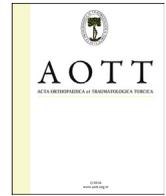




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Comparative investigation of percutaneous plating and intramedullary nailing effects on IL-6 production in patients with tibia shaft fracture



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ABSTRACT

Objective: The aim of this study was to analyze the effect of intramedullary nailing (IMN), open plating and percutaneous plating on the induction of IL-6 in patients with tibia fractures.

Methods: A total of 30 patients with tibia shaft fracture underwent either intramedullary nailing (IMN, n = 15; 14 males and 1 female; mean age: 32.1 ± 15.6), ORIF plating (n = 8; 5 males and 3 females; mean age: 60.0 ± 17.8), or percutaneous plating (n = 7; 6 males and 1 female; mean age: 43.1 ± 21.4). Serum IL-6 cytokine levels were measured prior to, and 6 and 24 h after the surgery, using a special ELISA kit.

Results: The IL-6 concentration increased to peak levels at 6 h in both IMN and percutaneous plating groups, and at 24 h in ORIF plating group ($p < 0.001$). The mean IL-6 concentration of percutaneous plating group was significantly lower than that of the IMN group at 6 h following the surgery ($p = 0.022$). In addition, the mean IL-6 concentration of ORIF plating group was significantly higher than that of the percutaneous plating group at 24 h post operation ($p = 0.009$).

Conclusion: Our results suggest that percutaneous plating compared to the IMN has lower effects on IL-6 production in patients with tibia fracture.

Level of evidence: Level III, therapeutic study

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Introduction

Tibial fractures, similar to femoral fractures or other traumas can be considered as a “first hit” causing an inflammatory response¹ that, if improperly managed during surgical procedure by the clinicians (second hit), may give rise to the production of inflammatory cytokine cascades leading to a condition, called systemic inflammatory response syndrome (SIRS), and eventually to multi-organ failure and patient's death.² It is widely accepted that adopting a suitable method of surgery with minimal challenge on the immune system will be of upmost contribution to decrease risk of developing the SIRS in severely injured patients. In other words, the less invasive is the surgery method, the more favorable outcome will be achieved, in terms of preventing the SIRS and subsequent respective complications.

Early total care (ETC) refers to any attempts that culminate in the earliest possible definitive osteosynthesis in order to allow subsequent operations on the patients.³ In addition to considerable contribution to osteosynthesis, such attempts have been shown to lessen pulmonary complications, and lower hospitalization duration and total expenditure. Although the emergence of damage control orthopedic (DCO) concept which prioritizes life-saving procedures has challenged the ETC pitfalls such as poor timing and higher blood loss; until now,⁴ no definite notion exists regarding the preference of each of the approaches over the other. Within the ETC, all long bone fractures are early stabilized using instruments such as IMN and plating, etc.⁵ In contrast, an external fixator serves as a workhorse of DCO⁶; though, some disadvantages of external fixation, such as higher contamination rates of the fixator, further surgery to remove the fixator and definite fixation, have shed doubt on the use of this method in DCO in the recent decades.⁷

Interleukin 6 (IL-6) is an inflammatory cytokine that its serum level systematically enhances following any trauma.⁸ Also, a fortified serum level of IL-6 in the traumatized has been suggested to

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reflect the second hit phenomenon leading to the SIRS. Particularly, it has been shown that the intramedullary nailing (IMN) of femoral fractures may be associated with induction of IL-6 and thereby increased risk of developing the SIRS in femoral fractures.⁹ However, the IMN impact on the induction of IL-6 in long bone fractures remains controversial.¹⁰

Regarding a very short line of evidence about the differences between effects of IMN and percutaneous plating on IL-6 level in tibial fractures as well as the uncertainty about the use of an external fixator in DCO management of patients with long bone fractures; herein, we ran a comparative investigation into the IMN, ORIF (open) plating and percutaneous (bridge) plating methods in terms of induction of IL-6 in patients with tibial shaft fractures.

Patients and methods

Study population

In a consecutive manner, 30 mono-trauma patients with tibia shaft fracture referring to Taleghani Hospital of Shahid Beheshti University of Medical Sciences, from August 2014 to May 2015, were entered to this study. To avoid complications associated with other injuries, only the patients with mono trauma and also close fractures were included. The type of fracture based on AO classification is was AO type A or B, and the type of soft tissue based on Tscherne classification was 0 or 1 diaphyseal or metaphyseal fracture. Those patients with multiple trauma, open fractures, and any medical conditions with elevated IL-6 such as; obesity, chronic heart failure, renal failure, ARDS, osteoporosis were excluded from the study. Also, the time between trauma and surgery in study groups was comparable; those with considerable difference regarding the duration between trauma and surgery were excluded, as well.

Standardized clinical examination of all patients was performed immediately after admission to the hospital. Then, according to the discretion of the physician and the extent of the fracture, the patients underwent one of three treatment surgery methods as follows; intramedullary nailing (IMN, $n = 15$), ORIF plating ($n = 8$), and percutaneous plating ($n = 7$), within 9 h, on average, after the admission. In order to avoid possible effect of tourniquet on IL-6 production, it was not used in the present study.

Monitoring serum IL-6 changes

Serum IL-6 cytokine level of all patients was measured prior to, and also 6 and 24 h post operation, using a special enzyme-linked immunosorbent assay (ELISA) kit (IL-6 ELISA MAX kit, BioLegend), according to the instructions of the kit's manufacturer. The test was performed in duplicates.

Ethics

The study's design and use of clinical information of the patients was approved by the ethics committee based at Research Deputy of Shahid Beheshti University of Medical Sciences. Also, an informed consent was obtained from patients or one of their first-grade relatives.

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS) software version 16 (IBM Co., Illinois, USA) and a graph was drawn using GraphPad Prism 5 software for windows (San Diego, CA, USA). The results were expressed as Mean \pm SD. Mean differences within and between the groups were compared by one-

way analysis of variance (ANOVA) followed by least-significant difference (LSD) PostHoc test. The differences with P value less than 0.05 were considered as statistically significant.

Results

Demographic characteristics

A total of 30 patients with tibia shaft fracture underwent close IMN, ORIF plating and percutaneous plating treatment surgery. Demographic characteristics of the patients are presented in Table 1; there was no significant difference among the groups regarding gender distribution of the patients ($P > 0.05$), while the mean age of patients in the ORIF plating group was significantly higher than that of the IMN group ($P = 0.001$).

Serum IL-6 changes

Results of the ELISA test on serum obtained from the patients before, and after the surgery showed that there were no significant difference between the serum IL-6 concentrations of the IMN, ORIF plating and percutaneous plating groups ($P > 0.05$), while significant changes in IL-6 concentrations were observed at 6 and 24 h post operation between the groups ($P < 0.05$). Also, the IL-6 concentration significantly increased to peak levels in both IMN and percutaneous plating groups at 6 h, whereas in ORIF plating group at 24 h post operation ($P < 0.001$). In addition, the IL-6 concentration showed a slight decrease at 24 h post procedure in both IMN and percutaneous plating groups ($P > 0.05$).

As depicted in Fig. 1 and Table 2, the mean IL-6 concentration of percutaneous plating group was significantly lower than that of the IMN group at 6 h after the surgery ($P = 0.022$), while no significant difference was seen neither between ORIF plating and the IMN groups ($P = 0.089$) nor between ORIF plating and percutaneous plating groups ($P = 0.516$). On the other hand, the mean IL-6 concentration of ORIF plating group at 24 h post operation was significantly higher than that of the percutaneous plating group ($P = 0.020$). Interestingly, no difference was found between the mean IL-6 concentrations of neither the ORIF plating and IMN groups ($P = 0.282$) nor the percutaneous plating and IMN groups ($P = 0.091$) at 24 h post operation.

Discussion

In this prospective cohort, we compared serum IL-6 changes between IMN, ORIF plating and percutaneous plating in patients with tibia fractures. To the best of our knowledge, our study is the first in this realm. Our findings revealed that percutaneous plating, compared to the IMN and ORIF plating less stimulated IL-6 production of IL-6 in patients with tibia shaft fractures.

Table 1

Demographic characteristics of the patient with tibia shaft fractures involved in the current study.

Variables	Intramedullary nailing (n = 15)	Open plating (n = 8)	Percutaneous plating (n = 7)	P value
Age (Mean \pm SD)	32.1 \pm 15.6	60.0 \pm 17.8	—	0.001 ^a
	—	60.0 \pm 17.8	43.1 \pm 21.4	0.075 ^a
Gender (M:F), n	32.1 \pm 15.6	—	43.1 \pm 21.4	0.183 ^a
	14:1	5:3	6:1	0.165 ^b

^a One-way analysis of variance (ANOVA) followed by least-significant difference (LSD) PostHoc test.

^b Pearson Chi-Square.

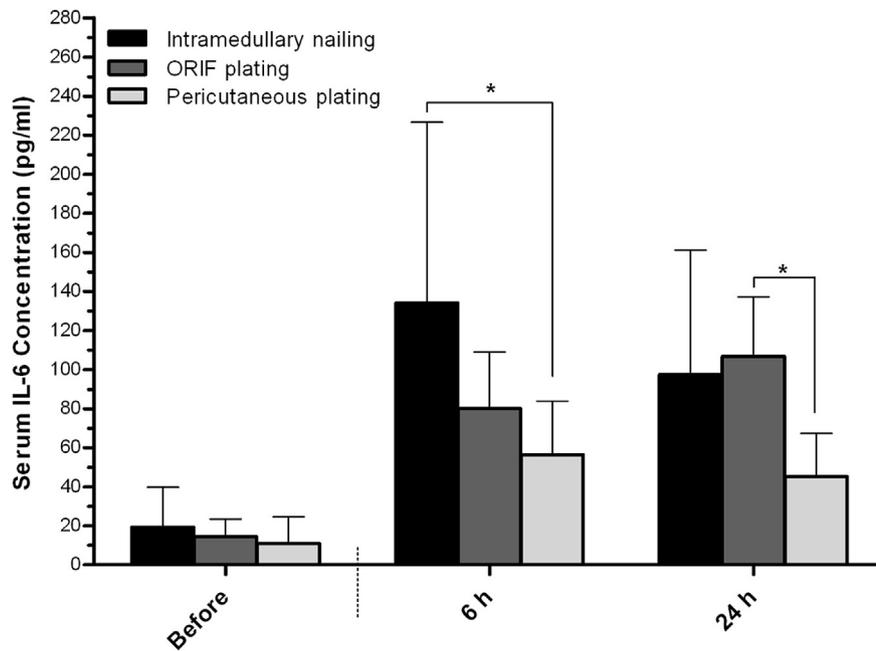


Fig. 1. Serum IL-6 level changes in the patient with tibia shaft fractures involved in the current study: The data are presented as Mean \pm SD. Mean difference between the groups was compared by one-way analysis of variance (ANOVA) followed by least-significant difference (LSD) PostHoc test. The differences with P value less than 0.05 were considered as statistically significant (*represents $P < 0.05$). IL-6 concentration in the percutaneous plating patients was significantly lower than that in the intramedullary nailing patients ($P = 0.022$) at 6 h following the operation. Also IL-6 concentration in the percutaneous plating patients was significantly lower than that in the open plating (ORIF) patients ($P = 0.020$) at 24 h following the operation.

There is increasing evidence that IL-6 correlates with the injury severity and plays a key role in developing the SIRS.¹¹ Therefore, IL-6 can be regarded as an inflammatory marker for monitoring extends of the SIRS in fracture surgeries.¹² Based on this hypothesis, our findings indicate that the plating, particularly percutaneous approach, might be more appropriate than the IMN for stabilization of tibial fractures in DCO, because the former compared to the latter exerts less impact on IL-6 production, and is thereby helpful to avoid or reduce risk of developing the SIRS. However, recently Hietbrink et al,¹⁰ in contrast to our findings, demonstrated that IMN of tibial fractures had no significant impact on serum IL-6 level and PMNs.

Although there is a paucity of evidence about association of the IMN and IL-6 production in tibial fractures, plethora of literature provides adequate proof that implementation of the IMN for stabilization of femoral fractures brings about to a considerable increment in IL-6 production early post operation, thus posing the patient at high risk of unfavorable complications.^{9,13–15} Hietbrink et al⁹ for instance, reported that the IMN of femoral fractures significantly enhanced IL-6 level compared to the isolated femoral

fractures. Houseboy et al¹⁴ demonstrated that the IMN of femur in pigs induced pronounced production of IL-6 in femoral vein blood, subsequently leading to death of two animals due to pulmonary embolism. In another investigation, they also showed that serum level of TNF α , IL-6 and IL-10 cytokines peaked on the first post-operative day in the poly-traumatized patients with femoral shaft fractures early stabilized with IMN.¹⁵ In addition, Pape et al¹³ found that application of ETC by early IMN of femoral shaft fractures in severely injured patients gave rise to a significant increase in IL-6 by 254 ± 55 pg/dL, within 24 h post operation, which was not observed in the patients subjected to DCO. Besides, Morley et al¹⁶ showed that the magnitude of IL-6 increase following the IMN of femoral fracture was independent of the ISS.

Up to now, there is not record of IL-6 level in tibial fractures subjected to the percutaneous plating. However, the percutaneous plating has been suggested as an effective treatment option in patients with tibial fractures presenting no infection risk.^{17,18} Since, our findings herein, in line with the antecedent evidence outlined above, indicated that the IMN of tibial fracture may exacerbate developing the SIRS compared to the percutaneous plating; thus, the percutaneous plating, despite modicum of proof, may preferably serve as a desirable surgery method of choice over the IMN, in DCO of these patients. Howbeit, the excessive time of operation required for percutaneous plating may still restrict use of this surgery method in DCO.

On the other hands, the advocates of the DCO are firmly of the belief that initial external fixation or delayed internal fixation bear advantages, including early skeletal stabilization with diminished blood loss,^{4,19,20} over early IMN and percutaneous plating. More importantly, external fixation does not enforce any secondary inflammatory reaction, termed as a second hit. For example, Scalea et al,⁶ demonstrated that temporary external fixation of multiple fractures is a valuable action to reduce complications associated with possible second hit, and can be later followed by IMN in stabilized patients.

Table 2

Serum IL-6 levels the patient with tibia shaft fractures undergoing intramedullary nailing, percutaneous plating, and open plating (ORIF). Values are given as pg/ml.

Time points	Groups	Minimum	Maximum	Mean	Std. deviation
Before	Intramedullary nailing	3	74	19.3	20.6
	Percutaneous plating	3	38	11.5	13.3
	ORIF	4	32	14.6	8.6
6 h	Intramedullary nailing	34	370	133.9	92.8
	Percutaneous plating	25	105	56.4	27.4
	ORIF	42	121	80.1	28.8
24 h	Intramedullary nailing	37	245	87.9	63.8
	Percutaneous plating	21	90	48.1	22.2
	ORIF	69	163	111.8	30.4

However, opposing views exist against the external instrumentation during DCO, restricting its application in only severe injuries with ISS > 17.⁴ Moreover, the external fixation has been shown to be associated with higher infection rate and longer length of hospitalization.^{21,22} As weakness of the current study, we did not include patients undergoing external fixation or a control group of splinted patients to examine and compare the differences between their IL-6 and that of the IMN and plating groups. Also, reviewing the literature, we could not find data regarding the IL-6 level in patients being applied external fixation.

In conclusion, although the IMN is often a treatment of choice for tibial shaft fractures, according to our results, it seems that percutaneous plating, because of lower induction of IL-6 might be recruited as an appropriate approach in DCO method, alternative to external fixation, in clinically stable patients, but who are at higher risk of developing the SIRS or patients with additional severe injuries to the head, chest, and pelvis who are borderline patients. However, due to the small sample size as a weakness of the present study, much more studies with larger sample size are required to confirm our results.

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