FAT EMBOLISM AND THE FAT EMBOLISM SYNDROME
A DOUBLE-BLIND THERAPEUTIC STUDY

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Fifty-five adults who sustained a tibial fracture, or a femoral fracture, or both, were subjected to a
double-blind randomised study to determine the efficacy of methylprednisolone in treating the fat embolism
syndrome. This drug maintained arterial oxygen levels, stabilised or reduced the serum level of free fatty
acids, and decreased the risk of the fat embolism syndrome in a statistically significant proportion of patients.

Gurd's criteria for the diagnosis of the fat embolism syndrome were found inadequate. Other more
sensitive criteria for early diagnosis and effective management were determined. There were no deaths or
serious morbidity in our series.

In a classic monograph on fat embolism, Sevitt (1962) wrote: "A hundred years after its first description, there
is lack of agreement and ... even confusion as to its frequency, aetiology, pathogenesis, clinical significance
and its clinical effect". This report represents an attempt to clarify some of the issues.

Weisz (1974) recounts the early history and refers to the first report, by Lower of Oxford (1669), who injected
milk intravenously into experimental animals and found fat globules in the pulmonary vessels at autopsy. Weisz
attributes the first histologically proven case of fat embolism to Zenker (1862), in a patient who died after a
severe crush injury; he also mentions Czerny's (1875) concept of the pathogenesis and the resulting symptoms,
and that Scriba (1880) attributed the illness to cerebral emboli.

In the early 1950s, Peltier's studies expanded our knowledge of the pathogenesis and he noted the toxic
effects of free fatty acids (Peltier 1956). The result was a description of the respiratory theory (Peltier 1969)
which is still valid and is the basis of current therapeutic

regimes. Szabó, Serényi and Kocsár (1963) reported the
post-mortem presence of pulmonary fat emboli in 100%
of a series of 10 000 victims of major accidental injuries.
Sevitt (1962) reported a 70% incidence in childhood
fatalities from injuries, and Peltier (1970) showed that
bone marrow fat matures to the adult pattern in children
at 3 to 11 years.

The term "fat embolism" denotes the presence of
globules of fat in the lung parenchyma and peripheral
circulation after a fracture of a long bone or other major
trauma; the complication arises in the vast majority of
such cases. The term "fat embolism syndrome" (FES)
denotes a more serious manifestation of the same
phenomenon, and occurs less frequently. Its incidence is
variably reported, from as low as 3.4% (Peltier 1969) to
as high as 29% in the present study, depending on the
criteria for a positive diagnosis (see below).

FES is a respiratory deficiency syndrome due to
decreased alveolar diffusion of oxygen. It occurs in three
degrees of severity: a subclinical, an overt clinical, and a
fulminating form. The latter is frequently fatal, while the
subclinical and clinical forms are amenable to treatment.

Gurd's (1970) criteria for a positive diagnosis are in
common usage and are grouped under major and minor
features (Gurd and Wilson 1974). The major features are
respiratory insufficiency, cerebral involvement and
petechial rash. The minor features are pyrexia, tachycardia,
retinal changes, jaundice and renal changes. A
positive diagnosis is made in the presence of at least one
major and four minor features, together with fat
macroglobulinaemia.

Recently other more sensitive features have been
determined, and various therapeutic measures
investigated. These include a comparison of the effect of
methylprednisolone vis-à-vis fluid loading, hypertonic
glucose, and aspirin by Shier et al. (1977) and hypertonic dextrose by Stoltenberg and Gustilo (1979).

This present study was performed to determine the efficacy of methylprednisolone, to seek earlier recognition of FES and to improve prognosis.

MATERIAL AND METHODS

There were 55 patients in the series, ranging in age from 16 to 54 years (average 27.5 years). They all had a fractured femur and/or tibia, with or without soft-tissue contusion and laceration, and were studied during the period from October 1984 to August 1985. Any patient with a history or evidence of any of the following conditions was excluded from the series: concomitant injuries of the skull, chest wall and lungs, abdominal cavity, pelvis or urogenital diaphragm; pregnancy; pathological fractures from whatever cause; pre-existing cardiac or pulmonary affections; or previous cortisone therapy. Uniformity of resuscitation and other therapeutic measures was maintained throughout; traction devices and surgical techniques were standardised.

A number of investigations were carried out on admission (baseline values), and again after 12, 24, 48 and 72 hours. Blood analysis included blood gas, serum complement (C5a), free fatty acids (palmitic, stearic and oleic), and serum protein levels; a full blood count and haematocrit were performed. The temperature, pulse rate, blood pressure and respiratory rate were measured four-hourly. The presence of any petechiae, and their sites was recorded.

Methylprednisolone or a placebo was administered intravenously on a double-blind randomised basis. The dosage was methylprednisolone 30 mg/kg body mass on admission, and a single repeat dose after four hours.

RESULTS

There were 48 men and seven women in this series. The average time between injury and admission was 1.6 hours (range 10 minutes to 4 hours). The injuries were mostly caused by road accidents, 32% being due to motor car accidents, 40% to motor cycle accidents and 9% to pedestrians, while 19% of injuries were from other causes. Closed fractures and open fractures were divided equally among the methylprednisolone and control groups; similarly, there was an equal proportion of those who on admission were found to have raised serum alcohol levels.

Petechiae occurred in only 39% of patients with a PaO₂ level of less than 60 mmHg. The common sites were in the axilla, the conjunctiva and the anterior chest wall. Arterial oxygen values. In the trial group, all 27 patients had an initial baseline PaO₂ value of more than 60 mmHg; in six of them (22%) this fell to below 60 mmHg during the trial. In the control group, 16 of the 28 patients (57%) had a similar fall in levels. These percentages differ significantly (χ² test: p<0.025), and reflect a 35% reduction in the incidence of FES in the trial group.

A fall in the PaO₂ level to below the critical level of 55 mmHg occurred in only three patients (11%) in the trial group; one dropped to 50.4 mmHg. By contrast, in the control group 13 patients (46%) dropped to below 55 mmHg, the lowest value recorded being 35.1 mmHg. These two percentages also differ significantly (χ² test: p<0.025).

The largest fall in PaO₂ value in the trial group was from 86.9 to 61.7 mmHg, in contrast to a fall from 89.1 to 47.0 mmHg in the control group. The average fall in the trial group was 10.4 mmHg, s.d. 7.1 mmHg (19 patients; range 0.3 to 25.2 mmHg), and in the control group 16.1 mmHg, s.d. 12.5 mmHg (24 patients; range 0.2 to 42.1 mmHg).

Free fatty acids. FFA values as such do not reflect the unbound active fraction of FFA due to the fact that more than 90% of FFA is bound to albumin. The serum FFA/albumin ratio reflects the bound and unbound forms of FFA. We could not determine a direct statistical relationship between PaO₂ values and FFA, but methylprednisolone stabilised the levels of the free fatty acids. Serum C5a (activated C5). We found that the majority of patients who sustained a long-bone fracture had raised levels of C5a regardless of the development of FES. C5a was present in equal amounts in the placebo and methylprednisolone groups but the levels of C5a bore no direct relationship to PaO₂ levels.

DISCUSSION

Fat embolism, with fat droplets larger than 20 μm in diameter, occurs in more than 90% of patients with long-bone fractures (Weisz 1974). The fat embolism syndrome denotes clinical or subclinical respiratory insufficiency developing in patients with long-bone fractures. It usually runs a mild course and responds well to measures for respiratory support. The subclinical form is detected by blood gas analysis and is associated with a PaO₂ value of less than 60 mmHg. The overt clinical form, which usually appears within 24 to 72 hours and presents the classic picture, is easy to diagnose. The severe, fulminant form, which develops within hours, deteriorates rapidly despite respiratory support and other resuscitative measures, and is frequently fatal. This form is caused by a massive embolism followed by a succession of further massive embolisms.

Criteria of FES. The clinical manifestations of FES may be absent and the syndrome overlooked if judged by Gurd's criteria only. This may prove disastrous, for the full respiratory deficiency syndrome may develop within hours, and the opportunity for early effective treatment be missed.

Instant recognition is possible only when blood gas levels are determined as a routine procedure, immediately
upon admission of a patient with a long-bone fracture. The diagnosis of FES is established in the presence of a $P_{O_2}$ value of less than 60 mmHg or of other criteria which are listed below. Measures for resuscitation may then be adopted without delay.

In the present series, the diagnosis of FES was positive in 7 of 55 cases (13%) when assessed in terms of Gurd’s criteria: two patients in the trial group who recovered promptly after respiratory support below baseline $P_{O_2}$ values of 66.4 mmHg; and five patients in the control group. In strong contrast, the diagnosis in terms of our criteria (see below) was positive in 16 of 55 cases (29%): three patients in the trial group and 13 patients in the control group. These percentages for the differing criteria differ significantly (McNemar test: p < 0.01).

We observed a number of patients who maintained a low $P_{O_2}$ value for some time before developing clinical signs. The classic criteria of Gurd (1970) never became a reality in these patients. For this reason we adhered to a simpler set of criteria, based on respiratory insufficiency alone.

**Proposed criteria** for a positive diagnosis of FES comprise the following factors.

1. A sustained $P_{O_2}$ of less than 60 mmHg.
2. A sustained $P_{CO_2}$ of more than 55 mmHg or a pH of less than 7.3.
3. A sustained respiratory rate of more than 35 breaths per minute even after adequate sedation.
4. Increased work of breathing – dyspnoea, the use of accessory respiratory muscles, and tachycardia – combined with anxiety. A patient showing at least one of the above criteria was judged to have developed FES.

**Methylprednisolone trial.** The $P_{O_2}$ reflects oxygen diffusion from the alveoli to the lung capillaries which is essential for tissue oxygenation. For this reason we used the $P_{O_2}$ values to compare the efficacy of methylprednisolone against a placebo. Methylprednisolone had a significant effect in preventing the development of the clinical and subclinical FES. It reduced the fall in $P_{O_2}$ and decreased the risk of a low $P_{O_2}$ level. A rise in the $P_{O_2}$ level was recorded in a few patients.

In the methylprednisolone group, eight patients had a baseline $P_{O_2}$ between 60 and 70 mmHg, three of whom (38%) dropped to below 60 mmHg during the following three days; 15 patients had a baseline $P_{O_2}$ above 70 mmHg, and three of these (20%) dropped to less than 60 mmHg. These figures show that a patient with a baseline $P_{O_2}$ less than 70 mmHg runs a higher risk of developing FES, despite methylprednisolone administration. The administration of oxygen at two litres per minute by mask and of lung physiotherapy must not be delayed, not even for one hour.

Methylprednisolone offers advantages but is not a “wonder drug”. The basic principles in the management of long-bone fractures remain inviolate. They include early aggressive resuscitation, adequate splinting of fractures, administration of intravenous analgesics, administration of blood through a 20 μm filter, and prevention of sepsis in compound fractures. When these conditions are fulfilled, methylprednisolone 30 mg/kg body mass, on admission and repeated after four hours, is 35% more effective in maintaining the $P_{O_2}$ level and in stabilising the free fatty acids than a placebo. The prognosis is improved. Methylprednisolone sodium succinate has a plasma half-life of approximately 200 minutes, but the duration of its pharmacological activity is 18 to 36 hours (Swartz and Dluby 1978).

In our series, the incidence of FES was 29%, judged in terms of the criteria established during the course of the study. This figure is considerably higher than that reported elsewhere, indicating our timely recognition of a threatening complication, and establishing the undisputed advantages of immediate treatment. The potential for the development of a serious form of FES in every case of long-bone fracture, whether in child or adult, should not be underestimated. Delay in recognising the complication may prove serious and even fatal.

**Relation to the adult respiratory distress syndrome (ARDS).** The terms ARDS, shock lung and FES are commonly being used interchangeably. ARDS or shock lung should be applied when the cause is a pathological condition other than fracture: these conditions include burns, septicaemia and hypovolaemic shock and may be associated with aspiration of gastric contents, multiple emergency transfusions and pulmonary contusion (Pepe et al. 1982). Full ARDS has a mortality rate of 20% to 50%. This is in contrast to FES which is characterised by a mild course, good response to respiratory support and, except in the rare fulminating form, a low mortality. The risk of developing a severe respiratory syndrome in long-bone fractures is low (1 in 12), and this risk is further reduced when oxygen therapy without intubation and physiotherapy are applied (Pepe et al. 1982).

The manner in which the alveolo-capillary membrane reacts to an insult is the same in both syndromes: interstitial oedema, accumulation of a transudate and later an exudate in the alveoli, the demise of the alveolar Type II cells, the formation of a protein-rich hyaline membrane in the alveoli – all leading to decreased oxygen diffusion from the alveoli to the lung capillaries.

The insult in long-bone fractures is not as severe as in septic shock and it is probably not the same mechanism which causes the damage. We believe that free fatty acids have an important role in FES because this was the only factor notably stabilised and/or reduced by methylprednisolone.

The role of C5a in FES is still unclear, and we were unable to find any relationship between the activation of C5 and the development of the subclinical or clinical FES. The in-vivo effect of methylprednisolone on serum C5a also remains unclear, and we were unable to demonstrate a reduction of C5a after the administration of methylprednisolone.
CONCLUSION

The routine early administration of intravenous methylprednisolone to patients admitted with long-bone fractures offers advantages in the maintenance of $P_2O_2$ levels and a reduction in the incidence of the fat embolism syndrome. Several problems remain, among them the role of the C5a factor, and the possible value of a more prolonged course of intravenous steroids.

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