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ORIGINAL ARTICLE

New 6% hydroxyethyl starch 130/0.4 does not increase blood loss during major abdominal surgery—A randomized, controlled trial☆

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KEYWORDS
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tissue perfusion

Background/Purpose: Ideal fluid management during surgery still poses a clinical dilemma gauging the benefits and adverse effects. This randomized controlled trial compared the tissue perfusion and coagulation profiles under clinically equivalent hydroxyethyl starch (HES 130/0.4) and lactated Ringer's solution (LR).

Methods: Eighty-four patients undergoing major abdominal surgery were randomized to receive either HES or LR. Tissue perfusion parameters using heart rate, arterial blood pressure, central venous pressure, cardiac index, stroke volume index, and central venous oxygen saturation were measured at T0 (baseline), T1 (start of surgery), T2 (1 hour after start of surgery), and T3 (end of surgery). Coagulation parameters using thrombelastography (TEG) were measured at T0 (baseline), T4 (after 15 mL/kg fluid transfused), and T5 (24 hours after baseline).

Results: The total amount of fluid administrated was 1547.9 ± 424.0 mL in HES group and 2303.1 ± 1033.7 mL in LR group ($p < 0.001$). The parameters of tissue perfusion and TEG did not differ significantly between groups at any time point except for a transient decrease in clot

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kinetic and clot strength at T4 for HES group. There was no significant difference in blood loss and consumption of blood products between the two fluids.
Conclusion: HES 130/0.4 is a more efficient intravascular volume expander to maintain tissue perfusion than conventional crystalloid. Transient hypocoagulability induced by HES 130/0.4 does not warrant excessive blood loss and blood transfusion.

Introduction

Perioperative fluid management for intravascular volume deficits has been, and still is, the focus of much debate in perioperative medicine.[1] The debate has primarily focused on the choice of the ideal fluid therapy with either crystalloid or colloid, or with either liberal or restrictive amount of fluid.[2–5] Large-volume crystalloid resuscitation is associated with an increase in tissue edema, which further jeopardizes tissue perfusion locally.[6] On the contrary, adverse effects of colloid therapy, such as anaphylaxis and hemostatic impairment, are of concern.[7]

In a major abdominal surgery, patients commonly suffer from absolute or relative intravascular volume deficits because of preoperative fasting, gastrointestinal preparation, perioperative bleeding, exposure evaporation, third-space losses, and vasodilation after general anesthesia.[8] Hypovolemia during surgery has been associated with intraoperative hemodynamic instability and tissue and/or organ hypoperfusion. Therefore, adequate restoration of intravascular volume is important to fulfill the nutritive role of the circulation and to have beneficial outcomes on both morbidity and mortality.

However, the optimal strategy remains controversial and uncertain, and mostly depends on the dogma and belief of the caring physician in spite of fluid therapy recommendations.[8] Recently, a new generation of hydroxyethyl starch (HES) preparation (Voluven®, 6% HES 130/0.4, Fresenius Kabi GmbH, Bad Homburg, Germany) was introduced. It has a lower mean molecular weight (130,000 Da), a lower degree of molar substitution (0.4), and a narrower molecular distribution profile; therefore, it is expected to have less hemostatic interference than other HES preparations.[1,9] However, interference with blood coagulation is still the main obstacle to its adoption in perioperative fluid management, especially in major surgery with potentially significant bleeding and fluid shift.[9] Therefore, this study was designed to assess the efficacy of this new HES preparation on tissue perfusion and coagulation in patients undergoing major abdominal surgery, compared to that of lactated Ringer's solution (LR), by the concept of goal-directed fluid management.[10,11]

Patients and methods

The study protocol was approved by our Research Ethics Committees, and 84 adult patients undergoing elective major abdominal surgery were included with their written informed consent. Inclusion criteria for participation in the study were loss of more than 500 mL blood during surgery and admission to an intensive care unit after the surgery. Patients with cardiac insufficiency (New York Heart Association class III–IV), renal impairment (serum creatinine >1.5 mg/dL), altered liver function (aspartate aminotransferase >40 U/L, alanine aminotransferase >40 U/L, or serum total bilirubin >2 mg/dL), preoperative anemia (hemoglobin <10 g/dL), preoperative coagulation abnormalities (platelet count $<100000/\mu L$; international normalized ratio >1.5), and known allergy to HES were excluded from the study.

Anesthesia was induced with thiopental (4–6 mg/kg) and fentanyl (3 μg/kg). Neuromuscular blockade was achieved with cisatracurium (0.2 mg/kg). Anesthesia was maintained by incremental doses of fentanyl, cisatracurium, and 1–2% isoflurane titrated accordingly. Mechanical ventilation was performed in all patients to maintain arterial oxygen saturation of $>95\%$ and end expiratory carbon dioxide concentration between 35 and 40 mmHg. Perioperative hemodynamic monitoring included continuous measurement of electrocardiogram, arterial blood pressure, and central venous pressure (CVP). Warming blanket device and fluid warmers were used to keep patients normothermic ($>36.0^{\circ}C$). The patients were managed perioperatively by anesthesiologists who were not involved in the study and process of randomization.

Patients were randomly assigned to two groups by using computer-generated random numbers. In HES group, patients received intravenous infusion of 0.6% HES 130/0.4 throughout the operation and, in LR group, LR was administered. Fluid was given to maintain a predefined target of mean arterial blood pressure (MAP) between 65 and 90 mmHg or CVP between 8 and 12 mmHg. Vasopressor or inotropic agents were added when volume administration was not effective in maintaining the predefined target blood pressure for 5 minutes.[10,11] Maximum allowed doses for HES and LR infusion were 15 and 45 mL/kg, respectively, which should be followed by other crystalloid infusion (e.g., 0.9% saline or 5% glucose water) if necessary. Packed red blood cell (RBC) was transfused when hemoglobin level dropped below 8 g/dL. At the end of surgery, endotracheal tube was removed at the discretion of the caring anesthesiologist. All patients were sent to the intensive care unit and mechanical ventilation continued if necessary. Intravenous morphine was used for postoperative pain management for patients who requested patient-controlled analgesia (PCA) prior to surgery. Those without consent for PCA received intravenous fentanyl infusion titrated as required in the intensive care unit.

Measurement of tissue perfusion

Tissue perfusion parameters were obtained by an uncalibrated arterial pressure-based cardiac output monitor

(FloTrac-Vigileo™ system, Edwards Lifesciences, Irvine, CA, USA).[12] Central venous oxygen saturation ($ScvO_2$) was obtained by a central venous oximetry catheter (PreSep®, Edwards Lifesciences).[13] Data including heart rate (HR), MAP, CVP, cardiac index (CI), stroke volume index (SVI), systemic vascular resistance, and $ScvO_2$ were recorded after induction of anesthesia (T0, baseline), start of surgery (T1), 1 hour after the start of surgery (T2), and at the end of the surgery (T3).

Measurement of coagulation

A blood sample of 3 mL was drawn from an arterial catheter into a citrated tube for coagulation test. Coagulation test was performed by a modified thrombelastography (TEG) [14] (TEG® 5000, Thrombelastograph Hemostasis Analyzer, Haemoscope Corporation, Niles, IL, USA) after induction of anesthesia but prior to fluid administration (T0, baseline), after 15 mL/kg of infused fluid in each study group (T4), and 24 hours after T0 (T5). The investigator responsible for the TEG analysis was blinded to the study group. TEG reagent (20 μL) containing calcium ion was added to 340 μL of kaolin-activated and citrated whole blood in a disposable cup for triggering the coagulation cascade. The cup was inserted in a rotating metal cuvette heated to 37.0°C. A piston with rotated motion was dropped into the blood sample. An electronic amplification system allowed the TEG tracing to be recorded. Standard TEG variables including clotting time (*R*), clot kinetics (*K* and alpha angle), and clot strength (maximum amplitude, MA) were measured.

Statistical analysis

Data are shown as mean ± standard deviation unless otherwise specified. Continuous, normally distributed data were compared by paired and unpaired Student's *t*-tests or analysis of variance for repeated measures. Mann–Whitney rank sum test was adopted whenever the analyzed data failed the normality test using Shapiro–Wilk test. The Bonferroni or Tukey test was applied when multiple comparisons were made for normally and non-normally distributed data, respectively. All *p* values were two sided, $p < 0.05$ was taken as significant, and all data were analyzed by SigmaPlot® software (version 12.0, Systat, San Jose, CA, USA).

Results

Eighty-four patients were enrolled in this study. Four patients withdrew from this study because of their reluctance to provide blood samples for TEG after surgery. Therefore, 41 and 39 patients were included in HES and LR group, respectively. Demographic characteristics of the patients and perioperative data were summarized in Table 1. There were no significant differences between the two groups with regard to age, sex, weight, height, preoperative hemoglobin level, cases of packed RBC usage, and type of surgery. All patients had a smooth recovery without complications. The duration of surgery in LR group (mean duration: 209.8 minutes) was longer than that in HES group (165.4 minutes), but did not reach significance ($p = 0.091$).

Table 1 Demographic and perioperative data.

Variables	HES group ($n = 41$)	LR group ($n = 39$)	*p*
Age (y)	48.0 ± 10.7	50.4 ± 8.7	0.276[a]
Sex (M/F)	23/18	25/14	0.616[c]
Weight (kg)	60.9 ± 19.0	65.6 ± 18.4	0.265[a]
Height (cm)	161.8 ± 8.7	163.7 ± 7.8	0.308[a]
Preoperative hemoglobin (g/dL)	13.2 ± 1.5	13.2 ± 1.8	> 0.99[a]
Packed RBC transfused (*n*)	1	5	0.201[b]
Duration of surgery (min)	165.4 ± 60.5	209.8 ± 154.3	0.091[a]
Type of surgery (*n*)			
UGI surgery	12	17	0.252[c]
LGI surgery	8	9	
Hepatobiliary surgery	21	13	
Survivors	41	39	> 0.99[b]

Data are presented as mean ± SD *n*.
HES = hydroxyethyl starch; LGI = lower gastrointestinal; LR = lactated Ringer's solution; RBC = red blood cell; SD = standard deviation; UGI = upper gastrointestinal.
[a] From *t* test.
[b] From Fisher's exact test.
[c] From chi-square test.

Intraoperative volume input and output

Patients in HES group were infused with 999.1 ± 369.3 mL of HES 130/0.4 during the period of the study, whereas those in LR group were administered 1760.8 ± 528.3 mL of LR (Table 2). Total amount of intravenous fluid transfused was 1547.9 ± 424.0 mL in HES group, which was significantly

Table 2 Intraoperative volume input and output.

Variables	HES group ($n = 41$)	LR group ($n = 39$)	*p*[a]
6% HES 130/0.4 (mL)	999.1 ± 369.3	Not infused	NA
LR (mL)	Not infused	1760.8 ± 528.3	NA
0.9% saline/D5W (mL)	548.8 ± 443.6	542.3 ± 733.7	0.271
Total amount of fluid administered (mL)	1547.9 ± 424.0	2303.1 ± 1033.7	<0.001
Packed RBC (units per group)	2	24	0.037
Blood loss (mL)	208.5 ± 150.6	421.3 ± 597.1	0.015
Urine output (mL)	304.8 ± 224.7	546.6 ± 418.5	<0.001

Data are presented as mean ± SD unless otherwise noted.
D5W = 5% dextrose water; HES = hydroxyethyl starch; LR = lactated Ringer's solution; NA = not applied; RBC = red blood cell; SD = standard deviation.
[a] From Mann–Whitney rank sum test.

different from 2303.1 ± 1033.7 mL transfused in LR group ($p < 0.001$). Blood loss and urine output were both less in HES group than in LR group, while amount of packed RBC usage was significantly higher in LR group than in HES group (Table 2).

Hemodynamics and tissue perfusion

Hemodynamics, including HR, MAP, CVP, CI, SVI, and $ScvO_2$, showed comparable courses in both groups (Table 3). SVI, CI, and MAP were significantly increased in each group compared to the baseline by a predefined goal-directed fluid management.

TEG coagulation parameters

All data in TEG analysis were within normal ranges at any time of the study (Table 4). TEG data at baseline was comparable between groups. After infusion of 15 mL/kg of HES 130/0.4 solution (T4), both clot kinetics and clot strength showed significant difference compared to the baseline(T0) (*K*: $p = 0.002$; alpha angle: $p = 0.003$; MA: $p < 0.001$), which was compatible with relative hypocoagulation in TEG. On the contrary, clot kinetics at T4 in LR group revealed an increase in clot kinetics with decreased *K* time and increased alpha angle (*K*: $p = 0.024$; alpha angle: $p = 0.046$). Therefore, the ultimate strength of clot (*G* index) was significantly different between groups at T4 (6.6 ± 2.2 vs. 7.8 ± 2.3, $p < 0.001$). All TEG coagulation parameters returned to the baseline 24 hours later (T5).

Discussion

In this study, the effects of intravascular fluid therapy with a new HES solution (Voluven, 6% HES 130/0.4) or LR on tissue perfusion and coagulation were investigated in patients undergoing major abdominal surgery. By using predefined cardiovascular variables (e.g., MAP and CVP) as targets to adjust the amount of fluid transfused,[10,11] HES 130/0.4 was shown to be a more efficient intravascular volume expander than LR, with less amount needed to maintain the tissue perfusion parameters, including HR, MAP, CI, SVI, and $ScvO_2$. However, these two groups showed significant difference with regard to coagulation status in TEG (*K* time, alpha angle, MA, and *G* index) after administration of 15 mL/kg of either HES or LR in comparison with the baseline and also between groups in different directions, i.e., mildly hypocoagulable in HES group and mildly hypercoagulable in LR group (Fig. 1). After 24 hours, the coagulation changes returned to baseline in both groups.

Table 3 Data of hemodynamics.

Variables	T0	T1	T2	T3	p[a]
HR (bpm)					
HES	72.4 ± 12.5	71.4 ± 12.5	70.5 ± 11.7	70.4 ± 13.4	0.387
LR	70.5 ± 12.0	70.5 ± 14.0	70.6 ± 14.8	71.8 ± 12.6	0.821
MAP (mmHg)					
HES	75.6 ± 12.5	86.5 ± 14.3*	83.9 ± 9.3*	81.5 ± 10.7*	<0.001
LR	72.4 ± 17.7	87.8 ± 17.1*	81.8 ± 12.2*	80.5 ± 11.5*	<0.001
CVP (mmHg)					
HES	7.0 ± 2.6	7.4 ± 3.1	9.0 ± 2.9*	8.9 ± 3.0*	<0.001
LR	7.2 ± 3.2	7.8 ± 3.1	7.8 ± 3.6	7.2 ± 3.3	0.554
CI (L/min/m^2)					
HES	2.8 ± 0.8	3.0 ± 0.7	3.0 ± 0.5*	3.0 ± 0.4*	0.004
LR	2.4 ± 0.6	2.8 ± 0.7*	2.8 ± 0.7*	2.8 ± 0.6*	<0.001
SVI (mL/m^2)					
HES	37.6 ± 7.0	42.3 ± 8.1*	42.8 ± 8.1*	43.4 ± 7.8*	<0.001
LR	34.2 ± 6.3	39.6 ± 9.0*	39.8 ± 6.7*	39.1 ± 8.1*	<0.001
SVR (dyne/s/cm^5)					
HES	1265.2 ± 234.1	1316.7 ± 249.7	1296.2 ± 289.6	1260.5 ± 259.2	0.085
LR	1287.5 ± 250.3	1406.0 ± 257.0*	1290.1 ± 265.8	1311.3 ± 258.5	0.002
$ScvO_2$ (%)					
HES	84.9 ± 5.0	85.3 ± 4.8	85.1 ± 4.8	85.5 ± 4.8	0.716
LR	83.7 ± 4.2	84.5 ± 5.4	84.3 ± 5.5	84.2 ± 5.9	0.908

Data are presented as mean ± SD.
*$p < 0.05$ compared with baseline (T0).
ANOVA = analysis of variance; CI = cardiac index; CVP = central venous pressure; HES = hydroxyethyl starch; HR = heart rate; LR = lactated Ringer's solution; MAP = mean arterial pressure; $ScvO_2$ = central venous oxygen saturation; SD = standard deviation; SVI = stroke volume index; SVR = systemic vascular resistance; T0 = baseline; T1 = start of surgery; T2 = 1 hour after the start of surgery; T3 = end of surgery.
[a] From one-way ANOVA and multiple-comparison procedures, which were performed if $p < 0.05$.

Table 4 Data of thromboelastography.

Variables	T0	T4	T5	p [a]
R (min)				
HES	5.7 ± 3.4	5.5 ± 2.4	5.5 ± 2.2	0.404
LR	5.3 ± 3.3	5.0 ± 2.0	5.2 ± 1.9	0.368
K (min)				
HES	2.3 ± 1.2	2.4 ± 0.9*,†	2.3 ± 1.0	0.002
LR	2.2 ± 1.0	1.9 ± 0.8*	2.1 ± 1.0	0.024
Alpha angle (°)				
HES	62.7 ± 11.2	60.4 ± 9.1*,†	61.2 ± 9.6	0.003
LR	62.3 ± 9.8	65.5 ± 8.1*	63.2 ± 8.7	0.046
MA (mm)				
HES	57.8 ± 9.1	55.4 ± 7.9*,†	58.4 ± 8.7	<0.001
LR	57.9 ± 7.9	59.7 ± 7.5	59.5 ± 5.5	0.176
G (kd/s)				
HES	7.5 ± 3.1	6.6 ± 2.2*,†	7.5 ± 2.5	<0.001
LR	7.3 ± 2.4	7.8 ± 2.3	7.6 ± 1.6	0.304

Data are presented as mean ± SD.
*$p < 0.05$ compared with baseline (T0).
†$p < 0.05$ between HES and LR groups.
ANOVA = analysis of variance; *G* = ultimate strength of clot; HES = hydroxyethyl starch; *K* = time to specific strength of clot; LR = lactated Ringer's solution; MA = maximal amplitude of clot; *R* = reaction time of clot formation; SD = standard deviation; T0 = baseline; T4 = after 15 mL/kg of infused solution; T5 = 24 hours after baseline (T0).
[a] From one-way ANOVA and multiple-comparison procedures, which were performed if $p < 0.05$.

Although TEG showed decreased hemostatic ability after transfusion of 15 mL/kg of HES 130/0.4, the amount of blood loss during the surgery was contrarily lower than in patients transfused with clinically equal amount of LR (208.5 ± 150.6 vs. 421.3 ± 597.1 mL, $p = 0.015$). Blood products were also transfused more in LR group. Specifically, three patients in LR group suffered from intraoperative blood loss of more than 1000 mL, who were transfused with 16 units of RBCs. Review of the TEG data of these three patients did not reveal any significant coagulopathic condition, and operation records also showed surgical difficulties with moderate to severe intra-abdominal adhesion and prolonged surgical time. A *post hoc* analysis after excluding these three patients still revealed more amount of blood loss in patients transfused with LR, but it was not statistically different. One may argue that the operation time was longer in the LR group (209.8 ± 154.3 vs. 165.4 ± 60.5 minutes, 95% CI: 96.1 to −7.3 minutes) and, therefore, blood loss increased. However, considering the fact that all the data from TEG analysis during the study period were within normal ranges at any time point, these TEG findings in HES group may not be clinically relevant in aspects of coagulopathy associated with fluid therapy and may not warrant excessive blood loss and blood transfusion by HES 130/0.4.

A hypercoagulable state after surgery is a quite common phenomenon and formed the basis for prophylactic management of perioperative thromboembolism.[15] While some suggest that surgery and stress response trigger the enhancement in coagulation by stimulating the release of procoagulants into the systemic circulation, Ruttmann and his colleagues[16–19] have demonstrated in serial studies that hemodilution *per se* is the most probable cause of postoperative hypercoagulability. Administration of crystalloid fluid (i.e., LR or 0.9% saline) results in an imbalance between the naturally occurring anticoagulants and activated procoagulants, thus leading to the enhanced coagulation.[17] However, this effect appears to be modulated by infusion of HES, which has been demonstrated to induce a von Willebrand-like syndrome with decreased factor VIII coagulant activity, and a von Willebrand factor antigen and factor VIII-related ristocetin cofactor,[9,20,21] thus decreasing platelet adhesion capacity by blocking platelet membrane receptor proteins GPIb and GPIIb/IIIa.[22] New HES 130/0.4 with lower molecular weight and a lower molar substitution has demonstrated to have less or even negligible negative effects on coagulation, compared to its preceding similar products, such as HES 450/0.7 and HES 200/0.6.[1,9,22,23] Our TEG data showed that a relative hypercoagulable state was observed in the LR group while a relative hypocoagulable state was observed in the HES group (Fig. 1). It is of interest that coagulability returned to its baseline in either group 24 hours after surgery. A similar result has also been demonstrated previously.[17] Considering the populations at risk of occlusive vascular events after surgery, enhancement of coagulation by crystalloid fluid should not be overlooked.[17] Since transfusion of HES 130/0.4 is not associated with increased blood loss and is demonstrated to attenuate hemodilution-induced enhancement of coagulation, it may be suggested for patients with increased risks of perioperative thromboembolism on the balance of hemostatic interferences.[17]

This study has several limitations. One is the choice of treatment target for fluid therapy. We used conventional targets such as MAP and CVP instead of functional hemodynamic variables, such as pulse-pressure variation, or mixed venous oxygen saturation mostly adopted in goal-directed fluid therapy.[10,11] In the meanwhile, the main indicators of tissue perfusion in this study were CI and $ScvO_2$, which are indicative of systemic tissue perfusion rather than microcirculatory tissue perfusion.[11–13] Since a marked increase in systemic blood flow does not guarantee a concurrent increase in regional blood flow such as intestinal blood flow, difference in specific tissue perfusion may still exist, but it could not be detected by our methods. Lang et al[24] reported that colloid administration resulted in an increased skeletal muscle oxygen tension in patients but administration of LR did not. Mythen and Webb[25] found improved gastric mucosa pH and outcome in patients receiving goal-directed administration of colloids compared with control patients. It is our goal to adopt a conventional target that can be accessible to every surgical patient and to compare the efficacy of the HES 130/0.4 as an intravascular volume expander on tissue perfusion with that of LR, which is more reflective of our everyday practice.

We tested the coagulation state after transfusion of 15 mL/kg of either HES 130/0.4 or LR, which was estimated to cause a 20–25% effect of hemodilution in our participants and was relatively restrictive in amount, compared to the daily allowance of HES 130/0.4 (50 mL/kg/d).[26] It was decided based on our experiences regarding the amount of intravenous fluid supplement needed in most major

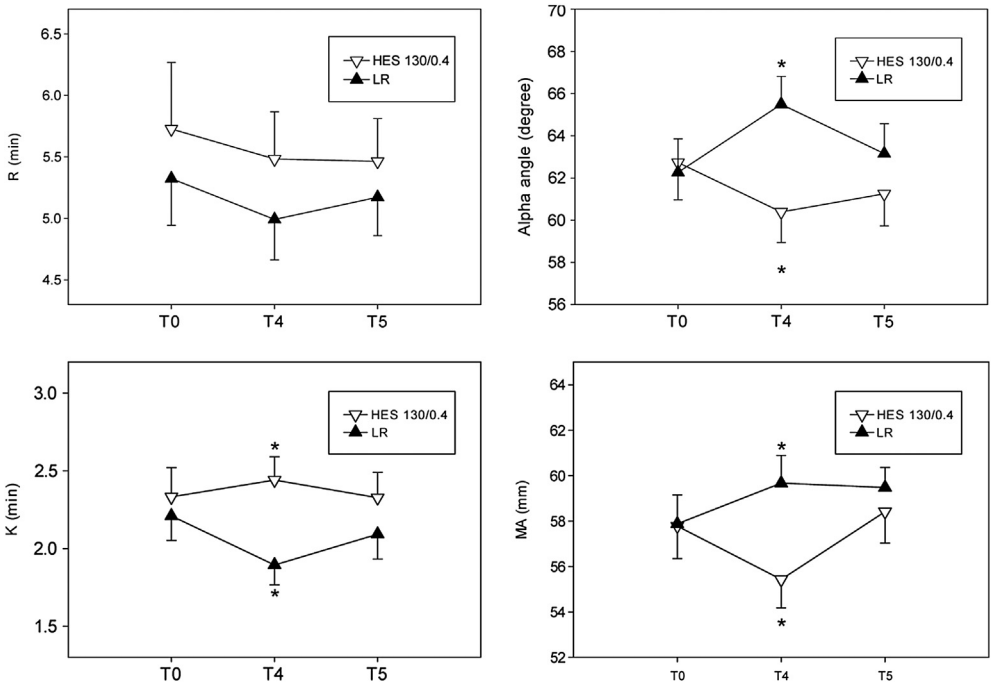

Figure 1 Changes in clotting time (*R*), clot kinetics (*K*, alpha angle), and clot strength (MA) using TEG. Data are presented as mean ± standard error. *$p < 0.05$ different from baseline data. HES = hydroxyethyl starch; *K* = time to specific strength of clot; LR = lactated Ringer's solution; MA = maximal amplitude of clot; *R* = reaction time of clot formation; T0 = baseline; T4 = after transfusion of 15 mL/kg of either HES 130/0.4 or LR; T5 = 24 hours after baseline.

abdominal surgery. Although our TEG data also showed a hypercoagulable state in the LR group, further hemodilution (50–60%) may compromise blood coagulation due to excessive hemodilutional coagulopathy.[23]

In summary, we demonstrated that HES 130/0.4 is a more efficient intravascular volume expander to maintain tissue perfusion than conventional crystalloid, LR. Although clot kinetics and strength (*K*, alpha angle, and MA) were mildly impaired after transfusion of 15 mL/kg of HES130/0.4, it was not associated with clinically significant bleeding during surgery and hence with the need of blood transfusion. The transient hypocoagulability was recovered within 24 hours after surgery.

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