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Serum complement-reactive protein (CRP) trends following local and free-tissue reconstructions for traumatic injuries or chronic wounds of the lower limb

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Summary *Background:* Soft-tissue reconstructions of the lower limb for open fractures, chronic infections and nonunion carry a high risk of infection, nonunion, osteomyelitis and amputation. Inflammatory markers can be difficult to interpret in the context of recent surgery and trauma and little is known of their behaviour.
Aim: To profile the behaviour of complement-reactive protein (CRP) following soft-tissue reconstructions for the lower limb performed for acute injuries(open fractures) and chronic wounds(nonunion and osteomyelitis).
Patients and methods: Patients who had soft-tissue reconstructions following open fractures of the lower limbs, chronic infection, osteomyelitis and nonunion were identified and their notes and postoperative CRP levels reviewed.
Results: 52 patients were identified. 41 reached peak CRP $\leq$4 days of surgery. A peak CRP $>$4 days indicated infection or further surgery ($p < 0.01$). Acute and chronic groups showed a peak in mean CRP at day 2. Chronic wound patients showed significantly elevated CRP levels compared to acute wound patients at day 7 ($p = 0.05$) and 8 ($p < 0.001$). Muscle and fasciocutaneous flaps showed similar CRP profiles. Patients with nonunion or deep infections showed persistently elevated CRP levels.
Conclusions: CRP peaks on day 2 following soft-tissue coverage and falls thereafter. Peaks after day 4 indicate infective complications or further surgery. Patients with chronic wounds show a slower decrease in their CRP. Persistently elevated CRP following surgery is associated with infection and nonunion.
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Open fractures of the lower limb carry a risk of nonunion, osteomyelitis, and subsequent amputation.[1] Treatment is excision of all non-viable tissues, osteosynthesis, and coverage with well-vascularised tissue. Post-operative monitoring aims to ensure the success of the reconstruction, and allow early detection and treatment of infection. Indicators of infection include physical signs, physiological observations, haematological markers e.g. white-cell count and erythrocyte sedimentation rate (ESR), Complement Reactive Protein (CRP) and blood and tissue cultures. CRP is a group of plasma proteins which are part of the innate immune system, first described in patients with pneumonia.[2] CRP is secreted by macrophages, adipocytes and hepatocytes in response to IL-6 released in response to trauma, infection and some malignancies. It has a constant half-life, making its serum levels reflective of the balance between production and degradation.

CRP has been investigated in elective orthopaedics,[3,4] trauma and fractures,[5] fracture fixation,[6,7] bone infection,[8] sepsis, burns[9] and some elective plastic surgical procedures.[10] CRP rises following closed tibial fractures, reaching a higher peak if the fracture is fixed reflecting additional surgical trauma. These studies found CRP peaks at day 3, and later peaks suggest infection.

Surgery for nonunion is a stimulus to a patient where fracture healing has ended without union. Osteomyelitis exerts an inflammatory effect, but surgery will superimpose a further stimulus and may re-activate infection by disturbing the sequestrum. Hence there are many confounding factors influencing serum CRP following surgery for nonunion.

Aim

To characterise the trend of serum CRP following soft-tissue reconstruction of the lower limb for trauma, nonunion, and osteomyelitis. These trends were analysed to see if they were predictive of healing or union, infection or other complications.

Patients and methods

Patients with soft-tissue reconstruction for open fractures, soft tissue injuries, osteomyelitis and nonunion were reviewed. Surgery was performed in a specialist centre by a multidisciplinary surgical team of plastic and orthopaedic surgeons with specialist interests in lower limb reconstruction. CRP levels were measured daily until discharge and then at intervals in a specialist lower limb clinic. Antibiotic therapy was guided by a consultant microbiologist.

During follow-up flap loss, wound breakdown, nonunion and further treatment were recorded. Time was measured from definitive soft-tissue coverage until final review. Absolute CRP values varied, so a patients CRP values were expressed as a percentage of their peak value. Percentages were averaged per day per group. The number of days taken for each individual to reach peak CRP were measured. Groups' mean CRP trends within the series were compared. Fishers exact test was used for parametric variables, and the unpaired t-test for continuous variables, $p < 0.05$ was taken as statistically significant.

Results

Fifty-two patients who had local or free-tissue transfer for trauma and chronic wound problems to the lower limb over a two-year period were identified (Table 1).

Forty-one (79%) of patients reached their peak CRP within 4 days, of whom 6 (15%) had an infective complication or further surgery. Of the 11 peaking after day 4, 9 (82%) had an infective complication or further surgery ($p < 0.01$) (Figure 1).

Having peaked at day 2, serum CRP levels fell in both groups. There was a second, smaller peak at day 8–9 in both groups, reflecting further surgery, or infection. There was a tendency for the chronic group CRP to fall more slowly and the second peak to be more pronounced. The divergence of the trend-lines greatest between 5 and 8 days (Figure 2) was statistically significant at days 7 ($p = 0.05$) and 8 ($p < 0.001$) (Table 2).

Mean CRP halved in 4 days in the acute group and 10 days in the chronic group. At 2 weeks both groups had fallen to 20% of their peak value including those with infections, or further surgery (Figure 2).

Twenty-five patients achieved union, or resolution of their chronic wounds or osteomyelitis while eight had ongoing problems such as nonunion, osteomyelitis or persistent wounds. We found the CRP level rose again in the nonunion/non-healing/ongoing treatment group after day 10. At union, all patients were noted to have a CRP <8 mg/L while those failing to unite had CRP levels persistently in excess of 8 mg/L.

Discussion

Flap coverage converts an open fracture to a closed fracture, and arrests the associated inflammation. CRP peaked most commonly 2 days following soft tissue coverage and fell thereafter. Any upward trends in serum CRP after day 4 resulted from further surgery, or infection. One patient developed pancytopenia following their injuries requiring Granulocyte Macrophage Colony Stimulating Factor (GMCSF). While the patient's neutrophil counts were meaningless, the patient's CRP showed a similar pattern to our main cohort.

Table 1 Patient presentations and reconstructions used

Presentation		Number in group
Acute ($n = 37$)	Soft-tissue alone	1
	Open fracture	36
Chronic ($n = 15$)	Non-healing wound	5
	Osteomyelitis	6
	Non-union	2
	Arthroplasty revision	2
Flap type		Number used
Local	Fasciocutaneous	9
	Muscle- gastrocnemius	4
Free	Fasciocutaneous	37
	Muscle	5

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