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Original Article

Effects of different types of hydroxyethyl starch (HES) on microcirculation perfusion and tissue oxygenation in patients undergoing liver surgery

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Abstract: To compare the effects of hydroxyethyl starch (HES) 130/0.4 and HES 200/0.5, which have different molecular weights and degrees of substitution, on microcirculation perfusion and tissue oxygenation in patients undergoing liver surgery. Thirty patients with an American Society of Anesthesiologists status I/II who were scheduled for liver surgery were randomly divided into two groups: one received an intraoperative HES 130/0.4 infusion equal to the amount of blood loss (HES 130/0.4 group, n=15), and the other received HES 200/0.5 equal to the amount of blood loss (HES 200/0.5 group, n=15). Gastric mucosal perfusion and tissue oxygenation were monitored by measuring the gastric mucosal pH (pH_i), which was determined using a carbon dioxide tonometer inserted through a nasogastric tube. Gastric mucosal pH_i, hemodynamic parameters, body temperature, and blood gas parameters were recorded upon entering the operating room, before skin incision, one hour and two hours after skin incision, and at the end of surgery. The intraoperative pH_i decreased in both groups of patients, but the decline in the HES 130/0.4 group was smaller than that of the HES 200/0.5 group. The pH_i of the HES 130/0.4 group was significantly higher than that of the HES 200/0.5 group two hours after skin incision and at the end of surgery ($P<0.05$). A multivariate analysis showed that the type of colloid used intraoperatively was the only variant that affected pH_i ($F=0.626$, $P<0.05$). Moreover, there were good correlation between pH_i at the end of surgery and the length of postoperative hospital stay ($r=-0.536$, $P<0.05$) and the time intervals from surgery to the passage of flatus ($r=-0.547$, $P<0.05$). Compared with HES 200/0.5, the use of HES 130/0.4 (with a relatively lower molecular weight and lower degree of substitution) could significantly improve internal organ perfusion and tissue oxygenation in patients undergoing liver surgery with a relatively large amount of blood loss.

Keywords: Hydroxyethyl starch, gastric mucosa, internal organs, blood loss, surgery

Introduction

Volume replacement treatment is a basic intervention during surgeries that entail a relatively large amount of blood loss because it helps to ensure a successful surgical outcome. Due to the loss and redistribution of body fluids, gastrointestinal ischemia and hypoxia can occur early and are the most serious complications, leading to bacterial translocation, endotoxin absorption, and ultimately multiple organ failure, which is one of the key factors affecting prognosis [1]. pH_i is a marker for the assessment of internal organ oxygenation, which can decrease during surgeries that involve a relatively large amount of blood loss, and is important for both the early assessment and prediction of perioperative complications in critically ill patients. Therefore, pH_i can act as a guide for volume replacement treatment [2]. Among the many volume expanders, hydroxyethyl starch (HES) has the advantages of limiting the degree of tissue edema and improving organ perfusion and tissue oxygenation [3-7]. There are few reports on whether different types of HES (with different molecular weights and degrees of substitution) perform differently in maintaining tissue oxygenation. Previous study in volunteers undergoing acute normovolemic hemodilution shows a larger and more rapid increase in skeletal muscle tpO_2 over baseline values with HES 130/0.4 than with HES 70/0.5 or HES 200/0.5

[8]. Therefore, in our study, by measuring pH_i, we investigated the effects of different types of HES on internal organ microcirculation perfusion and tissue oxygenation in patients undergoing liver surgery that involved extensive blood loss.

Materials and methods

This prospective, randomized, double-blinded, crossover study was approved by the Ethics Committee of the Harbin Medical University, and informed consent was obtained from the patients prior to study enrollment. Thirty patients with American Society of Anesthesiologists status I/II who were scheduled for elective liver surgery under general anesthesia (including vascular tumor enucleation and partial liver resection) were selected for this study. It was estimated that the amount of intraoperative blood loss would be greater than 400 ml and that the operation time would exceed two hours. Exclusion criteria were preoperative hemoglobin <10 g/dl; severe heart, lung, liver, or renal dysfunction; abnormal hemagglutination; known allergic reactions to colloids; and preoperative pH or electrolyte imbalance. All of the surgeries were performed by the same group of surgeons. Based on the intraoperative infusion of different types of HES, patients were randomly divided into two groups; one group received an intraoperative HES 130/0.4 infusion that was equal to the amount of blood loss (HES 130/0.4 group, n=15), and the other group received an intraoperative HES 200/0.5 infusion that was equal to the amount of blood loss (HES 200/0.5 group, n=15).

Anesthesia method

The patients received an intra-muscular injection of 0.5 mg atropine, an intravenous injection of 300 mg cimetidine, and 0.02 mg/kg body weight midazolam 30 minutes before surgery. After entering the operation room, the patients received a continuous intravenous infusion of either HES 130/0.4 or HES 200/0.5 (Fresinius, UK) at a dose of 10 ml/kg for approximately 30 minutes. Anesthesia was induced using 0.05 mg/kg midazolam, 2 μg/kg fentanyl, 0.1 mg/kg vecuronium ammonium, and 1-2 mg/kg propofol. Tracheal intubation and mechanical ventilation were used to maintain the end-expiratory partial pressure of carbon dioxide at ~35 mmHg. Anesthesia was maintained by isoflurane inhalation combined with a continuous intravenous infusion of remifentanil. An additional dose of 0.02 mg/kg vecuronium ammonium was given during surgery to maintain an appropriate depth of anesthesia.

Intraoperative monitoring

Left radial artery catheterization was performed to monitor arterial blood pressure and collect blood samples. Right internal jugular vein catheterization was performed to monitor central venous pressure and to infuse fluids. Core and peripheral temperatures were measured in the nasopharynx and between the right thumb and index finger, respectively. Air gastric tension nasogastric catheter was inserted into the stomach cavity according to the operation manual and was positioned using upper abdomen auscultation after air injection into the catheter. Every 10 min, a Tomometrics™ tonometer (Datex-Ohmeda, Finland) automatically and semi-continuously injected air into the balloon and measured gastric mucosal carbon dioxide partial pressure (P_gCO_2) after equilibrium was reached. Meanwhile, arterial blood samples were collected and measured for arterial pH (pH_a) and P_gCO_2. The measurement data were imported into the monitor, and pH_i was automatically exported. A Detex-Ohmeda S/5 (Datex-Ohmeda) monitor was used to monitor the heart rate (HR), electrocardiogram (ECG), oxygen saturation (SpO_2), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), central venous pressure (CVP), end-expiratory carbon dioxide partial pressure ($P_{ET}CO_2$), body temperature (difference between core and peripheral temperatures, T1-T2), gastric mucosal carbon dioxide partial pressure (P_gCO_2) and gastric mucosal pH (pH_i). Urine output and blood loss were monitored simultaneously. pH_i, P_gCO_2, and the intramucosal-arterial difference in CO_2 partial pressure ($P_{g-a}CO_2$) were recorded at the following five time points: entering the operation room (baseline value), before skin incision, one and two hours after skin incision, and at the end of surgery.

Fluid treatment

During surgery, patients routinely received a continuous infusion of Ringer's lactate at a dose of 10 ml/kg/h to complement the transfer of plasma volume, evaporation from the opera-

Table 1. Demographic data of patients

	HES 130/0.4	HES 200/0.5
Age (yr)	48.1 ± 8.3	49.7 ± 10.8
Gender (M/F)	6/9	7/8
Weight (kg)	61.2 ± 8.0	61.9 ± 7.8
Height (cm)	165.3 ± 6.8	165.1 ± 8.6
Duration of surgery (min)	209.2 ± 51.7	200.4 ± 57.7
Duration of anesthesia (min)	230.5 ± 123.3	222.3 ± 101.7
Type of surgery		
Hepatolobectomy	7	6
Liver hemangioma enucleation	8	9

Mean ± SD. *P*>0.05. There was no significant difference between the two groups.

Table 2. Fluid Intake and Output

	HES 130/0.4	HES 200/0.5
Colloid (ml)	1497 ± 345	1440 ± 330
Crystalloid (ml)	1984 ± 481	2090 ± 511
Red cell (ml)	111.3 ± 173.2	112.0 ± 224.8
Blood loss (ml)	846 ± 319	899 ± 525
Urine volume ($ml \cdot kg^{-1} \cdot h^{-1}$)	2.3 ± 0.8	2.7 ± 1.2
Passage of flatus (h)	22.8 ± 2.3	26.2 ± 5.6*
Hospital day (d)	11.5 ± 2.3	14.3 ± 5.7

Mean ± SD. *P<0.05 (difference between groups).

tion field, and undetected fluid loss. The intraoperative volume replacement treatment was performed according to the principles of the standard Berne concept of surgical component therapy [9]. Blood volume was estimated to be 70 ml/kg body weight in males and 65 ml/kg in females. The amount of bleeding was roughly estimated by measuring the blood volume in a suction bottle, weighing the blood-soaked gauze, and examining the amount of blood lost on the operation sheet. If the estimated blood loss was <18%, 6% HES 130/0.4 (maximum infusion volume was 50 ml/kg) or 6% HES 200/0.5 (maximum infusion volume was 33 ml/kg) was infused to replace the blood loss. If the estimated blood loss was >18% or if the hemoglobin concentration was <8 g/dl, 6% HES and concentrated red blood cells (at a volume ratio of 1:1) were transfused. If the estimated blood loss was >80%, concentrated red blood cells and fresh-frozen plasma (at a volume ratio of 1:1) were transfused.

Hemodynamic management

During surgery, MAP, CVP, and urine output were maintained at 60-90 mmHg, 6-9 mmHg, and >0.5 ml/kg/h, respectively. The rate of volume infusion was adjusted based on the patient's body weight, urine output, and hemodynamic parameters. If MAP was <60 mmHg and CVP was <6 mmHg, the infusion rate was accelerated. If CVP was >9 mmHg, the depth of anesthesia was reduced. When necessary, a continuous intravenous infusion of dopamine was given if adjusting the depth of anesthesia and the infusion rate were not effective. The time intervals from surgery to the passage of flatus and the length of each patient's postoperative hospital stay were also recorded.

Statistical analysis

The sample size of each experimental group was determined based on the mean and the standard deviation of the two samples obtained before the trial. Calculation of the sample size revealed that ≥12 patients in each group were needed; therefore, the sample size was set at 15. SPSS13.0 statistical software was utilized for statistical analysis. Measurement data are expressed as the mean ± standard deviation ($\chi \pm s$). Comparisons between groups were analyzed using the independent-samples t-test and repeated-measures analysis of variance (ANOVA). Count data were analyzed using Fisher's exact test. The relationships between pH_i and its influencing factors were analyzed using a bivariate correlation analysis and a multiple linear regression analysis. P<0.05 was considered statistically significant.

Results

General data and fluid intake and output

There were no significant differences in age, gender, body weight, body height, the type of surgery, or operation time between the two groups (P>0.05) (**Table 1**). In addition, there was no significant difference in the amount of colloid (1497 ± 345 ml vs 1440 ± 330 ml, P>0.05) or crystalloid (1984 ± 481 ml vs 2090 ± 511 ml, P>0.05) and concentrated red blood cells (111.3 ± 173.2 ml vs 112.0 ± 224.8 ml, P>0.05) fluids that were required during surgery between the two groups. Urine output was

Table 3. Hemodynamic Parameters

		Entering the OR	Before skin incision	One hour after skin incision	Two hours after skin incision	End of surgery
SBP (mmHg)	HES 130/0.4	123.2 ± 15.7	116.0 ± 23.8	119.5 ± 29.6	113.0 ± 19.9	120.3 ± 23.4
	HES 200/0.5	120.2 ± 23.2	112.8 ± 14.1	107.7 ± 19.1	115.5 ± 6.3	119.0 ± 21.8
DBP (mmHg)	HES 130/0.4	78.1 ± 17.8	75.3 ± 27.1	74.2 ± 33.5	71.8 ± 21.4	74.4 ± 16.6
	HES 200/0.5	79.7 ± 21.3	75.4 ± 25.0	71.8 ± 26.5	74.8 ± 25.6	76.6 ± 36.4
MAP (mmHg)	HES 130/0.4	93.5 ± 15.8	89.3 ± 26.7	90.4 ± 31.7	86.3 ± 18.0	87.3 ± 21.7
	HES 200/0.5	93.3 ± 18.8	87.6 ± 19.1	83.8 ± 20.4	87.9 ± 17.4	90.8 ± 28.2
HR (min^{-1})	HES 130/0.4	88.7 ± 25.8	92.3 ± 34.2	94.6 ± 34.6	87.3 ± 23.7	82.3 ± 32.2
	HES 200/0.5	91.8 ± 22.9	83.3 ± 20.8	87.9 ± 30.5	88.8 ± 27.7	84.8 ± 30.7
CVP (mmHg)	HES 130/0.4	5.0 ± 1.1	7.5 ± 1.0	7.3 ± 1.0	7.0 ± 1.4	7.8 ± 1.3
	HES 200/0.5	5.1 ± 1.1	7.5 ± 1.3	8.1 ± 1.6	7.9 ± 1.9	8.0 ± 1.5

Mean ± SD. *P*>0.05 there was no significant difference between the two groups.

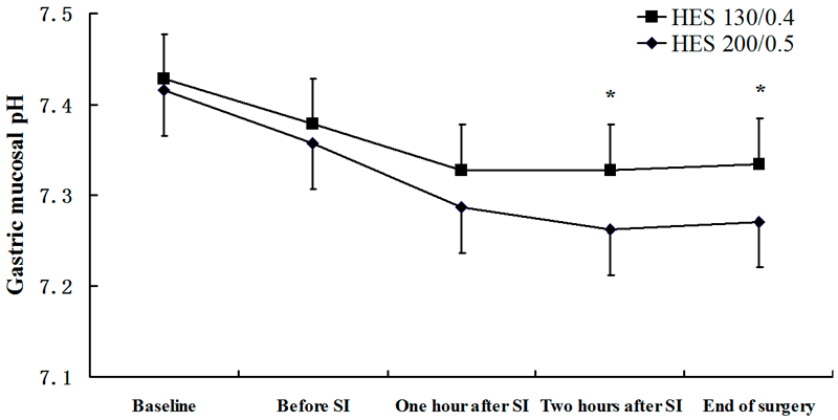

Figure 1. Gastric mucosal Ph. Mean ± SD. *P<0.05 (difference between groups). (Repeated-measures ANOVA showed significant differences in the effects of the two volume expanders on indicators of gastric mucosal pH. The spherical symmetry test criteria were not met, and after correction with the Greenhouse-Geisser method, comparisons of repeated measurement data at various time points within each group showed statistical significance (P<0.05).

maintained at a rate of ~2 ml/kg/h during surgery. Urine output was relatively large until the end of surgery, and volume replacement was adequate. There was no difference between the two groups in these parameters (**Table 2**).

Hemodynamic parameters

There were no significant differences in the hemodynamic parameters (SBP, SBP, MAP, HR, and CVP; **Table 3**) between the two groups (P>0.05). Both HES 130/0.4 and HES 200/0.5 maintained stable hemodynamics in patients, and there was no difference between the two groups.

The preoperative CVP of most patients was at the lower limit of the normal range, indicating widespread hypovolemia due to fasting diet and liquid. If hypovolemia is not corrected in time, it is difficult to guarantee the stability of circulation during major abdominal surgery and in the induction loop. Therefore, a pre-charge volume load of colloid at a dose of 10 ml/kg was given before surgery to avoid relative hypovolemia due to anesthesia and fasting and to maintain intraoperative hemodynamic stability.

Gastric mucosal carbon dioxide tension monitoring

pH_i gradually decreased during surgery (**Figure 1**). pH_i reached its nadir, 7.33, one hour after skin incision and then increased in the HES 130/0.4 group, whereas pH_i continued to drop to 7.26 in the HES 200/0.5 group. Therefore, the pH_i of the HES 200/0.5 group dropped further, and their hypoxia lasted longer. Two hours after skin incision and at the end of surgery, pH_i in the HES 130/0.4 group was higher than in the HES 200/0.5 group (7.33 ± 0.06 vs 7.26 ±

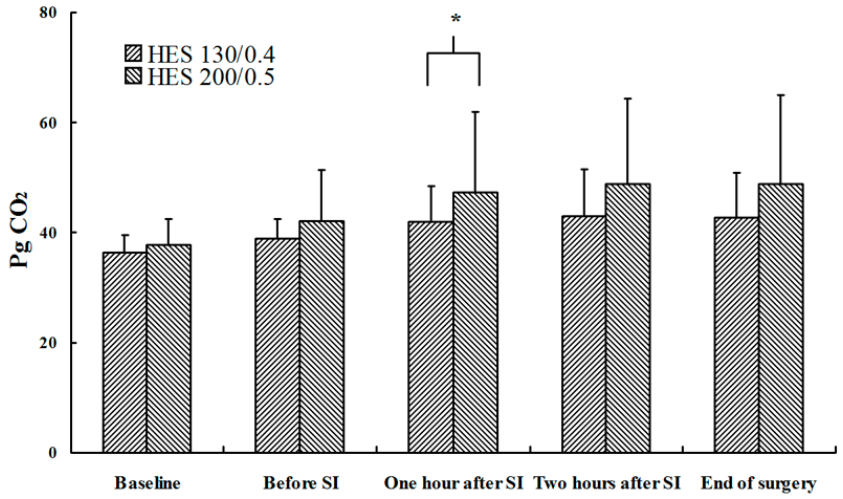

Figure 2. P_gCO_2. Mean ± SD. *P<0.05 (difference between groups). (Repeated-measures ANOVA showed significant differences in the effects of the two volume expanders on indicators of P_gCO_2. The spherical symmetry test criteria were not met, and after correction with the Greenhouse-Geisser method, comparisons of repeated measurement data at various time points within each group showed statistical significance (P<0.05).

0.06 and 7.33 ± 0.04 vs 7.27 ± 0.04, respectively, P<0.05) (**Figure 2**). P_gCO_2 and $P_{g-a}CO_2$ gradually increased in both groups, and there was a significant difference between the two groups (P<0.05) (**Table 4**, **Figure 3**), indicating that the effect of HES 130/0.4 on gastric mucosal tension was superior to that of HES 200/0.5. A multivariate analysis at various time points within each group showed no significance in the scale of pH_i recovery throughout surgery. These results indicate that mucosal ischemia led to local edema and an interruption of tissue oxygen supply that could not be corrected even with adequate reperfusion, which once again demonstrates the importance of preventive preoperative low-volume infusion.

Comparison of the effect of HES on homeostasis

There was no significant difference in sodium, potassium, calcium, pH_a, P_aCO_2, P_aO_2, BE or Hct before or after surgery between the two groups. The effects of HES 130/0.4 and HES 200/0.5 on maintaining homeostasis were similar (**Table 5**).

Changes in body temperature in the two groups of patients

There was no significant difference in the effects of the volume expanders on body temperature (P>0.05) (**Table 6**).

Multiple linear regression analysis showed that pH_i at the end of surgery was closely correlated with the type of colloid used during surgery (F=0.626, P<0.05) but not with arterial or venous pressure, crystalloid, colloid, red blood cell transfusion volume, operation time, anesthesia time, Hct, or hemoglobin concentration. Intraoperative pH_i was correlated with the T1-T2 difference (r=-0.344, P< 0.05), indicating the importance of the choice of colloid and the maintenance of body temperature in internal organ perfusion and tissue oxygen supply. In addition, the difference between core and peripheral temperatures could be used to roughly estimate the peripheral circulation (the correlation coefficient between T1-T2 and pH_i was less than 0.5; thus, the correlation was not close). The length of postoperative hospital stay in the HES 130/0.4 group was slightly but not significantly shorter than that of the HES 200/0.5 group (11.5 ± 2.3 days *vs.* 14.5 ± 5.7 days, P>0.05), while the time intervals from surgery to the passage of flatus were shorter in HES 130/0.4 Group (22.8 ± 2.3 h *vs.* 26.2 ± 5.6 h, P<0.05) (**Table 2**). Correlation analysis between the length of postoperative hospital stay and pH_i at the end of surgery showed a significantly negative correlation (r=-0.536, P<0.05), and also, correlation analysis between the time intervals from surgery to the passage of flatus and pH_i at the end of surgery showed a significantly negative correlation (r=-0.547, P<0.05).

Discussion

Our study showed that both HES 130/0.4 and HES 200/0.5 can effectively maintain hemodynamic stability and homeostasis, but compared with HES 200/0.5, HES 130/0.4 significantly improves internal organ perfusion and tissue oxygenation.

Table 4. Changes of gastric mucosal carbon dioxide tension

		Entering the OR	Before skin incision	One hour after skin incision	Two hours after skin incision	End of surgery
pH_i	HES 130/0.4	7.43 ± 0.04	7.38 ± 0.04	7.33 ± 0.07	7.33 ± 0.06*	7.33 ± 0.04*
	HES 200/0.5	7.42 ± 0.06	7.36 ± 0.05	7.29 ± 0.06	7.26 ± 0.06	7.27 ± 0.04
P_gCO_2 (mmHg)	HES 130/0.4	36.5 ± 3.01	38.8 ± 3.69	42.0 ± 6.44*	43.0 ± 8.56	42.7 ± 8.22
	HES 200/0.5	37.7 ± 4.73	42.1 ± 9.34	47.3 ± 14.61	48.7 ± 15.63	48.8 ± 16.2
$P_{g-a}CO_2$ (mmHg)	HES 130/0.4	0.3 ± 1.69	1.6 ± 5.89	3.0 ± 5.89*	4.7 ± 7.57	3.7 ± 7.28*
	HES 200/0.5	1.6 ± 4.99	3.9 ± 7.56	7.8 ± 11.69	8.5 ± 10.60	8.8 ± 10.82

Mean ± SD. *P<0.05 (difference between groups).

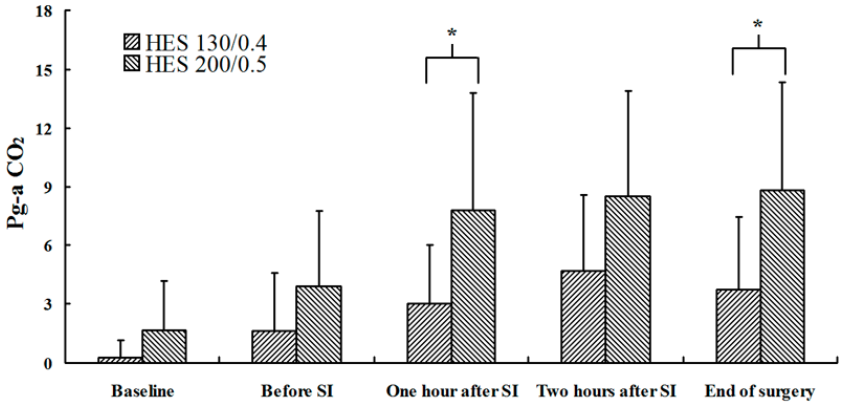

Figure 3. $P_{g-a}CO_2$. Mean ± SD. *P<0.05 (difference between groups). (Repeated-measures ANOVA showed significant differences in the effects of the two volume expanders on indicators of $P_{g-a}CO_2$. The spherical symmetry test criteria were not met, and after correction with the Greenhouse-Geisser method, comparisons of repeated measurement data at various time points within each group showed statistical significance (P<0.05).

The ultimate goal of volume replacement treatment is to maintain tissue perfusion and cell oxygenation; therefore, the observation of the related indicators can guidance fluid resuscitation. Gastric tonometry is the only method that could be used for monitoring in intervention studies during the perioperative period. As an end organ, the gastrointestinal tract is vulnerable to hypovolemic effects, and mucosal ischemia often occurs during major surgeries that involve extensive blood loss, such as liver surgery. Microcirculation problems may already be present in patients with normal circulation and can be reflected by pH_i. There was no difference in the parameters of hemodynamics and internal milieu between the two groups in our study, but there was a significant difference in pH_i, which confirmed the presence of possible microcirculation problems. Previous studies showed that when the body acid - base status were maintained within the normal range, and the $P_{g-a}CO_2$ gap and pH_i were already out of the normal range, it proved that $P_{g-a}CO_2$ gap and pH_i were more sensitive indicators than blood gas analysis for visceral perfusion. Arterial blood lactate level is also an indicator for tissue perfusion, but it is consistent with the changes of systemic acid - alkali state, compare with pH_i, arterial blood lactate level is not sensitive for visceral perfusion and oxygenation status [10]. A pH_i of 7.35 is considered to be the lower limit of normal [11]. In one study, the sensitivity and specificity of forecasting internal organ ischemia were 60% to 68% and 100%, respectively, when pH_i was <7.32 [12]. In our study, pH_i in the HES 130/0.4 group two hours after skin incision and at the end of surgery was significantly higher than that of the HES 200/0.5 group. The intraoperative pH_i ceased to decrease one hour later in the HES 200/0.5 group but not in the HES 130/0.4 group, and its decline was greater and lasted longer, which illustrated the more severe gastrointestinal mucosal ischemia in the HES 200/0.5 group. pH_i dropped to as low as 7.26 in the HES 200/0.5 group, whereas it never dropped below 7.33 in the HES 130/0.4 group.

The fundamental reasons for the difference between the two groups lie in the differences in molecular weight, the degree of substitution, and the ratio of C2/C6 replacement of the two HES. The molecular weight of HES 130/0.4 is

Table 5. Effect of HES on Homeostasis

		Entering the OR	Before skin incision	One hour after skin incision	Two hours after skin incision	End of surgery
PH_a	HES 130/0.4	7.40 ± 0.09	7.39 ± 0.05	7.36 ± 0.06	7.37 ± 0.05	7.37 ± 0.06
	HES 200/0.5	7.41 ± 0.08	7.39 ± 0.04	7.37 ± 0.04	7.35 ± 0.05	7.36 ± 0.11
P_aCO_2 (mmHg)	HES 130/0.4	38.8 ± 5.29	38.0 ± 3.35	39.2 ± 1.90	38.8 ± 2.35	39.4 ± 6.76
	HES 200/0.5	39.1 ± 9.74	38.9 ± 2.78	39.5 ± 2.90	40.4 ± 3.85	39.9 ± 7.55
Na^+ (mmol/L)	HES 130/0.4	140.7 ± 2.1	142 ± 2.82	139.3 ± 2.06	142.7 ± 2.09	140.6 ± 2.27
	HES 200/0.5	139.3 ± 3.65	140.7 ± 4.67	138.8 ± 1.05	140.8 ± 2.58	140.4 ± 2.28
K^+ (mmol/L)	HES 130/0.4	3.3 ± 0.38	3.2 ± 0.99	3.4 ± 0.91	3.38 ± 0.54	3.52 ± 0.72
	HES 200/0.5	3.5 ± 0.93	3.54 ± 0.9	3.68 ± 0.32	3.56 ± 0.38	3.51 ± 0.44
Ca^{2+} (mmol/L)	HES 130/0.4	1.19 ± 0.3	1.05 ± 0.1	1.04 ± 0.1	0.86 ± 0.1	1.02 ± 0.1
	HES 200/0.5	1.1 ± 0.1	1.09 ± 0.1	1.11 ± 0.1	1.08 ± 0.1	1.08 ± 0.1
BE (mmol/L)	HES 130/0.4	-2.0 ± 2.8	-2.5 ± 2.6	-3.30 ± 2.5	-2.73 ± 2.7	-2.6 ± 1.42
	HES 200/0.5	-1.6 ± 2.45	-1.7 ± 2.32	-2.7 ± 2.25	-3.5 ± 2.16	-2.9 ± 2.79
Hb (g/dl)	HES 130/0.4	11.9 ± 1.6	10.6 ± 0.8	8.8 ± 2.1	7.7 ± 1.3	8.6 ± 1.7
	HES 200/0.5	12.3 ± 1.6	11.4 ± 1.4	9.4 ± 2.2	8.0 ± 1.9	9.3 ± 2.0
Hct (%)	HES 130/0.4	35.0 ± 5.0	30.0 ± 2.8	26.7 ± 6.0	23.0 ± 3.7	26.0 ± 5.2
	HES 200/0.5	37.0 ± 4.5	35.1 ± 5.8	28.6 ± 4.7	25.1 ± 7.6	28.0 ± 6.0

Mean ± SD. $P>0.05$ there was no significant difference between the two groups.

Table 6. Changes in body temperature

		Entering the OR	Before skin incision	One hour after skin incision	Two hours after skin incision	End of surgery
Core temperature (°C)	HES 130/0.4	36.2 ± 0.4	35.8 ± 0.5	35.6 ± 0.5	35.2 ± 0.6	35.2 ± 1.0
	HES 200/0.5	36.7 ± 0.7	36.3 ± 0.8	36.2 ± 1.1	36.2 ± 1.2	36.1 ± 1.4
Peripheral temperature (°C)	HES 130/0.4	32.8 ± 2.1	32.1 ± 2.9	30.5 ± 3.7	30.9 ± 3.2	29.4 ± 3.2
	HES 200/0.5	32.7 ± 1.7	32.3 ± 2.0	31.3 ± 2.3	29.8 ± 2.5	29.0 ± 2.7
Temperature difference (°C)	HES 130/0.4	3.5 ± 2.3	3.7 ± 3.2	5.1 ± 3.9	4.8 ± 3.6	5.7 ± 3.7
	HES 200/0.5	4.0 ± 2.0	4.3 ± 2.3	4.9 ± 2.7	6.4 ± 2.8	7.1 ± 3.0

Mean ± SD. $P>0.05$ there was no significant difference between the two groups.

130,000, the degree of substitution 0.4, and the C2/C6 ratio 9:1, whereas in HES 200/0.5, these values are 200,000, 0.5, and 5:1, respectively. The average molecular weight determines the capacity to expand volume. The expansion effect of colloids, such as starch, depends on the number of active, osmotic pressure-maintaining particles in the circulation. The optimal molecular weight to improve hemodynamics and oxygen supply is between 60,000 and 130,000. Due to the difference in molecular weight, HES 130/0.4 can provide many active, osmotic pressure-maintaining particles of an appropriate molecular weight in the early stage [13, 14], whereas HES 200/0.5 can only exert its ideal effect on hemodynamics after its degradation into small particles after infusion [8]. This difference may explain the delayed effect of HES 200/0.5. The degree of substitution determines the rate of decomposition. The lower degree of substitution of HES 130/0.4 results in it being metabolized faster. Moreover, HES 130/0.4 particles that leak into interstitial areas will not accumulate within tissues, leading to smaller tissue colloid osmotic pressure. Therefore, the amount of fluid that crosses blood vessels into interstitial areas is reduced, and tissue edema is lessened [15-17]. In addition, the substitution pattern affects the degradation rate. The C2 hydroxy of a starch molecule is not prone to α-amylase hydrolysis, so the intravascular half-life is prolonged, and its plasma concentration is prevented from decreasing rapidly, which explains why HES 130/0.4 remains in blood vessels for a relatively long time.

Another factor is relevant to the effects of HES 130/0.4 and HES 200/0.5. They affect blood viscosity differently. Neff [18] demonstrated that blood viscosity was reduced to below baseline after HES 130/0.4 infusion, whereas HES 200/0.5 elevated blood viscosity. The four microcirculation determinants were perfusion pressure, vascular resistance, Hct, and the viscosity of the perfusate. Blood viscosity can be reduced to increase blood flow, reduce vascular resistance, and red blood cell aggregation, thereby improving the speed of blood flow to tissues and organs [19].

Our multiple linear regression analysis showed that the type of colloid was the only variable that affected pH_i at the end of surgery. Arterial and venous pressure, crystalloid, colloid, the amount of red blood cell transfusion, operation time, anesthesia time, Hct, and hemoglobin concentration did not affect pH_i at the end of surgery. This result is consistent with previous findings [5]. Intraoperative pH_i was correlated with T1-T2, and both could reflect the situation of peripheral circulation. When the body's circulating blood volume is insufficient, the blood and oxygen supply to vital organs are ensured at the expense of peripheral blood circulation, such as those of the gastrointestinal tract and skin. However, when the two groups were compared here, there was no significant difference in T1-T2, indicating that pH_i may be a more sensitive indicator to predict microcirculation ischemia. The length of postoperative hospital stay was negatively correlated with pH_i at the end of surgery, although the difference of the length of postoperative hospital stay between groups was not statistically significant, but there is a shorter endency in HES 130/0.4 group. Moreover, the recovery of gastrointestinal function and pH_i at the end of surgery showed a significantly negative correlation. This may be because that the mucosal ischemia leads to mucosal injury and infection, so, the recovery of gastrointestinal function was delayed, and eventually the length of postoperative hospital stay was prolonged [20]. All of those confirming once again that pH_i can be used as a reliable indicator of prognosis [11].

Many previous studies support the experimental results of our study or reached similar conclusions. Using a series of dilutions of healthy volunteers' blood, Stand [8] demonstrated that HES 130/0.4 was superior to HES 200/0.5 and HES 70/0.5 in tissue oxygenation via the determination of tissue oxygen partial pressure with skeletal muscle electrodes. Hoffmann [21] demonstrated that HES 130/0.4 could improve the microcirculation of normotensive endotoxemia and capillary leak syndrome. In animal experiments, Zilria et al. [7] demonstrated that tissue edema and capillary leak depended on the molecular weight and the degree of substitution of HES. That study indicated that the use of HES 200/0.5 alone demonstrates a leakage-preventive effect that is superior to any other colloid and that significantly reduces the plasma leakage and edema of damaged capillaries. Therefore, HES 200/0.5 can be used in critically ill patients with imminent or pre-existing organ failure and has the distinct advantage of preventing capillary leakage, low blood volume, and tissue edema.

There was no significant difference in the abilities of HES 130/0.4 and HES 200/0.5 to maintain hemodynamics and homeostasis, but HES 130/0.4 was superior to HES 200/0.5 in microcirculation perfusion and tissue oxygenation. For patients undergoing major abdominal surgeries that entail a large amount of blood loss, using HES 130/0.4 for volume replacement treatment may have potential benefit in internal organ perfusion.

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Disclosure of conflict of interest

None.

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