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Prevention of posttraumatic hypoxaemia in isolated lower limb long bone fractures with a minimal prophylactic dose of corticosteroids

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Summary The efficacy of a minimum dose of methylprednisolone for the prevention of posttraumatic hypoxaemia and fat embolism syndrome (FES) was prospectively studied in 87 patients with isolated, closed or grade I open, femoral and tibial fractures. On admission, the patients were randomly allocated either to a control group given placebo (40 patients) or to a methylprednisolone-treated group (47 patients). A total dose of 6 mg/kg BW methylprednisolone (SoluMedrol®, Upjohn) was administered intravenously, divided in six equal doses at 8 h intervals. Six patients (12.8%) in the control group and one patient (2.5%) in the trial group developed FES ($P = 0.079$) but the difference is not statistically significant. Twenty-four hours after admission, the steroid-treated patients displayed statistically significant higher p_{O_2} values compared to the control group ($P = 0.035$) and this difference persisted on the second and the third post-admission day as well ($P = 0.008$). No corticosteroid-related side-effects were noticed in any of the patients during hospitalisation. Our results support the prophylactic administration of methylprednisolone in small dosage to prevent post-traumatic hypoxaemia and probably FES in patients with isolated lower limb long bone fractures, especially when early fracture stabilisation is not possible.

Introduction

Microscopic systemic fat embolism occurs in almost every patient with a long bone fracture and is also evident following surgical procedures which involve intramedullary reaming.[6,11,20,28] However, fat embolism syndrome (FES) develops only in a small percentage of this patient population and represents a significant cause of morbidity but not mortality.[3,6,10,12,18,19,23] Hypoxia is common after long bone fractures and may pass unnoticed.[5,15,21] There is no clinical or experimental study until now to demonstrate beneficial effect of any drug on the clinical course of the syndrome,[26] so that prevention, early diagnosis and adequate symptomatic treatment are the mainstays of treatment of this condition.[18] Several pharmacological agents have been used as prophylactic treatment, such as hypertonic glucose,[31] aspirin,[30] dextrans[30] and corticosteroids with variable results.[16,19,31,34] In several clinical trials the use of corticosteroids in various pulmonary disorders and in FE was proven to be beneficial but their use remains controversial.

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Corticosteroids, primarily methylprednisolone were administered at doses as high as 180 mg/kg BW[2] and as low as 9 mg/kg BW.[16] Corticosteroids are effective when administered in high-risk patients prior to the onset of FES but their systemic use, especially in high dose, may be followed by several acute and chronic complications.[28,35] Even a single injection of high-dose methylprednisolone in animals was found to be capable of inducing complications such as multifocal osteonecrosis.[38] The reduction of the administered corticosteroid dosage is, therefore very important in order to reduce the drug-related complications.

This study was undertaken to determine the effect of a minimum dose of methylprednisolone (SoluMedrol®, Upjohn) on the respiratory function of young patients with isolated femoral or tibial fractures.

Patients and methods

The study was performed at the 401 General Army Hospital in Athens, Greece, between January 1995 and February 1998 and was approved by the hospital's Scientific and Human Ethics Committee. All patients gave informed consent. On admission, the patients were assigned in alternate sequence either to a group where methylprednisolone was administered or to a control group where normal saline was administered. All patients with severe injuries in other systems (central nervous system, gastrointestinal, urogenital and respiratory system) or with pre-existing pulmonary or other chronic diseases were excluded from the study. As a result out of the 124 patients who were admitted to hospital during this period with isolated closed and grade I open fractures of the femur and of the tibia 37 were excluded due to the co-existence of other injuries while nine other patients declined participation in the study. The remaining 87 patients have been allocated in two groups. The first group included 47 male patients treated with methylprednisolone (study group) while the second group included 40 male patients and served as control group. Initially, the two groups consisted of 40 patients each, but the encouraging results of methylprednisolone use forced us to include the last seven patients in the methylprednisolone and not in the placebo group. The patients' age ranged from 18 to 28 years (average 22.4 years). The average age in the first group was 22.68 ± 3.92 years and in the control group was 22.23 ± 4.48 years. In the steroid group were included 11 closed femoral, 22 closed tibial fractures, 6 open femoral and 8 open tibial fractures. In the placebo group were included 8 closed femoral, 19 closed tibial fractures, 4 open femoral and 9 open tibial fractures. There was no statistically significant difference between the two groups regarding the demographic characteristics of the patients (age, sex and body weight), the time from accident (in hours) and the distribution of open fractures and fractures of either bone, i.e. the tibia or the femur. The mean time from accident to admission was 4.9 ± 3.5 h. The cause of the fracture was motor vehicle accidents (56 patients, 64.36%), falls from height (17 patients, 19.54%) or other causes (14 patients, 16.1%). Resuscitation and restoration of the depleted intravascular volume was initiated at the Emergency Department and was completed at the surgical ward. Closed tibial fractures were placed in long leg splints, while grade I open fractures were treated with debridement and external fixation. All closed fractures and most open fractures were treated with secondary nailing within 5–14 days. Closed femoral fractures were placed in skeletal traction while grade I open fractures were stabilised with an external fixator. All femoral fractures were treated with secondary intramedullary nailing between 4 and 12 days after injury. All patients received subcutaneously low molecular weight heparin as thromboprophylaxis. The trial group received 1 mg methylprednisolone (SoluMedrol®, Upjohn)/kg body weight (BW) on admission and five more equal doses in 8 h intervals while the control group received placebo intravenously (5% dextrose in water). The totally administered dose of methylprednisolone was 6 mg/kg BW. The patients were monitored for 4 days following admission with daily clinical examination, recording of temperature, pulse rate, blood pressure and respiratory rate, observation for the presence of petechiae or central nervous system symptoms and when indicated with fundoscopy as well. Chest radiograph was performed daily for the first 4 days. Blood analysis including haematocrit, white cell count, CRP and arterial blood gas partial pressure measurement was carried out at presentation, 12 h later, twice on the first post-admission day and once during the following 2 days. There have been six measurements available for every patient. All specimens for blood gas analysis were taken by puncture of the radial or the femoral artery with the patient spontaneously breathing room air. Every day the fat embolism index score, according to Shier et al.,[31] employing clinical signs and laboratory findings, was derived for each patient from a blinded investigator (EA). The presence of petechiae was considered to be a highly indicative manifestation of FES and was assigned a score of 5, which was the minimum accepted score for the establishment of a positive diagnosis. Hypoxaemia

Table 1 Clinical features and Shier et al.'s index in patients with established FES

Patient	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Sex	Male	Male	Male	Male	Male	Male	Male
Age	18	18	21	23	19	24	25
p_{O_2}	45	40	49	55	41	52	43
Clinical presentation	Fever tachypnea	Confusion X-ray (+) fever tachycardia	Petechiae tachypnea	Confusion X-ray (+) fever tachypnea	Confusion X-ray (+) fever tachycardia	Petechiae tachypnea	Tachypnea tachycardia fever
Fat embolism index (Shier et al.)	5	10	9	10	10	9	6
Group	Steroid	Control	Control	Control	Control	Control	Control

with arterial oxygen partial pressure (p_{O_2}) lower than 60 mmHg was assigned a score of 4, positive X-ray findings a score of 3, while tachycardia, fever and tachypnea were assigned a score of 1. All patients were classified in six subgroups (three in the control and three in the trial group) according to their p_{O_2} values. We considered as hypoxaemia any $p_{O_2} < 70$ mmHg and classified all patients in three categories: severe hypoxaemia ($p_{O_2} < 60$ mmHg), mild hypoxaemia (60 mmHg $< p_{O_2} <$ 70 mmHg) and normal ($p_{O_2} > 70$ mmHg). The statistical evaluation was accomplished using the paired and the unpaired *t*-test, the Fisher's exact test and the x^2-test. A *P*-value less than 0.05 was considered to denote the presence of a statistically significant difference.

Results

The diagnosis of FES was established in seven patients, six from the control group (15%) and one from the trial group (2.1%). The clinical features and Shier et al.'s index[31] of the patients who developed the syndrome are presented in Table 1. Despite the fact that this difference is arithmetically significant the Pearson's x^2-value was 0.079,

Table 2 Arterial oxygen partial pressure (p_{O_2}) values according to the time elapsed since the traumatic incidence

Day	Measurement	Group	$p_{O_2} < 60$ mmHg	60 mmHg $< p_{O_2} <$ 70 mmHg	$p_{O_2} > 70$ mmHg
Admission	First	MP	1 (2.2%)	5 (10.9%)	41 (87%)
	First	PL	1 (2.5%)	12 (30%)	27 (67.5%)
		Total	2 (2.3%)	17 (19.8%)	68 (77.9%)
	Second	MP	1 (2.2%)	4 (8.9%)	42 (88.9%)
	Second	PL	1 (2.5%)	12 (30%)	27 (67.5%)
		Total	2 (2.4%)	16 (18.8%)	69 (78.8%)
1	First	MP	2 (4.3%)	4 (8.5%)	41 (87.2%)
	First	PL	5 (12.5%)	8 (20%)	27 (67.5%)
		Total	7 (8.7%)	12 (13.8%)	68 (78.2%)
	Second	MP	2 (4.3%)	4 (8.5%)	41 (87.2%)
	Second	PL	5 (12.5%)	9 (22.5%)	26 (65%)
		Total	7 (8%)	13 (14.9%)	67 (77%)
2		MP	0	4 (8.5%)	43 (91.5%)
		PL	6 (15%)	10 (25%)	24 (60%)
		Total	6 (6.9%)	14 (16.1%)	67 (77%)
3		MP	0	0	47 (100%)
		PL	5 (12.5%)	8 (20%)	27 (67.5%)
		Total	5 (5.7%)	8 (9.2%)	74 (85.1%)

MP, methylprednisolone group; PL, placebo group.

making it, therefore, statistically non-significant but rather indicating a trend. Perhaps, if more patients were included in the trial, the difference would be statistically significant. The study of the oxygen partial pressure in the arterial blood (p_{O_2}) yielded interesting results (Table 2, Fig. 1a–c). Within the first 12 h after admission, only a small number of patients of both groups presented $p_{O_2} <$ 60 mmHg, probably because during the first hours following the accident, the chemical phase of fat embolism in the lung parenchyma is still in progress. There were almost three times more patients in the control group with p_{O_2} between 60 and 70 mmHg than in the trial group ($P = 0.027$). There was a statistically significant difference in mildly hypoxaemic patients between the two groups at this time instant. On the first post-admission day, the number of patients with $p_{O_2} < 60$ mmHg increased from 2.2 to 4.3% in the trial group and from 2.5 to 12.5% in the control group, respectively ($P = 0.051$). On the second and the third post-admission days, there was no patient with $p_{O_2} < 60$ mmHg in the trial group,

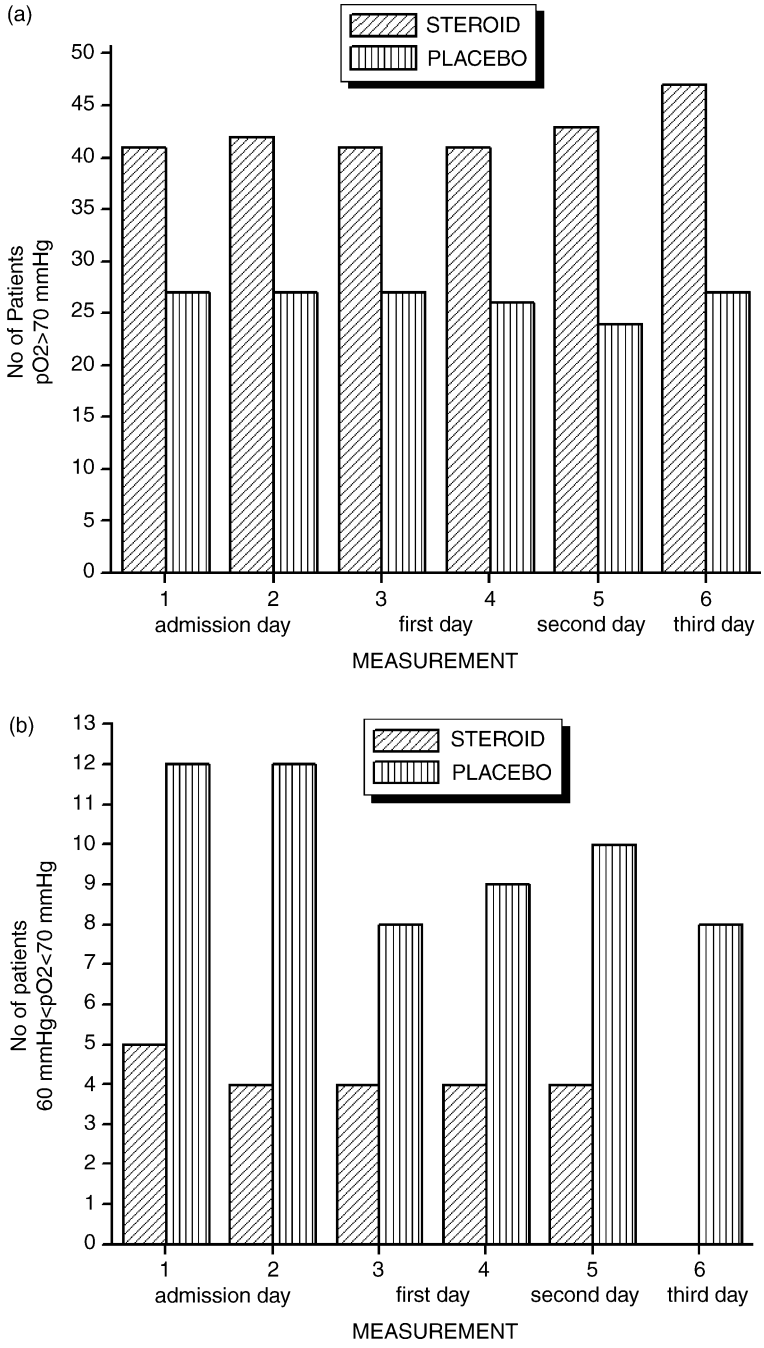

Figure 1 Graphic representation of Table 2 (a–c).

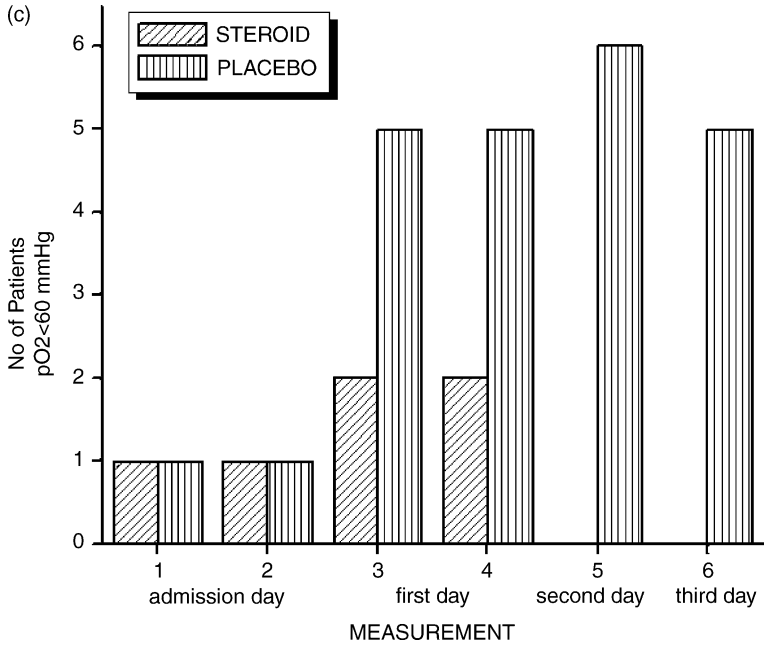

Figure 1. (*Continued*).

while in the control group 15 and 12.5% of the patients presented $p_{O_2} < 60$ mmHg ($P = 0.008$), respectively. On the third day, the difference was significant as there were no patients in the trial group with $p_{O_2} < 70$ mmHg, while in the control group 32.5% of the patients presented such p_{O_2} values ($P = 0.008$). This finding suggests that methylprednisolone administration may have prevented the development of posttraumatic hypoxaemia and may also have had a preventive role on the chemical phase of the FES, as this process starts 12—24 h after the traumatic event.[18,23,24] We also examined the average p_{O_2} values in each group, including all values of every given day (Table 3, Fig. 2). There was no statistically significant difference on admission ($P = 0.386$ and 0.467 for the first and the second p_{O_2} measurement), but this difference became statistically significant 24 h later ($P = 0.035$ and 0.018, respectively) as well as on the second and on the third post-admission days ($P = 0.008$ and 0.008, respectively). No patient died during this study. Infections occurred in five open fractures (four tibial and one femoral), three in the steroid-treated group and two in the placebo

Table 3 Distribution of p_{O_2} values in every patient group

Day	Measurement	Group	Patients	Average p_{O_2}	S.D.	*P*-value
Admission	First	MP	46	80.4	9.18	0.386
		PL	40	78.35	12.50	
	Second	MP	45	80.09	8.81	0.467
		PL	40	78.32	12.79	
1	First	MP	47	83.09	12.31	0.035*
		PL	40	77.22	13.17	
	Second	MP	47	82.98	12.04	0.018*
		PL	40	76.80	11.81	
2		MP	47	82.89	9.78	0.008*
		PL	40	73.52	12.09	
3		MP	47	88.21	8.99	0.008*
		PL	40	73.27	10.87	

The asterisk (*) denotes the presence of statistical significance. MP, methylprednisolone group; PL, placebo group.

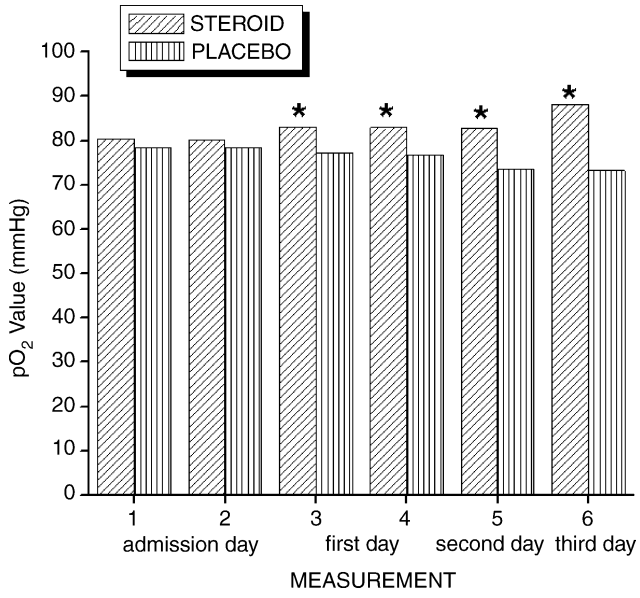

Figure 2 Bar graph representing the data presented in Table 3. The asterisk (∗) denotes the presence of statistical significance.

group. All infections were treated surgically with success. There were no significant corticosteroid-related complications during the hospitalisation period. During the first postoperative year, no case of osteonecrosis was noted in any of the patients.

Discussion

Pulmonary dysfunction after skeletal trauma may occur as a primary insult or as a secondary injury due to fat embolism and adult respiratory distress syndrome (ARDS).[5,6,25,28] The development of respiratory failure and hypoxaemia contributes to morbidity and mortality after trauma.[5,15,18] The term ''fat embolism'' refers to the presence of fat globules in the peripheral circulation (lipaemia) and the lung parenchyma after long bone fractures or other major trauma,[6,19] while FES is the result of an obstructive and chemical process that takes place in the lung capillaries and is caused by fat globule embolisation and hydrolysis of free fatty acids.[11,18,23,24] FES may become clinically evident or may present as subclinical respiratory insufficiency.[6,18,23] Full blown FES develops in 3—5% of trauma patients, but the incidence of the subclinical form of FES, which is manifested as hypoxaemia, is much more frequent. Only a small portion (0.5—10%) of patients with subclinical FES will develop full blown FES[11] with a mortality rate of 2.5—20%.[24] FES becomes apparent within 24 h in 50—60% of the cases and within 3 days in 90% of all cases.[6,24] The main clinical findings of the typical FES are the presence of petechiae, CNS depression and respiratory distress.[23] The more frequent subclinical type of the syndrome[21] is associated with $p_{O_2} < 60$ mmHg, is detected by blood gas analysis and may be easily overlooked.[19] It is not possible to diagnose FES on the basis of a single pathognomonic sign, symptom or laboratory measurement, as the evaluation of a whole series of parameters, signs and symptoms is required for the establishment of the diagnosis. The clinician may fail to diagnose the syndrome, if he relies on the criteria of Gurd and Wilson[12] who suggested that a positive diagnosis requires the presence of at least one major and four minor criteria. The careful analysis of our patients' symptoms showed that these criteria were inadequate to establish the diagnosis in patients Nos. 1 and 7 who developed the syndrome (Table 1). The same problem was recognised by other authors as well, who have proposed different protocols in order to increase the diagnostic accuracy.[19,31] We employed Shier et al.'s criteria[31] to detect milder cases as Lindeque et al.'s criteria[19] are exclusively based on the patient's respiratory status. According to Shier et al.'s criteria, total score of 5 or higher is suggestive of FES. The patients suspected of having developed the syndrome underwent bronchoalveolar lavage and those who were found positive had at least a score of 5. This test may confirm the diagnosis, although it is a rather demanding procedure and its results are not always conclusive.[4,6] The appearance of petechiae is a rather late occurrence.[6,7,18,23] In our study only two of the patients who developed the syndrome had petechiae and only three had a positive chest radiograph, while all of them were severely hypoxaemic ($p_{O_2} < 60$ mmHg) and reported anxiety.

Hypoxaemia was already discovered 24 h after admission. If Gurd and Wilson's[12] criteria were applied to our patients, the incidence of the syndrome would have been 2.3%. In our study, only patients with isolated fractures of the femur and the tibia have been included, a fact that may explain why the incidence of FES was not high (2.5% in the trial group and 12.8% in the control group). In other series, the incidence of FES varies between 2 and 29%.[2,6,12,18,19,23,24] The preferred method of fracture treatment is early stabilisation. In our study, all fractures underwent late surgical stabilisation, so that it may not reflect the clinical pictures seen when early fixation is undertaken.

FES is a self-limiting complication and its treatment is mainly supportive, aiming to restore the perfusion and the oxygenation of peripheral tissues. No laboratory test or physical findings can reliably predict the development of FES.[16,17,19,29,30,34] Thus, prevention and prophylactic treatment of this complication are of utmost importance. The incidence of FES can be reduced with adequate immobilisation of the fracture prior to patient transport, with early operative fixation, with avoidance of fracture manipulation and with the use of corticosteroids. In many different trials several forms of pharmaceutical treatment were employed to treat FES, such as ethyl alcohol (a lipase inhibitor), clofibrate (which increases free fatty acid metabolism), dextran, heparin and aspirin, fluid administration, fluid and salt restriction, hypertonic glucose and systemic corticosteroids. The use of corticosteroids for the prevention and treatment of FES is a subject of study and debate.[1,2,8,9,12–14,16,19–23,36] Corticosteroids are effective when they are administered in high-risk patients prior to the onset of FES, but there is variation in the literature regarding the dosage and the scheme of administration. The mechanism of steroid action is not ascertained. Steroids inhibit plasma complement activation, decrease leukocyte aggregation and decrease capillary leakage by stabilising capillary membranes[3] but may cause delayed wound healing and increase the infection rate.[16,29] The acute and systemic use of corticosteroids may be followed by several complications.[17] Even a single injection of high-dose methylprednisolone in animals was found to be capable of inducing complications as thrombocytopenia, hypofibrinogenaemia, hyperlipaemia and multifocal osteonecrosis in several bones.[38] Osteonecrosis is an unpredictable and severely disabling complication of corticosteroid therapy occuring in 5–25% of patients usually after 6 months of treatment.[33] The risk of osteonecrosis after systemic corticosteroid use is greater in patients treated for prolonged periods with high doses,[8] but there have also been reports of osteonecrosis in patients treated with high corticosteroid doses for a short time period.[29,35] Alho et al.[1] administered 30 mg/kg BW in three doses, Shier et al.[31] 30 mg/kg BW at presentation and 6 h later, Stoltenberg and Gustilo[34] 1 g/kg BW on admission and 8 and 16 h thereafter, Schonfeld et al.[30] 7.5 mg/kg BW every 6 h for 12 more doses, Lindeque et al.[19] 30 mg/kg BW every 2 h for two doses and Kallenbach et al.[16] 1.5 mg/kg BW every 8 h for four doses. The reported results of methylprednisolone administration are favourable with no significant side-effects. Methylprednisolone (125 mg i.v. bolus and 80 mg every 6 h for 3 days) was used to treat severe FES with favourable results.[9] The mechanism of methylprednisolone action has been shown to be activated in vitro by zymosan-activated plasma, when the concentration of methylprednisolone approximates 30 mg/kg bolus.[13] This knowledge led many authors to administer doses of 30 mg/kg BW or higher in established FES, resulting in side-effects such as delayed wound healing, sepsis, immunosuppression or even death.[32,37] However, the failure of these studies could have been foreseen, since the systemic use of any agent expected to act on the fat emboli is ineffective due to the occlusion of the pulmonary vessels by the fat droplets.[23] Bernard et al.[2] reported that high doses of methylprednisolone (120–180 mg/kg BW) administered to treat established ARDS had no effect on the survival rate or the reversal of the respiratory failure. Corticosteroids should therefore be administered prior to the appearance of FES in order to exert their action. In our study, we chose a low-dose scheme of up to 6 mg/kg BW in order to take advantage of the beneficial effects minimising the occurrence of side-effects. In fact, we did not notice increased time of wound healing or increased infection rate in our patients. The capability of methylprednisolone treatment to reduce posttraumatic hypoxaemia has also been demonstrated in previous studies.[16,19,34] In one study of 43 patients with long bone and pelvic fractures, 15 were found to be hypoxaemic with arterial oxygen saturation lower than 94% within the first 72 h, but the hypoxaemia was not present after 48 h from the initiation of the treatment.[21] In another study, isolated arterial hypoxaemia developed in 53.65% of patients with long bone fractures.[16] Hypoxaemia was severe in 21.9% of the controls and in 2.6% of the methylprednisolone-treated patients, while the overall incidence of arterial hypoxaemia was 67.1%.[16] In this study a low dose of methylprednisolone (6 mg/kg BW) was administered and the protective effect of methylprednisolone against both full blown FES and hypoxaemia was demonstrated, but one case of a fatal infection was also reported. In our series the incidence of FES was not statistically

significantly different between the corticosteroid-treated and the control group ($P = 0.079$), although this difference was significant in absolute numbers (one patient in the trial group versus six patients in the control group) indicating a possible protective effect of methylprednisolone. The sample number might have been inadequate to elucidate a probable difference. In our study, a significant number of patients developed hypoxaemia. Hypoxaemia with $p_{O_2} < 60$ mmHg was present in 2.3% of the patients of both groups 12 h after admission. The low incidence of hypoxaemia during the initial period can be explained by the fact that the chemical process of fat hydrolysis in the lung parenchyma is still in progress. Twenty-four hours later, the hypoxaemic patients in the control group were almost three times more than in the trial group. This difference was apparent both in severely ($p_{O_2} < 60$ mmHg) and mildly (60 mmHg $< p_{O_2} <$ 70 mmHg) hypoxaemic patients and was statistically significant ($P = 0.051$). On the second and third day post-admission, 15 and 12.5% of the patients in the control group had $p_{O_2} < 60$ mmHg compared to none in the trial group ($P = 0.008$), while this difference became higher on the third day regarding patients with p_{O_2} between 60 and 70 mmHg (20% in the control group and none in the trial group, $P = 0.001$).

In conclusion, in the patients of our study the administration of 6 mg/kg BW methylprednisolone, divided in six doses at 8 h intervals, initiated directly after patient admission, had reduced the incidence of posttraumatic hypoxaemia and has probably also reduced the incidence of FES. Repeated arterial blood gas analysis over the first 48 h in high-risk patients is extremely valuable in detecting and treating those patients with significant hypoxaemia and FES.[21,27]

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