Comparison of intrathecal and intravenous morphine for post-operative analgesia after single level spinal fusion surgery.

Adriaan Johannes Vlok

MB ChB, MMed (Neurosurgery), FC (Neurosurgery)

Dissertation presented for the Degree of Doctor of Philosophy in the Faculty of Medicine and Health Sciences, at Stellenbosch University

Supervisor: Prof Andre Coetzee

MB ChB M Med(Anes) FFA(SA) FFARCS PhD MD PhD DSc

March 2020

Declaration

By submitting this dissertation electronically, I declare that the entirety of the work contained therein is my own, original work, that I am the sole author thereof (save to the extent explicitly otherwise stated), that reproduction and publication thereof by Stellenbosch University will not infringe any third party rights and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

Date: March 2020

Abstract

The purpose of this study was to evaluate the efficacy, safety and cost effectiveness of a 0.005mg/kg, up to a maximum of 0.45mg, dose of intrathecal morphine in first-time single level spinal surgery. The study was conducted, and results apply, to a tertiary care public service hospital in South Africa.

This experimental intervention was compared to the institutional standard of care being the use of intravenous morphine via a patient-controlled device, administering 1mg of morphine intravenously every 7 minutes as required.

Efficacy was measured with reference to validated scoring systems which included the Oswestry disability index, Roland Morris questionnaire, EQ-5 score and visual analogue scale (VAS) to assess pain, analgesia and disability in the post-operative phase and subsequent follow up. A standardised physiotherapy regime was used to mobilize patients and the patients was discharged directly to their homes, specifically skipping a step-down facility.

Safety was assessed by monitoring the known side-effects of morphine (nausea, vomiting, pruritis), oxygen saturation, respiratory rate and sedation during the stay in the ICU. Inter alia, blood gases were analysed on 11 occasions within the first 24 hours. General patient follow-up occurred at 6 weeks, 3 and 6 months.

The study was conducted in a prospective double-blind, randomized placebo controlled fashion.

40 patients were enrolled (20 per group). The time to discharge for the intrathecal morphine group (IT) was statistically significantly shorter (3.68 days) compared to 5.61 days for the patient-controlled analgesia (PCA) group. This translated into a 43.5% saving for general ward stay costs.

VAS was assessed when lying still and moving and the difference between these values was used to quantify the intensity of pain. A significant difference was noted at 24 hours favouring the IT group. Significantly less supplemental analgesia was used in the IT group during the first 24 post-operative hours.

No significant difference in side-effects were noted between the groups. The initially elevated mean $PaCO_2$ in the IT group demonstrated a significant decrease from 4 hours up to 24 hours. An increase in mean respiratory rate was demonstrated from 10 hours onwards in both groups. Seven incidents of hypoxia (PaO_2 < 8kPa) were observed (IT=4, PCA=3). The 7 incidents were explained by either a low FiO_2 or a decrease in functional residual capacity (FRC) as

proven by the A-a gradient. No overt sedation was clinically demonstrated at the time the PaO_2 was less than 8.0 kPa.

Six week, 3-month and 6-month follow-up demonstrated significant improvement in all scoring modalities in both groups.

The intrathecal use of morphine had a direct effect on the μ-receptors in the spinal cord resulting in segmental analgesia allowing the patients to mobilize faster compared to the more central acting analgesic effects offered by intravenous morphine. The proposed dose proved to be safe with minimal side-effects, all of which were comparable to the PCA group. The application will be particularly useful in obese patients where the calculation of a safe intravenous dose can be challenging because of excess adipose tissue. When using IT or PCA morphine, supplemental oxygen is suggested for the first 4 hours post-operatively and continuous monitoring of respiratory rate, saturation and sedation should be done. Finally, it is recommended that it will be safer practice to reset the minimum cut-off value for saturation at a higher value than the conventional 90% level.

Abstrak

Die doel van die studie was om die effektiwiteit, veiligheid en koste-effektiwiteit van ‘n 0.005mg/kg, tot ‘n maksimum van 0.45mg, dosering van intratekale morfien te evalueer in eerste operasie, enkel vlak lumbale spinale fusie chirurgie. Die studie is uitgevoer in en resultate relevant tot ‘n tersiere vlak publieke diens hospitaal in Suid Afrika.

Die eksperimentele intervensie was vergelyk met standaard sorg vir hierdie tipe gevalle wat bestaan uit intraveneuse morfien toegedien deur ‘n pasient-beheerde toestel wat 1mg intravenuese morfien elke 7 minute toedien soos benodig.

Effektiwiteit is gemeet deur gevalideerde evaluerings sisteme wat insluit die “Oswestry disability index”, “Roland Morris questionnaire”, “EQ-5” telling asook die “visual analogue score (VAS)” om pyn en ongeskiktheid te evalueer, beide post-operatief asook tydens opvolg besoeke. ‘n Gestandardiseerde fisioterapie regime was gebruik om die pasiënte te mobiliseer en pasiënte is direk tuis ontslaan, sonder enige rehabilitasie fasiliteit.

Veiligheid is evalueer deur monitering van die bekende newe-effekte van morfien (naarheid, braking, pruritis), suurstof saturasie, asemhalingspoed en sedasie gedurende die intensiewe sorgeenheid verblyf. Bloedgas analises is gedoen op 11 geleenthede gedurende die eerste 24 post-operatiewe ure. Pasiënt opvolg het geskied op 6 weke, 3maande en 6 maande.

Die studie is uitgevoer as ‘n prospektiewe, dubbel-blind, gerandomiseerde placebo beheerde studie.

40 pasiënte is ingesluit (20 per groep). Die tyd tot ontslag vir die intratekale morfien (IT) groep was statisties beduidend minder (3.68 dae) as die 5.61 dae in die pasiënt-beheerde analgesie (PCA) groep. Dit het gelei tot ‘n 43.5% kostebesparing in algemene saal verblyf.

VAS was gemeet beide as die pasiënt stil lê en as hulle beweeg. Die verskil in die waardes is gebruik om intensiteit van pyn aan te dui. ‘n Statisties beduidende verskil is op 24 uur identifiseer ten gunste van die IT groep. Betekenisvol minder reddings-analgesie is gebruik in die IT groep oor die eerste 24 uur.

Geen beduidende verkil in newe-effekte kon identifiseer word nie. Die aanvanklike verhoogde gemiddelde $PaCO_2$ in die IT groep het ‘n statisties betekenisvolle uur tot uur daling getoon vanaf 4 tot 24 uur. Beide groepe het ‘n gemiddelde asemhalingspoed verbetering getoon vanaf 10 ure post-operatief aanwaards. Sewe insidente van hipoksie (PaO_2 < 8kPa) is identifiseer (IT=4, PCA=3). Die 7 insidente kon verduidelik word deur of ‘n lae FiO_2, of ‘n lae funksionele residuele kapasiteit aangedui deur die A-a gradient. Geen sedasie was assosieer met die insidente van PaO_2 < 8kPa nie.

Die 6 weke, 3 maande en 6 maande opvolge het statisties beduidende verbetering getoon in al die evaluerings sisteme.

Die intratekale gebruik van morfien het ‘n direkte effek op die μ-reseptore in die spinal koord wat lei tot segmentele analgesie wat die pasiente vinniger laat mobiliseer vergeleke met intraveneuse morfien wat ‘n meer sentrale meganisme van werking het. Die voorgestelde dosis is bewys as veilig met minimale newe-effekte vergeleke met die PCA groep. Dit is veral van belang in obees pasiënte waar dosis bepaling uitdagend is met die addisionele vetweefsel wat teenwoordig is. Supplementele suurstof word aanbeveel vir die eerste 4 ure vir beide groepe, met volgehoue monitering van asemhalingspoed, saturasie en sedasie. Laastens sal dit veiliger wees om die minimum aanvaarde waarde vir saturasie op ‘n hoër vlak te stel as die konvesionele 90%.

Acknowledgements

This dissertation could not have been completed without the support and contributions of many individuals, all to whom I am extremely grateful. I would like to thank the following people specifically:

Prof Andre Coetzee, my supervisor and previous head of Anaesthetics and Critical Care at the University of Stellenbosch. His guidance throughout this project from conception to completion has been the cornerstone in keeping me motivated and constantly improving my own ability to reason and discuss the scientific work. His professionalism and incredible work-ethic also provides me with the blueprint for a successful professional career.

Dr Nash Munthree, my neurosurgical colleague for his invaluable contributions as co-investigator.

Dr Alex van der Horst, my orthopaedic colleague for his help and support of this project.

Dr's Armin Gretschel and David Roytowski, my consultant colleagues at the Department of Neurosurgery for proving me the time to complete this work and their constant support throughout this project. Also, all the registrars and medical officers for their support.

Mrs Anneke Groenewald, typist, secretary and overall mother-figure to all passing through the Department of Neurosurgery. She was in constant communication with the patients and facilitated all the admissions, follow-ups and administrative challenges with this project. Her never-ending compassion to the patients and families is humbling.

Dr Guillaume Muller, anaesthetist, for his valuable contributions to the technical aspects of the anaesthetic components of this study.

My wife **Ingrid** and our three children **Adriaan, Leah and David** for their love, patience and support throughout this project. They symbolize the meaning of my life.

Above all, I would like to thank our heavenly Father. "I can do all things through Christ who strengthens me" (Phil 4:13). I experience your love on a daily basis.

I dedicate this work to my father Gert. You are and will always be my inspiration.

Table of contents

Abstract……1
Abstrak……3
Acknowledgements……5
1.
Literature review……10
1.1. Morphine……10
1.1.1. Mechanism of action……10
1.1.1.1. Intravenous morphine……11
1.1.1.2. Intrathecal morphine……12
1.2. Patient controlled analgesia……14
1.3. Lower backache and spinal surgery……17
1.3.1. Instruments to measure backache and disability……18
1.3.1.1. The Visual Analogue Scale (VAS)……19
1.3.1.2. The Oswestry Disability Index……20
1.3.1.3. The Euroqol-5D……23
1.3.1.4. The Roland-Morris disability questionnaire……25
1.3.2. Psychiatric disorder and spinal pathology……27
1.3.3. Physiotherapy……27
1.3.4. Obesity……30
1.4. Peri-operative pain……32
1.4.1. Non-steroidal anti-inflammatory drugs……33
1.4.2. Opioids……35
1.5. Intrathecal morphine in spinal surgery……42
2. Materials and methods……54
2.1. Informed consent……55
2.2. Randomisation……55
2.3. PCA……55
2.4. Scoring systems……57

2.5. General anaesthetic plan……..……..58

2.6. Single level fusion……...63

2.7. Intrathecal injection……64

2.8. Blood gas analysis……..64

2.9. High care unit……..……...65

2.10. Rescue analgesia……..……...65

2.11. Physiotherapy……..……..……65

2.12. Retrospective cohort……..……65

2.13. Direct costs……..……..……66

2.14. Statistical analysis……..……66

3. Results……..……70

3.1. General remarks……..……70

3.2. Group demographics……..……71

3.3. Pre-operative scoring……..……...72

3.4. Surgical detail……..……..……74

3.5. Post-operative course……...75

3.6. Intrathecal injection and morphine side effects……..……81

3.7. VAS scores during study period and supplemental analgesia……..……82

3.8. Mobilisation……..……87

3.9. Blood gas analysis……..……90

3.10. Post-operative scoring results……..……116

3.11. Retrospective review……..……124

3.12. Direct cost……..……...125

4. Discussion……..……126

4.1. Introduction……..……126

4.2. Mobilisation and discharge……..……...127

4.2.1. Disability of patients……...129

4.2.2. Pain……..……..131

4.2.3. Mobilisation……136

4.2.4. Efficacy of the intrathecal morphine dose…….……..139

4.3. Safety of the intrathecal injection of morphine……..……..146

4.3.1. Intra-operative injection……147

4.3.2. Respiratory depression…….……..149

4.3.3. Respiratory rate……...151

4.3.4. Sedation……153

4.3.5. Oxygen saturation……..……154

4.3.6. $PaCO_2$……155

4.3.7. PaO_2……..157

4.4. Direct cost……160

5. Conclusion……..……161

6. References……..……163

1. Literature review

Modern anaesthetics are constantly searching for ways in which to optimise analgesia during surgery, especially in the post-operative period. The shift in focus, from systemic opioids to more regional analgesic, underlines the efforts being made to overcome the side-effects of opioids such as respiratory depression, sedation, nausea, vomiting and decreased bowel mobility (Raffaeli, 2006). This constant drive to optimise analgesia, yet minimise side-effects, leads to innovative research in pain relief.

1.1 Morphine

The first opioid approved for neuraxial use by the United States Food and Drug Association (FDA) was morphine (DeSousa, 2014). It has several possible routes of administration with the most popular being intravenous. The intrathecal route provides the opioid with direct access to the neural structures, however, due to its many perceived dangers which include cerebrospinal fluid leakage from the access point as well as respiratory depression, this route of administration is not very popular (Raffaeli, 2006). Irrespective of the route of administration, a portion, if not all of the morphine will enter the bloodstream, be metabolised in the liver and ultimately cleared via the kidneys (Fukuda, 2009).

1.1.1 Mechanism of action

Opioids are effective as they directly inhibit the painful stimuli which ascend in the spinal cord. Concurrently descending pain control circuits, arising in the midbrain, are activated in the dorsal horn in the spinal cord by means of opioid receptors found in both pre- and post-synaptic neurons (Fukuda, 2009). Opioids can reach these sites by several different means of which intravenous administration is most commonly employed.

The opioid receptors are G-protein linked and specifically located in laminae I and II of the dorsal horn. Once bound to the receptors, calcium channels close and potassium channels open which reduce the level of intracellular calcium. Subsequently there is a reduction in excitatory transmitters (substance P and glutamate) from the pre-synaptic C-fibres and, although A-fibres are not affected, the result of these actions is a reduction in nociceptive transmission (Hindle, 2008).

1.1.1.1 Intravenous morphine

Once administered, intravenous morphine is metabolised in the liver. Compared to other opioids, morphine has a relatively low lipid solubility and its penetration in and out of the central neural tissues (thus crossing the blood-brain barrier) is presumably slower (Fukuda, 2009).

Its main metabolites are Morpine-3-Glucuronide (M3G), which is inactive, and Morphine-6-Glucuronide (M6G), which has a similar potency to morphine itself regarding its binding to the μ-receptors in neural tissue (Linares, 2009). The kidney is mainly responsible for the clearance of morphine and thus renal failure is a major risk factor for persistent morphine effect, both from morphine itself and M6G.

The intravenous administration of morphine faces several obstacles. To calculate the dosage needed, a dosage per total body weight will be accurate for a lean individual. However, the modern epidemic of obesity in the developed world (World Health Report, 2013) has resulted in body weight not being the only factor which needs to be considered.

The amount of adipose tissue in the body, partly due to its poor blood supply (Wulfsohn, 1969), does not resort under pharmacologically active mass but does, however, add significantly to total body weight. At the same time the increase in weight, due to the deposition of adipose tissue, is non-linear to the relative increase in muscle bulk and other organs (Coetzee, 2010). The accurate calculation of morphine requirements in the overweight patient is thus a challenging exercise. The inability to calculate a safe and optimum dose across the spectrum of differing weights creates the risk of undertreating pain but also the potential for overdosing with life-threatening results.

The more hydrophilic nature of morphine results in its crossing the blood-brain barrier slower than in the case of its more lipophilic counterparts, prolonging time to effect and resulting in more unpredictable outcomes when delivered intravenously. Green *et al*. (Green, 2010) concluded that total body weight can be used for dosage calculation of highly lipophilic drugs when these are given acutely (e.g. during anaesthesia) as these drugs are easily and quickly taken up due to the high lipid content of target cell membranes. However, once a drug is more hydrophilic (as with morphine), both the time to effect and dosage calculations become somewhat more challenging.

1.1.1.2 Intrathecal morphine

The identification of opioid receptors in the brain by Pert and Schnyder in 1973 (Pert, 1973) and, subsequently in the spinal cord in 1976 (LaMotte, 1976), heralded the use of intrathecal morphine for analgesia. This concept was successfully tested in the animal model in 1976 (LaMotte, 1976). A study by Yaksh *et al.,* published in *Science* in 1976, similarly concluded that narcotics acting only at the spinal level changed cord function to block not only spinal reflexes but also the operant response to painful stimuli (Yaksh, 1976).

Dorsal horn opioid receptors were identified by radioligand techniques and this subsequently led to further animal studies (DeSousa, 2014). A dose of 0.25ug morphine was intrathecally injected into rats by Wang *et al*. in 1976 (Wang, 1977). They concluded that intrathecal morphine provided potent analgesia which could be reversed with the administration of Naloxone. This paved the way for human application, a domain first studied by Wang in 1979. He successfully showed that the concept was valid in eight patients with genitourinary malignancy (Wang, 1979). Since then, intrathecal morphine has become widely used in an array of surgeries.

Studies by McQuay *et al*., published in 1989, demonstrated an inverse relationship between the lipophilic nature of the opioid and the potency thereof based on the ability of the opioid drug to cross the blood-brain barrier (McQuay, 1989).

Morphine administered intrathecally shows a high affinity for dorsal horn receptors. However, it does not exhibit the same characteristic for non-receptor sites in the myelin and white-matter (Hindle, 2008). This leads to a high concentration of morphine in the cerebrospinal fluid which is sustained by the more hydrophilic nature of morphine as opposed to other opiates, such as Fentanyl, which is much more lipophilic in nature and will thus cross the blood-brain barrier almost immediately (Fukuda, 2009). This then accounts for the spread of intrathecal morphine as well as the late, or later, onset of respiratory depression (Hindle, 2008). Said respiratory depression usually occurs after about 6 to 12 hours (Bujedo, 2012), once the morphine has spread more cephalad in the cerebrospinal fluid. A single dose of morphine, however, makes the timing and severity of respiratory depression more predictable and easier to avoid if safe dosages are applied, specifically when compared to continuous intravenous infusions and bolus intravenous doses (Bujedo, 2012).

The intrathecal morphine will cause an effective band of analgesia in the proximity of the area of administration in addition to systemic effects (Bujedo, 2012).

However, if the morphine dose is appropriate, it is possible to limit this cephalad spread and hence minimise the risk of respiratory depression. The combination of low lipophilicity and the

inherent lack of cephalad spread was proven by Kroin *et al*. in 1993 (Kroin, 1993). Results imply that it is possible to achieve a safe dose which would be almost completely risk free in terms of respiratory depression. Kroin noted a distinct decline in drug concentration in the cephalad region when cerebrospinal fluid was sampled from the cistern and lumbosacral areas (Kroin, 1993). This also confirmed that a direct intrathecal site of introduction, situated at the mid to lower lumbar area, would be associated with less ascent of the drug and thus curb its associated systemic, or central, effects.

However, several factors aid in the cephalad spread of intrathecally delivered drugs (Hindle, 2008). Cyclical thoracic pressure changes, associated with breathing, aid the flow of cerebrospinal fluid, both cranially and caudally. Brain expansion also occurs with the cardiac cycle and this, in turn, results in the flow of cerebrospinal fluid through the subarachnoid spaces. Both these mechanisms will thus aid in a lumbosacral delivered drug being distributed cranially, even if administered in lower concentrations (Hindle, 2008; Kroin, 1993).

If a safe concentration could be achieved through direct delivery of the drug at a lumbosacral level and minimal spread occurs due to the low concentration of the drug being administered, it thus follows that the risk of respiratory depression should be low.

An increase in the lumbosacral cerebrospinal fluid, adenosine, constitutes a further proposed mechanism of action. Adenosine opens potassium channels and subsequently decreases nerve fibre excitation due to hyperpolarisation which results in reduction of neural activity (Hindle, 2008; Kerchner, 2002). Intrathecally delivered morphine could also be taken up by the posterior radicular artery and this may result in its spreading to the brainstem. This mechanism was proven by autoradiographic studies in primates where an increased uptake of morphine in the respiratory centre was noted 60 minutes after it had been injected intrathecally (Hindle, 2008), even though the pharmacologically active amount of morphine had significantly diminished by then.

Morphine will ultimately cross the blood-brain barrier (Bujedo, 2012), be taken up via the epidural venous plexus and then be metabolised in the liver. This amount will be small and, after a single intrathecal dose, deemed clinically insignificant.

It was demonstrated in a pharmacokinetic study of intrathecal morphine in which the effect-site concentration of the morphine was well maintained over the first 6 hours whilst minimal plasma concentrations were detected (Sjöström, 1987). This phenomenon can be ascribed to the hydrophilic nature of morphine. The subsequent clinical effect was dose dependent and a slow elimination phase was noted which implies a lingering concentration of morphine in the CSF.

Intrathecal morphine has been widely adopted by several different surgical disciplines resulting in effective analgesia, without the addition of a local anaesthetic (Giovannelli, 2008). The American FDA approved preservative free morphine for intrathecal use in 1984 (Sultan, 2011).

1.2 Patient controlled analgesia

As early as 1953 Keats *et al*. (Keats, 1961) highlighted the inadequacies of post-surgical pain control. Somerville, in 1982, once again emphasised this fact and claimed that insufficient treatment of pain should be tantamount to negligence and a violation of patients' rights (Somerville, 1982; Brennan, 2007). The challenge, not only in high care settings but in general wards as well, was to address the delay in the initial administration of the drugs. A cycle of delayed administration was identified as a series of events initiated by the patient requesting pain medication. The nurse would take time to respond to the request, screen the patient, sign out the necessary medication, prepare an injection and finally administer it. This process, along with absorption time, resulted in a significant time interval to effect (Graves, 1983). The parenteral use of analgesia would facilitate a quicker response to medications and, having the patient administer the drug him/herself with certain safety measures in place, could break the cycle of delayed analgesia (Graves, 1983).

Nursing staff's influence on pain relief is dependent on their ability to assess said pain. Clarke *et al*., in a publication reporting on the impact of nursing characteristics and education on pain management, noted that the undertreatment of pain can be ascribed to nursing staff's lack of understanding regarding addiction, tolerance and dependence. This incomprehension ultimately creates a fear of potential complications and, as such, it results in insufficient treatment (Clarke, 1996). Dalton *et al*. identified a proportional relationship between the treating nurse's ability to assess pain and his/her years of nursing experience (Dalton, 1989). Holm also found that pain assessment, including emotional suffering and psychological distress, was significantly influenced by the nurse's own personal experiences and perception of pain, thus potentially resulting in undertreatment of a patient (Holm, 1989).

Patient-controlled analgesia (PCA) was first described in 1979 (Kranz, 1979) but PCA opioids only became universally accepted 15 years later. Today it is considered a valuable adjunct to post-operative analgesia because of its intravenous delivery of opioids and the lock-out period maintaining patient safety.

All patient-controlled analgesia devices operate in accordance with the same basic principles. The system comprises of an initial loading dose provided by the anaesthetist, a set demand dose which the patient will deliver themselves via the device, a lockout period which controls the amount provided and 1- and 4-hour dose limits (Grass, 2005).

The safety of the PCA device, however, is closely linked to the careful training of both the patient and nursing staff (Coetzee, 2013). Mishaps that do occur are often as a result of inappropriate dose programming and/or accidental bolus administration during preparation (White, 1987). A further safety feature lies in the fact that if the opiates do result in cerebral depression, the patient will sleep and not self-request further PCA doses.

Coetzee indicated, in his review on PCA usage, that education forms the cornerstone of achieving successful analgesia (Coetzee, 2013). As such, the patient needs to first understand the principles of PCA as well as the fact that despite the PCA device, pain will probably not be completely controlled. Monitoring of the patient will require waking him/her regularly to assess sedation and the patient should also be informed of this practice. Instruction should take place via interpersonal communication and a printed handout should also be supplied for perusal at the patient's leisure. Education should take place outside the theatre environment and during a pre-operative visit. Similarly, intensive care unit or general ward nursing staff must be aware of patients' monitoring requirements as well as the clinical signs of an overdose which include depression of consciousness, sedation and hypoventilation. Nursing staff should also be well versed in immediate treatment options if this should occur (Parker, 1991).

Greater efficacy of PCA has been demonstrated when a background infusion is run concurrently. This approach has, however, not been consistently described throughout the literature and has proven to be dangerous. Parker *et al*. studied 230 patients and their results could not demonstrate a difference in analgesia between 0.5, 1 or 2mg/h infusion rates running concurrently with on-demand PCA morphine delivering boluses of 1 - 2mg (Parker, 1991).

Sam *et al*. (Sam, 2011) assessed the pharmacokinetics of morphine and its metabolites (M6G and M3G) during PCA. Results clearly indicated that the effect-site concentrations increased with an increase in background infusion rates. Peak levels were achieved 8 to 24 hours after the infusion had started with the highest peaks occurring when a 2mg/hour infusion was used. Across the groups, the peak M6G concentration was measured at 25 hours after the infusion was started with the 2mg/hour infusion again yielding the highest levels. The initial peak at 8 hours was attributed to increased patient PCA usage immediately post-operatively in an attempt to achieve effective analgesia. The authors concluded that monitoring of patients with PCA devices, especially with a concurrent background infusion, should extend beyond 24 hours. These findings were reiterated by Flisberg *et al*. who concluded that a greater risk of

respiratory depression occurs when PCA analgesia is supplemented with a background infusion. They noted that adverse events usually occur in the first post-operative day rather than immediately post-surgery and, as such, the need for monitoring beyond the perceived high-risk period, immediately post-operation, was stressed (Flisberg, 2003).

The concern is that increasing the total dose of morphine will increase the risk of respiratory depression (Sam, 2011). Sidebotham *et al.* reviewed more than 6 000 patients who were treated with a PCA device after surgery. Their overall incidence of life-threatening complications was low at 0.28%, thus confirming the safety of the device (Sidebotham, 1997). A subgroup, however, was managed with a background infusion (n=276). When closely examined this subgroup revealed significant incidences of overdose related complications.

Similarly, Sidebotham *et al*. demonstrated that the PCA device was most frequently used in the first 24 hours after surgery. Thereafter a rapid decline in use was noted over the following 48 hours, irrespective of the type of surgery which had been performed (Sidebotham, 1997).

The volume of morphine distribution is 2 - 5L/kg which implies that it will not be contained in the plasma alone but that it will be distributed to other tissues as well (Linares, 2009). This might result in PCA morphine being ineffective and therefore prompt increased use or even a request for rescue analgesia. The preceding combination elevates the risk of respiratory depression and other opioid related side-effects occurring later than generally expected (Green, 2004). It would therefore be beneficial if the risk could be contained with the administration of a single dose, for instance intrathecally, rather than exposing the patient to an increased risk associated with the accumulation of morphine after repeated doses.

Coetzee, in his review on the safety of PCA devices (Coetzee, 2013), concluded that once a patient has recovered after surgery, it is the responsibility of the anaesthetist to titrate a volume of morphine to facilitate a starting point of very little to no pain prior to commencing the PCA. This process requires the doctor to exercise patience as the complete effect of a dose of morphine may only be demonstrated up to 45 minutes after titration.

Intravenous morphine might also have a sedative effect and although this is the fundamental concept on which the safety of the PCA method relies it may, on the other hand, compromise the effective use of the PCA device (Fukuda, 2009).

A further consideration in gauging the success of patient-controlled analgesia is the patient's willingness to use the PCA pump when prompted by their experience of pain. If the patient's expectations of post-operative pain were not properly discussed, inappropriate usage may ensue in which the patient will use the device constantly to prevent pain rather than in response to the stimulus of pain (Johnson, 1989). In theory, the lock-out period and

programmed maximum dose over any given period of time should limit this risk. Similarly, some patients may underutilise the PCA. This may be prompted by a perception that pain should be accepted and endured and/or a perceived risk associated with the PCA (Ferrante, 1988). In both these situations, training is paramount to ensure successful use of PCA. Patient compliance, however, can vary significantly (Coetzee, 2013).

1.3 Lower backache and spinal surgery

Lower backache is a condition which exerts a crippling effect on individual patients as well as economies worldwide. Not only does it negatively affect an individual's ability to earn an income, but the pain in itself demoralises and significantly reduces quality of life. The economy, in turn, is affected by loss of work days and the subsequent impact on productivity (Ekman, 2005). The prevalence of lower backache, as reported in different studies and quoted in a meta-analysis by Dagenais *et al*., varies from 5 - 65% with a mean of 18.7% (Dagenais, 2005). The impact of this condition is thus *directly* experienced by the patient, by virtue of direct costs accrued, and *indirectly* due to lost work days and the effect thereof on the broader economy (Dagenais, 2005). Direct costs involve peri-operative interventions which include chiropractors, physical therapists, peri- and intra-operative pharmacy costs, surgical cost (including anaesthetic, surgeon and facility costs), imaging ward costs and out-patient visits (Dagenais, 2005). These direct costs are generally easy to calculate as accounts and record keeping enable one to make a comparison across patient groups. Indirect costs, however, are more challenging to calculate and include factors such as impact of continual absenteeism on company and/or work productivity, early retirement, impact on the household, inactivity and sick leave (Dagenais, 2005).

Katz *et al.* attempted to assess the socio-economic impact of lower backache in the United States (Katz, 2006). They found that in 2005 the American Worker's Compensation expenditure exceeded 20 billion dollars for musculoskeletal disorders of which *backache* was noted as most prevalent. Lower back pain accounted for a loss of productivity equal to the bulk of 50 billion dollars. The total cost of lower back pain amounted to between 100 and 200 billion dollars for the year 2005 (Katz, 2006). Frymoyer reported this cost to be between 50 and 100 billion dollars per year in 1991 (Frymoyer, 1991).

Due to certain socio-economic, psychological and work-related reasons, some individuals unfortunately often settle on *backache* as a diagnosis of convenience. A reliable diagnosis is consequently a challenging task and the overall indirect cost nearly impossible to calculate (Andersson, 1999). At the same time, degenerative conditions of the spine are most likely to affect the older section of the population and this includes individuals who are already in the

latter part of their careers or who are approaching retirement (Andersson, 1999). The diagnosis of backache can thus either lead to or act as an incentive for early retirement. Hunter *et al.* studied 178 railroad workers with lower backache and, based on their observations, implemented a multidisciplinary rehabilitation programme (Hunter, 1998). The study recorded patient improvement in both subjective and objective measures, yet no impact was noted on long-term work status. These findings seem to imply that other factors, such as financial considerations, played a significant role.

Once neurological cause, malignancy or infective process has been excluded from the work-up of the chronic backache patient, the degenerative realm of disease comes to the fore (Chou, 2007). The afore-mentioned group resorting under malignancy and neurological fallout make up only 5% of lower backache patients (Wassenaar, 2011). The gold standard in lumbar spine imaging is the magnetic resonance imaging scan (MRI) which provides accurate soft issue information of the spinal nervous and ligamentous structures. It is the clinical correlation, however, that remains challenging. Wassenaar, in a systematic review pertaining to the correlation of MRI findings to lower backache in the absence of malignancy, infections or nerve root pathology (thus the chronic backache group), found that MRI findings were only 75% sensitive and 77% specific to clinical findings of spinal stenosis or degenerative disease and that a significant number of patients were over-diagnosed based on the MRI findings alone (Wassenaar, 2011). Sirvanci *et al*. attempted to ascertain a correlation between MRI findings and the Oswestry Disability Index (ODI) which is a validated scoring system used to define disability due to degenerative spinal pathology (Sirvanci, 2008). They could demonstrate no significant correlation between image findings and the ODI scores. However, the scan is almost routinely requested by clinicians prompted by a fear of missing some serious underlying pathology and/or in an effort to reassure patients (Ash, 2008).

1.3.1 Instruments to measure backache and disability

There are several scoring systems used to quantify backache and monitor the progression thereof. These scoring systems are also used to quantify the impact of the condition on daily living and quality of life.

1.3.1.1 The Visual Analogue Scale

The visual analogue scale (VAS) is one of the most popular measuring tools used in spinal pathology and spinal surgery (Gould, 2001). It is performed by evaluation of a horizontal line, typically 10cm in length, with word descriptors at both ends namely *no pain* and *worst pain ever*. The patient is required to indicate his/her current experience of pain upon the continuum scale. The result is filed enabling comparison to past tests, using the same scale.

Although the instrument can directly measure pain, it is reliant on the patient's perception and understanding of the instrument. This implies that the number allocated to a specific degree of pain cannot be compared to another patient's experience as perceptions of pain are unique to each individual. However, the trend of *decreasing* or *increasing* pain is relevant and will be indicated in terms of consecutive determinations of the scale. The patient quantifies his/her own pain and will then compare this experience at a specific time using a similar standard of interpretation.

The scale involves a horizontal line marked 0 to 10. The length of the horizontal line should exceed 10cm as a shorter line exerts an impact on scoring variance (Scott, 1976). Similarly, the ends of the line should have vertical bars to clearly delineate the borders of the scoring tool and so prevent patients from marking outside the scoring parameters (Huskisson, 1983).

The Visual Analogue Scale (VAS) was validated in 1983 (Price, 1983) and reviewed by Wewers *et al*. in 1990 (Wewers, 1990). It is a quick and easy-to-use tool which, in busy practices especially, can act as a handy guide to help the physician formulate an opinion as to the progress of a patient or the efficacy of an intervention. The VAS gives expression to an important fact that pain is a subjective experience and, as such, it allows for every individual to express his/her unique perception. The change in scoring can be reproduced reliably and measured across a study population.

The minimal clinical important difference was found to be 19mm, or two vertical lines as seen on Figure 1.1 (Hägg, 2003). Hägg concluded that a 19mm difference, or more, in scoring at two separate intervals can be accepted as indicative of a clinically significant change.

A variation of the VAS score exists in which the same line is used, but numbers ranging from 0 to 10 are spaced evenly in between the ends. In this way the scale is converted into a so-called numeric rating scale (NRS), or segmented numeric version of the VAS, as per Figure 1.1. The NRS differs very little from the traditional VAS score. A numerical value on the horizontal line, which correlates easily to pain, indicates the degree of pain being experienced by the patient (Hawker, 2011). The extremes of pain are also defined as per the VAS. The NRS is especially helpful when a patient is sleepy (such as the case might be in opioid

analgesia or post-operatively in spinal surgery) or is experiencing challenges in making a mark on the line depicting their pain (e.g. intravenous lines on the writing hand). The NRS can be conducted verbally (Jensen, 1986). Its validity has a high correlation with the VAS, and reliability in testing and re-testing is very high (Ferraz, 1990).

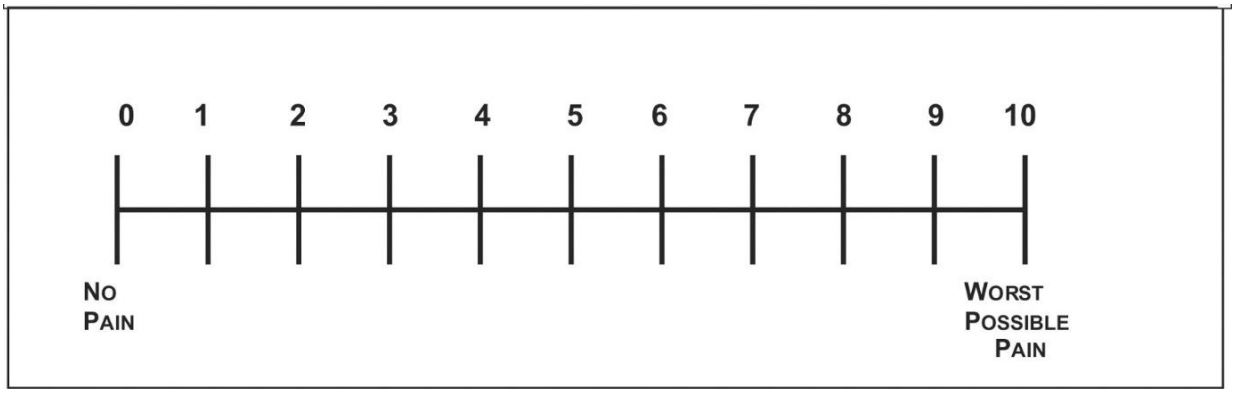

Figure 1.1: *The numeric rating scale (NRS) (Jensen, 1986)*

1.3.1.2 The Oswestry Disability Index

The Oswestry Disability Index (ODI) (Figure 1.2) is a condition specific outcome measuring tool aimed at spinal disorders. It is one of the most frequently used tools to estimate disability. It was first proposed in 1980 (Fairbank, 1980) and disseminated in 1981 at the International Society for the Study of the Lumbar Spine (ISSLS) meeting held in France. It contains 10 categories of activities associated with everyday living. Each activity has 6 possible options from which the respondent can choose with the best option (or top) scoring 0 and the worst option (or bottom) scoring 5. The total is multiplied by 2 (Fairbank, 2000). The result is categorised and interpreted in terms of a score where 0 reflects the *best* possible and 100 the *worst* possible state of health. The degree of disability is expressed in increments of 20 with 0 - 20% implying minimal disability, 20 - 40% moderate disability, 40 - 60% severe disability, 60 - 80% crippled and 80 - 100% bed-bound (Fairbank, 2000). It has been translated into numerous languages.

The daily living categories denote everyday activities to which patients can easily relate. These categories include: personal care, walking, standing, sitting, lifting, sex life, travelling, social life, sleeping and a personal interpretation of pain. It is condition specific to the degenerative spine and is advantageous as the self-assessment format contains items which can be easily

understood by the patient. The assessment takes less than 5 minutes to complete and less than 1 minute to score (Sirvanci, 2008). The patient need only tick the appropriate option in each category and is not privy to the score associated with that option.

This instrument was also intended for use at different time intervals, particularly to evaluate the effect of an intervention. It correlates significantly with the VAS ($p<0.01$) (Gronblad, 1997). Gronblad demonstrated increased VAS scores in relation to everyday activities whereas the ODI demonstrated a decrease in these activities, thus implying comparative conclusions in both scoring systems (Gronblad, 1997). The significant correlation was demonstrated in both females and males which confirmed that disability associated with degenerative spinal conditions is painful.

The inclusion of basic activities in the assessment makes this scoring system applicable to any individual, irrespective of facilities or social support structures, as it represents the impact of pain on the basic qualities of life. The ODI is easy and convenient to use in busy clinical environments seeing that it is reliable, short, reproducible and internally consistent within a practice (Sirvanci, 2008).

name ..... address ..... date .....
date of birth ..... age..... .....
occupation ....
how long have you had back pain? ..... years ..... months ..... weeks
how long have you had leg pain? ..... years ..... months ..... weeks

please read:

this questionnaire has been designed to give the doctor information as to how your back pain has affected your ability to manage in everyday life – please answer every section, & mark in each one only the *one box* which applies to you. we realise you may consider that 2 statements in any 1 section relate to you, but please *just mark the box which most closely describes your problem*

section 1 - pain intensity
- ❑ I can tolerate the pain I have without having to use pain killers
- ❑ the pain is bad but I manage without taking pain killers
- ❑ pain killers give complete relief from pain
- ❑ pain killers give moderate relief from pain
- ❑ pain killers give very little relief from pain
- ❑ pain killers have no effect on the pain and I do not use them

section 2 - personal care (washing, dressing, etc)
- ❑ I can look after myself normally without causing extra pain
- ❑ I can look after myself normally but it causes extra pain
- ❑ it is painful to look after myself and I am slow and careful
- ❑ I need some help but manage most of my personal care
- ❑ I need help every day in most aspects of self care
- ❑ I do not get dressed, wash with difficulty and stay in bed

section 3 - lifting
- ❑ I can lift heavy weights without extra pain
- ❑ I can lift heavy weights but it gives extra pain
- ❑ pain prevents me from lifting heavy weights off the floor, but I can manage if they are conveniently positioned, eg on a table
- ❑ pain prevents me from lifting heavy weights but I can manage light to medium weights if they are conveniently positioned
- ❑ I can lift only very light weights
- ❑ I cannot lift or carry anything at all

section 4 - walking
- ❑ pain does not prevent me walking any distance
- ❑ pain prevents me walking more than 1 mile
- ❑ pain prevents me walking more than 1/2 mile
- ❑ pain prevents me walking more than 1/4 mile
- ❑ I can only walk using a stick or crutches
- ❑ I am in bed most of the time and have to crawl to the toilet

section 5 - sitting
- ❑ I can sit in any chair as long as i like
- ❑ I can only sit in my favourite chair as long as i like
- ❑ pain prevents me from sitting more than 1 hour
- ❑ pain prevents me from sitting more than 1/2 hour
- ❑ pain prevents me from sitting more than 10 minutes
- ❑ pain prevents me from sitting at all

comments

section 6 - standing
- ❑ I can stand as long as I want without extra pain
- ❑ I can stand as long as I want but it gives me extra pain
- ❑ pain prevents me from standing for more than 1 hour
- ❑ pain prevents me from standing for more than 1/2 hour
- ❑ pain prevents me from standing for more than 10 minutes
- ❑ pain prevents me from standing at all

section 7 - sleeping
- ❑ pain does not prevent me from sleeping well
- ❑ I can sleep well only by using tablets
- ❑ even when I take tablets I have less than six hours sleep
- ❑ even when I take tablets I have less than four hours sleep
- ❑ even when I take tablets I have less than two hours sleep
- ❑ pain prevents me from sleeping at all

section 8 - sex life
- ❑ my sex life is normal and causes no extra pain
- ❑ my sex life is normal but causes some extra pain
- ❑ my sex life is nearly normal but is very painful
- ❑ my sex life is severely restricted by pain
- ❑ my sex life is nearly absent because of pain
- ❑ pain prevents any sex life at all

section 9 - social life
- ❑ my social life is normal and gives me no extra pain
- ❑ my social life is normal but increases the degree of pain
- ❑ pain has no significant effect on my social life apart from limiting my more energetic interests, eg dancing etc
- ❑ pain has restricted social life and I do not go out as often
- ❑ pain has restricted my social life to my home
- ❑ I have no social life because of pain

section 10 - travelling
- ❑ I can travel anywhere without extra pain
- ❑ I can travel anywhere but it gives me extra pain
- ❑ pain is bad but I manage journeys over two hours
- ❑ pain restricts me to journeys of less than one hour
- ❑ pain restricts me to short necessary journeys of less than 1/2 hour
- ❑ pain prevents me from travelling except to the doctor or hospital

from: Fairbank J C T, Couper J, Davies J B & O'Brien J P Physiotherapy 1980; 66: 271-73

Figure 1.2: *The Oswestry disability index (Fairbank, 2000)*

1.3.1.3 The Euroqol-5D

The Euroqol-5D (EQ-5D) scoring system, as per Figure 1.3, combines the clinical and economic impacts which an intervention, or disability, exert on a patient (The EuroQOL Group, 1990).

This scoring system tests 5 dimensions (mobility, self-care, activities of daily life, pain and anxiety/depression) with each dimension only allowing 3 options (no; mild to moderate; severe). The patient is requested to place a tick next to the sentence which best describes his/her condition at the time, allowing for comparison at a later stage. The scoring system can be applied to a great variety of conditions and is frequently used, and has been validated for use, in spinal surgery (The EuroQOL Group, 1990, Solberg, 2005). Each dimension has 3 options and thus 3^5 or 243 possible state of health combinations exist (Brooks, 1996). Apart from its ability to measure clinical and emotional improvement, or deterioration, the principle holds that a value can be allocated to a condition at a specific time (Williams, 1995).

Jansson *et al.* reported on 230 spinal stenosis patients in 2009 (Jansson, 2009). The EQ-5D scoring system was accurate in indicating both quality of life and clinical improvement in this patient cohort.

Solberg *et al*. attempted to assess the reliability, validity and responsiveness of the Euroqol 5-D in a prospective study assessing 326 patients undergoing spinal surgery for degenerative spine conditions (Solberg, 2005). They compared their results to the ODI and concluded that the EQ-5D was responsive, valid and reliable in the assessment and follow-up of patients undergoing lower back surgery.

The instrument was further validated for use in lumbar spinal pathology by Mueller *et al.* (Mueller, 2013). They concluded that it correlated well with existing validated scoring systems, such as the ODI, and ascertained that it could serve clinicians well as an effective measure of state of health and clinical outcome. The EQ-5D combines individual aspects, such as self-care and mobility, but also identifies patients' perception as to their activities, mobility and mood. The test does not take long to perform, and its worth lies, *inter alia,* in the fact that it can be quickly repeated.

By placing a tick in one box in each group below, please indicate which statement best describes your own health state today.

Do not tick more than one box in each group.

Mobility

I have no problems walking about ☐
I have some problems in walking about ☐
I am confined to bed ☐

Self-care

I have no problems with self-care ☐
I have some problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

Usual activities (e.g. work, study, housework, family or leisure activities)

I have no problems with performing my usual activities ☐
I have some problems with performing my usual activities ☐
I am unable to perform my usual activities ☐

Pain/Discomfort

I have no pain or discomfort ☐
I have moderate pain or discomfort ☐
I have extreme pain or discomfort ☐

Anxiety/Depression

I am not anxious or depressed ☐
I am moderately anxious or depressed ☐
I am extremely anxious or depressed ☐

Figure 1.3: *The Euroqol 5-D (The EuroQOL Group, 1990)*

1.3.1.4 The Roland-Morris disability questionnaire

The Roland-Morris disability questionnaire (RM) is specifically designed to detect physical disability as a result of lower back pain (Roland, 2000). It is a useful patient-friendly tool for monitoring progress, in both clinical practice and clinical trials, as it is short, easy to understand and can be completed quickly. The questionnaire originally contained 24 questions, all starting with the phrase “Because of my backache…” but as certain questions were viewed as redundant, it was later reduced to 18 questions (Stratford, 1997). Its successful application was evident in instances of short-term improvement in backache, often achieved through primary care level interventions. The questionnaire is thus a particularly useful tool when trying to assess the improvement, as experienced by the patient, after an intervention had been performed on the lower back. The score has little or no association with the sex and/or age of the patient. Patients presenting to primary care facilities typically achieved median scores of 11 (Roland, 1983). The score correlated well with other questionnaires, such as the ODI, used in assessing physical function (Stratford, 1994). The ODI and RM are complementary in tracking patients’ improvement at follow-up (Beurskens,1996). A difference in scoring of 5 is considered clinically significant (Stratford 1998).

Roland Morris Questionnaire:

When your back hurts, you may find it difficult to do some of the things you normally do. Mark only the sentences that describe you lately

1. [ ] I stay at home most of the time because of my back.
2. [ ] I walk more slowly than usual because of my back.
3. [ ] Because of my back, I am not doing any jobs that I usually do around the house.
4. [ ] Because of my back, I use a handrail to get upstairs.
5. [ ] Because of my back, I lie down to rest more often.
6. [ ] Because of my back, I have to hold onto something to get out of an easy chair.
7. [ ] Because of my back, I try to get other people to do things for me.
8. [ ] I get dressed more slowly than usual because of my back.
9. [ ] I stand up only for short periods of time because of my back.
10. [ ] Because of my back, I try not to bend or kneel down.
11. [ ] I find it difficult to get out of a chair because of my back.
12. [ ] My back or leg is painful almost all of the time.
13. [ ] I find it difficult to turn over in bed because of my back.
14. [ ] I have trouble putting on my socks (or stockings) because of pain in my back.
15. [ ] I sleep less well because of my back.
16. [ ] I avoid heavy jobs around the house because of my back.
17. [ ] Because of back pain, I am more irritable and bad tempered with people than usual.
18. [ ] Because of my back, I go upstairs more slowly than usual.

Figure 1.4: *The Roland Morris Questionnaire*

1.3.2 Psychiatric disorder and spinal pathology

Of very real concern is the effect of social and psychiatric conditions on pre-operative presentation of patients with lower backache as well as on outcome, should surgery be performed. Menendez *et al.* described the effect of psychiatric conditions on major spinal surgery outcomes and concluded that pre-operative psychiatric conditions, such as major depression, schizophrenia, anxiety disorders and dementia, were associated with higher rates of peri-operative adverse events whilst only dementia had an effect on mortality (Menendez, 2014). Anxiety and depression are very real concerns in modern society and are estimated to affect 7.3% and 6 - 10% of the global population. Slover *et al.* observed 3 482 patients undergoing lumbar spinal surgery and ascertained that the impact of depression was statistically significant when using the Oswestry Disability Index at both 1 and 3 years (Slover, 2006). They highlighted the fact that researchers and clinicians need to be mindful of the deleterious effect that depression has on clinical outcomes.

Chronic pain due to lumbar pathology has a negative effect on patients' social and professional lives. Demyttenaere *et al*., in a *World Mental Health Survey*, indicated that mood and anxiety disorders were more prevalent in patients who suffered from chronic lower back or neck pain (Demyttenaere, 2007). Population surveys from 18 countries, including South Africa, were used to specifically assess the consistent association of mood and anxiety disorders with chronic backache. From a total of 85 088 patients surveyed, the results indicated that patients suffering from chronic backache had a 2.2 times increased likelihood of suffering from anxiety disorder and a 2.3 times increased likelihood of suffering from a mood disorder. The pattern of disorder prevalence was consistent across developed and developing countries.

It is therefore important to determine whether a patient is being treated for depression, schizophrenia or anxiety disorder prior to enrolling him/her in a clinical trial (Slover, 2006) as this will impact the post-operative course and outcomes.

1.3.3 Physiotherapy

Several studies have proven that physiotherapy and a structured rehabilitation programme have a significant impact on spinal surgery outcomes. As early as 1964 Hansen described the benefits experienced by a physiotherapy trained group in comparison with an untrained group (Hansen, 1964). The results indicated improved outcomes after spinal surgery in the trained patients who, as a result of trunk extensor strengthening, presented with quicker post-operative recovery times.

Another study, evaluating patients undergoing spinal surgery, divided the patient cohort into 2 groups: those undergoing regular physiotherapy and those subjected to a regime of intense post-operative physiotherapy. The results indicated that the latter outscored their counterparts (i.e. the normal physiotherapy group) and thus highlighted the positive effects of intensive physiotherapy for patients subjected to spinal surgery (Manniche, 1993).

Patients find it difficult to do strengthening exercises when inhibited by backache, albeit from surgery or degenerative pathology. The performance of the group which underwent the intense regime is thus all the more remarkable as they had no fear of activity, even after having recently undergone spinal surgery. Unfortunately, most patients struggle to commit to a programme of strengthening exercises after surgery and this limits the practical implementation of an intense post-operative regime, *especially when pain is not well controlled.*

Scrimshaw *et al*., in a prospective study, attempted to add neural mobilisation techniques to already established and proven physiotherapy muscle strengthening regimes in the post-operative period to see whether this would further benefit the spinal surgery group (Scrimshaw, 2001). At 12-month follow-up no improvement in objective scoring or clinical analysis could be demonstrated. These results suggest that muscle strengthening, and training remains central to the basic advantages associated with physiotherapy after spinal surgery.

The immediate goal-orientated active mobilisation regime after spinal surgery has been proven to aid in initial rehabilitation as well as improve short- and long-term outcomes (Kjellby-Wendt, 1998). This regime is initiated in hospital and can be continued by the patient at home. The goal-orientated programme encourages the patient to initially sit, stand and walk and then to participate in daily activities such as showering and climbing the stairs as per Figure 1.5. Once mobile, the patient is discharged and issued with exercises which he/she has to perform at home (Kjellby-Wendt, 1998).

Physiotherapy progress sheet:

(Mark with an X in each column if achieved on that day)

	Log-roll and circulation exercises	Sit on side of bed	Stand next to bed	Mobilise a few steps next to bed	Walk to bathroom aided	Walk to bathroom unaided	Mobilise independently (including stairs)	Discharge
Day 1								
Day 2								
Day 3								
Day 4								
Day 5								
Day 6								
Day 7								

Figure 1.5: *Physiotherapy progress sheet*

1.3.4 Obesity

Obesity has been officially defined as a disease (ICD-10 E66.0). This condition refers to an abnormal accumulation of body fat, in excess of 20% of the normal ideal body weight, or a body-mass-index (BMI) of 30 or above. Morbid obesity is defined as a BMI of 40 or above (Agha, 2017).

The incidence of obesity is increasing across the world. In 1986 morbid obesity was observed in 1 in 200 adults in the United States. This figure escalated to 1 in 50 in 2004 and, by 2017, it had dramatically increased to 1 in 5 (Agha, 2017).

The use of opioid based analgesia in obese patients is complex and adverse effects are more often reported.

The risk of respiratory depression is generally increased in obese patients with a higher incidence (60 - 90%) of sleep apnoea syndrome (Rose, 1994, Benumof, 2001). The latter is due to the increased deposition of adipose tissue in the pharyngeal space which results in a smaller cross sectional total pharyngeal area. Should the upper airway muscles relax, the pharyngeal patency will be compromised earlier in obese patients (Benumof, 2001). Opioids diminish the action of pharyngeal dilator muscles, thus promoting collapse of the airway in obese patients with a fat-laden pharyngeal wall. In addition, this mechanical obstruction will further limit the ventilatory effort should hypercapnia and hypoxemia ensue once central respiratory depression occurs (Benumof, 2001).

Volume of distribution (V_D) of a drug is defined as the degree to which a drug is distributed in body tissue rather than the plasma itself. Thus, a higher V_D implies a greater distribution in the tissues. The V_D of morphine is 2 - 5L/kg body weight implying that it is widely distributed throughout the body as opposed to a drug with a smaller V_D which would imply that the drug is distributed in plasma and extracellular fluid only (Linares, 2009).

Considering morphine's mostly hydrophilic, yet also lipophilic properties, its distribution into tissues is affected by total body water, regional blood flow and body composition. In obese patients, the increased adipose tissue is associated with increased blood volume and cardiac output. In lean patients, total body water is distributed 35% extracellularly and 65% intracellularly. In obese patients, however, an expansion of the extracellular compartment relative to the intracellular compartment is noted which would consequently affect the V_D of morphine (Linares, 2009).

Glomerular filtration rate is also affected by obesity. A larger glomerular planar surface, which leads to a faster clearance of drugs, is noted in obese patients. In the case of drugs which are

more hydrophilic in nature, more frequent parenteral administration is required if the drug is to remain effective (Linares, 2009).

Should a drug be purely hydrophilic, lean body mass could be used to calculate the dose as it would have little affinity for the excess adipose tissue in obese patients. Hence it has less of an effect on the $V_{D.}$ If the drug has lipophilic properties, such as morphine, the total body weight should be considered as a parenteral route will lead to the drug being exposed to adipose tissues (Linares, 2009). It must be noted that although morphine is generally regarded as more hydrophilic and less lipophilic, it does have some lipophilic characteristics i.e. the lipophilic tendency is not zero.

Should a drug such as morphine, with a largely hydrophilic nature, be delivered intrathecally, its general kinetics will differ quite significantly from morphine administered parenterally in the obese patient. The hydrophilic nature of morphine, the smaller dose used and absorption into the spinal cord (myelin) will ensure a relatively constant cerebrospinal fluid concentration over time. Opposed to this, a systemically administered opiate in the obese patient will be widely distributed, *inter alia*, into the fat and brain and hence larger and more frequent doses will be required.

1.4 Peri-operative pain

A patient's recovery is adversely affected if post-operative pain management is not effective (McGuire, 2006). There are several options available and, depending on comorbid conditions, combinations of these are used for different surgeries and patient populations. The conventional approach includes non-steroidal anti-inflammatory drugs, local anaesthesia, Paracetamol and the opioid family of drugs, either administered alone or in combinations.

When instrumented spinal fusion surgery is considered, several factors could affect the outcome. With regards to the lumbar spine there are three general indications for surgery: neurology, instability and deformity (Weinstein, 2007). Should a patient be suffering from a neural compressive condition, the decompression surgery might affect the stability of the lumbar spine which would result in a fusion procedure. At the same time, an acquired degenerative instability might cause dynamic compression of a nerve in which case the instability becomes the primary indication for surgery which, in turn, would also require a fusion procedure (Weinstein, 2007; Eismont, 2014). The technique itself can be executed in many ways, yet the gold standard remains a midline approach with open, direct decompression of the neural structures and pedicle fixation with bone-graft augmentation of the fusion (Eismont, 2014; Watter, 2009). It is this bone graft on which a great deal of the outcome depends (Watter, 2009; Greenwald, 2001). The instrumentation merely acts as a scaffold to facilitate the formation of the new bone which would then, ultimately, stabilise the new construction and maintain the decompression (Greenwald, 2001). Should this new bone formation not be successful, failure of the construct and patient morbidity would ensue.

With this in mind, several considerations influence the choice of post-operative analgesia. Despite having been proven very efficient in the post-operative period in spinal decompression and fusion surgery (Nissen, 1992; Reuben, 1997), the non-steroidal family of drugs has an important negative effect on bony fusion (Glassman, 1998).

1.4.1 Non-steroidal anti-inflammatory drugs

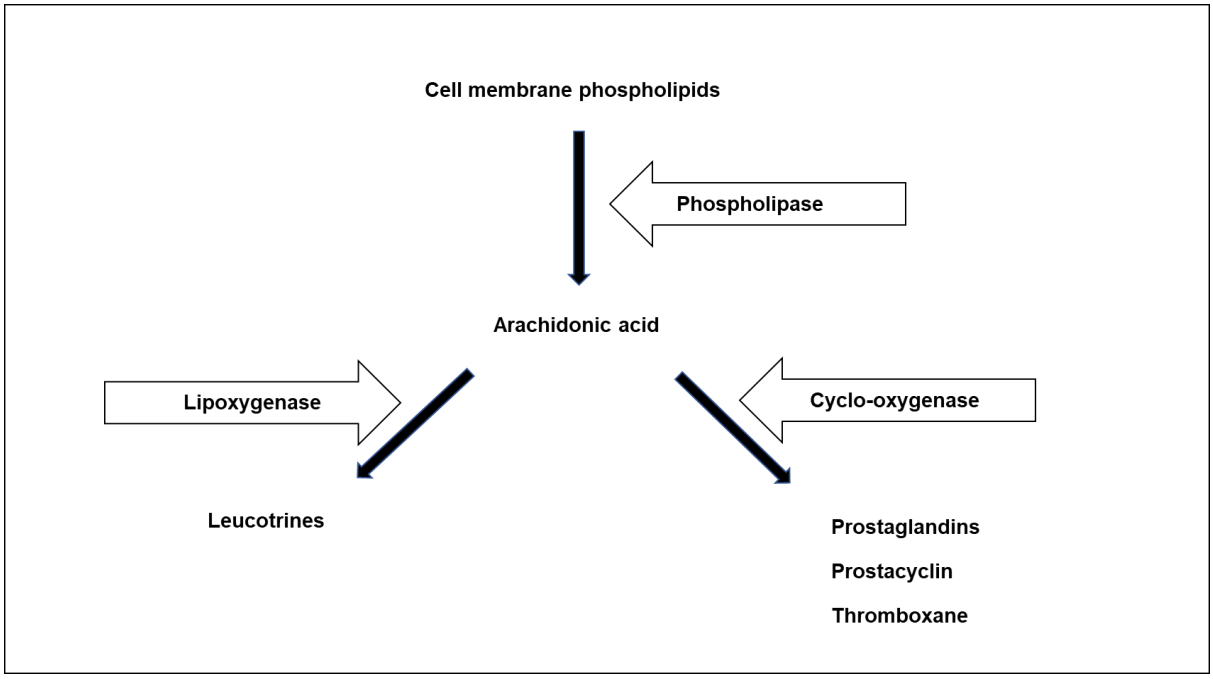

Figure 1.6: *Diagram illustrating the formation of leucotrines, thromboxane, prostacyclin and prostaglandins from the pre-cursor arachidonic acid*

Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit the enzyme cyclo-oxygenase (COX) which is essential in the formation of thromboxane, prostacyclin and prostaglandins from the arachidonic acid pre-cursor as per Figure 1.6.

Two forms of the COX enzyme exist namely: cyclo-oxygenase 1 (COX 1) and cyclo-oxygenase 2 (COX 2). COX 1, which is involved in everyday homeostasis, is found in nearly all tissues of the body yet most notably in the small intestine, stomach and platelets (Vane 1998). The COX 2 enzyme is mostly found in tissues of the musculoskeletal system, including bones and joints. Drugs which inhibit the enzyme are thus effective in managing musculoskeletal pain, especially considering that the COX 2 enzyme increases up to twenty-fold during an inflammatory state (Thaller 2005).

The response to inflammatory mediators, such as tumour necrosis factor, interleukin 1 and platelet derived growth factor, causes induction of the COX 2 enzyme in osteoblasts, chondrocytes, synoviocytes, monocytes and macrophages. Traditional NSAIDs, such as Ketorolac, Diclofenac and Ibuprofen, inhibit both the COX 1 and COX 2 enzymes which would

effectively address musculoskeletal pain, but would also explain the gastro enteral side-effects of abdominal discomfort and gastritis, especially during prolonged use.

The prostaglandins involved in bone metabolism, and which are primarily affected by the inhibition of the COX enzymes, are prostaglandin E1 and prostaglandin E2. They play an important role in both bone resorption and formation and the net gain of bone is negatively affected by the inhibition of these prostaglandins (Thaller, 2005). This inhibitory effect is used to advantage in arthroplasty surgery where heterotopic ossification is prevented by NSAID use in the post-operative period of hip replacement surgery (Fransen, 2013). However, it would lead to poorer outcomes if bone formation is an important factor in the final outcome of a procedure such as spinal fusion surgery.

Bone healing and new bone formation has been divided into three phases: the initial inflammatory phase, the reparative phase and the remodelling phase (Riew, 2003). The deleterious effect of anti-inflammatory drugs would potentially be most pronounced in the initial inflammatory phase. Riew *et al*. confirmed that the inflammatory phase occurs within the first week after surgery. In addition, they affirmed that this initial inflammatory phase was significantly affected if NSAID were used (Riew, 2003) with a trend towards non-union which persisted throughout the reparative and remodelling phases. However, the observed differences were not statistically significant.

Reuben *et al*. retrospectively studied the effect of Ketorolac on the fusion rate of 434 patients (Reuben, 2005). They concluded that a high dose of non-steroidal anti-inflammatory drugs impacts negatively on bony union and that it should therefore be avoided. They also identified smoking as a common co-factor in the development of non-union. The combination of these two factors seems to be a significant inhibitor to bone healing (Reuben, 2005). Interestingly, this is the same author who eight years previously had advocated the addition of Ketorolac to the immediate post-operative pain relief regime (Reuben, 1997). However, he subsequently changed his practice in the light of the research revealing non-union complications (Reuben, 2005).

Reuben's work is echoed by Glassman *et al.* who, already in 1998, published results garnered from 288 patients receiving non-steroidal drugs in the post-operative period after spinal fusion surgery (Glassman, 1998). They concluded that the non-steroidal drugs significantly reduced fusion rates. In addition, they noted increased non-union rates in all subgroups (men, women, smokers and non-smokers), thereby implying that NSAID were the most significant deterrent to bone fusion.

It is in the first post-operative week that analgesia is most needed, yet, the same inflammatory process which causes the pain is vital to the formation of new bone and thus provides the

foundation for successful fusion. Inhibition of this process might result in improved pain control, but the long-term effects could include failure of the procedure resulting from non-union of the fusion construct (Riew, 2003).

A meta-analysis on the effect of NSAID and spinal fusion rates concluded that there is a duration- and dose-dependent relationship (Sivaganesan, 2017).

Alternative therapy should thus be considered, and the emphasis falls on the use of opioids.

1.4.2 Opioids

The use of opioids in the post-operative setting is challenging. This family of drugs has many side effects albeit being an effective therapy. The secret lies in balancing the analgesic effects with possible side effects as the latter could not only significantly impact the patient but also give rise to financial implications (Rathmell, 2005; Raffaeli, 2006). The side-effect which is most dreaded is significant respiratory depression which is associated with hypoxia and permanent brain injury.

1.4.2.1 Respiratory depression

Despite this potentially devastating complication being well-known and a primary consideration, the incidence of significant respiratory depression remains around 0.1 - 1% in the peri-operative period, irrespective of the route of administration (Etches, 1994). Cashman *et al.* concurred with these findings and concluded that progression to death is rare (Cashman, 2004). This does not, however, exclude significant morbidity related to the event. Considering the vast number of patients treated with opioids in various forms, the figure of 1% adds up to a significant absolute number.

The pathophysiology was originally perceived to be linked to the interaction between the opioid and μ-receptors in the medulla. The pre-Bötzinger complex, situated in the medulla, has now been identified as the main cause of decreased respiratory drive after opioid usage (Montandon, 2011).

It should be understood that opioids cause dose dependant respiratory depression. Hence, once opioids have been selected, there will be some effect on the respiratory control mechanism. However, the risk lies in significant respiratory depression which may result in varying degrees of hypoxia.

Respiratory depression can occur via any of the following three mechanisms:

- Central respiratory depression leading to decreased respiratory drive and associated alveolar hypoventilation;
- Decreased genioglossus or tongue muscle tone causing obstruction of the upper airway;
- The sedative effect of opioids resulting in a decreased response to stimuli (Coetzee, 2013).

The fear of respiratory depression often results in insufficient analgesia being prescribed. This, in turn, leads to the under-treatment of pain which impacts upon length of hospital stay and the overall recovery of the patient (Rathmell, 2005; Brennan, 2007).

The challenge when using opioids, in the absence of other forms of analgesia, is to minimise the side-effect profile yet optimise analgesia to the patient. In addition, pain stimulates respiration and, by inference, once analgesia is effective the desired effect of pain relief may well accentuate the side-effect of respiratory depression (Borgbjerg, 1996). Dahan *et al*. used an integrated pharmacodynamic-pharmacokinetic model to simultaneously assess the analgesic effect of morphine and respiratory depression (Dahan, 2004). The study design involved four groups of healthy volunteers receiving a bolus of intravenous morphine, or placebo, at 09:00 and 18:00 to also evaluate sleeping hours (23:00 - 07:00). They concluded that despite inadequate pain relief, respiratory depression is still possible based upon the interaction of morphine and the μ-receptor. In addition, this unwanted side effect can occur later than what was generally anticipated.

The most common risk factors for acute and short-term opioid induced respiratory depression include: advanced age, high opioid blood and effector site concentration (either excessive dose *per se* or too short interval between administrations), respiratory acidosis as well as combined use with Benzodiazepines, or other central nervous system depressant drugs.

Due to the renal clearance of morphine and its metabolites, renal failure should also be considered as a known risk factor in cases where opioids are being used in repeated dosages. This becomes a significant consideration when the dose is constantly being *topped up* with a PCA device (Fukuda, 2009).

Delayed respiratory depression after morphine use, specifically with intrathecal administration, can be ascribed to the hydrophilic nature of the opioid (Sultan, 2011). Its slow rostral spread and delayed uptake into the brainstem can cause respiratory depression to present even later

than 6 hours post-administration. Its hydrophilic nature facilitates its strong affinity to the μ-receptors found at the dorsal horn in the spinal cord at the intrathecal injection site. It is, however, not absorbed into the white matter of the spinal cord and thus maintains a relatively constant concentration in the CSF (Hindle, 2008). In time, some cranial distribution does occur.

Methods used to monitor the side effects of the opiates include:

- The use of an opioid induced sedation scale is a valuable aid to guide the monitoring of patients with either intrathecal or patient-controlled intravenous morphine. As per Figure 1.7, the Pasero scale involves assessing the patient over a period of time (8, 24 and 48 hours) and is based on clinical parameters of sedation (Pasero, 2004). The sedation scale allows for the following manifestations: sleeping, awake and alert, occasionally drowsy but easy to rouse, frequently drowsy and drifts off to sleep or being somnolent and having minimal response to painful stimuli (Coetzee, 2013). This approach is valuable in the acute setting as less opioids are required to cause sedation than respiratory depression and sedation can thus act as an early marker for the risk of respiratory depression.
- Other clinical observations can provide additional valuable information regarding the deleterious effects of morphine. The most common reported finding indicative of significant respiratory depression in published literature is an oxygen saturation measurement less than 90%, especially in a patient who previously showed normal saturation (Cashman, 2004). They concluded that blood gas analysis, although accurate, is less frequently used due to its invasiveness than routine peripheral oxygen saturation measurement.
- Other clinical observations include respiratory frequency with a rate less than 10 breaths per minute commonly indicating significant respiratory depression (Cashman, 2004). The accuracy of respiratory rate as an indicator for respiratory depression has both been advocated and disputed. Camporesi *et al.* investigated the relationship between respiratory depression and CO_2 after both intravenous and epidural morphine administration in healthy volunteers (Camporesi, 1983). They demonstrated that blunting of the CO_2 response peaked at 10 hours post-intervention and could last up to 22 hours in the epidural group. This finding has to be considered within the context of the absence of painful stimuli, such as would typically occur after surgery. Although the pain will enhance respiratory drive, in principle, the observed length of potential respiratory depression is important for the post-surgical care environment. Camporesi *et al.* also concluded that respiratory rate was a poor indicator of respiratory

depression. They reported on several cases of respiratory rates of 14 - 15 having sudden prolonged spells of apnoea.

Overdyk highlighted the challenges of counting respiratory rate noting that it is done intermittently and an episode of bradypnea could therefor easily be missed (Overdyk, 2007). In addition, Catley *et al.* documented short-lived ventilatory pattern changes not identified by routine counting of respiratory rate (Catley, 1985). Furthermore, Overdyk found that supplemental oxygen could potentially mask desaturation in respiratory depression. He noted that in those patients, desaturation occurred along with bradypnea lasting a longer period, three minutes or longer. These findings were similar to reports by Fu *et al*. who ascertained that oximetry could be a late indicator of respiratory depression if oxygen is supplemented (Fu, 2004). In addition, nursing response to audible alarms adds another dimension to the time delay factor, more so in the general ward setting. Pin-point pupils is an indication of a significant opioid effect (Coetzee, 2013).

In order to be effective, these observations need to be repeated at close intervals. Patients should thus be cared for in a high care environment to ensure effective and repeated monitoring. In addition, the physician has to rely on the nursing staff's accurate monitoring and, given the ever-increasing pressure in health care environments, this is becoming more and more difficult. A combination of these observations, rather than any single parameter, would increase the early detection of opiate side effects. Macintyre emphasised this by stating that, despite monitoring clinical parameters, all patients receiving opioids should at least be monitored with the use of sedation scores (Macintyre, 2011).

Further morphine related side-effects include nausea, vomiting, pruritus and urinary retention. Post-operative nausea and vomiting remain one of the most common complaints, or complications, encountered in the post-operative recovery room setting (Hines, 1992, Habib, 2004). Although not conventionally life threatening, it is extremely uncomfortable and can result in significant morbidity.

The options for administration of opioids in the post-operative period include:

- intravenous (typically through a patient-controlled device);
- intrathecal morphine (delivered to the patient during the procedure);
- intramuscular administration;
- oral medications, although these are discouraged in the immediate post-operative period due to bowel immobility and unpredictable dose-response results (Fukuda, 2009).

Number	Description
S	Sleep, easily aroused
1	Awake and alert
2	Occasionally drowsy, easy to rouse
3	Frequently drowsy, rousable, drifts off to sleep during conversation
4	Somnolent, minimal or no response to stimuli

Figure 1.7: *Pasero's opioid-induced sedation scale (Pasero, 2004)*

1.4.2.2 Pruritus

Pruritus is defined as an unpleasant irritation, or sensation, resulting in an urge to scratch. With opioid use it typically presents in areas innervated by the trigeminal nerve due to an abundance of opioid receptors in its spinal nucleus which is the origin of pain and temperature perception in the face (Korhonen, 2003).

Pruritus, after the use of neuraxial opioids, can be explained by the following possible mechanisms (Gulhas, 2007):

- It is theorised that pruritus and pain are transmitted by the same sensory neurons (small unmyelinated nerves or C-fibres). It is these fibres that are affected by prostaglandin release (PGE1 and PGE2) which enhances the transmission of C-fibres to the central nervous system and potentiate pruritus.
- During neuraxial opioid delivery, cephalad spread of the drug occurs and the opioids act on the 5 Hydroxytryptamine (5HT3) receptors causing pruritus.

The incidence of pruritus after neuraxial use has been reported in the range of 20 to 100% (Ganesh, 2007). The high incidence has been ascribed to the interaction between eostrogen and the opioid receptors leading to a much higher incidence of pruritus in pregnant patients (Kumar, 2013; Charulaxananan, 2000). When excluding pregnant patients and assessing orthopaedic patients separately, the reported pruritus incidence ranges from 30 to 60% (Kumar, 2013) after intrathecal opioid use. This is comparable to the reported incidence of 10 to 50% (Gulhas, 2007) for intravenous use of morphine in an orthopaedic group of patients.

It is the more direct and immediate exposure to opioid receptors, via the intrathecal route, that could lead to a quicker onset of pruritus. The overall incidence between intrathecal and intravenous administration, however, is comparable in the non-pregnant group of patients (Gulhas, 2007).

Various drugs, the most successful being 5HT3 antagonists such as Ondansetron, have been used to decrease, or treat, pruritus after both neuraxial and parenteral opioid use. However, contradictory results regarding efficacy persists in literature. Korhonen *et al*. failed to demonstrate a decrease in pruritus in patients receiving intrathecal Fentanyl compared to placebo, yet they used only a small amount of intrathecal Fentanyl and postulated that it did not have significant cephalad spread to interact on 5HT3 receptors in the trigeminal cervical nucleus (Kerhonen, 2003). Gulhas, in turn, demonstrated a significant reduction in pruritus incidence when 8mg Ondansetron was administered intravenously within the first 24 hours after surgery (Gulhas, 2007). Considering its low side-effect profile, 5HT3 antagonist group of drugs are considered the drugs of choice in treating opioid related pruritus.

NSAIDs, due to their inhibitory effect on prostaglandin formation, could be effective in treating post-operative pruritus but they cannot be used in fusion surgery due to the deleterious effect on bone formation (Riew, 2013).

1.4.2.3 Nausea and vomiting

Nausea and vomiting can be caused by opioids and, as such, they count amongst the most distressing side effects associated with opioids in the post-operative period. The incidence of nausea is reported to be 20 to 33% with vomiting affecting more or less half of those patients (Smith, 2014). It appears, although the mechanism is not yet clear, that opioid stimulation of the vestibular apparatus chemoreceptor zone could trigger nausea and vomiting.

Ali *et al.* demonstrated that in patients undergoing major thoraco-abdominal surgery, opioid epidural analgesia provided better analgesia and improved short-term quality of life in comparison to PCA (Ali, 2010). They concluded that this short-term advantage was due to the lower incidences of nausea, vomiting and pain which then resulted in patients sleeping better. Their conclusions highlight the effect that nausea and vomiting have on patients' quality of recovery.

1.4.2.4 Opioid induced hyperalgesia

This side-effect of opioid use is defined as a paradoxical increase in painful sensation, despite the optimal usage of opioids (Lee, 2011). This sensitisation to noxious stimuli often leads to increased rescue dosages of opioids which, in turn, could lead to more severe side-effects such as respiratory depression. Respiratory depression, it has been proven, is linked to the interaction of opioids with the pre-Bötzinger complex in the medulla (Sultan, 2011). The paradoxical response in analgesia does not exhibit heightened respiratory depression yet, if safe opioid doses are exceeded, the standard risk regarding depression of ventilation still applies.

The mechanism of action is related to the interaction of opioids with the central glutaminergic system. The neurotransmitter N-methyl-D-aspartate (NMDA), which is excitatory in nature, is activated in the central nervous system and can trigger post-operative hyperalgesia. It has been shown that intra-operative use of Remifentanil is linked to opioid induced hyperalgesia due to the stimulation of these NMDA subunits (Joly, 2005). This phenomenon can be avoided with the use of a small Ketamine dose intra-operatively. The latter, in turn, increases the effectivity of the opioids as well (Joly, 2005).

1.5 Intrathecal morphine in spinal surgery

Spinal surgery, especially fusion surgery with extensive tissue mobilisation and bone work, results in significant pain in the immediate post-operative period. The analgesic modalities available need to be safe for the patient and not deleterious to the bony construct created and/or the fusion mass which needs to form. It is in this situation where opioids, when used safely and effectively, could assist in early mobilisation and rehabilitation.

Literature regarding the use of intrathecal morphine in spinal surgery provides several guidelines. Potentially good studies have, however, often been flawed by poor study designs and an incomplete understanding and interpretation of already published results.

O'Neill randomised 46 patients to 1mg intrathecal morphine, or no injection, after lumbar spinal surgery (O'Neill, 1985). The control group received the same analgesia used as rescue analgesia for the intrathecal group namely Papavaretum 15 to 20mg intramuscularly every 4 to 6 hours, as required. On all pain scoring modalities, the intrathecal group did significantly better up to 20 hours after which the difference in pain perception was not considered statistically significant any longer. This loss in significance was not addressed by the authors. It can be theorised, however, that the surgical procedures did not require extensive muscle dissection (no fusion-type surgeries were performed) which leans itself to less pain post-operatively and pain could therefore be treated effectively with intramuscular analgesia. The only side-effect noted was an increased tendency towards pruritus in the treatment group. The authors acknowledged the risk of respiratory depression in their discussion and commented that suggested doses for intrathecal use were, at that time, not yet firmly established. They cautioned that intrathecal opioid use was investigational and that the risk of respiratory depression should be weighed against intramuscular options to provide analgesia. A dose of 1mg of intrathecal morphine was given across the study population with no consideration to patient weight. Remarkably few complications were recorded, especially considering this high dose of morphine. The study thus proved the efficacy of the concept of intrathecal morphine.

Blacklock subsequently reported on 5 patients undergoing lumbar procedures who received 1mg of intrathecal morphine (test group). This patient cohort was compared to 10 control patients who received any of the following analgesics at the discretion of the nursing staff: intramuscular Meperidine (50 to 100mg), an oral Acetominophen and codeine combination, or Acetaminophen alone (Blacklock, 1996). He noted that, in the test subjects, affective analgesia resulted from the administration of intrathecal morphine with hardly any supplemental analgesic requirements. However, the test group used twice as much supplementary intramuscular narcotics (which were not named, nor were doses provided) after 24 hours when compared to the control group. The overall oral and intramuscular analgesic drug use across

both groups were comparable over the 5 days studied. However, procedures performed in the test and control groups did not include any fusion procedures, which require more muscle dissection and is intuitively more painful. This study also demonstrated that vigilance is required after the effect of the intrathecal morphine has worn off and that additional effective analgesia might then be needed.

Of significance was the finding that urinary retention, which lasted 24 to 36 hours, was noted in all 5 test subjects. No urinary retention was noted in any of the patients in the previously mentioned study published by O'Neill, despite the same dose of 1mg intrathecal morphine being used (O'Neill, 1985).

Blackman *et al*. studied the use of intrathecal morphine in a younger population (ranging from 11 to 16 years) in 1991 (Blackman, 1991). The study specifically addressed the issue of the efficacy of intrathecal morphine in scoliosis surgery as well as evaluating the risk of respiratory depression. Thirty-three patients were assessed, and it was concluded that efficient pain relief lasted between 8 and 40 hours (the patients thus required no supplemental analgesia). However, 2 patients reported no pain relief which could imply a technical failure in the delivery of the intrathecal morphine, most likely leakage through the small puncture in the dura. Significant respiratory depression in this study was defined as $PaCO_2$ equals to or more than 60mm Hg.

Four patients demonstrated $PaCO_2$ of more than 60mm Hg and were subsequently treated with intravenous Naloxone 6 hours after anaesthesia in order to reverse the opioid effect. All 4 patients had normal respiratory mechanical parameters and blood gas analysis, 30 minutes after extubating, diagnosed the respiratory depression. The literature does not state whether any of the patients were awake and responding to commands. There is also no reference to the PaO_2 level, or saturation, or the number of blood gas analyses done on each patient. The increased $PaCO_2$ could, in the author's opinion, have been easily managed by instructing the patient to breath deeper, or faster, or by increasing the inspired oxygen concentration. However, respiratory depression is a known side effect of opioids and nothing turns on this *provided* it does not result in hypoxia or somnolence i.e. the $PaCO_2$ level becomes very high. The absence of saturation data therefore limits the understanding of the respiratory risk associated with intrathecal opioids.

The authors concluded that intrathecal morphine provided noticeable pain relief in younger spinal fusion patients. They further asserted that possible side effects are easily recognisable in a high care setting and could be effectively managed with Naloxone, should the need arise.

The dose used was described in the materials and methods section as 0.01mg/kg with an added reference that the dose was varied to determine whether it changed the response. The doses ultimately used ranged from 0.007 to 0.019mg/kg which makes it difficult to draw a definite conclusion as to an effective dose and dose-related side-effects. One patient had to be ventilated for more than 24 hours. Scoliosis surgery is significant spinal surgery and the resultant effective analgesia achieved by intrathecal morphine in this study strongly suggests that the approach holds promise in terms of analgesia. The study, however, also highlights the important risks associated with intrathecal opiates.

Ross *et al.* reported on the use of intrathecal morphine in spinal surgery (Ross, 1991). They randomised patients to doses of 0.125, 0.25 and 0.5mg and compared this to a placebo group receiving normal saline intrathecal injection (placebo). The results showed that the 0.125mg and placebo group experienced similar degrees of pain relief and that the 0.25 and 0.5mg groups both showed improved pain scores and shorter hospital stays. The rescue analgesia of choice was subcutaneous morphine. Their protocol required clinical respiratory frequency measurements every 30 minutes for 12 hours in a high care environment and no respiratory complications were noted. No blood gas analyses were done to support any potential respiratory complications. It is now accepted that reliance on respiratory rate, as an indication of opioid respiratory depression, is neither accurate nor safe (Coetzee, 2013).

Generally, the study was well designed and proved the efficacy of the 0.25 and 0.5mg doses. However, the surgical procedures were not standardised, nor equally distributed amongst the groups. No fusion procedures were performed in this study. These observations raise questions regarding the randomisation of the study. None of the procedures performed (which included discectomy, hemilaminectomy, laminectomy and foraminotomy) required significant muscle stripping as part of the surgical intervention. This is important as muscle stripping is a significant contributor to post-operative pain in many surgical procedures performed on the spine. The amount of surgical levels operated on were also unequally spread, as some procedures, such as discectomy and hemilaminectomy, will require no more than two days hospital stay in conventional spinal surgical practice. This normal post-operative course could have significantly influenced the authors' conclusions regarding reduced hospital stay and improved pain scores as baseline expectation was neither severe pain nor extended hospital stay. The randomisation apparently did not address this variable. No body-weight adaptations of the doses were used, an approach which could have skewed the results and influenced potential respiratory complications. The time to first supplemental narcotic was 20 hours in the 0.5mg group compared to 13.5 hours in the 0.25mg group. Despite having no respiratory complications, the authors still recommended a regime of intensive post-operative respiratory monitoring, wisely so, but perhaps also because they understood that their data were

insufficient to ignore the potential risk of respiratory depression. Finally, the authors did not express an opinion regarding the safety of the 0.5mg intrathecal morphine dose. They recommended that the treating physician should decide whether he/she wanted to perform intensive monitoring on the patient for the added benefit of longer and improved analgesia.

The studies by Blackman (Blackman, 1991) and Ross (Ross, 1991) evaluated respiratory complications associated with the use of intrathecal morphine. Despite comparable dose regimes, conflicting results were reported. This difference could be ascribed to the fact that Ross did not study arterial blood gases and relied on respiratory rate. There is a right shift in the minute ventilation vs $PaCO_2$ response curve which confirms the notion that opioids depress respiration, but this may not necessarily find expression in the respiratory rate (Loeschke, 1953). It is well known that a reliance on respiratory rate as an index of respiratory depression associated with morphine, is unreliable and even unsafe. In addition, the study by Ross did not use a weight-calculated dose, complicating any conclusion regarding safety. Both studies were promising inasmuch as effective analgesia was achieved but they failed to provide specific information regarding effective vs safe doses.

Two years after Ross *et al*. reported on their experience with intrathecal morphine, Bernard *et al.* published their experience comparing an intrathecal morphine dosage of 0.3mg to a continuous intravenous infusion of Clonidine and Fentanyl. Patients undergoing major spinal surgery (scoliosis correction) were randomly assigned to groups in a double-blinded fashion (Bernard, 1993). A standardised anaesthetic regime was used. All patients were kept intubated after surgery and were only extubated approximately 4 hours after administration of the drugs. The study design identified a $PaCO_2$ of 50mm Hg as trigger to reverse the opioid effect with Naloxone. A rise in $PaCO_2$ was noted in the first 2 hours after extubating in the intrathecal morphine group with 4 patients reaching $PaCO_2$ levels in excess of 50mm Hg. Although no hypoxia was recorded, the authors concluded that a significant respiratory depression risk exists with the use of intrathecal morphine. Similarly, no decrease in saturation below 90% was noted in either group. The PaO_2 and saturation remained at control values between the 2 groups for the duration of the study and no patient's respiratory rate decreased below 10 breaths per minute. All patients received a facemask oxygen (FiO_2 0.4) and all patients were reported to be easy to rouse post-operatively. No significant difference could be demonstrated between the 2 groups with regards to analgesia. The intrathecal dose of 0.3mg was used in all the patients although the Fentanyl and Clonidine infusions were adapted for weight, making it difficult to compare efficacy. All patients received Ketoprofen (NSAID) as rescue analgesia and its use in the groups was similar. However, the use of NSAID drugs in the post-operative period after spinal fusion surgery is deemed inappropriate. Further, the use of the drugs in these studies obscured the effectiveness of the opiates used in different modes.

France *et al*. published a comparative study of intrathecal morphine to intrathecal 0.9% normal saline injection (placebo group) (France, 1997). All 77 patients in the study population received a PCA pump to control breakthrough pain. The intrathecal morphine dosage used was 0.011mg/kg, implying that a 100kg patient would receive a single intrathecal dosage of 1.1mg morphine. This would be considered a high dose according to the literature at the time.

The patient-controlled analgesia solution was not standardised, and 3 different drugs were administered non-randomly to provide additional analgesia. The drugs used were morphine, Demerol (Meperidine) and Dilaudid (Hydromorphone). The management of breakthrough pain was left to the discretion of the pain management team of the hospital thus making it difficult to draw reasoned conclusions regarding the findings. It would have increased the benefit of the study had a single drug been selected as PCA escape as this would have facilitated a comparison regarding the amount used over a specific time period. This was, however, not done.

All patients remained in ICU post-operatively and were monitored for apnoea. The study also evaluated hospital length-of-stay.

Naloxone was administered to 3 patients as their respiratory rates decreased below 8 per minute. An additional 9 patients, all belonging to the intrathecal placebo group, were removed from the study as their PCA was changed to continuous infusion, implying ineffective analgesia associated with PCA as single treating modality. No blood gas analyses were done to objectively examine the respiratory effects of the intrathecal morphine. The frequency of 8 breaths per minute as trigger for Naloxone administration was part of the study design, yet none of the 3 three patients who were given Naloxone showed any clinical signs of respiratory compromise, nor difficulty being roused. It is thus uncertain why Naloxone was administered.

The authors did not evaluate other breakthrough pain analgesic options but recorded a decreased use of PCA in the group which had received intrathecal morphine by comparing post-surgical PCA volumes and attempted use (within the lock-out period) between the groups. No mention was made of a standardised anaesthetic and the intrathecal morphine injection was administered approximately 30 minutes before the surgical procedure was completed. The end of surgery was adopted as time zero i.e. the start of time-based data collection for this study. This being so, the type of anaesthesia, especially intra-operative opiate use, was of significant importance in the interpretation of their results.

No difference could be demonstrated in the length of stay between the 2 groups. As regards the side-effects of morphine, the dose of 0.011mg/kg could be criticised due to the known respiratory effects associated with a higher dose of intrathecal morphine (Rathmell, 2005). Three patients had to be given Naloxone. However, other morphine related side-effects were

minimal. Pruritus was documented in 8 intrathecal morphine patients and in 2 control patients. The authors described this as a “minor nuisance” and regarded it as not being significant.

No pain scoring was done after 32 hours and no other analgesic regime, other than PCA, was used. Upon post-operative arrival in the intermediate care unit, the mean VAS was statistically significant in favour of the intrathecal group. However, this significance diminished towards the end of the first day (p=0.1) and a statistically significant reversal occurred in favour of the control group at 36 hours post-operatively. The authors highlighted the importance of breakthrough pain after 24 hours where the PCA demand exceeded that of the control group. The attempted PCA use was consistently lower in the intrathecal morphine group, initially coinciding with the better VAS scores. However, during the second 24 hours post-operatively the use increased to more than that of the control group which implied that the breakthrough pain regime was not fully effective. PCA as standalone entity could thus provide some analgesia, but not comparable to that of the intrathecal morphine.

Boezaart *et al*. (Boezaart, 1999) attempted to provide a dose regime for analgesia after spinal surgery which would balance optimal analgesia with minimal side effects, specifically with reference to respiratory depression. Sixty patients, scheduled for spinal surgery, were divided into 3 groups of 20 patients each. At the end of surgery, before wound closure, 0.2, 0.3 and 0.4mg morphine was intrathecally administered to the 3 groups. Pain was scored by means of the Visual Analogue Scale at 6, 12, 18 and 24 hours post-operatively. However, no randomisation occurred, and doses used were not based on body mass. The surgery itself entailed fusion-type procedures with, or without, a decompression. The time to wound closure as well as the time it took to wake the patient up was not recorded thus making it difficult to extrapolate a time to effective analgesia from the initial administration of intrathecal morphine. Also, the anaesthetic regime was not standardised. This implies that intra-operative opioids might have influenced the outcome, at least for the first few hours after the patient woke up. Diclofenac was prescribed and only required in the 0.2mg intrathecal morphine group where 40% of the patients received the drug. The amount of times Diclofenac was used was not noted. In the initial 24 hours post-operatively, the ineffectiveness of the 0.2mg dose was notable. If an additional 24 hours had been studied, the dose to weight discrepancies (the doses were not scaled to body weight) in the higher intrathecal doses would probably have come to the fore. Effectiveness in the 0.3 and 0.4mg groups were comparable between groups and demonstrated for up to 24 hours.

The changes in $PaCO_2$ were not significant across the groups and the highest single level measured was 6.4kPa (48mm Hg). All 3 groups followed the same overall trend of a decreasing $PaCO_2$ over the 24 hours measured. Despite a blood gas analysis being done 6-

hourly, no mention is made of PaO_2 or SaO_2. Respiratory rate was significantly less in the 0.3mg group when compared to the other 2 groups, yet the lowest value was 13 breaths per minute. No comment was made regarding how easily these patients could be roused. The oxygenation status and level of sedation were important factors which informed the decision as to whether or not the respiratory depression, as gauged from the elevated $PaCO_2$, was of clinical significance.

Urban *et al*. also published results in 2002 on the use of intrathecal morphine in spinal surgery (Urban, 2002). Sixty-five patients were randomised into 3 groups and given a bolus of 10ug/kg, 20ug/kg intrathecally or no intrathecal injection. All patients received morphine PCA post-operatively for 72 hours and were monitored for respiratory depression. The authors defined oxygen saturation as less than 90% and sedation which was graded on a scale of 1 to 5 with 1 being awake and 5 unconscious. The larger dose intrathecal morphine group remained pain free for the longest period of time followed by the group who had received 10ug/kg. The placebo group predictably used the PCA device most often. All groups were, however, comparable after 12 hours.

The study adopted a standardised anaesthetic regime as guideline. However, the large variety of surgical procedures, and especially the length of surgery (not quantified, yet implied), exposes this part of the protocol to uncertainty. Neither the surgeon nor the ICU staff were blinded to the intrathecal morphine groups and although no respiratory complications were mentioned in the results, the discussion mentions that the author, as standard practice outside of this study, used Naloxone to treat perceived respiratory depression based on hypercapnia. The study design did not mention any threshold value used to initiate treatment for hypercapnia, neither did it address the role of PaO_2, SaO_2 and/or respiratory rate. Prolonged ICU stay was required for 15 patients, yet this was due to pre-existing pulmonary disease, extensive and prolonged surgery as well as ventilator support beyond the first post-operative night. The number of patients who required ventilator support were significantly more in the placebo group than the high dose intrathecal morphine group. Incidences of pruritis were higher in the larger dose group, yet instances of nausea and vomiting were similar, even in the placebo group.

Ultimately this study design added no new information to the known literature regarding intrathecal morphine. It is this author's considered opinion that the higher doses of intrathecal opiate potentially endangered the patients. The higher dose of intrathecal morphine provided a longer analgesic effect and Urban *et al.* commented on its efficacy in spinal surgery, yet the affirmation was not supported with appropriate pain scores. The discussion did not involve any ideal dose nor was the role of supplemental analgesia addressed.

Gehling *et al.* performed a multi-centre placebo-controlled trial between 2002 and 2003 on orthopaedic patients receiving spinal anaesthesia (Gehling, 2009). They postulated that patient-controlled devices could be avoided if intrathecal morphine was given in addition to the conventional spinal anaesthesia. They randomised patients into 3 groups: placebo (zero morphine), 0.1 and 0.2mg intrathecal morphine injections. These were administered in addition to the spinal anaesthesia of 15mg intrathecal Bupivacaine given to all 3 groups. An intravenous dose of 5mg morphine was prescribed for rescue analgesia and could be given every 10 minutes, if necessary. In addition, all patients received an intravenous infusion of 1000mg Metamizol over 30 minutes which could be repeated according to protocol every 4 hours to a maximum dosage of 6000mg.

They concluded that the higher dose of intrathecal morphine resulted in longer post-operative analgesia and less additional opioid requirements, confirming the analgesic potency of intrathecal morphine. After 24 hours, additional opioids were required in 51% of patients who had received 0.1mg intrathecal morphine and 31% in those who had received 0.2mg. The placebo group, with only the spinal anaesthetic, had a 71% additional opioid requirement, predictably starting at around 6 hours post administration. Of all the patients who had received intrathecal morphine, only 40% required additional narcotics after 24 hours. All patients were kept in a high care facility (PACU) for 3 hours only and then transferred to a general ward once circulatory and respiratory parameters were deemed normal where hourly observations were performed.

Of the 188 patients studied, no respiratory complications were reported. However, no blood gas analyses were done, and respiratory frequency was the only parameter used to assess respiratory complications with a rate of 10 breaths per minute as trigger for intravenous Naloxone to reverse the opioid effect. The intrathecal morphine dose was not adapted to weight, making it difficult to draw a final and definitive conclusion as to its effectiveness in relation to a specific dose. By not subjecting the patients to general anaesthesia, this study eliminated intra-operative administration of opiates (as part of the anaesthesia) as a confounding factor. The authors proved the efficacy of intrathecal morphine. The lack of standardised surgical procedures and standard doses (scales to the patient size), however, once again makes it difficult to draw more specific conclusions besides confirming that the technique is, indeed, effective.

Techanivate performed a prospective randomised controlled study on 40 patients which were allocated to 2 groups (Techanivate, 2003). All patients received spinal fusion procedures and were randomised to a morphine (0.3mg) intrathecal injection or intrathecal 0.9% normal saline injection (both in a volume of 0.3ml). Similar to other studies, all patients received PCA for

breakthrough pain in the post-operative period. Their results indicated that less patient-controlled analgesia was required and longer time to first use of the PCA was present in the morphine group (131.7 to first use vs 29.6min). Both groups had similar incidences of nausea and vomiting, and no respiratory depression was documented. No complications were noted regarding the dural puncture site for the intrathecal injections.

Again, albeit indirectly, the authors confirmed that spinal opiate administration is effective. The lack of puncture site complications is comforting to those who fear cerebrospinal fluid leaks and complications thereof.

A case report by Law *et al*. (Law, 2009) demonstrated severe respiratory depression in a post-operative patient after an intrathecal morphine injection. The patient recovered after Naloxone had been administered. The patient received a dose of 0.4mg intrathecal morphine, which is lower than most guidelines available at the time. In particular, a patient group in the Boezaart study (Boezaart, 1999) received 0.4mg intrathecal morphine and no similar complications occurred. On closer analysis of this single case, it appears as if the patient received a dose of 0.0068mg/kg which is indeed higher than what the literature at that time suggested (Boezaart, 1999), although other studies used higher doses. Blackman *et al.* (Blackman, 1991) reported 4 cases of respiratory depression in their series, but the doses used exceeded the dose used in the case report on by Law. In this case report, the intrathecal injection was combined with 5mg Bupivacaine. A 3mg intravenous morphine bolus was administered at the end of surgery and a PCA device, charged with morphine, showed that 1.5mg was used in the first 5 hours post-operatively. In the absence of pain, the combined effect of the different morphine sources led to the respiratory depression. This publication highlights the risk of a fixed dose of morphine, in addition to the spinal morphine, rather than administering the additional morphine with a PCA only. The latter combination relies on the safeguard that the PCA cannot over administer and also, presumably, a PCA request cannot be delivered when the patient is deeply sedated by the morphine. This case report simply confirms what is already well known regarding the consequences of excessive doses of morphine being administered.

Ziegeler *et al.* (Ziegeler, 2008) included 52 randomised patients undergoing spinal fusion surgery in a study where patients were then randomly allocated an intrathecal morphine injection or placebo 0.9% normal saline injection intrathecally. All patients in the study population received a PCA pump containing Piritramide for post-operative treatment. The study participants were administered a single dose of 0.4mg of intrathecal morphine, irrespective of weight, and all patients were prescribed an intravenous regime of 5mg Piritramide in bolus doses for breakthrough analgesia. All patients received 100mg Diclofenac suppositories post-operatively at 4 and 16 hours. The authors limited their analysis to 20 hours

post-operatively. Their results showed a significantly superior analgesia in the first 8 hours after surgery in the morphine group with the mean VAS scores being significantly better when compared to placebo (22 in the morphine group vs 30 in the placebo group). The PCA use was significantly more frequent in the placebo group when compared to the morphine group for the first 3 time periods up to 8 hours post-operatively. Between 8 and 20 hours the absolute PCA use was more frequent in the placebo group, yet this result did not achieve statistical significance. This could perhaps be attributed to the Diclofenac administered to all the study participants knowing that Diclofenac is very effective in managing musculoskeletal pain (Thaller, 2005.) Intravenous bolus use of Piritramide was higher in the immediate post-operative period in the placebo group with 13 patients requiring additional doses compared to 5 in the morphine group. The number of times it was required is not described.

The authors could not detect statistically significant differences in the side-effect profile, which included respiratory depression. The latter was measured using PaO_2 and $PaCO_2$ at 3 time intervals post-operatively (30 minutes, 4 hours and 16 hours). All patients received supplemental oxygen via nasal cannula. The results indicated no difference in PaO_2 between the groups, however, the intrathecal morphine group at 4 hours had a statistically significantly greater change in $PaCO_2$ values (9.8mm Hg vs 5.2mm Hg). No clinically relevant respiratory depression requiring Naloxone was documented, yet the criteria used for Naloxone administration was not recorded in the study. No difference in saturation between the groups could be demonstrated. Other side-effects measured were: pruritus, cerebrospinal fluid leakage from the puncture site, nausea and vomiting and the use of antihistamine and antiemetic medication. No statistically significant difference could be detected in any of these.

The single dose for intrathecal morphine (0.4mg, irrespective of patients' size) could potentially be a dangerous dose for a smaller patient. The authors did attempt to standardise the anaesthetic regime and both study groups had access to PCA. Although the latter was necessary to provide for escape treatment, in this author's opinion it makes for a difficult evaluation of the intrathecal morphine as treatment alone. The impact which Diclofenac had on the pain measurements is also not discussed. This study is comparable to that of France *et al*. (France, 1997) who reported similar results. The short post-operative study period of 20 hours avoided the critical analysis of breakthrough pain. The PCA use was meant to demonstrate breakthrough pain but the 20 hours study period was too short to fully evaluate this phenomenon.

Airamo Morselli *et al*. attempted to compare the efficacy of a fixed intrathecal dose of 100ug to a standardised intravenous regime of approximately 5mg intravenous morphine, administered over 24 hours as an infusion, in minimally invasive spinal fusion procedures.

Patients were observed for 24 hours (Airamo Morselli, 2017). No rescue analgesia was permitted in either group.

A single anaesthetist managed all the cases with a standardised anaesthetic regime. The intrathecal dose, not calculated to weight, was given prior to commencing surgery soon after induction of anaesthesia. The intravenous dose was calculated to weight (0.06 - 0.08mg/kg) and given as a 24-hour infusion. The intrathecal group received a similar infusion of normal saline. All patients were observed in a general ward and transferred to ICU only if the respiratory rate was less than 8 breaths per minute.

Fifty patients were recruited to take part in the study. The intrathecal group demonstrated statistically significantly lower VAS scores compared to the intravenous morphine group (mean VAS of 0.72 vs 3.08 at 6 hours, 0.72 vs 3.56 at 12 hours and 1.36 vs 3.64 at 24 hours). Eighteen patients in the intrathecal group underwent early mobilisation vs 10 only in the intravenous morphine group. This significant difference meant that the intrathecal group had a shorter hospital stay than the intravenous morphine group (3 vs 6.44 days). No nausea and vomiting, pruritis or respiratory depression was encountered in either group. Respiratory depression was defined as a respiratory rate less than 8 breaths per minute.

The authors acknowledged the limitations of their study, including the small sample size and the inherent nature of the minimal invasive procedure, which in its own right is meant to be much less painful than open spinal surgery. However, one has to keep in mind that the placebo group had similar surgery and the comparison is therefor still valid. The reader can interpolate but can naturally not extrapolate to more painful surgery, such as conventional spinal surgery.

Once again, no dose-per-weight calculation was made for the intrathecal group. This is a problem which occurs in many studies as it complicates the making of a comparison.

In summary, with regards to the use of intrathecal morphine in lumbar spinal surgery, the available literature shows:

1. Support for the efficacy of this approach.
2. Significant variations occur as to the doses used.
3. Significant variations occur as to possible side-effects.
4. Variations often occur as a result of poor study design.
5. The natural history of this technique shows that progressively smaller doses are being used. This approach is driven by the fear of complications, of which respiratory depression would be foremost.

6. Multiple factors could influence the measurement of pain in the post-operative period. These include a non-standardised anaesthetic regime and non-standardised procedures which could result in variations regarding the amount of tissue dissected to perform the procedure, and ultimately how painful the procedure might be.
7. PCA is mostly used in conjunction with intrathecal morphine which makes it difficult, if not nearly impossible, to make valid conclusions regarding dose and dose-related side effect.

In view of the uncertainties, safety for effectiveness, a standardised evaluation of intrathecal morphine is necessary. The surgical and anaesthetic procedure must both be standardised; the dose of intrathecal morphine should be calculated to body weight and the post-operative management standardised with reference to escape analgesia and management of side effects. The presence and extent of respiratory depression need to be objectively quantified to properly gauge the perceived respiratory risk. The study proposed in this thesis aims to address the above questions.

2. Materials and methods

This study was conducted in the Department of Neurosurgery at Tygerberg Academic Hospital in the Western Cape province of South Africa.

Ethical approval was obtained from the University of Stellenbosch's Health and Ethics committee (REF:M15/09/039).

Approval to conduct the research at Tygerberg Academic Hospital was obtained from the Provincial Government of the Western Cape (22/11/2018).

Public healthcare patients presenting for surgery to the department were recruited via standard out-patient visits as first contact. Surgery was only offered once conservative measures had been exhausted. Inclusion criteria for the study were: patients should not have undergone previous spinal surgery and should be classified as American Society of Anaesthesiologists (ASA) grade I or II.

At the last out-patient visit, prior to surgery, patients were educated regarding the use of the patient-controlled analgesia (PCA) device.

Patients were admitted to hospital one day prior to surgery and informed consent was obtained for both the procedure and participation in the study.

The surgical procedure, a first surgery single level fusion of 2 lumbar vertebrae, was performed in the elective operating room environment.

Prior to administration of the anaesthesia, the anaesthetist received an envelope allocating the patient to either the intrathecal morphine or the PCA group. This information was only communicated to the anaesthetist and neither the surgeon nor the patient had insight as to allocation. The anaesthetist then prepared the appropriate solutions for both the intrathecal injection and the PCA. All patients received a PCA device and an intra-operative intrathecal injection with one containing the appropriate dose of morphine and the other normal saline, as determined by randomisation. Each patient was thus subjected to either morphine or saline injected intrathecally as well as a PCA containing either morphine or saline.

Pre-operative scoring was conducted by the author and co-investigators. Post-operative scoring was conducted in-hospital until discharge, at 6 weeks, 3 months and 6 months follow-up.

2.1 Informed consent

Informed consent for the study was obtained during admission for surgery. Informed consent for the surgical procedure was dealt with separately and procedural risks, benefits and possible complications were explained.

Consent forms for the study, which all participants were required to sign, were made available in Afrikaans, English and Xhosa. It was explained that both methods of analgesia are effective and that the doses studied fall within the recommended doses for the drug morphine. Patients participated in the study of their own volition and were afforded the opportunity to ask questions related to the study, admission as well as the procedure.

2.2 Randomisation

As previously noted, patients were allocated to one of the study options per sequentially numbered envelope which contained a descriptor for the anaesthetist allocating the patient to either the intrathecal morphine (thus PCA normal saline) or intrathecal placebo or saline (thus PCA morphine) group.

Randomisation was done by an independent third party. Block randomisation occurred allowing for 5 of each study group per 10 patients recruited. The unblinded information was filed and locked in a secure location in the departmental office, close to the ICU, should the necessity for unblinding arise during the study.

2.3 PCA

Depending on the group to which the patient had been randomised, he/she received a PCA device which contained either morphine, or normal saline. In the PCA morphine group, the device was loaded with a 1mg/ml concentration of morphine in normal saline. The 7 minute lock-out period allowed a maximum dose of 8 mg morphine per hour.

In the immediate post-operative period, the anaesthetist titrated small doses (1 - 2mg) of morphine until the patient was pain free on his/her arrival in the recovery room. The patient was then given the PCA device and could thus control his/her analgesia for the next 24 hours.

2.3.1 PCA Education

Patients who could not understand the principles of PCA analgesia, or how to use the device, were excluded from the study.

PCA education took place on two occasions prior to the procedure: once pre-operatively on the day of admission and the second immediately pre-operatively, just prior to induction of anaesthesia. Post-operatively, once they had recovered form anaesthesia, patients were again reminded of the PCA facility.

During the first PCA education session, which occurred in the ward on the day of admission, the device was shown to the patient and the mechanism of action was explained. Emphasis was placed on the lock-out period of 7 minutes between available dosages.

The same education was re-emphasised in the induction room prior to anaesthesia being administered. Once the patient had been recovered and he/she was in the recovery room, the use of the device was emphasised again.

2.4 Scoring systems

2.4.1. Oswestry disability index

The patient was requested to complete an Oswestry disability index (ODI), as illustrated in Figure 1.2, pre-operatively and then again at the 6-week, 3-month and 6-month follow-up visits.

2.4.2. Visual analogue scale

The patient was given a visual analogue scale (VAS), as per Figure 1.1. This instrument constitutes a horizontal line, at least 10cm in length, and marked from 1 to 10 with clear borders at 0 and 10 on an otherwise blank sheet of paper. The investigator explained that 0 signifies a complete absence of pain whilst 10 indicates the worst pain imaginable. The patient was then requested to draw a mark at the number which most appropriately represented his/her current pain. This process was done pre-operatively, and then at 8, 24 and 48 hours post-operatively and thereafter every 24 hours until the patient was discharged.

2.4.3. Euroqol-5D

This scoring system, as illustrated in Figure 1.3, was employed pre-operatively and then again at 6 weeks, 3 months and 6 months post-operatively.

2.4.4. Roland Morris

The patient completed this scoring sheet, as per Figure 1.4, pre-operatively. The process was repeated at 6 weeks, 3 months and 6 months post-operatively.

2.4.5. Opioid induced sedation scale

In conjunction with blood gas analysis, this scale is used to evaluate a patient's state of sedation in the first 24 hours post-operatively. The evaluation process, as per Figure 1.7, is repeated every hour for the first 4 hours post-operatively, 2-hourly for the next 8 hours and then 4-hourly for up to 24 hours post-operatively. A total of 11 blood gas analyses was done per patient using the same machine in the neurosurgical ICU (Gem Premier 3500, Instrumentation Laboratory, Bedford MA, United States). The analyser has an auto-calibration function to ensure the same quality of analysis across all samples.

2.5 General anaesthetic plan

2.5.1 Pre-operatively

The patient's medical risk factors and fitness for surgery were optimised.

Special investigations were directed by the patient's underlying medical comorbidities but a full blood count (FBC), urea and electrolytes (U/E) and electrocardiogram (ECG) were recommended for all patients 40 years and older.

An active crossmatch for all patients was sent to the blood bank in the event of an intra-operative blood transfusion being required.

Diabetics were to stop oral hypoglycaemic agents and were managed in accordance with a subcutaneous short-acting insulin sliding scale on the day before surgery.

All anti-hypertensive medication and diuretics were continued pre-operatively, except Angiotensin converting enzyme inhibitors and Angiotensin II receptor blockers which were omitted the morning of surgery.

2.5.2 Premedication

No sedatives or anxiolytics were given to patients with anticipated airway difficulties or to patients suffering from obstructive sleep apnoea.

All other patients received Midazolam 0.5mg/kg orally, to a maximum dose of 15mg 30 minutes pre-induction, or Lorazepam 1 - 2mg sublingually 30 minutes pre-induction.

Paracetamol 1g orally was given as a pre-medication as intravenous Paracetamol is not reliably available.

No intramuscular morphine or other oral opioid equivalent medication was given as a pre-medication.

2.5.3 Intra-operative

Standard monitoring techniques were done. These included: non-invasive blood pressure measurements, oxygen saturation, 3 - 5 lead ECG, agent and oxygen analyser, expired carbon dioxide and core temperature (Carescape Monitor B650, Helsinki, Finland).

As additional monitoring requirement, all study patients had an intra-arterial line insertion for haemodynamic monitoring and arterial blood gas analysis intra- and post-operatively in the ICU. This was inserted whilst the patient was under general anaesthesia and had specifically been consented to pre-operatively.

Other monitoring requirements were dictated by the patient's underlying physical/functional status and any concurrent medical co-morbidities.

A single 16g/18g peripheral intravenous line with Ringer's Lactate or Balanced Solution (Balsol) was placed to help maintain fluid requirements.

A central venous catheter was not mandatory and placement of such was guided by the patient's underlying medical co-morbidities, or if peripheral venous access proved to be difficult.

An upper or under body forced air warming blanket (Bair Hugger) was used to ensure that the patient's core body temperature was maintained at 36 to 37^{o}C.

2.5.4 Induction

Intra-operative analgesia was provided by an effect site target-controlled infusion (Cet TCI) of 50ug/ml (2mg in 40ml 0.9% normal saline) Remifentanil using the Minto pharmacokinetic-pharmacodynamic model. (Minto, 1997) The aim was to achieve an induction effect site concentration of 4 - 6ng/ml. A maintenance dose of 2 - 5ng/ml was titrated to the patient's analgesic requirements intra-operatively.

Depending on its availability, intravenous Paracetamol (Perfalgan) 15mg/kg IVI was infused slowly. This was done only if Paracetamol had not been administered as a pre-medication.

Hypnosis was initiated with an intravenous dose of 1% Propofol/Propoven titrated slowly to effect with a dosage range of 0.5 - 2mg/kg.

Muscle relaxation was facilitated with a non-depolarising muscle relaxant, Rocuronium, at a dosage of 0.6mg/kg. Residual neuromuscular paralysis was monitored using a standard train of four count (TOF), aiming for a TOF count of 1 (NMT TOF module, GE Healthcare, Helsinki Finland).

Cefazolin 25 - 30mg/kg was administered as prophylactic antibiotic, provided no allergic contraindication existed. If so, an alternative antibiotic was selected in consultation with the surgeon.

Dexamethasone 8mg IVI was given to each patient to decrease the incidence of post-operative nausea and vomiting (PONV).

Anaesthesia was maintained using a volatile based technique with either Isoflurane or Sevoflurane, depending on availability, in an oxygen/air blend aiming for 0.8 - 1 minimum alveolar concentration (MAC), depending on the patient's age and underlying comorbidities/functional class. The minimum inspired oxygen was 40%. Patients were mechanically ventilated using tidal volumes of 6-8ml/kg and adjusting the respiratory rate to ensure the expired carbon dioxide was 4 - 5%.
The patient was hand ventilated and full muscle relaxation was achieved in about 2 to 3 minutes. The trachea was then intubated using the appropriate size armoured endotracheal tube. The latter was securely fastened to ensure that it did not dislodge. An oral or nasal temperature probe was placed, and the patient's eyes were adequately padded and closed using ophthalmic pads.

A urinary catheter was inserted.

The patient was placed in the prone position. Care was taken to not dislodge any lines or the endotracheal tube and to support the patient's head and neck. The upper chest and pelvis were supported with a prone pillow allowing minimal pressure on the abdomen so as to not impede mechanical ventilation. The head and neck were kept in in a neutral position and the forehead was supported on a gel face pillow with no pressure being exerted on the eyes, nose or mouth. The temperature probe and endotracheal tube were positioned free from impingement on the patient's facial tissues. The patient's arms faced forward in a 90% flexion on arm boards resulting in minimal tension at the shoulder and elbow joints. Arm position was at the surgeon's discretion. All pressure points were protected with gel/foam pads and the patient's hips, knees and ankles were adequately supported. The urinary catheter was suspended from the bed allowing the anaesthetist easy access to assess urinary output.

The haemodynamic goal during surgery was to maintain mean arterial blood pressure (MAP) within 20% of pre-induction baseline values. This was achieved using appropriate fluid therapy (crystalloid/colloid) to maintain euvolemia and appropriately directed vasopressor/inotropic support to maintain adequate myocardial contractility and afterload, as needed.

Transfusion requirements were directed by the patient's underlying starting haemoglobin level, co-morbidities (transfusion trigger), as well as indicators of inadequate delivery of oxygen and intra-operative blood loss.

The surgeon delivered an intrathecal injection of preservative free morphine sulphate at a dose of 5ug/kg to a maximum dose of 450ug, or a placebo of normal saline (similar volume) under direct vision during surgery. The dose calculation was made based on the relationship of height to weight with the theory that the length of a person and thus the length of the spinal column will be related to the weight. However after 90kg, additional weight is theorised to be as a result of more adipose tissue, hence the upper limit of 450ug.

A PCA pump primed with morphine sulphate 1mg/ml or normal saline placebo was attached to an independent intravenous cannula for post-operative use.

2.5.5 Emergence

Upon completion of surgery, the Remifentanil TCI was weaned timeously to a Cet of 1ng/ml, which allowed for adequate return of spontaneous ventilation on emergence from anaesthesia.

Muscle relaxation was reversed using Neostigmine 25 - 50ug/kg in combination with Glycopyrrolate 4 - 6ug/kg or, for an average adult patient, 2.5mg Neostigmine with 0.5mg Glycopyrrolate. If Glycopyrrolate was unavailable, Atropine was used in a dose of 0.6 -1.2mg.

Adequate muscle reversal is demonstrated when the TOF ratio T4:T1 is >95%.

Upon adequate reversal, the volatile agent was terminated, and the patient woke up from anaesthesia. The patient's oropharynx was adequately suctioned under direct vision and the patient was extubated when awake and breathing adequately.

The patient was turned onto his/her back prior to terminating the anaesthesia.

2.5.6 Post-operative

The patient was transferred to the recovery room for further post-operative monitoring and to complete emergence.

A face-mask oxygen with a FiO_2 of 0.4 was administered to all study patients for the first 24 hours post-operatively.

Either the nursing staff or anaesthetist reinforced PCA pump function availability and its use as soon as the patient was fully awake.

When fully awake and stable the patient was sent to the Neurosurgery Intensive Care Unit (ICU) for further care and monitoring of study variables which included: blood gas analysis, oxygen saturation, respiratory rate, sedation scoring, pain scoring, blood loss and haemodynamic monitoring.

2.6 Single level fusion

Once general anaesthesia had been administered, the surgeon or assistant surgeon placed and secured a catheter. The patient was then placed in a prone position. Once prone, the surgical level was confirmed with fluoroscopy.

Routine surgical site preparation followed which involved the cleaning of the site with an antiseptic solution by the surgeon, assistant surgeon or nursing staff. Thereafter a sterile draping was placed.

A midline incision was performed, and the para-spinal muscles were stripped to the lumbar lamina. This dissection was then extended beyond the facet joints to expose the lateral gutters and transverse processes. Fluoroscopy was once again used to confirm the surgical level.

This was followed by the placement of pedicle screws in the relevant pedicles (4 in total as it is a single level fusion). This involved intra-operative identification of the pars interarticularis, transverse processes and facet joints. Screw lengths were estimated pre-operatively and optimal lengths to use intra-operatively were guided by clinical probing of the pedicle, to ensure no breaches, and intra-operative fluoroscopy.

This was followed by a laminectomy and decompression of the neural structures.

A laminectomy or hemi-laminectomy was performed to access and decompress the relevant neural structures. Care was taken to preserve the interspinous ligament of the more cranial vertebra involved in the fusion construct.

The use of a transforaminal lumbar interbody fusion (TLIF) was done at the discretion of the surgeon. This involved a facetectomy, discectomy and placement of an interbody cage. This added approximately 20 to 30 minutes to the total procedure time and caused no additional muscle trauma.

Prior to insertion of the rods, the intrathecal injection was administered. The rods were placed in the screw heads and secured with locking caps. A locally harvested bone graft was placed in decorticated lateral gutters. A surgical site drain was placed, and the wound was closed using continuous, interrupted and subcutaneous sutures. Surgical site clips were used if deemed appropriate by the surgeon.

The Intra-operative data captured included: surgical time, blood loss, complications, surgical sets used, surgeon/assistant details, time of intrathecal injection and anaesthetic charts.

2.7 Intrathecal injection

Depending on the group to which the patient had been randomised, the anaesthetist prepared a solution containing 1mg/ml of morphine in normal saline or a placebo. The surgeon, using a sterile insulin needle, drew up the appropriate volume from the solution provided by the anaesthetist (Figure 2.1). If the patient had been randomised to the intrathecal group, the dose administered was 0.005mg/kg to a maximum dose of 0.45mg. The volume matched the total milligram in millilitres, thus 0.45mg was 0.45ml. If the patient had been allocated to the placebo group, the solution contained normal saline only, applying a similar volume calculation as per the weight of the patient.

The intrathecal injection was performed at the most cranial point of the exposed dura mater. The dura mater at the caudal border of the lamina at the cranial end of the decompression was depressed using a blunt instrument. The spinal needle was then passed through the dura in the midline effectively under the cranial lamina. This technique provided a tamponade of the needle site with the lamina limiting a cerebrospinal fluid (CSF) leak and potential complication (Figure 2.2).

Once the needle had been correctly placed, cerebrospinal fluid (CSF) was aspirated to ensure correct positioning of the needle within the thecal sac. The solution was then *slowly administered.* The needle was not removed until 30 seconds *after* the entire content had been delivered. This slow delivery aided the spread of the solution within the CSF space. Considering that the remainder of the surgical procedure involved placement of the rods, bone graft and closure of the wound, the intrathecal solution was administered roughly 30 to 45 minutes prior to the end of the procedure.

Time point 0 was fixed as the time of the patient's arrival in the recovery room.

2.8 Blood gas analyses

Blood gas analyses were performed at the following time points for the first 24 hours post-surgically: hourly for the first 4 hours, 2-hourly for the next 8 hours and 4-hourly for the next 12 hours resulting in 11 samples in total. These arterial samples were analysed by the same calibrated blood gas machine. The parameters evaluated were: PaO2, PaCO2, oxygen saturation, FiO2, HCO_3, TCO2 (total carbon dioxide), haematocrit, base excess, haemoglobin, lactate and pH. The patient respiratory rate was documented per each sample taken.

2.9 High care unit

Routine observations were performed and included: blood pressure, mean arterial pressure, pulse rate, oxygen saturation, respiratory rate, opioid induced sedation scale, urinary output and intravenous fluid use.

2.10 Rescue analgesia

Additional analgesia consisted of intravenous paracetamol (Perfalgan®) 6 hourly for 48 hours.

An intramuscular dose of 5mg morphine was prescribed as rescue analgesia to be administered 4 - 6 hourly should the VAS score be 4 or above.

2.11 Physiotherapy

Physiotherapy was standardised throughout the study population with the same endpoints to be achieved and recorded. These endpoints included: log-roll and circulation exercise in the bed, sitting on the side of the bed, standing next to bed, mobilising a few steps next to bed, walking to the bathroom aided, walking to the bathroom unaided, mobilising independently and then discharge (Figure 1.5). These were recorded on the post-operative day that the target was achieved.

2.12 Retrospective cohort

A size matched retrospective cohort was enrolled from consecutive patients in the public sector who had their surgical procedures performed by the author and who were managed in the same neurosurgical unit where the prospective arm was conducted.

The data collected in the groups included demographics (age, gender) and length of hospital stay measured in days.

2.13 Direct costs

The length of stay of each patient was converted to a Rand value and a direct cost implication was calculated. Other factors which affected cost included: materials cost (e.g. PCA pump), drugs used and physiotherapy costs.

2.14 Statistical analysis

The statistical analysis was done by Ms Tonya Esterhuizen from the Biostatistics Unit, Division of Epidemiology and Biostatistics, Stellenbosch University with support from the Dean's Fund.

Group sample sizes of 37 and 37 was calculated to achieve 80% power to detect a change in mean duration of stay of 1.0 day between the PCA group and intrathecal morphine group. Group standard deviations of 1.5 (a conservative estimate) were assumed for the purposes of the sample size calculation. A significance level (alpha) of 0.05 using a two-sided Mann-Whitney test was used assuming that the actual distribution is uniform.

IBM SPSS version 25 was used to analyse the data. A p-value <0.05 was considered as statistically significant. However, clinical significance was also considered in the interpretation of the results.

Descriptive analysis:

Continuous variables were analysed descriptively using means and standard deviations if data was normally-distributed and medians and interquartile ranges if the data was non-normally distributed. 95% Confidence intervals were presented for population means and medians were presented when appropriate. Histograms were used to present the data visually. Nominal data was presented using frequency distributions and bar charts. 95% Confidence intervals for binary proportions were presented. Ordinal data was presented as medians and interquartile ranges.

Hypothesis testing:

Due to the randomisation of treatments in this study, where simple comparison of the outcomes between the two groups were required, a general framework of analysis was applied. The relationship between two nominal variables were investigated with contingency tables and likelihood ratio chi-square tests. Relationships between two continuous variables were analysed with regression analysis and the strength of the relationship measured with the Pearson correlation, or Spearman correlation, if the continuous variables were not normally distributed. If one continuous response variable was to be related to several other continuous

input variables, multiple regression analysis was used, and the strength of the relationship was measured with regression coefficients. The relationships between continuous response variables and nominal input variables were analysed using appropriate analysis of variance (ANOVA). When ordinal response variables were compared versus a nominal input variable, non-parametric ANOVA methods was used. For comparison of non-normally distributed outcomes, for example volume of PCA used, between the two treatment groups, the Mann-Whitney tests were used. Continuous normally distributed baseline variables were compared between the two treatment groups using independent t-tests,

In accordance with good clinical practice regarding a prospective clinical trial, an interim analysis was performed once twenty patients per group were recruited.

The **primary objective** of the study was to determine whether there is a decrease in the median duration of stay between the PCA and intrathecal morphine arms of the prospective groups. Assumptions of normality was tested using normal probability plots and found to be not normally distributed. Non parametric Mann-Whitney tests were used to compare median days to discharge as well other end points between the groups.

Another important objective of the study was to test for differences in side-effects and efficacy (measured by VAS scores and mobilisation) between the groups. Side effects are measured at 8, 24 and 48-hour post-operative time points as well as 11 blood_gas analysis values in the first 24 hours post-operatively. Repeated measures ANOVA models were employed, with time as a within-subjects factor and intervention group as the between-subjects factor. Interactions between time and intervention group were interpreted as treatment effects. Profile plots of mean outcome measures over time were shown by treatment group to visually assess the presence of an interaction or treatment effect. Assumptions of normality was tested using normal probability plots. Similar analyses were carried out for pain questionnaires (e.g. ODI, RM, EQ-5 and VAS), however the measurement intervals differ and include pre-operative, 6-week, 3 month and 6-month time points.

Figure 2.1: *A sterile insulin needle was used to deliver the prepared solution intrathecally. The anaesthetist prepared the appropriate solution and the surgeon then drew it into the syringe from a sterile container*

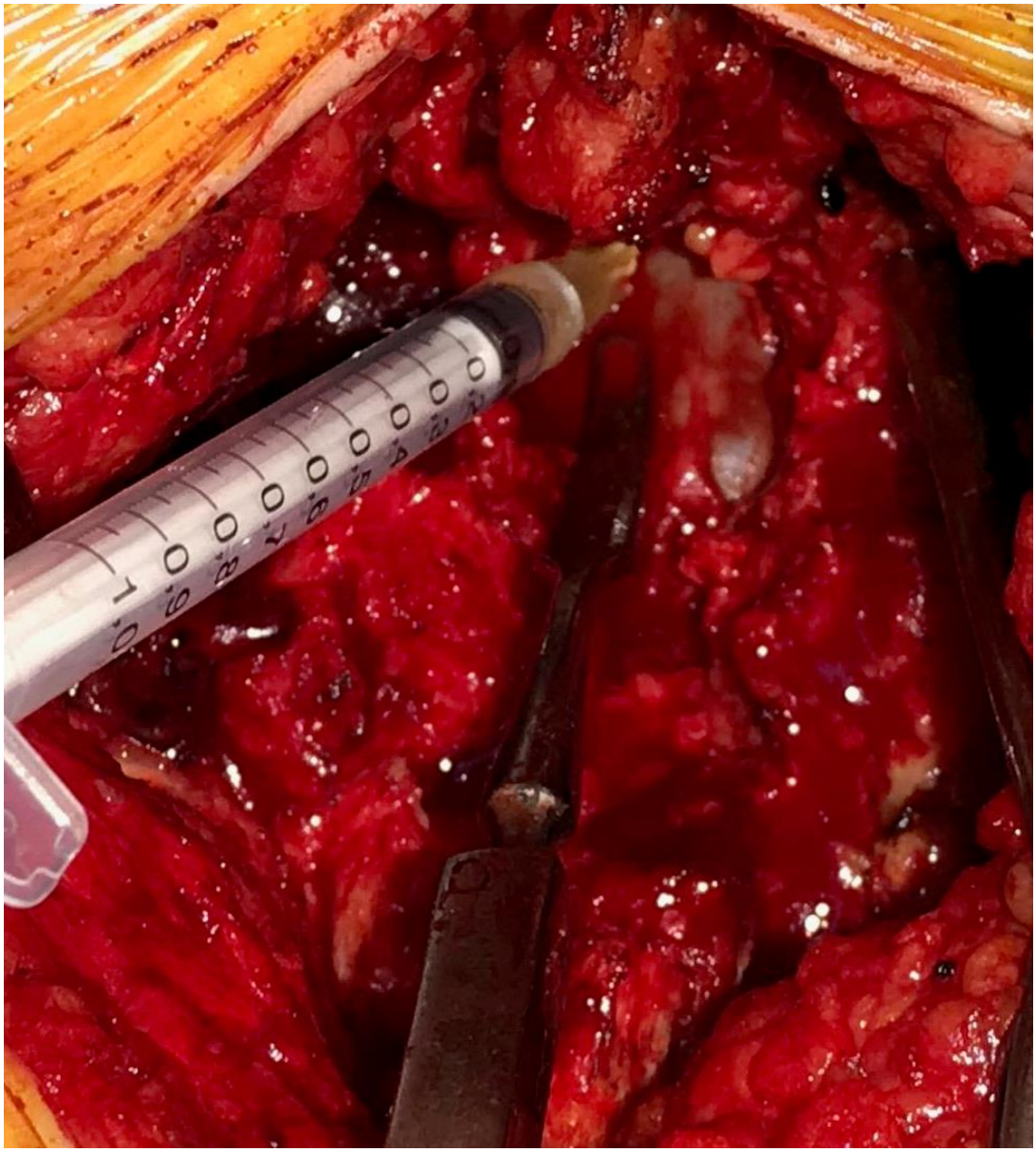

Figure 2.2: *The thecal sac is depressed under the cranial lamina and the intrathecal solution is then delivered. When the syringe is removed, the lamina will tamponade the puncture site in the dura.*

3. Results

3.1 General remarks

A sample size calculation was performed after 40 patients had been recruited. The total sample size resulted in the study being powered at 90% with a significance level of 0.01.

The block randomisation allowed for 20 patients per group (PCA and IT). Three patients were withdrawn from the study for reasons detailed in the following section:

- The first patient suffered a cardiac arrest whilst walking to the X-ray division for post-operative x-rays. The patient was successfully resuscitated and taken to cardiac angiography suite. Cardiac angiography demonstrated closure of a coronary vessel. The vessel was successfully stented, and re-perfusion occurred. The patient woke up and was transferred to the cardiac ICU. Later that evening she suffered another cardiac arrest and she could not be resuscitated. The case was reported as a serious adverse event (SAE) and was considered not related to the study.
- The second patient suffered from cannabis withdrawal during the first post-operative day. The patient pulled out all intravenous lines as well as the arterial line and needed sedation to control the withdrawal event. The patient, who had not disclosed any substance abuse or addiction prior to being enrolled, was subsequently withdrawn from the study.
- The third patient had a misplaced screw identified on post-operative X-rays. This required another surgery during the same admission. The post-operative blood gas data obtained in the first 24 hours were analysed. Length of stay, however, could not be used.

3.2 Group demographics

3.2.1 Intrathecal morphine group (IT group)

This group contained 11 female and 8 male patients. Seven patients were actively working at the time of the surgery. Ten patients were unemployed and 2 were retired and/or pensioners. Sixteen patients in the group were treated pre-operatively with oral opioid drugs (Tramadol).

3.2.2 Patient controlled analgesia group (PCA group)

There were 16 female and 2 male patients in the group. Four patients were actively working at the time of the surgery. Nine patients were unemployed and 5 were retired and/or pensioners. Seventeen patients in this group were treated with oral opioid drugs (Tramadol) pre-operatively.

3.2.3 Body mass index, body fat and muscle percentage

The mean body mass index (BMI) in the IT group was 29.18kg/m^2. Eleven patients had a BMI of more than 30kg/m^2 (58%). The mean body fat percentage was 37.4% and the mean muscle percentage was 35.16%.

The mean BMI in the PCA group was 34.31. Twelve patients had a BMI of more than 30 (67%). The mean body fat percentage was 44.65% and the mean muscle percentage was 32.37%.

The median BMI in the PCA group was 33kg/m^2 and 30.9kg/m^2 in the IT group.

There was a significant difference in mean BMI between the groups (p=0.011) and median BMI (p=0.033).

As per Table 3.1, the difference in total body fat percentage was not significant (p=0.075).

BMI and Body fat %				
		Mean	Std. Deviation	p-value
BMI (kg/m²)	PCA	34.31	6.52	0.01
	IT	29.18	5.24	
Body fat %	PCA	44.65	10.89	0.075
	IT	37.40	13.40	
Body muscle %	PCA	32.37	9.23	0.06
	IT	35.16	7.02	

Table 3.1: *BMI, bodyfat percentage and body muscle percentage in the intrathecal morphine and PCA groups*

3.3 Pre-operative scoring

3.3.1 Quadruple Visual Analogue Score

In the IT group the following average Quadruple Visual Analogue Score (QVAS) scores were recorded:

Pain right now at 7.16

Pain on average at 6.37

Pain at its best at 3.37

Pain at its worst at 9.42

In the PCA group the following average QVAS scores were recorded:

Pain right now at 6.05

Pain on average at 6.00

Pain at its best at 2.79

Pain at its worst at 8.84

3.3.2 EQ-5

The average Best/Worst imaginable health state, as measured out of 100, was 34.21 in the IT group and 36.05 in the PCA group.

3.3.3 Oswestry disability index

The average Oswestry disability index (ODI) percentage for the IT group was 63.79 and 63.47 in the PCA.

3.3.4 Roland Morris (RM)

The mean total in the IT group was 16.11 and in the PCA group 16.37.

	IT	**PCA**
QVAS Pain right now	7.16	6.05
QVAS Pain on average	6.37	6
QVAS Pain at its best	3.37	2.79
QVAS Pain at its worst	9.42	8.84
EQ-5	34.21	36.05
ODI percentage	63.79	63.47
RM	16.11	16.37

Table 3.2: *The mean pre-operative scores in the IT and PCA groups (no statistically significant difference between groups)*

3.4 Surgical detail

The index procedure to be included in the study was first-time spinal surgery namely a single level lumbar fusion.

The most common levels at which the procedure was performed was:

L4/L5 (n=23, 62.2%)

L5/S1 (n=10, 27%)

L3/L4 (n=2, 5.4%)

L2/L3 (n=2, 5.4%)

The breakdown per study group for surgical levels is as follows:

IT:

L4/L5 (n=12)

L5/S1 (n=6)

L2/L3 (n=1)

PCA:

L4/L5 (n=11)

L5/S1 (n=4)

L3/L4 (n=2)

L2/L3 (n=1)

For the IT group, the average intra-operative blood loss was 434.2ml and surgical time 129.2 minutes.

For the PCA group, the average intra-operative blood loss was 538.9ml and surgical time 129.9 minutes.

The average time from the intrathecal injection until closure of the skin was 29.58 minutes in the IT group and 28.83 in the PCA group. Overall, the average time was 28.21 minutes between the intrathecal injection and skin closure. Surgical detail is presented in Table 3.3.

	IT	PCA	Overall
Blood loss (ml)	434.2	538.9	486.55
Surgical time (minutes)	129.2	129.9	129.55
Intrathecal injection until skin closure (minutes)	29.58	28.83	28.21

Table 3.3: *Intra-operative detail in the IT group, PCA group and overall (no statistical difference between groups)*

3.5 Post-operative course

The VAS scores were taken at 8 hours post-operatively both when the patient was lying still and when he/she was moving. Possible side-effects related to the intrathecal injection and morphine (itching, headaches, nausea and vomiting, feeling of heavy breathing) were recorded.

The post-operative results are presented per each time point (8, 24, 48, 72, 96 and 120 hours post-operatively). A summary of the side-effects, VAS scores and supplementary analgesia used are presented as per each point in time.

3.5.1 Eight (8) hours post-operatively

3.5.1.1 IT group

There were 4 incidences of itching, 3 cases of headache, 1 incident of nausea and vomiting and 1 incident of a feeling of heavy breathing (Table 3.5).

The average VAS lying still was 2.26 and moving 4. The average difference between lying still and moving was 1.74.

3.5.1.2 PCA group

There was 1 incident of itching, 3 incidences of headache, 0 incidences of nausea and vomiting and none of a feeling of heavy breathing (Table 3.5).

The average VAS lying still was 2.68 and moving 4.79. The average difference between lying still and moving was 2.11.

3.5.1.3 Supplemental analgesia

There was no supplemental analgesia required for either group.

3.5.2 Twenty-four (24) hours post-operatively

3.5.2.1 IT group

There were 5 incidents of itching, 2 incidents of headache, 1 incident of nausea and vomiting and 0 incidences of a feeling of heavy breathing (Table 3.5).

The average VAS lying still was 3.16 and moving 4.79. The average difference between lying still and moving was 1.63.

3.5.2.2 PCA group

There was 1 incident of itching, 2 incidents of headache, 0 incidence of nausea and vomiting and none of a feeling of heavy breathing (Table 3.5).

The average VAS lying still was 2.26 and moving 4.68. The average difference between lying still and moving was 2.42.

3.5.2.3 PCA volume used

The volume of PCA used was calculated for both groups. The volume used in the IT group was 22ml and 43ml in the PCA group (p=0.057). Refer to Table 3.4 and Figure 3.1.

		PCA	IT	p-value
PCA volume used	Median	43.0	22.0	0.057
	Percentile 25	20	12	
	Percentile 75	55	47	

Table 3.4: *PCA volume used in the IT and PCA groups*

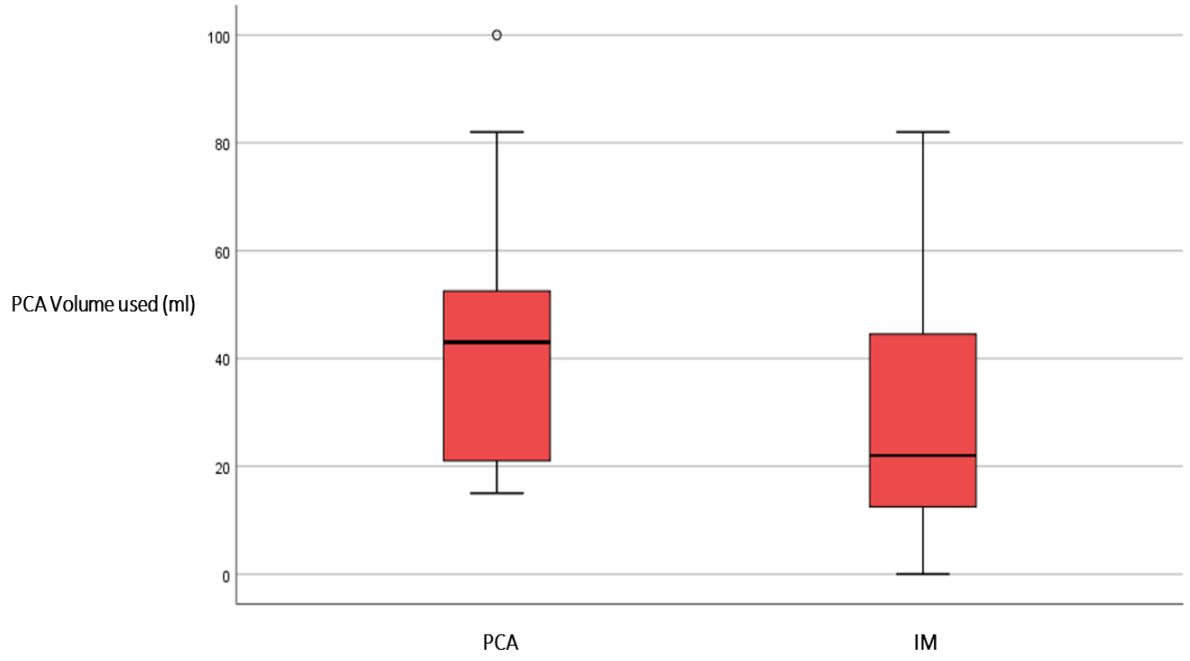

Figure 3.1: *PCA volume used in PCA and IT groups (no statistically significant difference, p=0.057)*

3.5.2.4 Supplemental analgesia

There were 2 patients who required supplemental analgesia in the IT group and 8 patients in the PCA group. This difference was statistically significant as indicated in Table 3.12.

3.5.3 Forty-eight (48) hours post-operatively

3.5.3.1 IT group

There was 1 incident of itching, 3 incidents of headache, 1 incident of nausea and vomiting and 0 incidences of a feeling of heavy breathing (see Table 3.5).

The average VAS lying still was 3.22 and moving 5.1. The average difference between lying still and moving was 1.88.

3.5.3.2 PCA group

There were 0 incidents of itching, 4 incidents of headache, 1 incident of nausea and vomiting and 0 incidences of a feeling of heavy breathing (Table 3.5).

The average VAS lying still was 3.32 and moving 5.21. The average difference between lying still and moving was 1.89.

3.5.3.3 Supplemental analgesia

There were 5 patients who required supplemental analgesia in the IT group and 8 patients in the PCA group (see Table 3.12).

3.5.3.4 VAS difference over the first 48 hours

The VAS scores were recorded both when the patient was *lying still*, and when the patient was *asked to move*. The difference between these two measures is presented in Figure 3.2.

The difference is most pronounced at 24 hours and was statistically significant (p=0.032).

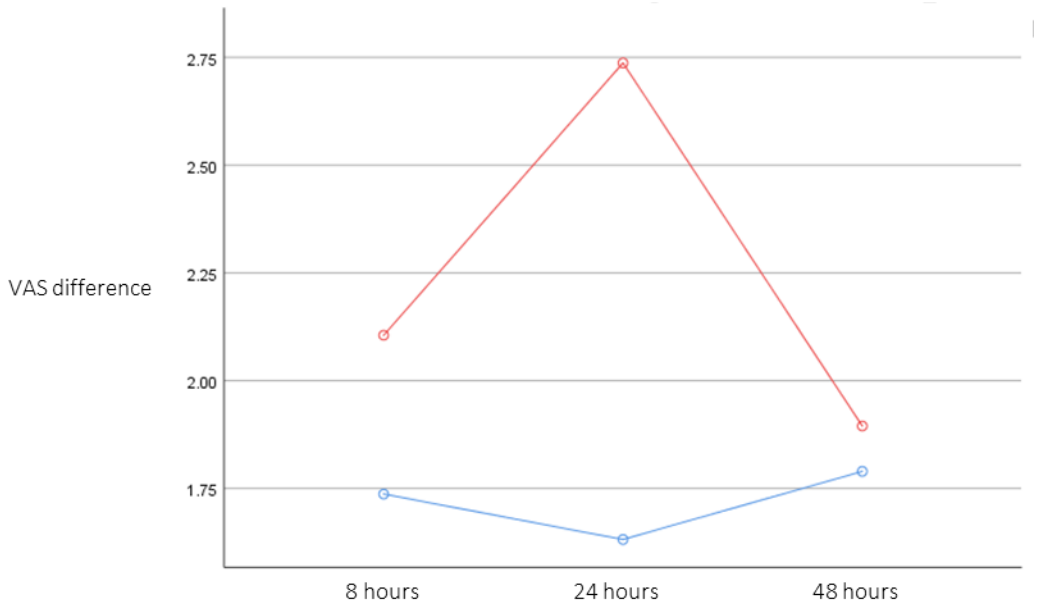

Figure 3.2: *The difference in VAS scores for the IT group (blue line) and the PCA group (red line) at 8, 24 and 48 hours*

3.5.3.5 VAS sub analysis at 24 hours post-operatively

When the difference in VAS lying still and VAS moving were compared between the IT and PCA groups, and the patients with a BMI of less than 30 were removed (n=14), a statistically significant difference occurred in favour of the IT group (p=0.03).

3.5.4 Seventy-two (72) hours post-operatively (n=32)

3.5.4.1 IT group

The average VAS lying still was 2.21 and moving 4.14. The average difference between lying still and moving was 1.93.

3.5.4.2 PCA group

The average VAS lying still was 2.28 and moving 4. The average difference between lying still and moving was 1.72.

3.5.4.3 Supplemental analgesia

There was 1 patient who required supplemental analgesia in the IT group and 4 patients in the PCA group (see Table 3.12).

3.5.5 Ninety-six (96) hours post-operatively (n=24)

3.5.5.1 IT group

The average VAS lying still was 1.56 and moving 3.67. The average difference between lying still and moving was 2.11.

3.5.5.2 PCA group

The average VAS lying still was 2.67 and moving 4.2. The average difference between lying still and moving was 1.53.

3.5.5.3 Supplemental analgesia

There was 1 patient who required supplemental analgesia in the IT group and 3 patients in the PCA group (see Table 3.12).

3.5.6 One-hundred and twenty (120) hours post-operatively (n=20)

3.5.6.1 IT group

The average VAS lying still was 1 and moving 2.17. The average difference between lying still and moving was 1.17.

3.5.6.2 PCA group

The average VAS lying still was 2.64 and moving 3.86. The average difference between lying still and moving was 1.21.

3.5.6.3 Supplemental analgesia

No patients required supplemental analgesia in the IT group and 2 patients required analgesia in the PCA group (Table 3.12).

3.6 Intrathecal injection and morphine side effects

Patients were assessed for the following possible side effects of the intrathecal injection (with or without morphine) and morphine itself: headache, nausea and vomiting, itching and a sense of heavy breathing. The incidences are described for each time point (8 hours, 24 hours and 48 hours) and proved to not be statistically different.

	IT group incidences	**PCA group incidences**	**p-value**
8 hours headache	3	3	1.000
8 hours nausea and vomiting	1	0	1.000
8 hours itching	4	1	0.340
8 hours feeling of heavy breathing	1	0	1.000
24 hours headache	2	2	1.000
24 hours nausea and vomiting	1	0	1.000
24 hours itching	5	1	0.180
24 hours feeling of heavy breathing	0	0	1.000
48 hours headache	3	4	0.565
48 hours nausea and vomiting	1	1	0.598
48 hours itching	1	0	0.486
48 hours feeling of heavy breathing	0	0	0.311

Table 3.5: *Summary of the side effects related to the intrathecal injection and morphine in the IT and PCA groups with no statistically significant difference between the groups*

3.7 VAS scores during study period and supplemental analgesia

3.7.1 VAS lying still

The VAS scores lying still over the study period is presented in Table 3.6 and Figure 3.3. There was a significant difference at 120 hours post-operatively between the IT and PCA groups (p=0.029).

VAS lying still	IT	PCA	p-value
8 hours	2.26	2.68	0.552
24 hours	3.16	2.26	0.237
48 hours	3.22	3.32	0.938
72 hours	2.21	2.28	0.924
96 hours	1.56	2.67	0.174
120 hours	1	2.64	**0.029**

Table 3.6: *The mean VAS values of the IT and PCA groups when lying still over the first 120 hours post-operatively*

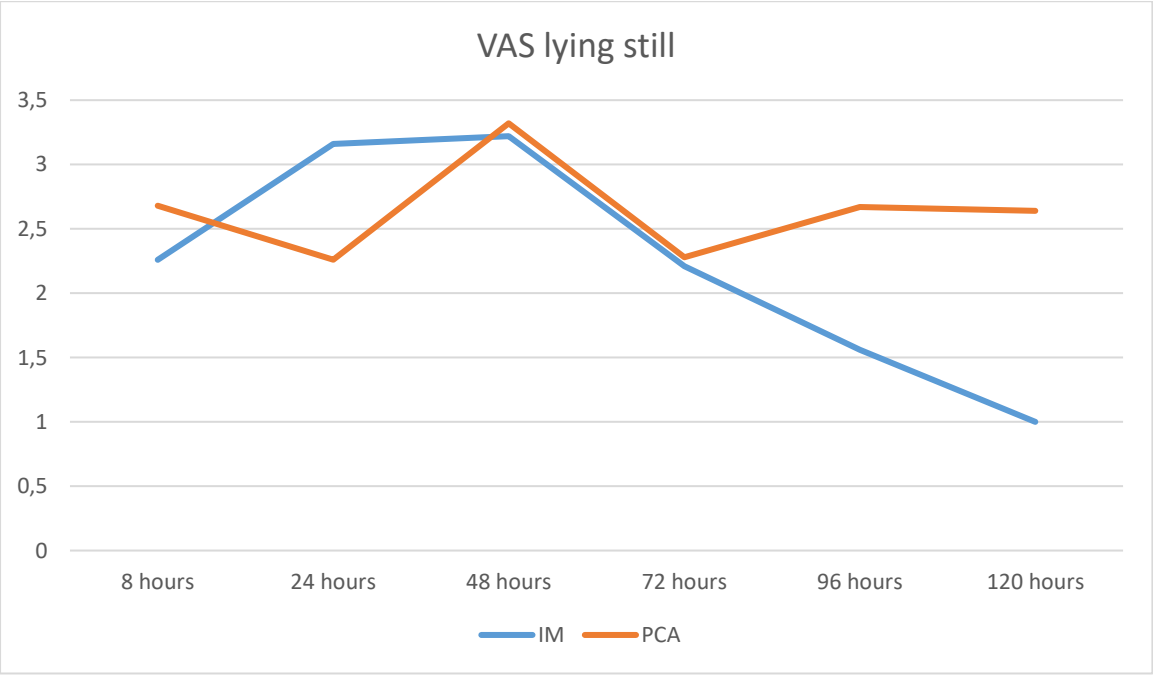

Figure 3.3: *The mean VAS values of the IT and PCA groups when lying still over the first 120 hours post-operatively*

3.7.2 VAS moving

The VAS scores while moving are presented in Table 3.7 and Figure 3.4. There was a significant difference at 120 hours post-operatively between the IT and PCA groups (p=0.026).

When using the median values, a significant difference was also detected at 120 hours (p=0.033).

VAS moving	IT	PCA	p-value
8 hours	4	4.79	0.422
24 hours	4.79	4.68	0.953
48 hours	5.1	5.21	0.835
72 hours	4.14	4	0.831
96 hours	3.67	4.2	0.487
120 hours	2.17	3.86	**0.026**

Table 3.7: *The mean VAS values of the IT and PCA groups when moving over the first 120 hours post-operatively*

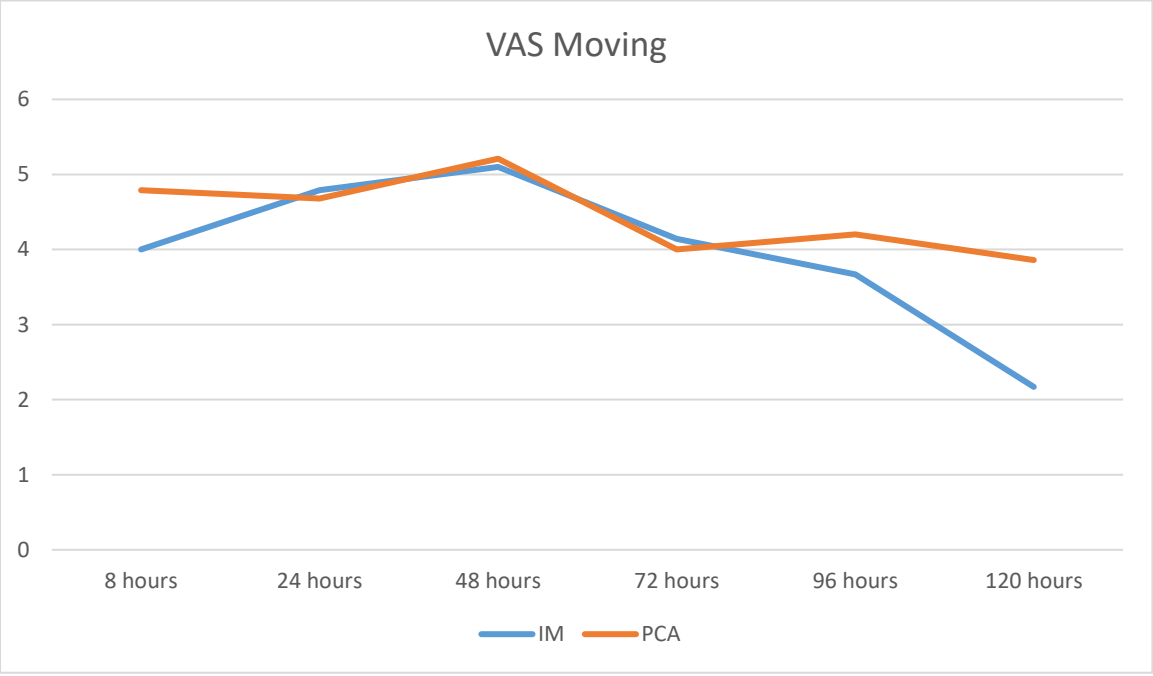

Figure 3.4: *The mean VAS values of the IT and PCA groups when moving over the first 120 hours post-operatively*

3.7.3 VAS difference

The difference in VAS scores over the study period is presented in Table 3.8 and Figure 3.5.

A statistically significant difference was noted at 24 hours favouring the IT group.

VAS difference	IT	PCA	p-value
8 hours	1.74	2.11	0.507
24 hours	1.63	2.42	**0.034**
48 hours	1.88	1.89	0.810
72 hours	1.93	1.72	
96 hours	2.11	1.53	
120 hours	1.17	1.21	

Table 3.8: *The mean difference in VAS values of the IT and PCA groups over the first 120 hours post-operatively*

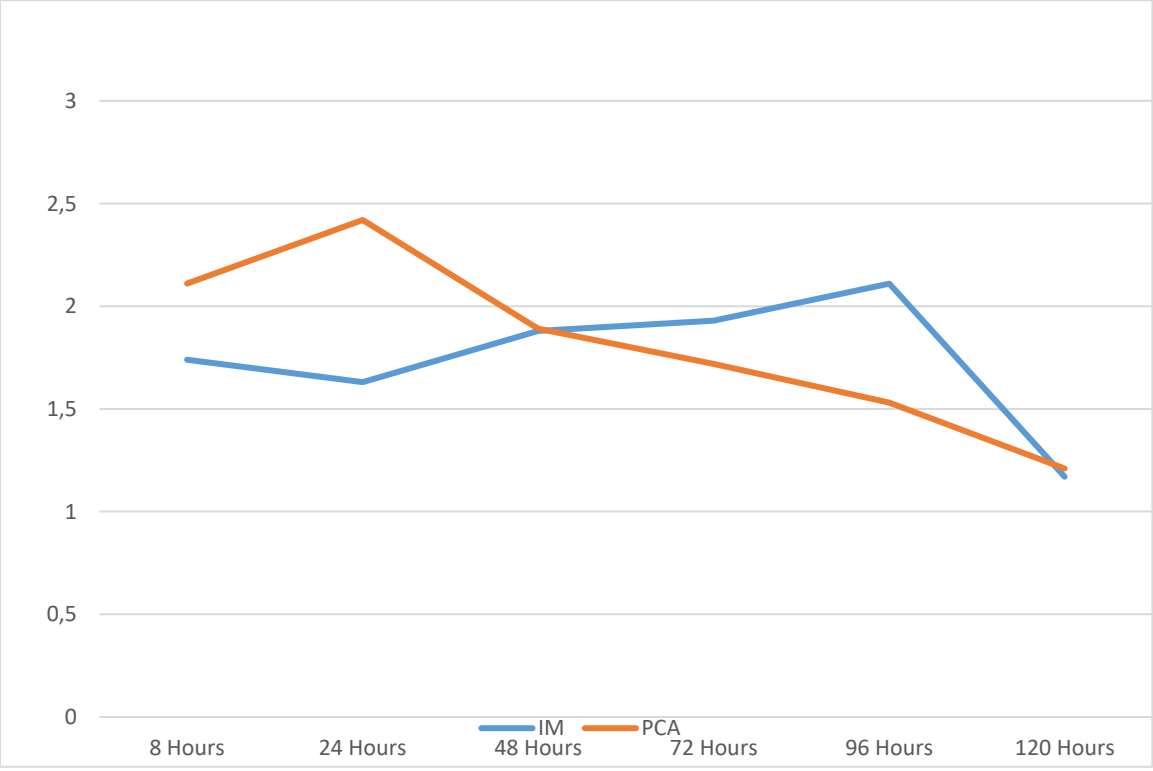

Figure 3.5: *The mean difference in VAS values of the IT and PCA groups over the first 120 hours post-operatively*

VAS Lying still	**IT**	**IT** when mobilization (**sitting**) is corrected for	**PCA**	**PCA** when mobilization (**sitting**) is corrected for	**p-value**
8 hours	2.26	2.39	2.68	2.42	0.066
24 hours	3.16	3.34	2.26	1.65	
48 hours	3.22	3.19	3.32	2.91	

Table 3.9: *The mean VAS Lying still values for the IT and PCA group for 8, 24 and 48 hours post-operatively both before and when corrected for the effect of sitting. The impact of sitting was not statistically significant (p=0.066)*

VAS Lying still	**IT**	**IT** when mobilization (**standing**) is corrected for	**PCA**	**PCA** when mobilization (**standing**) is corrected for	**p-value**
8 hours	2.26	2.57	2.68	2.23	0.045
24 hours	3.16	3.55	2.26	1.43	
48 hours	3.22	3.28	3.32	2.81	

Table 3.10: *The mean VAS Lying still values for the IT and PCA group for 8, 24 and 48 hours post-operatively both before and when corrected for the effect of standing. The impact of standing was statistically significant (p=0.045)*

VAS Lying still	**IT**	**IT** when mobilization (**steps**) is corrected for	**PCA**	**PCA** when mobilization (**steps**) is corrected for	**p-value**
8 hours	2.26	2.57	2.68	2.24	0.052
24 hours	3.16	3.52	2.26	1.45	
48 hours	3.22	3.27	3.32	2.83	

Table 3.11: *The mean VAS Lying still values for the IT and PCA group for 8, 24 and 48 hours post-operatively both before and when corrected for the effect of taking steps. The impact of taking steps was not statistically significant (p=0.052)*

3.7.4 Supplemental analgesia required

There was a significant difference in supplemental analgesia use at 24 hours between the 2 groups.

	IT	**PCA**	**p-value**
24 hours	2	8	**0.02**
48 hours	5	8	0.25
72 hours	1	4	0.24
96 hours	1	3	0.57
120 hours	0	2	0.33

Table 3.12: *The supplemental analgesia requirements presented for each group over the study period*

3.8 Mobilisation

Mobilisation was measured in accordance with targets achieved for each patient. These targets were: logroll, sit on the side of the bed, stand next to the bed, mobilise a few steps, walk to the bathroom aided, walk to the bathroom unaided, mobilise independently and discharge.

The average length of stay in the IT group was 3.68 days and in the PCA group 5.61 days. These results are depicted in Figures 3.6 and 3.7.

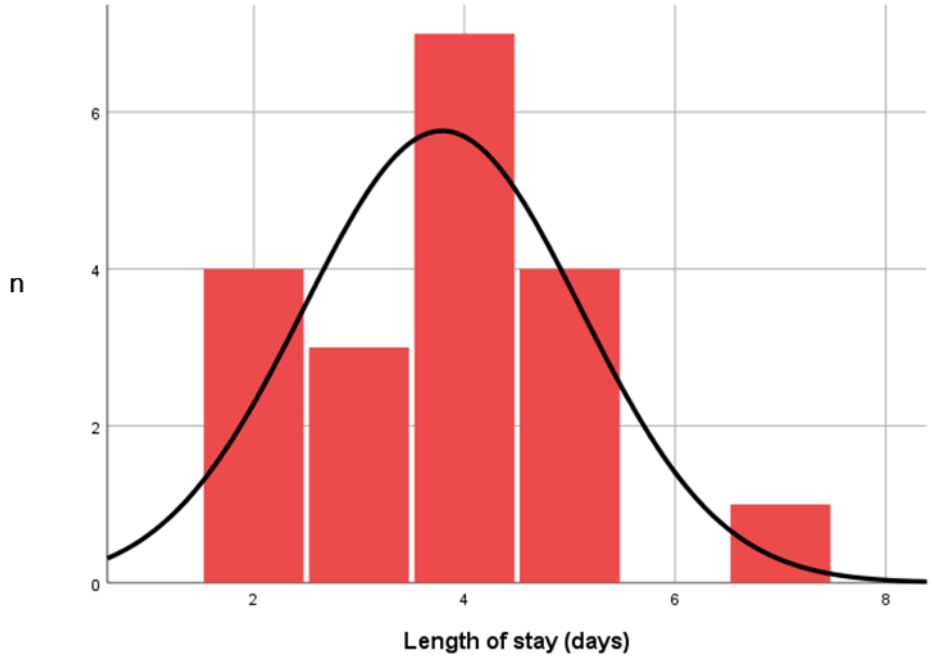

Figure 3.6: *Histogram presenting the IT group length of stay*

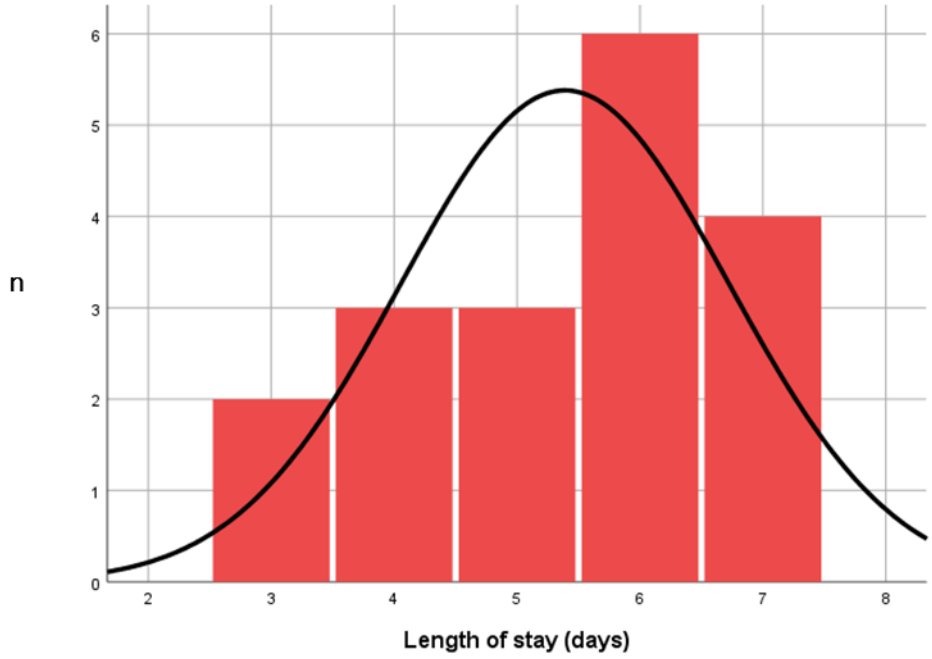

Figure 3.7: *Histogram presenting the PCA group length of stay*

The results for each of the individual mobilisation targets are presented in Table 3.13.

There was a significant difference between the IT and PCA groups for days to mobilising independently (p=0.009) and days to discharge (p=0.001).

		PCA	IT	p-value
Days to logroll	Median	1	1	0.988
Days to sit	Median	2	1	0.298
Days to stand	Median	2	2	0.134
Days to a few steps	Median	3	2	0.105
Days to walking aided	Median	3	3	0.480
Days to walking unaided	Median	4	4	0.126
Days to mobilising independently	Median	5	4	**0.009**
Days to discharge	Median	6	4	**0.001**

Table 3.13: *The median days to achieving mobilisation targets for the IT and PCA groups*

The individual distributions of mobilisation targets per group is presented in Figure 3.8.

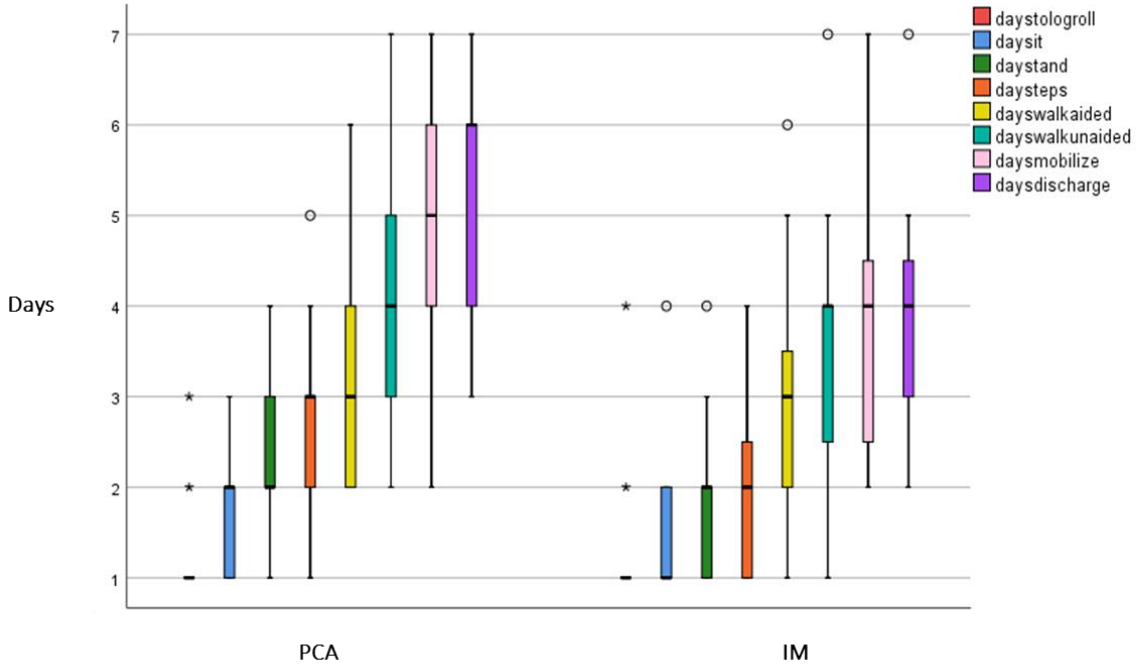

Figure 3.8: *The individual distributions of mobilisation targets*

3.9 Blood gas analysis

Blood gas analysis was performed on each patient: every hour for 4 hours, 2-hourly for a further 8 hours and then 4-hourly up to 24 hours post arrival in the recovery room after surgery. Each patient thus contributed 11 samples post-operatively to the data. A pre-operative blood gas analysis was also performed on each patient.

The following parameters were also assessed at the same time as the blood gas analysis: respiratory rate (RR), FiO_2 and the opioid induced sedation scale (OISS).

The following were considered risk factors for respiratory depression: RR less than 10 breaths per minute, oxygen saturation (SATS) less than 90%, $PaCO_2$ more than 6kPa, PaO_2 less than 8kPa and an OISS score of 2 or more. The results were also assessed during ICU sleep time (22:00 – 06:00) and awake time (06:00 – 22:00) and also if the patient had a BMI of >30kg/m².

3.9.1 Respiratory rate

Considering a rate of less than 10 breaths per minute as an indicator for respiratory depression, very few incidents occurred within the first 24 hours post-operatively in both the PCA and IT groups.

A total of 5 incidents were observed of which 3 were in the IT group and 2 in the PCA group. No incidence of RR <10 breaths per minute were recorded prior to 6 hours post-operatively (Table 3.14). These 5 incidents were observed in 2 patients (3 incidents in an IT patient, 2 incidents in a PCA patient).

The mean respiratory rate (mRR) at each timepoint demonstrated a slightly higher mRR at the first hour post-operatively and both groups (PCA and IT) demonstrated a steady increase in mRR for the first 24 hours measured (see Figure 3.9). Neither of the groups had any mRR of concern. A gradual increase in mRR was seen in both groups from approximately 6 hours post-operatively onwards.

			PCA group		IT group	
			n	percentage	n	percentage
	1hr	RR<10	0	0.0%	0	0.0%
	2hr	RR<10	0	0.0%	0	0.0%
	3hr	RR<10	0	0.0%	0	0.0%
	4hr	RR<10	0	0.0%	0	0.0%
	6hr	RR<10	1	5.3%	1	5.3%
	8hr	RR<10	0	0.0%	0	0.0%
	10hr	RR<10	1	5.9%	0	0.0%
	12hr	RR<10	0	0.0%	1	5.3%
	16hr	RR<10	0	0.0%	0	0.0%
	20hr	RR<10	0	0.0%	1	5.3%
	24hr	RR<10	0	0.0%	0	0.0%

Table 3.14: *Incidences of mean respiratory rate under 10 breaths per minute between the PCA and Intrathecal morphine groups over the first 24 hours post-operatively with no statistically significant difference*

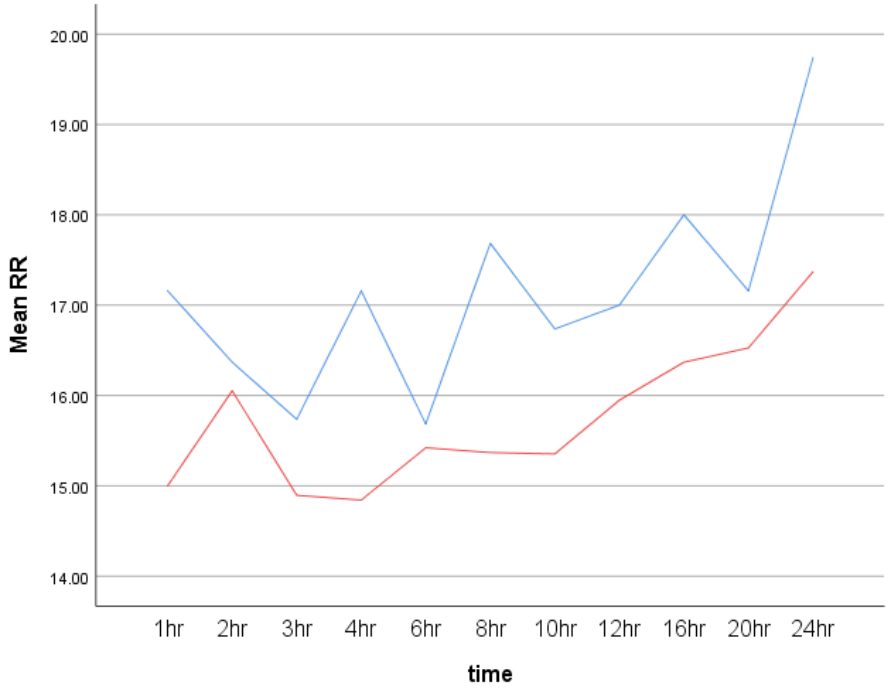

Figure 3.9: *The mean respiratory rate of the patients in the PCA group (red line) and IT group (blue line) as observed over the first 24 hours*

3.9.2 Oxygen saturation

SATS of less than 90% was defined as a parameter for respiratory depression. Seven incidents occurred where the SATS decreased to less than 90%. This occurred 4 times in the IT group and 3 times in the PCA group (Table 3.15).

Five of the above occurred while the patient was on supplemental oxygen and 2 occurred on room air. Of these 5, 3 occurred in the IT group, and 2 in the PCA group.

The mean SATS values for both groups demonstrated a sharp rise until 3 hours post-operatively after which a steady decline took place over the next 24 hours. This subsequent decline never decreased to below 95% (Figure 3.10).

When the parameters of RR and SATS were cross tabulated, no incidents of RR below 10 breaths per minute and SATS of less than 90% occurred at the same time over the first 24 hours post-operatively.

				PCA		IT	
				n	%	n	%
	1hr	SATS	<90	1	5.3%	1	5.3%
	2hr	SATS	<90	0	0.0%	0	0.0%
	3hr	SATS	<90	0	0.0%	0	0.0%
	4hr	SATS	<90	0	0.0%	0	0.0%
	6hr	SATS	<90	0	0.0%	0	0.0%
	8hr	SATS	<90	0	0.0%	1	5.6%
	10hr	SATS	<90	1	5.9%	0	0.0%
	12hr	SATS	<90	0	0.0%	1	5.3%
	16hr	SATS	<90	1	5.3%	1	5.3%
	20hr	SATS	<90	0	0.0%	0	0.0%
	24hr	SATS	<90	0	0.0%	0	0.0%

***Table 3.15**: Incidence of SATS being less than 90% between the s PCA and IT groups over the first 24 hours post-operatively with no statistically significant difference*

Figure 3.10: *The mean SATS of the patients in the PCA group (red line) and IT group (blue line) as observed over the first 24 hours*

3.9.3 $PaCO_2$

$PaCO_2$ of higher than 6kPa was defined as indicative of significant alveolar hypoventilation because of central respiratory depression. This occurred 41 times (19.8%) in the PCA group and 57 times (27.9%) in the IT group over the first 24 hours post-operatively.

In the IT group, 52.6% had $PaCO_2$ in excess of 6kPa at the first hour post-operatively and 66.7% at hour 2. The percentage gradually decreased over the following 22 hours, yet never reached 0%. This gradual decrease is seen in both PCA and IT groups (Table 3.16).

There was no statistically significant difference detected between the mean $PaCO_2$ in both groups (p=0.175).

When a $PaCO_2$ of higher than 6.5kPa was considered, 21.1% of PCA and 26.3% of IT patients exceeded this threshold at the first hour post-operatively (Table 3.17). The PCA group then presented a sudden decrease and maintained a low incidence throughout the rest of the 24 hours. The IT group maintained a higher incidence for the first 8 hours, where after it decreased to 0% barring a small spike of 5.3% at 12 hours (Table 3.17). The total incidence of patients exceeding this threshold was 7.7% in the PCA and 13.2 % in the IT group.

The mean $PaCO_2$ of both the PCA and IT group rapidly decreased 4 hours post-operatively (Figure 3.11). From 10 hours post-operatively onwards they followed a similar trend.

The decrease in PaCO2 in the IT group demonstrated a statistically significant decrease starting at 4 hours post-operatively and continuing until 24 hours post-operatively and in the PCA group from 16 hours until 24 hours post-operatively (Table 3.18).

			PCA		IT	
			n	%	n	%
1hr	$PaCO_2$	>6	6	31.6%	10	52.6%
2hr	$PaCO_2$	>6	6	31.6%	12	66.7%
3hr	$PaCO_2$	>6	6	31.6%	8	42.1%
4hr	$PaCO_2$	>6	4	21.1%	8	42.1%
6hr	$PaCO_2$	>6	4	21.1%	6	33.3%
8hr	$PaCO_2$	>6	1	5.3%	5	27.8%
10hr	$PaCO_2$	>6	4	23.5%	2	11.8%
12hr	$PaCO_2$	>6	4	21.1%	1	5.3%
16hr	$PaCO_2$	>6	4	21.1%	1	5.3%
20hr	$PaCO_2$	>6	1	5.3%	2	10.5%
24hr	$PaCO_2$	>6	1	5.3%	2	10.5%
Total	$PaCO_2$	>6	41	19.8%	57	27.9%

Table 3.16: *Incidence of $PaCO_2$ being higher than 6kPa between the PCA and IT groups over the first 24 hours post-operatively. No statistically significant difference was detected (p=0.175)*

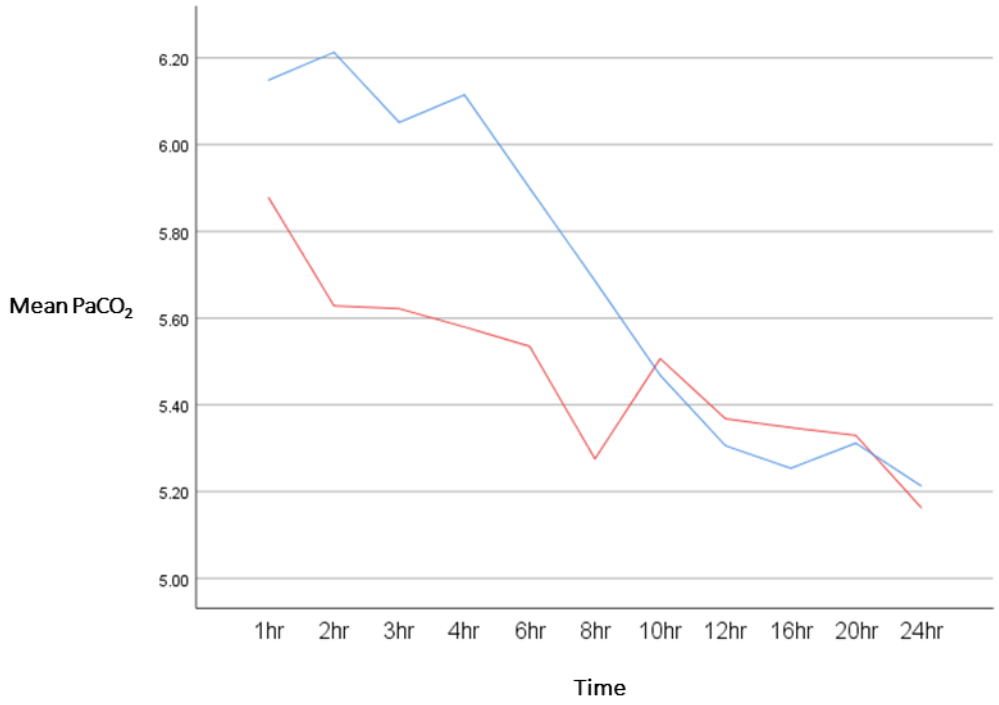

Figure 3.11: *The mean $PaCO_2$ of the patients in the PCA group (red line) and IT group (blue line) as observed over the first 24 hours*

The incidence of a $PaCO_2$ higher than 6.5kPa is presented in Table 3.17. There were 43 incidences in total (16 in the PCA group and 27 in the IT group). No statistically significant difference was detected between the groups.

			PCA		IT	
			n	%	n	%
1hr	$PaCO_2$	>6.5	4	21.1%	5	26.3%
2hr	$PaCO_2$	>6.5	0	0.0%	6	33.3%
3hr	$PaCO_2$	>6.5	1	5.3%	4	21.1%
4hr	$PaCO_2$	>6.5	1	5.3%	5	26.3%
6hr	$PaCO_2$	>6.5	1	5.3%	3	16.7%
8hr	$PaCO_2$	>6.5	1	5.3%	3	16.7%
10hr	$PaCO_2$	>6.5	2	11.8%	0	0.0%
12hr	$PaCO_2$	>6.5	2	10.5%	1	5.3%
16hr	$PaCO_2$	>6.5	2	10.5%	0	0.0%
20hr	$PaCO_2$	>6.5	1	5.3%	0	0.0%
24hr	$PaCO_2$	>6.5	1	5.3%	0	0.0%
Total	$PaCO_2$	>6.5	16	7.7%	27	13.2%

Table 3.17: *Incidence of $PaCO_2$ being higher than 6.5kPa between the PCA and IT groups over the first 24 hours post-operatively*

	Time	IT group p-value	PCA group p-value
Mean $PaCO_2$	1hr vs 2hr	0.623	0.086
	2hr vs 3hr	0.530	0.241
	3hr vs 4hr	0.807	0.259
	4hr vs 6hr	**0.012**	0.250
	6hr vs 8 hr	**0.004**	0.051
	8hr vs 10hr	**0.000**	0.589
	10hr vs 12hr	**0.000**	0.247
	12hr vs 16hr	**0.000**	0.122
	16hr vs 20hr	**0.000**	**0.032**
	20hr vs 24 hr	**0.000**	**0.016**

Table 3.18: *The statistical difference in change in $PaCO_2$ between post-operative time points in the intrathecal morphine and PCA groups. A statistically significant decrease in $PaCO_2$ occurs from 4 hours up to 24 hours post-operatively in the IT group, and from 16 hours up to 24 hours post-operatively in the PCA group.*

The incidence of a $PaCO_2$ higher than 7kPa is presented in Table 3.19. There were 9 incidences in total (3 in the PCA group and 6 in the IT group). Four incidents occurred in the first 4 hours post-operatively in the IT group, 1 at 8 hours post-operatively and none thereafter. The 3 incidences in the PCA group occurred at 1, 12 and 24 hours.

With regards to the $PaCO_2$ higher than 7kPa in the IT group, the following are individual additional details:

- The first patient had a $PaCO_2$ of 7.2kPa at 1 hour post-operatively. The PaO_2 was 7.7, the respiratory rate 15 breaths per minute, the SATS 89%, the FiO_2 0.21 and the OISS was 1. The same patient had a second event of $PaCO_2$ of 7.2kPa at 4 hours post-operatively. The PaO_2 was 16.9kPa, the respiratory rate 15 breaths per minute, the SATS 99%, FiO_2 0.4 and the OISS was 1.
- The second patient had a $PaCO_2$ of 7.3kPa at 2 hours post-operatively. The PaO_2 was 10.3kPa, the respiratory rate 14 breaths per minute, the SATS 94%, the FiO_2 0.4 and the OISS was s (sleeping, easily rousable).
- The third patient had a $PaCO_2$ of 7.3kPa at 4 hours post-operatively. The PaO_2 was 16.3kPa, the respiratory rate 13 breaths per minute, the SATS 98%, the FiO_2 0.21 and the OISS was s.
- The fourth patient had a $PaCO_2$ of 7.1kPa at 4 hours post-operatively. The PaO_2 was 9.1kPa, the respiratory rate was 15 breaths per minute, the SATS 92%, the FiO_2 0.4 and the OISS was 1.
- The fifth patient had a $PaCO_2$ of 7.25kPa at 8 hours post-operatively. The PaO_2 was 8.83, the respiratory rate was 23 breaths per minute, the SATS was 89.5%, the FiO_2 0.4 and the OISS was 1.

With regards to the $PaCO_2$ being higher than 7kPa in the PCA group, the following were individual additional details:

- The first patient had a $PaCO_2$ of 7.1kPa at the first hour post-operatively. The PaO_2 was 10.9kPa, the respiratory rate 16 breaths per minute, the SATS 95%, the FiO_2 0.4 and the OISS was 1.
- The second patient had a $PaCO_2$ of 7.2kPa at hour 12 post-operatively. The PaO_2 was 16kPa, the respiratory rate was 13 breaths per minute, the SATS 98%, the FiO_2 0.4 and the OISS was s.
- The third patient had a $PaCO_2$ of 7.1kPa at hour 24 post-operatively. The PaO_2 was 10.9kPa, the respiratory rate was 22 breaths per minute, the SATS 95%, the FiO_2 0.28 and the OISS was 1.

			PCA		IT	
			n	%	n	%
1hr	$PaCO_2$	>7	1	5.3%	1	5.3%
2hr	$PaCO_2$	>7	0	0.0%	1	5.6%
3hr	$PaCO_2$	>7	0	0.0%	0	0.0%
4hr	$PaCO_2$	>7	0	0.0%	3	15.8%
6hr	$PaCO_2$	>7	0	0.0%	0	0.0%
8hr	$PaCO_2$	>7	0	0.0%	1	5.6%
10hr	$PaCO_2$	>7	0	0.0%	0	0.0%
12hr	$PaCO_2$	>7	1	5.3%	0	0.0%
16hr	$PaCO_2$	>7	0	0.0%	0	0.0%
20hr	$PaCO_2$	>7	0	0.0%	0	0.0%
24hr	$PaCO_2$	>7	1	5.3%	0	0.0%

Table 3.19: *Incidences of $PaCO_2$ being higher than 7kPa between the PCA and IT group over the first 24 hours post-operatively*

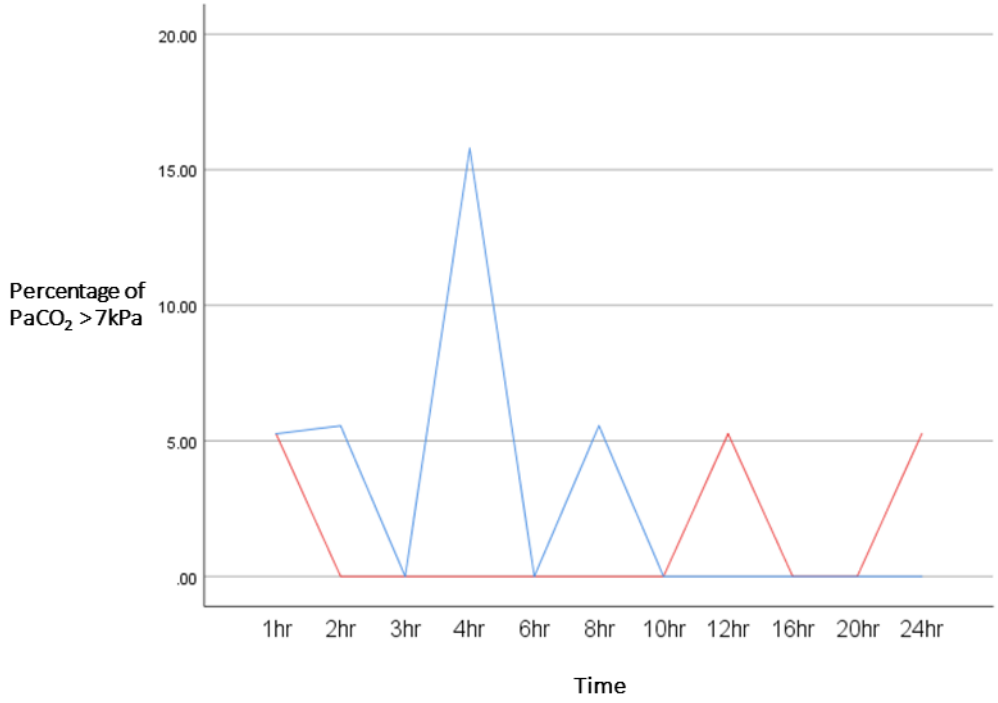

Figure 3.12: *The percentage of $PaCO_2$ in excess of 7kPa in the PCA group (red line) and IT group (blue line) as observed over the first 24 hours*

3.9.4 Awake and sleep time

The incidence of the $PaCO_2$ being in excess of 6kPa was correlated with the occurrence thereof in day time (06:00 – 22:00) and during sleep time (22:00 – 06:00). In the PCA group, the total incidence was 21.1% during day time and 16.4% during sleep. In the IT group, the incidence was 32.5% in the day time and 14% during sleep time. The breakdown for all the time points are depicted in Table 3.20.

				PCA		IT	
				n	%	n	%
1hr	awake time 6am - 10pm	$PaCO_2$	<=6	12	66.7%	9	47.4%
			>6	6	33.3%	10	52.6%
	sleep time 10pm - 6am	$PaCO_2$	<=6	1	100.0%	0	0.0%
			>6	0	0.0%	0	0.0%
2hr	awake time 6am - 10pm	$PaCO_2$	<=6	12	66.7%	6	33.3%
			>6	6	33.3%	12	66.7%
	sleep time 10pm - 6am	$PaCO_2$	<=6	1	100.0%	0	0.0%
			>6	0	0.0%	0	0.0%
3hr	awake time 6am-10pm	$PaCO_2$	<=6	12	66.7%	11	57.9%
			>6	6	33.3%	8	42.1%
	sleep time 10pm - 6am	$PaCO_2$	<=6	1	100.0%	0	0.0%
			>6	0	0.0%	0	0.0%
4hr	awake time 6am - 10pm	$PaCO_2$	<=6	14	77.8%	11	61.1%
			>6	4	22.2%	7	38.9%
	sleep time 10pm - 6am	$PaCO_2$	<=6	1	100.0%	0	0.0%
			>6	0	0.0%	1	100.0%
6hr	awake time 6am - 10pm	$PaCO_2$	<=6	12	75.0%	11	73.3%
			>6	4	25.0%	4	26.7%
	sleep time 10pm - 6am	$PaCO_2$	<=6	3	100.0%	1	33.3%
			>6	0	0.0%	2	66.7%
8hr	awake time 6am - 10pm	$PaCO_2$	<=6	10	90.9%	10	76.9%
			>6	1	9.1%	3	23.1%
	sleep time 10pm - 6am	$PaCO_2$	<=6	8	100.0%	3	60.0%
			>6	0	0.0%	2	40.0%
10hr	awake time 6am - 10pm	$PaCO_2$	<=6	5	83.3%	7	87.5%
			>6	1	16.7%	1	12.5%

	sleep time 10pm - 6am	$PaCO_2$	<=6	8	72.7%	8	88.9%
			>6	3	27.3%	1	11.1%
12hr	awake time 6am - 10pm	$PaCO_2$	<=6	1	100.0%	0	0.0%
			>6	0	0.0%	0	0.0%
	sleep time 10pm - 6am	$PaCO_2$	<=6	14	77.8%	18	94.7%
			>6	4	22.2%	1	5.3%
16hr	awake time 6am - 10pm	$PaCO_2$	<=6	6	75.0%	5	83.3%
			>6	2	25.0%	1	16.7%
	sleep time 10pm - 6am	$PaCO_2$	<=6	9	81.8%	13	100.0%
			>6	2	18.2%	0	0.0%
20hr	awake time 6am - 10pm	$PaCO_2$	<=6	18	94.7%	17	89.5%
			>6	1	5.3%	2	10.5%
	sleep time 10pm - 6am	$PaCO_2$	<=6	0	0.0%	0	0.0%
			>6	0	0.0%	0	0.0%
24hr	awake time 6am - 10pm	$PaCO_2$	<=6	18	94.7%	17	89.5%
			>6	1	5.3%	2	10.5%
	sleep time 10pm - 6am	$PaCO_2$	<=6	0	0.0%	0	0.0%
			>6	0	0.0%	0	0.0%
Total	awake time 6am - 10pm	$PaCO_2$	<=6	120	78.9%	104	67.5%
			>6	32	21.1%	50	32.5%
	sleep time 10pm - 6am	$PaCO_2$	<=6	46	83.6%	43	86.0%
			>6	9	16.4%	7	14.0%

Table 3.20: *Incidence of $PaCO_2$ being higher than 6kPa between the PCA and IT group during the day time (06:00 – 22:00) and sleep time (22:00 – 06:00) over the first 24 hours post-operatively*

The incidence of SATS decreasing below 90% was analysed with reference to it occurring in day time or night time. The overall incidence of SATS below 90% in the PCA group during day time was 2% and during sleep time 1.4%. In the IT group during the day time the incidence was 1.3% and during sleep time 2%.

The incidence of RR decreasing below 10 breaths per minute was analysed for day and night time. This occurred twice in both the PCA and IT groups during day and only once in the IT group during sleep compared to no events in the PCA during sleep.

A crosstabulation of RR less than 10 breaths per minute and $PaCO_2$ higher than 6kPa revealed no co-occurrence.

When RR, SATS and $PaCO_2$ higher than 6kPa were compared, 5 incidents were identified where SATS was below 90% together with $PaCO_2$ in excess of 6kPa. In all these events the RR remained more than 10 breaths per minute.

- The first patient was in the PCA group and had SATS of 88%, $PaCO_2$ of 6.1kPa and a RR of 20 breaths per minute on room air (FiO_2 0.21). This occurred at hour 1 after arrival in the recovery room. The OISS was 1 (awake and alert).
- The second patient was in the IT group and had SATS of 89%, $PaCO_2$ of 7.2kPa and a RR of 15 breaths per minute. This also occurred 1 hour after arrival in the recovery room whilst the patient was on room air (FiO_2 0.21). The OISS was 1 (awake and alert).
- The third patient was in the IT group and had 2 episodes. The first was at hour 8 post-surgery with SATS of 89.5% and $PaCO_2$ of 7.25kPa. The RR was 23 breaths per minute, the FiO_2 0.4 and the OISS was 1 (awake). The second episode in this patient occurred at hour 12 post-surgery. The SATS was 89.9%, the $PaCO_2$ was 6.51kPa, FiO_2 0.4 and the RR 15 breaths per minute. The OISS was 1 (awake and alert).
- The fourth patient was in the IT group and had SATS of 88%, $PaCO_2$ of 6.1kPa, the FiO_2 0.4 and the RR 14 breaths per minute. The OISS was 1 (awake and alert).

3.9.5 OISS

The OISS was recorded while arterial blood gas was taken for analysis. Each patient had 11 recordings over the first 24 hours post-operatively. Three patients in the PCA group collectively had 19 events of OISS of 2, no episodes in the IT group were recorded. There were no values of 3 or 4 recorded.

- The first patient was in the PCA group and had all 11 time points recorded as 2 on the OISS. At each of these time points both the SATS and $PaCO_2$ were over 90% and under 6kPa. In 2 of the 11 episodes, the RR was below 10 breaths per minute.
- The second patient was in the PCA group and had 7 time points recorded as OISS 2. At all those time points, the SATS were more than 90%, the $PaCO_2$ equal or less than 6kPa and the respiratory rate in excess of 10 breaths per minute. There were 2 episodes of $PaCO_2$ being 6kPa exactly.
- The third patient was in the PCA group and the event was recorded (OISS of 2) hour 1 post-operatively. The SATS was 98% on room air and the respiratory rate was 12 breaths per minute. The $PaCO_2$ was 6.9kPa.

3.9.6 PaO_2

A PaO_2 value of less than 8kPa was considered abnormal. This occurred 3 times (1.8%) in the PCA group and 4 times (2%) in the IT group (see Table 3.21). One patient had 2 episodes of PaO_2 being less than 8kPa.

- The first patient had a PaO_2 of 7.5kPa at 1 hour in the PCA group. The $PaCO_2$ was 6.1kPa, the SATS 88%, the RR 20 breaths per minute and the OISS 1. The FiO_2 was 0.21.
- The second patient had a PaO_2 of 7.7kPa at 1 hour in the IT group. The SATS was 89%, the $PaCO_2$ 7.2kPa, the RR 15 breaths per minute and the OISS 1. The FiO_2 was 0.21.
- The third patient had a PaO_2 of 7.69kPa 16 hours post-operatively in the PCA group. The SATS was 88.6%, $PaCO_2$ 4.8kPa, RR 12 breaths per minute and OISS 1. The FiO_2 was 0.4.
- The fourth patient had a PaO_2 of 7.3kPa 16 hours post-operatively in the IT group. The SATS was 88%, $PaCO_2$ 6.1kPa, RR 14 breaths per minute and OISS 1. The FiO_2 was 0.4.
- The fifth patient had a PaO_2 of 7.7kPa 20 hours post-operatively in the IT group. The SATS was 90%, $PaCO_2$ 6.4kPa, RR 17 breaths per minute and OISS s. The FiO_2 was 0.21. This patient had a second incident 1 hour later with a PaO_2 of 7.5kPa. The SATS remained 90%, the RR increased to 18 breaths per minute and the OISS was s. The $PaCO_2$ decreased to 6.1kPa.
- The sixth patient had a PaO_2 of 7.6kPa 20 hours post-operatively in the PCA group. The SATS was 90%, $PaCO_2$ 6.7kPa, RR 16 breaths per minute and OISS 1.

A graph comparing the mean PaO_2 between the PCA and IT groups demonstrated an increase in the mean PaO_2 over the first 3 hours post-operatively. There is a decline after that up to the 24 hours. The PCA group mean PaO_2 is consistently below the mean PaO_2 of the IT group, except for the 20 hour time point and 6 hour point (Figure 3.13).

Figure 3.14 depicts the mean PaO_2 and $PaCO_2$ of the IT group over the first 24 hours post-operatively. It demonstrates a higher mean $PaCO_2$ than the PCA group (see Figure 3.15) and the rapid increase of PaO_2 seen up to 3 hours post-operatively did not alter the slow descending trend of the $PaCO_2$.

			PCA		IT	
			n	%	n	%
1hr	PaO_2	<8	1	5.3%	1	5.3%
2hr	PaO_2	<8	0	0.0%	0	0.0%
3hr	PaO_2	<8	0	0.0%	0	0.0%
4hr	PaO_2	<8	0	0.0%	0	0.0%
6hr	PaO_2	<8	0	0.0%	0	0.0%
8hr	PaO_2	<8	0	0.0%	0	0.0%
10hr	PaO_2	<8	0	0.0%	0	0.0%
12hr	PaO_2	<8	0	0.0%	0	0.0%
16hr	PaO_2	<8	1	5.3%	1	5.3%
20hr	PaO_2	<8	1	5.3%	1	5.3%
24hr	PaO_2	<8	0	0.0%	1	5.3%
Total	PaO_2	<8	3	1.4%	4	2.0%

Table 3.21: *Incidence of the PaO_2 lower than 8kPa comparing PCA and IT group over the first 24 hours post-operatively with no statistically significant difference between the groups*

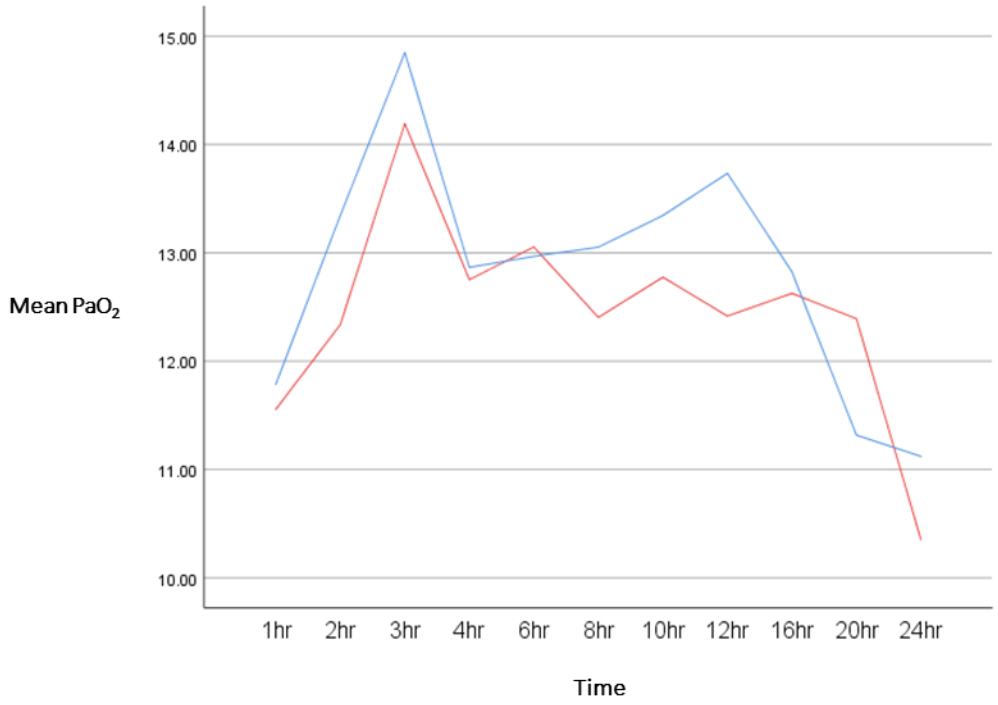

Figure 3.13: *The mean PaO_2 of the patients in the PCA group (red line) and IT group (blue line) as observed over the first 24 hours*

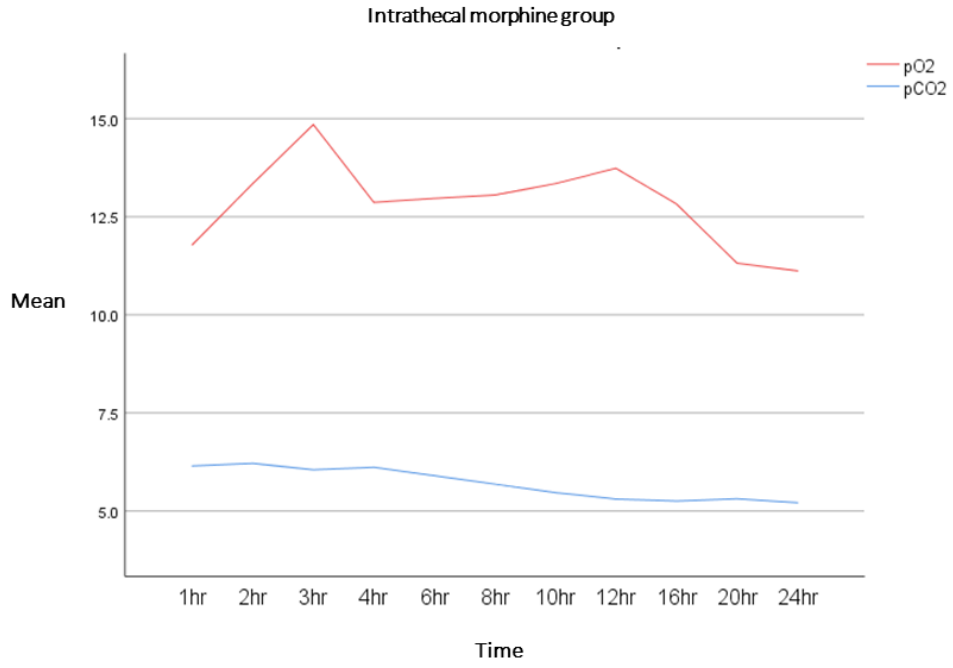

Figure 3.14: *The mean PaO_2 (red line) and mean $PaCO_2$ (blue line) in the IT group over the first 24 hours post-operatively*

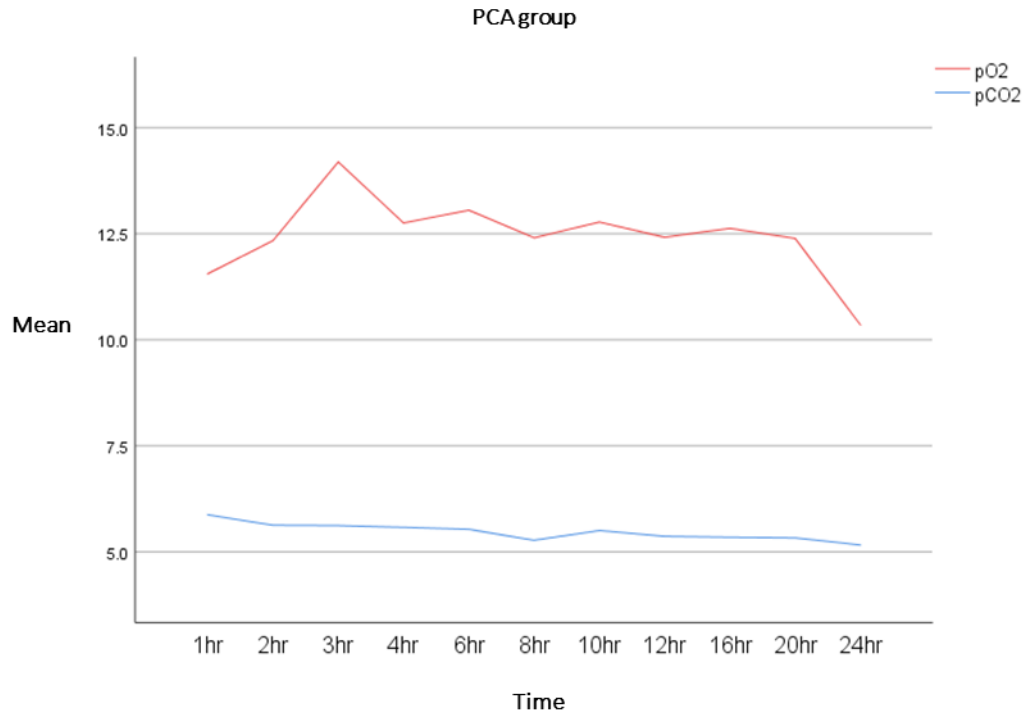

Figure 3.15: *The mean PaO_2 (red line) and mean $PaCO_2$ (blue line) in the PCA group over the first 24 hours post-operatively*

3.9.7 BMI

A BMI of 30kg/m² was considered a risk factor which could affect respiration. The incidents where BMI equals or is more than 30kg/m² and $PaCO_2$ higher than 6kPa occurred together are presented in Table 3.22.

There were 33 incidences of both occurring in the PCA group (23.2% of cases) and 38 in the IT group (31.9% of cases).

				PCA		IT	
				n	%	n	%
BMI	<30	$PaCO_2$	<=6 kPa	57	87.7%	66	77.6%
			>6kPa	8	12.3%	19	22.4%
	>=30	$PaCO_2$	<=6 kPa	109	76.8%	81	68.1%
			>6kPa	33	23.2%	38	31.9%

Table 3.22: *The incidents of BMI less and more than 30kg/m² together with $PaCO_2$ less and more than 6kPa*

3.9.8 Alveolar oxygen tension

The partial pressure of oxygen in the alveoli (P_AO_2) is calculated with the abbreviated alveolar gas equation: P_AO_2 (mm Hg) = (Patm - PH_2O) FiO_2 - $PaCO_2$ / RQ.

Both groups followed a similar trend with a peak between 2 and 3 hours post-operatively, a steady trend up to 12 hours post-operatively and then a rapid decline with the PCA group decline at 24 hours being much more than the IT decline (see Figure 3.16).

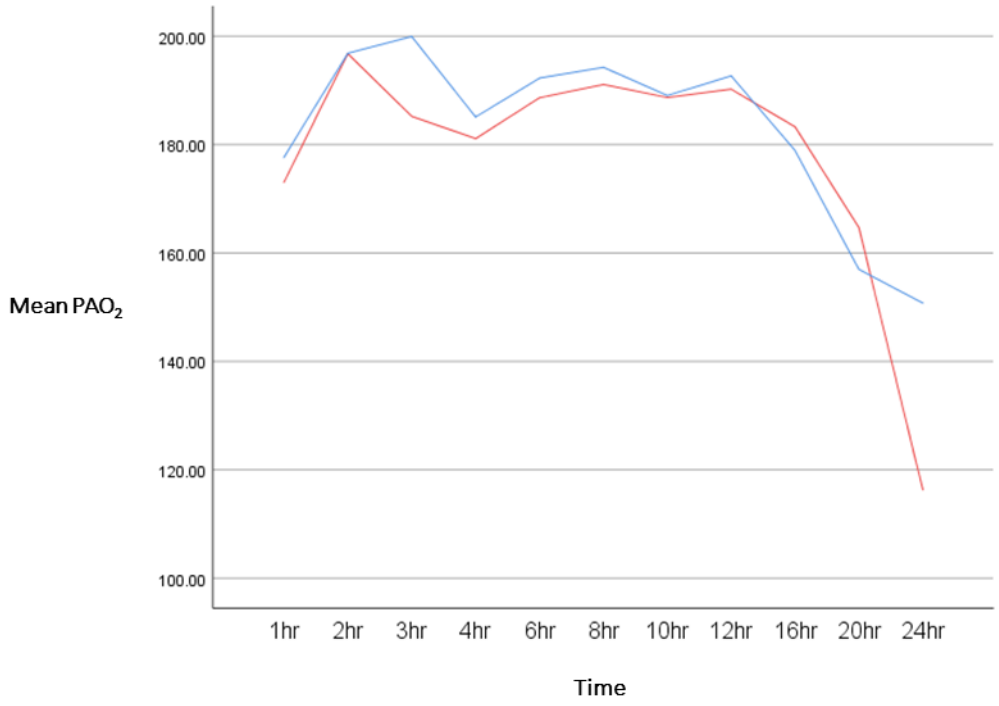

Figure 3.16: *The alveolar partial pressure of oxygen (PAO_2) in mm Hg for the PCA (red line) and IT (blue line) group*

3.9.9 PaO_2 / FiO_2 ratio

The mean PaO_2 / FiO_2 ratio is presented in Figure 3.17 for the first 24 hours post-operatively.

Both groups followed s similar trend over the first 24 hours with a peak at 3 hours and a gradual increase up to 24 hours.

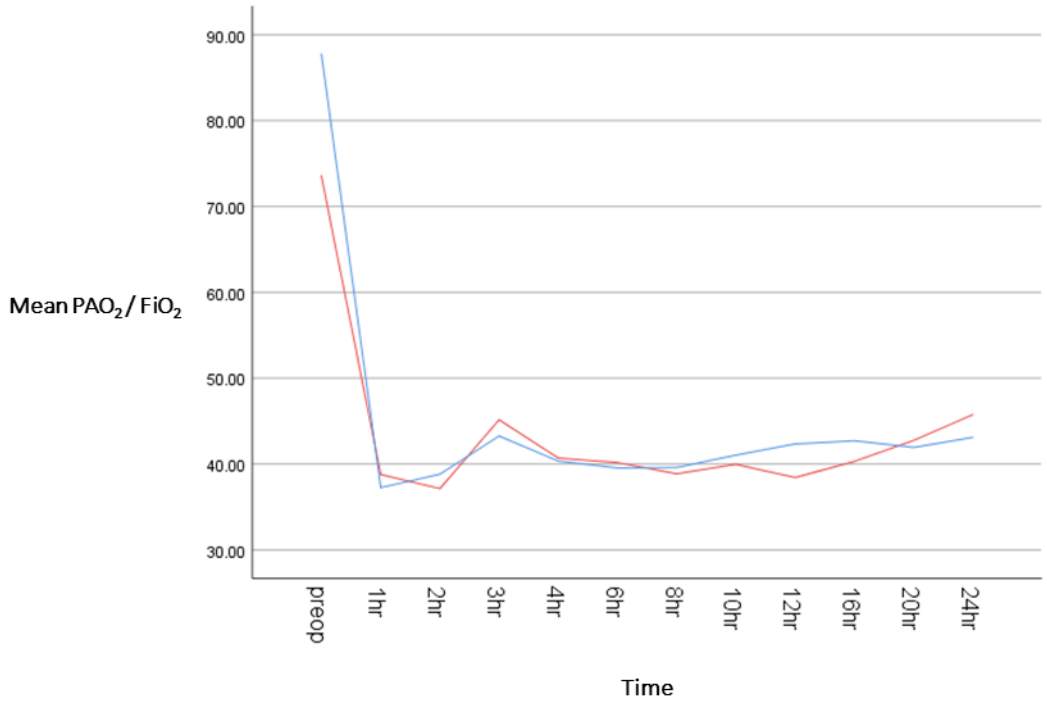

Figure 3.17: *The mean P_AO_2 (mm Hg)/ FiO_2 ratio for the IT group (blue line) and PCA group (red line) over the first 24 hours post-operatively*

3.9.10 A-a gradient

The A-a gradient is calculated as $P_AO_2 – PaO_2$. The mean A-a gradient in both IT and PCA group follow a similar trend with an initial spike at 1 to 3 hours post-operatively, followed by a dip between 3 and 6 hours post-operatively. It then remains steady until a gradual decrease up to 24 hours with the PCA group presenting a more profound decrease (Figure 3.18).

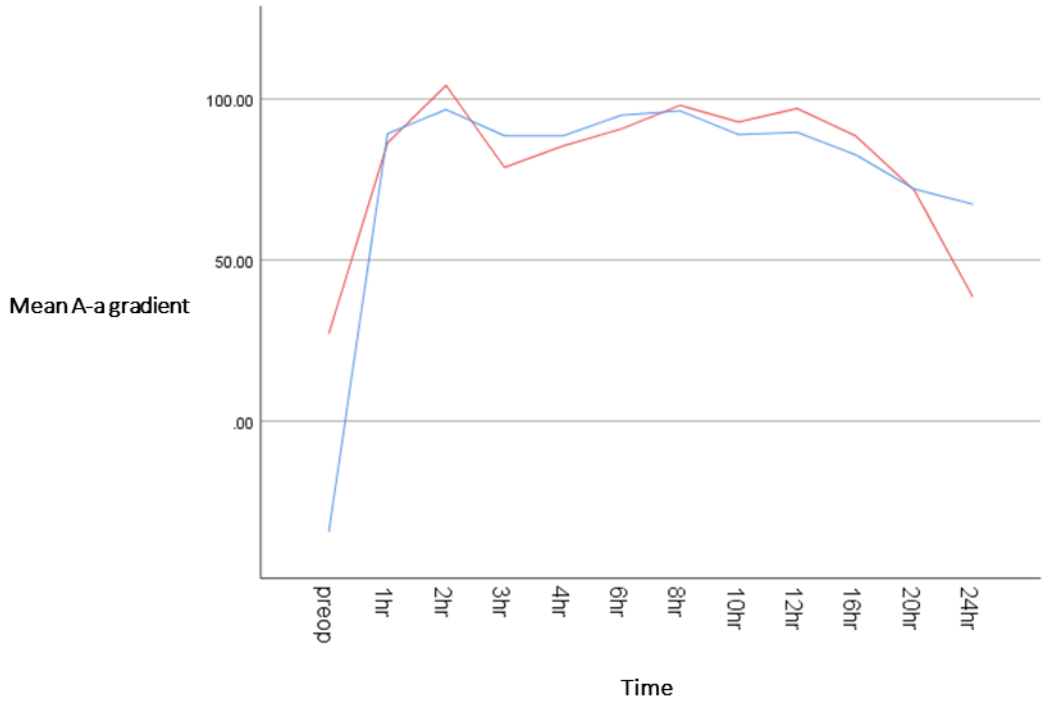

Figure 3.18: *The mean A-a gradient ratio for the IT group (blue line) and PCA group (red line) over the first 24 hours post-operatively*

The P_AO_2, P_AO_2 / FiO_2 ratio and A-a gradient are presented for both IT and PCA groups in Table 3.23.

		PCA			IT		
		PAO_2	PaO_2/FiO_2	A-a gradient	PAO_2	PaO_2/FiO_2	A-a gradient
Pre-op	**Mean**	221.11	73.56	27.28	220.26	87.72	-34.21
	Standard deviation	123.78	54.89	136.51	80.10	36.37	98.38
1hr	**Mean**	173.06	38.78	86.39	177.64	37.26	89.24
	Standard deviation	69.28	13.19	65.26	67.42	8.88	56.16
2hr	**Mean**	196.78	37.14	104.25	196.85	38.82	96.75
	Standard deviation	58.47	10.21	53.39	56.40	13.43	56.74
3hr	**Mean**	185.21	45.16	78.76	199.95	43.27	88.57
	Standard deviation	61.26	13.99	56.34	55.95	15.37	57.00
4hr	**Mean**	181.10	40.70	85.45	185.09	40.34	88.59
	Standard deviation	60.65	8.76	49.47	66.19	14.18	63.65
6hr	**Mean**	188.65	40.17	90.74	192.26	39.54	95.00
	Standard deviation	60.01	9.01	50.56	61.15	15.37	63.60
8hr	**Mean**	191.08	38.86	98.05	194.26	39.59	96.35
	Standard deviation	61.21	11.36	57.46	61.28	13.78	60.73
10hr	**Mean**	188.70	39.96	92.88	189.05	41.05	88.96
	Standard deviation	60.14	11.23	54.55	62.70	12.13	55.25
12hr	**Mean**	190.22	38.42	97.09	192.67	42.33	89.66
	Standard deviation	57.17	10.52	50.43	62.19	13.55	58.10
16hr	**Mean**	183.28	40.31	88.58	178.90	42.72	82.71

		Standard deviation	60.21	9.37	51.09	66.81	14.04	63.66
	20hr	**Mean**	164.68	42.75	71.74	156.97	41.93	72.09
		Standard deviation	62.92	9.80	49.95	68.15	13.70	63.70
	24hr	**Mean**	116.33	45.75	38.68	150.76	43.10	67.35
		Standard deviation	33.33	8.10	29.46	67.46	13.66	65.30

Table 3.23: *The mean P_AO_2, PaO_2 / FiO_2 ratio and A-a gradient for the IT and PCA groups over the first 24 hours per time point assessed*

3.10 Post-operative scoring results

3.10.1 QVAS

Pre-operative QVAS scores (*pain right now*, *pain on average*, *pain at its best*, *pain at its worst*) is described in Table 3.2.

The follow-up time points were at 6 weeks, 3 months and 6 months.

3.10.1.1 QVAS at 6 weeks

The 6-week QVAS scores are presented in Table 3.24. There was no statistical difference noted between any of the parameters assessed.

		PCA group	IT group
6wk QVAS Pain right now	Median	1	2
6wk QVAS Pain on average	Median	2.0	2.0
6wk QVAS Pain at its best	Median	0	0
6wk QVAS Pain at its worst	Median	3	4

Table 3.24: *The median values for 6-week QVAS scores with no statistically significant difference between the groups on all parameters*

3.10.1.2 QVAS at 3 months

The 3-month QVAS scores are presented in Table 3.25. There was no statistical difference noted between any of the parameters assessed. Six patients, 3 per group, were lost to the 3-month follow-up (n=31).

		PCA group	IT group
3m QVAS Pain right now	Median	1	1
3m QVAS Pain on average	Median	2	2
3m QVAS Pain at its best	Median	0	0
3m QVAS Pain at its worst	Median	3	3

Table 3.25: *The median values for 3-month QVAS scores with no statistically significant difference between the groups on all parameters*

3.10.1.3 QVAS at 6 months

The 6-month QVAS scores are presented in Table 3.26. There was no statistical difference noted between any of the parameters assessed. Six patients, 3 per group, were lost to the 6-month follow-up (n=31).

		PCA group	IT group
6m QVAS Pain right now	Median	0	1
6m QVAS Pain on average	Median	1	2
6m QVAS Pain at its best	Median	0	0
6m QVAS Pain at its worst	Median	2	3

Table 3.26: *The median values for 6-month QVAS scores with no statistically significant difference between the groups on all parameters*

The median QVAS (pain right now) is presented in Figure 3.19. There was a statistically significant improvement in both groups between the pre-operative values and the 6 weeks, 3 months and 6 months values.

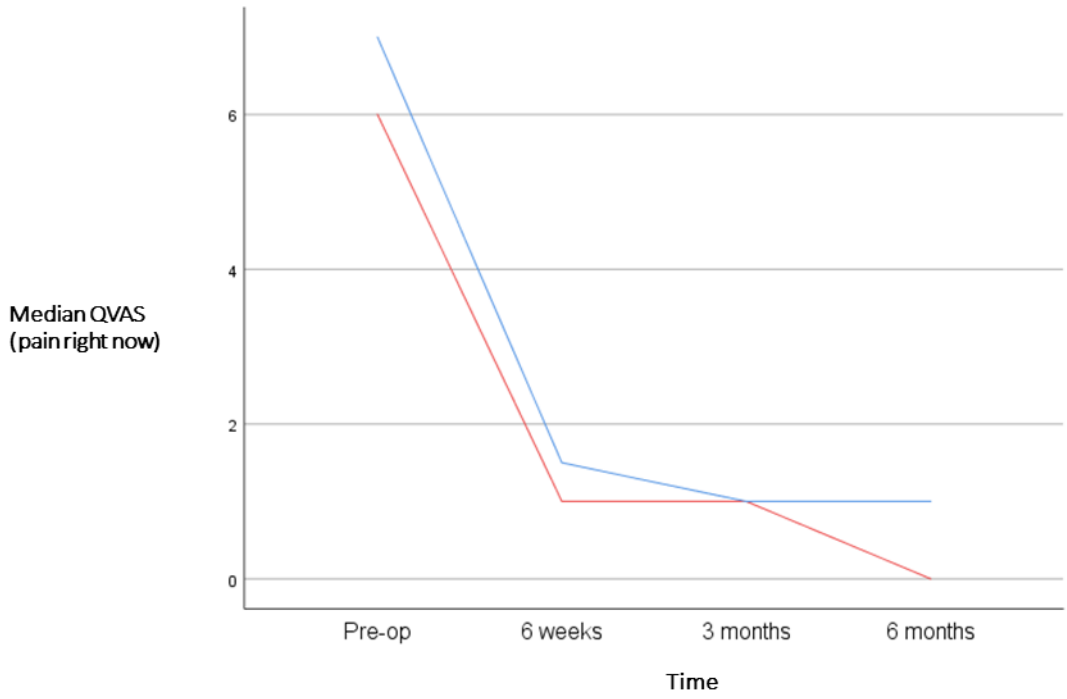

Figure 3.19: *The median QVAS (pain right now) presented for the IT group (blue line) and PCA group (red line) for the time periods: pre-operative, 6 weeks, 3 months and 6 months*

The median QVAS (pain on average) is presented in Figure 3.20. There was a statistically significant improvement in both groups between the pre-operative values and the 6 weeks, 3 months and 6 months values.

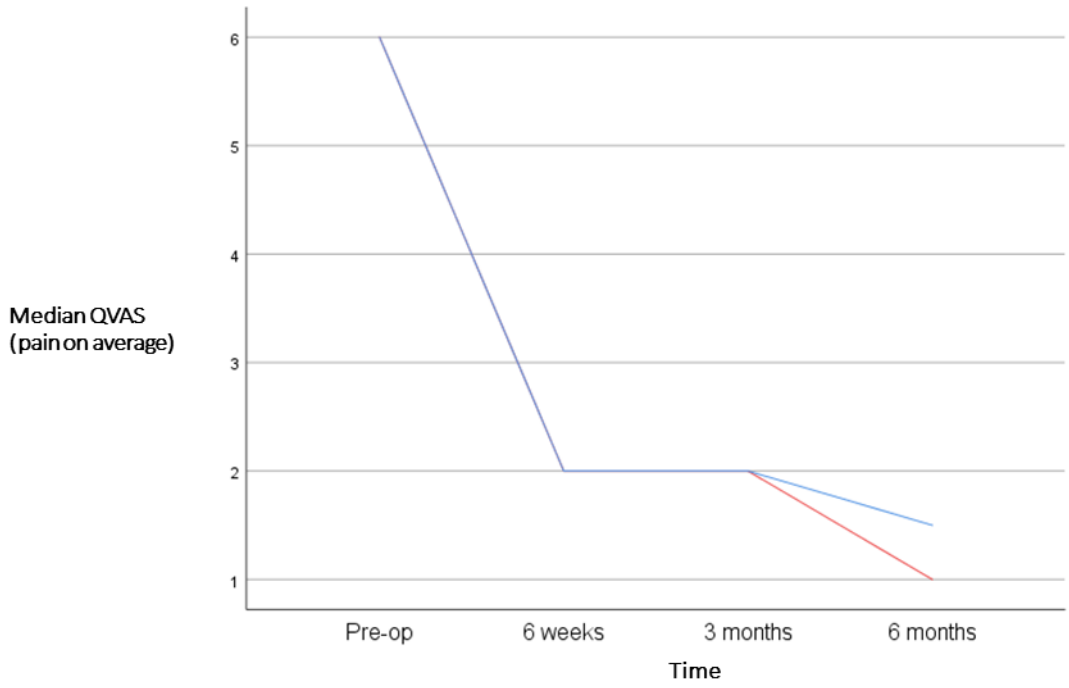

Figure 3.20: *The median QVAS (pain on average) presented for the IT group (blue line) and PCA group (red line) for the time periods: pre-operative, 6 weeks,3 months and 6 months. The lines were identical thus superimposed up to the 3 month time point in the figure.*

The median QVAS (pain at its best) is presented in Figure 3.21. There was a statistically significant improvement in both groups between the pre-operative values and the 6 weeks, 3 months and 6 months values. The values were identical for both groups (IT and PCA).

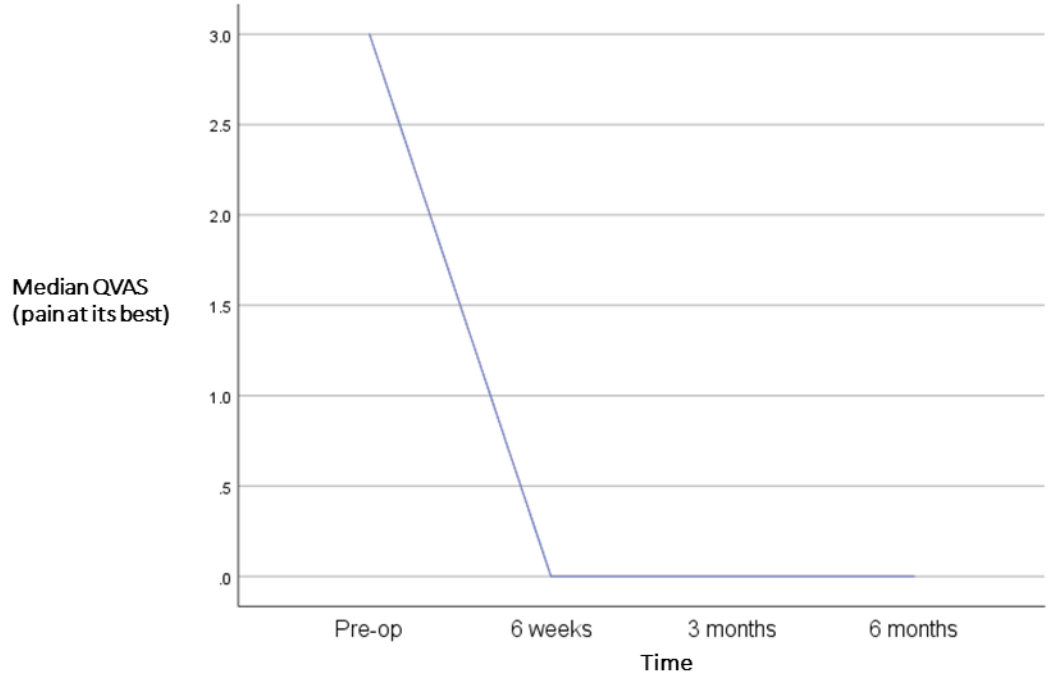

Figure 3.21: *The median QVAS (pain at its best) presented for the IT group (blue line) and PCA group (red line) for the time periods: pre-operative, 6 weeks, 3 months and 6 months. The lines were identical thus superimposed in the figure.*

The median QVAS (pain at its worst) is presented in Figure 3.22. There was a statistically significant improvement in both groups between the pre-operative values and the 6 weeks, 3 months and 6 months values.

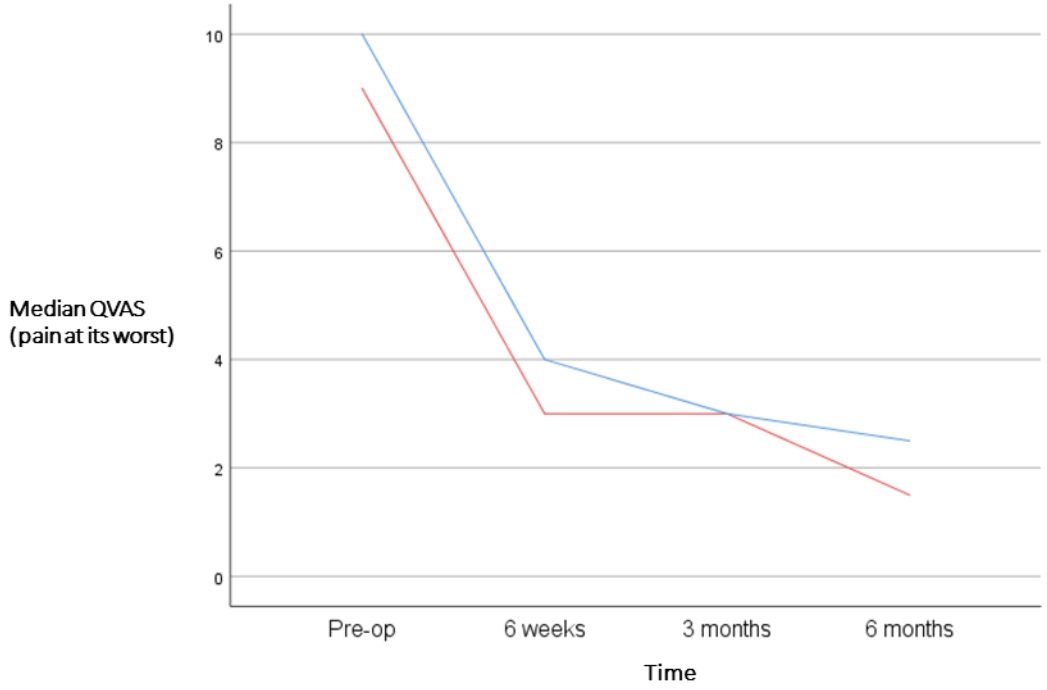

Figure 3.22: *The median QVAS (pain at its worst) presented for the IT group (blue line) and PCA group (red line) for the time periods: pre-operative, 6 weeks, 3 months and 6 months*

3.10.2 EQ-5

The best/worst health state as depicted in a vertical line ranging from 0 to 100 (best health state = 100) provided a significant improvement in the score between pre-operative, 6 weeks, 3 months and 6 months. There was a statistical significance between the pre-operative values and the rest for both groups, but none between the groups themselves (Figure 3.23).

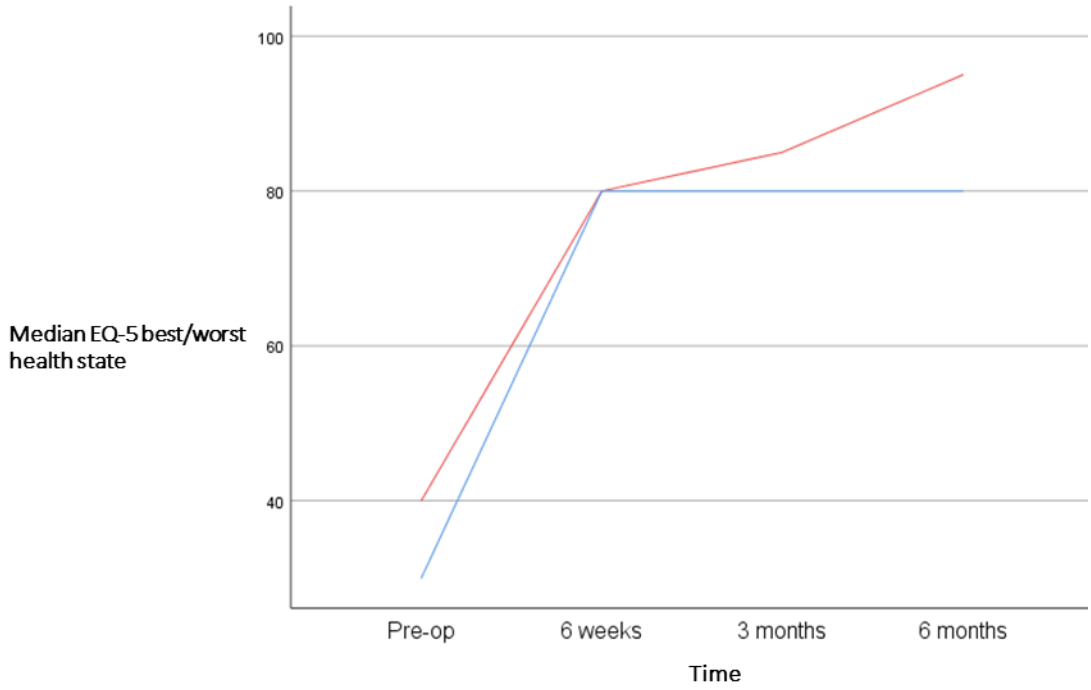

Figure 3.23: *The median EQ-5 best/worst health state values presented for the IT group (blue line) and PCA group (red line) for the time periods: pre-operative, 6 weeks, 3 months and 6 months*

3.10.3 ODI

The ODI is expressed as a percentage with a higher value indicating more disability.

The values significantly drop from pre-operative up to 6 weeks and are then maintained up to 6 months in both groups. There is no statistical difference between the 2 groups (Figure 3.24).

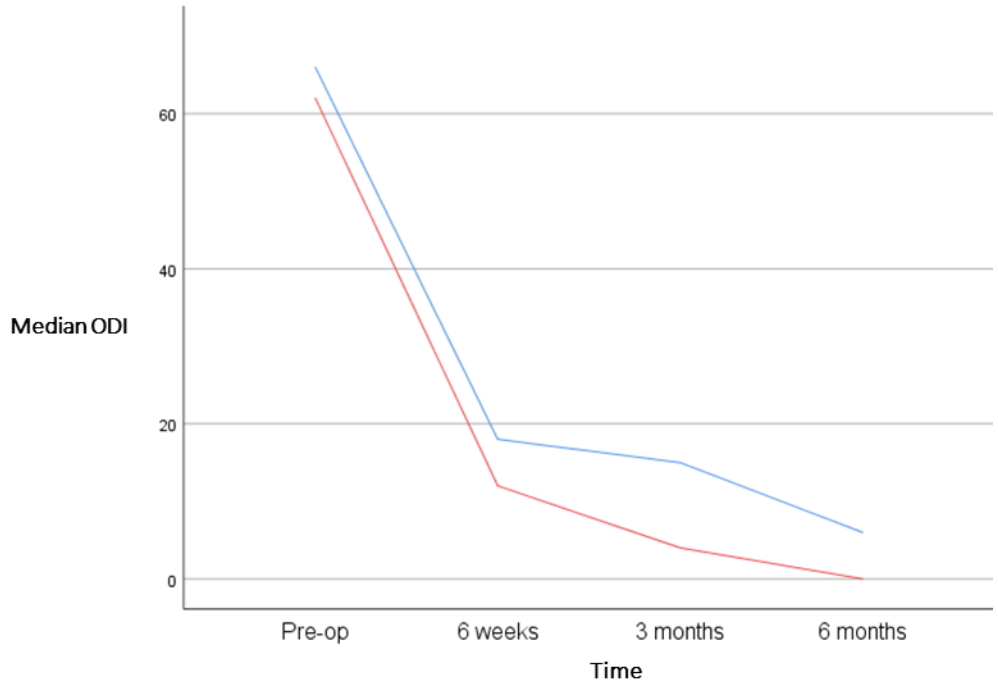

Figure 3.24: *The median ODI values presented for the IT group (blue line) and PCA group (red line) for the time periods: pre-operative, 6 weeks, 3 months and 6 months*

3.10.4 RM

The RM collates a value out of 18 with a higher value indicating increased disability. The mean values in both groups demonstrate a significant drop from pre-operative values up to 6 weeks which then gradually declines further up to 6 months. No significant difference was noted between the 2 groups (Figure 3.25).

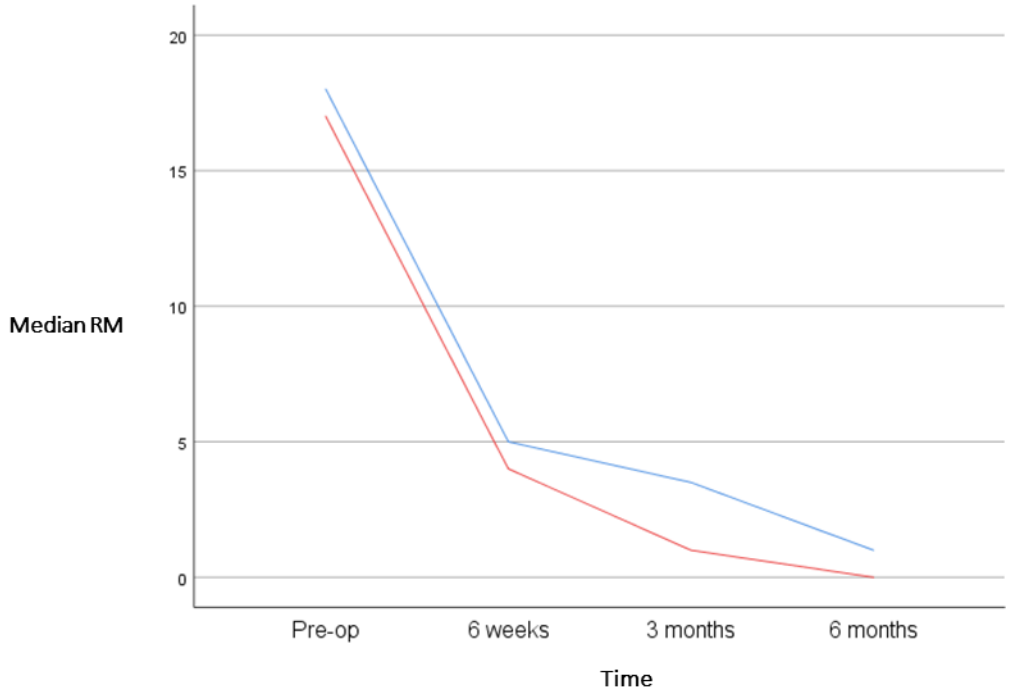

Figure 3.25: *The median RM values presented for the IT group (blue line) and PCA group (red line) for the time periods: pre-operative, 6 weeks, 3 months and 6 months*

3.11 Retrospective review

A departmental surgical database was interrogated for first lumbar spine surgery single level fusion patients. Thirty-seven patients were identified. Four were removed from the dataset as they had prolonged stay (1 re-operation and 3 social circumstances preventing them from going home).

The mean length of stay was 6.23 days.

3.12 Direct cost

The direct cost involved were calculated according to the billing practices of Tygerberg Hospital.

The management of the patients in both groups were standardized therefore the following costs were the same: pre-operative imaging, intraoperative cost, spinal implants and ICU stay. The length of stay in the general ward differed where the IT group stayed 2 full days less than the PCA group (see section 3.8). The percentage cost saving on general ward stay was 43.5%. The overall saving was 5%. The costs for both groups are expressed in Table 3.27.

Cost description	**IT group**	**PCA group**	**Percentage difference**
Total Surgical ward	3172	5612	**43.5**
Total ICU	1688.80	1688.80	0
Pre-operative imaging	222	222	0
Intraoperative cost	21572.60	21572.60	0
Spinal implants	19526.50	19526.50	0
Total cost (Rand)	**46181.9**	**48621.90**	**5**

Table 3.27: *The direct costs for the IT and PCA group expressed in Rand for the total length of stay*

4. Discussion

4.1 Introduction

The rationale behind this study is based on the ever-increasing pressure exerted by the vast volume of patients requiring tertiary medical care in the South African public health service, in general, and the Western Cape Department of Health, in particular. This pressing need for health services, coupled with a trauma epidemic, is placing available resources under significant pressure and is fuelling the need to create solutions whereby scarce resources, such as ICU and general ward beds, could be optimised. When opioid analgesia is the only effective option for post-operative analgesia, patients often require a high care or ICU environment in order to monitor for opioid related side-effects and complications.

The single level spinal fusion patient fits the profile of a patient who is suffering from a debilitating condition which requires surgery. The use of systemic opioid analgesia is associated with significant challenges in mobilizing and discharging patients due to the extent of the surgery and the associated pain.

The author noted that, in the past the use of intrathecal morphine has resulted in patients apparently mobilising quicker. However, dose and safety concerns have always remained a serious consideration. Unfortunately, in the author's opinion, literature does not address these issues satisfactorily. A prospective, double-blind randomised controlled trial was thus designed in an attempt to prove the efficacy and safety of intrathecal morphine when compared to the more standard analgesic approach of patient controlled analgesic (PCA).

The **primary hypothesis** stated that a proposed dose of 0.005mg/kg intrathecal morphine, up to a maximum dose of 0.45mg, would be effective in ensuring **earlier mobilisation and earlier discharge** from hospital. Generally, in the public health sector where no step-down facilities are available, discharge from hospital occurs between 5 to 7 days after surgery.

Furthermore, but also of significant importance, it was hypothesised that the proposed intrathecal morphine dose would be **safe** and **effective in controlling pain.** When considering safe and effective analgesia as well as early mobilisation, it was envisaged that this approach could result in **cost savings** to the health system.

The number of patients that needed to be operated to prove these hypotheses were calculated at 72 in consultation with a biostatistician. As this was a prospective trial, the study was subjected to an interim analysis which was done after 40 patients had been operated on. The block randomisation occurred with each group of 10 patients containing 5 intrathecal morphine

(IT) and 5 patient-controlled analgesia (PCA) patients. In addition, the study had progressed past the half-way point at this time.

An independent statistician was appointed to review the available data and to consequently recommend whether or not the study should continue. The data were unblinded and results indicated that the primary hypothesis had already been proven as both groups had equal distribution and the study was powered at 90% with a significance level of 0.001. It was therefore decided to terminate the study at the interim point.

4.2 Mobilisation and discharge

The challenge when performing a single level fusion procedure of the spine lies in effectively managing the initial pathology of the patient and thereby relieve the symptoms.

To a large extent, degenerative spine disease is associated with advanced age and hence the patient profile is often that of an older patient who presents with medical co-morbidities (Andersson, 1999). The ideal would be an effective procedure which not only relieves the patient's symptoms but also enables him/her to mobilise rapidly in order to reduce morbidity and cost to the patient (Dagenais, 2005). Effective analgesia is mandatory as it aids in mobilisation, but it should not negatively influence the result of the index procedure.

A patient may experience several limitations to post-operative mobilisation after spinal surgery. The most prominent limitation is pain which stems from the procedure itself. Pain is an entity which clinicians should be able to control (Somerville, 1982; Brennan, 2007), but some otherwise effective analgesics, such as non-steroid anti-inflammatory analgesics (NSAID), could significantly affect the outcome of bony fusion. The use of these drugs as an effective analgesic option are thus limited (Thaller, 2005).

The very nature of the initial presenting pathology is an instability between two lumbar vertebrae which results in neurological impairment. In principle, management of the primary cause for the symptoms and signs is to unite (fuse) these vertebrae and maintain the union.

The surgical technique involves pedicular screws in each vertebra, connected by a rod and secured with locking caps, resulting in a scaffold which creates immediate stability between the vertebrae. Care should however be taken to decorticate the transverse processes and pars interarticularis for the effective grafting of autologous bone, usually harvested during the decompression of the spinous processes and laminae. The new bone will ultimately form and unite the vertebrae. The screws, if unsupported by new bone formation, will break and result in morbidity. The modifiable aspects in creating the bony union is meticulous harvesting of the

bone (i.e. removal of all soft tissues to create the largest possible surface area of cancellous bone) and preparation of the transverse processes and pars interarticularis by decorticating them as much as possible.

The effect of NSAIDs on post-operative fusion has been repeatedly discussed in the literature (Riew, 2003; Reuben, 2005; Li, 2011). Li *et al.* conducted a meta-analysis on the deleterious effects of NSAIDS on spinal fusion rates which highlighted a significant reduction in fusion rate when accompanied by high doses of Ketorolac. The authors, however, were ambivalent regarding normal dosages and short periods of use (Li, 2011). A statistically significant association between NSAID use and decrease in bony fusion could not be established. However, they did report a wide confidence interval, ranging from 0.74 - 2.61, and concluded that there *might* be a dose-dependent inverse relationship between NSAID dose and fusion rates. The same finding was reported in a further meta-analysis of NSAID's use and it's relationship with spinal fusion highlighting dose- and duration dependency (Sivaganesan, 2017).

The data itself creates an ethical conundrum as there now is a known effect of NSAID's on bone fusion (Thaller, 2005, Riew, 2003) and therefore, to study a possible dose dependant relationship, with non-union as a potential outcome, would be ethically unacceptable. This is further highlighted by the fact that impairment of bone formation as a result of NSAID's is effectively used to curb heterotopic ossification in hip arthroplasty surgery (Fransen, 2013).

The surgeon is ethically bound to maximise the possible outcome for the patient, in this case bone formation. Certain factors which affect bony fusion such as age, nutrition and smoking are, to some extent, beyond the control of the surgeon and thus he/she should implement factors which can be controlled. One of the factors which lie within the surgeon's sphere of control is the choice of drugs to be used. As such, the choice should be carefully considered to avoid a negative impact on the formation of bone in spinal surgery. Effective analgesia, as obtained from NSAIDs, can thus no longer be considered a completely safe option. Therefore, it is becoming increasingly important to identify effective and safe alternative/s in the opioid family of medications to obtain effective analgesia without negatively affecting time to mobilisation.

4.2.1 Disability of patients

Pre-existing morbidity was assessed through the use of several scoring systems. As explained in Chapter 1.3.1, these scoring systems were used to define the disability of the patient (ODI, RM and EQ-5) as well as ascertain their pain (VAS). These scoring systems are key in establishing the effect of spinal instability and neurological fallout on the patient. In addition, they help to ascertain the effect/s of the intervention (surgery) on the patient/s. The power of these scoring systems lies in their repetition to monitor a trend (Wewers, 1990; Hawker, 2011; Fairbank, 2000; The EuroQOL Group, 1990; Beurskens, 1996).

The ODI was chosen as it interrogates activities associated with daily living. Irrespective of the age of the patient, the ODI provides a relevant score which relates to that particular patient (Fairbank, 1980). Similarly, the RM reviews physical disability (Roland, 2000), specifically as it relates to the lower back. This scoring system was thus particularly appropriate to this study cohort which included older patients who are more prone to degenerative or age-related conditions of the spine. It is known that a correlation exists between the ODI and RM questionnaires (Beurskens, 1996). One would thus expect a similar response to the procedure and the same degree of disability post-surgery.

The mean pre-operative ODI for the IT group was 63.79% and 63.47% for the PCA group, thus placing them in the severe disability group (Fairbank, 2000). The same pre-operative level of disability was expressed in the RM scores with the mean being 16.11 in the IT group and 16.37 in the PCA group out of a total of 18 questions posed (Roland, 2000). The very fact that both groups ticked nearly all the disability related questions in the RM questionnaire highlights the extent to which the pre-operative condition affected patient profiles as reflected with the ODI. The status quo was echoed by the EQ-5 health state in which a value is assigned out of a possible total of 100 with a score of 100 denoting the best possible state of health for a patient (The EuroQOL Group, 1990). Both groups recorded values averaging in the 30s with the IT group scoring 34.21 and the PCA group 36.05.

All three these modalities were clinically significant for pre-operative disability and demonstrated appropriate indications for surgical intervention. The two groups demonstrated near similar levels of disability for all three questionnaires. This suggests that the starting point for the study was similar for the two arms of the study.

To facilitate the appropriate assessment of the IT and PCA morphine interventions, the index procedure should remove potential confounders including pre-operative pain as the ideal post-operative score must reflect surgically inflicted pain only. Similarly, the pain created by the pre-operative pathology must be relieved in order to mobilise appropriately.

This was evident in the post-operative scoring done during follow-up at 6 weeks, 3 months and 6 months post-operatively. As illustrated in Figures 3.19 to 3.25, there was a significant clinical and statistical decrease in the disability experienced by both groups when compared to the pre-operative scoring. There was no statistical difference between the 2 groups, indicating that the procedure was effective in treating the initial pathology. It must be noted that the pre-operative scores were similar i.e. the groups started with a similar disability. The equal decrease in disability, as measured at 6 weeks, 3 months and 6 months post-surgery in both arms of the study, suggests that the procedure itself was successful and that the 2 groups did not experience significantly different outcomes. This is not surprising as patients admitted to the study were carefully selected in accordance with accepted criteria, the surgical procedures were similar, and the patients were properly randomised.

One would not expect a long-term advantage from immediate post-operative analgesia. The hypothesis stated that post-operative mobility and pain would favour the intrathecal group but once the patient had been mobilised, this shorter term advantage would fall away.

Despite the IT group mobilising quicker, no long-term difference was noted between the 2 groups. This could most likely be ascribed to factors which affect rehabilitation at home as different socio-economic environments either add to *or* detract from rehabilitation. This is especially apt when considering all modalities which quantify disability in the ODI, for example sleep, lifting weights, standing, walking and sitting, as per Figure 1.2. These variables will naturally differ between patients but due to effective randomisation and sufficient power in the number of patients analysed, one can safely assume that the variables would be equally distributed between the two arms of the study.

The results indicate that the index procedure effectively addressed the primary pathology. In addition, any difference/s noted in early mobilisation and post-operative analgesia did not carry over into the medium and long term well-being of the patients.

4.2.2 Pain

The QVAS score captured patients' pain as associated with the pre-existing condition. This score includes the conventional VAS methodology of a horizontal line depicting a score between 0 and 10. In addition, it reflects the best, worst and average pain experienced by the patient. Each of the entities is depicted on a separate line which illustrates the degree in which the patient is experiencing the disabling primary pathology as translated into pain.

It is important to note that the conducted VAS scores were numbered, thus effectively converting the scale into a numeric rating scale (NRS). This differs very little from a traditional VAS score. A numerical value on the horizontal line, familiar to the patient and easy to correlate with his/her experience of the pain, is used as an indication of said pain (Hawker, 2011). The numerical values were added to facilitate easier recording of the score. In the traditional VAS the patient is asked to make a mark on a 100mm unnumbered line to indicate his/her pain. A drowsy patient or one that is experiencing pain or who is unwilling to write at that specific time can seriously affect this process. The NRS allows a patient to verbalise and define the intensity of the pain, especially if they cannot or choose not to write at that time. It can thus be specifically helpful in the context of potential sedation as a result of morphine (Karcioglu 2018). Both scores measure pain intensity in addition to being reproducible and reliable per patient (Hawker, 2011). It is still referred to as VAS in the discussion.

Pre-operative scores in 3 QVAS modalities (pain right now, pain on average, pain at its worst) were in excess of 6 out of 10 (Table 3.2). There was no significant difference between the 2 groups, once again confirming both the proper randomisation of patients and equal starting point for the study. The *pain at its best* scores were under 4 in both groups and no difference between groups could be demonstrated.

When the patients were counselled on how to complete the VAS scores, a value of 4 was used to indicate pain which needed *treatment by injection*. This same value was used as a trigger for *supplemental analgesia* in the post-operative period should the patient require additional analgesia.

The VAS score is also valuable as a repetitive measurement. Changes of 1.9 out of 10 is considered a clinically significant difference, whether reflecting more, or less pain (Hägg, 2003). This change was evident in all 4 modalities when the 6 weeks, 3 month and 6 month scores were collated as per Figures 3.19 to 3.22. A clinically and statistically significant change was noted in the values, thus echoing results observed in the scores measuring disability (EQ-5, RM, ODI). These values reflect the effect of the procedure on the initial pathology. It also indicates that pain, as measured with the VAS immediately post-operatively, was largely a

result of muscle and surgical trauma related to the procedure itself rather than remaining primary pathology (radiculopathy and instability). Selection criteria for the study also dictated that the index procedure be the first lumbar spinal surgery undergone by the patient. The patient's post-operative pain would thus be a new experience, devoid of any previous reference, which could possibly then create a subjective expectation.

Direct vision of the nerve roots intra-operatively would confirm that they are free from compression thus resolving the radiculopathy. The pain generated by instability (mechanical backache) would also be resolved as the 2 unstable vertebrae would now be united. However, the decompression requires bony excision which, in itself, can be a pain generator, albeit short-lived. This implies that the main sources of immediate post-operative pain would be surgical trauma to the musculature, to facilitate access, and surgical trauma to the bone as a result of the decompression. These should occur equally between the 2 groups.

During the post-operative period the VAS score was assessed for 2 scenarios: lying still and moving in bed. Pain is a unique and individual experience. A pain score of 2 out of 10 for one person might thus very well be a 4 out of 10 for another person (Wewers,1990). During pre-operative counselling, attempts were made to educate patients regarding the use of the VAS to help in standardising the scale. However, this proved difficult due to the subjective nature of pain. A value of 4 out of 10 was determined to indicate a level at which pain would usually require an injection. In addition, the advantage of the study was that every patient acted as his/her own *control.* This implied that the psychological aspect of pain probably did not differ.

The surgical procedure resolved the pre-existing pathological pain, yet it also inflicted pain. This was most prominently as a result of the erector spinae and multifidus muscles undergoing dissection off their medial attachments and being mobilised to access the transverse processes and facet joints. Even though they remained physically intact, these injured muscles present a significant generator of pain. This is particularly true in the first 2 post-operative days when the bruised muscles need to be used to effect mobilisation.

Activation of these trunk muscles will be a significant pain generator and will thus hamper mobilisation. The muscles controlling the trunk have been grouped into 2: those muscles that control spinal segmental stabilisation (multifidus, internal oblique and transversus abdominus) and those muscles controlling gross trunk movement (erector spinae, rectus abdominus and external oblique) (Bergmark, 1989). The erector spinae muscles, or pain generators, are not as active when the patient is sitting but play an important role in maintaining posture. These muscles are thus strongly activated when standing and mobilising to the erect position (O'Sullivan, 2002). It then stands to reason that in the relaxed position (or when lying still), the pain, as a result of the muscles involved in the surgery, would be much less than when active

movement is being attempted. In accordance with this tenet, VAS was measured when the patient was *lying still* in bed and when the patient *was moving*. This was done in an attempt to quantify the intensity of the pain given the perspective set out above.

As illustrated in Table 3.8, the difference in VAS for the first 48 hours post-operatively demonstrated a lesser difference (and thus less pain) in the IT group, significantly so at 24 hours. After 48 hours this relationship reversed. As per Figure 3.5, the difference in VAS scores were less in the PCA group than in the IT group from 48 hours onwards up to 120 hours post-operatively.

Considering the earlier mobilisation noted in the IT group, these patients should naturally have experienced more discomfort when activating the erector spinae muscles, particularly in trying to stand for the first time post-operatively. The direct comparison of the mean *VAS lying still* favours the PCA group, yet the values become near equal at 48 hours and follow the same trend up to 72 hours where the IT group continues with a downward trend and demonstrated a statistical difference at 120 hours (Table 3.6 and Figure 3.3).

In the *VAS moving* analysis, a non-significant difference favouring the IT group is seen up to 24 hours, after which both groups followed a similar trend up to 72 hours, upon which the groups once again deviated to a statistical difference favouring IT at 120 hours (refer Table 3.7 and Figure 3.4).

At first glance it would seem as if the scores did not differ that much and the question therefore begs to be asked: Why did one group then mobilise significantly faster than the other, considering that nearly all variables were accounted for? This can be explained by the fact that the actual mobilisation itself generates pain by activating the core muscles, specifically the first attempt at standing upright which would activate the erector spinae muscles, argued to be the main muscle used in maintaining standing posture and hence the biggest pain generator (O'Sullivan, 2002).

One must then consider the impact that the quicker mobilisation had on the pain itself as well as pondering the question whether the VAS scores of the groups are, in fact, comparable. The IT group fully mobilised a mean of 1.93 days earlier than the PCA group which was statistically significant in days to independent mobilisation as per Table 3.10. A multivariate analysis was conducted which included 3 mobilisation end-points (sitting, standing, taking a few steps) which were the most likely actions to impact the VAS scores in first 48 hours when the difference in the interventions are deemed to be most pronounced.

There was no statistical evidence using VAS *lying still* or *moving* of a differential treatment effect over the first 48 hours between the 2 groups when mobilisation was **not** considered.

However, when *mobilisation* targets were considered, it demonstrated that the act of standing significantly affected the apparent non-significant mean VAS values (Table 3.10). This would imply that standing after a single level fusion procedure has a significant impact on mobilisation and that intrathecal morphine provided a statistically significant advantage over the conventional PCA regimen. The acts of sitting and taking steps also provided near-significant advantages over the PCA and merits reporting (Tables 3.9 - 3.11).

The fact that the act of standing significantly influenced the pain perceived by the patient, supports the argument that the erector spinae muscles were the biggest pain generators in the first 48 hours post-operatively. This is where the strong segmental analgesia associated with the intrathecal morphine provided advantage when compared to the more central effects of the intravenous morphine. This makes for a compelling argument as to the use of IT morphine.

Overall, the results indicate that the direct measures of VAS, as observed in the *VAS lying still* and *VAS moving* groups, seem equal. Yet, the scores are significantly affected by the mobilisation attempts of the patient. In effect, the use of the IT allowed for earlier mobilisation and although this comes at a price, namely an increase in pain, this method of analgesia was still effective to ensure acceptable analgesia while obtaining the advantage of earlier mobilisation. This important concept and the interrelationship between attempting to obtain early mobilisation but, at the same time, provide effective analgesia is, in the author's view, an important concept supporting the use of IT morphine. Specific qualification of this interaction is difficult to achieve but, on a conceptual basis, the author argues that this view and conceptual interpretation of the data are valid.

When the *VAS difference* values were compared (a measure of the intensity of pain), a statistically significant difference at 24 hours favouring the IT group was noted (Table 3.8). This difference between the values directly reflects the ability of a patient to mobilise as the patient is experiencing the pain associated with the movement i.e. originating from the muscles involved. In the IT group, the experience of pain was similar to the pain experienced when lying still (keep in mind the additional pain generator). The acceptable pain levels during movement will also bolster the patient's confidence to mobilise without fearing the pain usually associated with movement.

In addition, as to the impact of mobilisation on the VAS scores, one must consider *supplemental analgesia* use between the groups. The PCA group, as per Table 3.9, used significantly more supplemental analgesia than the IT group in the first 24 hours post-operatively. The use of supplemental analgesia is a clinical validator which indicates whether the analgesic regimen used is effective or ineffective at that time (Farrar, 2000). All patients in

the PCA group who required supplemental analgesia had a BMI in excess of 30kg/m^2 (the remaining patient's BMI was 29.5kg/m^2).

This finding underscores the fact that excessive adipose tissue does not form part of the pharmacologically active mass. It can, however, absorb morphine and thus potentially yield a less effective result (Linares, 2009). In addition, the administration of morphine in obese patients can be dangerous. The calculation of the correct dose is a challenging endeavour which needs to take into account the delayed release of morphine from the adipose tissues which can result in dangerous levels of morphine in the blood (Coetzee, 2010).

Therefore, when interpreting the results, one must recognise the impact of *supplemental analgesia* on the VAS values as well as the *lack of mobilisation* in the PCA group. Despite additional analgesia, mobilisation targets were still achieved significantly quicker in the IT group as illustrated in Table 3.10.

A sub-analysis was performed in which all patients with a BMI of less than 30kg/m^2 were removed. The results demonstrated a statistically significant difference in the *VAS difference* scores at 24 hours between the groups, favouring the IT group. The intravenous morphine group (PCA) experienced analgesia from the interaction of the morphine with the cranial μ-receptors whilst the intrathecal morphine group experienced strong segmental analgesia. In the obese group of patients, adipose tissue does not form part of the pharmacologically active tissues. However, the partly lipophilic nature of morphine could result in absorption of the drug (Linares, 2009) thus affecting the available drug at the target receptors. This consideration emphasises the idea that the effectiveness and accuracy of analgesia could be enhanced by adopting an intrathecal route for morphine delivery (i.e. at the locus of pain) thus rendering considerations as to the effect of excess adipose tissue obsolete.

In summary, the results showed that mobilisation was indeed achieved at 24 hours earlier in the intrathecal morphine group. The pain associated with this mobilisation process remained at acceptable pain levels. The author would speculate that this earlier mobilisation would increase patient confidence which, in turn, would motivate them to continue with the mobilisation. For reasons explained earlier, the advantage seems to be more pertinent in the obese group.

4.2.3 Mobilisation

The primary hypothesis of the study was that the IT group would fully mobilise and be discharged quicker than the PCA group. The IT group were fully mobilised and discharged home after a mean of 3.68 days and the PCA group after 5.61 days.

The mobilisation regime was standardised for all patients with several targets which had to be achieved. The attainment of each of the mobilisation gaols was recorded and included: log-roll in bed, sit on the side of the bed, stand next to the bed, mobilise a few steps, walk aided, walk unaided and ultimately discharged with full independent mobilisation having been achieved. It is noteworthy that some steps in the mobilisation regime are generally easier to achieve as they cause less pain and discomfort. These steps relate to activities which facilitate the activation of the trunk muscles when erect (erector spinae) and their relaxing in passive positions such as sitting. However, when sitting the multifidus muscle, another pain generator which was influenced by surgery, is activated. Thus, a log roll, by inference, would use very few of the surgically affected muscles whilst sitting and standing upright would mobilise most muscle groups (O'Sullivan, 2002).

Most patients thus easily achieved a log roll in bed on day 1 post-operatively as per Table 3.10. Sitting up and sitting upright on the side of the bed does not require significant weight bearing and result in limited activation of the back muscles, particularly the erector spinae (Bergmark, 1989). Although painful at times, it is generally regarded as bearable. Standing upright next to the bed is considered a full weightbearing activity which results in full activation of the posterior lumbar muscles. In the recently operated patient, especially when one considers the extent of muscle mobilisation in lumbar fusion surgery, this is associated with significant pain (O'Sullivan, 2002; Bergmark, 1989).

As per Figure 3.8, the mobilisation pattern noted in the 2 groups started diverging when patients were required to stand next to the bed and/or take a few steps. The data in a multivariate analysis showed that mobilisation significantly affected the VAS reported by the patients (Tables 3.9 to 3.11). The relationship between the pain scores and level of mobilisation achieved can be ascribed to mobilisation resulting in additional pain. This occurrence had to be considered when interpreting VAS and analgesia requirements.

The difference in VAS, viewed as an indication of pain intensity, was most pronounced at 24 hours with the IT group displaying significantly better pain control at this point. This was illustrated by the significant difference in VAS scores with the IT group attaining 1.63 and the PCA group attaining 2.42. This difference can be ascribed to the efficacy of the IT on the μ-receptor expressed in both pre- and post-synaptic neurons at the spinal cord (Fukuda, 2009)

which directly relate to the surgical site with direct administration of morphine into the intrathecal space reaching high concentrations at that target site (Bujedo, 2012). This advantage is further emphasised when one considers the increased expression of the μ-receptors in the presence of inflammation (Linares, 2009).

PCA administration results in a blood concentration of the opiate which must cross the blood-brain barrier to reach the effected site in order to deliver pain relief. Due to its hydrophilic nature, morphine does not have a strong tendency to diffuse into the fatty neural tissue and it thus remains available in the cerebrospinal fluid in order to bind to the μ-receptors. In addition, it remains in the cerebrospinal fluid for a longer period of time thus resulting in a prolonged action when compared to a single bolus dose of morphine administered intravenously or intramuscularly (Hindle, 2008).

Intrathecal morphine is also in direct contact with the μ-receptors. In the author's opinion, this assists in earlier mobilisation as all nociceptive nerve traffic from the afferent sensory neurons, responding to painful triggers, is effectively suppressed and controlled (Linares, 2009). Patients also quickly learn and obtain confidence that they will not be in severe pain when they start moving if they had intrathecal morphine. Given human nature and the power wielded by experience, patients would probably find it easier to overcome anxiety associated with the unknown once they had experienced that moving did not result in severe pain if intrathecal analgesia had been administered. Apart from the reality of pain itself, the fear of pain is a significant limiting factor in making progress to mobilisation. The fear of pain can even prompt patients to use the PCA device in the absence of pain (Johnson, 1989). Hence, effective analgesia, obtained through the use of intrathecal morphine, made it physically easier for patients to start mobilising. Once these patients were up and experiencing effective pain relief, they gained confidence which, in turn, assisted in further mobilisation.

This does not imply that the PCA did not provide reasonable analgesia. However, once it reaches beyond the blood-brain barrier, it is dispersed throughout the central nervous system rather than being concentrated at the spinal target site, as is the case with intrathecal morphine introduced into the lumbar thecal sac. In the event of systemic opiates, the general dispersion would affect all susceptible areas in the brain. However, a simple and straight comparison of the 2 techniques, as well as the concentration of morphine achieved in the cerebrospinal fluid at the level of the brain, is beyond the scope of this study. It could, however, be considered as an informative topic for a research project.

The calculation of an effective dose also gains relevance with the increase of adipose tissue, associated with a higher BMI, as noted in most of the trial patients. The higher BMI could very well interfere with the availability of systemically administered morphine (Linares, 2009).

It is estimated that the intrathecal dose would be effective for approximately 24 hours (Sjöström, 1987). At this point the PCA device would have been removed and both groups would have been placed on the same analgesic regime. Sidebotham *et al*. demonstrated that the use of a PCA device was most effective in the first 24 hours post-operatively, irrespective of the type of surgery performed. The device was therefore removed after 24 hours in an attempt to standardise the effect of the interventions (Sidebotham, 1997).

The expected *difference* between the 2 groups would be most pronounced in the first 48 hours post-operatively as both groups received the same standardised analgesic regimen from 24 hours post-operatively onwards. The effects of the initial analgesic intervention would wear off by 48 hours.

The argument has been made that sitting up, standing and taking a few steps would be most challenging to the patient as these activities directly involve muscles which had recently been mobilised during surgery. These muscles thus act as pain generators and, as such, their use would hinder mobilisation.

The VAS scores, both in *lying still* and *moving*, did not demonstrate significant differences between the groups. The *difference in VAS* between moving and not moving was however significant.

Discharge within the public service does not usually involve step-down facilities. This means that patients have to be able to return home and essentially care for themselves within the broader context of their local support system. The mandate for physiotherapy was that the patient must be able to mobilise independently on oral analgesics alone, and that he/she should be able to repeat the activities at home within limits of pain. The final discharge, after physiotherapy had cleared the patient, was done by the surgeon who inspected the wound, reviewed post-operative x-rays and determined that the level of analgesia was adequate.

4.2.4 Efficacy of the intrathecal morphine dose

A first-time lumbar surgery, single level fusion procedure was used in an attempt to standardise surgical injury to patients and thus facilitate comparable pain responses when comparing intrathecal vs PCA morphine interventions. In addition, this selection guaranteed that the patient had not previously undergone a lumbar rehabilitation and mobilisation programme.

As evident from Table 3.1, a significant difference in BMI existed between the groups. The mean BMI in the intrathecal morphine group was 29.18kg/m^2 and in the PCA group 34.31kg/m^2. The median values, 30.9kg/m^2 in the intrathecal group and 33kg/m^2 in the PCA group, represented a more accurate value as outliers were accounted for. This significance was not evident in the mean body fat percentage of the groups implying that either patients' length or an increased muscle component affected the BMI as BMI cannot distinguish between larger than normal muscle mass or adipose tissue (Green, 2004). In both groups these patients were classified as *obese*. As Table 3.1 illustrates, no statistical difference could be detected between body fat percentage and body muscle percentage in the 2 groups.

The fact that the median BMI values in both groups classified them as *obese*, played a significant role in attempting to find the safe morphine dose. Although morphine is primarily hydrophilic, the excess adipose tissue still needs to be considered along with the pharmacokinetics of the drug when administered intravenously (Coetzee, 2010). As obesity is considered a growing epidemic (Agha, 2017), this becomes a very relevant consideration in a frequently used drug such as morphine.

One of the dangers in attempting to calculate a safe dose is that the administered dose may not effectively control pain, and this may very well prompt the use of rescue analgesia. In doing so, a compound effect could occur which could result in delayed onset respiratory depression and other side-effects (Coetzee, 2013).

For the intrathecal group, a dose of 0.005mg/kg up to a maximum of 0.45mg intrathecal morphine was proposed and used by the author. This implied that a patient with a weight of 90kg and/or more would have received the same dose of intrathecal morphine.

In general, it is the author's view that above 90kg the percentage body fat becomes more significant unless the person is a particular large and muscular individual. This value of 90kg was chosen based on the average height of males which resides at 168cm in South Africa and up to 183cm in the Netherlands (Average height of men and women worldwide [Internet]). When one correlates this with a standard BMI table, the corresponding weight *prior* to being classified as obese is approximately 90kg (Ulijaszek 2000, Agha 2017)

In addition, available literature on the intrathecal use of morphine in spinal surgery afforded some insight into potentially dangerous and effective doses (Boezaart, 1999; O'Neill, 1985; Ross, 1991).

Intuitively, one would expect a dose-response relationship to intrathecal morphine. This is however only partially true. To fully understand this relationship, or lack thereof, one must carefully scrutinise the pharmacokinetics and dynamics of morphine when administered both intravenously and intrathecally.

The effect that the opioid has on the pain sensation is based on its interaction with μ-receptors situated in the dorsal horn where it enters the spinal cord, as well as centrally in both the midbrain (periaqueductal grey matter) and the medulla (pre-Bötzinger complex). The latter area is also associated with opioid induced respiratory depression (Montandon, 2011). Nausea, vomiting and pruritis are side-effects which stem from the central action of morphine (Gulhas, 2007).

In order to be effective, one must appreciate the obstacles which the drug has to overcome to reach these target sites. Segmental spinal analgesia will be achieved through interaction with the μ-receptors at the dorsal horn in the spinal cord. This is the *safe target* and will yield an ideal result as effective interaction here will have no significant side effects such as respiratory depression. It will thus provide post-surgical analgesia related to the surgical site, in this case the lumbar spine.

The physiochemical properties of the drugs *inter alia* dictate the efficacy and side-effect profile of the opioids. The effect of the drug is determined by the cerebrospinal fluid and spinal cord concentrations of the freely diffusible opioid as these conditions are favoured by more hydrophilic drugs (Ummenhofer, 2000). Morphine is (mostly) a hydrophilic drug and has a strong affinity to the μ-receptors. These receptors are situated in the grey matter of the spinal cord which contains no myelin and thus pose no obstacle for the more hydrophilic drug. The opposite is true for the white matter which, as a result of the myelin sheaths, is made up of up to 80% lipids (Bernards, 2002; Hindle, 2008). Therefore, once the drug arrives at the spinal cord, by whichever route, the more hydrophilic drug will diffuse through the extracellular space of the white matter cells and reach its target receptors. Hardly any of the morphine will partition into the white matter therefore resulting in an increased bioavailability to the receptors, as long as the drug is not actively cleared (Bernards, 2002). It has been shown that meningeal permeability is inversely proportional to the hydrophilic nature of a drug, implying that morphine will have a low permeability potential through the meninges and will thus remain

within the CSF space (Ummenhofer, 2000). This characteristic is useful if prolonged analgesia is required.

.

The high affinity of morphine to the μ-receptor provides effective analgesia mainly in relation to the spinal segments where the drug is inserted. If a discrete concentration of morphine remains available, it would suggest prolonged analgesia until the available concentration of morphine becomes negligible. Morphine effect-site pharmacokinetics could differ from cerebrospinal fluid pharmacokinetics implying that, despite the cerebrospinal fluid morphine being eliminated, morphine at the receptor level can persists (Bernards, 2002). This ensures that a clinical effect is present for up to 12 hours (Hindle, 2008). Ummenhofer demonstrated the extracellular spinal cord bioavailability of morphine at level L2/3, even after 6 hours post-intrathecal injection (Ummenhofer, 2000).

For intravenous morphine to reach this site, it must cross the layers of the meninges. The dura mater has a rich capillary network of which the endothelial cells will act as a barrier to more hydrophilic drugs (Bernards, 2002). This capillary network is also an important site for clearance of the drug from the cerebrospinal space. This also favours the more hydrophilic drug if the intention is for the drug to remain in the cerebrospinal fluid for as long as possible. Hence, morphine would be the more ideal drug to use.

Despite the dura mater being the thickest layer of the meninges, the arachnoid mater accounts for 90% of resistance to drug diffusion. It is also impermeable to cerebrospinal fluid and thus contains the cerebrospinal fluid and its contents in the subarachnoid space, unless being actively cleared (Bernards, 1990). The arachnoid has tightly junctioned flat epithelial cells which pose resistance to more hydrophilic drugs (Nabeshima, 1975). Both these layers will provide an obstacle to the diffusion of morphine if the drug arrives at the spinal cord via the intravenous route.

The pia mater consists of a single cellular layer and it poses very little resistance. There is no difference between opioids injected directly into the cerebrospinal fluid space and those arriving through diffusion, therefore, once *in* the cerebrospinal fluid, the effect will be comparable (Bernards, 2002), although dependent on the concentration present.

As regards the dose-response relationship of intrathecal morphine, Jiang demonstrated a clear dose-response relationship for doses ranging from 0.025 - 0.125mg regarding the *duration of analgesia* observed (Jiang, 1991) but not the *degree of analgesia*. A larger dose

did have a longer effect well in excess of the expected cerebrospinal fluid half-life of morphine. At the same time, increased incidents of pruritis were observed with increased doses which would support the contention of a supraspinal effect of intrathecal morphine in larger doses. It then stands to reason that the clinical analgesic effect, observed *beyond* the expected duration at the spinal segmental level, is due to the interaction of morphine with the central receptors.

Palmer *et al.* assessed different doses of intrathecal morphine in post-caesarean section patients ranging from 0.0mg as placebo up to 0.5mg with supplementary PCA morphine use noted as a measure of effective pain relief. Their initial hypothesis was that an expected inverse linear dose-response relationship would be present. However, they were surprised to observe a ceiling for analgesia (or similar PCA morphine use) of doses starting at 0.075mg up to 0.5mg. They did however notice an increase in pruritis, nausea and vomiting as the dose increased. Because the study was not designed to assess respiratory depression, they did not offer comments on this important topic (Palmer, 1999). They concluded that an increase in dose beyond 0.025mg *will not* provide an increase in the quality of analgesia. They concluded that the analgesia provided by the intrathecal dose was not perfect and that even their maximum intrathecal dose of 0.5mg was not sufficient to activate supraspinal mediated analgesia via cephalad spread. They recommended that PCA morphine support should be considered in addition to the intrathecal dose (even 0.5mg) to provide a supraspinal analgesic effect.

The latter conclusion can, however, be disputed as the cerebrospinal fluid terminal elimination half-life of morphine has been demonstrated to be between 42 and 136 minutes (Sjöström, 1987). Thus, a supraspinal analgesic effect had to occur if pain relief had lasted 24 hours, as per the study, most likely due to supraspinal spread of the morphine in the cerebrospinal fluid. This potential misinterpretation could be explained by PCA morphine use being adopted as a *measure of pain* rather than the pain scores themselves. This approach is fraught with inaccuracies (Johnson, 1989; Ferrante, 1988; Macintyre, 2001). In addition, the dose-related increase in pruritis, nausea and vomiting described in the study would suggest cephalad spread of the intrathecal morphine due to the interaction with the 5HT3 receptors in the trigeminal cervical nucleus for pruritis (Kerhonen, 2003) and the chemoreceptor trigger zone in the floor of the fourth ventricle for nausea and vomiting (Smith, 2014).

These supraspinal, or central effects of morphine can be used to the clinician's advantage when prolonged and effective analgesia is being sought, although achieved against the backdrop of potential side-effects of which respiratory depression is an obvious and dangerous risk.

The method by which intrathecal morphine is introduced can also play a role in the movement of morphine to the medulla and other supraspinal areas. The main method of cephalad spread is bulk cerebrospinal fluid flow resulting from the pulsating brain and cyclical thoracic pressure associated with respiration (Kroin, 1993; Hindle, 2008).

The pharmacokinetics of morphine in the cerebrospinal fluid is poorly understood and hampered by the logistics of studying the subject i.e. taking repeated fluid samples. This procedure will potentially dilute the available intrathecal drug and repeated samples of spinal cord tissue and fluid cannot be obtained in clinical practice (Ummenhofer, 2000). Kroin *et al.* studied the distribution of a hydrophilic compound along the length of the spinal cord. They demonstrated a 57% decrease in concentration over the length of the thoracic spinal cord (20cm). Considering minimal capillary losses due to the hydrophilic nature of the compound, they ascribed the change in concentration to the increase in volume the drug is exposed to as well as a two-compartment model of cerebrospinal fluid interchange involving the spinal and cranial spaces (Kroin, 1993).

In a cadaveric study, Parese *et al.* demonstrated that the overall length of the spinal cord varied ranging from 36.2 to 45.7cm (Parese, 1959). Effectively, the key in predicting a dose that would be effective both in the spinal and cranial areas would be linked to the *length of the patient* which is an indirect reflection of the length of the spinal cord and spinal canal cerebrospinal fluid volume. As the relationship between length and weight is generally defined in BMI (Agha, 2017), it stands to reason that a weight based dose should be effective to manage the supraspinal effects of the intrathecal morphine, reverting back to the original proposed dose of 0.005mg/kg up to a maximum of 0.45mg. Given the variance in achieving the BMI, i.e. for instance being very short and very fat vs being tall and fat, will obviously result in different cord lengths. Based on this observation, one can perhaps argue that the patient's length may very well be an equally good, if not better, determinant for the dose. This topic has not been examined but provides an interesting topic for further research.

A further uncertainty which affects the calculation of intrathecal morphine doses is the question of whether or not any relationship exists between the body's fat component and the volume of the CSF. The author believes that this is unlikely, and that CSF volume more closely relates to ideal body weight rather than total body weight. The already speculative and tenuous relationship between the cerebrospinal fluid and total body weight will probably become even more inaccurate as the fat component increases i.e. the patient is more obese. Hogan *et al.*,

in fact, described a smaller total spinal cerebrospinal fluid volume in obese patients as a result of raised intra-abdominal pressure (Hogan, 1996).

Matsumae *et al.* could demonstrate a mean difference of 21cm^3 of total cranial CSF volume between males and females. However, in both sexes the total cerebrospinal fluid volume amounted to 11.4% of the total intracranial volume (Matsumae, 1996). These findings were not coupled to length, yet it seems as if a relationship existed between total cranial cerebrospinal fluid volume and length with males being generally taller than females.

The PCA device was primed with a 1mg/ml concentration of morphine in normal saline. The device delivered a 1mg bolus intravenously on demand with a 7-minute lockout period. This would allow a patient up to 8mg of intravenous morphine per hour. Owen *et al*. compared the concentrations of 0, 5, 1 and 2mg/ml of morphine in normal saline and concluded that 1mg/ml is optimal and effective for post-operative analgesia (Owen, 1989; Macintyre, 2001). The recommended lockout period for morphine PCA is 7 - 11 minutes (Macintyre, 2001). This concentration and total potential dose per hour also conform to the institutional standard of care at Tygerberg Academic Hospital.

The efficacy of the doses was evident in the VAS scores assessed throughout the study. The difference in VAS *lying still* and VAS *moving*, as a measure of pain intensity, demonstrated efficacy of the proposed dose. Moreover, the earlier mobilisation emphasised this conclusion as well. During the retrospective review, prior to embarking on this study, the average stay was 6.23 days for the same surgery in the department of Neurosurgery at Tygerberg Academic Hospital. This was similar to the length of stay in the PCA group (5.61 days).

The volume of PCA used was more in the PCA group compared to the intrathecal group (which was primed with normal saline as placebo), yet this was not deemed statistically significant (p=0.057). The box and whisker plot (Figure 3.1) demonstrate outliers affecting the median volume which was used. The fact that the median PCA volume used in the intrathecal group was 22ml, emphasises the point made by Johnson that *fear of potential pain* may well drive the use of the PCA (Johnson, 1989). Given that the placebo was normal saline, it could however not influence the pain scores.

In the intrathecal group, the quicker mobilisation achieved in a short time is testament to adequate analgesia. However, the fear of potential pain should not be underestimated. Even if present, the early mobilisation targets achieved are remarkable considering patients' potential fear. The fact that minimal rescue analgesia was requested, despite the mobilisation, supports the contention that the dose of intrathecal morphine was effective and that the particular level VAS could be accepted as an indication that patients were not experiencing severe pain or discomfort.

The double-blinded nature of the study assured that the PCA volume used was an acceptable indirect reflection of both the pain experienced by a patient as well as the fear of possible pain. Given that the latter is a uniquely individual experience, and as such not quantified in this study, the author asserts that the total pain perception of any particular patient needs to be addressed by the attending doctor who has to consider both the physical manifestation of pain as well as the psychological component of his/her patient. In addition, the volume of morphine used in the PCA group could also be less than potentially necessary as the sedative effect of morphine could result in a patient falling asleep and waking only when the pain becomes excessive (Coetzee, 2013). However, one has to keep in mind that the patient with significant pain is unlikely to fall asleep in the first instance.

All these factors make a compelling argument that when opioid analgesia is relied upon, the intrathecal route results in effective analgesia, significantly so at 24 hours post-operatively.

4.3 Safety of the intrathecal injection of morphine

The use of morphine, both via the intravenous and intrathecal routes, will expose the patient to certain risks concerning the side effects of the drug.

The bioavailability of a drug refers to its ability to distribute from its site of injection to its site of action and, in the case of spinal surgery, spinal segmental analgesia is the goal. This is easily achieved when introducing the drug intrathecally as the calculated dose will be delivered directly to the target site.

Morphine, administered intravenously, will be distributed throughout various body compartments. The working of the drug will also be influenced by other tissues, such as fat (Bernards, 2002), where the physiochemical properties of the opioid and those of the tissue determine the interaction. The volume of distribution (Vd) is defined as the distribution of a medication between the plasma and the rest of the body. It can be expressed in the following formula:

Vd = total amount of the drug in the body / total amount of drug in the plasma

The Vd of morphine is 1 - 6L/kg which implies that it will be absorbed in other tissues of the body as well (Glare, 1991). Even though it is considered a mostly hydrophilic drug, it will be partially absorbed in adipose tissue (Linares, 2009). Should this component of the body habitus be significant, it could affect the bioavailability of the drug to target receptors. This will affect the efficacy of the drug and prompt the use of rescue analgesia or result in persistent and higher volume PCA use. A potential build-up of the drug should thus be considered along with later than expected clinical effects and, specifically, side-effects (Coetzee, 2010).
Once distributed in the plasma, the drug will become available to all areas of target receptors with equal amounts being available to both the spinal and cranial μ-receptors. Considering that the respiratory control centre and receptors in the spinal cord would be affected, it follows that an increased dose, or cumulative doses, would increase the potential for side-effects. This, in contrast to the intrathecal route of administration, could present with earlier onset significant side-effects where the exposure of intrathecally introduced morphine to the cranial receptors only occur at a later stage.

The key, when using intrathecal morphine, would then be to administer an effective dose which would provide prolonged analgesia. When the morphine ascends to the levels of the midbrain

and medulla, however, the ideal is that it would be sufficiently diluted to not cause significant side-effects such as respiratory depression and excessive somnolence.

Based on the above rationale, morphine is the better choice for intrathecal use as: it has a high affinity for the μ-receptors at the injection site, it does not absorb into the fatty myelin and it will persist in the cerebrospinal fluid for a lengthy period of time. However, it will have cephalic spread in the cerebrospinal fluid which is an unavoidable occurrence. The accurate calculation of a safe dose in a safe volume thus becomes imperative. The safety of the dose should be critically evaluated in accordance to parameters related to respiratory depression and level of consciousness.

In order to critically evaluate the effects of the intrathecal opiates on the brain, as opposed to the spinal cord, blood gas analysis, monitoring of the respiratory rate, the determination of the OISS and FiO_2 were done at various time intervals. These observations were done at 11 predetermined time points post-operatively over the first 24 hours. It was envisaged that this exercise would define the risk in addition to providing valuable information to be used in suggesting a safe approach to the use of the intrathecal morphine.

4.3.1 Intra-operative injection

Initially there was some concern that intrathecal administration could result in a cerebrospinal fluid leak which could potentially affect the patient's recovery and result in the loss of some morphine which was, in fact, supposed to remain in the CSF.

The intrathecal injection was performed once the pedicular screws had been placed and the decompression had been completed. This allowed adequate time for the drug to work considering the remaining steps in the procedure and emergence from anaesthesia.

To minimise the risk of a potential CSF leak, the author used a blunt instrument to depress the thecal sac in the midline at the border of the thecal sac and the cranial lamina within the surgical field. The injection was performed with a sterile insulin needle and syringe which is the smallest bore needle available. The anaesthetist was asked to prepare a solution of 1mg/ml of morphine in normal saline and the surgeon drew the correct dose as it related to millilitres with 1ml being 1mg of morphine.

The rationale for this injection site is that the inherent pressure within the thecal sac would tamponade the small puncture site onto the ventral surface of the lamina, thus reducing the chance of a cerebrospinal fluid leak. An even better scenario is the presence of epidural fat

which could then be mobilised gently, or the needle could be passed through said fatty tissue to further minimise a potential leak, as per Figure 2.2.

By using a small volume (no more than 0.45ml for the maximum dose), the volume added to the thecal content is minimal and therefore it does not affect the pressure in the thecal sac. Consequently, it is thus extremely unlikely to perpetuate a leak. The expectation was further that the small volume added to the existing cerebrospinal spaces would limit the immediate rostral ascension of the drug. It is important to keep the needle in situ for approximately 30 seconds to allow the injected content to disperse as it is a small volume with a high concentration of morphine. Cerebrospinal fluid pulsation associated with the normal cardiac cycle will allow the content to disperse locally within that time and when the needle is removed, the potential small flush of cerebrospinal fluid will unlikely contain a high concentration of morphine. Considering the small volume that is introduced into the thecal sac and knowing that spinal cord concentrations could be maintained up to 12 hours, it is important not to lose some of the morphine in this small back flush (Hindle, 2008).

Once the injection had been performed, the rods were placed and secured, and the autologous bone graft was placed in the decorticated lateral gutters prior to commencing closure. This resulted in an average time from injection until skin closure of 28.21 minutes. It has been shown that maximum concentrations of intrathecal morphine are achieved at the target receptors in the spinal cord between 5 and 30 minutes post-injection (Sjöström, 1987). This does not mean that optimal analgesia has been achieved as the morphine still has to bind to the μ-receptor. This makes it even more important that the anaesthetist titrate analgesia in the recovery room should the patient be uncomfortable. Morphine has a high affinity for the μ-receptor which makes this time short and the approximate 45 minutes it would take from injection until emergence of the patient from anaesthesia should be sufficient time for the administered dose to take effect.

Complications related to cerebrospinal fluid leak include headache and a cerebrospinal fluid leak through the surgical site. In this study, no patient presented with a cerebrospinal fluid leak. Six incidents of headache were recorded at 8 hours, 4 at 24 hours and 7 at 48 hours post-operatively. Whether these headaches were related to a potential cerebrospinal fluid leak is uncertain.

The surgical site drain was assessed for clotting in the draining tube towards the reservoir and if clotted, it was removed. All drains were removed after 24 hours.

This technique has proved to be safe in limiting cerebrospinal fluid leak and related complications but effective in administering a concentrated small volume intrathecal dose.

4.3.2 Respiratory depression

Rhythmic breathing, generated by a complex neuronal network found in the brainstem, is essential to life (Montandon, 2011). The rhythm generated by the pre-Bötzinger complex found in the medulla is thus considered critical for maintaining breathing (Gray, 2001) and, ultimately, for the oxygenation of tissues. Opioids have a dose-dependent interaction with this area in the medulla which consequently affects the rhythm of breathing and which may result in a decrease in respiratory drive (Montandon, 2011). Not only do opioids effect the rhythm of breathing, they also influence the respiratory system and airway as they decrease the genioglossus muscle tone. This could cause potential airway obstruction and result in a sedatory effect which decreases response to stimuli (Coetzee, 2013) whilst, on the other hand, wakefulness is a stimulus to normal breathing (Talbot, 2003).

In addition, a patient who is sleeping *normally* could present with rhythm disturbances related to rapid eye movement (REM) and non-REM phases of sleep. Krieger *et al.* studied 20 young (average age 24 years) and 20 older (average age 65.5 years) healthy patients with no previous history of sleep disturbances (Krieger, 1983). Hypopnea was defined as a 50% decrease in tidal volume in 1 minute compared to the tidal volume recorded during quiet wakefulness for a 3 minute period. Apnoea, defined as a complete cessation of air flow, was divided into central or obstructive apnoea. The authors reported a decrease in tidal volume for all patients during light sleep and a further decrease during deeper sleep. Hypopnea was demonstrated in 85% of the older group (more than 5 events per sleep hour) and apnoea in 35%. Hypopnea was seen in 65% of the younger group and apnoea in 55%. They concluded that advanced age was a risk factor for sleep related respiratory events. Given the influence which sleep exerts on the respiratory system it follows that the presence of opiates, with their well-defined depressing effect on the respiratory control system, would introduce a heightened risk of severe respiratory depressive effects during sleep. In the light of this, it is specifically important to monitor patients during sleep periods when they are being exposed to opiate therapy.

In the event of opioid related respiratory depression, the primary result is hypercarbia. This can be explained at the hand of the following formula:

$PaCO_2 = k \times VCO_2/VA$ (Equation 4.1)

Where VCO_2 is carbon dioxide production (which remains relatively constant) and VA refers to alveolar ventilation (Talbot, 2003). If the alveolar ventilation decreases, as seen in respiratory depression, the VCO_2/VA will increase and finally result in hypercarbia.

The question is whether this hypercarbia is dangerous to the patient. Permissive hypercapnia has long since been an accepted strategy in managing acute respiratory distress syndrome (ARDS) where the low-stretch ability of the lung prevents clearance of CO_2 (Kregenow, 2002). Systemic effects of hypercarbia include, amongst others: increased ventilatory stimulation, cerebral vasodilation, increased sympathetic tone and it can also lead to reduced oxygen consumption (Kregenow, 2002). Hence, one can safely conclude that mild hypercarbia is not a life-threatening condition and that it only becomes such if and when hypoxia ensues. The interaction between hypercarbia and hypoxia is best illustrated with reference to the abbreviated alveolar gas equation:

$P_AO_2 = FiO_2(PB – PH_2O) – PaCO_2/0.8$ (Equation 4.2)

Where P_AO_2 = alveolar oxygen tension (in mm Hg), PB = barometric pressure, PH_2O the saturated vapor pressure in the alveolus which is taken as a constant of 47mm Hg at 37^oC and $PaCO_2$ is the arterial carbon dioxide tension in mm Hg. With regards to the latter, the assumption is (correctly) made that the alveolar and arterial carbon dioxide tension are approximately similar. Note that a gradient exists from the alveolar PO_2 to the capillary and arterial PO_2 but, for the purposes of this discussion, this is assumed to remain constant.

From this equation it is clear that as the alveolar ventilation decreases and the carbon dioxide increases (Equation 4.2), the alveolar P_AO_2 will decrease in a ratio of 1.2 i.e. for every 1 unit increase in $PaCO_2$ there will be n decrease in P_AO_2 of 1.2. Hence, if alveolar ventilation is significantly depressed, the patient may become hypoxic. Hypoxia, for purposes of clinical medicine and in patients with normal lungs, is defined as a PaO_2 less than 60mm Hg (or 7.99kPa) based on the assumption that the oxyhaemoglobin dissociation curve is normal when this level of oxygenation is associated with a saturation of 90%.

From Equation 4.2 it is also clear that, within limits, arterial oxygen partial pressure and thus saturation may well be maintained if inspired oxygen is raised.

Furthermore, in wards and units where saturation is constantly displayed, staff and practitioners use the 90% cut off with impunity as the measurement is available and physiology is known to be normal. However, if the oxyhaemoglobin dissociation curve is shifted, with either a decrease or increase in P_{50}, the relationship between the saturation and the partial pressure for oxygen will change. In the presence of uncompensated hypercarbia, the P_{50} will increase and the critical PaO_2 will be associated with a lower saturation (less than 90%). Although this can be viewed as incorrect medical science, the error favours safety.

Therefore, when assessing the side-effects of morphine, specifically for respiratory depression, one must carefully evaluate individual parameters but also appraise them within the broader context of facilitating a pain free, comfortable and safe patient.

4.3.3 Respiratory rate (RR)

When trying to assess the safe use of morphine, respiratory rate is often one of the factors closely monitored. However, the definition of bradypnea is not clear-cut and often varies across studies referencing morphine and the safe usage thereof (Ko, 2003). The challenge in using RR to define respiratory depression is that its monitoring usually forms part of hourly observations in a high care unit or at an even longer intervals in a general ward. Once assessed by nursing staff, respiratory rate represents, at best, a snapshot in time of a ventilatory pattern which may very well vary between observations.

Similarly, the action of assessing RR or the mere presence of the nurse may disturb, or wake, the patient resulting in a less depressed state being recorded which, in reality, confounds the actual state of sedation. The inadequacies of this monitoring method have been highlighted before and recommendations have been made that this phenomenon not be used as a single or reliable reflection of respiratory depression (Coetzee, 2013).

Only 5 incidents of low respiratory rate were recorded in this study and none prior to 6 hours post-operatively (Table 3.14). These low respiratory rates were not associated with a decrease in saturation below 90% nor an increase in $PaCO_2$ over 6kPa. The OISS in the IT patient did not signify any dangerous sedation, yet a score of 2 was noted in the PCA patient during both incidents of bradypnea. This illustrates a sedate patient, yet the $PaCO_2$ remained below 6kPa throughout the 24 hours observed. Additionally, the patient presented with a PaO_2 of 11.6 and 13.5kPa implying good oxygenation despite the low respiratory rate. It is thus justified to ask whether a “snapshot” count of respiratory rate could truly represent any form of respiratory distress or wellbeing.

The value, or lack thereof, of considering RR can be placed in perspective by considering Equation 4.2 and the role of, for instance, elevated inspired oxygen.

If one assumes the A-a gradient to be normal (healthy lungs) in association with a FiO_2 supply of 0.21, then to achieve the minimal acceptable P_AO_2 of 60mm Hg (or 8kPa), the $PaCO_2$ must rise to 72mm Hg (or 9.6kPa)! This was not the case in incidents observed in the study with a RR less than 10 breaths per minute. This emphasised the fact that all *abnormal values* were in fact *snapshots* and, as such, they did not represent a trend or lengthy period of bradypnea

at the time. In real terms this implies that minute ventilation must be reduced by approximately 50% over a period of time, once again emphasising the limitation of intermittent counting of respiration.

It is safe to say that a low RR (less than 10 breaths per minute) is always concerning and requires prompt verification. Data garnered from this study, however, does not support RR to be of positive predictive value i.e. indicating severe hypercarbia and associated hypoxia. The author suggests that this parameter should be used as but one in a battery of observations continuously applied when monitoring the respiratory effects of opiates (Coetzee, 2013).

The mean respiratory rates for both groups demonstrated a steady increase over 24 hours post-operatively. This increase was noted to start between 6 and 8 hours post-operatively, as per Figure 3.9. As wakefulness is a stimulus for respiration (Talbot, 2003), the steady increase is most-likely a reflection of increased activity in the ICU the following morning after the procedure at approximately 16 hours post-operatively on average. At this stage nursing activities would intensify in the ICU with patients being washed and active attempts at mobilisation being initiated.

However, an increase in observed mean RR commences at more or less 6 to 8 hours post-operatively, thus effectively during the night for most patients. This could indicate that during the first 6 to 8 hours post-operatively, the effect of morphine may well have played a role in the pattern of respiration. A decreasing trend is noted in both groups up to 3 hours post-operatively. Admittedly, this mean rate is between 15 and 16 breaths per minute with the PCA group showing a decrease, albeit briefly, below 15 breaths per minute between 3 and 4 hours post-operatively. The mean RR for the PCA group is consistently less than that of the intrathecal group over the initial 24 hours post-operatively. The upward trend which was noted, particularly from 10 hours onwards, suggests that RR will no longer be a real concern from 10 hours post-surgery.

After 6 hours, a steady increase in mean RR for both groups was noted. Overall, however, the checking of RR did not contribute significantly to the successful monitoring of the effect of the opiates on the respiratory drive. In summary, little difference was noted between the intrathecal and PCA morphine groups. Perhaps the RR trend is noteworthy inasmuch as RR increased from 10 hours onwards thus suggestive of a diminished opiate effect at this time and subsequent to 10 hours.

4.3.4 Sedation

The OISS is not a direct measure of respiratory depression but rather focuses on the level of sedation of a patient. Sedation is a central action, or side-effect, of morphine and would thus indicate, in the case of intrathecal morphine, that a cranial spread of the drug had occurred (Kroin, 1993).

Its association with respiratory depression is two-fold. Firstly, less opioids are required to affect sedation than respiratory depression. Sedation, therefore, could be considered an early warning sign for respiratory depression (Coetzee, 2013). Secondly, in obese patients, increased fat deposition in the pharyngeal wall will cause a smaller pharyngeal volume which when relaxed, such as in the case of sedation, can cause potential airway collapse and compromise (Benumof, 2001).

As argued by Coetzee *et al.*, the use of a sedation scale should be afforded preference over counting the RR and should be used in the monitoring of all patients who have received opioids (Coetzee, 2010). The values of s (asleep, easily aroused) and 1 (awake and alert) indicate patients not experiencing sedatory effects. In the study population used for this thesis, only 3 patients recorded a value of 2 and no values of 3 or 4 were documented. These occurred *only in the PCA group* and amounted to 19 events. The benefit of this study is that during the evaluation of sedation (OISS), an arterial blood gas analysis was also performed which accurately defined the impact on PaO_2 and $PaCO_2$.

One patient was evaluated as a 2 at 11 time-points, yet at no point did saturation register under 90% and $PaCO_2$ remained in excess of 6kPa. The respiratory rate decreased to below 10 breaths per minute at 2 of these time points. This patient was comfortable and had no subsequent deleterious effects related to the opioids received, but his RR certainly warranted close observation. The FiO_2 was 0.4 throughout the first 23 hours and at 24 hours it was recorded at 0.21. The second patient recorded OISS 2 at 7 time-points, yet no events of saturation, RR and $PaCO_2$ were noted which would suggest possible respiratory depression. The same applied to the third patient who had a single OISS value of 2. This patient had normal saturation and RR, yet an elevated $PaCO_2$ (6.9kPa) was noted.

The fact that very few of the parameters which suggest respiratory depression occurred in the abnormal range verifies that patients can experience the sedatory effect of morphine without suffering respiratory depression. However, if the scale does indicate that a patient is suffering from the sedatory effects of an opioid, it is imperative that monitoring be continuous and that other parameters be carefully evaluated as well. The opinion of the author in this regard is that the patient should be placed on elevated inspired oxygen as a mandatory intervention and

that arterial blood gas (in particular) should be done to place the occurrence of sedation within the correct perspective.

No patient in the IT group recorded any OISS values beyond 1. The conclusion is that there was limited cranial spread of the intrathecal morphine in the doses used. To some extent this is a reassuring observation as, already discussed, patients experienced effective analgesia at the doses used. Therefore, it seems as if the elected dose was not excessive inasmuch as it resulted in significant cranial spread in the cerebrospinal fluid.

4.3.5 Oxygen saturation

The use of oxygen saturation, as a single observation, to detect respiratory depression is a dangerous practice. If an opioid induced respiratory depression does take place, alveolar ventilation is affected, and this could result in hypoxia, hypercarbia and desaturation. In this cascade of events, once desaturation does occur as a late warning sign, the patient would already be in significant danger. This already dire situation could be compounded when oxygen is supplemented as this procedure could mask potential depression with, what may well *appear* to be, an acceptable saturation while, in fact, significant respiratory depression is occurring as per Equation 4.2 (Fu, 2004).

The mean saturation in both groups demonstrated the same trend of a sharp rise until 3 hours post-operatively with a steady decline up to 24 hours post-operatively. This could represent the use of supplemental oxygen on arrival in the neurosurgical ICU for the first few hours (Figure 3.10).

When cross-tabulated, no incidents of RR decreasing below 10 breaths per minute coinciding with saturation of less than 90% occurred. However, in view of the elevated $PaCO_2$ which was commonly noted (19.8% incidence overall), respiratory depression had, in fact, occurred but it was either not severe enough and/or the effect on oxygenation was masked by an elevated inspired oxygen (Fu, 2004).

Of the saturations below 90%, 5 were supplemented with oxygen at the time (FiO_2 0.4). None of these were associated with bradypnea. In all 5 these cases, the A-a gradient ranged between 151 and 182.52 mm Hg suggesting abnormal lung parenchymal function, most likely related to a decreased functional residual capacity secondary to atelectasis post-anaesthetic. It highlights the fact that vigilance is required even in the absence of potential respiratory depressant drugs.

Another aspect worth considering with pulse oximetry is a possible poor contact between the patient's finger and the sensor or inadequate pulsatile flow being registered for a number of reasons. If the contact is poor, a false measurement will be noted. This is a common occurrence in ICUs where nursing staff become desensitised to the alarms and, consequently a decrease in saturation may be wholly disregarded or the response to a monitor alarm may not be as prompt as one would wish.

In this study the author had the advantage of monitoring blood gases. Generally, *saturation*, a parameter which is continuously available, was tracked to indicate whether effective oxygenation was taking place.

4.3.6 $PaCO_2$

A $PaCO_2$ in excess of 6kPa in a normal patient is indicative of some depression of the alveolar ventilation if not associated with an elevated standard bicarbonate and normal pH, in which case it would, from a physiological perspective, be regarded as a normal value. It should be reiterated that type 2 respiratory failure, in a patient with prior normal lungs, is defined in terms of an elevation of the $PaCO_2$ in excess of 8kPa. An elevated $PaCO_2$ must be considered in the context of how it relates to the alveolar ventilation. Equation 4.1 ($PaCO_2 = k \times VCO_2/VA$) indicates that a rise in $PaCO_2$ would directly be as a result of alveolar hypoventilation. The latter can either be as a result of a decreased tidal volume, or slow RR, or a combination of these two. This deduction rests on the assumption that the VCO_2 remains constant (which it usually does) and that only in conditions of hypermetabolism (such as an elevated temperature, thyroid toxicosis or excessive metabolism of fat) would the VCO_2 increase per se. However, notwithstanding these possible explanations, the chemoreceptors in the brain monitor pH and the maintenance of a normal pH is a priority in human physiology. Given that, according to the Henderson Hasselbalch equation (Po, 2001) pH is mainly determined by the $HCO_3/PaCO_2$ ratio, it follows that in cases where the production of carbon dioxide thus increases, the onus rests on the brain to increase the minute ventilation to maintain the $PaCO_2$ within the normal range.

Equation 4.2 summarises the relationship between $PaCO_2$ and alveolar oxygenation and thus arterial oxygenation.

As per Figure 3.11, the graph depicting the mean $PaCO_2$ values between the PCA and intrathecal morphine groups demonstrate a rapid decrease in values from 4 hours post-operatively and onwards. This implies that in both groups, vigilance is required and, where either of the analgesic interventions are used, potential supplemental oxygen should be

administered in the first 4 hours post-operatively. A similar trend of gradual decrease is noted from 10 hours onwards with the mean $PaCO_2$ of both groups recorded below 6kPa. In an attempt to pinpoint a period of risk associated with hypoventilation, statistical analysis indicates a significant decrease in the mean $PaCO_2$ in the IT group from 4 hours up to 24 hours post-operatively for every time-point's data collected (Table 3.18). The mean $PaCO_2$ in the PCA group had a statistically significant decrease from 16 hours up to 24 hours post-operatively. This significance supports the use of supplemental oxygen to counter any deleterious effects of potentially elevated $PaCO_2$ for the first 4 hours post-operatively in the IT group.

Crosstabulation between incidences of bradypnea and elevated $PaCO_2$ (higher than 6kPa) revealed no coinciding events. This is comforting as it shows that an adequate RR was maintained in all instances of an elevated $PaCO_2$. These results have to be considered in the context of respiratory rate being a snapshot in a ventilatory pattern which could, potentially, include episodes of bradypnea (Catley, 1985). It also raises queries as to why the $PaCO_2$ was elevated if the RR was maintained. The only explanations being that the tidal volume decreased and/or the VCO_2 increased and was not matched by the increase in tidal volume (McCrimmon, 2003).

Furthermore, in nearly all ICU settings the diurnal cycle of a patient is respected, with a designated "sleep time" thus being set to ensure maximum rest. In the Neurosurgery ICU at Tygerberg Academic Hospital, this "sleep time" is from 22:00 until 06:00 the following day. During this time every attempt is made to curb noise within the ICU and to minimise activity in an effort to ensure that patients obtain adequate sleep. However, all essential and prescribed monitoring activities continue. It is this prolonged period of sleep that could pose a risk to patients, especially if they are obese (Rose, 1994; Benumof, 2001). Nurse observations are sometimes fragmentary during the sleep period and staff often hesitate to wake a patient to check on his/her level of sedation. Hence, nursing staff often rely on the RR and saturation, with both of these having clear limitations. Not checking the sedation level though may very well constitute the omission of a crucial part of a required set of observations if patients with opiate analgesia are to be successfully protected against the risky effects of the morphine.

Obese patients possess an additional chest weight which could potentially restrict normal respiration and thus result in shallower breathing. If the rate does not accommodate the smaller tidal volume, the potential for heightened $PaCO_2$ increases. This, if occurring in combination with potential respiratory depression, could pose an additional risk to the patient. When incidences of increased $PaCO_2$ (as defined by a $PaCO_2$ higher than 6kPa) were correlated with *awake time* and *sleep time*, results revealed higher incidences of $PaCO_2$ being

in excess of 6kPa during the day time for both groups (PCA 21.1%, intrathecal morphine 32.5%). These values were both higher than the sleep time percentages of 16.4% in the PCA group and 14% in the intrathecal morphine group. This is an unexplained but reassuring finding because the median BMI was in excess of 30kg/m2 in both groups, suggesting that BMI had no significant impact in the study population.

4.3.7 PaO_2

Hypoxia is the biggest danger when using drugs that could interfere with respiratory control mechanisms. Effectively, the elevation of $PaCO_2$ (within limits) is not dangerous in itself and the body normally responds to the elevated levels by increasing respiratory drive in the short term and bicarbonate retention in the longer term (Kregenow, 2002). It is when the respiratory drive is decreased, as the case may be when opioids are administered, that hypoxia could become a significant risk.

As previously explained, Equation 4.2 the abbreviated alveolar gas equation, summarises the risk associated with alveolar hypoventilation in the following way: P_AO_2 (mm Hg) = (PB – PH_2O) FiO_2 - $PaCO_2$/RQ. This implies that once the P_AO_2 has decreased to dangerous levels, considered to be less than 8kPa or 60mm Hg, the $PaCO_2$ increases to severe levels. This interaction is, as already mentioned, subject to the level of inspiratory oxygen which could serve to overcome the effect of hypercarbia on the arterial oxygen tension but may also mask the depression of the alveolar ventilation in the presence of opiates. The attending practitioner must understand this interaction when considering the alveolar gas equation.

There were only 7 incidences of PaO_2 decreasing below 8kPa in both study groups with 3 instances in the PCA group and 4 in the intrathecal morphine group. Of these 7 incidents, 2 occurred in the first post-operative hours and the other 5 occurred at hours 16 (n=3) and 20 (n=2) post-operatively.

- The first instance was in the PCA group at the first hour post-operatively with a PaO_2 of 7.5kPa. This occurred in the high care unit in an awake patient with a RR of 20 breaths per minute with the warning sign being a saturation of 88%. The patient was on room air. It seems as if the low PaO_2 was not related to the opioid as no apparent sedation was present, nor was the $PaCO_2$ markedly elevated (6.1kPa). This patient's FiO_2 was increased to 0.4 which improved the PaO_2 to 16.4kPa and the saturation to 99% with the RR consequently decreasing to 15.

- The second case belonging to the intrathecal group, with a PaO_2 of 7.7kPa, presented at one hour post-operatively. This was a similar presentation where the only parameter suggesting concern was a saturation of 89%. The RR was 15 breaths per minute and the patient was awake and not sedated. The patient was on room air. The $PaCO_2$ showed an increase to 7.2kPa. The patient's FiO_2 was increased to 0.4 resulting in the PaO_2 increasing to 21.3 kPa and the saturation to 99%.

With both incidents occurring in the first post-operative hour, the probability exists that the functional residual capacity of the lungs was decreased due to the recent anaesthesia which is known to reduce the FRC (Hewlett, 1974; Rutherford, 1994; Don 1972). In addition, age and body habitus may also have played a role (Nunn, 2006). The saturation was the only measurable warning sign and appropriate action (increasing the FiO_2) had the appropriate result i.e. improved oxygenation. The fact that both patients were awake would suggest that very little central action of morphine was present.

The remaining 5 incidents of PaO_2 less than 8kPa all occurred at either 16 or 20 hours post-operatively.

- The third patient was in the PCA group and at 16 hours presented a PaO_2 of 7.69kPa. The patient was awake, had a RR of 12 and FiO_2 was 0.4. The saturation was 88.6%. The $PaCO_2$ was normal at 4.8kPa. The following blood gas one hour later revealed a PaO_2 of 20.33kPa and saturation of 99% with FiO_2 of 0.4. Minimal change in the other parameters was noted. The low PaO_2 at the 16 hour mark was not due to alveolar hypoventilation (i.e. a central respiratory drive effect) as the $PaCO_2$ was normal. The A-a gradient was 182.52mm Hg which would suggest a decreased FRC as a cause for the hypoxia.
- Two other patients, one in the PCA and one in the intrathecal group, presented at 20 hours post-operatively with PaO_2 less than 8kPa. In both cases there was no bradypnea and no evidence of sedation. The saturations were 90% in both patients on room air. In both cases the $PaCO_2$ was elevated (6.7 and 6.4kPa). The patient in the intrathecal group did not receive supplementary oxygen. One hour later there still was no bradypnea, no sedation was noted, and saturation remained 90%. The $PaCO_2$ decreased to 6.1kPa. The patient in the PCA group did not receive supplemental oxygen, was not sedated, had no bradypnea and the saturation improved to 94% with the $PaCO_2$ decreasing to 5.6kPa. In both these cases alveolar hypoventilation played a small role in the reduction of the PaO_2, but this can only explain a small portion of the reduced oxygenation. The remainder can probably be ascribed to residual reduction in the FRC which was initiated during anaesthesia and carried over into the post-operative period (Liu, 1995).

Clinical parameters set to prompt responses for ICU nursing staff were: RR, OISS and saturation. Considering that neither of these elements were abnormal, no action was taken. In hindsight, it is important to reflect on the saturation of 90% and the low PaO_2 which is associated with it. Firstly, it relates to the relationship between oxygen tension and saturation via the oxyhaemoglobin dissociation curve which, as already alluded to, may vary depending on the P_{50}. Secondly it will be prudent to rather select a saturation of 92 to 94% as a cut-off criterion in light of the fact that the decrease in saturation will be a relatively late marker of impending problems.

- The sixth patient was in the intrathecal group and whilst on 40% facemask oxygen, a desaturation to 88% was noted. The RR was 14 breaths per minute and the OISS 1. The PaO_2 was 7.3kPa and $PaCO_2$ 6.1kPa. The next saturation improved to 92% and the RR remained unchanged. However, one hour later, the FiO_2 was recorded as 0.21 and the OISS remained 1. The patient was fully awake and cooperative. In this instance the alveolar hypoventilation did play a role in the reduction of the PaO_2 and it could have been addressed with ease if the inspired oxygen had been sufficiently elevated.

It is evident that the clinical parameters set to recognise hypoxia might not be stringent enough. In hindsight, all parameters were close to the thresholds set for alerts. One must appreciate that there is a slow deterioration in these parameters and in an environment where alarms measure absolute values and not trends (such as decreasing RR or saturation over time), a hypo-ventilating patient could present rather suddenly in the absence of prior warnings. In addition, it may be prudent to supply a minimum of 28% oxygen in the post-operative period and the prescription issued by the practitioner must clearly state the remedy if and when the saturation decreases below say 92%. The remedy is simply to increase the inspired oxygen to 40% and continuously observe the patient.

None of the patients in which PaO_2 less than 8kPa was measured had evidence of sedation which is regarded as a constant finding when opioid induced respiratory depression is present (Coetzee, 2013).

4.4 Direct cost

The direct costs involved in the complete management of the patients in both groups *only differed in length of stay in the general wards*. The pre-admission, surgical procedure and ICU stay was standardized and the same for each patient.

The billing practices at each institution differs and thus it is very difficult to provide an accurate figure to the general l saving generated by the earlier mobilization and discharge as was demonstrated in the earlier discharge of 2 days. The data represented here applies to our institution and obviously the 2 days saving will depend on the cost per ward day of any particular institution.

The cost saved per day in the ward, amounts to 43.5 % saving on the ward day cost. However, in the total cost per procedure, the cost saved was 5%. The cost saving favoured the IT group. This however is in context of the heavily subsidized public service pricing model implying that the cost of a general ward stay is much less than for example the surgical implants and this will differ between institutions and both private and public facilities. However, if the total number of procedures are considered, it may well amount to a large cumulative value.

The 2 day saving is not only important as a cost saver. In an environment where bed availability is progressively becoming more problematic, making beds available are of enormous importance. Approximately 60 such procedures are annually performed at Tygerberg Hospital which will translate in 120 available bed days in the neurosurgical service.

This will potentially add improved service delivery and efficacy of the service.

5. Conclusion

The purpose of this study was to evaluate the safety, efficacy and cost-effectiveness of a proposed dose of intrathecal morphine when comparing it to the standard of care practice at a tertiary public service hospital in South Africa. This was tested in first time, single level lumbar spinal fusion surgery in a prospective, double blind, randomized placebo controlled fashion.

The first question was whether the proposed dose of 0.005mg/kg of intrathecal morphine up to a maximum dose of 0.45mg was effective. The intervention was compared to the standard of care which is a patient controlled analgesia device able to deliver 1mg of intravenous morphine every 7 minutes. The primary hypothesis that the proposed dose will result in faster mobilization and shorter hospital stay was proven when the intrathecal morphine (IT) group mobilized a statistically significant 1.93 days faster than the patient controlled analgesia (PCA) group. This was ascribed to the interaction of the directly introduced morphine to the μ-receptors in the spinal cord resulting in segmental analgesia to counter painful stimuli from the surgical site.

The visual analogue scores (VAS) were recorded when the patient was lying still and moving during the post-operative course. The difference between these scores represented the intensity of pain when moving. A statistically significant difference was noted at 24 hours post-operatively in favour of the IT group. This was further emphasized when the effect of mobilization on the VAS demonstrated a statistically significant effect in favour of the IT group implying that despite the active mobilization occurring in the group, the IT morphine group had better pain control at 24 hours. It must be emphasized that the PCA group also had excellent analgesia with mean VAS lying still values always less than 3 for the first 24 hours post-operatively.

The second question of safety of the proposed dose was evaluated by clinically assessing the known side-effects of morphine which included nausea and vomiting, pruritis and respiratory depression. The later was clinically assessed by means of the respiratory rate, the oxygen saturation and by using an opioid induced sedation scale (OISS). These were further supported by 11 arterial blood gas analyses within the first 24 post-operative hours. No statistically significant difference could be demonstrated between the two groups when nausea and vomiting and pruritis was assessed.

The mean respiratory rate in both groups demonstrated an increasing trend after 10 hours post-operatively and this trend was maintained up to 24 hours (increasing implying that the

probable effect of the opiates became less). Furthermore, the mean $PaCO_2$ in the IT group was initially elevated for up to 4 hours after which a statistically significant decrease was noted up to 24 hours. Seven incidents of hypoxia (PaO_2 < 8kPa) were observed in 4 of the IT group and 3 in the PCA group. All seven incidents could be explained by either a low FiO_2 or a decreased functional residual capacity, as demonstrated by the A-a gradient, and some degree of hypoventilation i.e. the effect of the opiate. In none of the patients where the PaO_2 less than 8kPa were recorded, were the patients overtly sedated. These findings highlighted the fact that the conventional lowest acceptable oxygen saturation level of 90% should be higher in order to define patients at risk at an earlier stage. Similarly, supplemental oxygen is advised for all patients, irrespective of the analgesic technique used, for up to 10 hours post-operatively. Monitoring should include no single parameter, but a combination of respiratory rate, saturation and sedation as no single entity warned of the risk of desaturation.

The third question of a direct economic impact was answered when calculating the effect of an earlier mobilization on both the patient and the hospital. Due to the fact that the admission time, surgical procedure and ICU stay were equal for both groups, the saving occurred in the general ward stay which translated to 43.5% in favour of the IT group.

In addition, the saving of two ward days occupancy has profound implications for a burdened public service where these beds can be utilized for the next patient requiring surgical admission and intervention. An estimated 120 bed-days per year are expected to be saved by means of the intrathecal morphine intervention in the Department of Neurosurgery at Tygerberg Academic Hospital.

The study proved that the proposed intrathecal morphine dose of 0.005mg/kg up to a maximum of 0.45mg was safe, effective and cost-effective.

6. References

Agha M, Agha R. The rising prevalence of obesity. International Journal of Surgery Oncology. 2017;2(7):e17.

Araimo Morselli F, Zuccarini F, Caporlingua F, Scarpa I, Imperiale C, Caporlingua A et al. Intrathecal Versus Intravenous Morphine in Minimally Invasive Posterior Lumbar Fusion. Spine. 2017;42(5):281-284.

Ali M, Winter D, Hanly A, O'Hagan C, Keaveny J, Broe P. Prospective, randomized, controlled trial of thoracic epidural or patient-controlled opiate analgesia on perioperative quality of life. British Journal of Anaesthesia. 2010;104(3):292-297.

Andersson G. Epidemiological features of chronic low-back pain. The Lancet. 1999;354(9178):581-585.

Ash L, Modic M, Obuchowski N, Ross J, Brant-Zawadzki M, Grooff P. Effects of Diagnostic Information, Per Se, on Patient Outcomes in Acute Radiculopathy and Low Back Pain. American Journal of Neuroradiology. 2008;29(6):1098-1103.

Average height of men and women worldwide [Internet]. Worlddata.info. 2019 [cited 17 September 2019]. Available from: https://www.worlddata.info/average-bodyheight.php

Baxter A, Scott K, Vos T, Whiteford H. Global prevalence of anxiety disorders: a systematic review and meta-regression. Psychological Medicine. 2012;43(5):897-910.

Benumof J. Obstructive sleep apnea in the adult obese patient: implications for airway management. Journal of Clinical Anesthesia. 2001;13(2):144-156.

Bergmark A. Stability of the lumbar spine. Acta Orthopaedica Scandinavica. 1989;60(sup230):1-54.

Bernard J, Hommeril J, Legendre M, Passuti N, Pinaud M. Spinal or systemic analgesia after extensive spinal surgery: Comparison between intrathecal morphine and intravenous fentanyl plus clonidine. Journal of Clinical Anesthesia. 1993;5(3):231-236.

Bernards C. Understanding the physiology and pharmacology of epidural and intrathecal opioids. Best Practice & Research Clinical Anaesthesiology. 2002;16(4):489-505.

Bernards C, Hill H. Morphine and Alfentanil Permeability Through the Spinal Dura, Arachnoid, and Pia Mater of Dogs and Monkeys. Anesthesiology. 1990;73(6):1214-1219.

Beurskens A, de Vet H, Köke A. Responsiveness of functional status in low back pain: a comparison of different instruments. Pain. 1996;65(1):71-76.

Blacklock B, Rea G, Maxwell R. Intrathecal Morphine during Lumbar Spine Operation for Postoperative Pain Control. Neurosurgery. 1986;18(3):341-344.

Blackman RG, Reymonds J, Shively J. Intrathecal morphine: dosage and efficacy in younger patients for control of postoperative pain following spinal fusion. Orthopedics 1991;14:555—557.

Boezaart A, Eksteen J, Spuy G, Rossouw P, Knipe M. Intrathecal Morphine. Spine. 1999;24(11):1131-1137.

Borgbjerg M, Nielsen K, Franks J. Experimental pain stimulates respiration and attenuates morphine-induced respiratory depression: a controlled study in human volunteers. Pain. 1996;64(1):123-128.

Brennan F, Carr D, Cousins M. Pain Management: A Fundamental Human Right. Anesthesia & Analgesia. 2007;105(1):205-221.

Brooks R. EuroQol: the current state of play. Health Policy. 1996;37(1):53-72.

Bujedo B. A Clinical Approach to Neuraxial Morphine for the Treatment of Postoperative Pain. Pain Research and Treatment. 2012;11:1-11.

Burns J, Hodsman N, McLintock T, Gillies G, Kenny G, McArdle C. The influence of patient characteristics on the requirements for postoperative analgesia. Anaesthesia. 1989;44(1):2-6.

Camporesi E, Nielsen C, Bromage P, Durant P. Ventilatory CO_2 Sensitivity after Intravenous and Epidural Morphine in Volunteers. Anesthesia & Analgesia. 1983;62(7):633-640.

Cashman J, Dolin S. Respiratory and haemodynamic effects of acute postoperative pain management: evidence from published data. British Journal of Anaesthesia. 2004;93(2):212-223.

Catley D, Thornton C, Jordan C, Lehane J, Royston D, Jones J. Pronounced, Episodic Oxygen Desaturation in the Postoperative Period. Anesthesiology. 1985;63(1):20-28.

Charuluxananan S, Somboonviboon W, Kyokong O, Nimcharoendee K. Ondansetron for Treatment of Intrathecal Morphine-Induced Pruritus After Cesarean Delivery. Regional Anesthesia and Pain Medicine. 2000;25(5):535-539.

Clarke E, French B, Bilodeau M, Capasso V, Edwards A, Empoliti J. Pain management knowledge, attitudes and clinical practice: The impact of nurses' characteristics and education. Journal of Pain and Symptom Management. 1996;11(1):18-31.

Coetzee J. Ensuring that patient-controlled anaesthesia is safe. Southern African Journal of Anaesthesia and Analgesia. 2013;19(1):8-10.

Coetzee J. Safety of pain control with morphine: new (and old) aspects of morphine pharmacokinetics and pharmacodynamics. Southern African Journal of Anaesthesia and Analgesia. 2010;16(2):7-15.

Chou R, Qaseem A, Snow V, Casey D, Cross J, Shekelle P et al. Diagnosis and Treatment of Low Back Pain: A Joint Clinical Practice Guideline from the American College of Physicians and the American Pain Society. Annals of Internal Medicine. 2007;147(7):478.

Cruickshank S, Hirschauer N. The alveolar gas equation. Continuing Education in Anaesthesia Critical Care & Pain. 2004;4(1):24-27.

Dagenais S, Caro J, Haldeman S. A systematic review of low back pain cost of illness studies in the United States and internationally. The Spine Journal. 2008;8(1):8-20.

Dahan A, Romberg R, Teppema L, Sarton E, Bijl H, Olofsen E. Simultaneous Measurement and Integrated Analysis of Analgesia and Respiration after an Intravenous Morphine Infusion. Anesthesiology. 2004;101(5):1201-1209.

Dalton J. Nurses' perception of their pain assessment skills, pain management practices, and attitudes towards pain. Oncology Nursing Forum 1989;16:225-231.

Demyttenaere K, Bruffaerts R, Lee S, Posada-Villa J, Kovess V, Angermeyer M et al. Mental disorders among persons with chronic back or neck pain: Results from the world mental health surveys. Pain. 2007;129(3):332-342.

DeSousa K. Intrathecal morphine for postoperative analgesia: Current trends. World Journal of Anesthesiology. 2014;3(3):191-202.

Deyo R, Battie M, Beurskens A, Bombardier C, Croft P, Koes B et al. Outcome Measures for Low Back Pain Research. Spine. 1998;23(18):2003-2013.

Don H, Wahba W, Craig D. Airway Closure, Gas Trapping, and the Functional Residual Capacity during Anesthesia. Anesthesiology. 1972;36(6):533-539.

Dumont A, Verma S, Dumont R, Hurlbert R. Nonsteroidal anti-inflammatory drugs and bone metabolism in spinal fusion surgery. Journal of Pharmacological and Toxicological Methods. 2000;43(1):31-39.

Eismont F, Norton R, Hirsch B. Surgical Management of Lumbar Degenerative Spondylolisthesis. Journal of the American Academy of Orthopaedic Surgeons. 2014;22(4):203-213.

Ekman M, Johnell O, Lidgren L. The economic cost of low back pain in Sweden in 2001. Acta Orthopaedica. 2005;76(2):275-284.

Etches R. Respiratory depression associated with patient-controlled analgesia: a review of eight cases. Canadian Journal of Anaesthesia. 1994;41(2):125-132.

EuroQol - a new facility for the measurement of health-related quality of life. Health Policy. 1990;16(3):199-208.

Fairbank J, Couper J, Davies J, et al. The Oswestry low back pain questionnaire. Physiotherapy. 1980;66:271–273.

Fairbank J, Pynsent P. The Oswestry Disability Index. Spine. 2000;25(22):2940-2953.

Ferrante F, Orav E, Rocco A, Gallo J. A Statistical Model for Pain in Patient-Controlled Analgesia and Conventional Intramuscular Opioid Regimens. Anesthesia & Analgesia. 1988;67(5):457-461.

Ferraz M, Quaresma M, Aquino L, Atra E, Tugwell P, Goldsmith C. Reliability of pain scales in the assessment of literate and illiterate patients with rheumatoid arthritis. The Journal of Rheumatology. 1990;17:1022–1024.

Flisberg P, Rudin A, Linner R, Lundberg C. Pain relief and safety after major surgery A prospective study of epidural and intravenous analgesia in 2696 patients. Acta Anaesthesiologica Scandinavica. 2003;47(4):457-465.

France J, Jorgenson S, Lowe T, Dwyer A. The Use of Intrathecal Morphine for Analgesia After Posterolateral Lumbar Fusion. Spine. 1997;22(19):2272-2277.

Fransen M, Neal B. Non-steroidal anti-inflammatory drugs for preventing heterotopic bone formation after hip arthroplasty. Cochrane Database of Systematic Reviews. 2013; CD001160.

Frymoyer J, Cats-Baril W. An overview of the incidences and costs of low back pain. The Orthopedic Clinics of North America. 1991;22:263-271.

Fu E, Downs J, Schweiger J, Miguel R, Smith R. Supplemental Oxygen Impairs Detection of Hypoventilation by Pulse Oximetry. Chest. 2004;126(5):1552-1558.

Fukuda, K. Chapter 27, Opioids, Miller's Anesthesia, Seventh Edition. Ronald D. Miller. Churchill Livingstone, London, 2009, 769 – 824.

Ganesh A, Maxwell L. Pathophysiology and Management of Opioid-Induced Pruritus. Drugs. 2007;67(16):2323-2333.

Gehling M, Luesebrink T, Kulka P, Tryba M. The effective duration of analgesia after intrathecal morphine in patients without additional opioid analgesia: a randomized double-blind multicentre study on orthopaedic patients. European Journal of Anaesthesiology. 2009;26(8):683-688.

Giovannelli M, Bedforth N, Aitkenhead A. Survey of intrathecal opioid usage in the UK. European Journal of Anaesthesiology. 2008;25(2):118-122.

Glassman S, Rose S, Dimar J, Puno R, Campbell M, Johnson J. The Effect of Postoperative Nonsteroidal Anti-inflammatory Drug Administration on Spinal Fusion. Spine. 1998;23(7):834-838.

Glare P, Walsh T. Clinical Pharmacokinetics of Morphine. Therapeutic Drug Monitoring. 1991;13(1):1-23.

Gould, D et al. Information point: Visual Analogue Scale (VAS). Journal of Clinical Nursing 2001; 10(5): 697-706.

Grass J. Patient-Controlled Analgesia. Anesthesia & Analgesia. 2005;101(Supplement):S44-S61.

Gray P, Janczewski W, Mellen N, McCrimmon D, Feldman J. Normal breathing requires preBötzinger complex neurokinin-1 receptor-expressing neurons. Nature Neuroscience. 2001;4(9):927-930.

Graves D, Foster T, Batenhorst R, Bennett RL, Baumann TJ. Patient controlled analgesia. Annals of Internal Medicine. 1983; 99:360-366.

Green B, Duffull S. What is the best size descriptor to use for pharmacokinetic studies in the obese? British Journal of Clinical Pharmacology. 2004;58(2):119-133.

Greenwald A, Boden S, Goldberg V, Khan Y, Laurencin C, Rosier R. Bone-Graft Substitutes: Facts, Fictions, and Applications. The Journal of Bone and Joint Surgery-American Volume. 2001;83:98-103.

Gronblad M, Hurri H, Kouri JP. Relationships between spinal mobility, physical performance tests, pain intensity and disability assessments in chronic low back pain patients. Scandinavian Journal of Rehabilitation Medicine. 1997; 29:17–24.

Gulhas N, Erdil F, Sagir O, Gedik E, Togal T, Begec Z et al. Lornoxicam and ondansetron for the prevention of intrathecal fentanyl-induced pruritus. Journal of Anesthesia. 2007;21(2):159-163.

Habib A, White W, Eubanks S, Pappas T, Gan T. A Randomized Comparison of a Multimodal Management Strategy Versus Combination Antiemetics for the Prevention of Postoperative Nausea and Vomiting. Anesthesia & Analgesia. 2004;99(1):77-81.

Hägg O, Fritzell P, Nordwall A. The clinical importance of changes in outcome scores after treatment for chronic low back pain. European Spine Journal. 2003;12:12–20.

Hansen J. Postoperative Management in Lumbar Disc Protrusions: I Indications, Method and Results, II Follow-up on a Trained and an Untrained Group of Patients. Acta Orthopaedica Scandinavica. 1964;35(sup71):32-47.

Hawker G, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF. Arthritis Care & Research. 2011;63(S11):S240-S252.

Hewlett A, Hulands G, Nunn J. Heath J. Functional residual capacity during anaesthesia II: Spontaneous respiration. British Journal of Anaesthesia. 1974;46(7):486-494.

Hindle A. Intrathecal opioids in the management of acute postoperative pain. Continuing Education in Anaesthesia Critical Care & Pain. 2008;8(3):81-85.

Hines R, Barash P, Watrous G, O'Connor T. Complications Occurring in the Postanesthesia Care Unit. Anesthesia & Analgesia. 1992;74(4):503-509.

Holm K, Cohen F, Dudas S, Medema P, Allen B. Effect of Personal Pain Experience on Pain Assessment. Image: the Journal of Nursing Scholarship. 1989;21(2):72-75.

Hogan Q, Prost R, Kulier A, Taylor M, Liu S, Mark L. Magnetic Resonance Imaging of Cerebrospinal Fluid Volume and the Influence of Body Habitus and Abdominal Pressure. Anesthesiology. 1996;84(6):1341-1349.

Hunter S, Shaha S, Flint D, Tracy D. Predicting Return To Work. Spine. 1998;23(21):2319-2328.

Huskisson E C. Visual Analogue Scales. Pain measurement and assessment. 1983; 33-40.

Jansson K, Németh G, Granath F, Jönsson B, Blomqvist P. Health-related quality of life (EQ-5D) before and one year after surgery for lumbar spinal stenosis. The Journal of Bone and Joint Surgery British volume. 2009;91-B(2):210-216.

Jensen M, Karoly P, Braver S. The measurement of clinical pain intensity: a comparison of six methods. Pain. 1986;27(1):117-126.

Jiang CJ, Chi-Ching C et al. Mini-dose intrathecal morphine for post-cesarean section analgesia. Acta Anaesthesiologica Sinica. 1991; 29:683-689.

Johnson L, Magnani B, Chan V, Ferrante M. Modifiers of patient-controlled analgesia efficacy. I. Locus of control. Pain. 1989;39(1):17-22.

Joly V, Richebe P, Guignard B, Fletcher D, Maurette P, Sessler D et al. Remifentanil-induced Postoperative Hyperalgesia and Its Prevention with Small-dose Ketamine. Anesthesiology. 2005;103(1):147-155.

Joshi G, Duffy L, Chehade J, Wesevich J, Gajraj N, Johnson E. Effects of Prophylactic Nalmefene on the Incidence of Morphine-related Side Effects in Patients Receiving Intravenous Patient-controlled Analgesia. Anesthesiology. 1999;90(4):1007-1011.

Katz, Jeffrey N. Lumbar Disc Disorders and Low-Back Pain: Socioeconomic Factors and Consequences. The Journal of Bone and Joint Surgery-American Volume. 2006; 88:21-24.

Karcioglu O, Topacoglu H, Dikme O, Dikme O. A systematic review of the pain scales in adults: Which to use? The American Journal of Emergency Medicine. 2018;36(4):707-714.

Keats AS, Telford J, Kurosu Y. "Potentiation" of meperidine by promethazine. Anesthesiology. 1961;22(1):34-41.

Kerchner G, Zhuo M. Presynaptic Suppression of Dorsal Horn Inhibitory Transmission by μ-Opioid Receptors. Journal of Neurophysiology. 2002;88(1):520-522.

Kjellby-Wendt G, Styf J. Early Active Training After Lumbar Discectomy. Spine. 1998;23(21):2345-2351.

Ko S, Goldstein D, VanDenKerkhof E. Definitions of “respiratory depression” with intrathecal morphine postoperative analgesia: a review of the literature. Canadian Journal of Anesthesia/Journal canadien d'anesthésie. 2003;50(7):679-688.

Korhonen A, Valanne J, Jokela R, Ravaska P, Korttila K. Ondansetron does not prevent pruritus induced by low-dose intrathecal fentanyl. Acta Anaesthesiologica Scandinavica. 2003;47(10):1292-1297.

Kranz JC jr. Pain—man's ruthless enemy. West Virginia Medical Journal. 1979; 75:60-61.

Kregenow D, Swenson E. The lung and carbon dioxide: implications for permissive and therapeutic hypercapnia. European Respiratory Journal. 2002;20(1):6-11.

Krieger J, Thrlot J, Mangin P, Kurtz D. Breathing During Sieep in Normal Young and Elderly Subjects: Hypopneas, Apneas, and Correlated Factors. Sleep. 1983;6(2):108-120.

Kroin J, Ali A, York M, Penn R. The Distribution of Medication along the Spinal Canal after Chronic Intrathecal Administration. Neurosurgery. 1993;33(2):226-230.

Kumar K, Singh S. Neuraxial opioid-induced pruritus: An update. Journal of Anaesthesiology Clinical Pharmacology. 2013;29(3):303-307.

Lamotte C, Pert C, Snyder S. Opiate receptor binding in primate spinal cord: distribution and changes after dorsal root section. Brain Research. 1976;112(2):407-412.

Law C, Visser E. Unconsciousness and severe respiratory depression following intrathecal morphine analgesia for lumbar spinal surgery. Acute Pain. 2007;9(3):163-167.

Lee M, Silverman S. A Comprehensive Review of Opioid-Induced Hyperalgesia. Pain Physician, 2011; 14:145-161.

Li Q, Zhang Z, Cai Z. High-Dose Ketorolac Affects Adult Spinal Fusion. Spine. 2011;36(7):E461-E468.

Linares C, Declèves X, Oppert J, Basdevant A, Clement K, Bardin C et al. Pharmacology of Morphine in Obese Patients. Clinical Pharmacokinetics. 2009;48(10):635-651.

Liu S, Carpenter R, Neal J. Epidural Anesthesia and Analgesia. Anesthesiology. 1995;82(6):1474-1506.

Loeschke H, Sweel A, Kough R, Lambertson C. The effect of morphine and of meperidine (dolantin, Demerol) upon respiratory response of normal men to low concentrations of inspired carbon dioxide. Journal of Pharmacology and Experimental Therapeutics. 1953;108:376-383.

Macintyre P. Safety and efficacy of patient-controlled analgesia. British Journal of Anaesthesia. 2001;87(1):36-46.

Manniche C, Skall H, Braendholt L, Christensen B, Christophersen L, Ellegaard B et al. Clinical Trial of Postoperative Dynamic Back Exercises After First Lumbar Discectomy. Spine. 1993;18(1):92-97.

Matsumae M, Kikinis R, Mórocz I, Lorenzo A, Sándor T, Albert M et al. Age-related changes in intracranial compartment volumes in normal adults assessed by magnetic resonance imaging. Journal of Neurosurgery. 1996;84(6):982-991.

McCrimmon D, Alheid G. On the opiate trail of respiratory depression. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology. 2003;285(6):R1274-R1275.

McGuire L, Heffner K, Glaser R, Needleman B, Malarkey W, Dickinson S et al. Pain and wound healing in surgical patients. Annals of Behavioral Medicine. 2006;31(2):165-172.

McQuay H, Sullivan A, Smallman K, Dickenson A. Intrathecal opioids, potency and lipophilicity. Pain. 1989;36(1):111-115.

Menendez M, Neuhaus V, Bot A, Ring D, Cha T. Psychiatric Disorders and Major Spine Surgery. Spine. 2014;39(2):E111-E122.

Minto C, Schnider T, Shafer S. Pharmacokinetics and Pharmacodynamics of Remifentanil. Anesthesiology. 1997;86(1):24-33.

Montandon G, Qin W, Liu H, Ren J, Greer J, Horner R. PreBotzinger Complex Neurokinin-1 Receptor-Expressing Neurons Mediate Opioid-Induced Respiratory Depression. Journal of Neuroscience. 2011;31(4):1292-1301.

Mueller B, Carreon L, Glassman S. Comparison of the EuroQOL-5D With the Oswestry Disability Index, Back and Leg Pain Scores in Patients With Degenerative Lumbar Spine Pathology. Spine. 2013;38(9):757-761.

Nabeshima S, Reese T, Landis D, Brightman M. Junctions in the meninges and marginal glia. The Journal of Comparative Neurology. 1975;164(2):127-169.

Nissen, I., Jensen, K. A., Ohrstrom, J. K. Indomethacin in the management of postoperative pain. British Journal of Anaesthesia. 1992;69(3):304-306.

Nunn, JF In: Nunn's Applied Respiratory Physiology, Ed A Lumb. 6th Ed, Elsevier Philadelphia, USA, 2006, 25-36.

O'Neill P, Knickenberg C, Bogahalanda S, Booth A. Use of intrathecal morphine for postoperative pain relief following lumbar spine surgery. Journal of Neurosurgery. 1985;63(3):413-416.

O'Sullivan P, Grahamslaw K, Kendell M, Lapenskie S, Möller N, Richards K. The Effect of Different Standing and Sitting Postures on Trunk Muscle Activity in a Pain-Free Population. Spine. 2002;27(11):1238-1244.

Owen H, Plummer J, Armstrong I, Mather L, Cousins M. Variables of patient-controlled analgesia 1. bolus size. Anaesthesia. 1989;44(1):7-10.

Palmer C, Emerson S, Volgoropolous D, Alves D. Dose-Response Relationship of Intrathecal Morphine for Postcesarean Analgesia. Anesthesiology. 1999;90(2):437-444.

Parker RK, Holtmann B, White PF. Patient-controlled analgesia. Does a concurrent opioid infusion improve pain management after surgery? JAMA. 1991;266(14):1947.

Pasero C, McCaffery M. Safe use of a continuous infusion with IV PCA. Journal of PeriAnesthesia Nursing. 2004;19(1):42-45.

Pert C, Snyder S. Opiate Receptor: Demonstration in Nervous Tissue. Science. 1973;179(4077):1011-1014.

Po H, Senozan N. The Henderson-Hasselbalch Equation: Its History and Limitations. Journal of Chemical Education. 2001;78(11):1499.

Price D, McGrath P, Rafii A, Buckingham B. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. Pain. 1983;17(1):45-56.

Raffaeli W, Marconi G, Fanelli G, Taddei S, Borghi G, Casati A. Opioid-related side-effects after intrathecal morphine. European Journal of Anaesthesiology. 2006;23(7):605-610.

Rathmell J, Lair T, Nauman B. The Role of Intrathecal Drugs in the Treatment of Acute Pain. Anesthesia & Analgesia. 2005;101(Supplement):S30-S43.

Reuben S, Ablett D, Kaye R. High dose nonsteroidal anti-inflammatory drugs compromise spinal fusion. Canadian Journal of Anesthesia/Journal canadien d'anesthésie. 2005;52(5):506-512.

Reuben S, Connelly N, Steinberg R. Ketorolac as an adjunct to patient-controlled morphine in postoperative spine surgery patients. Regional Anesthesia and Pain Medicine. 1997;22(4):343-346.

Reynolds C, Cuijpers P, Patel V, Cohen A, Dias A, Chowdhary N et al. Early Intervention to Reduce the Global Health and Economic Burden of Major Depression in Older Adults. Annual Review of Public Health. 2012;33(1):123-135.

Riew K, Long J, Rhee J, Lewis S, Kuklo T, Kim Y et al. Time-dependant inhibitory effects of indomethacin on spinal fusion. The Journal of Bone and Joint Surgery-American Volume. 2003;85(4):632-634.

Roland M, Fairbank J. The Roland–Morris Disability Questionnaire and the Oswestry Disability Questionnaire. Spine. 2000;25(24):3115-3124.

Roland M, Morris R. A Study of the Natural History of Low-Back Pain. Spine. 1983;8(2):145-150.

Rose D, Cohen M, Wigglesworth D, DeBoer D. Critical Respiratory Events in the Postanesthesia Care Unit. Anesthesiology. 1994;81(2):410-418.

Ross D, Drasner K, Weinstein P, Flaherty J, Barbaro N. Use of Intrathecally Administered Morphine in the Treatment of Postoperative Pain after Lumbar Spinal Surgery: A Prospective, Double-Blind, Placebo-Controlled Study. Neurosurgery. 1991;28(5):700-704.

Ross J, Robertson J, Frederickson R, Petrie J, Obuchowski N, Modic M et al. Association Between Peridural Scar and Recurrent Radicular Pain After Lumbar Discectomy: Magnetic Resonance Evaluation. Neurosurgery. 1996;38(4):855-863.

Rutherford J, Logan M, Drummond G. Changes in end-expiratory lung volume on induction of anaesthesia with thiopentone or propofol. British Journal of Anaesthesia. 1994;73(5):579-582.

Sam W, MacKey S, Lötsch J, Drover D. Morphine and its metabolites after patient-controlled analgesia: considerations for respiratory depression. Journal of Clinical Anesthesia. 2011;23(2):102-106.

Scott J, Huskisson E. Graphic representation of pain. Pain. 1976;2(2):175-184.

Scrimshaw S, Maher C. Randomized Controlled Trial of Neural Mobilization After Spinal Surgery. Spine. 2001;26(24):2647-2652.

Sidebotham D, Dijkhuizen M, Schug S. The safety and utilization of patient-controlled analgesia. Journal of Pain and Symptom Management. 1997;14(4):202-209.

Sirvanci M, Bhatia M, Ganiyusufoglu K, Duran C, Tezer M, Ozturk C et al. Degenerative lumbar spinal stenosis: correlation with Oswestry Disability Index and MR Imaging. European Spine Journal. 2008;17(5):679-685.

Sivaganesan A, Chotai S, White-Dzuro G, McGirt M, Devin C. The effect of NSAIDs on spinal fusion: a cross-disciplinary review of biochemical, animal, and human studies. European Spine Journal. 2017;26(11):2719-2728.

Sjöström S, Tamsen A, Persson M, Hartvig P. Pharmacokinetics of Intrathecal Morphine and Meperidine in Humans. Anesthesiology. 1987;67(6):889-895.

Slover J, Abdu W, Hanscom B, Weinstein J. The Impact of Comorbidities on the Change in Short-Form 36 and Oswestry Scores Following Lumbar Spine Surgery. Spine. 2006;31(17):1974-1980.

Smith H, Laufer A. Opioid induced nausea and vomiting. European Journal of Pharmacology. 2014;722:67-78.

Solberg T, Olsen J, Ingebrigtsen T, Hofoss D, Nygaard Ø. Health-related quality of life assessment by the EuroQol-5D can provide cost-utility data in the field of low-back surgery. European Spine Journal. 2005;14(10):1000-1007.

Somerville MA. Inadequate treatment of pain in hospitalized patients [Letter], New England Journal of Medicine. 1982;307(1):55.

Stratford P, Binkley J. Measurement Properties of the RM-18. Spine. 1997;22(20):2416-2421.

Stratford P, Binkley J, Riddle D, Guyatt G. Sensitivity to Change of the Roland-Morris Back Pain Questionnaire: Part 1. Physical Therapy. 1998;78(11):1186-1196.

Stratford P, Binkley J, Solomon P, Gill C, Finch E. Assessing Change Over Time in Patients with Low Back Pain. Physical Therapy. 1994;74(6):528-533.

Sultan P, Gutierrez M, Carvalho B. Neuraxial Morphine and Respiratory Depression. Drugs. 2011;71(14):1807-1819.

Talbot N, Dorrington K. Mechanics and Control of Ventilation. Surgery (Oxford). 2003;21(3):iii-vi.

Techanivate A, Kiatgungwanglia P, Yingsakmongkol W. Spinal morphine for post-operative analgesia after lumbar laminectomy with fusion. Journal of the Medical Association of Thailand. 2003;86:262-269.

Thaller J, Walker M, Kline A, Anderson D. The Effect of Nonsteroidal Anti-Inflammatory Agents on Spinal Fusion. Orthopedics. 2005; 28:299-303.

Ulijaszek S. Obesity: Preventing and Managing the Global Epidemic. Report of a WHO Consultation. WHO Technical Report Series 894. Pp. 252. (World Health Organization, Geneva, 2000.) SFr 56.00, ISBN 92-4-120894-5, paperback. Journal of Biosocial Science. 2003;35(4):624-625.

Ummenhofer W, Arends R, Shen D, Bernards C. Comparative Spinal Distribution and Clearance Kinetics of Intrathecally Administered Morphine, Fentanyl, Alfentanil, and Sufentanil. Anesthesiology. 2000;92(3):739-753.

Urban M, Jules-Elysee K, Urquhart B, Cammisa F, Boachie-Adjei O. Reduction in Postoperative Pain After Spinal Fusion With Instrumentation Using Intrathecal Morphine. Spine. 2002;27(5):535-537.

Vane J, Botting R. Anti-inflammatory drugs and their mechanism of action. Inflammation Research. 1998;47(0):78-87.

Wang JK. Analgesic effect of intrathecally administered morphine. Regional Anaesthesia. 1977; 2:3–8.

Wang J, Nauss L, Thomas J. Pain Relief by Intrathecally Applied Morphine in Man. Anesthesiology. 1979;50(2):149-151.

Wassenaar M, van Rijn R, van Tulder M, Verhagen A, van der Windt D, Koes B et al. Magnetic resonance imaging for diagnosing lumbar spinal pathology in adult patients with low back pain or sciatica: a diagnostic systematic review. European Spine Journal. 2011;21(2):220-227.

Watters W, Bono C, Gilbert T, Kreiner D, Mazanec D, Shaffer W et al. An evidence-based clinical guideline for the diagnosis and treatment of degenerative lumbar spondylolisthesis. The Spine Journal. 2009;9(7):609-614.

Weinstein J, Lurie J, Tosteson T, Hanscom B, Tosteson A, Blood E et al. Surgical versus Nonsurgical Treatment for Lumbar Degenerative Spondylolisthesis. New England Journal of Medicine. 2007;356(22):2257-2270.

Wewers M, Lowe N. A critical review of visual analogue scales in the measurement of clinical phenomena. Research in Nursing & Health. 1990;13(4):227-236.

White P. Mishaps with Patient-controlled Analgesia. Anesthesiology. 1987;66(1):81-82.

Williams A. The Role of the EuroQol Instrument in QALY Calculations, Discussion Paper 130, Centre for Health Economics, York, 1995.

Wulfsohn N, Joshi C. Thiopentone dosage based on lean body mass British Journal of Anaesthesia. 1969;41(6):516-521.

Yaksh T, Rudy T. Analgesia mediated by a direct spinal action of narcotics. Science. 1976;192(4246):1357-1358.

Ziegeler S, Fritsch E, Bauer C, Mencke T, Müller B, Soltesz S et al. Therapeutic Effect of Intrathecal Morphine After Posterior Lumbar Interbody Fusion Surgery. Spine. 2008;33(22):2379-2386.

World Health Report, 2013.