Role of Interleukin-6 as an Early Marker of Fat Embolism Syndrome: A Clinical Study

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Abstract

Background A few animal studies have shown that IL-6 can serve as an early marker of fat embolism syndrome. The degree to which this is true in human trauma victims is unknown.

Questions/purposes In this clinical study, we sought to determine (1) whether elevated serum IL-6 levels at 6, 12, and 24 hours in patients with skeletal trauma were associated with the development of fat embolism syndrome (FES) within 72 hours after injury, and (2) at what time after trauma peak IL-6 levels are observed.

Each author certifies that he or she, or a member of his or her immediate family, has no funding or commercial associations (eg, consultancies, stock ownership, equity interest, patent/licensing arrangements, etc) that might pose a conflict of interest in connection with the submitted article.

All ICMJE Conflict of Interest Forms for authors and *Clinical Orthopaedics and Related Research* editors and board members are on file with the publication and can be viewed on request. Each author certifies that his or her institution approved the human protocol for this investigation, that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained. This work was performed at the Department of Orthopaedics, Postgraduate Institute of Medical Education and Research, Chandigarh, India.

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Methods Forty-eight patients between 16 and 40 years old who presented to our tertiary trauma center within 6 hours of injury with long bone and/or pelvic fractures were included in this study. Serum IL-6 levels were measured at 6, 12, and 24 hours after injury. The patients were observed clinically and monitored for 72 hours for development of FES symptoms. Gurd's criteria were used to diagnose FES.

Results Elevated serum IL-6 levels 12 hours after trauma correlated with an increased likelihood of having FES develop; no significant relationship was observed between IL-6 levels at 6 or 24 hours and the development of FES. Patients with FES had a mean IL-6 level of 131 pg/mL, whereas those without FES had a mean IL-6 level of 72 pg/mL. Peak IL-6 levels were observed at 12 hours.

Conclusions An elevated serum IL-6 level may be useful as an early marker of FES in patients with isolated skeletal trauma.

Level of Evidence Level II, diagnostic study. See Guidelines for Authors for a complete description of levels of evidence.

Introduction

Fat embolism syndrome (FES) is a serious manifestation of long bone fractures characterized clinically by a triad of

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dyspnea, petechiae, and mental confusion [1, 11]. The reported incidence of FES is 2% to 22% in patients with skeletal injury. It is fatal in 10% to 36% of patients [24]. The diagnosis of FES is supported by few clinical signs and symptoms, and there is no specific test to confirm the diagnosis. Its pathogenesis is based on mechanical and biochemical theories: the former including fat droplets from the bone marrow embolizing to the lung and brain as a consequence of the fracture, and the latter including local reaction of the lungs to the emboli and toxic effect of free fatty acids in the pulmonary system [21]. The ultimate manifestation of FES is dependent on the inflammatory response of the lungs to the fat emboli and its toxic products [5]. Several cytokines such as tumor necrosis factor- α , CD-11b expression, IL-1, IL-6, phospholipase A2, E-selectin, and elastase have been implicated in the pathogenesis of lung changes following fat embolism [6, 8].

IL-6 is a multifunctional glycoprotein that plays an important role in host defense, acute phase reactions, immune response, and hematopoiesis. IL-6 correlates well with the degree of injury and appears to be a reliable index of the magnitude of systemic inflammation [18]. After trauma, the IL-6 level has been shown to rise substantially and proportionally to the extent of injury [20]. A few animal studies have shown IL-6 can act as an early marker of FES [23, 27]. The degree to which this is true in human trauma victims is unknown.

In this clinical study, we sought to determine (1) whether elevated serum IL-6 levels at 6, 12, and 24 hours in patients with skeletal trauma were associated with the development of FES within 72 hours after injury, and (2) at what time after trauma are peak IL-6 levels observed?

Patients and Methods

We designed a prospective study to evaluate the role of IL-6 as a serologic marker in FES. The study period was 18 months, starting from July 2010 to December 2011. We obtained ethical clearance from the institutional board before the study was initiated. All patients with orthopaedic trauma admitted to our Level I trauma center were evaluated by the emergency trauma team for possible inclusion in this study. Initial resuscitative measures were provided and then splintage and radiographs of the body part with suspected musculoskeletal injuries were obtained. The magnitude of injury was assessed using the New Injury Severity Score (NISS) [17]. A NISS greater than 16 was considered for diagnosis of polytrauma.

We included patients between 16 and 40 years old with normal BMI (between 19 and 25 kg/m²) who presented within 6 hours of their injury with long bone fractures (isolated femur fracture or multiple long bone fractures)

and/or pelvic fracture. Presence of open or pathologic fracture, cardiac or respiratory disease, smoking history, major systemic illness, or other systemic injury (head, chest, or abdominal injuries) were contraindications for inclusion in this study. We obtained written informed consent from all patients before recruiting them in this study.

Of 6124 patients with trauma with an orthopaedic element, 48 (38 males, 10 females; mean age, 27.5 years) met the inclusion criteria (Fig. 1). Thirty-five patients had a NISS greater than 16 and 13 had a NISS of 16 or less. The patients were admitted to the trauma ward with intensive care facilities. They were monitored for 72 hours and were observed closely for manifestations of FES regardless of intermediate surgical intervention. The fractures were treated using standard surgical techniques. Six patients underwent surgery within 24 to 48 hours and remaining 42 patients underwent surgery within 48 to 72 hours.

We monitored the following clinical and laboratory parameters regularly during this period: (1) petechiae (axillary/subconjunctival); (2) complete records of temperature, pulse rate, blood pressure, and respiratory rate were maintained every 4 hours; (3) fundus examination was performed at least once a day for 3 days; (4) a posteroanterior radiograph of the chest was taken at the time of admission and then every 24 hours for the initial 72 hours; (5) blood parameters (at 6, 24, 48, and 72 hours) including hemoglobin, erythrocyte sedimentation rate (ESR), coagulation profile (prothrombin time, partial thromboplastin time, fibrinogen, D-dimer), platelet count, and blood gas analysis; (6) serologic estimation of IL-6 (at 6, 12, and 24 hours after injury); and (7) urine was examined for presence of fat globules once daily for 3 days.

The patients were evaluated for FES as per Gurd's criteria [13]. The clinical diagnosis of FES was made by at least two major symptoms or signs, or one major and four minor symptoms or signs.

The blood samples (volume 5 mL) were drawn from the peripheral vein (brachial vein or femoral vein) and collected in a pyrogen and endotoxin-free collecting tube for serologic estimation of IL-6 at 6 hours, 12 hours, and 24 hours after injury. The sample was allowed to clot and then it was centrifuged for 10 minutes to extract serum. The serum was preserved in a CryoVial[®] (Biomax Corporation, Chandigarh, India) in a frozen condition (−70° C). On the day of analysis, samples were thawed to room temperature. IL-6 level was estimated using Gen-Probe Human IL-6 enzyme-linked immunosorbent assay kit (Gen-Probe Diacclone, Besançon, France) per the manufacturer's instructions by the quantitative sandwich immunoassay technique.

We analyzed the clinical, biochemical, and hematologic parameters at different intervals to observe their sequential

Fig. 1 The flow chart shows the selection method for recruitment of patients in this study.

changes in patients diagnosed with and without FES. Similarly, serum IL-6 level changes between patients with and without FES were analyzed. We used a descriptive statistical test to evaluate the mean and SE. The changes of IL-6 in patients at different intervals were analyzed using a paired t-test. An independent sample test was used for comparison of IL-6 levels between patients who were diagnosed as having FES or not having FES according to Gurd's criteria. The difference was considered significant with a p less than 0.05.

Results

Eleven of 48 patients (23%) had FES develop within 72 hours of injury; five patients had FES develop between 24 and 48 hours and six patients between 48 and 72 hours (Table 1). Fourteen patients had hypoxic changes, and 10 of these 14 had FES. Petechiae and central nervous system depression were seen in nine of 11 patients who had FES develop. The classical triad of FES symptoms was seen in six patients (55%). Elevated serum IL-6 levels 12 hours after trauma correlated with an increased likelihood of having FES develop; no significant relationship was observed between IL-6 levels at 6 or 24 hours and the development of FES (Fig. 2). Patients with FES had a mean IL-6 level of 131 pg/mL, while those without FES had a mean IL-6 level of 72 pg/mL at 12 hours of injury ($p < 0.0001$, Table 2). Analysis with coordinates of the curve revealed that serum IL-6 level greater than

134 pg/mL at 12 hours has a sensitivity of 73% and specificity of 92% in diagnosis of FES.

The peak IL-6 levels were observed at 12 hours in all patients (Fig. 2). Whereas the increase in serum IL-6 between 6 and 12 hours was significant only in patients with FES ($p < 0.0001$, Table 3), the decrease in its level between 12 and 24 hours was significant in both groups of patients (with FES, $p < 0.0001$ and without FES, $p = 0.045$).

Discussion

In this clinical study, we sought to determine whether elevated serum IL-6 levels at 6, 12, and 24 hours in patients with skeletal trauma were associated with the development of FES within 72 hours after injury, and at what time after trauma are peak IL-6 levels observed? The diagnosis of FES is still based on clinical examination and there is no laboratory marker available to confirm the diagnosis [1, 11, 14]. Researchers have proposed several cytokines that can be used as early markers of FES [6, 8, 23, 25, 27], however a proper clinical study on human trauma victims on these markers is lacking. IL-6 is one of the early inflammatory mediators of FES that has been studied in a few animal studies [23, 27]. Sears et al. [23] observed a major increase in IL-6 levels in serum and lung tissue at 6 hours after injury in rats after bilateral femur fracture. They advocated that IL-6 concentration in lung tissues correlates with the serum level. In a similar animal study, Yoga et al. [27] simulated fat embolism in rats by putting an intramedullary pin in the femur. The amount of fat

Table 1. Demographic characteristics of patients

Patient	Age (years)/sex	NISS	Mode of injury	Injury details	FES	Time to development of FES
1	40/M	27	RSA	BL SOF, SPR, IPR, proximal tibia	Absent	—
2	40/M	18	RSA	SOF, mandible	Absent	—
3	28/F	27	RSA	IT with SOF, lateral condyle humerus	Absent	—
4	38/M	22	RSA	SOF, iliac blade, BB forearm	Absent	—
5	18/M	18	RSA	SOF, radius	Absent	—
6	22/M	22	RSA	SOF, BB leg	Present	48–72 hours
7	25/M	18	RSA	BL SOF	Absent	—
8	40/M	27	RSA	SOF, segmental BB leg, acetabulum	Absent	—
9	19/F	14	RSA	SOF	Absent	—
10	21/M	27	RSA	SOF, malleolus, pelvis	Absent	—
11	19/M	22	RSA	SOF, BB leg	Present	48–72 hours
12	18/F	19	RSA	SOF,SPR IPR	Absent	—
13	32/M	14	RSA	SOF	Present	24–48 hours
14	24/M	14	RSA	SOF	Absent	—
15	28/F	22	RSA	SOF, BB leg	Absent	—
16	25/M	22	RSA	SOF, patella	Absent	—
17	22/M	19	RSA	SOF, knee DL	Present	48–72 hours
18	25/F	13	RSA	SOF	Absent	—
19	23/M	27	RSA	SOF, NOF, BB leg	Absent	—
20	20/F	22	RSA	SOF, NOF	Absent	—
21	21/M	27	RSA	SOF, acetabulum, distal radius	Present	24–48 hours
22	35/M	22	RSA	SOF, BB forearm	Absent	—
23	40/M	14	RSA	SOF	Absent	—
24	32/M	22	RSA	SOF, patella	Absent	—
25	21/F	13	RSA	SOF	Present	24–48 hours
26	25/M	27	FALL	SOF, calcaneum, patella	Absent	—
27	40/M	14	RSA	SOF	Absent	—
28	20/M	22	RSA	SOF, BB leg	Absent	—
29	24/M	27	RSA	SOF with ST femur, iliac blade	Present	48–72 hours
30	35/M	14	RSA	SOF	Absent	—
31	18/M	22	RSA	SOF, BB leg	Absent	—
32	40/M	19	RSA	SOF, patella	Present	24–48 hours
33	39/F	27	RSA	SOF, BB forearm, BB leg	Absent	—
34	30/M	19	RSA	SOF, proximal tibia	Present	48–72 hours
35	30/M	22	RSA	SOF, 3 rd ,4 th ,5 th metatarsals	Absent	—
36	25/M	22	RSA	SOF, SOH	Absent	—
37	30/M	22	RSA	SOF, distal humerus,	Absent	—
38	35/M	14	Fall	SOF	Absent	—
39	25/F	13	RSA	SOF	Absent	—
40	40/M	27	RSA	SOF, BB forearm, SOH	Absent	—
41	36/F	22	RSA	SOF, BB leg	Present	24–48 hours
42	16/M	22	RSA	SOF, BB leg	Absent	—
43	28/M	13	RSA	SOF,	Absent	—
44	20/M	14	RSA	SOF	Absent	—
45	26/M	27	RSA	BL SOF, BB leg	Absent	—
46	20/M	27	RSA	SOF, BB forearm, BB leg	Present	48–72 hours
47	23/M	14	RSA	SOF	Absent	—

Table 1. continued

Patient	Age (years)/sex	NISS	Mode of injury	Injury details	FES	Time to development of FES
48	21/M	22	RSA	SOF, SOH,	Absent	–

NISS = New Injury Severity Score; FES = fat embolism syndrome; RSA = road side accident; BL = bilateral; DL = dislocation; BB = both bones; SOF = shaft of femur; SPR = superior pubic rami; IPR = inferior pubic rami; NOF = neck of femur; ST = subtrochanteric; IT = intertrochanteric; SOH = shaft of humerus.

Fig. 2 Serum IL-6 level in patients with and without FES at various times. FES = fat embolism syndrome; P = present, A = absent.**Table 2.** Serum IL-6 level at 6, 12, and 24 hours of injury

IL-6 samples	FES	Number of patients	Mean (pg/mL)	Standard error of mean	Difference in IL-6 level between both groups (t-test)
6 hours	Present	11	78.55	9.783	$p = 0.374$
	Absent	37	66.54	6.667	
12 hours	Present	11	130.91	15.098	$p = 0.000$
	Absent	37	72.00	7.063	
24 hours	Present	11	76.36	8.984	$p = 0.316$
	Absent	37	63.62	6.294	

FES = fat embolism syndrome.

Table 3. Statistical analysis of changes in serum IL-6 level at different intervals*

Pair number	Paired samples	Patients with FES p value	Patients without FES p value
Pair 1	Samples at 6–12 hours	0.000	0.218
Pair 2	Samples at 6–24 hours	0.777	0.494
Pair 3	Samples at 12–24 hours	0.000	0.045

* Paired t-test; FES = fat embolism syndrome.

droplets seen in the lungs was correlated with serum IL-6 levels, and they concluded that IL-6 level at 12 hours after injury can serve as an early marker of FES. To our knowledge, our study is first clinical study on human trauma victims to prove this inflammatory mediator as an early marker of FES.

There are a few limitations in this study. The sample size was small and clinical diagnosis of FES was established using Gurd's criteria [13], which have not been proved as the gold standard clinical diagnostic criteria of FES. Although some researchers believe that Gurd's criteria may underdiagnose FES, there is in fact no gold standard diagnostic criterion to identify this condition and Gurd's criteria are still the most frequently used diagnostic criteria of FES [12, 14, 15, 22]. Some researchers believe that a high index of suspicion and close observation for the subtle signs of FES in vulnerable patients may diagnose the syndrome accurately [12, 14, 24]. The selective inclusion of healthy young patients with long bone or pelvic fractures in our study screened the most vulnerable trauma victims who are likely to have FES develop. The pathognomonic sign of FES, the rash (petechiae), was observed in 82% of patients with FES and the clinical triad was observed in 54% of patients with FES in our study. The most common manifestation of FES is respiratory (hypoxia, usually seen in 96% patients [1, 12, 14, 24]) and it was observed in 91% of patients with FES. Among 14 patients with hypoxic features, 10 were diagnosed with FES taking other major and minor signs and symptoms of Gurd's criteria into consideration. Thus, we believe we could diagnose FES accurately with Gurd's clinical criteria. The prospective nature of the study and close observations of patients for the initial 72 hours by an experienced trauma team further clarified the accuracy of diagnosis. Despite the small sample size, the study has shown a highly significant correlation between IL-6 at 12 hours and FES and therefore proves its role as an inflammatory marker in FES.

It also has been proven that the level of serum IL-6 can be altered with fracture fixation types (for example, intramedullary nailing increases serum IL-6 level), blood loss, and timing of surgery [10]. However, these variables are unlikely to compromise the conclusion of the study. None of the patients in this study underwent surgery within 24 hours and therefore there were no effects of fracture fixation types, blood loss, and

timing of surgery on serum IL-6 level. We followed a standard treatment protocol for all our patients, therefore the treatment modality for both groups of patients remained uniform.

Serum IL-6 at 12 hours after injury correlated significantly with subsequent development of FES. Although increase in serum IL-6 levels between 6 and 12 hours after injury were observed in all patients, the increase in IL-6 were significant only in the patients in whom FES developed and they were moderate in patients who did not have FES develop. The difference in serum IL-6 levels between both groups of patients was significant only at 12 hours after injury. Severe inflammatory reactions in the lung parenchyma of patients with FES may be the possible explanation for the excessive increase in serum IL-6 level in this group of patients. Fat embolism occurs in almost all cases of long bone fractures; however, FES develops only in a few of them. The pathogenesis of FES involves an inflammatory response to embolized fat droplets and their toxic metabolic products in the lung parenchyma leading to hemorrhage and leakage of proteins into the alveoli. IL-6 acts as an early inflammatory mediator in this pathogenesis and is believed to correlate with disease severity [8, 10]. Few other functions further explain the surplus increase of IL-6 in patients with FES. IL-6 is responsible for adipose tissue metabolism, lipoprotein lipase activity, and hepatic triglyceride secretion [2]. The IL-6 gene shows polymorphism and variable expressions leading to abnormalities in IL-6 transcription rate. Experimental studies in humans comparing the activity of this gene have shown patients with polymorphism of IL-6 gene are prone to lipid abnormalities [3]. Yoga et al. hypothesized this abnormal IL-6 transcription could lead to an abnormal reaction to fat emboli in the lungs and development of full-blown FES [27].

The peak in serum IL-6 level was observed at 12 hours in this study in all trauma patients. Numerous authors have reported stimulation of the inflammatory system after trauma and we had a similar observation [4, 7–9, 16–19, 26]. Serum IL-6 level is associated with inflammatory activity and exhibits more rapid increase and quicker return to normal values than C-reactive protein and ESR [26]. The IL-6 level typically increases after surgery and attains a peak in the first 6 to 12 hours. It then decreases and returns to its baseline range by 48 to 72 hours postoperatively [26]. As none of our patients underwent surgery within 24 hours of injury, we confirmed that following skeletal injury serum IL-6 level increases and attains its peak at 12 hours and then shows a declining trend.

This prospective study confirmed the role of IL-6 as an early marker of FES. In isolated skeletal injuries, the IL-6 level at 12 hours after injury predicts subsequent development of FES. The future directions of research should focus on this inflammatory mediator if it can be used to prognosticate the outcome of FES. Future studies also are needed to gather information regarding IL-6 expression

and its molecular mechanism in FES so that new methods of treatment including IL-6 receptor antibodies or antagonists can be developed for the management of FES.

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