PAIN MANAGEMENT PROTOCOL FOR OOCYTE RETRIEVAL IN LOW-RESOURCE SETTING ASSISTED REPRODUCTIVE TECHNOLOGY: PATIENT SURVEY

By

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DECLARATION

I, Ronia Hendrina Gerardo hereby declare that the work contained in this thesis is my own original work (except where acknowledgements indicate otherwise) and that neither part or the whole work of it has been submitted for another degree in this or any other university.

Signature:

Date:

DEDICATION

I dedicate this dissertation to my family, my bible study family in Cape Town and Dr N. Amagulu.

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I would like to extend my great gratitude and appreciation to the following people:

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ABSTRACT

Introduction:

Assisted reproductive technology (ART) involves a series of procedures, the cost of which may prevent many from achieving reproduction desires. To cut on the cost, oocyte retrieval has evolved into an affordable day procedure that still requires analgesia. The goal of this study is to evaluate the level of acceptance and tolerance of the Tygerberg Fertility pain management protocol (a combination of intramuscular pethidine and paracervical block) during oocyte retrieval.

Method:

This was a cross-sectional study/patient survey. A questionnaire was compiled in an attempt to evaluate participants' perspectives regarding the pain management using a Likert scale. Participants completed the questionnaire after the procedure. Participants who did not return the questionnaire were excluded.

Study setting: Tygerberg Reproductive Medicine Unit

Results:

The study recruited 100 women and 80 completed and returned the questionnaires. A total of 73.8% participants tolerated the pain with the current pain management method. Only 6.3% could not tolerate the pain. The majority of participants (71.3%) found the protocol acceptable and over 90% of the participants would recommend the method to others as well as accept it in future.

Conclusions:

The study showed that a combination of intramuscular pethidine and paracervical block is an acceptable and tolerable method of pain management during ultrasound-guided oocyte retrieval in a low-resource setting environment.

Keywords: pain management, oocyte retrieval, acceptance, and tolerance

ACRONYMS

ART	Assisted Reproductive Technology
BMI	Body Mass Index
FSH	Follicle Stimulating Hormone
GIFT	Gamete Intrafallopian Transfer
ICSI	Intracytoplasmic Sperm Injection
IVF	In-Vitro Fertilization
RMU	Reproductive Medicine Unit
TBH	Tygerberg Hospital
TIVA	Total Intravenous anaesthesia
TUGOR	Transvaginal Ultrasound-Guided Oocyte Retrieval

CHAPTER 1

ORIENTATION OF THE STUDY

Introduction

The number of individuals struggling with natural conception is rising, with a prevalence of about 15% world-wide. Meanwhile, advancing technology in the field of assisted reproduction has helped many individuals world-wide to win the battle with infertility. In the beginning, oocytes were obtained by laparotomy during In-vitro Fertilisation (IVF) process(1). Subsequently, laparoscopy became the technique of choice for oocyte aspiration during IVF(2). However, general anaesthesia was routinely utilised/necessary and local anaesthesia performed only in selected cases. Both laparotomy and laparoscopy are relatively expensive and invasive procedures that expose healthy women to the risks of surgery(1). Even in those cases where laparoscopy was performed using local anaesthesia, it was still expensive, requiring expensive instruments and laparoscopically trained health professionals to carry out the procedure. The practice has since evolved to a stage whereby oocytes retrieval can be performed safely and efficiently via transvaginal ultrasound-guided approach(1,3). This method does not require an operating theatre and could be performed following various methods of analgesia for pain management(1,4–6). One approach is not deemed superior to the other and the method chosen is guided by available resources and patient acceptance and comfort. The most used method of pain relief during transvaginal ultrasound-guided oocyte retrieval (TUGOR) is light sedation and local anaesthesia(4,7–9).

Literature review

IVF refers to advanced techniques that aid fertilization in a couple diagnosed with infertility such as in women who have irreversible fallopian tube damage or cervical and/or uterine problems. It is one of the most performed treatments for infertility. The procedure involves a complex series of steps, such as: controlled ovarian hyperstimulation, oocyte retrieval, fertilization, culture of the embryo and uterine transfer. The first successful birth following IVF was achieved in a spontaneous ovulatory cycle; a single oocyte was retrieved, and a single embryo was transferred into the uterine cavity(1). Success rates using spontaneous ovulatory cycles were low and most investigators adopted the use of ovarian stimulation strategies to achieve synchronous development of multiple follicles(10). Ovaries are stimulated by several ovulation-inducing agents, which include Clomiphene with or without human menopausal gonadotropins and/or human chorionic gonadotropin, pure follicle-stimulating hormone (FSH), human gonadotropin-releasing hormones and their analogues(11). One or more oocytes are aspirated from the ovarian follicles. The retrieved oocytes are then fertilized in the laboratory (in-vitro), after which, one or more embryo(s) are transferred into the uterine cavity(12). The transfer of more than one embryo at a time increased the chance that at least one would implant and result in a successful live birth.

The ability to retrieve oocyte serves a very important step in IVF(9). In the early stages of in-vitro fertilization, oocytes were retrieved by laparotomy(13). Due to high morbidity and the evolvement of laparoscopic surgery the method of oocyte retrieval by laparotomy was replaced by laparoscopy. The technique was developed during the collaboration between Robert Edwards, the scientist with the knowledge of how to fertilize and culture human oocytes in vitro, and Patrick Steptoe, a clinician who master a technique that could be used to harvest oocyte in women with tubal infertility(1,14). The role of laparoscopic adhesiolysis in IVF

program has expanded with the realization that the laparoscope can be used to optimize ovarian access(15). Laparoscopy subsequently became the method of choice for oocyte retrieval during the first 10 years of clinical IVF era(1). This method is still occasionally used in conjunction with Gamete Intra-Fallopian Tube Transfer (GIFT), in women whose ovaries are not in the pelvis(16), or if the patient has no vaginal canal(16).

For more than 20 years, oocytes are retrieved almost exclusively using the TUGOR method(1). This method does not only help to avoid exposing women to major surgery and general anaesthesia, but it also helps to minimize the cost of oocyte retrieval. Although no large prospective-controlled, randomized trial comparing laparoscopic-guided and transvaginal-guided oocyte retrieval has ever been performed, the latter has become the method of choice(1). Most ultrasound machines with a vaginal transducer can be used during TUGOR. A frequency of 5-7MHz gives a sufficient penetration depth and enough resolution for accurate visualization of the lower pelvis(1). It is essential to choose a fairly long (40-50 cm length) transducer, which makes it easy to handle during the procedure(1).

David K Gardner et al, explains the procedure in detail, in section II, chapters 7-8 in the "Textbook of Assisted Reproductive Techniques. Laboratory and clinical perspectives". 2012, fourth edition. The woman must meet criteria for oocyte retrieval depending on the ovarian stimulation protocol provided at the IVF Centre. It is important to take note that transvaginal oocyte retrieval is the most painful component of IVF treatment(1,17). During TUGOR women do experience discomfort and pain which is caused by the aspirating needle puncturing the vaginal skin and ovarian capsule and during manipulation within the ovary(18). In addition, one needs to consider the aspirating needle design and its effect on pain during TUGOR(19). The sharpness of the needle is the most important factor, the sharper the needle the less the pain is encountered if the procedure is performed under some form of analgesia(1). A

randomized controlled study comparing pain experience between a standard needle size (outer diameter of 1.4mm and inner diameter of 1 mm for the whole length) and a newly designed thin tip needle (outer diameter of 0.9 mm and inner diameter 0.6 mm for the last 50 mm from the tip; and the remaining length with outer diameter of 1.4 mm and inner diameter of 1 mm) showed that oocyte retrieval with a thin tip needle resulted in significantly less overall pain and less vaginal bleeding(19).

Despite the technical aspect in contribution to the pain experienced during TUGOR, the psychological status of the client should also be addressed. Infertility can be a very stressful experience to many if not all couples(20). Women have different coping strategies for pain and their tolerance of pain might also be influenced by socio-cultural factors. High-anxiety clients have shown to require more sedation than low-anxiety clients(21,22). Clients that are well informed and educated preoperatively tend to experience less anxiety and pain perception, and has shown to be more satisfied, and have a positive effect on post-operative outcome(17).

TUGOR is regarded as a relatively invasive short procedure. Like many short surgical procedures such as gastroscopy, colonoscopy, superficial biopsies, ophthalmological and dental short procedures etc., it is performed under light sedation. According to The American Society of Anaesthesiologists, there are four levels of sedation: minimal, moderate, deep sedation, and general anaesthesia(23). During moderate or conscious sedation, the client can maintain unassisted airway with an altered level of consciousness and less pain(23). TUGOR is a relatively invasive short procedure lasting about 20-30 minutes but can still be painful without adequate analgesia or anaesthesia. Therefore, it requires a short acting form of anaesthesia with minimal side effects(8). Different IVF centres use various anaesthetic modalities such as: monitored anaesthesia care, conscious sedation, general anaesthesia, local injections as paracervical block, epidural block, total intravenous anaesthesia (TIVA), patient-

controlled anaesthesia and acupuncture(18,24). Pain management protocols include local anaesthesia, opioids, benzodiazepines and electro acupuncture(6,9,25,26). The most used drugs for anaesthesia during oocyte retrieval in recent years are opioids such as: pethidine, morphine, fentanyl and remifentanil(27). The conclusion was drawn from the systematic review by Kwan I et al, that the use of more than one method of analgesia and pain relief is more effective than a single modality(6). Kwan et al reviewed 21 randomized controlled trials including 2974 women undergoing oocyte retrieval, where they compared five different categories of conscious sedation and analgesia: 1) conscious sedation and analgesia versus placebo; 2) conscious sedation and analgesia versus other active interventions such as general and acupuncture anaesthesia; 3) conscious sedation and analgesia plus paracervical block versus other active interventions such as general, spinal and acupuncture anaesthesia; 4) patient-controlled conscious sedation and analgesia versus physician-administered conscious sedation and analgesia; and 5) conscious sedation and analgesia with different agents or dosage(6). No particular method of analgesia has proved to be superior in providing pain relief, during and after oocyte retrieval(6). In low-income settings, the combination of conscious sedation and paracervical block can be an option that offer adequate pain relief and still be cost effective.(28) Pain is subjective and unique for everyone. Intensity and characteristics of pain during follicle aspiration are influenced by the type of aspiration needle, puncture of the vaginal wall and the ovarian capsule, number of follicles and position of and access to ovaries(17). These are the factors to be considered when choosing an appropriate analgesia for individual clients. The method of anaesthesia the practitioner chooses must be both effective and safe; anaesthesia should be easy to administer and monitor, short acting and readily reversible; it should have less side effects while providing adequate analgesia(25). The need for adequate pain relief is not only for the comfort of the woman but also necessary for immobilization and to avoid the danger of piercing the surrounding vessels.(25) A recent survey by Tobler et al.

inquired about the use of anaesthesia during oocyte retrieval in programs of the Society of Assisted Reproductive Technology, 95% of the respondents indicated the use of conscious sedation(29). The use of midazolam, pethidine and paracervical block has shown to be an acceptable and safe method of pain relief(8,28,30).

Although TUGOR is now the gold standard of oocyte pickup, careful attention should be given to the possible complications that may arise during or following the procedure. The complications cannot be compared to that of oocyte retrieval by laparotomy or laparoscopy, where the procedure is much more invasive and time consuming. TUGOR is less invasive, shorter in duration and technically less challenging. This also makes it more affordable than laparotomy or laparoscopy. Despite all the benefits that comes along with TUGOR, the aspiration needle may injure pelvic organs and vessels, leading to more serious complications(1,31). Most encountered complications include bleeding, injury to bladder or rectum and pelvic infections(1). The use of prophylactic antibiotics during TUGOR is debatable and it is currently not a standard practice(31). However, prophylactic antibiotics may be considered in the presence of risk factors. The rate of injury to intraperitoneal and retroperitoneal vessels have been reported to be between 0%-1.3%(1). Hemodynamic and physical changes during or after the procedure should be evaluated closely to exclude any vessel injury. The effect of various anaesthetic drugs used during TUGOR on oocyte or pregnancy remains a topic of debate and still needs to be investigated further. A retrospective study in Turkey by Urfalioglu A. et al, showed no negative effect with the use of Propofol, Ketamine, Remifentanyl and Sevoflurane during general anaesthesia(32). In an endeavour towards making assisted reproductive technologies (ART) accessible and simplified(5), the aim of our study is to evaluate the acceptance and tolerance levels of pain management protocol during TUGOR at Tygerberg Academic Hospital, Reproductive Medicine Unit (RMU).

Aim of the study

The aim of this study was to evaluate the level of tolerance and acceptance of pain management protocol (using intramuscular pethidine and paracervical block) for oocyte retrieval by patients undergoing assisted reproductive technology (ART) treatment.

Objectives of the study

The primary objectives of this study was to evaluate how patients tolerated the light sedation protocol and to evaluate how patients accepted the pain management protocol for oocyte retrieval using a Likert scale. The secondary objectives of the study was to determine how many participants would be willing to accept the current pain management protocol and how many would recommend the protocol to other women who would require the same procedure.

Definition of protocol

The pain management protocol in this study included the use of Pethidine 50-100mg intramuscularly (IM) with an appropriate anti-emetic approximately 15-30 minutes before the procedure. In addition, a paracervical block was performed by infiltrating 20 ml of 1% Lignocaine in the posterior fornix of the vagina following a good vaginal lavage.

Rationale of the study

Laboratory costs of ART (IVF/ICSI) are extremely high and anaesthesia together with the anaesthetist fees contributes significantly. In low-resource setting this approach is often unavailable (limited number of anaesthetists) and unaffordable. Therefore, the study illustrated a less expensive protocol that can possibly be adopted in many ART units.

CHAPTER 2

RESEARCH METHODOLOGY

Study design and population

This was a prospective, cross-sectional study. A survey was conducted at the Reproductive Medicine Unit (RMU) of Tygerberg Hospital (TBH) in the Western Cape province of South Africa. The study considered all women who were referred to TBH for oocyte retrieval for IVF or ICSI (intracytoplasmic sperm injection). All women who were eligible for and underwent oocyte retrieval who were willing to participate were included in the study. There were no specific exclusion criteria unless the woman declined to participate in the study.

Sample size

The sample size was estimated using 95% confidence intervals around a proportion for tolerability and acceptance of light sedation. We aimed at recruiting sample size of more than 100 women between November 2019 and December 2020, in order to achieve a precision of between 13.9% and 9.8% (half –width of the 95% confidence interval). Due to the COVID-19 virus pandemic, the study was interrupted, and we were unable to recruit more than 100 women. The sampling period was extended beyond the first wave of corona virus pandemic. All women who met inclusion criteria who presented between November 2019 and April 2021 were included in the study, provided they were willing to participate and signed the consent form. This was a random sample of the population who underwent oocyte retrieval, thus sampling bias was minimal.

Recruitment of patients

Women who were scheduled for oocyte retrieval were approached prior to the procedure. The study was explained to them and information leaflets (Appendix A) with contact details of the principal researcher and the Research Ethics Committee approval (Appendix B) were given to each participant. Participants were assured that participating in the study was voluntary and declining to participate would not compromise their level of care. The participants signed an informed consent prior to oocyte retrieval. Provision of the interpreter was considered for any participants who did not understand the information provided. However, none of the participants required an interpreter. Study number was allocated to each participant. Participants were informed to complete the questionnaire (Appendix C) following oocyte retrieval and to return it to the research investigator.

Data collection and statistical analysis

Participants provided general information as part of the questionnaire. Data was obtained from patients using a structured questionnaire presented as appendix C. Data was collected using the patients' folder number only and no names or identifiable information was used. Data from the questionnaire was captured into a Microsoft excel spreadsheet for analysis. A biostatistician from the Division of Epidemiology and Biostatistics (Ms T. Esterhuizen) was consulted for data analysis. Analysis of the data was done using the latest version of SPSS.

Continuous data was analysed descriptively using means and standard deviations for normally distributed, and medians and interquartile ranges for non-normally distributed data. The 95% confidence interval was calculated. Nominal data was presented using absolute and relative frequencies with 95% confidence intervals being used for binomial proportions.

Ethical consideration

Ethics approval (Appendix A) was obtained from the Health Research Ethics Committee of the Faculty of Medicine and Health Sciences, Stellenbosch University, prior to commencement of the study.

Confidentiality

All participants were assigned an individual study number that was not linked to their names or hospital numbers to protect their identity and to maintain confidentiality. Identity of patients was only known to the principal investigator who kept the details of the information in a secure office and was the only one with access to the information on the computer that was password protected.

CHAPTER 3

RESULTS

Recruitment and Demographic characteristics

The study recruited a total of 100 women between November 2019 and April 2021, but 80 participants completed and returned the questionnaires. Patient demographics and characteristics are listed in Table 1. The mean age of the study participants was 34.7 (24-42). The mean body mass index (BMI) was 28.6 with a range of 19-40 (Table 1).

Majority of women (78.8%) had no previous births (Table 1). Sixty-five (65)% of study participants had primary infertility. Almost a third (28, 7%) of the patients had one previous miscarriage and approximately 9% had at least one ectopic pregnancy (Table 1). Over 60% of the participants were undergoing IVF for the first time and the remaining 38% were on their second or more treatment cycles of IVF (Table 1). More than half (56.3%) of the participants had previous gynaecological surgery (mostly laparoscopic surgery for salpingectomy, ectopic pregnancy, myomectomies and/or excision of endometriosis). Most of the participants were healthy with no known medical co-morbidities, and only 13.8% had underlying co-morbidities including diabetes mellitus and/or hypertension. Only 2.5% of the participants reported any mental conditions and they were bipolar mood disorder and depression. The duration of infertility varied widely from 6-240 months.

Primary objectives

The study showed that most of the patients (61.3%) tolerated the pain during the procedure with the current method, and 12.5% strongly tolerated the pain during the procedure (Fig 1).

Only 6.3% of the patients could not tolerate the pain. One (1) participant was unable to give an answer on how she tolerated the pain (1.2%). The pain management protocol was acceptable to 51.3% of the participants, and strongly acceptable to 20% of the participants (Fig 2). The pain management protocol was strongly unacceptable to 1.3% of the participants.

Secondary objectives

Majority of the participants (65%) would easily accept the method, and 1.25% will strongly decline the current protocol (Fig 3). Most of the participants (54.4%) would recommend the current protocol, but 3,8% were unsure and 2.5% will not recommend the current protocol (Fig 4). Most patients received IVF (57%) treatment (Table 2). Overall, 95% of the study participants felt the information provided with regards to pain management during TUGOR was sufficient (Table 2). Despite more than 96% of the participants reporting that the procedure was explained, approximately 60% of the participants reported to be anxious before the procedure (Table 2). Forty percent (40%) of the participants reported discomfort during the procedure, 48% reported pain ranging from mild to moderate, and only 6% reported severe pain (Table 2). Overall, more than 60% of the participants reported to tolerate the pain during the procedure and 90% of the participants felt they were taken care of. It is also important to note that 90% of the participants were not aware of other alternative methods of pain management (Table 2). Over 95% of the participants reported the current pain management protocol to be safe (Table 2).

CHAPTER 4

DISCUSSION

The findings of this study showed that 73.8% and 71.3% of the participants tolerated and accepted light sedation protocol for oocyte retrieval respectively (Fig 1&2). The findings are similar to the report from a recent survey by Tobler et al., that evaluated the use of anaesthesia during oocyte retrieval in programs of the Society of Assisted Reproductive Technology, and 95% of the respondents indicated the use of conscious sedation as the preferred method(29). The use of midazolam, pethidine and paracervical block has shown to be an acceptable and safe method of pain relief(8,28,30).

At Tygerberg Academic Hospital, Reproductive Medicine Unit, a unit in a low-resource setting, the pain management protocol offered during TUGOR include, the use of Pethidine 50-100mg intramuscularly (IM) with an appropriate anti-emetic approximately 15-30 minutes before the procedure. In addition, a paracervical block was performed by infiltrating 20ml of 1% Lignocaine in the posterior fornix of the vagina following a good vaginal lavage. As demonstrated by the study findings, majority of the patients accepted the current method. In a systematic review by Kwan I et al, they also showed that the use of combination method of sedation and pain relief was more effective(6,7,33).

Over 90% (Fig 3) of the study participants were willing to have the same pain management protocol should there be a need to repeat IVF/ICSI cycle in the future. Unfortunately, a large proportion of the study participants (90%) were not aware of other alternative methods of pain management during TUGOR (Table 2). Different alternative methods include: monitored anaesthesia care, conscious sedation, general anaesthesia, local injections as paracervical block, epidural block, total intravenous anaesthesia (TIVA), patient-controlled anaesthesia and

acupuncture(24,34). In many private centres, the method of choice is general anaesthesia with the use of laryngeal mask, and this method requires anaesthetic machine and the expertise of an anaesthetist. In a study by Lucie Rolland and colleagues, they found that general anaesthesia was associated with less pain and was the most satisfactory method of anaesthesia for oocyte retrieval(6). In a resource restricted settings as it may be in the majority of low- and middle-income countries (LMIC), this method will not always be feasible from the costs and human resource point of view(5). Therefore, the method defined in this study could be a viable option, with high patient's tolerance and acceptability. In the very small number of participants (2, 5%) who found the method unacceptable, and would not recommend it to anyone, it may be advisable to discuss alternative methods and possibly refer to centres with adequate resources(35).

Infertility can be a very stressful experience to many if not all couples. Women have different coping strategies for pain and their tolerance of pain might also be influenced by socio-cultural factors(17,22). In this study, 95% of the participants felt the information provided with regards to the procedure and pain management during TUGOR was sufficient (Table 2). However, approximately 60% of the participants reported to be anxious before the procedure. High-anxiety clients have shown to require more sedation than low-anxiety clients(17,36). It is therefore important to assess the client's level of anxiety before the day of the procedure and during the procedure because by simply addressing their fears and concerns can go a long way with pain perception during any minor procedure. In the unit, client communication and reassurance are one of our key strategies when preparing for oocyte retrieval procedure. Clients that are well informed and educated pre-operatively tend to experience less anxiety and pain perception, and has shown to be more satisfied, and have a positive effect on post-operative outcome.

Forty percent (40%) of the study participants reported discomfort during the procedure, 48% reported pain ranging from mild to moderate, and only 6% reported severe pain (Table 2). These findings were similar to the report by Yoon et al., in their study they found that approximately 7% of women found the oocyte retrieval procedure to be very or extremely painful(22). Similar results were also reported by Hojgaard and colleagues where they found that 6% of women reported unacceptable pain levels.

That being said, more than 60% of our study participants reported to tolerate the pain during the procedure and 90% of the participants felt they were taken care of. This is also another key strategy, to show compassionate for these women during the procedure as that will reduce the need for medical intervention and make their experience less traumatic(17).

Over 95% of the participants reported the current pain management protocol to be safe (Table 2), which is comforting. Although 78% of the study participants felt that the side effects were manageable, 20% did not appreciate nausea and vomiting, while 38% were unhappy with the feeling of dizziness. Again, a good preparation to inform women on what to expect and to implement interventions to minimize the degree of the side effects should form part of the service to improve women care during oocyte retrieval. At the end of the day, the method of anaesthesia the practitioner or the facility chooses must be both effective and safe; anaesthesia should be easy to administer and monitor, short acting and readily reversible; it should have less side effects while providing adequate analgesia.

Strengths of the study

This is the first prospective study assessing client's acceptance and tolerance of the pain management protocol at our unit and in the region. Client's opinion with regards to any treatment is very important and the authors are of the opinion that this study has provided some insight on pain management options that can be simple, feasible for most settings and not very costly.

Weaknesses of the study

The timing of the survey was affected by the COVID-19 pandemic because we believe that it contributed to the anxiety level of our participants. Some clients had to be rescheduled and some postponed the procedure due to financial implication as the result of the pandemic. All these factors influenced the client's response to the questionnaire and affected the number of participants, hence the sample size. All participants received the same method of pain control and results could not be compared to any other method of analgesia. The study did not distinguish between women who were more likely and those who were less likely to be anxious

CHAPTER 5

CONCLUSION AND RECOMMENDATIONS

Conclusion

In conclusion, the study showed that the level of pain experienced during the procedure was acceptable to clients. The study has also showed that the majority of clients were able to tolerate the procedure relatively well. This form of pain control precludes the need for sophisticated and expensive equipment required for general anaesthesia. The pain management protocol in this study is also reported to be safe with manageable side effects. Additionally, the study showed that despite adequate information about the procedure and the type of pain management regimen some clients will still be anxious on the day of the procedure. It is thus important to continue to reassure the clients until the procedure is completed. Furthermore, showing compassion and the sense that one cares will possibly reduce the pain perception and make the experience less traumatic.

Recommendations

It will be of interest to compare various methods of pain management during oocyte retrieval, looking at effectiveness, safety, and costs.

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APPENDIX

Appendix *A*

PARTICIPANT INFORMATION LEAFLET AND CONSENT FORM

TITLE OF THE RESEARCH PROJECT: PAIN MANAGEMENT PROTOCOL FOR OOCYTE RETRIEVAL IN LOW-RESOURCE SETTING ASSISTED REPRODUCTIVE TECHNOLOGY

REFERENCE NUMBER:

PRINCIPAL INVESTIGATOR: Ronia Gerardo, Dr

ADDRESS: Tygerberg Hospital

CONTACT NUMBER: 0712453433/ 021 938 4432

You are being invited to take part in a research project. Please take some time to read the information presented here, which will explain the details of this project. Please ask the study staff or doctor any questions about any part of this project that you do not fully understand. It is very important that you are fully satisfied that you clearly understand what this research entails and how you could be involved. Also, your participation is **entirely voluntary** and you are free to decline to participate. If you say no, this will not affect you nor your treatment negatively in any way. You are also free to withdraw from the study at any point, even if you do agree to take part.

This study has been approved by the **Health Research Ethics Committee at Stellenbosch University** and will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

What is this research study all about?

- ***Where will the study be conducted; are there other sites; total number of participants to be recruited at your site and altogether:***

The study will be conducted only at Tygerberg Hospital Reproduction Medicine Unit; the number of participants will be determined by the number of clients receiving treatment within a period of 6 months

- ***Explain in participant friendly language what your project aims to do and why you are doing it?***

  The project aim to find out whether the light sedation protocol at TBH RMU during egg pick up is efficient and acceptable to the patients who undergo IVF.

- ***Explain all procedures.***

  The In vitro fertilization procedure involves a complex series of steps, such as: controlled ovarian hyperstimulation, oocyte retrieval, fertilization, culture of the embryo and uterine transfer. The ability to retrieve oocyte serves a very important step in IVF.

  Oocytes are retrieved almost exclusively by the use of Transvaginal Ultrasound-Guided Oocyte Retrieval (TUGOR) method. TUGOR is regarded as a relatively invasive short procedure that requires some form of analgesia. The woman is put in a lithotomy position (laying on her back with the legs up). Analgesia is administered prior to oocyte pickup. The vagina is cleaned. A vaginal ultrasound probe and the aspirating needle is introduced into the vagina and follicles are aspirated under ultrasound vision.

- ***Explain any randomization process that may occur.***

  None

- ***Explain the use of any medication, if applicable.***

  Light sedation protocol during TUGOR include the use of Pethidine 50-100mg intramuscularly (IM) with an appropriate anti emetic approximately 15-30mins before the procedure. In addition, 20 ml of 1% Lignocaine is infiltrated in the posterior fornix of the vaginal following a good vaginal lavage for paracervical block.

Why have you been invited to participate?

- *Because you are undergoing IVF procedure and you are entitled to receive light sedation during egg pickup. We would like to hear your view regarding pain management protocol at TBH RMU.*

What will your responsibilities be?

- *Read the information leaflet. If you are willing to participate in the study then you should give consent. Complete the questionnaire and return it to the investigator.*

Will you benefit from taking part in this research?

- *We would like to know if you are satisfied with the sedation protocol in use. Should there be a need to adjust the protocol, this will be beneficial to patients in future and to you, should you require another IVF procedure in future. We will try to improve the service and consider other options of pain management.*

Are there in risks involved in your taking part in this research?

- *No*

If you do not agree to take part, what alternatives do you have?

- *The decline to take part in this study will not affect your treatment in any negative way.*
- *At the moment egg pick is offered under light sedation and no alternatives offered at this unit.*

Who will have access to your medical records?

- All patients will be assigned an individual study number that will not be linked to their names or hospital numbers in order to protect their identity and to maintain confidentiality. Identity of patients will only be known to the principal investigator who will keep the details of the information in a secure office and will only access the information for verification purposes. The computer used for coding and storing patients' information will be password protected.

What will happen in the unlikely event of some form injury occurring as a direct result of your taking part in this research study?

- *Please take note that this is not a trial of medication study. The medications used for pain management are regarded as standard practice. Any complications encountered during the study will be related to the IVF procedure in general. The doctor in charge will attend to any complications that may arise during the procedure and manage accordingly.*

Will you be paid to take part in this study and are there any costs involved?

No you will not be paid to take part in the study. There will be no costs involved for you, if you do take part.

Is there anything else that you should know or do?

- You should inform your family practitioner or usual doctor that you are taking part in a research study: NOT applicable
- You should also inform your medical insurance company that you are participating in a research study: NOT applicable
- You can contact Dr Ronia Gerardo at tel 0712453433 if you have any further queries or encounter any problems.
- You can contact the Health Research Ethics Committee at 021-938 9207 if you have any concerns or complaints that have not been adequately addressed by your study doctor.
- You will receive a copy of this information and consent form for your own records.

Declaration by participant

By signing below, I …… agree to take part in a research study entitled *"Light sedation protocol for oocyte retrieval I low resource setting assisted reproductive therapy"*.

I declare that:

- I have read or had read to me this information and consent form and it is written in a language with which I am fluent and comfortable.
- I have had a chance to ask questions and all my questions have been adequately answered.
- I understand that taking part in this study is **voluntary** and I have not been pressurised to take part.
- I may choose to leave the study at any time and will not be penalised or prejudiced in any way.
- I may be asked to leave the study before it has finished, if the study doctor or researcher feels it is in my best interests, or if I do not follow the study plan, as agreed to.

Signed at (*place*) ..... on (*date*) …….. 2019.

…… ……

Signature of participant **Signature of witness**

Declaration by investigator

I ……. declare that:

- I explained the information in this document to the participants
- I encouraged him/her to ask questions and took adequate time to answer them.
- I am satisfied that he/she adequately understands all aspects of the research, as discussed above
- I did/did not use a interpreter. (*If a interpreter is used then the interpreter must sign the declaration below.*

Signed at…… Tygerberg on……..2019

…… ……

Signature of investigator **Signature of witness**

Declaration by interpreter

I *(name)* …… declare that:

- I assisted the investigator (*name*) …… to explain the information in this document to (*name of participant*) …….. using the language medium of Afrikaans/Xhosa.

- We encouraged him/her to ask questions and took adequate time to answer them.
- I conveyed a factually correct version of what was related to me.
- I am satisfied that the participant fully understands the content of this informed consent document and has had all his/her question satisfactorily answered.

Signed at (*place*) ..... on (*date*) ……..……..

…… ……

Signature of interpreter **Signature of witness**

Appendix B

UNIVERSITEIT
STELLENBOSCH
UNIVERSITY

Approval Notice

New Application

05/11/2019

Project ID :10827

HREC Reference No: S19/07/133

Project Title: Pain management protocol for oocyte retrieval

Dear Dr Ronia Gerardo

The **New Application** received on 28/10/2019 16:02 was reviewed by members of **Health Research Ethics Committee** via **expedited** review procedures on 05/11/2019 and was approved.

Please note the following information about your approved research protocol:

Protocol Approval Date: 05 November 2019

Protocol Expiry Date: 04 November 2020

Please remember to use your Project ID 10827 and Ethics Reference Number S19/07/133 on any documents or correspondence with the HREC concerning your research protocol.

Please note that the HREC has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

After Ethical Review

Translation of the informed consent document(s) to the language(s) applicable to your study participants should now be submitted to the HREC.

Please note you can submit your progress report through the online ethics application process, available at: Links Application Form Direct Link and the application should be submitted to the HREC before the year has expired. Please see *Forms and Instructions* on our HREC website (www.sun.ac.za/healthresearchethics) for guidance on how to submit a progress report.

The HREC will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit.

Provincial and City of Cape Town Approval

Please note that for research at a primary or secondary healthcare facility, permission must still be obtained from the relevant authorities (Western Cape Department of Health and/or City Health) to conduct the research as stated in the protocol. Please consult the Western Cape Government website for access to the online Health Research Approval Process, see: https://www.westerncape.gov.za/general-publication/health-research-approval-process. Research that will be conducted at any tertiary academic institution requires approval from the relevant hospital manager. Ethics approval is required BEFORE approval can be obtained from these health authorities.

We wish you the best as you conduct your research.

For standard HREC forms and instructions, please visit: Forms and Instructions on our HREC website https://applyethics.sun.ac.za/ProjectView/Index/10827

If you have any questions or need further assistance, please contact the HREC office at 021 938 9677.

Yours sincerely,

Ms Elvira Rohland
Health Research Ethics Committee 1 (HREC1)

National Health Research Ethics Council (NHREC) Registration Number:

REC-130408-012 (HREC1)•REC-230208-010 (HREC2)

Federal Wide Assurance Number: 00001372
Office of Human Research Protections (OHRP) Institutional Review Board (IRB) Number:

Appendix C

PATIENT QUESTIONNAIRE

This questionnaire is designed to evaluate your treatment experience with regard to pain management during transvaginal ultrasound guided oocyte retrieval (TUGOR) during in vitro fertilization treatment.

Date of treatment……

Study number……..

Hospital number……..

Please complete the survey below and return it to the investigator.
Your feedback is valuable and allows TBH RMU to continue to improve while delivering the best possible care.
Please choose the most suitable answer to the following questions.

FOR EASY DATA CAPTURING AND MONITORING, STICK TO LIKERT SCALE FORMAT: 1-5
1 = LESS SATISFIED OR MOST UNACCEPTABLE OR LESS TOLERATED
5 = MOST SATISFIED OR MOST ACCEPTABLE OR MOST/STRONGLY TOLERATED
DEFINE THEM FOR EVERY QUESTION IF YOU HAVE TO.

A) General information

1. Age……
2. Number of pregnancies…… Number of children……
3. Weight (Kg)……Height (m)
4. Ethnicity……..
5. Marital status……
6. Level of education: Matric □ Higher education□ Other (Specify)
7. Duration of infertility (in months)……..
8. Previous cycles of IVF: ICSI□ IVF□ None
9. Number of previous egg pick-up attempts ……
10. Previous operations…….

    ……..
11. Chronic disease…….

    ……..
12. Mental condition……

B) Treatment

1. IVF☐ ICSI☐
2. Were eggs picked up during your procedure: Yes☐ No☐

1. **How adequate was the information (pain management and egg pick-up) provided to you before the procedure?**

1 =very insufficient	2=only sufficient to understand but needed more	3=not sure	4=sufficient enough to understand	5=very sufficient

Comment:

2. **How well was the procedure explained to you and your partner?**

1=very insufficient	2=only sufficient to understand but needed more	3=not sure	4=sufficient	5=excellent

Comment:

3. **How much pain did you experience during the procedure?**

1=none	2=discomfort but not pain	3=mild pain	4=moderate pain	5=severe

Comment:

4. **When did you experience the most pain?**

1=just before the egg pick-up	2=during the egg pick-up	3=after the egg pick-up

Comment:

5. **What is your general tolerance to any painful procedure?**

1=very well	2=well enough	3=not sure	4=poor	5=very poor

Comment:

6. **How would you rate your level of anxiety in general?**

1=very high	2=high	3=fairly acceptable	4=low	5=very low

Comment:

7. **When do you think you were most anxious during your egg pick-up procedure?**

1=before the procedure	2=during the procedure	3=after the procedure

Comment:

8. What is your level of acceptance of pain management during egg pick-up?

1=strongly unacceptable	2=unacceptable	3=fairly acceptable	4=acceptable	5=strongly acceptable

Comment:

9. Please rate your level of tolerance for pain during the procedure.

1=completely intolerable	2=intolerable	3=fairly tolerable	4=tolerable	5=strongly tolerable

Comment:

10. Please rate the level of medication side effects.

1=completely unmanageable	2=unmanageable	3=fairly manageable	4=manageable	5=strongly manageable

Comment:

11. Could you specify the common side effect of pain management that was intolerable?

1=nausea and vomiting	2=dizziness	3=loss of memory	4=inability to recognize oneself & surrounding	5=none

Comment:

12. Could you rate the doctor performing the procedure's level of sympathy and understanding towards your reaction to pain?

1=did not care	2=minimal understanding/caring	3=moderate understanding/care	4=caring	5=very caring

Comment:

13. Please rate the laboratory staff assisting with the procedure's level of sympathy and understanding towards your reaction to pain?

1=did not care	2=minimal understanding/care	3=moderate understanding/care	4=caring	5=very caring

Comment:

14. If you must undergo IVF (assisted reproduction) and egg pick-up procedure again in future, would you accept the same pain management method?

1=strongly decline	2=unacceptable	3=fairly accept	4=accept	5=easily

Comment:

15. Would you recommend the current pain management method during egg pick-up to anyone else?

1=strongly not	2=not at all	3=unsure	4=yes	5=strong yes

Comment:

16. Are you aware of any other forms of pain management during egg pick-up for assisted reproduction treatment?

Yes ☐ No☐ if yes, which one?.....

17. **If you answered yes, to question 16, how strongly will you recommend other methods over pain management offered in this facility)**?

1=strongly not recommend	2=not recommend	3=unsure	4=recommend	5=strongly recommend

Comment:

18. In your overall opinion, do you think pain management offered in this facility) during egg pick-up is safe?

1=strongly unsafe	2=unsafe	3= unsure	4=safe	5=very safe

Comment:

19. **Overall, do you think pain management offered in this facility for egg pick-up is an acceptable form of pain management during IVF treatment?**

1=strongly unacceptable	2=unacceptable	3=unsure	4=acceptable	5=strongly acceptable

Comment:

Thank you for your time.

Table 1: Demographic characteristics

Characteristics	**Distribution**
Age(years)	34.7(24-42)*
Body mass index(kg/m^2)	28.6(19-40)*
Ethnicity	**n(%)**
Black	14(18.2)
Coloured	41(53.2)
White	22(28.6)
Marital status	**n(%)**
Single	5(6.3)
Married	74(93.7)
Level of education	**n(%)**
Matric	25(32.5)
Higher education	44(57.1)
Other	8(10.4)
Previous births	**n(%)**
0	63(78.8)
1	11(13.8)
2	5(6.3)
3	1(1.3)
Previous miscarriages	**n(%)**
0	52(65)
1	23(28.7)
2	4(5.0)
6	1(1.3)
Previous ectopic pregnancies	**n(%)**
0	68(85.0)
1	7(8.8)
2	5(6.3)
Previous cycles of IVF	**n(%)**
No	48(62.3)
Yes	29(37.7)
Previous operations	**n(%)**
No	35(43.8)
Yes	45(56.3)
Chronic diseases	**n(%)**
No	69(86.3)
Yes	11(13.8)
Mental conditions	**n(%)**
No	78(97.5)
Yes	2(2.5)
Number of previous pregnancies	1(0-7)
Duration of infertility (months)	60(6-240)
Previous egg-pick up attempts	0(0-7)

*mean(range)

Table 2: Additional findings (variables)

Findings	Distribution
Treatment received	**n(%)**
IVF	57(71.3)
ICSI	22(27.5)
Missing	1
Treatment information provided	**n(%)**
Very insufficient	3(3.8)
Only sufficient to understand but needed more	1(1.3)
Sufficient enough	42(53.2)
Very sufficient	33(41.8)
Procedure explanation	**n(%)**
Very insufficient	2(2.5)
Only sufficient to understand but needed more	1(1.3)
Sufficient	33(41.8)
Excellent	43(54.4)
Doctor's level of sympathy and understanding n(%)	
Caring	4(10)
Very caring	72(90)
Laboratory staff level of sympathy and understanding n(%)	
Moderate understanding	1(1.3)
Caring	6(7.5)
Very caring	73(91.3)
Pain experienced during the procedure	**n(%)**
None	3(3.8)
Discomfort but not pain	32(40.0)
Mild pain	18(22.5)
Moderate pain	21(26.3)
Severe pain	5(6.3)
Missing response	1(1.3)
Timing of pain	
Just before the procedure	8(10.0)
During the procedure	40(50.0)
After the egg pick-up	21(26.3)
Missing response	11(13.8)
General pain tolerance	**n(%)**
Very well	12(15.0)
Well enough	39(48.8)
Not sure	11(13.8)
Poor	10(12.5)
Very poor	2(2.5)
Missing response	6(7.5)

Anxiety level	**n(%)**
Very high	4(5.0)
High	13(16.3)
Fairly acceptable	37(46.3)
Low	17(21.3)
Very low	4(5.0)
Missing response	5(6.3)
Timing of anxiety	**n(%)**
Before the procedure	48(60.0)
During the procedure	18(22.5)
After the procedure	9(11.3)
Missing response	5(6.3)
Management of side effects	**n(%)**
Completely unmanageable	1(1.3)
Unmanageable	2(2.5)
Fairly manageable	14(17.5)
Manageable	37(46.3)
Strongly manageable	26(32.)
Intolerable common side effects	**n(%)**
Nausea, vomiting	16(20.0)
Dizziness	31(38.8)
None	31(38.8)
Missing	2(2.5)
Awareness of alternative pain management protocol	**n(%)**
No	72(90)
Yes	7(8.8)
Missing response	1(1.3)
Safety of protocol	**n(%)**
Unsafe	1(1.3)
Unsure	1(1.3)
Safe	38(47.5)
Very safe	38(47.5)
Missing response	2(2.5)

Figure 1: Pain tolerance

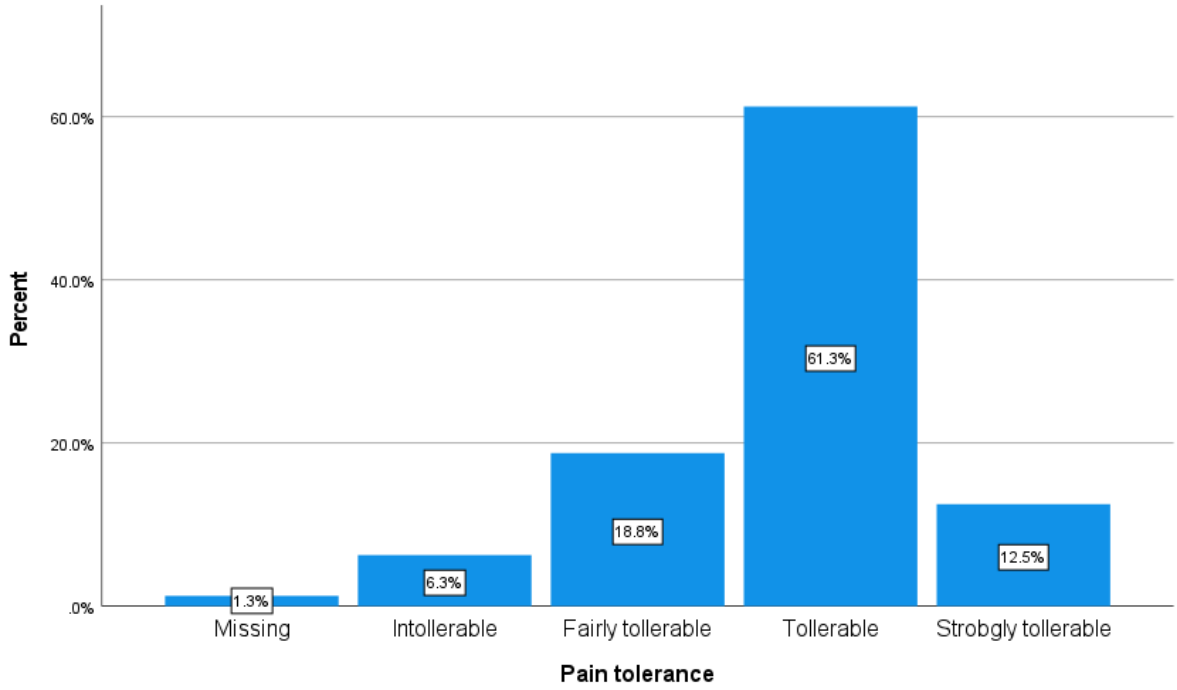

Figure 2: Pain management acceptance

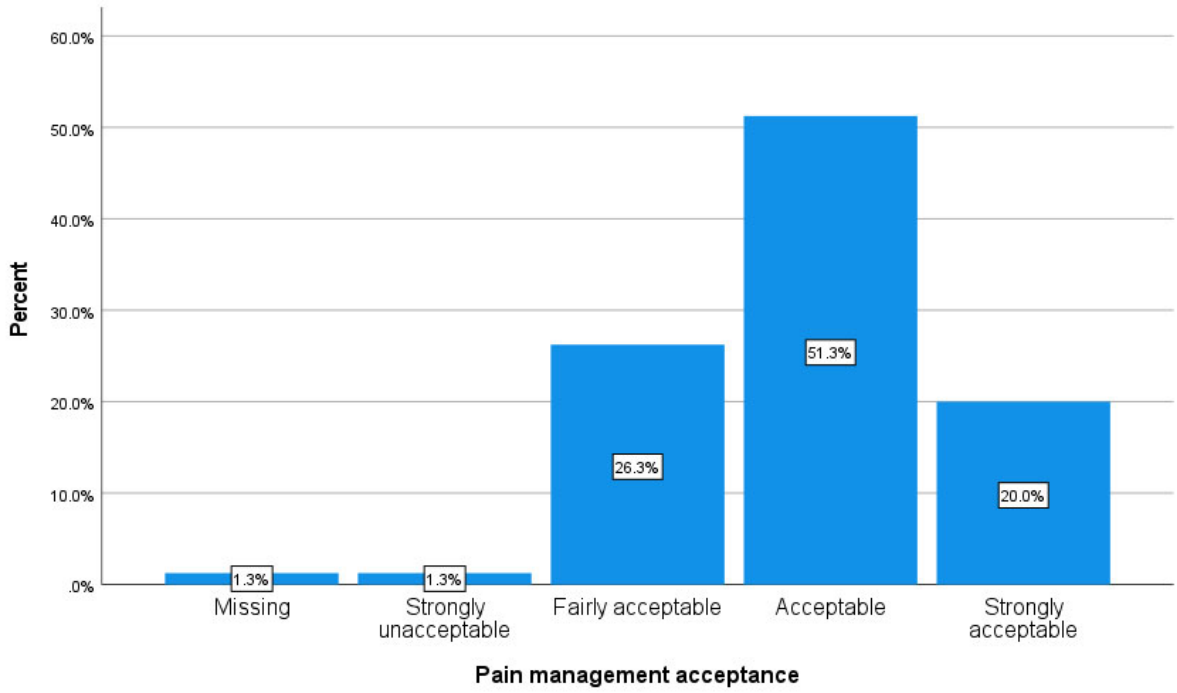

Figure 3: Pain management protocol repeat in the future.

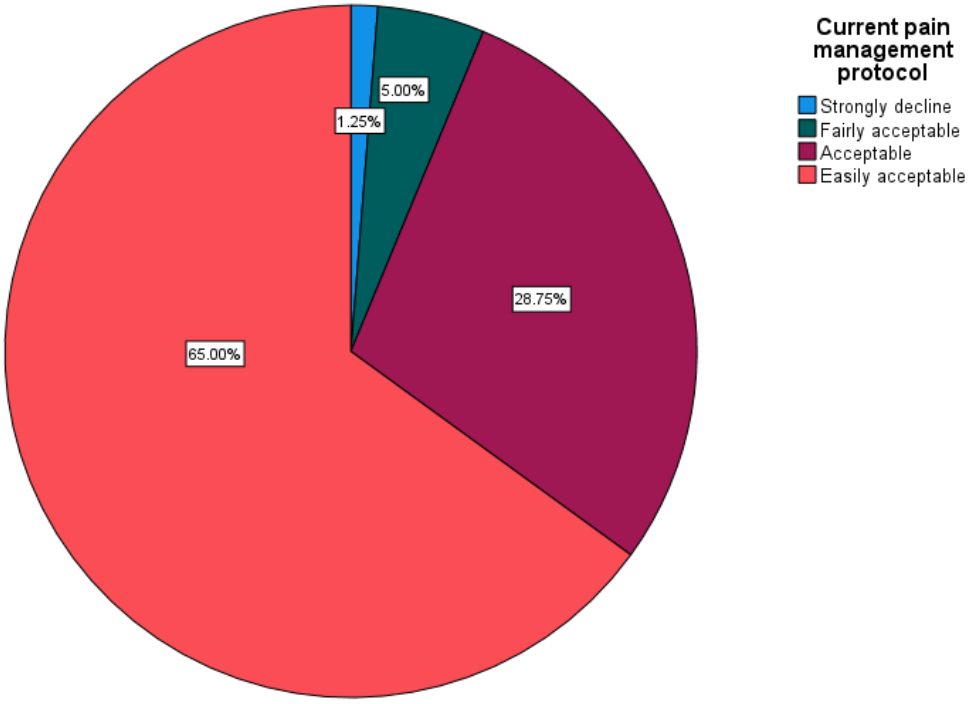

Figure 4: pain management protocol – recommendation