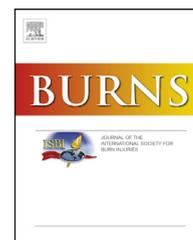


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Editorial

What about HES in burn patients?[☆]

Evaluation of the actual evidence

Following the 2013 alert by the European Medicines Agency (EMA) discouraging the use of hydroxyethyl-starch solutions (HES) in critically ill and burn patients [1], most specialized units treating burn victims have stopped using HES in this population. But, how well-founded was the EMA alert in this specific type of patient?

A major burn patient is defined as one with burn injury affecting at least 20% or 30% of the body surface area (BSA). At this percentage, the patient experiences a systemic impact, characterized by an inflammatory response with microvascular changes that lead to altered capillary permeability, and hypovolemic and cell shock, commonly known as *burn shock* [2]. It is recognized that intravenous fluid resuscitation is essential to improve survival in major burn patients, as they are in an exceptionally severe clinical state. In addition to the above-mentioned systemic changes, they may experience massive bleeding when undergoing surgical treatment for their injuries and are highly susceptible to the development of infection. But not all victims of burn injury are major burn patients, and not all develop sepsis or have the same systemic repercussions. The different etiologies and severity of the lesions makes this a very heterogeneous patient population, and it is surprising that the European Medicines Agency considers them all in the same manner with respect to HES administration.

We believe that the alert emitted, which explicitly says "Hydroxyethyl-starches (HES) should no longer be used in patients with sepsis, burn injuries or critically ill patients" [1] lacks specific information. Given that there is considerable variability in the characteristics of burn patients and that these require advanced fluid therapy management [2], data are needed on the severity of the injury, the affected BSA, systemic involvement, and the time during which this recommendation should be applied.

Several questions come to mind in relation to this recommendation: Should solar burns or 1% burns be taken into account in a trauma patient with bleeding? Is it only appropriate for major burns? How long should it be applied? During the first 24h, as is done with the remaining colloids in patients with burns? One week? One month? And what is quite

important: on what basis did this specific recommendation for burn patients emerge?

When the alert was communicated, it was based on a series of large, recently published studies: 6S [3], CRYSTMAS [4], CHEST [5], CRISTAL [6], and VISEP [7]. But, were burn patients actually included in these studies? To answer our concerns about the current recommendations for these patients, we set out to review the methods used in these studies, and here we present our results.

The 6S study [3], involving 798 patients and excluding those with burns affecting >10% BSA, compared mortality and acute kidney injury after initial resuscitation with Ringer's acetate (RA) versus HES 130/0.42. It is surprising that only burns involving <10% BSA were accepted, when these patients are not usually considered critically ill and are unlikely to develop severe sepsis. The study concluded that patients with severe sepsis or septic shock receiving HES had a higher risk of death and renal replacement requirement at 90 days than those given RA. Of note, patients were randomized after the first 24h, once they had been stabilized and when they may already have received 1 liter of synthetic colloids, as in the majority of these studies [3,5,8]. Furthermore, 38 patients in the RA group received synthetic colloids without being excluded from the statistical analysis. As to the results, there were no significant differences in mortality at 28 days, but differences were seen at 90 days. Mortality was related to the requirement for renal replacement therapy (RRT), but the indications for this therapy were not defined in the study protocol and were left to the discretion of the attending physician. The number of patients with a definite RRT requirement was exactly the same in the two groups. There were no significant differences between the groups for the authors' defined measure of renal failure, for the urinary output (UO) values, or for patients with doubling of plasma creatinine levels. With regard to the RIFLE score, the raw data were given in an appendix, but statistical significance was not calculated. No significant differences were seen for the overall SOFA score, but the renal subscore data were not provided; instead, they were combined with those of patients undergoing RRT.

[☆] This manuscript was not screened for plagiarism.

Table 1 – The evidence on the use of HES in burn patients.

Design	Interventions	Burns	N	Type of HES	Mortality	Renal failure	RIFLE score	RRT	Creatinine	SOFA score	UO
6S [3]	Prospective randomized double-blind multicenter parallel-group Septic patients	Fluid resuscitation with Ringer's acetate vs HES	798	130/0/42	No significant differences at 28 days Significantly higher in the HES group at 90 days	Defined as RRT or SOFA kidney score ≥ 3 No significant differences	Raw data. No data on statistical significance	Indication criteria not established in the protocol Significantly higher in the HES group	Patients doubling baseline creatinine No significant differences	Data are mixed with RRT No separate data on renal SOFA Overall SOFA showed no significant differences	No significant differences
CRYSTMAS [4]	Prospective randomized double-blind multicenter Septic patients	No information	96	130/0/4	No significant differences at 28 or 90 days	Defined as doubling creatinine levels or RRT No significant differences	No significant differences AKIN score also showed no statistical differences	-	No significant differences	No separate data on renal SOFA Overall SOFA showed no significant differences	-
CHEST [5]	Prospective randomized blinded multicenter parallel-group Critically ill patients	Excluded	7000	130/0/4	No significant differences at 90 days	Not defined as such	R: Statistically significant in favor of HES I: Statistically significant in favor of HES F: No significant differences Data on the remaining states not provided	Indication criteria not established in the protocol Significantly higher in the HES group	Significantly higher in the HES group	No overall data on renal subscore Significantly lower in the HES group	-
CRISTAL [6]	Prospective randomized Patients with hypovolemic shock	>20% BSA excluded	2857	Colloids	No significant differences at 24 days Significantly lower in the colloid group at 90 days	-	-	Indication criteria not established in the protocol No significant differences	-	No separate data on renal SOFA Overall SOFA showed no significant differences	-
VISEP [7]	Multicenter randomized open-label two-by-two factorial trial	No information	537	200/0/5	No significant differences	Considered as such with doubling of baseline creatinine levels Significantly higher in the HES group	-	Indication criteria not established in the protocol Significantly higher in the HES group	-	Significantly higher in the HES group	-

Table 1 (continued)

Design	Interventions	Burns	N	Type of HES	Mortality	Renal failure	RIFLE score	RRT	Creatinine	SOFA score	UO
Long-term and cost-effectiveness CHEST analysis [14]	Fluid resuscitation with Ringer's acetate vs HES	Excluded	2857	130/0.4	No significant differences at 6 months or 24 months	-	-	-	-	-	-
Prospective randomized parallel-group Septic patients Béchir [9]	Fluid resuscitation with Ringer's lactate vs Ringer's lactate +HES	>20% BSA included	30	200/0.5	Higher in HES group, but no significant differences	Considered as such with RRT requirement Higher in the HES group, but non-significant	-	Indication criteria not established in the protocol Higher in the HES group, but not significant	Higher in the HES group, but not significant	-	Lower in the HES group, but no significant differences
Prospective, randomized double-blind Béchir [10]	Fluid resuscitation with Ringer's lactate vs Ringer's lactate +HES	>15% BSA included	48	130/0.4	No significant differences	No significant differences	-	Indication criteria not established in the protocol. No significant differences	No significant differences	-	No significant differences

AKIN, acute kidney injury network; HES, hydroxyethyl starch; RIFLE, risk, injury, failure, loss, end-stage renal disease; RRT, renal replacement therapy; SOFA, sequential organ failure assessment; UO, urinary output.

The multicenter CRYSTMAS [4] study, including 196 patients with severe sepsis, compared the volume of HES (130/0.4) versus 0.9% saline needed to hemodynamically stabilize patients, and concluded that a significantly lower volume of HES was infused on the first day. There were no significant differences in 28- and 90-days mortality, volume infused in the first 4 days, hemostatic changes, or incidence of acute kidney injury. Furthermore, urinary biomarkers showed no significant differences regarding tubular or glomerular involvement. There was no information on whether burn patients were included.

CHEST [5], another important multicenter study, analyzed 7000 patients, and burns were considered an exclusion criterion. HES (130/0.4) was compared with 0.9% saline for resuscitation in intensive care patients. In this study HES was associated with a higher incidence of renal replacement therapy as indicated by the attending doctor, although there were no significant differences in the severity of acute kidney injury estimated by the RIFLE score, and more patients were classified in the risk and injury stage in the saline group. No significant differences were found for 90-days mortality, ICU stay, or hospital stay. Creatinine concentration and UO were significantly higher in patients receiving saline, but in the HES group creatinine values were around 100 $\mu\text{mol/L}$ and diuresis 1500 mL/day; hence the differences would seem to have little clinical relevance.

In CRISTAL [6], a multicenter study including 2857 patients, burn victims with >20% BSA involvement were excluded. Resuscitation with colloids (HES, dextrans, gelatins, and albumin) or crystalloids (0.9% saline, hypertonic solutions, and Ringer's lactate [RL]) was compared in intensive care patients in hypovolemic shock. There were no significant differences in mortality at 28 days, but the survival rate was higher in colloid-treated patients at 90 days. The colloid group remained more days without vasopressor therapy and had a lower incidence of mechanical ventilation. Of note, the study population was very heterogeneous and there were differences in mortality between centers. This study also provided separate data on mortality in HES-treated patients. This group also showed no significant differences with regard to mortality at 28 or 90 days except in the comparison of patients who received only one type of fluid. In this analysis, 90 days mortality was significantly lower in patients receiving HES than in those given isotonic saline solution.

As to the VISEP [7] study, it is important to note that the starch used was hypertonic pentastarch, a formula that differs completely from the fourth-generation isotonic starches currently used in Europe. Hence, as these are different products, the results obtained should not be extrapolated to other starches. VISEP was a randomized multicenter study including 537 patients with sepsis who underwent resuscitation with HES 200/0.5 (10%) or RL. Mortality did not differ between the groups, but renal failure and RRT rates were significantly higher in the HES group. There was no mention of burn patients at any point in the article. Furthermore, the authors reported protocol violations and stated that the HES dose administered was 2400 mL in 24 h, an amount almost double the maximum dose used in Europe.

Two studies specifically assessing HES use in burn patients are available, both by the same author [9,10]. The first, published in 2010 [9], included 30 patients and compared resuscitation using mixed therapy (crystalloids+HES 200/0.5 [10%]) with RL-based therapy. Mortality and renal failure were somewhat higher in the HES group, but the results were not significant. The second study, published in 2013, was a randomized, double-blind study with 48 patients comparing resuscitation with RL or with mixed therapy (RL+HES 130/0.4 [6%]). In this case there were no differences in terms of mortality, renal failure, or other associated morbidities between the two groups [10].

Following the HES alert, various authors have voiced concern about the methodology used in the studies upon which it was based [11,12], and several new studies and reviews on HES use in different types of patients have emerged. More than 20 new related studies are registered in Clinical Trials, and one of them, still to be published, is in burn patients [13]. In addition, a long-term, cost-effectiveness study was carried out in a CHEST cohort in 2016 that found no differences in mortality or any of the other indicators evaluated at long term between the HES and 0.9% saline groups [14]. For our part, we conducted a retrospective study whose preliminary results were recently presented in the 2017 European Anaesthesiology Congress. The study, performed in major burn patients, found no significant differences in mortality at 28 or 90 days associated with administration of HES 130/0.4 versus other fluids [15].

The results of the analysis of these studies are shown in Table 1. It is surprising that only one study in 798 patients actually found a higher mortality rate in patients receiving HES 130/0.42 and only at 90 days, not at 28 days. Moreover, the authors reported a greater RRT requirement without specifying whether the indication was for renal failure. Finally, major burn patients were excluded from this study [3]. None of the available studies performed with HES 130/0.4 found differences in mortality in burn patients or critically ill patients.

As is well recognized, RRT use cannot be equated with end-stage renal failure and even less so if the criteria for starting RRT are not clearly established in the study protocol. Various reasons apart from renal failure can prompt the clinician to decide on RRT. We consider the lack of information on what constituted severe renal failure in these studies to be a limitation affecting the interpretation of the results.

This analysis of the current evidence regarding HES use in major burn patients leads us to conclude that despite the European Medicines Agency recommendations set down four years ago, to this day there is still no scientific evidence supporting a contraindication for last-generation HES use in patients with burn injuries. None of the related studies have shown an increase in mortality or renal failure in major burn patients treated with HES.

Conflicts of interest

All authors declare no conflicts of interest.

Authors contribution

Patricia Guilabert helped design the study, conducted the study, analyzed the data, wrote the manuscript, and reviews.

Luis Abarca, Nuria Martin and Gemma Usua analyzed the data, and wrote the manuscript.

Juan P Barret helped final approval.

Maria J Colomina wrote the manuscript and reviews and helped final approval.

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