Original Article

Inflammatory Factors Before and After Orthopedic Surgery in Patients with Fractures Following Trauma

Gholamreza Khosravi, Meysam Mahmodi Khaledi[1], Alireza Abedi, Mohammad Javad Azad Chehr[2], Mohammad Mahdi Heidari[3]

Trauma Research Center, Kashan University of Medical Sciences, [2]Biostatistics, Kashan University of Medical Sciences, Departments of [1]Orthopedic and [3]Pediatric, Student Research Committee, Faculty of Medicine, Kashan University of Medical Sciences, Kashan, Iran

ORCID:

Meysam Mahmodi Khaledi: https://orcid.org/0000-0001-8840-9035
Alireza Abedi: https://orcid.org/0000-0003-0569-8922
Mohammad Javad Azad Chehr: https://orcid.org/0000-0001-6877-8896
Mohammad Mahdi Heidari: https://orcid.org/0000-0003-4183-4995

Abstract

Background and Objectives: Inflammatory factors are indicators of complications such as infection following trauma fracture healing that is necessary to identify the process of changes after surgery and the factors affecting it. Therefore, this study aimed to evaluate the extent of inflammatory factors before and after surgery in patients with fractures following trauma. **Materials and Methods:** This prospective study was performed on 200 patients with fractures requiring surgery. After obtaining patient satisfaction and recording demographic information, the white blood cells (WBC) count, erythrocyte sedimentation rate (ESR), and serum levels of C-reactive protein (CRP) changes before and during the first 6 weeks of the postoperative period were recorded. Repeated measure ANOVA and mixed ANOVA tests were used to compare the data. **Results:** According to our results, the day after surgery all inflammatory factors including WBC, ESR, and CRP increased significantly, and 2 weeks after surgery serum levels of WBC and CRP decreased, while ESR serum levels were still high and decreased from the 4th week. **Conclusions:** The results of this study showed the deviation of inflammation factors from the normal ranges and increase and decrease after surgery can indicate the presence of complications such as infection after surgery. Since CRP changes were more sensitive than ESR, it is recommended to check WBC and CRP changes to evaluate infection because ESR was elevated for a longer duration.

Keywords: Bone fracture, inflammatory factors, surgery, trauma

Introduction

Bone fracture following trauma and subsequent repair is important issues in orthopedic departments. A clear understanding of the factors affecting repair after bone fracture is essential for the treatment and prevention of complications such as nonunions, bone infection, osteonecrosis, osteoporosis, arthritis, metabolic bone disease, and other diseases affecting bone. Otherwise, complications of bone fracture repairs have great clinical and economic importance that 100,000 fractures develop a nonunion each year in the USA,[1] which make extra cost approximately US$11,333.[2] Moreover, osteoporosis secondary to bone fracture is a major source of pain and disability and affects 25%–50% of cases over the age of 50 years,[3] which will cost over US$25 billion by 2025.[4] Therefore, recognizing physiological pathways in healing fractures may help us to prevent complications and increase the quality of life after repairing fractures. Bone healing after the injury is a complex biomechanical and biological process. Recently, studies reported an association between inflammatory cells and cells related to bone healing and remodeling.[5] Furthermore, some studies demonstrated that acute inflammation is the first stage of fracture healing, but is

Access this article online

Quick Response Code:

Website: www.archtrauma.com

DOI: 10.4103/atr.atr_22_22

Address for correspondence: Dr. Gholamreza Khosravi, Trauma Research Center, Kashan University of Medical Sciences, Kashan, Iran.
E-mail: ghkhosravi@yahoo.com

How to cite this article: Khosravi G, Khaledi MM, Abedi A, Azad Chehr MJ, Heidari MM. Inflammatory factors before and after orthopedic surgery in patients with fractures following trauma. Arch Trauma Res 2022;11:184-8.

Received: 09-04-2022, **Revised:** 16-01-2023,
Accepted: 18-01-2023, **Published:** 28-02-2023.

less studied.[6] Bone healing can be grouped into three stages which have partially overlap including the inflammatory phase, the repair phase, and finally the remodeling phase.[7] Studies reported that healing is more dependent on the initial phase, which is affected by both the local and systemic inflammatory responses to the injurious stimulus.[8] Thus, understanding and regulating inflammation processes is one of the key factors for successful, robust bone healing for the prevention of secondary complications. To the best of our knowledge, there is not enough prospective study about the changes in inflammation processes following bone healing after fracture, therefore, this study was designed to evaluate changes in inflammatory factors before and after surgery in patients with fractures following trauma.

Materials and Methods

Target group

This prospective study was conducted in the Orthopedic Department of Kashan Shahid Beheshti Hospital, the center of Iran from February 2021 to May 2021. The changes in inflammatory factors after surgery were compared to the changes before the surgery (at baseline [presurgery]). Inclusion criteria included patients referred to the orthopedic department with a diagnosis of bone fracture following trauma who needed surgery process, who signed a consent form to participate in the study (patients and their family) and aged between 18 and 60 years. Exclusion criteria consisted of patients with underlying diseases, inflammatory diseases in the past two months, rheumatic and autoimmune diseases, history of anemia, and all diseases affecting the level of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), receiving blood during surgery, history of recent infection, history of smoking, drug consumption, age below 18 years or more than 60 years, and dissatisfaction to continue participation in the study. We also excluded patients with uncompleted data.

Study design

The study flowchart is shown in Figure 1. Two hundred and fifty-four patients with a diagnosis of bone fracture following trauma, who had been diagnosed by an orthopedist and based on clinical and paraclinical findings and inclusion and exclusion criteria were included. It should be mentioned that using the findings of Honsawek *et al*.,[9] the mean ESR in two weeks and six weeks after surgery was 58 ± 28.3 and 42 ± 27.2, respectively, and using the following formula, the minimum required sample size was 156.

$$n = \frac{\left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)^2 s_d^2}{\left(\bar{x}_{24\ hours} - \bar{x}_{6\ weeks}\right)^2} = \frac{(1.96 + 1.645)^2 \times 55.5^2}{(58 - 42)^2} \cong 156$$

$$s_d = \sqrt{s_{24\ hours}^2 + s_{6\ weeks}^2 - 2rs_{24\ hours}s_{6\ weeks}}$$
$$= \sqrt{28.3^2 + 27.2^2 - 2(-1)28.3 \times 27.2} = 55.5$$

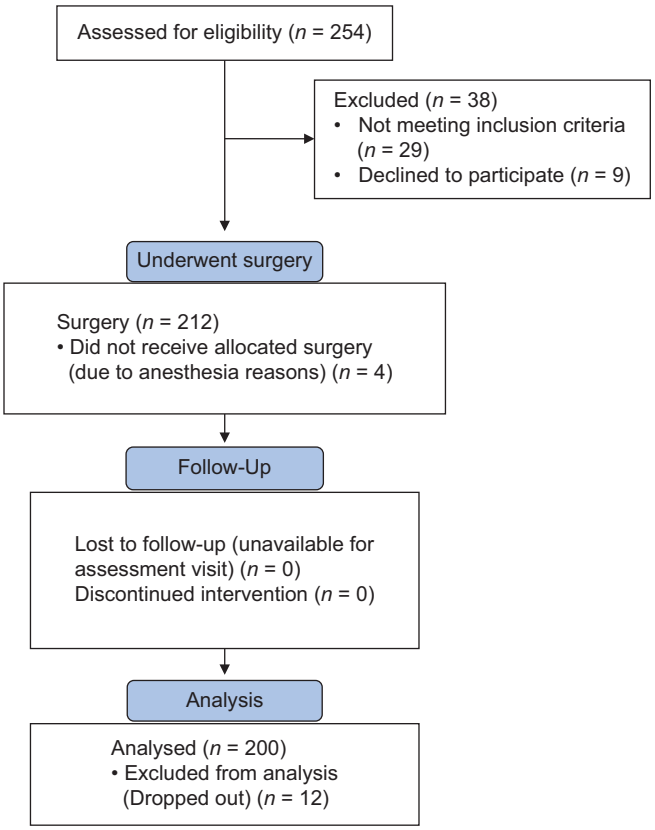

Figure 1: Study flowchart

The study received ethics approval from the Ethics Committee of Kashan University of Medical Sciences (IR.KAUMS.MEDNT.REC.1399.223), and all participants gave written informed consent.

After obtaining informed consent, eligible patients were enrolled. Data collection was based on an assessment protocol for gathering data on sociodemographic, clinical, and inflammatory variables. Patients were evaluated at baseline (before surgery) and during the first 6 weeks of the postoperative period.

At each time, 5 ccs of venous blood were taken from the patients to measure the inflammatory variables. Nonfasting peripheral blood samples were collected from an antecubital vein into ethylenediaminetetraacetic acid-containing tubes. White blood cells (WBC) were measured by a cell counter and serum CRP was measured by latex agglutination and ESR was measured manually by a laboratory expert according to the manufacturer's instructions. To minimize the biological variation of these inflammatory variables, sampling time was fixed at the morning hours between 8:00 and 9:00 a.m.

Data analysis

Data were analyzed and reported only for patients with completed information. Statistical analysis of data was performed using the SPSS version 22 software (SPSS Inc., Chicago, IL, USA). Repeated measures ANOVA (within group) was used to compare the mean inflammatory factors at

different measurement times (before and after surgery) and mixed ANOVA was used to compare the mean inflammatory indices at different measurement times (before and after surgery) based on the duration of surgery and location of fractures (within-between groups). $P < 0.05$ was considered statistically significant.

Results

In this study, 200 patients were enrolled. The mean age of the subjects was 31.8 49 9.49 years (18–60 years). Of the 200 patients included in the study, 162 (81%) were male and 38 (19%) were female. The most common locations of fractures were ankle (16%), tibia and fibula (15%), femoral shaft and intertrochanteric fracture (14.5%), and forearm (14%), respectively. In addition, the proportion of patients whose surgery lasted less (49%) than an hour was approximately equal to patients whose surgery lasted more than an hour (51%).

Mean serum levels of WBC and CRP increased immediately after surgery and decreased from the 2nd week of the postoperative period, while in relation to ESR, the mean increased until the 2nd week and decreased from the 4th week of the postoperative period. Moreover, the within-group effect (time) was significant in each of the three inflammatory factors ($P < 0.001$) [Table 1].

By grouping patients based on the duration of surgery, within-group effects (time) were significant in each of the inflammatory factors ($P < 0.001$). In other words, regardless of the duration of surgery, the mean inflammatory factors between different time intervals were significantly different. Furthermore, between-group effects were not significant in any of the inflammatory factors ($P > 0.05$). In other words, regardless of the effect of time, the mean inflammatory factors did not differ significantly between patients whose surgery lasted less than an hour as compared to patients whose surgery lasted more than an hour. In addition, interactions (within-between groups) were significant only in WBC ($P < 0.05$). In other words, the serum levels of WBC vary significantly between the studied groups (duration of surgery) at different times [Table 2].

By grouping patients based on the location of fractures, within-group effects (time) were significant in each of the inflammatory factors ($P < 0.001$). In other words, regardless of the location of the fracture, the mean of inflammatory factors varies significantly between different time intervals. Moreover, between-group effects were significant only in WBC ($P = 0.046$), and the serum levels of WBC in patients with hip fractures were significantly higher than in other groups (except shoulder and ankle). In addition, interactions were significant in each of the inflammatory factors ($P < 0.05$). In other words, the mean of inflammatory factors varies significantly between the studied groups (location of fracture) at different times [Table 3].

Discussion

According to our results, the day after surgery all inflammatory factors including WBC, ESR, and CRP increased significantly,

Table 1: Mean changes in inflammatory factors before and after surgery

Inflammation factors	Before surgery	After surgery				*F*	*P*
		Immediately	Second week	Forth week	Sixth week		
WBC	7.30±2.40	11.28±4.61	7.86±3.13	7.55±2.81	6.81±2.68	180.82	0.000
ESR	11.07±6.30	31.68±23.82	43.23±29.46	23.78±18.68	7.70±4.80	205.93	0.000
CRP	8.96±8.92	23.12±24.22	9.25±11.81	7.99±10.71	5.50±5.96	97.163	0.000

WBC: White blood cell, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein

Table 2: Mean changes in inflammatory factors before and after surgery based on the duration of surgery

Inflammation factors	Before surgery	After surgery				*F*	*P*
		Immediately	Second week	Forth week	Sixth week		
WBC (min)							
<60	7.30±2.46	10.61±4.22	7.48±2.89	7.40±2.78	6.83±2.60	Within-group: 182.98	0.000
≤60	7.29±2.35	11.91±4.89	8.22±3.33	7.69±2.84	6.79±2.77	Between-group: 1.36	0.244
						Within between*: 4.64	0.016
ESR (min)							
<60	10.82±6.25	29.61±23.49	43.69±30.57	23.72±19.35	7.97±4.95	Within-group: 205.70	0.000
≤60	11.30±6.38	33.67±24.07	42.79±28.49	23.84±18.11	7.45±4.65	Between-group: 0.10	0.749
						Within between*: 0.94	0.400
CRP (min)							
<60	8.58±8.52	20.80±23.79	10.15±14.44	8.55±12.68	5.31±6.40	Within-group: 97.54	0.000
≤60	9.32±9.05	25.34±24.53	8.38±8.54	7.45±8.42	5.69±5.52	Between-group: 0.14	0.711
						Within between*: 3.05	0.056

WBC: White blood cells, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein

Table 3: Mean changes in inflammatory factors before and after surgery based on the location of fractures

Inflammation factors	Before surgery	After surgery				*F*	*P*
		Immediately	Second week	Forth week	Sixth week		
WBC							
Shoulder	7.84±3.19	11.43±4.49	7.79±3.65	7.73±3.55	7.26±3.42	Within-group: 206.90	0.000
Humeral shaft	7.10±2.70	9.56±3.79	7.35±3.01	7.69±3.11	7.10±2.76	Between-group: 2.018	0.046
Elbow	6.83±1.56	9.26±3.31	7.22±1.58	7.11±1.34	6.48±1.17	Within between*: 7.89	0.000
Forearm	7.08±2.42	10.33±3.95	7.16±2.99	7.12±2.95	6.61±2.82		
Hip	6.52±1.59	16.66±3.65	12.09±2.23	8.64±2.24	6.54±2.97		
Intertrochanteric and femoral shaft	7.59±2.68	12.30±5.60	7.49±2.91	7.65±2.98	6.94±2.56		
Knee	6.71±1.79	9.89±4.53	7.21±2.31	7.14±2.17	6.47±2.15		
Tibia and fibula	7.07±1.50	10.00±3.46	6.93±2.17	6.91±1.92	6.32±1.97		
Ankle	8.15±2.92	11.72±4.46	8.16±3.58	7.98±3.54	7.31±3.28		
ESR							
Shoulder	12.65±7.49	35.06±28.15	47.06±31.03	24.47±20.16	8.17±5.91	Within-group: 196.29	0.000
Humeral shaft	10.68±7.29	22.16±15.08	40.16±33.08	24.84±22.24	8.21±6.18	Between-group: 0.46	0.884
Elbow	10.64±5.11	35.36±22.96	52.00±31.09	31.71±21.61	7.93±4.01	Within between*: 1.99	0.012
Forearm	11.00±6.63	27.78±23.45	41.82±31.57	22.39±20.46	6.71±4.47		
Hip	9.83±5.45	52.05±15.94	36.94±17.99	18.94±14.32	8.05±4.45		
Intertrochanteric and femoral shaft	11.34±6.71	30.93±28.01	39.10±30.38	24.55±17.23	6.83±4.38		
Knee	9.92±6.41	24.92±24.40	42.46±31.73	20.15±15.19	7.69±4.77		
Tibia and fibula	10.80±5.55	27.36±20.01	45.42±28.09	21.50±17.12	6.97±3.50		
Ankle	11.87±6.39	33.34±24.18	45.97±30.40	26.19±19.42	9.22±5.48		
CRP							
Shoulder	9.68±8.31	22.66±24.47	8.84±7.81	8.75±8.41	6.03±6.29	Within-group: 91.09	0.000
Humeral shaft	9.40±8.83	16.65±14.05	6.83±8.98	6.18±8.72	4.78±4.16	Between-group: 1.24	0.278
Elbow	9.50±9.39	23.57±25.72	11.56±13.27	9.21±11.33	5.26±7.17	Within between*: 1.95	0.020
Forearm	8.31±8.75	20.17±25.10	8.34±12.40	7.42±12.05	5.71±6.87		
Hip	10.29±11.33	42.00±22.45	13.02±12.50	11.60±12.62	7.89±6.85		
Intertrochanteric and femoral shaft	8.55±8.85	25.64±28.92	7.35±7.19	6.65±7.18	5.15±5.24		
Knee	6.66±5.37	14.32±23.54	7.07±9.28	5.91±9.24	2.72±2.67		
Tibia and fibula	8.40±8.31	18.12±20.11	8.08±12.36	6.75±10.43	5.58±6.25		
Ankle	9.71±10.20	24.93±24.18	12.28±16.40	9.80±13.68	5.63±6.14		

WBC: White blood cell, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein

and 2 weeks after surgery serum levels of WBC and CRP decreased, while ESR serum levels were still high and decreased from the 4th week. Considering the regular trend of ESR and CRP factors, it can be concluded that the deviation of these factors from the normal ranges and increase and decrease after surgery can indicate the presence of a complication such as infection after surgery. Since CRP changes were more sensitive and systematic than ESR, it is recommended to check WBC and CRP changes to evaluate infection because ESR was elevated for a longer duration.

Ellitsgaard *et al*. evaluated changes in CRP, WBC, and ESR in patients with hip fractures, and reported that the ESR was high 1 week after surgery. While CRP levels on the 2nd day of surgery reached their peak and returned to normal within a week.[10] The findings of the study regarding the increase in ESR a few days after surgery are quite similar to the findings of our study. Moreover, like Ellitsgaard *et al*.'s study, CRP changes were similar to WBC and were high after surgery but then begin to decrease and were normal in the 2nd week. Mun *et al*. (2005) showed that if CRP increased steadily for 1 week after surgery, it could be a serious sign of wound infection.[11] However, we found that high CRP levels may occur after surgery without infection. Therefore, the patient cannot be suspected of infection by CRP alone, and clinical examinations and other laboratory findings should be evaluated along with CRP to correctly identify cases with infection. Gelalis *et al*. in a prospective clinical study found that a combination of WBC, ESR, and CRP at normal levels reliably predicted the absence of infection after elective surgery,[12] while our study found that in the early days after surgery, an increase in ESR, CRP, and WBC levels was observed, and additional evaluation such laboratory findings, other symptoms, especially fever, and clinical examination should be performed. Moreover, we found that 2 weeks after surgery, a reduction in these inflammatory factors was observed, which indicates that after 2 weeks from surgery, the elevation of inflammatory factors such as WBC and CRP may manifest in infection.

Most researchers believe that the natural process of increasing and decreasing ESR and CRP is regular, so deviating from this

natural process can indicate the occurrence of a complication such as infection. The results of the present study, which was performed on 200 patients who underwent orthopedic surgery, were similar to the results of published studies.[13] In this study, it was found that WBC in all patients on the 1st day after surgery was maximal and the changes were irregular, similar to the results obtained from Giehl's studies. After the operation, WBC was slowly reduced and returned to normal after 4 weeks. In extensive surgeries, including hip surgery, higher inflammation factor levels and longer inflammatory factors such as ESR were observed. This result is similar to a study by Giehl, who stated that extensive surgeries make higher inflammation factor levels such as ESR. Furthermore, the time to reach the peak of ESR, like Giehl's study, was on days 5 or 6.[13]

In the present study, CRP peaked with regular changes but faster than ESR on the day after surgery and in most cases was negative after 2 weeks, and its positive rate was directly related to the extent of surgery. While the relationship between CRP and the extent of surgery was similar to the results of Giehl and Larrasson's studies, the time for CRP to normalize in the Larrasson study was reported to be approximately 21 days after surgery.[13,14]

Choi *et al*. evaluated the extent of WBC, CRP, and ESR in spinal surgery: comparison of lumbar open discectomy (LOD) and posterior lumbar interbody fusion (PLIF) found that different surgical methods and length of operation can affect ESR and CRP. They also found a significant decrease in CRP in the LOD group on day 3. Seven postoperatively and in the PLIF group, a significant increase in ESR was observed. In this study, they concluded that CRP is a more effective indicator for the early detection of infectious complications of CRP than early WBC and ESR.[15] Although the design of this study was not similar to our study, the findings were quite consistent with the findings of our study and based on the findings of both studies, we observed an increase in inflammatory factors after surgery, but CRP was less affected as compared to ESR and began to decline rapidly in the days after surgery.

Conclusions

The results of this study showed the deviation of inflammation factors from the normal ranges and increase and decrease after surgery can indicate the presence of a complication such as infection after surgery. Since CRP changes were more sensitive than ESR, it is recommended to check WBC and CRP changes to evaluate infection because ESR was elevated for a longer duration.

Acknowledgments

This study was financially supported by Kashan Medical Sciences University, Isfahan, Iran. We gratefully acknowledge the dedicated efforts of the investigators, the coordinators, Clinical research development unit of kashan Shahid Beheshti hospital, and the volunteer patients who participated in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Miranda MA, Moon MS. Treatment strategy for nonunions and malunions. In: Stannard JP, Schmidt AH, Kregor PJ, editors. Surgical Treatment of Orthopaedic Trauma. New York: Thieme; 2007. p. 77-100.
2. Hak DJ, Fitzpatrick D, Bishop JA, Marsh JL, Tilp S, Schnettler R, *et al.* Delayed union and nonunions: Epidemiology, clinical issues, and financial aspects. Injury 2014;45 Suppl 2:S3-7.
3. Pisani P, Renna MD, Conversano F, Casciaro E, Di Paola M, Quarta E, *et al*. Major osteoporotic fragility fractures: Risk factor updates and societal impact. World journal of orthopedics 2016;7:171.
4. Jahangir AA, Nunley RM, Mehta S, Sharan A, Fellows TW. Bone-graft substitutes in orthopaedic surgery. AAOS Now 2008;2:1-5.
5. Mountziaris PM, Spicer PP, Kasper FK, Mikos AG. Harnessing and modulating inflammation in strategies for bone regeneration. Tissue Eng Part B Rev 2011;17:393-402.
6. Marsell R, Einhorn TA. The biology of fracture healing. Injury 2011;42:551-5.
7. Claes L, Recknagel S, Ignatius A. Fracture healing under healthy and inflammatory conditions. Nat Rev Rheumatol 2012;8:133-43.
8. Maruyama M, Rhee C, Utsunomiya T, Zhang N, Ueno M, Yao Z, *et al.* Modulation of the inflammatory response and bone healing. Front Endocrinol (Lausanne) 2020;11:386.
9. Honsawek S, Deepaisarnsakul B, Tanavalee A, Sakdinakiattikoon M, Ngarmukos S, Preativatanyou K, *et al.* Relationship of serum IL-6, C-reactive protein, erythrocyte sedimentation rate, and knee skin temperature after total knee arthroplasty: A prospective study. Int Orthop 2011;35:31-5.
10. Ellitsgaard N, Andersson AP, Jensen KV, Jorgensen M. Changes in C-reactive protein and erythrocyte sedimentation rate after hip fractures. Int Orthop 1991;15:311-4.
11. Mun JH, Kim DH, Ryu KS, Park CK, Kim MC. Diagnostic value of early inflammatory reaction in postoperative infection of the lumbar spine. J Korean Neurosurg Soc 2005;38:206-10.
12. Gelalis ID, Arnaoutoglou CM, Politis AN, Batzaleksis NA, Katonis PG, Xenakis TA. Bacterial wound contamination during simple and complex spinal procedures. A prospective clinical study. Spine J 2011;11:1042-8.
13. Giehl JP, Kluba T, Lebherz C. The course of inflammatory mediators after elective orthopedic interventions. Z Orthop Ihre Grenzgeb 2000;138:181-4.
14. Larsson S, Thelander U, Friberg S. C-reactive protein (CRP) levels after elective orthopedic surgery. Clinical Orthopaedics and Related Research (1976-2007). 1992;275:237-42.
15. Choi MK, Kim SB, Kim KD, Ament JD. Sequential changes of plasma C-reactive protein, erythrocyte sedimentation rate and white blood cell count in spine surgery: Comparison between lumbar open discectomy and posterior lumbar interbody fusion. J Korean Neurosurg Soc 2014;56:218-23.