Review Article

FAT EMBOLISM SYNDROME: A REVIEW OF THE LITERATURE

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ABSTRACT

Fat embolism syndrome is a serious manifestation of fat embolism phenomenon characterized clinically by triad of dyspnoea, petechiae and mental confusion and usually follows long bone fractures. Its classic presentation consists of an asymptomatic interval followed by pulmonary and neurologic manifestations combined with petechial haemorrhages. The syndrome follows a biphasic clinical course. Unlike other embolic events, the vascular occlusion in fat embolism is often temporary or incomplete since fat globules do not completely obstruct capillary blood flow because of their fluidity and deformability.The late presentation is thought to be a result of hydrolysis of the fat to more irritating free fatty acids which then migrate to other organs via the systemic circulation. There is no specific therapy for fat embolism syndrome; prevention, early diagnosis, and adequate symptomatic treatment are of paramount importance. It is a self-limiting disease and treatment is mainly supportive

KEYWORDS: Long bone fracture, fat emboli, petechiae and supportive treatment.

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INTRODUCTION

The term 'Fat embolism' indicates the presence of fat globules in the peripheral circulation and lung parenchyma after fracture of long bones, pelvis or other major trauma.

Fat embolism syndrome is a collection of respiratory, haematological neurological and cutaneous symptoms and signs associated with trauma and other disparate surgical and medical conditions.

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HISTORICAL PERSPECTIVES

The first animal model of fat embolism was described over 330 years ago by Lower who injected intravenous milk into dogs[1]. Magendie performed more elaborate studies in the early 19th century and observed that intravenous injection of oil led to mechanical obstruction of small vessels by fat globules[1].

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In 1861, Zenger described fat droplets in the lung capillaries of railroad worker who sustained a fatal thoraco-abdominal crush injury[2].

In 1873, Von Bergmann was first to establish the clinical diagnosis of fat embolism syndrome[3]. In 1914, Tanton proposed that adequate fracture immobilization could help prevent the syndrome [4].

EPIDEMIOLOGY

Although fat embolism may occur in up to 90% of trauma patients[5], fat embolism syndrome occurs in only 2-5% of patients with long bone fractures[6].Patient with a single long bone fracture have a 1- 3 percent chance of developing FES, this increases in correlation with the number of fractures.

Fat embolism and FES are also more likely to occur after closed, rather than open fractures. Two events promote entrance of marrow contents into the circulation following a fracture i.e movement of unstable bone fragments and reaming of the medullary centre during placement of an internal fixation device.

It was also observed that the incidence of FES is lower (0.9%) when clinical criteria are used to diagnose FES as compared to post-mortem examination with incidence as high as 20% [7].

Incidence is also higher in young men as they are more prone to high velocity road traffic accidents. The syndrome occurs mostly in adults and rarely in children, as in children, the bone marrow contain more of hematopoietic tissue and less of fat.

CAUSES/RISK FACTORS

FES is commonly associated with traumatic fracture of femur,pelvis and tibia and postoperatively, after intramedullary nailing and pelvic and knee arthroplasty. Some non-traumatic conditions like diabetes pancreatitis etc have been found to be associated with this condition [8,9]. (See Table 1)

PATHOGENESIS/PATHOPHYSIOLOGY

Three major theories have been proposed [10]

1) **The Mechanical Theory**

According to this theory, proposed by Gauss in 1924, trauma to long bones release fat droplets by disrupting fat cell in the fractured bone or in adipose tissue. These fat droplets enter the torn veins near long bone. This occurs when the intramedullary pressure is higher than venous pressure. Fat droplets are then transported to pulmonary vascular bed where large fat globules result in mechanical obstruction and are trapped as emboli in the lung capillaries. Some of these fat droplets may pass through the lung and reach systemic circulation causing embolization to the brain, skin ,kidney or retina.

Fat droplets can also pass to the systemic circulation via pulmonary precapillary shunts and existing pathological venous-arterial communication such as patent foramen ovale[11,12].

2) **Biochemical Theory**

It was given by Lehmann and Moore in 1927, which states that embolized fat is degraded in plasma to free fatty acids. These free fatty acids have also been associated with cardiac contractile dysfunction, a feature of fat embolism syndrome.

Serum from acutely ill patients has been shown to have the capacity to agglutinate chylomicrons ,low density lipoproteins, and liposomes of nutritional fat emulsions. C-reactive protein, which is elevated in these patients, appears to be responsible for lipid agglutination and may also participate in the mechanism of non-traumatic FES. Co-existing shock, hypovolemia and sepsis ,impaired liver function augment toxic effects of free fatty acids.

3) **Coagulation Theory**

This states that tissue thromboplastin is released with marrow elements following long bone fractures. This activates the complement system and extrinsic coagulation cascade via direct activation of factor VII that leads to the production of intravascular coagulation products such as fibrin and fibrin degradation products.

These products along with leucocytes,platelets and fat globules combine to increase pulmonary vascular permeability ,both by their direct actions on the endothelial lining and through the release of numerous vasoactive substances. These substances also cause platelet activation[13,14].

CLINICAL FEATURES

Fat embolism syndrome typically presents 12-72 hours after the initial injury. Rarely, cases occur as early as 12hours or as much as 2weeks later[15].Patients present with a classic triad of : respiratory manifestations(95%), cerebral effects(60%) and petechiae(33%)[16,17].

Respiratory changes are often the first clinical feature to present. Dyspnoea, tachypnoea and hypoxemia are the most frequent early findings. Hypoxemia may be detected hours before the onset of respiratory complaints[18].The severity of these symptoms vary but a number of cases may progress to respiratory failure(10% of cases). A syndrome indistinguishable from acute respiratory distress syndrome(ARDS) may develop. Approximately one-half of the patients with FES caused by long bone fractures develop severe hypoxemia and respiratory insufficiency and require mechanical ventilation[19].

CNS manifestations result from cerebral embolism frequently present in the early stages and often occur after the development of respiratory distress. These changes are non-specific, ranging from acute confusion to drowsiness, rigidity, convulsions or coma. Focal neurological signs like hemiplegia, aphasia ,apraxia, visual field disturbances and anisocoria have been described. Cerebral edema contributes to the neurological deterioration[20], although almost all neurological deficits are transient and fully reversible[21]

Dermatological manifestations may be the last component of the triad to develop with characteristic petechial rash. It is due to embolization of small dermal capillaries leading to extravasation of erythrocytes. This rash(reddish-brown) appears on the upper part of the body especially the neck, chest, axilla, shoulder, upper arm, oral mucous membranes and conjunctivae[22].

It is believed to be the only pathognomic feature of fat embolism syndrome and usually appears within the first 36hours and is self-limiting ,disappearing completely within 7days.

Ocular manifestations, Purtscher's retinopathy (on fundoscopy) may be seen consisting of cotton wool exudates ,macular edema and macular haemorrhage.

Other manifestations are non-specific which include tachycardia , pyrexia(mild but may increase up to 39oC) , lipuria, oligura or anuria jaundice. There may be history of orthopaedic or plastic surgical procedure or parenteral lipid transfusion.

INVESTIGATIONS

A wide range of investigations have been used to identify FES. However, none of these is 100% specific. These investigations are usually performed to support the clinical diagnosis or to monitor therapy. They include:

Haematology and Biochemistry:- Thrombocytopenia (platelet count <150 x 109/L in up to 50% of patients) and unexplained anemia(70% of patients) are common. Blood lipid concentration is not helpful for diagnosis because circulating fat concentrations do not correlate with the severity of FES. Hypocalcemia(due to binding of free fatty acids to calcium) and elevated serum lipase have also been reported[21].Hypofibrinogenemia ,raised ESR and prolongation of prothrombin time may be seen.[16,23]

Arterial blood gases:- This reveals a low partial pressure of oxygen(often below60mmHg) and a low partial pressure of carbon dioxide with respiratory alkalosis. An unexplained increase in pulmonary shunt fraction alveolar-to-arterial oxygen tension difference, especially within 24-48hours of potentially causative event is strongly suggestive of FES.

Cytologic examination of urine, blood and sputum with Sudan or oil red O staining may detect fat globules that are either free or in macrophages. This test is not sensitive, however ,and does not rule out fat embolism.

Chest X-ray:- The chest X-ray is often normal initially but in some patients bilateral fluffy shadows develop as respiratory insufficiency worsens. A minority has diffuse or patchy air space consolidation due to oedema or alveolar haemorrhage(most prominent in the periphery and bases). The classical finding on CXR is multiple flocculent shadows (snow storm appearance), which may remain up to 3weeks.[24]

CT Chest- Focal areas of ground glass opacification with interlobular septal thickening are generally seen on chest CT but ill-defined centrilobular and subpleural nodules representing alveolar oedema, micro-haemorrhage and inflammatory response secondary to ischaemia and cytotoxic emboli may be seen[25]

Lung scans:- It may show ventilation perfusion mismatch. In the initial phase ,the V/Q ratio is often high and this phase merges imperceptibly with the stage characterized by low V/Q and fulfilling Gurd's criteria.[26]

ECG :- It is usually normal except for non-specific sinus tachycardia. However, non-specifc ST-T changes, right axis deviation and RBBB may be seen in fulminant cases.

Transoesophageal echocardiography:- may be of use in evaluating intra-operative release of marrow contents into blood stream during intramedullary reaming and nailing. The density of the echogenic material passing through the right side of the heart correlates with the degree of reduction in arterial oxygen saturation. Embolization of marrow contents through patent foramen ovale also has been noted.

Bronchoalveolar lavage(BAL):- The use of bronchoscopy with BAL to detect fat droplets in alveolar macrophages has been described in trauma patients and sickle cell patients with acute chest syndrome. However, diagnostic criteria vary and the sensitivity and specificity are unknown.

CT Brain:- Findings may be normal or may reveal diffuse white matter petechial haemorrhages consistent with microvascular injury. It may show generalized cerebral oedema or atrophy in patients with severe cerebral fat embolism[27].

BrainMRI:- Spotty areas of high intensity may be seen on T2 weighted image. It may be useful in patients with neurological features of fat embolism and a normal CT scan[28].It has been shown to be useful in early diagnosis of FES.

DIAGNOSIS

Clinical examination preferred over diagnostic.There are different criteria which are Gurd'scriteria, Lindeque's criteria and Schonfeld'scriteria.

GURD'S CRITERIA

Major Criteria

- Axillary or subconjuctivalpetechiae
- Hypoxaemia PaO_2<60mmHg, FI o2 =0.4
- Central nervous system depression disproportionate to hypoxaemia
- Pulmonary edema

Minor Criteria

- Tachycardia <110bpm
- Pyrexia< 38.5^{O}C
- Emboli present in the retina on fundoscopy
- Fat globules present in urine
- A sudden inexplicable drop in haematocrit or platelet values
- Increasing ESR
- Fat globules present in sputum
- Renal changes(anuria or oliguria)
- Jaundice

The diagnosis of FES requires at least 1 major and 4 minor criteria plus fat macroglobulaemia

LINDEQUE'S CRITERIA

1. A sustained Pa O2 < 8kpa
2. A sustained Pa CO2 >7.3 kpa or a pH<7.3
3. A sustained respiratory rate >35breaths/min, despite sedation
4. Increased work of breathing judged by dyspnoea, accessory muscle use, tachycardia, anxiety

Diagnosis is based on femur fracture +/- tibia fracture + 1 feature

SCHONFELD'S CRITERIA(Fat embolism index)

Clinical features	Scores
Petechiae	5
Chest X-ray changes(diffuse alveolar infiltrates)	4
Hypoxemia (Pa O2 <9.3 kpa)	3
Fever (>38oc)	1
Tachycardia(>120bpm)	1
Tachypnoea(>30breaths/min)	1
Confusion	1

Cumulative score >5 required for diagnosis

MANAGEMENT

Management involves both medical and surgical treatment.

Medical therapy includes adequate oxygenation and ventilation ,blood and blood products, crystalloid and colloids as clinically indicated ,hydration , prophylaxis of deep vein thrombosis and stress related gastrointestinal bleeding and nutrition.

Various drugs have been tried but with inconclusive results. These include:

- **Corticosteroids:-** The mechanism of action is largely as an anti-inflammatory agent, reducing the perivascular haemorrhage and oedema. Other possible beneficial effects includestabilization of the pulmonary capillary membrane, stabilizing complement system activation and inhibiting platelet aggregation. The use of methylprednisolone (9 -90 mg/kg in divided doses) has been shown to have these beneficial effects[28]
- **Aspirin:-** It blocks the production of thromboxane which occurs in animal models of Fat embolism[29, 30]. Studies have shown that patients with uncomplicated fractures treated with aspirin resulted in significant

normalization of blood gases ,coagulation proteins, and platelet numbers when compared with controls.[21]

- **Heparin:-** It is known to clear lipaemic serum by stimulating lipase activity and has been advocated for the treatment of FES. However, the evidence for heparin treatment in FES is contradictory[31,32]. There is also a possibility of increased risk of bleeding in patients with multiple trauma treated with heparin[21]. Heparin reduces platelet adhesiveness and thus reduce formation of microaggregates.
- **N-acetylcysteine:-** It was observed that posttreatment with N-acetylcysteine abrogated changes induced by fat embolism in rat lungs which include increase protein concentration in BALpulmonary hypertension, increased capillary coefficient etc.
- **Human albumin:-** Albumin's properties are that of chelating free fatty acids and avoiding their toxicity. Based on this evidence, the use of Albumin-IV was proposed and tested for FES treatment, but has never been adopted due to lack of benefit evidences[33,34,35]

So, there is no specific therapy for fat embolism syndrome; prevention, early diagnosis, and adequate symptomatic treatment are of paramount importance. It is a self-limiting disease and treatment is mainly supportive which includes:

1. **Spontaneous ventilation:-** This should be the initial management of hypoxia done by administering oxygen using facemask and high flow gas delivery system (delivers FIO2 of 50-80%).
2. **CPAP and non-invasive ventilation:-** Continuous positive airway pressure(CPAP) may be added to improve PaO2 without increasing FIo2 .Mechanical ventilation may also be applied via CPAP mask and has been used successfully in patients.
3. **Mechanical ventilation and PEEP:-** If a FIo2 of >60% and CPAP of >10cm are required to achieve a PaO2>60mmHg, then endotracheal intubation, mechanical ventilation with PEEP. The principal objective of PEEP and mechanical ventilation is to accomplish adequate gas exchange without inflicting further lung injury. While PEEP may be associated with an increase in PaO2 occasionally it can decrease the PaO2 by increasing right atrial pressure and decreasing cardiac output. Therefore, close monitoring of arterial blood gases and haemodynamic status is required when PEEP and mechanical ventilation are used.
4. Vasoactive drugs e.gdopamine, dobutamine, noradrenaline may be used if volume restoration is not adequate despite use of crystalloids or colloids.

SURGICAL THERAPY

Early immobolization of fractures reduces the incidence of FES and the risk is further reduced by operative correction rather than conservative management. Another strategy to prevent FES is to limit the elevation in intraosseous pressure during orthopaedic procedures, in order to reduce the intravasation of intramedullary fat and other debris[36]

Other operative refinements may also serve to limit intraosseous pressure including the use of cementless fixation of hip prostheses and undreamed intramedullary femoral shaft stabilization[36]

PROPHYLACTIC TREATMENT

Albumin has been recommended for volume resusucitation ,especially in cases of hypoproteinaemia ,because it not only restores blood volume but also binds fatty acids and may increase the extent of lung injury[10]. The use of corticosteroids for prophylaxis is controversial.

COMPLICATIONS

1. Pulmonary fat embolism –can lead to death
2. Systemic fat embolism -These may get lodged in capillaries of organs like brain ,kidney, skin etc. Causing haemorrhage and microinfarcts
3. Corpulmonale –may occur if adequate compensatory pulmonary vasodilation does not occur.

PROGNOSIS

The major cause of death in FES patients is progressive respiratory failure. The duration of FES is difficult to predict. Prognosis is good except in fulminant cases. Mortality is estimated to be 5-15% overall, but most patients will recover fully[37,38]

Table 1: Conditions associated with fat embolism

Trauma-related	
	Long bone fractures
	Pelvic fractures
	Fractures of other marrow-containing bones
	Orthopaedic procedures
	Soft tissue injuries(e.g chest compression with or without rib fractures)
	Burns
	Liposuction
	Bone marrow harvesting and transplant
Non-trauma related	
Pancreatitis	
	Diabetes mellitus
	Osteomyelitis and panniculitis
	Bone tumour lysis
	Steroid therapy
	Sickle cell haemoglobinopathies
	Alcoholic (fatty) liver disease Lipid infusion ; Cyclosporine A solvent

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