

## Case Series

# An assessment of the C-reactive protein, erythrocyte sedimentation rate and white blood cell count, values during the post-operative period of infected tibial nonunions treated with antibiotic-loaded PMMA-coated nails

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## ABSTRACT

In this study, our aim was to assess the changes in the serum C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and white blood cell count (WBC) values during the follow-up period of infected tibial pseudoarthrosis treated using antibiotic-loaded nails. Three patients with infected femoral nonunions and 11 patients with infected tibial nonunions were included in the study. All patients were treated with intramedullary nails coated with antibiotic-loaded PMMA after local extensive debridement. Postoperatively, parenteral antibiotic therapy was administered. The CRP, ESR and WBC values were noted preoperatively and on the first day, and then on the second, sixth, and 12<sup>th</sup> weeks postoperatively. The changes in these values over time were analyzed comparatively. The preoperative CRP level was found to be significantly lower than the early postoperative period (1<sup>st</sup> day), while no significant differences were detected during the follow-up period. The CRP level constantly decreased between the first postoperative control (1<sup>st</sup> day) and the final follow-up time (12<sup>th</sup> week). The postoperative ESR showed a significant difference when compared to the preoperative value, and also showed a decreasing trend in the postoperative period, having its highest value on the first day. The WBC did not exhibit a significant difference when comparing the preoperative and postoperative values. C-reactive protein level and ESR can be used to monitor the adequacy of the treatment after antibiotic-loaded nail application, whereas WBC may be insufficient in the diagnosis and follow-up of osteomyelitis treated with antibiotic-loaded nails.

**Keywords:** CRP, ESR, WBC count, Antibiotic, Coating, Nailing

## INTRODUCTION

Infection after surgical treatment of fractures is one of the most important complications in orthopedic trauma surgery with their diagnosis, treatment, and follow-up strategies constantly evolving and changing.<sup>1</sup> Diagnosis is made by imaging and examining the blood values and

physical examination findings such as the sinus tract. Recommended diagnostic criteria include the measurement of the C-reactive protein (CRP) level, erythrocyte sedimentation rate (ESR), and white blood count (WBC); if these values are high, an infection is likely to occur.<sup>2</sup> The adequacy and validity of the abovementioned laboratory values have been mainly

investigated in prosthetic joint infection cases and patients with osteomyelitis due to diabetic foot disease.<sup>3-5</sup>

Although the surgical techniques regarding antibiotic-loaded nail applications in infected long bone non-unions are described in detail in the literature, there is lack of evidence-based information on the amount of change in serum biomarker values during the follow-up period, and therefore objective protocols are needed in this regard.<sup>6-8</sup> The limited evidence in the literature could not indicate the role of serum inflammatory markers in the diagnostic algorithm of fracture-related infections. An important issue in the management of patients with osteomyelitis is monitoring the response to treatment. There are no guidelines for the follow-up of such patients; their management is basically empirical.<sup>8</sup> In addition, there are no data regarding the changes in the levels of serum infection markers over the treatment period to guide clinicians.

In study, aim was to examine perioperative changes in the serum inflammatory markers such as CRP, ESR and WBC values in follow-up period of infected pseudoarthrosis patients treated using antibiotic-loaded nails.

## CASE SERIES

Fourteen patients (four females, 10 males) with Cierny-Mader stage 4 infected non-unions of the tibia and the femur were included in the study. During their clinical examinations, all patients had pain with weight-bearing and local palpation in the involved extremity. Five patients without any implants exhibited pathological movements. All patients had a fistula opening with discharge of a low flowrate.

In the conventional X-ray evaluation, no patients were found to have cortical continuity in the fracture line. According to Ilizarov's classification of non-unions, eleven patients had hypertrophic pseudoarthrosis and three had atrophic pseudoarthrosis. According to the Cierny-Mader classification, three patients had one systemic risk factor (stage 4S). No local risk factors were observed in any patient. Diagnosis was made in the presence of a pseudoarthrosis picture during the physical examination, conventional radiography and surgery, and culture sampling. The average number of surgeries for the same area of fracture was 3.1 (range: 1 to 6). The CRP, ESR, and WBC values were measured, culture samples were collected from the fistula discharge and conventional radiographs were taken before the treatment.

Following local wound debridement, 3.6 gm of teicoplanin was added to 40 gm of PMMA bone cement, and the intramedullary nail was coated with this mixture and inserted in accordance with the standard surgical technique. Culture sampling was repeated during surgery. Empirical anti biotherapy (cefazolin sodium 3x1 gm) was started postoperatively. According to the results of deep tissue culture, appropriate anti biotherapy was initiated

(Table 1). The CRP, ESR, and WBC values were recorded on the first day, then on the second, sixth and 12<sup>th</sup> weeks postoperatively. Conventional radiographs were taken at 1.5-month intervals and were checked for the state of union. In addition, the discharge from the fistula and weight-bearing on the extremities were monitored.

Analyses were performed with the SPSS v.15.0 statistical package software using Fisher's exact and repeated measures ANOVA tests. The significance level was set at  $p < 0.05$ .

The patients had a mean age of 51.2 years (range: 30 to 84 years) at the time of surgery and they were followed up for a period of 24.7 months (range: 8 months to 37 months) on average. The preoperative and perioperative results of the culture samples were different in eight patients. No bacterial growth was observed in the preoperative samples of six patients. At the end of the follow-up period, the infection had regressed in 85.7% of the patients (12 patients), however, a late recurrence of infection was detected in one patient at the end of the first year. Non-union was observed in four patients, while union was observed in 10 patients (71.4%). Infection had continued in two of the non-union patients (Table 1).

Preoperatively, the mean CRP level was 24.6 mg/l (range: 8 to 55 mg/l), ESR was 37.1 mm/h (range: 14 to 64 mm/h), and WBC was  $7.6 \times 10^9/l$  (range:  $3.5$  to  $9.5 \times 10^9/l$ ).

According to the first day results of the blood count, the mean CRP level was 51.1 mg/l (range: 14 to 234 mg/l), ESR was 51.2 mm/h (range: 23 to 87 mm/h), and WBC was  $9 \times 10^9/l$  (range: 4.4 to  $11.5 \times 10^9/l$ ).

The second week blood count results revealed a mean CRP level of 31.8 mg/l (range: 5 to 178 mg/L), ESR of 37.9 mm/h (range: 10 to 77 mm/h), and WBC of  $9 \times 10^9/l$  (range: 3.9 to  $14.6 \times 10^9/l$ ).

On the sixth postoperative week, the mean CRP level was 18.6 mg/L (range: 5 to 63 mg/l), ESR was 27.1 mm/h (range: 6 to 47 mm/h), and WBC was  $7.8 \times 10^9/l$  (range: 3.8 to  $11 \times 10^9/l$ ).

Twelve weeks after the surgery, the mean CRP level was 23.9 mg/l (range: 7 to 57 mg/l) and ESR was 28.9 mm/h (range: 7 to 45 mm/h), while WBC was  $7.6 \times 10^9/l$  (range: 3.6 to  $10.9 \times 10^9/l$ ) (Table 2).

CRP and ESR values significantly improved with the cessation of the discharge. Repeated ANOVA values were found to be statistically significant ( $F=4.205$ ,  $p=0.030$ ).

The preoperative CRP values increased significantly in the postoperative first day, and the postoperative first day CRP values decreased significantly on the second, sixth, and 12<sup>th</sup> weeks ( $p < 0.05$ , post-hoc LSD pairwise comparison).

**Table 1: Demographic data, culture results, antibiotic preferences and treatment results.**

Patient no.	Age/Gender (Years)	Fracture site	Culture from the sinus tract	Peri-operative culturing result	Choice of antibiotics	Infection eradication	Union
1	37/M	Tibia	<i>Staphylococcus aureus</i> (MRSA)	<i>Staphylococcus aureus</i> (MRSA)	Teicoplanin	Yes	Yes
2	39/M	Tibia	No growth	No growth	Cefazolin	Yes	Yes
3	35/M	Tibia	<i>Staphylococcus aureus</i> (MRSA)	<i>Staphylococcus aureus</i> (MRSA)	Teicoplanin	Yes	Yes
4	48/M	Tibia	<i>Staphylococcus aureus</i> (MRSA)	<i>Staphylococcus aureus</i> (MRSA)	Teicoplanin	Yes	Yes
5	44/M	Femur	<i>Staphylococcus epidermidis</i> (MRSE)	<i>Staphylococcus epidermidis</i> (MRSE)	Teicoplanin	No	No
6	49/M	Femur	<i>Staphylococcus capitis</i>	<i>Proteus mirabilis</i>	Ciprofloxacin	No	No
7	56/M	Tibia	<i>Staphylococcus auricularis</i>	<i>Pseudomonas aeruginosa</i>	Ciprofloxacin	Yes	No
8	32/M	Tibia	<i>Enterobacter cloacae</i>	<i>Pseudomonas aeruginosa</i>	Ciprofloxacin	Yes	Yes
9	63/F	Tibia	No growth	No growth	Cefazolin	Yes	Yes
10	30/M	Tibia	No growth	<i>Staphylococcus aureus</i> (MRSA)	Teicoplanin	Yes (recurrence after one year)	Yes
11	80/F	Tibia	No growth	No growth	Cefazolin	Yes	Yes
12	84/F	Femur	<i>Escherichia coli</i>	<i>Escherichia coli</i>	Fusidic acid	Yes	Yes
13	57/F	Tibia	No growth	<i>Staphylococcus aureus</i> (MRSA)	Teicoplanin	Yes	Yes
14	63/M	Tibia	No growth	<i>Staphylococcus aureus</i> (MRSA)	Teicoplanin	Yes	No

**Table 2: Distribution of the serum marker results by patient and according to the time of measurement.**

Patient no.	Pre-operative values			Early post-operative values (1 <sup>st</sup> day)			Post-operative 2 <sup>nd</sup> week values			Post-operative 6 <sup>th</sup> week values			Post-operative 12 <sup>nd</sup> week values		
	CRP*	ESR	WBC**	CRP	ESR	WBC	CRP <sup>#</sup>	ESR <sup>\$</sup>	WBC	CRP	ESR	WBC	CRP	ESR	WBC
1	16	41	7.4	30	64	5.9	5	28	6	13	47	6.6	14	40	6.9
2	17	50	6.1	14	40	8.5	5	20	14.2	13	14	8	28	39	6.5
3	18	30	8.3	40	50	10.4	22	42	8.4	13	36	8	14	27	8.4
4	22	45	7.2	35	50	9.8	16	59	6.6	13	35	9	33	33	5.8
5	50	59	9.5	54	83	10.1	46	70	10	63	40	9.8	57	35	8.8
6	20	55	4.5	53	87	4.4	11	48	4.5	5	30	4.5	57	45	6
7	18	17	7.6	30	34	7.3	9	10	6.0	9	6	6.5	7	7	7.8
8	17	40	9.3	29	42	10.4	15	33	7.4	8	10	9.2	15	14	9
9	8	30	8.3	17	58	11.5	37	33	11.3	28	33	6.5	15	30	7
10	26	14	9.3	47	23	10.2	20	12	14.6	13	14	10.8	12	15	10
11	18	30	8	40	50	10	22	42	8.4	13	36	8	14	27	8.4
12	55	64	3.5	234	64	5.8	178	77	3.9	40	29	3.8	40	44	3.6
13	34	30	8.7	46	40	11.3	39	30	10	13	25	7.9	15	26	7
14	26	14	9.3	47	32	10.2	20	26	14.6	17	24	11	14	23	10.9

\*CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, \*\*WBC: white blood count. <sup>#</sup>CRP values are given in mg/L, <sup>\$</sup>ESR values in mm/h, WBC values in  $\times 10^9/L$

The preoperative ESR increased significantly on the postoperative first day, while it showed a significant decrease on the second, sixth and 12<sup>th</sup> weeks after the surgery ( $p < 0.05$ , post-hoc LSD pairwise comparison).

As for the WBC, the values did not show a significant difference with the cessation of the discharge ( $p = 0.069$ ). The CRP and ESR values remained above normal in two patients in which we failed in infection eradication. In one patient who encountered a delayed recurrence of osteomyelitis, the CRP and ESR values were higher than normal values.

## DISCUSSION

In orthopedic surgery, the most commonly used serum inflammation markers in the diagnosis of post-fracture infections are CRP, ESR, and WBC. In our study, the serum CRP level and ESR showed a statistically significantly better performance in comparison to serum WBC during the postoperative follow-up of infected tibial pseudoarthrosis treated with antibiotic-loaded nails. Although the sensitivity and specificity of these markers are poor, they are still widely used in the diagnosis of infections after trauma surgery and in the follow-up of antimicrobial therapy.<sup>9</sup> However, the variability of inflammatory markers during the follow-up should still be closely monitored.<sup>10</sup>

It is recommended that the CRP and ESR values always be evaluated under the guidance of clinical information. Harris et al reported that in cases of high clinical suspicion or high-risk factors for osteomyelitis, normal ESR and CRP values do not rule out osteomyelitis.<sup>11</sup> In addition, the authors emphasized the need for further diagnostic investigation in cases where ESR level is  $> 30$  mm/h and/or CRP level is  $> 10$  mg/L, even if there is little clinical suspicion, adding that WBC count has no place in the diagnosis of osteomyelitis. In our study, the mean CRP level was 24.6 mg/L and the mean ESR was 37.1 mm/h in the serum samples, while the mean WBC was  $7.6 \times 10^9/L$  and was within normal limits. We determined that the WBC did not exceed the normal range in the diagnosis of osteomyelitis; a finding in accordance with those from the literature.

Unkila-Kallio et al measured the WBC, CRP, and ESR values on the 3<sup>rd</sup>, 5<sup>th</sup>, 7<sup>th</sup>, 10<sup>th</sup>, 14<sup>th</sup>, 19<sup>th</sup> and 29<sup>th</sup> day during the follow-up of children treated for hematogenous osteomyelitis and found that the ESR was high ( $> 20$  mm/h) in 92% of the cases.<sup>12</sup> The authors found that in the follow-up period, ESR had reached its highest level between the third and fifth day, and then returned to normal levels on the third week after an average of 18 days. According to the same study, the CRP level was high ( $> 19$  mg/L) in 98% of the patients. While the CRP level reached its highest value on the second day (71 mg/L), it returned to normal levels at the end of the first week, showing a rapid improvement. The WBC values were found to be above normal in only 35% of the patients in

the acute period and it was accepted as a weak marker in diagnosis. In this study, the most sensitive value was considered as CRP.

It has been reported that in postoperative infections, the CRP, ESR, and WBC values tend to decrease after four weeks of treatment. Despite the decrease in sedimentation, the difference between the pre- and post-antibiotic therapy results was not statistically significant.<sup>13</sup> In our study, we found that the CRP and ESR values reached their highest levels in the early postoperative period (1<sup>st</sup> day) (mean CRP: 51.1 m/L, mean ESR: 51.2 mm/h) and showed a significant decrease at the end of the second week after surgery (mean CRP: 31.8 m/L, mean ESR: 37.9 mm/h). The mean WBC was  $9 \times 10^9/L$  both in the early postoperative period and at the end of the second week.

Inflammatory markers such as CRP, ESR, and WBC show an increase after intramedullary nailing with surgical debridement. In addition, the antibiotics and the debridement applied in this surgery have a reducing effect on the very same serum infection markers. In our operated cohort, the surgical intervention and the antibiotics administered had counter effects, while the first increased inflammation and the latter reduced it. To the best of our knowledge, there are no publications examining the changes in serum inflammation markers over time in such group of patients.

In our study, the preoperative CRP value was found to be statistically lower than that in the early postoperative period, while it did not show a statistically significant difference with the values recorded on the postoperative second, sixth, and 12<sup>th</sup> week. In addition, the CRP level showed a tendency to decrease between the postoperative first day and 12<sup>th</sup> week follow-up. As for the ESR values, there was a significant difference between the preoperative value and all postoperative follow-up values. The ESR value was at its highest on the first postoperative day and showed a continuous decline as in the CRP levels. The comparison of preoperative and postoperative WBC values demonstrated no significant difference. The CRP level and ESR remained above normal values in two patients in which we failed in infection eradication. In addition, in one patient that encountered a late recurrence, the CRP level and ESR were again above normal values. We believe that these findings are important in showing the sensitivity of these serum markers during the clinical follow-up of the patients.

The absence of a control group and its retrospective design seem to be the main drawbacks of our study. However, we believe that the number of cases with this rare disease renders our study a valuable one.

## CONCLUSION

CRP level and ESR can be used to monitor the adequacy of the treatment after antibiotic-loaded nail application, whereas WBC may be insufficient in the diagnosis and

follow-up of osteomyelitis treated with antibiotic-loaded nails.

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## REFERENCES

1. Govaert GAM, Glaudemans AWJM, Ploegmakers JJW, Viddeleer AR, Wendt KW, Reininga IHF. Diagnostic strategies for posttraumatic osteomyelitis: a survey amongst Dutch medical specialists demonstrates the need for a consensus protocol. *Eur J Trauma Emerg Surg.* 2018;44(3):417-26.
2. Metsemakers WJ, Morgenstern M, McNally MA, Moriarty TF, McFadyen I et al. Fracture-related infection: A consensus on definition from an international expert group. *Injury.* 2018;49(3):505-10.
3. Parvizi J, Tan TL, Goswami K, Higuera C, Valle DC, Chen AF et al. The 2018 Definition of Periprosthetic hip and knee infection: An evidence-based and validated criterion. *J Arthroplasty.* 2018;33(5):1309-14.e2.
4. Moallemi SK, Niroomand M, Tadayon N, Forouzanfar MM, Fatemi A. Diagnostic value of erythrocyte sedimentation rate and C reactive protein in detecting diabetic foot osteomyelitis; a cross-sectional study. *Arch Acad Emerg Med.* 2020;8(1):e71.
5. Lavery LA, Ahn J, Ryan EC, Bhavan K, Oz OK. What are the optimal cutoff values for ESR and CRP to diagnose osteomyelitis in patients with diabetes-related foot infections? *Clin Orthop Relat Res.* 2019;477(7):1594-602.
6. Pradhan C, Patil A, Puram C, Attarde D, Sancheti P. Can antibiotic impregnated cement nail achieve both infection control and bony union in infected diaphyseal femoral non-unions? *Injury.* 2017;48(2):S66-71.
7. Bhatia C, Tiwari AK, Sharma SB, Thalanki S, Rai A. Role of antibiotic cement coated nailing in infected nonunion of tibia. *Malays Orthop J.* 2017;11(1):6-11.
8. Makhdom AM, Buksbaum J, Rozbruch SR, Da Cunha R, Fragomen AT. Antibiotic cement-coated interlocking intramedullary nails in the treatment of septic complex lower extremity reconstruction; a retrospective analysis with two year minimum follow up. *J Bone Jt Infect.* 2020;5(4):176-83.
9. Williams DT, Hilton JR, Harding KG. Diagnosing foot infection in diabetes. *Clin Infect Dis.* 2004;39(2):S83-6.
10. Govaert GAM, Kuehl R, Atkins BL, Trampuz A, Morgenstern M. Fracture-Related Infection (FRI) Consensus Group. Diagnosing fracture-related infection: Current concepts and recommendations. *J Orthop Trauma.* 2020;34(1):8-17.
11. Harris JC, Caesar DH, Davison C, Phibbs R, Than MP. How useful are laboratory investigations in the emergency department evaluation of possible osteomyelitis? *Emerg Med Australas.* 2011;23(3):317-30.
12. Unkila-Kallio L, Kallio MJ, Eskola J, Peltola H. Serum C-reactive protein, erythrocyte sedimentation rate, and white blood cell count in acute hematogenous osteomyelitis of children. *Pediatrics.* 1994;93(1):59-62.
13. Lee Y, Lim J, Choi SW, Han S, Park B et al. Changes of biomarkers before and after antibiotic treatment in spinal infection. *Korean J Neurotrauma.* 2019;15(2):143-9.

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