

Research article

Reliability of inflammatory markers as predictors of infection in open long bone fracturesHaridas Somayaji¹, Ashwin Shetty¹, Visakh Pandikasalayil², Anoop Hegde³Department of Orthopedics, K.S. Hegde Medical Academy, Nitte (Deemed to be) University,
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Corresponding author: **Haridas Somayaji**. Email: hari81somayaji@gmail.com**ABSTRACT**

Introduction and Aim: Open fractures are associated complications such as infections, osteomyelitis, non-union. Levels of CRP, ESR and TLC increases during various types of tissue injury. This study aimed at estimating the effect of deranged peri-operative CRP, ESR, in patients with open long bone fractures and to assess them as significant peri-operative markers of postoperative infection.

Methodology: Patients with open long bone fractures during the period Jan 2019 to June 2020 were selected for the study. Serum CRP, ESR and TLC levels were measured preoperatively and on postoperative days 3 and 10. Patients were followed up in the ward for 14 days and after 6 weeks for signs of infection. These pre-operative, post-operative data and incidence of infection were estimated.

Results: In the present study 5 out of 32 cases developed infection. In infected cases CRP values were persistently elevated on post-operative day 3 and 10 while in non-infection group it elevated on postoperative day 3 and dropped to lower levels by postoperative day 10. It was statistically significant on preoperative data and on post-operative 10th day data. While the ESR and total WBC count showed no such correlation.

Conclusion: Serial CRP measurements can be considered as a more definitive reliable inflammatory marker as compared to ESR and total white blood cell count, in predicting postoperative infections in open long bone fractures. The elevated serial CRP levels postoperatively and their continued persistence in open fractures is potentially an early screening tool for infection before clinical signs of infection appear.

Keywords: Open fracture; C-reactive protein; erythrocyte sedimentation rate; total leukocyte count; acute phase response; acute phase protein.

INTRODUCTION

Open fractures are associated with higher chances of postoperative infections. Morbidity and mortality following postoperative infection can be minimized by early detection (1). The management of these fractures are comparatively difficult because of the disruption of the blood supply and soft tissue coverage. The amount of initial comminution, displacement, and amount of contamination of the fracture site determines the overall prognosis. Due to the communication with external environment and contamination, open fractures are very prone for infections. Even though prophylactic antibiotics are being used before and after surgery, the post-operative infection rates are high. Post-operative infections remain a big challenge to operating surgeons as it can lead to various complications such as osteomyelitis, delayed union, non-union, failure of surgery, discharging sinus, need for multiple surgeries (2). For minimizing morbidity and mortality, early detection of postoperative infection is essential. Systemic clinical features of infection or sepsis are difficult to distinguish from the effects of surgery which will mask initial signs and clinical symptoms of infection during the initial

postoperative period and makes it difficult to diagnose any impending postoperative infections. CRP, ESR, TLC are few of the fastest reacting and therefore can be used as a useful marker for early diagnosis of infection. Their levels are increased in the serum due to tissue damage and inflammation. There are several fold increases in concentration of those reactants in response to the stimuli in a limited period when compared to their basal levels which make them apt for monitoring. A single value will give a limited information and therefore the trend followed by these markers will give an idea for its maximum utilization in detecting and monitoring treatment of postoperative infections. The current study aims to assess the relationship between perioperative CRP, ESR and TLC values with postoperative infections in long bone fractures and to assess their usefulness as a biomarker and to find out a variation in their levels perioperative.

MATERIALS AND METHODS**Study design**

A prospective study was conducted at Justice K.S. Hegde Charitable Hospital, Mangalore, between January 2019 to June 2020. Total 32 cases were considered satisfying inclusion criteria during the

period of study. Inclusion criteria were the patients in the age group 18 to 70 years, with open long bone fractures undergoing surgery within 24 hours of trauma. Exclusion criteria were patients below the age of 18 years and above age of 70 years; patients with pre-existing clinically detectable infections like urinary tract infections, pneumonia, Patients with rheumatoid arthritis and tuberculous arthritis, Pregnancy, chronic smokers, patients on treatment with steroids, Open long bone fractures with vascular injury- Gustilo - Anderson Type IIIC.

Methodology

Serum CRP, ESR and TLC levels will be measured preoperatively and on postoperative days 3 and 10. Patients were followed up in the ward for 14 days and after 6 weeks for signs of infection. The diagnosis of infection is confirmed by culture of bacteria by taking swab from the operated site. CRP, TLC and ESR are quantified by well-known and established laboratory testing.

CRP was measured using Nephelometry (Agappe-MISPA I2). A CRP concentration of ≥ 6 $\mu\text{g/ml}$ was considered positive as indicated by the presence of agglutination. ESR was measured using Wintrobe method. An ESR level of $>20\text{mm}$ is taken as high. Total count is measured using Automatic Cell Counter. Reference value of TLC ranges from 4000 – 11000 cells/ mm^3 .

Patients who met the inclusion criteria and were without exclusion criteria, pre- operative and post-operative assessment were documented.

Statistical analysis

Collected information about infection was summarized by using frequency and percentage. Mean and standard deviation were used to summarize CRP, WBC, and ESR levels. To compare CRP, WBC and ESR between positive and negative cases, independent sample 't' test was used. If data was not following normal distribution Mann –Whitney U test was used. The P -value < 0.05 was considered significant.

RESULTS

In this prospective study of 32 cases of open fractures treated at our hospital, maximum number patients were in the age group between 31-35 years. The mean age was 40.3 years $\text{SD} \pm 14.061$ minimum age in the study was 19 years while maximum age in the study was 62 years. 26 cases were males (81.25%) while 6 cases were females (18.75%). The most common mode of injury was road traffic accident which was about 20 cases (62.50%), followed by slip and fall which included 6 cases (18.75%). The most common side of injury was right in 18 (56.3%) cases followed by left 14 (43.7%).

Based on the type of open fracture according to Gustilo Anderson classification, we had 12 cases of type I, 5 cases of type II, 6 cases of type III A and 9 cases of type III B fractures.

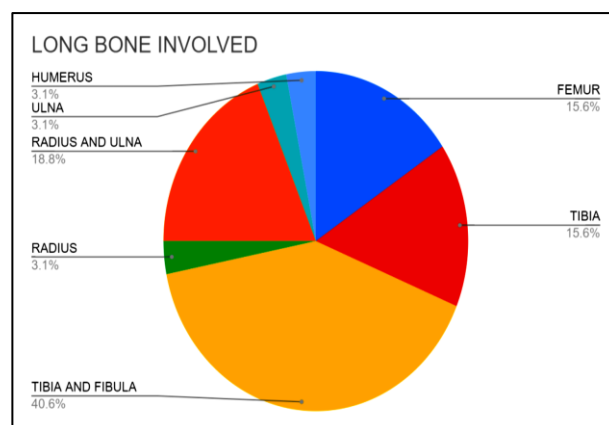


Fig. 1: Long bone involved

It was noted that 5 out of 32 cases (15.63%) were infected. Infected cases showed *Enterobacter cloacae* complex, MRSA, Pseudomonas, Pseudomonas with acinetobacter and Pseudomonas with *Staphylococcus aureus*. As per our study maximum incidence of infection was in GA type III B fractures.

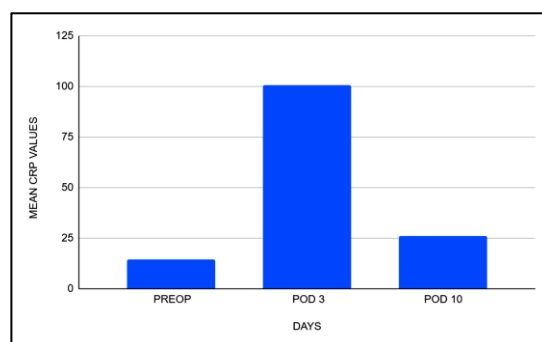


Fig. 2: CRP at various time intervals

In the infection group the mean CRP value preoperatively was 46.532 mg/dl, on post operative day 3 it was 138 mg/dl and post operative at day 10 it was 64.294 mg/dl. In the non-infection group the mean CRP value preoperatively was 8.30 mg/dl, on post operative day 3 it was 93.81mg/dl and post-operative at day 10 it was 19.29 mg/dl. Among infected cases CRP values were persistently elevated on postoperative day 3 and 10 while in non- infected group it elevated on postoperative day 3 and dropped to lower levels by postoperative day 10. Mann-Whitney Test used to find out relation between CRP and infection showed that it was statistically significant on preoperative and on POD 10 while not on POD 3.

In the infection group the mean ESR value preoperatively was 19.8 mm/h, on post-operative day 3 it was 81 mm/h and post operative at day 10 it was 52 mm/h. In the non-infection group the mean ESR value preoperatively was 13.66 mm/h, on post operative day 3 it was 56.92 mm/h and post operative

day 10 it was 46.55 mm/h. In both infection and non-infection group ESR levels were elevated on postoperative day 3 and 10 and showed very gradual decline in levels in no infection group even on postoperative day 10. Mann-Whitney Test used to find out any relation between ESR and infection showed no association between ESR and infection on preoperative, POD 3 and POD 10.

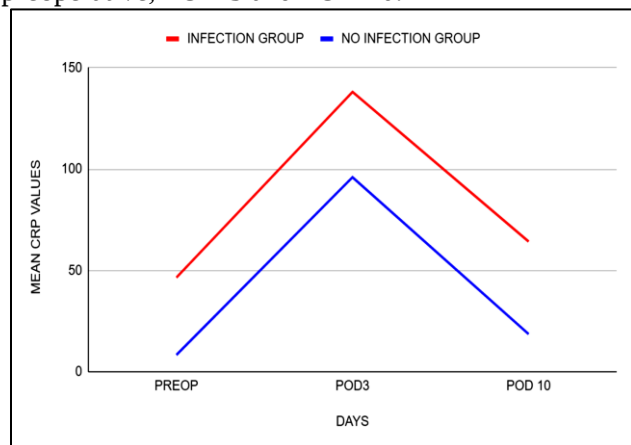


Fig. 3: Comparison of mean CRP in infection and no infection group

In the infection group the mean Total count value preoperatively was 13620, on post operative day 3 it was 9660 and post operative day 10 it was 11640. In the non-infection group the mean Total count value preoperatively was 11154.44, on post operative day 3 it was 8333.333 and post operative day 10 it was 8751.852. On day 10, the Total Count values had reduced to normal in the 22 out of 27 patients with non-infection and other 5 patients had elevated total count. In contrast, in the 5 patients with infection, the Total count concentration on day 10 was persistently elevated only in 3 patients. In contrast, of the total 32 patients on POD 10, 8 patients had elevated total count concentration ($\geq 11,000$ cells/mm³), but only 3 of them had local infection. In our study most of the patients had a drop in WBC counts by postoperative day 3 and were not following a typical postoperative profile. Independent „t“ test used to find out any relation between total count and infection showed that it was significant only on POD 10.

DISCUSSION

Dealing with postoperative infections in open long bone fractures with delayed presentations often have been difficult. In most of the cases clinical examinations do not indicate an underlying infection. Even when patients are under the cover of prophylactic antibiotics the occurrence of early infections are still high. Though clinical signs and symptoms are noted during a developing and progressing infection, the same can also be a part of response to surgery which makes it difficult to differentiate from an underlying infection. The above reasons put forward the requirement of simple, economical, dependable, and early monitoring of

postoperative complications.

In our study we used CRP, ESR and Total Leukocyte Count to monitor the course of infection. In our study mean CRP level preoperatively was 14.28 mg/dl, on post-operative day 3 was 49.06 mg/dl and on post-operative day 10 was 10.58 mg/dl. Kallio *et al.* in a study on patients with closed tibial fractures noted that the mean preoperative CRP was 9 mg/l which was less compared to patients in our study where mean preoperative CRP was 14.28. This can probably be explained because of the severity and nature of injury of our patients which included only open fractures. In our study where mean preoperative CRP was 46.532 in infection group which is high probably due to increased number of GA type III B cases among the infected group where the severity of injury and soft tissue damage is more compared to other types of open fractures (3).

Our study showed maximum peak CRP value on postoperative day 3 which was like some of the studies. In a study done by Thelander *et al.*, on change in levels of CRP and ESR after 4 types of uncomplicated spinal operations he noted peak values of CRP 2-3 days after surgery (4). Kang *et al.*, had done a retrospective study where serial CRP and WBC levels were measured to identify postoperative infections in patients who underwent primary spinal fusion surgery and revision fusion surgery which showed a peak CRP level on postoperative day 3 (5). In a prospective study done by Ayo, on 48 patients over 6 months on open tibia diaphyseal fractures, they noted increased CRP levels on day 3 after surgery (6). Studies have shown that in uncomplicated cases CRP levels dropped back to almost normal levels by postoperative day 10. Ellitsgard *et al.*, conducted a study on serial CRP and ESR values in 140 patients with hip fractures which showed a drop in CRP values in uncomplicated cases by 7th day (7). Neumaier *et al.*, conducted a study on perioperative CRP values to find out the kinetics of CRP following fracture surgery study showed a decline of CRP values to normal by 12 days (8). Retrospective study done by Kraft *et al.*, where CRP and WBC levels were assessed in 347 patients who underwent open posterior lumbar interlaminar fusion surgery and endoscopically assisted lumbar discectomy showed a rapid fall in CRP values 4-6 days postoperatively in both groups, almost reaching normal values in 14 days (9).

According to our study it was noted that all the patients infected postoperatively had persistent elevated CRP levels on postoperative day 10 which was like some of the studies. A study by Ayo on 48 patients over 6 months on open tibia diaphyseal fractures showed persistent elevated CRP levels up to 14 postoperative day (6). Aono *et al.*, had conducted a study on 143 patients who underwent instrumented posterior lumbar interbody fusion to assess the

changes in inflammatory markers perioperatively which concluded that elevated CRP values beyond POD-4 may be indicative of impending infection (10). Meyer *et al.*, showed the use of CRP, WBC, and ESR for early detection of postoperative infection after lumbar microdiscectomy. It was noted that CRP levels continued to be elevated on postoperative day 10 in infected cases (11). Our study showed elevated ESR levels on postoperative day 3 in both the infected and non-infected groups. But ESR levels were still persistently elevated in non-infected groups by postoperative day 10. This was like some of the studies conducted by Thelander *et al.*, on change in levels of CRP and ESR after 4 types of uncomplicated spinal operations. It was noted that ESR levels increased by 5 days after surgery which was followed by an irregular gradual drop to normal limits by 21-42 days (4). In a study conducted by Ellitsgard *et al.*, serial CRP and ESR values were measured in 140 patients with hip fractures which showed that in uncomplicated cases ESR values were elevated during the first week and had dropped to normal in a few weeks (7).

A study by Deirmengian *et al.*, on leukocytosis following total hip and knee arthroplasty to find out the natural history of WBC values following these surgeries showed an elevated WBC counts by POD-2 with a decline to normal levels which was not like our results (12). In our study most of the patients had a drop in WBC counts by postoperative day 3 and were not following a typical postoperative profile. Retrospective study by Kraft *et al.*, in 347 patients who underwent open posterior lumbar interlaminar fusion surgery and endoscopically assisted lumbar discectomy had similar results as our study where the postoperative profile of WBC counts was atypical and unreliable (9). All the 5 infected patients had features of localized warmth, induration, and discharge from wound and infection was confirmed bacteriologically with cultures from the same. CRP, ESR, and total counts have been used for detection of insidious infections. But our studies have shown that serial measurement of CRP as a better indicator than ESR and total count in predicting postoperative infection in open long bone fractures. High index of suspicion of infection and correlation with clinical signs and symptoms is of paramount importance in early diagnosis of postoperative infection. Clinical correlation with careful administration of these tests will help in early appropriate therapeutic management of the patients.

Limitation of the study

The study results must be interpreted in view of certain limitations with the sample size of the study

being small.

CONCLUSION

Serial CRP measurements can be considered as a more definitive reliable inflammatory marker as compared to ESR and total count in predicting postoperative infections in open long bone fractures. Serial measurements of total counts are not a reliable inflammatory marker for predicting postoperative infections in open long bone fractures. Clinical signs and symptoms associated with raised index of suspicion is important in early diagnosis of postoperative infection. The elevated serial CRP level postoperatively and their continued persistence in open fractures is potentially an early screening tool for infection before clinical signs of infection appear.

CONFLICT OF INTEREST

Authors declare no conflicts of interest.

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