CORRELATION BETWEEN SERUM CONCENTRATION OF IL-6, IL-10 AND TIMING AS WELL AS EARLY RESULTS OF FIXATION OF MAJOR FRACTURE IN POLYTRAUMA PATIENTS

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SUMMARY

Objectives: *To determine the relationship between serum concentration of IL-6, IL-10 and timing as well as early results of fixation of major fracture in polytrauma patients.*

Subjects and methods: *A prospective study was conducted on 59 polytrauma patients with major fracture who were treated at Military Hospital 103. Injury severity and patient's status of multiple trauma patients were assessed by ISS and RTS score. IL-6 and IL-10 level were tested at time of admission or 6 hours after injury (T0), T1, T2, T3, T4 (12, 24, 48 and 72 hours after injury), T5 (surgery time point), T6 (the first day after surgery).* ***Results:*** *The rate of femoral, pelvic, tibia and arm fracture was 71.2%, 27.1%, 22%, 15.3% respectively. There were 24 patients (40.6%) who got fracture fixation from day 2nd to 4th and 35 patients (59.4%) after day 5th after trauma. Postoperative serum concentration of IL-6 and IL-10 were higher in patients who underwent fixation from 2nd to 4th day than surgical patients after day 5th (p < 0.05). Concentration IL-6 and the ratio of IL-6/IL-10 before surgery were significant higher in patient with postoperative complications than patients without complications. Concentration of IL-6 and IL-6/IL-10 ratio before and after surgery had prognostic values with ROC > 0.7 for postoperative complications.* ***Conclusions:*** *The rate of early postoperative complications was higher in patients undergoing surgery from day 2nd to 4th after trauma and the concentration of IL-6, IL-10 among these patients were also significantly higher than those who had operation after day 5th. IL-6, IL-10 level and the ratio of IL-6/IL-10 on the first day after surgery were higher in patients with complications. IL-6 level and IL-6/IL-10 ratio had a prognostic value for postoperative complications.*

** Keywords: IL-6, IL-10; Multiple trauma; Major fracture; Timing of fracture fixation.*

INTRODUCTION

Strategies as well as techniques for fracture management in poly-trauma have made some progresses in recent years. However, timing as well as the optimal techniques of fixation has been controversial. Interleukin-6 (IL-6) and interleukin-10 (IL-10) were biological markers released in poly-trauma setting. While IL-6 stimulates local and systemic inflammation response, IL-10 has an anti-inflammatory role. Total early care *involves* definitive surgical stabilization of all long-bone fractures during the *early* phase of treatment (24 - 48h) [2]. Early fracture fixation reduces the incidence of fracture-related complications and shortens hospital stay [4].

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However, the variation of IL levels as well as the correlation with the timing of fracture fixation and early results of poly-trauma with major fractures still need further research. Therefore, the aim of this article is: *To determine the correlation between IL-6, IL-10 level and timing as well as early results of fixation of major fracture in polytrauma patients.*

SUBJECTS AND METHODS

1. Subjects

59 poly-trauma patients with major fracture were treated at Military Hospital 103 from July, 2015 to January, 2018.

* *Inclusion criteria:*

- Polytrauma was diagnosed according to Patel A (1971) and Trentz O. (2000): Patients with two or more severely injuried body regions or organ systems (ISS score ≥ 18), and at least one lesion affects survival ability.

- Polytrauma patients with major fracture including femoral, pelvic, tibia, arm fractures.

* *Exclusion criteria:*

- Patients who were definitively treated at other hospital before-transfer.

- Patients who were was intubated, had tracheotomy, ventilated, using vasocontriction agents, anesthetic or sedation agents before hospital admision.

- Patients were sent to other hospital before discharge.

- Patients died pre-operation.

- Insufficient data colection.

2. Methods

* *Study design:* Prospective study

* *Assessment tools:*

- Patients were assessed by Revised Trauma Score/RTS at the time admission:

+ Neurology: Glasgow Coma Scale (GCS).

+ Respiratory rate per minute.

+ Blood pressure was monitored by monitoring.

- Severe injury was assessed by Injury Severity Score/ISS:

+ Evaluate damaged organs with Computer Tomography, ultrasound or during surgery.

+ Assess local injury severity by Abbreviated Injury Scale/AIS.

+ Calculate Injury Severity Score according to Baker SP. et al 1974.

+ Fixation was indicated in case of stable hemodynamics

- IL-6 and IL-10 tests:

+ Timing for data collection and biochemical tests: T0: within 6 hours after trauma or at the timepoints of admission if the patients were admitted after 6 hours of trauma; T1: 12 hours after trauma; T2: 24 hours after trauma; T3: 48 hours after trauma; T4: 72 hours after trauma; T5: timepoints of fracture fixation; T6: the first day after fracture fixation.

+ Method: Biochemical test by kit of AviBion - Orgenium company, Finland and ELISA analyze by BECKMAN-COULTER-DTX 880 machine from America at the center of Medical -Pharmaceutical research, Vietnam Military Medical University.

- Evaluate early results after fracture fixation in polytrauma patients with major fractures.

* *Data analysis:* By SPSS 22.0 software. The correlation was calculated by Pearson Correlation.

RERULTS

1. General characteristics of patients

Table 1: General characteristics

General characteristi	Number of patients (n)	Percentage (%)
Mean age *(years):*	37.39 ± 15.82 (from 13 to 78)	
Gender		
Male	45	76.3
Female	14	23.7
Causes:		
Traffic accidents	44	74.6
Fall from height	13	22.0
Others	02	3.4
Mean time of admission (hours)	2.58 ± 1.08	
Types of trauma		
Pelvic fracture	16	27.1
Femoral fracture	42	71.2
Tibial fracture	13	22.0
Arm fracture	9	15.3
Timing of fixation (days)		
From day 2^{nd}- 4^{th} after trauma	24	40.6

2. Correlation between cytokine concentration, timing of fixation and early results

Table 2: Variation of IL-6, IL-10 concentration pre- and post-operation (**n = 59**).

Cytokine concentration	Pre-operation	1^{st} day post-operation	p
IL-6 (ng/L)	74.23 ± 63.61	120.10 ± 76.85	< 0.05
IL-10 (ng/L)	204.17 ± 96.97	264.12 ± 118.96	< 0.05
IL-6/IL-10	0.41 ± 0.40	0.48 ± 0.35	< 0.05

Table 3: Variation of IL-6, IL-10 concentration and ~~timing~~ fixation timing

Fixation timing / Cytokine concentration	Day 2^{nd} to 4^{th}	From day 5^{th}	p
IL-6 T6 (ng/L)	160.29 ± 75.45	92.55 ± 65.59	**< 0.05**
IL-10 T6 (ng/L)	332.26 ± 131.46	217.40 ± 83.22	**< 0.05**
IL-6/IL-10 T6	0.55 ± 0.41	0.44 ± 0.30	> 0.05

Table 4: Variation of IL-6, IL-10 concentration and early results.

Cytokine level		Patients with complications	Patients without complications	p
Preoperation	IL-6 T5	123.45 ± 71.24	44.97 ± 34.61	< 0.05
	IL-10 T5	223.72 ± 99.93	192.55 ± 94.62	> 0.05
	IL-6/IL10 T5	0.71 ± 0.52	0.23 ± 0.13	< 0.05
postoperation	IL-6 T6	186.31 ± 79.85	80.74 ± 39.04	< 0.05
	IL10 T6	311.44 ± 125.20	235.99 ± 107.11	< 0.05
	IL-6/IL10 T6	0.70 ± 0.46	0.35 ± 0.15	< 0.05

Table 5: Timing of fracture fixation and early results.

Timing of fixation / Early complications	Day 2nd to 4th	From day 5th	p
Infectious incision	13 (76.5%)	4 (23.5%)	0.000
Pneumonia	9 (75%)	3 (25%)	0.007
Multiple organ failure	11 (78.6%)	3 (21.4%)	0.001
Sepsis	10 (76.9%)	3 (23.1%)	0.003
Motarity	9 (60%)	6 (40%)	0.078

3. Prognostic value for complications of IL-6, IL-10 and the rate of IL6/IL-10

Table 6: Prognostic value for complications of IL-6, IL-10 and the rate of IL-6/IL-10.

ROC / Cytokine	Multi organ failure (n = 45)	Sepsis (n = 13)	Pneumonia (n = 12)	Infectious incision (n = 17)
IL-6 T5	0.843*	0.851*	0.803*	0.867*
IL-6 T6	0.865*	0.950*	0.849*	0.919*
IL-10 T5	0.719*	0.580	0.635	0.513
IL-10 T6	0.763*	0.678	0.672	0.631
IL-6/IL-10 T5	0.730*	0.791*	0.723*	0.908*
IL-6/IL-10 T5	0.700*	0.799*	0.693*	0.818*

(*p < 0.05)

DISCUSSION

1. General characteristics

Patient's median age was 37.39 ± 15.82 years in which the age group from 20 - 60 accounted for the highest rate (83.06%) and 49.15% aged from 20 - 39 years. Male outnumbered female with corresonding rate of 76.3% and 23.7%. There were 71.2% of femoral fracture, 27.1% of pelvis fracture, 22% of tibial fracture and 15.3% of arm fracture. The rate of fracture fixation from day 2nd to 4th was 40.6% and 59.4% from day 5th (*table 1*).

2. Correlation between IL-6, IL-10 concentration, timing of fracture fixation and early results

The timing of fixation for major fracture in multiple trauma patients has still been under debate. As early as the 1980s, a series of early total care studies were published. Bone LB. and et al conducted a study on 178 patients with femoral fractures who were divided into two groups: bone surgery in the first 24 hours and surgery after 48 hours. The results showed that latter had higher respiratory complications (pneumonia, ARDS), longer hospitalization and ICU care. Choosing the optimal time for a second procedure remains controversial for most surgeons. The right time for the fracture fixation affects the outcomes of treatment, prognosis, and rehabilitation. The best time for surgery based on systemic factor, severity injury of multiple trauma. The aim of the second fracture surgery for major fracture is to obtain a stable fixation of fractured bones. These techniques are performed in case the overall condition of the patient is stable and he/she is able to withstand the operation [5].

However, some studies have found that early fracture fixation did not bring good effects, especially in critical ill patients. Patients with chest, abdominal, or brain lesions accompanied or associated with major fractures are likely to have higher rate of mortality and complications. Therefore, in addition to intensive care, temporary fixation using external fixators to delay the second surgery until the patients' status is probably and more favorable option. Thus, starting from the 1990s, for the high-risk patients who will be given temporary fixation of fractures and second surgery will be conducted later when the condition is stable and can tolerate the effects of surgery [6]. This is the basis of new approach, damage control orthopedic surgery (DCO). The retrospective study by Pape et al (2002) also found that there was a significant reduction in the incidence of multiple organ failure (MOF) when switching from early total care to damage control surgery. The strategy of damage control surgery is more effective for high-risk patients of developing systemic complications after multiple trauma such as ARDS, MOF ...

The results of this study showed that the serum concentration of IL-6, IL-10 after fixation increased much more than pre-surgery with $p < 0.05$ (*table 2*). Multiple trauma patients who underwent fracture fixation surgery on day 2nd - 4th had higher post-surgery plasma levels of IL-6 and IL-10 than patients with fixation surgery from day 5th with $p < 0.05$ (*table 3*). Stahel P.F et al. (2005) suggested that progress of systemic inflammatory response and immune response was the crucial factor for the time of second surgery. Starting from 24 hours after trauma,

based on systemic inflammatory and immune response, polytrauma can be divided into four stages: phase of increased systemic inflammatory response (day 2^{nd}- 4^{th}), window period (day 5^{th}- 10^{th}), immunodeficiency period (week 3^{rd}) and recovery period (after 3 weeks). The author suggested that the second surgery should be performed at the window period and the recovery period after trauma. In contrast, if surgery performs during the period of increased systemic inflammation and immunodeficiency stage, postoperative complication rate will be so high [9].

The results in table 4 showed that serum concentration of IL-6 and the rate of IL-6/IL-10 preoperation were higher in patients with complications compared to those without complications ($p > 0.05$). Pape et al. (2002) studied 128 polytrauma patients, of whom 71 cases were performed early fixation surgery (day 2^{nd} - 4^{th}) and 57 cases with second fixation surgery (day 5^{th}- 8^{th}). The author suggested that definitive surgery should be performed at day 5^{th}- 8^{th} days after trauma in severe patients with IL-6 > 500 pg/dL [9]. Schreiber et al. (2011) comparing the timing of fracture fixation surgery among major trauma centers in the US and Germany found that this time should be after day 5^{th}. Specifically, fixation timing in the US and Germany was as follows: pelvic fracture 5 ± 2.8 days and 7.1 ± 9.6 days; femur fracture 7.9 ± 8.3 days and 5.5 ± 7.9 days; tibial fracture 6.2 ± 5.6 days and 6.2 ± 9.1 days; arm fracture 5 ± 3.7 days and 6.6 ± 6.1 days, respectively [8].

The method of internal fracture fixation had advantages such as adjusting the fracture to the correct anatomical position and firmly fixing it to help the patient recover early movement after surgery. Currently, this is the main and most widely method used for fracture treatment. In the past, external fixation frames were all indicated for open fracture cases; however, internal fixation combined with antibiotic are now indicated for Grade I and II open fractures, early admission, less contamination [6]. Each fracture fixation method has its advantages and limitations, the selection of the optimal method depends on the surgeon's experience, the patient's status and characteristics of fracture.

Our results showed that the concentration IL-6 and IL-10 were increased not only after trauma but also after surgery. One of the widely accepted theories about the pathogenesis of inflammatory responses in multiple trauma was the mechanism of the second - hit. In particular, the first hit is that the initial damage activates the immune system to release cytokines leading to inflammatory response. The surgical interventions act as the second hit which again affects the immune system and trigger the body inflammatory response [3]. Our results showed that not only after trauma, serum levels of IL-6 and IL-10 also increased on the first day after surgery (*table 2)*. The reduction of IL-6/IL-10 ratio may partly indicate that the change of IL-10 after surgery is greater than that of IL-6.

Unlike IL-6, there are still different opinions about the changes of concentration and prognostic value of IL-10, an anti-inflammatory cytokine in polytrauma patients. Sapan et al. (2016) studied 54 polytrauma patients and found that IL-10 levels increased ranging 21 - 340.7 pg/mL

(average value was 83.71 pg/mL). Elevated serum IL-10 levels in polytrauma patients, after major surgery, and associated with severity of injury. IL-10 is an anti-inflammatory cytokine that is also an important component of negative feedback to pro-inflammatory cytokines. The change of IL-10 level is dependent on trauma mechanisms and this variation may help restore the inflammatory response [7].

Results from table 5 showed that the incidence of complications such as infectious incision, pneumonia, multi-organ failure and sepsis in polytrauma patients who were performed fracture fixation on day 2^{nd} - 4^{th} was higher than those who were operated on day 5^{th} ($p < 0.05$). Mortality rate did not differ between the two groups. The cytokines reflect the body's inflammatory response, or the body's response to surgery, the second hit after trauma. Excessive increasing or decreasing of this process leads to the risk of postoperative complications such as surgical site infections, sepsis, respiratory failure, multiple organ failure and even a high risk of mortality.

3. Prognostic value for complication of IL-6, IL-10 andIL-6/IL-10 ratio

Early postoperative complications such as surgical site infection, pneumonia, sepsis or multiple organ failure, level of IL-6 and IL-6/IL-10 ratio before surgery and the first day after surgery were all prognostic value with the ROC greater than 0.7. Whereas IL-10 levels before surgery and the first day after surgery are only prognostic values for multiple organ failure (*table 6)*. The role of cytokines in prognosis of multiple trauma patients has also been demonstrated by many studies. Dekker et al analyzed from 42 studies which were published from 1988 to 2015, found that IL-6 had prognostic value for multi-organ dysfunction, multiple organ failure and mortality while IL-10 was only a prognosis for multiple organ failure. In another study on 100 patients with multiple trauma, the authors found that IL-10 was a valuable factor in the prognosis of acute respiratory failure following trauma. Level of IL-6 had also been shown to be valuable in the prognosis of multiple organ failure, duration in ICU, duration of mechanical ventilation, length of hospital stay, infection and risk of mortality in patients with multiple trauma. Postoperative systemic inflammatory response is one of the most important factors for early outcomes of treatment [1, 9, 10].

In our study, the incidence of early complications such as surgical site infection, pneumonia, sepsis and multiple organ failure was higher in the group that got fracture fixation on the day 2^{nd} - 4^{th} compared to post-operation day 5^{th}. At the same time, postoperative IL-6 and IL-10 levels were also higher in patients who received fixation surgery from day 2^{nd} - 4^{th} than those with surgery from day 5^{th} (*table 5*). According to Stahel PF et al. (2005), if polytrauma patients had operation during the stage of increased systemic inflammation (from day 2^{nd}- 4^{th}) and stage of immunodeficiency (week 3^{rd}), the rate of postoperative complications would be very high [9].

To conclude, choosing the optimal time for fracture fixation surgery for polytrauma patients remains a matter of debate.

After the day 2nd - 4th of trauma is the time of "increased inflammation response", in other words, this is the time when the inflammatory response of the immune system to the trauma is most powerful. Therefore, if fracture fixation surgery is performed at this stage, the effect of surgical intervention as a "second hit" will exacerbate previously activated inflammatory response. These problems will lead to a higher risk of systemic complications as well as local fractures, prolonging hospitalization and recovery time. During this period, minimal interventions, life-saving surgeries and damage control surgeries should be carried out. Second-fracture fixation surgeries should be conducted at a time after day 5th when the inflammatory response has been well controlled and the patient's condition is stable.

CONCLUSION

The rate of early postoperative complications was higher in patients who had surgery during the day 2nd to 4th after trauma and the concentration of IL-6, IL-10 of these patients were significantly higher than those who had operation after day 5th. IL-6, IL-10 level and the rate of IL-6/IL-10 on the first day after surgery were higher in patients with complications. IL-6 level and-IL-6/IL-10 ratio had a prognostic value for postoperative complications.

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