Nikolaos Kanakaris - Owais Ahmed

RQ [##]:

Should early conversion from external to internal fixation be guided by serum procalcitonin trends rather than fixed time intervals?

Section 1: Background (<300 words):

Temporary fixation of open fractures (bridging external fixation) remains one of the mainstay strategies of modern orthopaedic traumatology. It is a form of damage control orthopaedics (DCO) which is applied in the presence of other associated severe injuries (polytrauma scenarios), or in isolated injuries (monotrauma - MuST surgery (musculoskeletal temporary surgery)) when an acute "fix and cover" surgery is not feasible due to clinical or logistic reasons. (1)

The presence of the temporary external fixator raises concerns for a potential deep-seated contamination at the area of the pin sites which may predispose to a secondary fracture related infection (FRI) in the presence of future definitive internal fixation devices. (2)

A debate exists between using the absolute value or the trending of the value of biochemical markers (like serum procalcitonin) versus fixed time intervals or other clinical means (inspection of pin sites) to decide when it is relatively safe to shift from the temporary fracture fixation (bridging external fixation) to the definitive fixation especially via internal fixation (plates, intramedullary nails). (3)

The risk factors of an FRI when managing open fractures are apparently multiple. They include parameters relevant to the injury mechanism and levels of initial contamination, features of the pathogens, systemic host parameters relevant to certain comorbidities and the quality of resuscitation, as well as management related parameters (including the timing and conditions of soft tissue reconstruction and open fracture fixation). (4)

Serum procalcitonin (s-PCT), is a pro-hormone of calcitonin considered as a highly specific (85-90%) biomarker of bacterial infections, with improved diagnostic features in comparison to other biomarkers (i.e. C-reactive protein - CRP, erythrocyte sedimentation rate - ESR, white blood cell count - WBC). However, the sensitivity of s-PCT is low (60-70%) and is mostly used in the trauma setting to "rule in" bacterial infections and to differentiate from the systemic inflammatory reaction that follows a severe injury. In contrast to the CRP that has more of a delayed response to an infection (12-48 hours), s-PCT begins to raise

within 2-4 hours and peaks at 24 hours. It is also nonaffected in the presence of neutropenia and other immunosuppressive conditions, and its levels correlate well also with the severity of a bacterial infection. (5-7)

A literature review was performed to identify the presence and quality of published evidence on balancing decisions on serum procalcitonin rather than fixed time intervals.

Section 2: Data extraction table

S. no	Author, year of publication, Country	Study Design (level of evidence)	Sample Size	Study population (Inclusion and exclusion criteria)	Groups compared	Results	COMMENTS
1	Groznik et al. 2019, Slovenia (8)	prospective nonrandomised cohort study (IVI)	86	- Tibial fractures treated with definitive internal fixation. - EF converted to plate or IMN (11 cases).	- POMs (20) vs. non POMs (66) patients - levels of WBC, CRP, s-PCT, Alb, serum IL-6, IL-10 and TNFα - on admission, on POD1 and POD4	- Inflammatory marker values after surgical procedures were elevated, as expected, reaching a peak value on POD1 (CRP, s-PCT) and later decreasing. - did not find any statistically significantly elevated levels of s-PCT in POM compared to control group.	- A statistically high number of patients (35%) that had EF conversion developed POM in comparison to any other operative strategy. - Perioperative dynamics of CRP (increase at POD1 compared to the admission value) and a lower Alb value on POD4 should be warning signs for POMs.
2	D Souza et al, 2024, India (6)	prospective case control (III)	40	- All open fractures, presenting within 24hrs from trauma, undergoing internal fixation. - Exclusion of patients with pre-existing clinically evident infections.	- FRI (9) vs. non-FRI (31) patients - s-PCT levels (preop + 1day + 5days postop)	- open injuries of variable severity. (*GA: IIIB 18; IIIC 9; IIIA 7) - variable anatomical sites (*24 tibias, 7 hands, 6 femurs) - preop s-PCT had a steady raise postop in all groups (influence of surgical hit). - preop s-PCT levels > 0.5ng/ml predicted, whilst levels <0.1 ng/ml excluded the development of postop FRI (p<0.05).	- Indirect evidence on the potential use of s-PCT as a marker of secondary wound infection. - No subgroup analysis between different fixation methods, or the use of staged protocols including the use of an external fixation. - No inclusion of patients that underwent delayed definitive fixation.
3	Huang et al. 2026, j Orth Sc, China (9)	prospective randomised (II)	60	- All non-healing wounds of open GAIII fractures.	- Standard Dressing (30) vs. Nano Silver with VSD (30)	- The levels of s-PCT between both groups before treatment were elevated >0.5 mg/ml and post treatment dropped to <0.3 mg/ml without statistically significant difference (P > 0.05) between the two groups.	- Study has used the s-PCT levels but refers to established infections with soft tissue complications. - No reference or subgroup analysis on patients initially managed with an external fixation.

Alb: serum albumin; EF: external fixation; FRI: fracture related infection; GA: Gustilo Anderson classification system; IL: interleukin; mg/ml: milligram / millilitre; POD: postop day; POMs: post-traumatic osteomyelitis; postop: postoperative; preop: preoperative; s-PCT: serum procalcitonin; TNF: tumour necrosis factor; vs: versus; VSD: vacuum sealed drainage.

* 3 most common in this study

Section 3: Results summary write-up (up to 500 words)

Three studies were identified as relevant to the question. The literature review expanded to 3 databases (PubMed, Embase, and Scopus) using the Rayyan software. The title, abstract, and full text were screened as well as the references of the retrieved studies for the extraction of all possible relevant studies.

There was no study directly addressing the validity of using s-PCT levels and their trend to rationalise the transition from an external fixator of an open fracture to internal fixation, minimising the incidence of a subsequent fracture related infection.

In the study of the D Souza et al (6), the s-PCT were measured in three different time periods following admission for an acute open fracture of variable severity and anatomical locations. A prospective cohort of 40 patients was followed up and an subgroup analysis followed between those that developed signs of infection (wound discharge, fever, local induration, gaping of the wound and bacterial growth on wound cultures over a period of one month) (9, 22.5%), and those that did not (31, 77.5%). Although the numbers were small, the period of follow up short, and the definition of the infection did not follow fully the contemporary consensus on FRI (10), the authors demonstrated a statistically significant increase of the s-PCT in both groups from the values measured on admission to those measured at day 1 and 5 postoperatively, indicating probably the effect of the surgical hit. The mean s-PCT in all different time points was x10 times higher in the group that developed and infection. Among the developing infection patients, the mean preoperative s-PCT was 1.02 ± 0.56, increasing to 1.08 ± 0.62 on day 1 and 1.16 ± 0.57 on day 5. In contrast, for patients without infections, the mean preoperative PCT levels were 0.13 ± 0.14, increasing to 0.19 ± 0.18 on day 1 and 0.25 ± 0.3 on day 5. Preoperative s-PCT value >0.5 ng/mL predicted postoperative wound infection. In contrast, values <0.1 ng/mL excluded the likelihood of infection within 1 month from the admission. Although this study points towards using admission levels of s-PCT as an indicator of a future wound infection, no subgroup analysis between different fixation methods, or the use of staged protocols including the use of an external fixation was explored, neither the effect of delayed definitive fixation following a period in an external fixator was studied.

The study of Groznik et al (8), assessed a prospective cohort of 86 tibial fractures, managed with different methods (11 included the exchange of an initial external fixator to internal fixation). The authors compared those that developed a posttraumatic osteomyelitis (POM) in a period of 12 weeks of follow up to those that did not. POM was

defined as an acute exogenous osteomyelitis based on the assessment of clinical and laboratory findings. The monitored biomarkers including the c-reactive protein (CRP), white blood cell count (WBC), albumin, tumour necrosis factor-a (TFNa), interleukins 6 and 10 (IL6, IL10) and s-PCT measured on admission, at day 1 and day 4 postoperatively. No statistically significant elevated levels of s-PCT were found in the group that developed an infection. The procalcitonin was shown to be a poorly sensitive marker with high specificity at a cut-off of 0.5ng/ml. According to these authors, the s-PCT should not be used as a screening marker for identifying reliably the patients who would develop bone and joint infections.

The third study of Huang et al (9), was a randomised trial comparing the management of non healing wounds of open fractures with conventional wound dressings versus a vacuum sealing drainage combined with nanosilver dressings. They did use the expression of s-PCT and CRP together with wound exudate growth factors to assess the effectiveness of the different management strategies, The relevance of this study to the question we are studying was minimal as they assessed the s-PCT values at a later stage, when the wound problems and infection are established. Therefore their results, that the levels of both cytokines drastically improved following treatment, apply mainly to the value of s-PCT as a marker of response to a certain therapy of wound problems and infection following an open fracture.

Section 4: Discussion (<1000 words)

Prompt identification of patients with open fractures at risk of developing fracture related infections is critical for surgical planning and the employment of preventative and early treatment measures. The medical and socioeconomic costs of postoperative complications like FRI or septic non-unions, both needing secondary admissions and surgical interventions (11, 12), justify the efforts to employ advanced techniques and laboratory tests including different cytokines as biomarkers. (13) Past research has explored several inflammatory markers for their prognostic value, without any molecule proving as a perfect fit for screening purposes.

Often a staged management strategy is applied, including the use of a spanning external fixator at the time of the initial debridement of the open fracture site. Especially when definitive fixation plans pertain internal osteosynthesis devices there are concerns that a secondary FRI may occur. The overlap of the internal fixation device with the pin

sites, as well as a prolonged period in an external fixator during the ward or intensive care unit hospitalisation can lead to deep infection with often resilient and multiresistant pathogens. (14)

In contemporary practice, certain fixed time intervals are considered as more or less safe for a transition to internal fixation. Early conversion within 2 weeks is considered as safe, after 2 weeks and before 4 weeks of intermediate risk and after 4 weeks of high risk for infection. (3, 15, 16)

The main limitations of such an approach, is it is based on older observational studies, which in large understood that mature biofilm formation would take days to weeks to form, making the first 14 days to appear as safe enough. However, more recent evidence shows that mature bacterial biofilm formation takes less than 40 hours to develop. (17, 18) Even more, it should be anticipated that time intervals as such do not take much into account individual host related parameters, neither other contributing factors, which always exist making such horizontal approaches to a complex dynamic problem less convincing.

Theoretically if we could identify a biomarker, or a combination of biomarkers that could be used effectively for the screening of the patients in an external fixator and their safe transition to internal fixation. Such a test should be readily available, cost effective, sensitive and specific enough to the prognosis of a feature FRI at the setting of acute trauma.

The procalcitonin is a polypeptide precursor of calcitonin produced by the C cells of the thyroid gland. Usual serum levels are very low (<0.05ng/ml). As a response to bacterial endotoxins and pro-inflammatory cytokines, various cell types produce procalcitonin rapidly raising its serum levels int the presence of severe inflammation, especially in severe sepsis. Due to the reliable kinetics and unique characteristics of the PCT it has emerged as a key biomarker of bacterial infections. (19) The early elevation of s-PCT is related to the magnitude of the first hit and the severity of the injury. The levels of this initial elevation are mild and settle relatively fast unless a bacterial infection is added to the clinical picture. The trend of the s-PCT levels following its initial peak can reliably differentiate between an infectious and non-infectious inflammatory response (SIRS). (20, 21)

Since the increase of s-PCT is quite prompt in the process of developing a bacterial infection (increases within 6 hours, peaking at 24), it precedes any clinical findings and symptoms and is faster to its peak than the common infection biomarkers CRP, ESR, WBC.

(19, 20) The latter are acute phase reactants lacking in specificity for infections and have a peak at 48 plus hours. They are used mostly for monitoring response to therapy rather than diagnosis. (22) The IL6 has similar kinetics with the PCT but is more expensive to test and cannot differentiate as well between SIRS and an infection. Interferon γ (INFγ) is released in viral infections and has a downregulating effect to the s-PCT, meaning that the procalcitonin can also be used to differentiate between a bacterial and a viral infection. (23)

According to the existing evidence, baseline s-PCT levels taken on admission and immediately following the initial external fixation, with subsequent monitoring of its trends could be an molecule to study further. In the absence of a bacterial infection a downward trend of s-PCT should lead to a safe transition to internal fixation, when its levels cross a safety cut off (usually <0.25-0.5ng/ml). (6, 24)

Therefore, s-PCT could be considered as promising screening biomarker to identify patients with a developing FRI following an open fracture that should be treated aggressively or may better avoid the insertion of an internal fixation device if it that can be avoided. It could also help identify patients that need to be treated more aggressively with the use of additional debridement, tissue sampling and local delivery of high dose of antibiotics at the same time or before the definitive osteosynthesis. Unfortunately, the review we performed failed to identify any published study with a specific enough design and robust methodology exploring the above hypothesis.

There are of course a few studies challenging the role of s-PCT, highlighting its relatively lower sensitivity (down to 25% in paediatric series of patients). (25) Additionally, biofilm embedded bacteria, which may be present at the pin sites, rarely trigger a systemic rise of s-PCT. (17)

Early conversion from external to internal fixation should at present be guided by the retrospectively assessed and generally accepted “fixed time” windows, the state of the local soft tissue and a comprehensive panel of systemic inflammatory markers. Preferably prospective randomized controlled multicentre open-label intervention studies are necessary to investigate the impact of procalcitonin-guided decision-making on the clinical outcomes in the trauma setting and more specifically to the management of open fractures.

Section 5: Risk of bias of included studies

The overall risk of bias was assessed as **moderate**. All three included studies were prospective in nature, all offered had a control group, however the only randomised one was only indirectly related to the question under investigation. Of note is that all three studies defined differently infections and did not use the established defining criteria of FRI.

Section 5: Response/Recommendation (1-2 lines as a conclusion and recommendation statement for the question)

The use of serum procalcitonin levels in isolation to justify or guide the timing of conversion from a temporary external fixation to a definitive internal fixation cannot be supported due to absence of relevant strong evidence.

An individualised approach from open fracture trauma specialists should be adopted, considering injury and patient's parameters, the fixed safe time windows, the state of local soft-tissues, a comprehensive panel of systemic inflammatory markers would be a more reliable strategy at present.

Section 6: Level/ strength of Evidence:

LOW.

No studies that explored specifically the raised question of The use of serum procalcitonin levels to justify or guide the timing of conversion from a temporary external fixation to a definitive internal fixation.

Small number of studies (Table above) referring to the use of serum procalcitonin levels or their trends as a predictor of developing a fracture related infection.

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