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Review

Extracorporeal blood purification in burns: A review

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ABSTRACT

A prolonged and fulminant inflammatory state, with high levels of pro- and anti-inflammatory mediators, is seen after extensive thermal injury. Blood purification techniques including plasma exchange, continuous venovenous hemofiltration, and adsorbing membranes have the potential to modulate this response, thereby improving outcomes. This article describes the scientific rationale behind blood purification in burns and offers a review of literature regarding its potential application in this patient cohort.

Contents

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1. Introduction

Immune modulation by extracorporeal blood purification has been studied as a potential treatment for a variety of acute inflammatory states such as sepsis, pancreatitis, and after cardiac arrest [1,2]. Extracorporeal techniques have also been suggested to improve outcomes in patients with burns in the setting of organ dysfunction and refractory burn shock [3,4]. The purpose of this manuscript is to describe the scientific rationale behind extracorporeal blood purification, review the literature as this concept applies to the management of burn patients and review promising extracorporeal therapies.

2. Rationale for blood purification

There is a large body of evidence with respect to the inflammatory state associated with sepsis in critically ill patients [5]. This understanding may be applicable to the burn population because the genomic response in humans to inflammatory diseases is highly correlated, irrespective to the source of the insult [6]. The human response may represent a ''final common pathway'' that can be manipulated regardless of the source of inflammation. Therefore, our current understanding of sepsis should provide some insight into the processes related to the inflammatory state seen in burn patients. Sepsis is associated with a systemic inflammatory response syndrome (SIRS) which occurs due to increased expression of pro- and anti-inflammatory mediators [5,7,8]. In the early phase of SIRS, pro-inflammatory cytokines predominate [5]. This is followed by a phase of high expression of anti-inflammatory cytokines sometimes referred to as compensatory anti-inflammatory response syndrome (CARS), which leads to immunosuppression [5,9]. It is hypothesized that this ''cytokine storm'' results in multiple-organ dysfunction (MOD) and subsequent mortality. On the other hand, depressed or impaired cytokine production has also been seen in severe sepsis with high mortality [5]. A balanced level of inflammatory mediators seems to be necessary to survive sepsis. Based on this understanding, agents targeted to specific cytokines and key mediators have been examined in clinical trials. Interleukin-1 (IL-1) receptor antagonists, antibradykinin agents, anti-tumor necrosis factor (TNF) antibodies, toll-like receptor blockers and platelet-activating factor receptor antagonists have been studied, but none have demonstrated a survival benefit in phase III trials [5,10,11]. Recombinant human activated protein C was the only agent to make it to market; however, it was subsequently withdrawn due to unfavorable post-marketing data and lack of benefit in follow-on studies [12]. A plausible hypothesis for the inability of specific targeted therapies to improve clinical outcomes is the relative complexity and redundancy of the human body, with different cytokine profiles and host pathogen-interactions [13] as well as the considerable variability in responses to a severe insult. The above factors make detailed understanding and selection of therapeutics problematic. Thus, a non-selective approach via extracorporeal blood purification is an attractive treatment option while the pathophysiology of the inflammatory response is elucidated. Three hypotheses exist about the possible regulation of cytokine levels. The first one, the so called ''peak concentration hypothesis,'' states that by reducing total cytokine levels in the early pro-inflammatory phase, subsequent MOD and mortality may be prevented. In contrast, the second one, called ''threshold immunomodulation theory,'' has a dynamic view of the different compartments. By non-selectively removing cytokines from the blood, cytokines from the interstitium and tissues will also be reduced because they will follow the concentration gradient until a new equilibrium is achieved. At this point, the cascade of overwhelming inflammation should stop and organ damage could be prevented. Additionally, efficiency of mediator clearance is highly dependent on the concentration of the mediator. As such, mediators that are present at higher concentrations are likely to be cleared more effectively. In the third hypothesis, the ''mediator delivery hypothesis,'' the use of high replacement volumes may increase lymphatic flow, which helps to transport and deliver cytokines to the blood compartment where they can be removed using blood purification techniques [7,14]. Non-selective blood purification does not target a specific mediator but removes cytokines based on their blood concentrations. By this approach, it is thought that abundant cytokines can be removed and a balanced state can be achieved. Still, we do not know all the components and regulation mechanisms of this complex system. One must be wary of possible unforeseen effects when modulating the inflammatory response in the face of these unknowns.

3. Pathophysiology of burns and why blood purification makes sense

Cytokines are elevated early in the course of burn injury without signs of sepsis [15–17]. Finnerty et al. examined the cytokine profile of children and adults after burn. This group found a greater inflammatory response in adults, compared to children, with high levels of IL-6, IL-8, IL-10, IL-4, IL-17, granulocyte macrophage colony-stimulating factor (GM-CSF) and interferon gamma (INF-γ). IL-6, IL-8, IL-1β, IL-18 and IL-10 showed the highest elevations during the first week after the burn injury [18,19]. Enhanced catabolism and metabolism, which have an important impact on prolonged morbidity and mortality, are associated with high levels of pro-inflammatory cytokines in burns [15,20]. The inflammatory and hypermetabolic response has been shown to begin early, within the first 24 h after the