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Inflammatory response after nailing

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ABSTRACT

Intramedullary nailing, as the gold standard stabilisation method of most long bones, has been tailed by its extensive use as the basic tool of investigating the immune response to trauma in many large and small animal models, as well as at the clinical setting.

Over the last few decades a complex map of interactions between pro and anti-inflammatory pathways has been the result of these significant global research efforts.

Parallel to the evolution of modern nailing and reaming techniques, significant developments at the fields of other disciplines relevant to trauma care, has improved the contemporary management of injured patients, challenging previous concepts and altering clinical barriers.

The current article aims to summarise the current understanding of the effect of instrumenting the medullary canal after trauma, and hint on potential future directions.

Introduction

The instrumentation of the medullary canal of long bones was conceived even before the 16th century, since anthropologists in Mexico witnessed such a procedure of Aztec surgeons, inserting wooden sticks into long bone fractures [1]. Intramedullary instrumentation at the developed world was further recorded in the late 19th century by different surgeons describing the concept of interlocking devices from metal, autogenous or bovine bone, or ivory. At that point of time, long before the era of antibiotics and the evolution of medical metallurgy, all these were heavily criticized, as they were associated with early failures due to high rates of infection, instability, metal electrolysis and fatigue failure [2].

Only after the end of World War II and the wider acknowledgement of "marrow nailing" as that described by Gerhard Küntscher, this type of procedures started building their reputation as an effective and safe fixation method of long bones. Since then, intramedullary nailing has evolved extensively, including mainly the introduction of flexible reaming of the medullary canal, which allowed the increase of the contact area between the nail and the endosteum, and the incorporation of the interlocking screws, which increased the control of rotational and length deforming forces. More recent advances include the mechanical characteristics of newer alloys, the anatomic design of the modern nails, the incorporation of interfragmentary compression options, angular stability of the interlocking screws, antibiotic coating of the nails, as well as reaming irrigating and aspirating systems.

Immune response to trauma

The contemporary understanding of the physiologic response to trauma is that this includes a complex network of interactions, regulated by mediators of inflammation and coagulation. Basic objectives of this response is to dispose the damaged tissues, initiate tissue repair, and protect against infection, (Fig. 1). The dominating effect of the magnitude and of the nature of the "first

Abbreviations: ALI, acute lung injury; ARDS, acute respiratory distress syndrome; CARS, compensatory anti-inflammatory response syndrome; CD-11, cluster of differentiation molecule 11; CRP, c-reactive protein; DAMPs, damage-associated molecular patterns; FES, fat embolism syndrome; HLA-DR, human leucocyte antigens – antigen D related; IL, interleukin; LBP, lipopolysaccharide binding protein; MODS, multiple organ distress syndrome; MOF, multiple organ failure; PAMPs, pathogen associated molecular patterns; PCT, procalcitonin; s-ICAM-1, soluble intercellular adhesion molecule- 1; SIRS, systemic inflammatory response syndrome; TNF, tumor necrosis factor.

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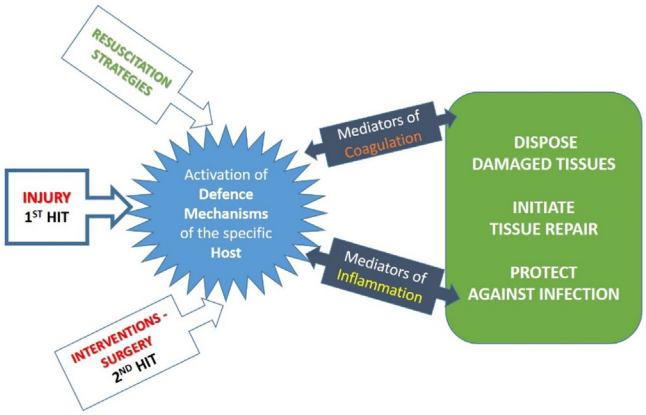

Fig. 1. Schematic representation of the network of interactions following an injury, including the effect of administered resuscitation and surgical interventions, regulated by mediators of the immune and coagulation systems, with main goals the clearance of the damaged tissues, initiate tissue repair, and protect against infection.

hit" on the defence mechanisms of the host, is also associated to the exaggerated response to any secondary physiologic insults – second hits/interventions.

As far as the timeline of the immune response, this is currently assumed to include the early innate phase of hyper-inflammation, the delayed adaptive, and late adaptive phases, (Fig. 2). The initial tissue damage and haemorrhage, via the activation of coagulation, tissue hypoperfusion and neuroendocrine stress response pathways, ignite the pro-inflammatory stage [3]. The extracellular release of damage-associated molecular patterns (DAMPs) and the resultant stimulation of the immune cells (polymorphonuclear leukocytes, monocytes, macrophages, natural killer cells) via chemokines, as the IL-8 and the complement fragment C5a, and initial stage mediators as the IL-6, TNF-a and the IL-1, lead to the activation of endothelial cells. The role of the endothelial system dominates the complications of these early days post trauma via the increased vascular permeability, tissue oedema, loss of endothelial integrity, and the clinical manifestations of FES, ALI/ARDS, MODS, and MOF (respectively, fatty embolism syndrome, acute lung injury/acute respiratory distress syndrome, multiple organ distress syndrome, and multiple organ failure) [4].

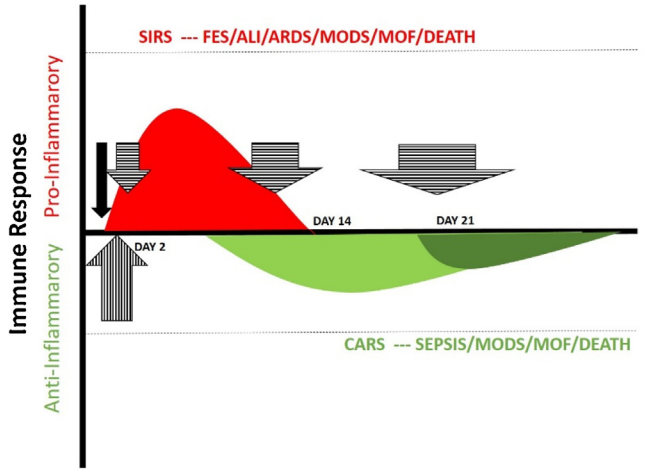

Fig. 2. Schematic representation of the understanding of the timeline of the immune response following a traumatic event ("first hit" – black dense arrow), the initial resuscitation effort (arrow with vertical lines), the surgical interventions ("second hits" – arrows with horizontal). The hyper-inflammatory phase in red (innate immune response) is followed by the delayed adaptive anti-inflammatory phase in light green and the late adaptive phase in darker green. Exacerbation of the hyper inflammatory state may lead to manifestations of SIRS, and subsequent ALI, ARDS, MODS, MOF or even death. The same adverse outcome may be reached when the anti-inflammatory state prevails leading to immune paralysis of the patient – CARS and sepsis.

The delayed adaptive phase is characterised by immune-suppression, where endogenous triggers – alarmins and CD5+ B cells, part of the delayed DAMPs, lead to an autoimmune regulated tissue destruction after the first ten days from trauma. The subsequent late adaptive phase is characterised by immune-proliferation, where pathogen associated molecular patterns (PAMPs), via T- and B- lymphocyte mediators and the production of conventional antibodies, gradually restore the equilibrium of the immune response [5,6].

The immune response following an injury, fluctuates between two extremes conditions. That of the systemic inflammatory response syndrome (SIRS) of the acute phase, and subsequently the compensatory anti-inflammatory response syndrome (CARS), influenced by a number of factors including the initial injury, the physiologic reserves of the individual, the timing and nature of secondary interventions, and the effectiveness of the delivered resuscitation [3].

Role of intramedullary nailing

From the era of Gerhard Küntscher, it was recognised that the intramedullary instrumentation of the long bones was a surgical technique that influenced gravely the outcome of patients under special conditions. Back in the early 50s, he was clearly recommending extra caution when "marrow nailing" was performed in the presence of multiple other associated injuries, or at the early period after the traumatic event, or in the presence of an expressed fatty embolism [7]. Thereafter, remarkable scientific effort has been made to expand our understanding on the significance of the magnitude and nature of the initial trauma or else called "first hit", together with that of the additional burden of comorbidities and of the physiological age of the patient, as well as the importance of all resuscitative and restorative interventions, or else called "second hit", to the outcome of injured patients [8,9].

The great clinical significance of intramedullary nailing as the gold standard method of stabilisation of most long bones, has been tailed by its extensive use as the example of the "second hit" phenomenon to most "in vivo" studies in large and small animal models [10], as well as in many clinical studies exploring the physiologic response to trauma [11]. These studies over the last decades include the assessment of both physical and biological adverse effects of intramedullary nailing to the patients physiology. The current article aims to summarise the current understanding of this important aspect of the effect of intramedullary instrumentation of the medullary canal and hint on its potential future directions.

Intramedullary pressure and fat intravasation

The early studies of the physiologic response to the instrumentation of the canal of long bones identified the increase of the intramedullary pressures, as well as that of embolic showers and fat intravasation, during the different stages of nailing (entry point preparation, insertion of guide wire, insertion of series of flexible reamers, insertion of the nail, insertion of interlocking screws) [12,13]. Evidence supports that even subtle manoeuvres of the canal, as opening of the canal or insertion of the guide wire [14], or even simple bone endoscopy [15] lead to increased pressures. The range of values of these pressures is relevant to a number of parameters as the anatomical site, the size of the long bone, the reaming technique, and the specific features of the reaming system. Whilst an increase of just 40 mmHg [16] is associated to