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Review

Peri-operative changes in serum immune markers after trauma: A systematic review

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ABSTRACT

Introduction: Surgery is a posttraumatic immune stimulus which contributes to the systemic inflammatory response syndrome and multiple organ failure (MOF). Serum markers may facilitate post-injury immune monitoring, predict complications and guide the timing of surgery.
Aim: To evaluate whether immune markers increase after surgery in trauma patients, if this is affected by the timing of surgery, and whether immune markers correlate with clinical outcomes.
Patients and methods: Systematic review of MEDLINE, Cochrane and EMBASE using a combination of keywords including trauma, biological markers, immune monitoring, and surgical procedures. The last search was performed on 26/11/13. The search considered English language studies enrolling adult trauma patients. Outcomes were perioperative immune markers plus clinical outcomes including mortality, MOF, sepsis.
Results: 1612 Articles were identified using the search strategy. 1548 Articles were excluded by title and 40 excluded by abstract, leaving 24 articles for full text review. Of these articles, fifteen studies were eligible for study inclusion. The disparity in interventions and outcome measures precluded combined statistical analysis. The surgical intervention studied was mostly intramedullary nailing of long bone fractures. All articles described a postoperative increase in at least one marker. Interleukin (IL)-6 and IL-10 were consistently elevated and tested in the greatest number of patients. Many studies did not correlate markers with clinical outcomes and few significant associations were demonstrated. Two studies considered the timing of surgery and showed greater increase in IL-6 after "early" surgery, though definitions of timing were dissimilar.
Discussion: An increase in posttraumatic serum cytokines has been demonstrated after surgery, but without consistent clinical associations. The timing of surgery may modulate this increase. Future research directions include confirmation of findings in larger populations, clarifying clinical associations, and evaluation of other surgical interventions.

Contents

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Introduction

Multiple organ failure (MOF) is the leading cause of deaths in intensive care units [1,2], and is responsible for at least 10% of traumatic deaths [3,4]. The reported incidence in trauma patients is around 20% [5,6], with mortality reported to be between 4 and 50% in affected patients [6–8]. Tissue trauma is known to cause an immune response and release of inflammatory mediators described as the systemic inflammatory response syndrome (SIRS) [9]. While SIRS is essential for the organism to cope with injury, exaggerated or prolonged SIRS is thought to result in secondary/remote organ damage manifesting as MOF [10].

The two-hit theory postulates that the initial injury results in priming of neutrophils, which are then vulnerable to activation in the event of further inflammatory stimuli ("second hits"). Thus subsequent events such as surgical interventions, infection, periods of hypoxia, hypovolemia, and blood transfusions can trigger and worsen the hyperinflammation that leads to MOF [11]. Surgical interventions have generated particular interest as they represent a major modifiable risk factor for complications, and the timing of surgery may modulate the resultant immune response. "Damage control" surgery after trauma involves an initial more minor procedure (e.g. stabilisation of fractures with external fixation, haemostasis and decontamination at laparotomy) with delayed definitive management. This approach has been adopted in unstable patients to allow optimisation of physiology [12–14] and abatement of the systemic inflammatory response [15] prior to a major intervention.

More recent studies have evaluated the post-traumatic immune response at the level of gene expression. They saw no evidence of a second hit, instead observing changes consistent with a prolonged response to the primary injury [16]. This research has called into question the very existence of second hits. However, if real, they represent a major consideration for surgeons as vulnerable patients may be at risk of developing organ failure after surgical intervention [17,18]. In addition, the optimal timing of surgery in clinically and haemodynamically "borderline" patients is currently controversial [19,20], and at present no immune parameters are available to guide decision making. Further advances in trauma care would include utilising markers of immune status to guide an individualised approach to the timing of major surgery [15].

The aim of this review was to evaluate the following questions:

1. Has current research in trauma patients demonstrated a measurable "second hit" phenomenon in immune markers associated with surgical intervention?
2. Does the timing of surgery modulate these changes?
3. Do the alterations in serum markers correlate with clinical outcomes?

Patients and methods

Studies addressing the research questions were identified by searches of the databases MEDLINE (1946-present), Cochrane and EMBASE (1947-present), as well as reviewing the reference lists of included articles. The last full search was run on 23/10/12; an update search was performed on 26/11/13. The search was limited to English language studies of adult patients published in the last 25 years, and case reports were excluded. Eligible studies enrolled adult trauma patients age $\geq$15 years undergoing surgical procedures of any kind, excluding isolated low energy injuries (e.g. ligamentous injuries, hip fractures). Study outcomes were alterations in serum or plasma immunological markers in conjunction with clinical outcomes reflective of immune dysfunction. These included mortality, infectious complications and sepsis, acute respiratory distress syndrome (ARDS), acute lung injury (ALI), and MOF. Immunological markers measured in other samples (e.g. wound exudate, synovial fluid) were not included, as alterations in the local inflammatory milieu may not be reflective of systemic changes in immune status. In addition, the immune markers targeted were directly measured serum levels, excluding ex vivo experimental studies evaluating cytokine production by artificially stimulated immune cells. The increase in serum markers could be compared before and after surgical intervention in the same patients, or between groups of trauma patients who did or did not undergo surgical intervention.

MEDLINE was searched using the keywords trauma OR wounds and injuries AND biological markers OR immunologic monitoring OR immune OR second hit AND surgical procedures OR second hit. EMBASE was searched using the keywords immune function test OR immune response OR immune OR immune dysregulation OR immune status OR immune system AND trauma OR injury AND surgery. Cochrane was searched using only the words "surgery" and "trauma" in title, abstract or keywords. Information was obtained from each article regarding study design, patient population (eligibility criteria for study inclusion, injury severity), surgical intervention performed and timing of surgery, immune markers measured and timing of samples, as well as corresponding clinical outcomes. There was no intention to perform a combined statistical analysis of the studies in the form of a meta-analysis as it was anticipated that there would be disparity in the study populations, interventions, and outcome measures between the included articles.

Results

The search strategies yielded a total of 1612 potential articles. The process of review and study selection is outlined in Fig. 1. 1548 Articles were excluded by title and a further 40 by abstract because they were clearly irrelevant to the study question. Twenty-four full text articles were reviewed of which five articles did not evaluate the target population and four studies measured the immune impact of the trauma rather than surgical intervention. Only fifteen articles were eligible for study inclusion.

Impact of surgical intervention on serum markers and clinical outcomes

Fourteen studies addressed the immune impact of surgical procedures. A detailed summary of the studies is shown in Table 1.

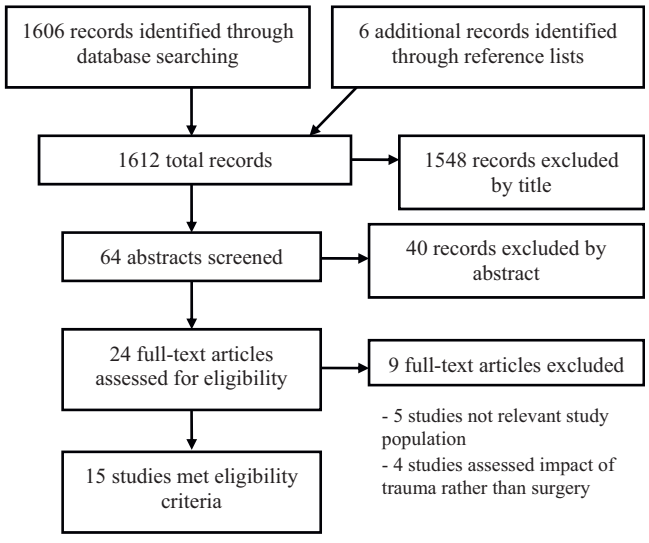

Figure 1. Flowchart of study selection.