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Comparison of 6% hydroxyethyl starch 130/0.4 and saline solution for resuscitation of the microcirculation during the early goal-directed therapy of septic patients☆,☆☆

Arnaldo Dubin MD[a,b,*], Mario O. Pozo MD[c], Christian A. Casabella MD[a], Gastón Murias MD[c], Fernando Pálizas Jr. MD[c], Miriam C. Moseinco MD[a], Vanina S. Kanoore Edul MD[a,b], Fernando Pálizas MD[c], Elisa Estenssoro MD[d], Can Ince PhD[e,1]

[a]*Servicio de Terapia Intensiva, Sanatorio Otamendi y Miroli, Azcuénaga 870, Buenos Aires C1115AAB, Argentina*
[b]*Cátedra de Farmacología Aplicada, Facultad de Ciencias Médicas, Universidad Nacional de La Plata, 60 y 120, La Plata 1900, Argentina*
[c]*Servicio de Terapia Intensiva, Clínica Bazterrica, Juncal 3002, Buenos Aires C1425AYN, Argentina*
[d]*Servicio de Terapia Intensiva, Hospital San Martín, 1 y 70, La Plata 1900, Argentina*
[e]*Translational Physiology, Academic Medical Center, University of Amsterdam, Meibergdreef 9, Amsterdam 1105 AZ, The Netherlands*

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Abstract

Purpose: The aim of this study was to show that 6% hydroxyethyl starch (HES) 130/0.4 achieves a better resuscitation of the microcirculation than normal saline solution (SS), during early goal-directed therapy (EGDT) in septic patients.

Materials and Methods: Patients with severe sepsis were randomized for EGDT with 6% HES 130/0.4 (n = 9) or SS (n = 11). Sublingual microcirculation was evaluated by sidestream dark field imaging 24 hours after the beginning of EGDT.

Results: On admission, there were no differences in Sequential Organ Failure Assessment score, mean arterial pressure, lactate, or central venous oxygen saturation. After 24 hours, no difference arose in those parameters. Sublingual capillary density was similar in both groups (21 ± 8 versus 20 ± 3 vessels/mm^2); but capillary microvascular flow index, percent of perfused capillaries, and perfused capillary density were higher in 6% HES 130/0.4 (2.5 ± 0.5 versus 1.6 ± 0.7, 84 ± 15 versus 53 ± 26%, and 19 ± 6 versus 11 ± 5 vessels/mm^2, respectively, $P < .005$).

Conclusions: Fluid resuscitation with 6% HES 130/0.4 may have advantages over SS to improve sublingual microcirculation. A greater number of patients would be necessary to confirm these findings.

☆ Trial registration: The study was registered in ClinicalTrials.gov. ClinicalTrials.gov Identifier: NCT00799916.

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* Corresponding author. Servicio de Terapia Intensiva, Sanatorio Otamendi y Miroli, Azcuénaga 870, Buenos Aires C1115AAB, Argentina.
E-mail address: arnaldodubin@speedy.com.ar (A. Dubin).

[1] Prof. Ince is Chief Scientific Officer of MicroVision Medical (a university-based company manufacturing sidestream dark field devices) and holds patents and stock related to sidestream dark field imaging. The remaining authors have not disclosed any potential conflicts of interest.

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1. Introduction

The early goal-directed therapy (EGDT) is one of the cornerstones of the therapeutic management of sepsis-induced hypoperfusion [1]. Therefore, aggressive resuscitation aimed at reaching a mean arterial pressure (MAP) level of 65 mm Hg or higher and a central venous oxygen saturation ($ScvO_2$) of 70% or greater is now considered a standard of care and represents an attempt to overcome tissue hypoperfusion [2]. The extent of multiorgan failure depends on the severity of tissue hypoperfusion. Recently, clinical studies showed a strong relationship between outcome and cardiovascular dysfunction plus alterations in sublingual microcirculation [3]. In accordance with these findings, increases in microcirculatory perfusion during resuscitation are associated with improvements in organ dysfunctions [4].

The Surviving Sepsis Campaign guidelines recommend fluid resuscitation with either natural/artificial colloids or crystalloids and state that there is no evidence-based support for one type of fluid over another [2]. Despite the lack of clinical evidence, experimental studies showed beneficial effects of starches on the microcirculation of septic animals [5-7]. To our knowledge, the effects of different fluids on the microvascular perfusion of septic patients have not yet been evaluated. We performed this pilot controlled randomized study to compare the effects of 2 commonly used solutions—1 colloid, 1 crystalloid—on the sublingual microcirculation of septic patients. Our hypothesis was that the utilization of hydroxyethyl starch (HES) 130/0.4 achieves a better resuscitation of the microcirculation than normal saline solution during the EGDT of septic patients.

2. Methods

This study was approved by the respective ethics committees of the 2 participating hospitals and was registered in ClinicalTrials.gov (ClinicalTrials.gov Identifier: NCT00799916). Informed consent was obtained from each next of kin.

2.1. Setting

The study was conducted in 2 teaching intensive care units.

2.2. Design

This is a randomized controlled pilot study.

2.3. Patients

Inclusion criteria were as follows: (1) 18 years or older, (2) confirmed or suspected infection plus 2 or more signs of the systemic inflammatory response syndrome (definition of sepsis by American College of Chest Physicians/Society of Critical Care Medicine criteria) [8], and (3) tissue hypoperfusion (MAP <65 mm Hg despite a crystalloid fluid challenge of 20 mL/kg or blood lactate concentration of 4 mmol/L or higher) [2].

Exclusion criteria were impossibility to perform sublingual videomicroscopy, age greater than 18 years, pregnancy, stroke, acute coronary syndrome, hydrostatic pulmonary edema, status asthmaticus, cardiac arrhythmias (as a main diagnosis), contraindication for central venous catheterization, active gastrointestinal hemorrhage, seizures, drug intoxications, burns, trauma, need of immediate surgery, terminal cancer, immunosuppression (organ transplant or systemic illness), no resuscitation order, delayed admission to the intensive care unit from the emergency department (more than 4 hours), or previous resuscitation with more than 1500 mL of fluids.

2.4. Measurements and derived calculations

Serial measurements of heart rate, MAP, central venous pressure (CVP), arterial and central venous gases, and oxygen saturations (AVL OMNI 9; Roche Diagnostics, Graz, Austria); [Na^+], [K^{+}], and [Cl^-] (ion-selective electrode (AEROSET; Abbott Laboratories, Abbott Park, Ill); and [albumin] (Bromcresol-sulfonphthaleinyl method) and [lactate] (ion-selective electrode, AVL OMNI 9; Roche Diagnostics) were performed. Derived acid-base variables from the conventional and the Stewart approaches were calculated [9].

2.5. Microvideoscopic measurements and analysis

The microcirculatory network was evaluated in the sublingual mucosa by means of a sidestream dark field imaging device (Microscan; MicroVision Medical, Amsterdam, Netherlands) [10].

Different precautions and specific steps were followed to obtain images of adequate quality and to ensure good reproducibility. Video acquisition and image analyses were performed by well-trained researchers. After gentle removal of saliva by isotonic saline-drenched gauze, steady images of at least 20 seconds were obtained while avoiding pressure artifacts via a portable computer and an analog/digital video converter (ADVC110; Canopus Co, San Jose, Calif). Sidestream dark field images were acquired from at least 5 different sites. Adequate focus and contrast adjustment were verified and images of poor quality discarded. The entire sequence was used to characterize the semiquantitative characteristics of microvascular blood flow, particularly the presence of stopped or intermittent flow.

Video clips were analyzed blindly and randomly through different approaches. First, we used a previously validated semiquantitative score [11]. It distinguishes between no flow

(0), intermittent flow (1), sluggish flow (2), and continuous flow (3). A value was assigned to each individual vessel. The overall score, called the microvascular flow index (MFI), is the average of the individual values. For each patient, the values from 5 videos were averaged. In addition, vascular density was quantified as the number of vessels per millimeters squared. To determine heterogeneity of perfusion, the flow heterogeneity index was calculated as the highest MFI minus the lowest MFI divided by the mean MFI [3]. Finally, the percent of perfused vessels and the total and capillary perfused vascular densities were calculated [12,13]. The percent of perfused vessels was calculated as the number of vessels with flows 2 and 3 divided by the total number of vessels and multiplied by 100. The perfused vascular density was calculated as the number of vessels multiplied by the fraction of perfused vessels. These quantifications of flow were made per group of vessel diameter: small (capillaries), 10 to 20 μm; medium, 21 to 50 μm; and large, 51 to 100 μm.

2.6. Study protocol

A simple randomization by the use of sealed envelopes was used to allocate patients to EGDT with 6% HES 130/0.4 in saline solution (Voluven; Fresenius-Kabi France, Sèvres, France) or isotonic saline solution (ClNa 0.9%). Clinical personnel were not blinded to the study solution. The cardiovascular support of both groups consisted in an adaptation of the protocol from Rivers et al [1]. Stated in brief, intravenous volume expansion (6% HES/0.4 or saline solution) and (if needed) vasopressors, dobutamine, or blood transfusions were administered to achieve CVP 8 to 12 mm Hg, MAP 65 mm Hg or greater, and $ScvO_2$ 70% or greater. Measurements of $ScvO_2$ were intermittently performed in the presence of any change in MAP, vasopressor requirements, heart rate, arterial oxygen saturation, or urine output after every therapeutic intervention or routinely every 2 hours.

2.7. Data analysis

The primary measures of outcome were microcirculatory parameters after 24 hours of resuscitation. Because there were no data available about the values of microcirculatory parameters during the EGDT in septic shock, this pilot study was firstly planned as a rough estimation to enroll 30 patients. Thereafter, Trzeciak and colleagues [3] showed that in these patients, the sublingual capillary MFI is 1.48 ± 0.4. Based on these data, the sample was recalculated. Consequently, using the sublingual capillary MFI as the primary outcome measure, we calculated that a study of 20 patients would have an 80% power of detecting an increase in MFI to 2.0 in the 6% HES/0.4 group with a certainty of 95%. After showing a normal distribution, data were

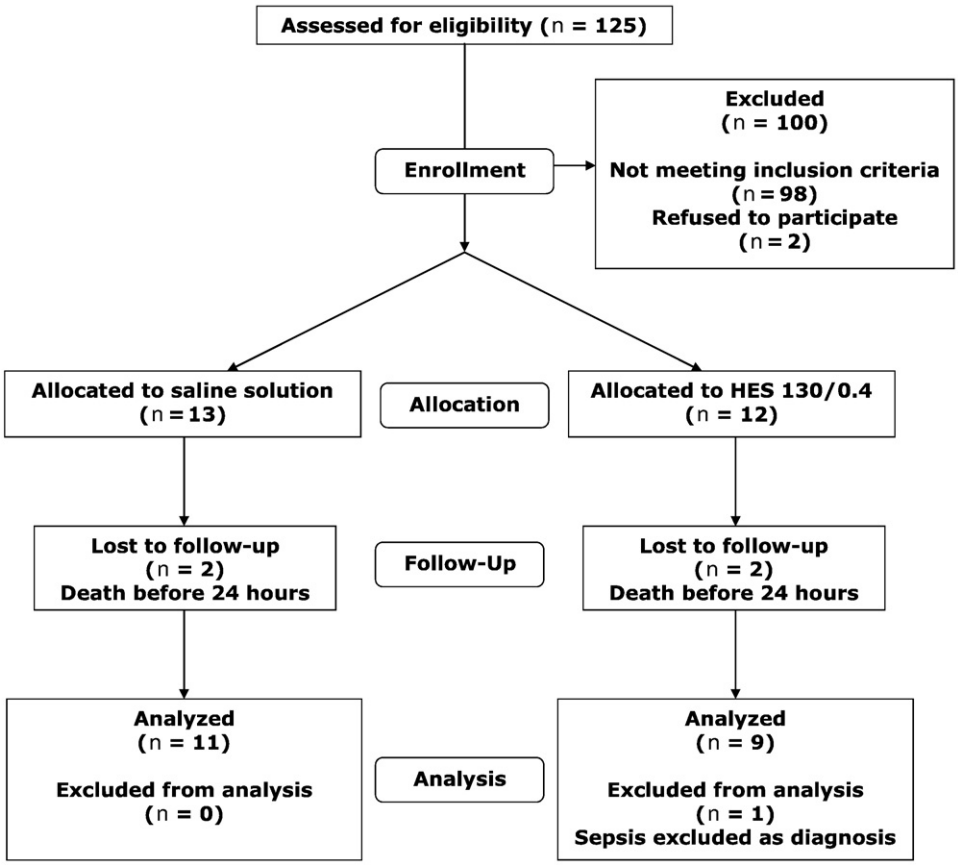

Fig. 1 CONSORT (CONsolidated Standards of Reporting Trials) patient flow diagram.

compared by the Student t test and 95% confidence intervals for continuous data and the χ^2 test for categorical data. A P value less than .05 was considered significant. Data are expressed as mean ± SD.

3. Results

Twenty-five patients were enrolled. Four patients died before the microcirculatory measurements were performed, 2 in each group. A patient in the 6% HES/0.4 was excluded because a pulmonary embolism was diagnosed and sepsis was ruled out as the cause of inflammatory response and shock. These patients were excluded from the analysis. Consequently, saline solution group comprised 11 patients, and the 6% HES/0.4 group comprised 9 patients (Fig. 1).

Table 1 Clinical and epidemiologic characteristics of saline solution and 6% HES 130/0.4 groups

	Saline solution	6% HES 130/0.4	*P*
Age (y)	65 ± 12	62 ± 21	.7517
Sex, male (%)	55	67	.5820
Infection site (%)			
Pulmonary	36	44	.8809
Abdominal	45	11	.0954
Urinary	9	11	.8809
Intravascular	9	11	.8809
Gynecologic tract	0	11	.2567
Soft tissue	0	11	.2567
SOFA score on admission	8.9 ± 3.6	8.1 ± 2.5	.5853
SOFA score 24 h	8.4 ± 3.7	6.9 ± 2.6	.3252
TISS score 24 h	31 ± 10	29 ± 10	.7370
Mechanical ventilation 24 h (%)	91.0	78.0	.4132
Swan Ganz catheter (%)	64.0	56.0	.7136
Total fluid intake	8368 ± 2405	4682 ± 1371	.0008
Hydration plan [a] (mL/24 h)	2114 ± 726	2071 ± 486	.8740
Volume expansion (mL/24 h)	6254 ± 2603	2610 ± 885	.0015
Urine output (mL/24 h)	1507 ± 1350	1825 ± 863	.5680
Fluid balance (mL/24 h)	6606 ± 2669	2857 ± 1596	.0026
Transfusions (% patients)	18	22	.8222
Norepinephrine ($\mu g\ kg^{-1}\ min^{-1}$)	1.1 ± 1.2	0.4 ± 0.3	.1783
Dopamine ($\mu g\ kg^{-1}\ min^{-1}$)	8 ± 4	14 ± 6	.3029
Urea on admission (mg/dL)	81 ± 63	59 ± 37	.3582
Urea 24 h (mg/dL)	84 ± 73	62 ± 28	.3974
Creatinine on admission (mg/dL)	2.1 ± 1.2	1.2 ± 0.3	.0480
Creatinine 24 h (mg/dL)	2.3 ± 1.6	1.5 ± 0.5	.1471
Mortality (%)	45.0	11.1	.0954

[a] The hydration plan mainly consisted in dextrose 5% in saline solution.

Epidemiologic and clinical characteristics are shown in Table 1. There were no significant differences between both groups except for lower values of blood creatinine levels in the 6% HES/0.4 group. In particular, Sequential Organ Failure Assessment (SOFA) and Simplified Therapeutic Intervention Scoring System (TISS) scores were similar. All patients received vasopressors. Norepinephrine was used in 10 patients in the saline solution group and in 6 patients in the 6% HES/0.4 group (P = .18). Dopamine was administered in 2 and 4 patients, respectively (P = .20; Table 1). Dobutamine was given in 3 and 2 patients, respectively (P = .80). Neither corticosteroids nor activated protein C was administered during the study.

On admission, both groups showed a similar degree of arterial hypotension. The resuscitation increased MAP in both groups, along with increases in CVP. The $ScvO_2$ was within the targeted values from the beginning of the study and remained unchanged in both groups (Fig. 2).

The saline solution group received more fluids for intravascular volume expansion and had higher positive fluid balance than the 6% HES/0.4 group. The urine output was similar (Table 1).

Despite a trend toward a higher degree of metabolic acidosis in the saline solution group, there were no significant differences in acid-base parameters (Table 2).

After 24 hours of resuscitation, sublingual capillary density was similar in both groups, but capillary MFI, percent of perfused capillaries, and perfused capillary density were higher in the 6% HES/0.4 group (Fig. 3). The capillary heterogeneity index was higher in the saline solution group (Fig. 3). Table 3 displays the different microcirculatory parameters in medium and large vessels. The large-vessel capillary density was slightly but significantly higher in the saline solution group. The medium- and large-vessel MFI and percent of perfused vessels were higher in the 6% HES/0.4 group, but the heterogeneity flow index was higher in the saline solution group. The total perfused vascular density was higher in the 6% HES/0.4 group (Table 3).

4. Discussion

The main finding of this study is that in septic patients, the EGDT is associated with an improved sublingual microcirculation when 6% HES/0.4 is used for the intravascular volume expansion compared with the use of saline solution.

In this study, the goals of resuscitation were reached in both groups, following a modification of an algorithm proposed by Rivers et al [1] and adopted by international guidelines [2]. Because of its lower volume of distribution, the administration of 6% HES/0.4 required the infusion of lower volumes (ratio 1.0:2.4) and generated lower positive fluid balance (2857 ± 1596 versus 6606 ± 2669 mL/24 hours) than saline solution to attain the same therapeutic aims. After 6-hour resuscitation, the goals of resuscitation (MAP, CVP,

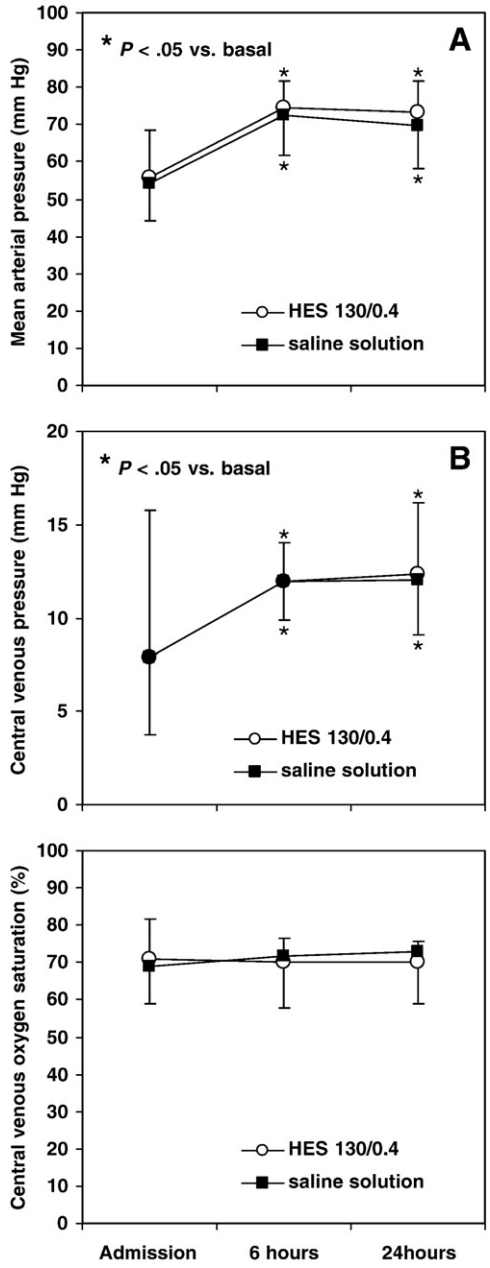

Fig. 2 Values of MAP, CVP, and central venous oxygen saturation, on admission and after 6 and 24 hours of resuscitation, in saline solution and HES 130/0.4 groups.

and $ScvO_2$) were similarly reached. After 24 hours of resuscitation, no differences arose in these parameters and other systemic variables, including those related to acid-base metabolism. Like saline solution, 6% HES 130/0.4 dissolved in saline has a strong ion difference of zero. Indeed, for an equivalent degree of intravascular volume expansion, ability of 6% HES/0.4 to induce hyperchloremic metabolic acidosis is the same as saline solution [14].

Despite the fact that similar goals of resuscitation such as MAP, CVP, $ScvO_2$, and urine output were achieved in both groups, the characteristics of the microcirculation were quite different. This finding highlights the concept that microcirculation is an organ with distinctive features compared with the rest of cardiovascular system. Furthermore, microcirculatory responses to therapeutic interventions may differ from those of the systemic circulation.

Severe microcirculatoty alterations were present in saline solution group despite that the resuscitation goals were reached. Experimental models of resuscitated septic shock show that microvascular perfusion is altered despite the normalization of systemic and regional hemodynamics [15]. In addition, septic patients systematically exhibit severe disorders in sublingual microcirculation that are strongly associated with organ failures and outcome [12,16]. The ability to improve sublingual microcirculation has also been related to survival [16]. Moreover, sublingual perfusion has been enhanced by different therapeutic strategies that include the use of vasoactive drugs [17]. In this way, improving

Table 2 Acid-base parameters in saline solution and 6% HES 130/0.4 groups on admission and after 24 hours of therapy

		Admission	24 h
Lactate (mmol/L)	Saline solution	3.8 ± 2.3	3.2 ± 3.2
	HES 130/0.4	3.0 ± 1.1	2.1 ± 0.7
Albumin (g/L)	Saline solution	2.7 ± 0.4	2.5 ± 0.3
	HES 130/0.4	2.8 ± 0.7	2.5 ± 0.5
pH (mm Hg)	Saline solution	7.23 ± 0.11	7.26 ± 0.12
	HES 130/0.4	7.28 ± 0.10	7.31 ± 0.09
P_{CO_2} (mm Hg)	Saline solution	42.7 ± 13.4	40.1 ± 10.7
	HES 130/0.4	40.5 ± 9.6	39.8 ± 10.8
P_{O_2} (mm Hg)	Saline solution	136.5 ± 92.0	95.8 ± 24.0
	HES 130/0.4	124.0 ± 48.1	110.1 ± 32.0
$[HCO_3^-]$ (mmol/L)	Saline solution	17.1 ± 4.1	18.0 ± 3.9
	HES 130/0.4	19.7 ± 4.3	19.6 ± 3.6
[BE] (mmol/L)	Saline solution	-9.1 ± 4.9	-7.8 ± 4.7
	HES 130/0.4	-6.0 ± 4.4	-5.7 ± 3.5
$[AG]_{corrected}$ (mmol/L)	Saline solution	18.7 ± 5.4	19.6 ± 5.4
	HES 130/0.4	19.5 ± 5.6	17.0 ± 3.1
$[Cl^-]_{corrected}$ (mmol/L)	Saline solution	111.4 ± 4.4	111.0 ± 6.2
	HES 130/0.4	107.2 ± 6.1	111.5 ± 3.6
$[SID]_{effective}$ (mmol/L)	Saline solution	26.8 ± 4.2	27.2 ± 3.9
	HES 130/0.4	29.2 ± 5.0	28.1 ± 4.2
[SIG] (mmol/L)	Saline solution	7.4 ± 5.3	8.3 ± 4.8
	HES 130/0.4	8.0 ± 5.7	5.5 ± 3.2

$[HCO_3^-]$ indicates plasma concentration of bicarbonate; [BE], base excess; $[AG]_{corrected}$, anion gap corrected for abnormal albumin concentration; $[Cl^-]_{corrected}$, $[Cl^-]$ corrected for water excess/deficit; $[SID]_{effective}$, effective strong ion difference concentration; [SIG], strong ion gap concentration.

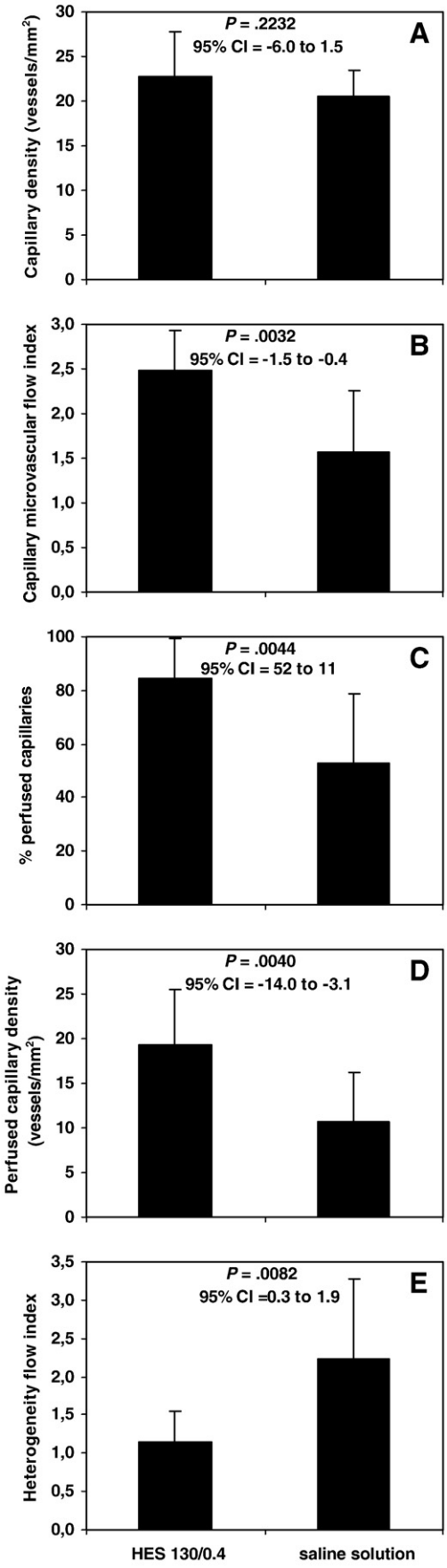

Table 3 Microcirculatory variables (medium and large vessels) in saline solution and 6% HES 130/0.4 groups after 24 hours of therapy

Vascular density (vessels/mm^2)			
Medium vessels	Saline solution	15.2 ± 3.7	0.5674
	HES 130/0.4	14.5 ± 1.5	
Large vessels	Saline solution	12.6 ± 2.4	0.0112
	HES 130/0.4	10.0 ± 1.2	
MFI			
Medium vessels	Saline solution	1.8 ± 0.7	0.0074
	HES130/0.4	2.6 ± 0.4	
Large vessels	Saline solution	1.9 ± 0.8	0.0131
	HES130/0.4	2.7 ± 0.3	
Percent of perfused vessels			
Medium vessels	Saline solution	78 ± 12	0.0002
	HES130/0.4	97 ± 3	
Large vessels	Saline solution	90 ± 5	0.0001
	HES 130/0.4	99 ± 1	
Heterogeneity flow index			
Medium vessels	Saline solution	1.8 ± 0.8	0.0094
	HES 130/0.4	1.0 ± 0.5	
Large vessels	Saline solution	1.8 ± 1.2	0.0355
	HES 130/0.4	0.8 ± 0.4	
Perfused density(vessels/mm^2)			
Medium vessels	Saline solution	12.0 ± 3.9	0.1615
	HES 130/0.4	14.0 ± 1.4	
Large vessels	Saline solution	11.4 ± 2.4	0.1257
	HES 130/0.4	10.0 ± 1.3	
Total	Saline solution	33.1 ± 9.8	0.0228
	HES 130/0.4	42.4 ± 5.9	

microcirculation could be considered an important goal in the resuscitation of septic shock.

This study is the first to evaluate the effects of different fluids on the sublingual microcirculation of septic patients during the initial period of resuscitation. We used a comprehensive approach for the analysis of the microcirculation. A round table has recently pointed out that the ideal analysis report should include evaluations of vessel density (total vessel and perfused vessel densities), perfusion indices (proportion of perfused vessels and MFI), and heterogeneity [13]. All these analyses were performed in our study. Consequently, we were able to identify significant microcirculatory differences between both groups, which were mainly localized at the capillary level. The capillaries are the essential components of the microcirculation that facilitate the exchange of oxygen, fluids, and metabolites with the tissues. In addition, the compromise of microvascular perfusion in sepsis is more severe in capillaries [12]. Therefore, we found that the use of 6% HES/0.4 was

Fig. 3 Values of capillary density (A), capillary MFI (B), percent of perfused capillaries (C), perfused capillary density (D), and capillary heterogeneity flow index (E) in saline solution and HES 130/0.4 groups. Each figure shows the *p* value and the 95% confidence interval (CI).

associated with improvements in capillary density, perfusion, and heterogeneity.

Despite the lack of clinical studies focused on the effects of different fluids on the microcirculation, research performed in relevant experimental models has shown similar results to those of our study. Morisaki et al [5] found in septic sheep that starch administration for 48 hours decreases tissue injury compared with Ringer lactate solution. Although systemic and regional oxygen transport were similar, greater capillary luminal areas with less endothelial swelling and less parenchymal injury were found in septic sheep treated with pentastarch versus Ringer lactate infusion in cardiac and skeletal muscles.

Several mechanisms such as the dysfunction of endothelial cells and their interaction with leukocytes, regional alterations in nitric oxide production, a decrease in deformability and an increase in the aggregability of red blood cells, alterations of coagulation and fibrinolysis, changes in the glycocalyx, and inflammatory injury might be involved in the development of septic microvascular dysfunction [18]. The beneficial effects of 6% HES/0.4 on sublingual microcirculation seen in this study might be related to the effects of infusion with the starch on these mechanisms.

In patients with severe sepsis and septic shock, fluid resuscitation and restoration of tissue perfusion are associated with decreases in systemic markers of inflammation [19]. Consequently, the fluids used in the resuscitation could modulate the inflammatory response and thus protect the microcirculation. The infusion of HES is associated with reductions in extravascular fluid losses and endothelial cell activation in vascular surgery, trauma, and other critically ill patients [20,21]. In experimental models, HES inhibits neutrophil adhesion and transendothelial migration [7,22]. In a rat model of normotensive endotoxemia, Hoffmann et al [6] showed that 6% HES/0.4 decreases leukocyte adherence. In addition, the lipopolysaccharide-induced decrease in functional capillary density and increase in macromolecular leakage were significantly attenuated by 6% HES/0.4 but not by saline solution. Moreover, Schäper et al [23] showed that 6% HES/0.4 preserves the intestinal microvascular perfusion despite the absence of antiinflammatory effects.

Other mechanisms could also contribute to the increase in microcirculatory perfusion with 6% HES/0.4, such as reductions in platelet aggregation [24] and decreases in blood viscosity secondary to improved erythrocyte deformability and aggregability [25]. Conversely, Castro et al [26] found that these last variables are adversely affected by HES. Finally, 6% HES might also increase microvascular perfusion by enhanced fibrinolysis [27] and decreased oxidative stress [28]. Finally, other explanations for the favorable effects of 6% HES/0.4 could be a better intravascular volume expansion and less edema formation. Zakaria et al [29] showed that cellular edema regulates capillary perfusion.

This study has several limitations. This is a pilot trial that included a small number of patients. Accordingly, some imbalance might have occurred in randomization. Patients assigned to the saline solution group had higher blood creatinine levels, showed a tendency toward a higher degree of metabolic acidosis on admission, and received higher doses of norepinephrine during the first day. Consequently, we could speculate that these patients could be sicker than those in 6% HES group and could have more profound microcirculatory alterations. Nevertheless, SOFA score, MAP, CVP, and ScvO2 were similar on admission in both groups. These findings suggest that the extent of multiorgan failure and the hemodynamic alterations were comparable at baseline. Because the basal cardiovascular profile before the use of vasopressors seems similar, the higher norepinephrine needs in the saline solution group could well be reflecting the response to the particular volume expansion. The overall differences in the use of vasopressors, however, is not as pronounced as indicated by the norepinephrine doses because these patients also required lower doses of dopamine than 6% HES/0.4 group.

Another important shortcoming in this study is the lack of microcirculatory assessments at baseline. Unfortunately, the characteristics of the study precluded such measurements because of the rapidity of group allocation and onset of resuscitation. Finally, this study was not designed to evaluate either the potential mechanisms of the solutions on microcirculation or the possible side effects of starches, such as nephrotoxicity and coagulopathy. Recent studies, however, have shown that starches, especially those of high molecular weight, can have nephrotoxic effects that can worsen the outcome of septic patients [30].

In conclusion, the results of this controlled randomized pilot study suggest that in patients with sepsis-induced hypoperfusion, the EGDT may allow a better recruitment of the microcirculation when 6% HES/0.4 is used for the expansion of intravascular volume compared with saline solution. These findings justify a larger clinical trial to confirm the beneficial effects of 6% HES/0.4 on microvascular perfusion and to determine if these improved parameters are associated with an improved outcome.

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