Methylprednisolone and the adult respiratory distress syndrome

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Summary

Total hip replacement was carried out on 22 patients under general anaesthesia. Of these, 10 were pre-treated with methylprednisolone (30 mg/kg); 1 of these developed the adult respiratory distress syndrome (ARDS) and had high levels of thromboxane B_2 (TXB_2) 5 minutes after fixation of the femoral prosthesis and at the end of the operation. The other 12 patients served as controls; 5 of them developed ARDS and had statistically significant higher TXB_2 levels than the other 7 control patients who remained well. All patients who did not develop ARDS had low TXB_2 levels. TXB_2 and ß-thromboglobulin levels followed the same trend and there was good correlation ($r=0,6806$; $P<0,01$) at the end of the operation in the control group patients who developed ARDS. There was no statistical difference in 6-keto-$PGF_{1\alpha}$ levels between the patients who developed ARDS and those in the control group who remained well. Steroids reduce arachidonic acid metabolism by inhibiting the release of substrate for cyclo-oxygenase and lipoxygenase activity. Patients prone to ARDS thus benefit from methylprednisolone administration.

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Ashbaugh and Petty[1] first reported the beneficial effects of steroid treatment in 2 patients with clinical fat embolism, subsequently referred to as adult respiratory distress syndrome (ARDS). Since then many authors[2-4] have had similar results with steroid treatment of fat embolic syndrome (FES). Alho *et al.*[2] stated that the beneficial effects of methylprednisolone on manifestations of FES may result from its ability to protect cell membranes against noxious agents. Lefer[5] extended this theory by presenting a unifying concept of cellular and lysosomal membrane stabilization.

Of these theories, Peltier's[6] mechanical-chemical fat theory was the first attempt at presenting possible aetiological factors for ARDS and it is still accepted by some authors[4] although questioned by others.[7,8] More recently the investigations of Hammerschmidt *et al.*[9] demonstrated that complement activation by trauma causes polymorphonuclear neutrophil (PMN) aggregation, and they suggested that this is an aetiological factor in ARDS. In animal experiments Borg *et al.*[10] demonstrated that infusion of complement-activated plasma resulted in PMN aggregation and an increase in total pulmonary vascular resistance. Pretreatment with indomethacin inhibited the vascular response but did not prevent PMN aggregation, suggesting that prostaglandin synthesis is involved in the pulmonary vascular response of ARDS.

In view of the beneficial effects of methylprednisolone and its influence on some of the aetiological factors in ARDS, we postulated that this steroid could be of value in the prevention of ARDS in patients undergoing total hip replacement (THR). We report on 22 patients who underwent THR under general anaesthesia. Plasma values of the two prostaglandins thromboxane A_2 (TXA_2) and prostacyclin (PGI_2) as well as the incidence of ARDS were examined in these patients. A definite relationship between TXA_2 levels and ARDS was found.

Patients and methods

Twenty-two patients with no history of major systemic illness and normal pre-operative ECG and lung function test results who were to undergo THR for osteo-arthritis under general anaesthesia were studied. No antiprostaglandins or steroids were administered during the 8 days preceding the operation. Ten patients with a mean age of 72 years (range 54 - 83 years) were given methylprednisolone 30 mg/kg intravenously at a mean of 34 minutes (range 25 - 55 minutes) before the induction of anaesthesia and 12 patients with a mean age of 71 years (range 56 - 83 years) served as a control group.

Anaesthetic management

Patients were given premedication with pethidine hydrochloride and promethazine hydrochloride, the former alone being favoured for older patients. Anaesthesia was induced with thiopentone 1 - 2 mg/kg followed by alcuronium 0,25 mg/kg. The patients were ventilated with a fractional inspired oxygen concentration (FiO_2) of 0,4 in nitrous oxide. The trachea was sprayed with 4% lignocaine and a No. 8 or 9 cuffed endotracheal tube was inserted. Appropriate doses of fentanyl (0,1 - 0,2 mg) and a low concentration of enflurane (< 1,0%) were used for maintenance of anaesthesia. A Bird MK II-Ventviva combination in a closed circuit, incorporating a warm-water humidifier, was used for ventilation. Expired carbon dioxide was monitored with a Godart infant capnograph and ventilation was adjusted accordingly. At the end of the operation curarization was reversed with atropine and prostigmine. Postoperatively the patients were exposed to an FiO_2 of 0,4 for 24 hours using a Mixomask.

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Monitoring

A 20 G radial artery catheter was inserted and arterial pressures were continuously monitored by an AE 840 pressure transducer and oscilloscope with digital display. A central venous line was inserted via a basilic vein. Chest radiography to confirm the position of the catheter was not carried out, a swing of at least 1 cm H_2O with respiration being taken as reasonable evidence of central placement. The pulse rate, ECG and temperature were also continuously monitored.

Measurement times

Blood samples were withdrawn at set measurement times: (*i*) before operation; (*ii*) after ± 30 minutes of stable anaesthesia; (*iii*) 5 minutes after fixation of the femoral prosthesis; (*iv*) at the end of the operation; and (*v*) ± 24 hours after the operation. The FiO_2 varied at the different times (Fig. 1).

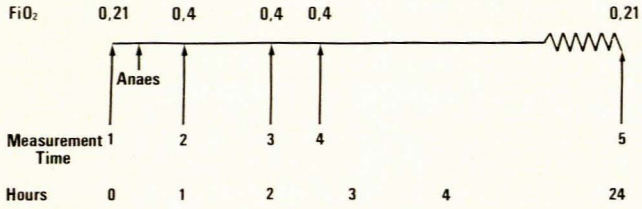

Fig. 1. Measurement times: 1 = pre-operative; 2 = after ± 30 minutes of stable anaesthesia; 3 = 5 minutes after fixation of the femoral prosthesis; 4 = at the end of the operation; 5 = ± 24 hours after the operation.

Sampling

Preparation of tubes for prostaglandin and ß-thromboglobulin (ß-TG) specimens. Stock solutions were prepared as follows: EDTA 10 g/dl and theophylline 540 mg/dl were dissolved in distilled water and the pH was adjusted to 7,0. Aspirin (120 mg) was added to 1 ml methyl alcohol. On the day of the operation 40 µl of aspirin solution was added to 200 µl theophylline-EDTA solution in polypropylene collecting tubes. Five millilitres of radial arterial blood was collected into each tube and mixed. The tube was immediately put into crushed ice and transported to the laboratory where it was centrifuged at 4°C and 1 500 *g* for 10 minutes. The top of the serum layer was removed and the centrifugation and sampling were repeated. The specimens were stored at -20°C until assayed. Because of the short half-life of TXA_2 and PGI_2, the stable metabolites — thromboxane B_2 (TXB_2) and 6-keto-$PGF_{1\alpha}$ — and also ß-TG were radio-immunoassayed. The assays were carried out directly on the stored plasma without prior extraction or chromatography. This gives a sensitivity of 50 - 100 pg/ml for the prostaglandin and 10 ng/ml for the ß-TG. Lower concentrations of prostaglandins were assayed after acidification of the plasma (1,0 ml) with 1M HCl (500 µl) and immediate extraction into diethyl ether (10 ml). Recoveries were quantitated using ^3H-$PGF_{2\alpha}$ and the specimens were taken up in assay buffer (250 µl) to give a fourfold concentrate for assay. Specimens of 100 µl each were used for each assay; extracted blank values were inluded with each specimen analysed.

Diagnosis of ARDS

Clinical features of FES usually present on the second postoperative day. Gurd and Wilson[11] have presented elaborate criteria for detecting FES, but we prefer our simpler criteria to detect pulmonary dysfunction.[12] Our patients were examined twice daily for 1 week. Usually the patients appeared well at a postoperative visit but at the next visit complained of shortness of breath and 'feeling out of sorts'. Examination revealed the following: (*i*) tachypnoea (> 20/min); (*ii*) tachycardia (> 110/min); (*iii*) partial arterial oxygen pressure (Pa_{O_2}) significantly lower than the pre-operative level (paired Student's *t* test; $P < 0{,}001$); and (*iv*) partial arterial carbon dioxide pressure (Pa_{CO_2}) values at the lower limits of normal with a mean of 4,2 kPa.

Raised temperatures were not a feature and clinical examination of the patients' lungs were negative, while chest radiography and flow-perfusion pulmonary scans revealed no abnormalities. These criteria correspond to Gomez's type I ARDS classification.[13]

Results

Incidence of ARDS

Of the 10 patients pretreated with methylprednisolone, 1 (10%) developed ARDS. Stoltenberg and Gustilo[4] used a different steroid dosage treatment regimen, and 15% of their 104 patients developed subclinical FES. Of our 12 controls, 5 (42%) developed ARDS. In a series of 124 patients with long-bone fractures Stoltenberg and Gustilo[4] found a 39% incidence of subclinical FES, which compares favourably with our results.

TXA_2

Of the patients treated with methylprednisolone, the 1 who developed ARDS had a TXB_2 level 10 times higher than the mean for the other 9 who remained well after the insertion of the femoral prosthesis.

The 5 control patients who developed ARDS had significantly higher TXB_2 levels 5 minutes after insertion of the femoral prosthesis ($P < 0{,}05$) and at the end of the operation ($P < 0{,}02$) than the other 7 patients in this group who did not develop ARDS (unpaired Student's *t* test).

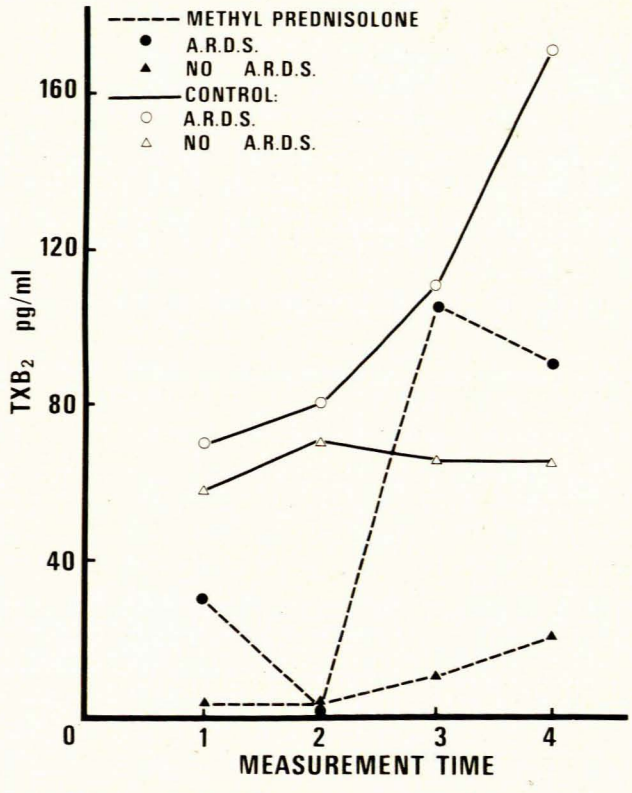

Fig. 2. TXB_2 levels at the different measurement times.

Of all those who did not develop ARDS, the controls had significantly higher TXB_2 levels than the methylprednisolone-treated patients (Table I, Fig. 2) suggesting steroid-depressed synthesis of TXA_2. At no measurement time in any of the groups was there a significant correlation between TXB_2 and PaO_2 levels.

ß-TG

This is a protein, probably unique to platelets. Its concentration in plasma is raised in situations associated with intravascular platelet aggregation and release (Table II).[14] Goldstein *et al.*[15] demonstrated TXA_2 release by PMNs, but whether these cells synthesize ß-TG is unknown. We found good correlation between TXA_2 and ß-TG levels ($r = 0{,}6806$; $P < 0{,}01$) at measurement time 4 in the control group patients who developed ARDS, suggesting that platelets were mainly responsible for TXA_2 synthesis (Figs 2 and 3).

PGI_2

We were unable to determine 6-keto-$PGF_{1\alpha}$ levels in the patients given methylprednisolone because of the low values. Attempts to assay these low values after plasma extraction and concentration of the extract were unsuccessful, or high blank values invalidated the results. Apart from different basal values (Table III), probably because of the small series, the shapes of the graphs of patients who developed ARDS and those who

TABLE I. TXB_2 LEVELS IN THE CONTROL AND METHYLPREDNISOLONE GROUPS AT THE DIFFERENT MEASUREMENT TIMES

	No.	TXB_2 levels at measurement times (mean ± SE; pg/ml)			
		1	2	3	4
Control group					
ARDS	**5**	**71 ± 27**	**78 ± 27**	**109 ± 20**	**169 ± 37**
No ARDS	**7**	**57 ± 7**	**70 ± 17**	**66 ± 7**	**67 ± 14**
***P* value**		***P* = NS**	***P* = NS**	***P* < 0,05**	***P* < 0,02**
		1	2	3	4	5
Methylprednisolone group						
ARDS	**1**	**31**	**0**	**105**	**90**	**0**
No ARDS	**9**	**4 ± 4**	**3 ± 3**	**10 ± 7**	**20 ± 11**	**21 ± 11**

NS = not significant.

TABLE II. ß-TG LEVELS IN THE CONTROL AND METHYLPREDNISOLONE GROUPS AT THE DIFFERENT MEASUREMENT TIMES

	No.	ß-TG levels at measurement times (mean ± SE; ng/ml)			
		1	2	3	4
Control group					
ARDS	**5**	**53 ± 6**	**48 ± 5**	**420 ± 174**	**467 ± 187**
No ARDS	**7**	**50 ± 14**	**55 ± 14**	**229 ± 52**	**253 ± 66**
***P* value**		***P* = NS**	***P* = NS**	***P* = NS**	***P* = NS**
		1	2	3	4	5
Methylprednisolone group						
ARDS	**1**	**49**	**37**	**640**	**525**	**30**
No ARDS	**8***	**67 ± 9**	**69 ± 7**	**152 ± 50**	**177 ± 34**	**88 ± 31**

NS = not significant.
*One patient omitted here since specimens for measurement times 3 and 4 never reached the laboratory.

TABLE III. 6-KETO-$PGF_{1\alpha}$ LEVELS IN THE CONTROL GROUP AT THE DIFFERENT MEASUREMENT TIMES

	No.	6-keto-$PGF_{1\alpha}$ levels at measurement times (mean ± SE; pg/ml)			
		1	2	3	4
ARDS	**5**	**228 ± 25**	**249 ± 22**	**254 ± 47**	**204 ± 27**
No ARDS	**7**	**115 ± 42**	**135 ± 36**	**178 ± 41**	**150 ± 35**
***P* value**		***P* = NS**	***P* < 0,05**	***P* = NS**	***P* = NS**

NS = not significant.

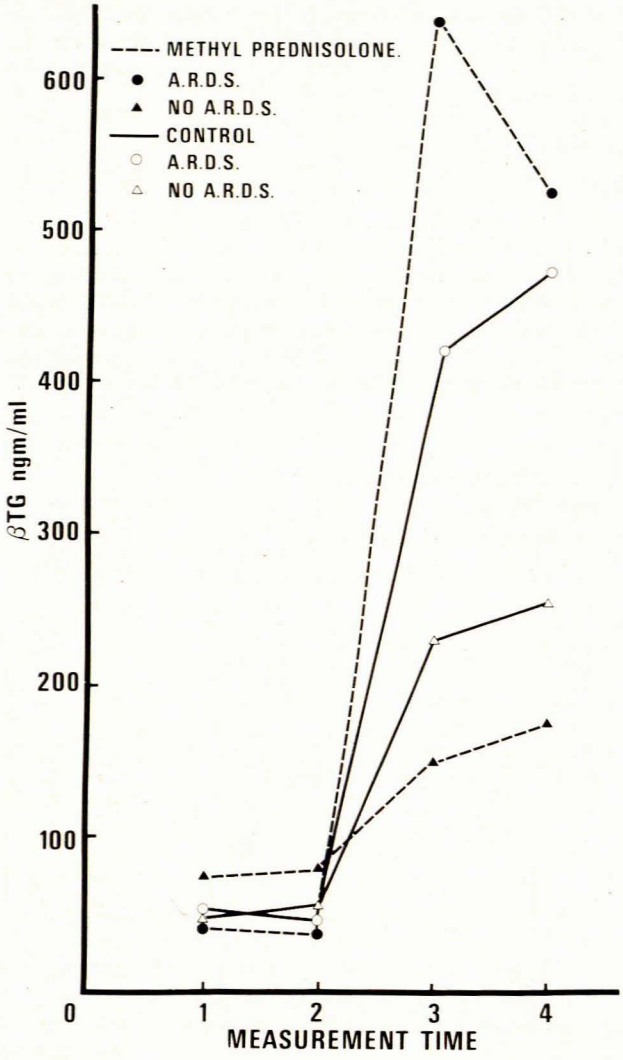

Fig. 3. ß-TG levels at the different measurement times.

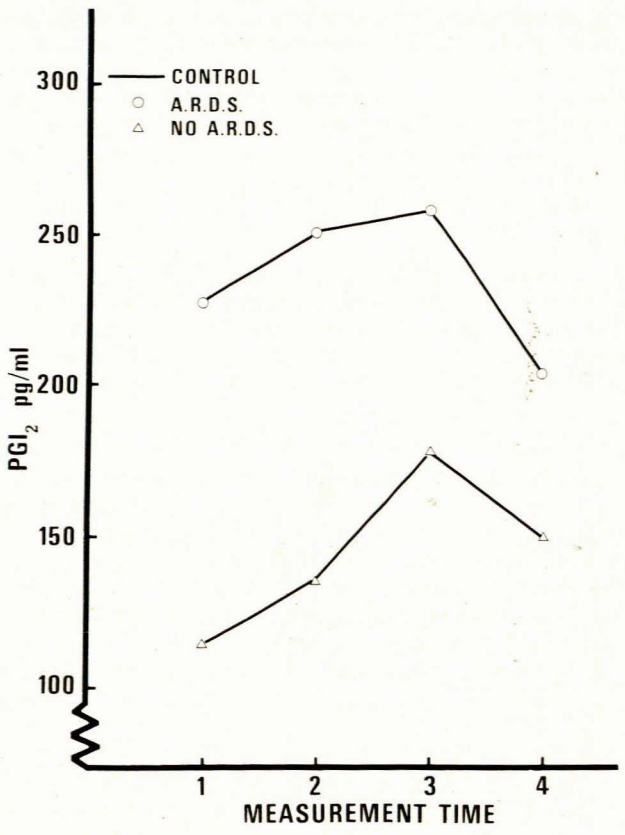

Fig. 4. 6-keto-PGF$_{1\alpha}$ levels at the different measurement times.

remained well are almost identical (Fig. 4). It therefore appears that PGI_2 levels are not changed by ARDS.

Thrombo-embolic events

All patients with pulmonary dysfunction underwent chest radiography and flow-perfusion pulmonary scans. No pulmonary emboli or other space-occupying lesions were found. Bergqvist *et al.*[16] retrospectively studied 350 patients who underwent hip surgery. They utilized pre- and postoperative chest radiographs and pulmonary perfusion scintigrams and found scintigraphic evidence of pulmonary embolism in 15,4% of patients.

Discussion

ARDS is caused by the interaction of the effects of trauma (THR) and blood-borne mediators. Peltier[6] proposed that mechanical obstruction of lung capillaries by fat emboli and subsequent chemical damage caused by fatty acids were responsible for ARDS.

More recently, Craddock *et al.*[17] stated that embolization of granulocyte aggregates might be a previously unsuspected cause of leucostasis and pulmonary damage in various clinical situations where intravascular complement activation occurs, C5 being the component responsible. Subsequently[18] they demonstrated that infusion of activated complement into sheep produced pulmonary vessel leucostasis, pulmonary arterial hypertension and pulmonary oedema with protein-rich fluid, suggesting pulmonary endothelial damage. In *in vitro* studies this damage was shown to be mediated by toxic oxygen metabolites released by the stimulated granulocytes.[18] However, since these oxygen radicals dissipate rapidly, it seems likely that close physical contact between leucocytes and endothelium would be necessary for significant cellular damage to occur by this mechanism.[18] From these considerations they postulated that excessive complement activation may initiate or amplify ARDS.[9] Craddock's group also thought that prostaglandin synthesis might play an important role in the pathogenesis of ARDS.[19]

In addition to the above views, our experimental evidence leads us to believe that stimulation of the arachidonic acid cascade may explain some aspects of the pathogenesis of ARDS.

Arachidonic acid metabolism (Fig. 5)

Arachidonic acid is found in the phospholipid cell membrane. Phospholipases liberate arachidonic acid for metabolism.[20] In the platelet and the leucocyte,[15] arachidonic acid may be metabolized in the lipoxygenase or cyclo-oxygenase pathways.[21] In the lipoxygenase pathway, arachidonic acid is oxidized to 12-L-hydroperoxy-5,8,10,14-eicosatetra-enoic acid (HPETE). Further metabolism results in the formation of 12-L-hydroxy-5,8,10,14-eicosatetra-enoic acid (HETE) and toxic oxygen radicals.[22] Trauma probably steps up synthesis in the lipoxygenase pathway as well as activating complement. The excess toxic oxygen radicals produced could be responsible for the cellular damage demonstrated by Craddock *et al.*[17] HETE, which is chemotactic for leucocytes, is probably responsible for leuco-embolization.

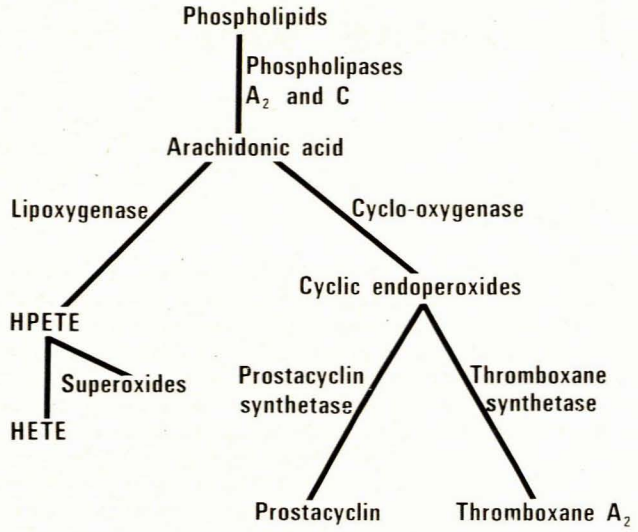

Fig. 5. Arachidonic acid metabolism — HPETE = 12-L-hydroperoxy-5,8,10,14-eicosatetra-enoic acid, HETE = 12-L-hydroxy-5,8,10,14-eicosatetra-enoic acid.

In the platelet cyclo-oxygenase pathway arachidonic acid is oxygenated to produce cyclic endoperoxides.[23] These endoperoxides are metabolized by thromboxane synthetase to TXA_2. If the cyclo-oxygenase activity of platelets is blocked by drugs (e.g. indomethacin), arachidonic acid is shunted to the lipoxygenase pathway and platelets then produce large quantities of HETE.[23] This explains the inability of indomethacin to prevent ARDS.

Borg *et al.*[10] infused pigs with complement-activated plasma and demonstrated transient trapping of leucocytes but not platelets in the pulmonary circulation. They also demonstrated a dose-dependent transient pulmonary arterial and venous constriction. This vascular response was not due to PMN aggregates as such, but was mediated by substances released from activated leucocytes and was prevented by pretreatment with indomethacin, suggesting that prostaglandin synthesis is involved in the pulmonary vascular response. Prostaglandin synthesis has therefore been suggested by Hammerschmidt *et al.*[19] and Borg *et al.*[10] as probably being involved in the pathogenesis of ARDS.

In the group that received methylprednisolone, the patients who remained well had low TXB_2 levels. In the 1 patient who developed ARDS the TXB_2 measurement (after insertion of the femoral prosthesis) was at the same level as in the 5 controls who developed ARDS. This patient also had a pre-anaesthetic level of TXB_2 7 times higher than the mean for the other methylprednisolone-treated patients. The mechanism responsible for this high pre-operative level of TXB_2 is unclear, as is the correct treatment in such cases. Of the 12 control patients who underwent THR, 5 developed ARDS. These patients had significantly higher TXB_2 levels (Fig. 2) after insertion of the femoral prosthesis and at the end of the operation than did the patients who did not develop ARDS.

We postulate that the synthesis of TXA_2, the most potent platelet aggregator and vasoconstrictor in the body, and the activation of complement are the basic requirements for the development of ARDS of any aetiology. Different aetiological factors trigger this basic mechanism and thus cause ARDS.

Steroids reduce arachidonic acid metabolism by inhibiting phospholipases and thus arachidonic acid substrate release from the phospholipid cell membrane. As a result, neither the lipoxygenase nor the cyclo-oxygenase pathway can function well. We therefore identify ourselves with Craddock's group[19] in stating that pretreatment with methylprednisolone in high doses (30 mg/kg body weight) will benefit patients prone to the development of ARDS.

Platelet aggregation and release instigated by TXA_2 play a prominent role in blood coagulation.[24] Since this aggregation is the starting point of thrombosis, methylprednisolone, with its inhibitory effect on platelet aggregation, may be of value in patients prone to the development of thrombo-embolic phenomena after surgery.

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