A Prospective, Randomized Comparison of Thromboelastographic Coagulation Profile in Patients Receiving Lactated Ringer's Solution, 6% Hetastarch in a Balanced-Saline Vehicle, or 6% Hetastarch in Saline During Major Surgery

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Objectives: **To compare the effects of lactated Ringer's solution (LR), 6% hetastarch in a balanced-saline vehicle (HS-BS), and 6% hetastarch in normal saline (HS-NS) on coagulation using thromboelastography.**

Design: **Prospective, randomized double-blinded evaluation of previously published clinical trial.**

Setting: **Tertiary-care medical center.**

Participants: **Patients undergoing elective noncardiac surgery with an anticipated blood loss >500 mL. A total of 90 patients were enrolled with 30 patients in each group.**

Interventions: **Patients received a standardized anesthetic. LR, HS-BS, and HS-NS were administered intraoperatively based on a fluid administration algorithm. Hemodynamic targets included maintenance of arterial blood pressure, heart rate, and urine output within a predefined range.**

Measurements and Main Results: **Thromboelastography variables for r time, k time, maximum amplitude, and α angle (mean ± SD) were recorded at induction of anesthesia, at the end of surgery, and 24 hours postoperatively. Patients in the LR group showed a state of hypercoagulation at the end of surgery with reductions ($p < 0.005$) in r time (−3.8 ± 6.7 mm) and k time (−1.7 ± 2.5 mm). This state of hypercoagulation continued into the postoperative period. Patients in the HS-NS group showed a state of hypocoagulation with increases ($p < 0.05$) in r time (+6.2 ± 8.5 mm) and k time (+1.7 ± 3.9 mm) and a reduction in maximum amplitude (−8.0 ± 9.8 mm) at the end of surgery. This state of hypocoagulation was reduced in the postoperative period. Patients in the HS-BS group showed no significant changes in coagulation status at end of surgery, with the smallest changes in r time (−0.3 ± 4.1 mm), k time (+0.1 ± 3.1 mm), maximum amplitude (−5.4 ± 12.3 mm), and α angle (0.3 ± 12.5°).**

Conclusion: **LR-treated patients exhibited a hypercoagulative profile that persisted into the postoperative period. HS-BS administration was associated with a lesser change in the coagulation profile compared with HS-NS, which was associated with a hypocoagulative state.**

KEY WORDS: colloid, crystalloid, hemostasis, 6% hetastarch, thromboelastography, coagulation, surgery

COAGULATION DISTURBANCES are deleterious to patients having any major surgery including cardiac[1] and noncardiac procedures.[2,3] Hypocoagulation can lead to bleeding, the administration of blood products, and return to the operating room for reexploration. At the other extreme, hypercoagulation may be a cause for many thromboembolic and graft occlusion complications observed after cardiac surgery,[4,5] vascular surgery,[6,7] and other types of noncardiac surgery.[8-11]

In a prospective, randomized, double-blinded trial of patients undergoing major elective surgery, the effect of lactated Ringer's solution (LR), 6% hetastarch in a balanced-saline vehicle (HS-BS) (Hextend), and 6% hetastarch in normal saline (HS-NS) (Hespan) on coagulation as determined by thromboelastography was compared. This was an investigator-initiated evaluation of a previous Food and Drug Administration–guided phase III parent study examining the efficacy of HS-BS versus HS-NS.[12] The sole objective of this evaluation was to assess the effects of different fluids on the coagulation profile as determined by thromboelastography. A third arm of LR was added to this evaluation to assess the effect of the commonly used crystalloid LR. The new study also included a third time point to test whether the coagulation changes continue into the postoperative period.

METHODS

Institutional review board approval and written informed patient consent were obtained. Adult patients with an American Society of Anesthesiologists physical status 1 through 3 were enrolled into this double-blind prospective study. Patients undergoing major elective noncardiac surgery with an anticipated blood loss >500 mL were approached at Duke University Medical Center. Patients with coagulopathy, significant hepatic or renal dysfunction, congestive heart failure; patients who had received an investigational drug within the last 30 days; and patients with known hypersensitivity to hydroxyethyl starches were excluded.

The anesthetic protocol used during this study was similar to that used in a previous study at this institution.[12] Before the start of anesthesia, all patients received an intravenous bolus of 7 mL/kg of LR solution, followed by an intravenous infusion at a rate of 5 mL/kg/h throughout the surgery. Anesthesia was induced with thiopental and maintained with a balanced inhalation technique incorporating isoflurane, nitrous oxide, and oxygen with neuromuscular blockade supplied by vecuronium. Anesthesia was maintained as judged by standard clinical criteria. Blood and blood product usage, types and volumes of all fluids administered intraoperatively, and an estimation of blood loss were recorded.

The placement of an epidural catheter for postoperative pain relief was not prohibited, but regional anesthesia was not used intraoperatively. The only local anesthetic used perioperatively was a 3-mL test dose consisting of lidocaine 1.5% with 1: 200,000 epinephrine, administered to ensure correct placement of the epidural catheter and to prevent hemodynamic alterations, which may affect fluid and pharmacologic management.

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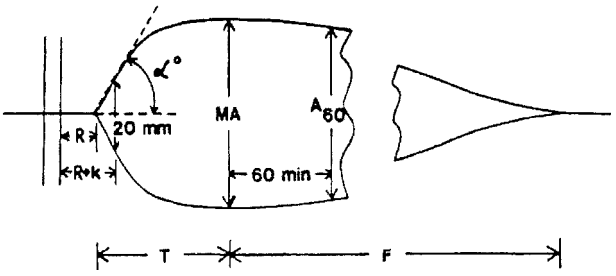

Fig 1. A normal thromboelastography trace: r time is measured from placing the sample in the cuvette until the tracing amplitude reaches 2 mm (normal range, 19 to 28 mm); k time is measured from the r time to the point where the amplitude of the tracing reaches 20 mm (normal range, 8 to 13 mm); α angle (α°) is the angle formed by the slope of the thromboelastography tracing from the r to the k value (normal range, 29° to 43°); maximum amplitude (MA) is the greatest amplitude on the thromboelastography trace (normal range, 48 to 60 mm).[13]

Thromboelastography enables a global assessment of hemostatic function, taking into account the interaction of platelets with the protein coagulation cascade from the time of the initial platelet-fibrin interaction, through platelet aggregation, clot strengthening, and fibrin cross-linkage to eventual clot lysis. Patients had a blood sample drawn before induction, at the end of the surgical procedure, and 24 hours postoperatively for thromboelastography analysis. The sample was transferred within 4 minutes to prewarmed cuvettes of a thromboelastography device (TEG; Haemoscope Corp, Skokie, IL). All thromboelastography tests were performed in duplicate. A piston is suspended in the blood, and as coagulation proceeds, fibrin strands form between the walls of the cuvette and the piston. The piston becomes increasingly coupled to the motion of the cuvette; the shearing elasticity of the evolving blood clot is detected to yield the thromboelastography trace. Parameters recorded included r time (normal range, 19 to 28 mm), which denotes the rate of initial fibrin formation and is functionally related to plasma coagulation factors, and k time (normal range, 8 to 13 mm), which represents the time it takes for a fixed degree of viscoelasticity to be achieved by the forming clot. The k time is affected by the activity of the intrinsic coagulation factors, fibrinogen and platelets. Maximum amplitude (normal range, 48 to 60 mm) is a reflection of the absolute strength of the fibrin clot and can be altered by qualitative and quantitative platelet abnormalities; α angle (normal range, 29° to 43°) denotes the rate at which a clot is formed. A normal thromboelastography trace is depicted in Fig 1.

In this double-blind study, patients were randomized to receive LR, HS-BS, or HS-NS for the treatment of hypovolemia according to a fluid management algorithm as previously reported (Fig 2) .[12] Hextend is a new plasma volume expander containing 6% hetastarch (mean molecular weight, 550 kD), balanced electrolytes (Na^+, K^+, Ca^{++}, Mg^{++}, and Cl^-), lactated buffer, and physiologic levels of glucose (90 mg/dL). Hespan, in contrast to Hextend, consists of 6% hetastarch in 0.9% saline without added electrolytes. Based on this algorithm, hemodynamic targets included maintenance of arterial blood pressure, heart rate, and urine output within a predefined range. Blood products (platelets, fresh frozen plasma, cryoprecipitate, or fibrinogen) were administered when clinically indicated and supported by the laboratory evidence of abnormal coagulation: platelet count, $<100{,}000/\mu L$; prothrombin time, >1.5 times control; activated partial thromboplastin time, >1.5 times control; and fibrinogen, <100 mg/dL.

Based on pilot data, power calculation revealed that 30 patients per group were adequate to determine a 25% difference in r time with $\alpha = 0.05$ and $\beta = 0.2$. Data were analyzed using the Kruskal-Wallis, Fisher exact test, and analysis of variance test as appropriate. Results are presented as mean ± SD or median (interquartile range). A p value < 0.05 was considered statistically significant.

RESULTS

Ninety patients were enrolled overall, with 30 patients in each group. The demographic data for the 3 groups were similar (Table 1). There was no statistically significant difference in the hematocrit and electrolytes among the 3 groups at baseline and end of surgery (Table 2). The previous study reported the thromboelastography data for the 2 colloid groups at baseline and end of surgery.[12] This study reports the thromboelastography changes at baseline, end of surgery, and postoperative day 1 for LR, HS-BS, and HS-NS groups.

The mean changes in r and k time, maximum amplitude, and α angle for the LR, HS-BS, and HS-NS groups are shown in Fig 3. The results are given as mean change ± SD. LR showed a state of hypercoagulation at the end of surgery compared with baseline with a reduction ($p < 0.001$) in r (−3.7 ± 6.7 mm) and k (−1.7 ± 2.5 mm) time. This state of hypercoagulation continued up to postoperative day 1 with continued decreases ($p < 0.003$) in r (−8.8 ± 8.6 mm) and k (−2.6 ± 3.8 mm) time and an increase in α angle (+11.3 ± 13.9°) compared with baseline. HS-NS showed a state of hypocoagulation with increases ($p < 0.05$) in r (+6.2 ± 8.5 mm) and k (+1.7 ± 3.9 mm) time and a reduction in maximum amplitude (−8.0 ± 9.8) at the end of surgery compared with baseline. No difference in thromboelastography variables was seen between postoperative day 1 and baseline. HS-BS showed no significant disturbance in coagulation at the end of surgery compared with baseline with the smallest changes in r (−0.3 ± 4.1 mm) and k (+0.1 ± 3.1 mm) time, maximum amplitude (−5.4 ± 12.3 mm), and α angle (+0.3 ± 12.5°). In the postoperative period up to postoperative day 1, HS-BS showed a degree of hypercoagulation with a change ($p < 0.0001$) in r time (−7.0 ± 8.2 mm) compared with baseline. There was no difference in intraoperative blood loss, red blood cells, or blood product utilization among the 3 groups. (Table 2)

DISCUSSION

In contrast to the previous study,[12] this study reports the effect of LR on thromboelastography and added an additional time point at 24 hours postoperatively to assess how thromboelastography variables change in the early postoperative period. Some of the major postoperative complications that occur, such as hemostatic disorders, deep vein thrombosis, and pulmonary embolism, may be related to the use of different types of fluids intraoperatively.[8,13,14] By adding this third time point, the effects of LR, HS-BS, and HS-NS on coagulation can be assessed at 24 hours postoperatively.

The administration of LR was associated with a hypercoagulable state with reductions in r and k time and an increase in maximum amplitude. This hypercoagulable state continued into the postoperative period up to postoperative day 1. HS-NS treatment was associated with a hypocoagulable state with prolongation of the r and k times and a reduction in maximum amplitude. This hypocoagulable abnormality was normalized by day 1 postoperatively. HS-BS showed a better coagulation

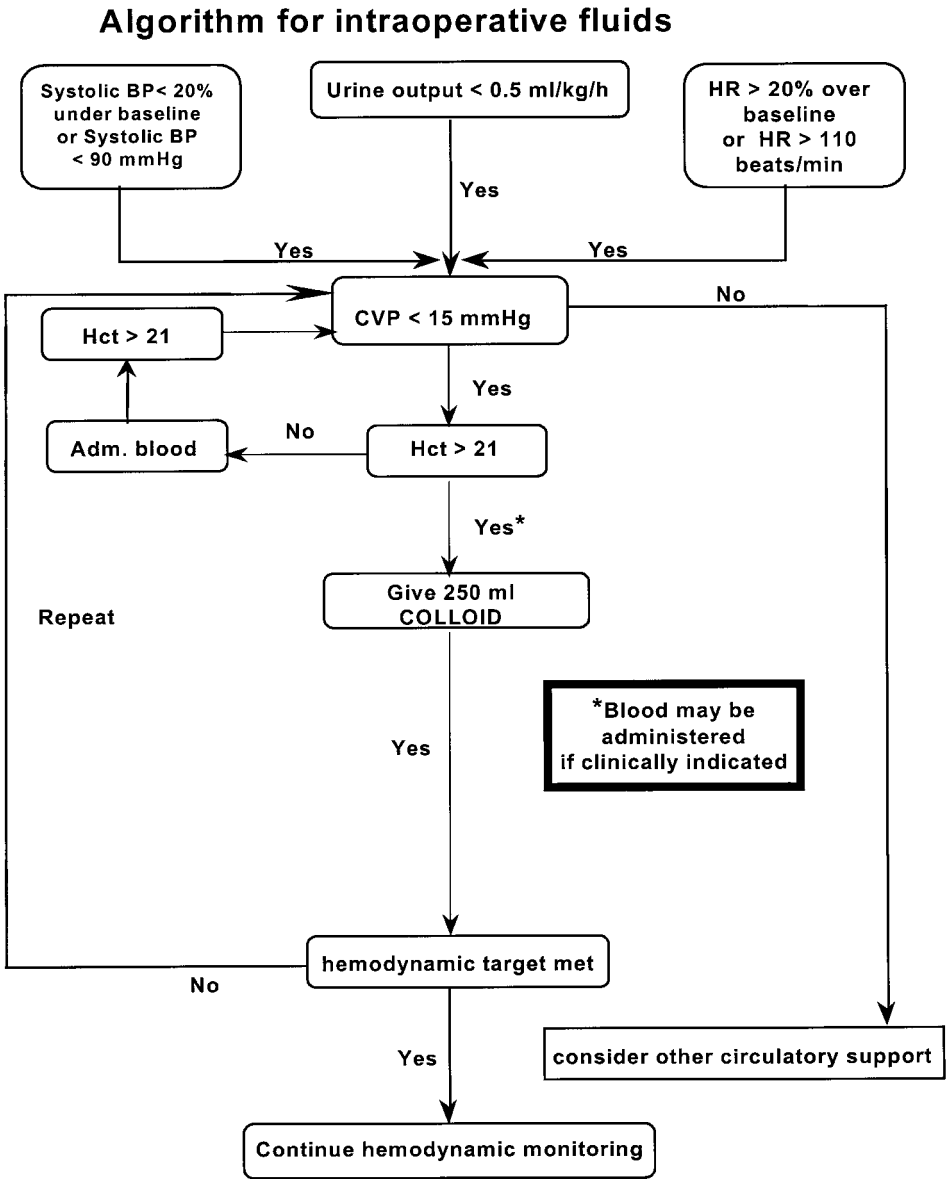

Fig 2. Algorithm for intraoperative colloid and crystalloid administration. BP, blood pressure; HR, heart rate; Hct, hematocrit; CVP, central venous pressure.[12]

profile compared with HS-NS or LR when used intraoperatively to treat hypovolemia. The thromboelastography profiles in HS-BS-treated patients showed the least change at the end of surgery. At postoperative day 1, HS-BS-treated patients exhibited an element of hypercoagulation as shown by a decrease in r time (Fig 3A and B).

The administration of LR in this study was associated with a procoagulant effect at the end of surgery and postoperative day 1 (Fig 3A and B). It is possible to speculate that this procoagulant effect may lead to an increased incidence of side effects, such as deep vein thrombosis and pulmonary embolism. These results are compatible with previous studies that showed this procoagulant effect of crystalloids *in vitro*[15,16] and *in vivo*.[8,17] Janvrin et al[8] not only showed a procoagulant effect because of hemodilution with crystalloid, but also an increased risk of deep vein thrombosis.[8] Patients who received normal saline had a 30% incidence of deep vein thrombosis, but only a 7% incidence was observed in patients who had a restricted fluid regimen. All these previous studies assessed the effect of saline solutions and not LR on coagulation. These findings of a hypocoagulant state in LR-treated patients suggest that this putative procoagulant state may be due to crystalloids regardless of their formulation.

This study has also shown that this procoagulant effect continues at least until 24 hours postoperatively (Fig 3A and B). The authors can only surmise on the cause of this state of hypercoagulation. The procoagulant state may predominate at moderate degrees of hemodilution. With increasing hemodilution, the procoagulant mechanisms may become increasingly affected, resulting in hypocoagulation. Another possible mechanism by which crystalloids cause this procoagulant effect may be due to the rapid loss of the fluid from the intravascular space

Table 1. Demographic Data

	6% Hetastarch in Normal Saline (n = 30)	6% Hetastarch in Balanced Saline (n = 30)	Lactated Ringer's Solution (n = 30)
Age (y)	58 ± 11	59 ± 8	58 ± 8
Weight (kg)	79.3 ± 24.5	79.1 ± 16.8	82.8 ± 21.3
Height (cm)	168.5 ± 8.0	167.9 ± 15.9	173 ± 9.2
ASA			
1	2	1	1
2	13	15	14
3	15	14	15
Surgical type			
Gynecology	11	10	5
Urology	11	11	14
General	8	9	11

NOTE. Data are either mean ± SD or number of patients.
Abbreviation: ASA, American Society of Anesthesiologists.

into the interstitial fluid, which results in hemoconcentration of coagulation factors and other blood elements. The finding that LR-treated and HS-BS-treated patients exhibited a degree of hypercoagulation in the first 24 hours postoperatively may be related to the inhibition of the fibrinolytic system that can occur in major abdominal and orthopedic surgery postoperatively.[18-20] This phenomenon has been described as fibrinolytic shutdown and has been attributed to an imbalance between tissue-type plasminogen activator and plasminogen activator inhibitor that occurs postoperatively.

HS-NS is a commonly used colloid in the United States. This study showed a hypocoagulant effect of HS-NS at end of surgery compared with baseline. Decreases in factor VIII, fibrinogen, and von Willebrand's factor and increases in prothrombin time, partial thromboplastin time, and bleeding time[13,14,21-23] are potential mechanisms for HS-NS-induced hypocoagulation.[24-27] In a literature review of the last 30 years by Warren and Durieux[28] in which 18 clinical studies were included, they concluded that there was insufficient evidence from adequately controlled trials to address the question of whether the administration of HS-NS results in more clinically significant bleeding. The effects may be independent of the dose given. These investigators believed that it was difficult to recommend a maximum safe dosage because patients' responses were variable. The package insert for HS-NS does not specify a maximum safe dosage. By 24 hours postoperatively, the thromboelastography variables in HS-NS-treated patients had returned to baseline, suggesting that there may be no long-lasting hypocoagulant effect attributed to HS-NS.

HS-BS may have a minimal effect on hemostasis. In an *in vitro* study, Bick[29] serially diluted normal plasma samples with HS-BS or saline. HS-BS had no adverse effect on prothrombin time, partial thromboplastin time, factor X, fibrinogen levels, and factor VIII complex, and rendered the same effect as dilution of plasma in saline. At all levels of dilutions with HS-BS, there was less prolongation of the prothrombin and partial thromboplastin times and smaller decreases in factor X, fibrinogen, and factor VIII complex levels. In this study, HS-BS compared with HS-NS and LR had a minimal effect on coagulation as assessed by thromboelastography at the end of surgery compared with baseline. This finding is in agreement with another study at this institution, which showed a statistically significant reduction in blood loss intraoperatively when comparing HS-BS, HS-NS, and LR.[30]

There are several possible mechanisms that could account for the observed differences in coagulation profiles between HS-BS and HS-NS. HS-BS, in contrast to HS-NS, is formulated in a balanced electrolyte solution including the presence of calcium (5 mEq/L). Calcium plays an important part not only in platelet activation, but also in the coagulation cascade. It is conceivable that the administration of larger volumes of HS-NS might be associated with hypocalcemia and impaired coagulation. Another possible explanation may lie in the difference in electrolyte composition. The level of chloride in HS-BS is 124 mEq/L versus 154 mEq/L in HS-NS. Large volumes of saline with its nonphysiologic levels of chloride have been associated with the development of a hyperchloremic acidosis. In a study by Scheingraber et al,[31] the rapid infusion of 0.9% saline but not LR caused a metabolic acidosis with hyperchloremic acidosis. There have been many reports of the association between the development of hyperchloremic acidosis and rapid saline infusion, leading to the use of the term *dilutional acidosis*.[32,33] The lower levels of chloride in HS-BS compared with HS-NS may account for these putative differences in coagulation profile through some yet undetermined mechanism.

Table 2. Intraoperative Fluids, Estimated Blood Loss, Hematocrit, and Blood and Blood Products Administration

	6% Hetastarch in Normal Saline (n = 30)	6% Hetastarch in Balanced Saline (n = 30)	Lactated Ringer's Solution (n = 30)
Volume of study fluid (mL)	1,301 ± 1,079	1,448 ± 759	5,946 ± 1,909*
Lactated Ringer's Solution (mL)	3,050 ± 1,531	3,242 ± 1,308	5,946 ± 1,909*
Hematocrit (%)			
Baseline	33.7 ± 6.03	35.4 ± 4.68	36.6 ± 3.60
End of surgery	28.9 ± 5.52	30.5 ± 3.92	32.1 ± 4.40
Red blood cells (mL)	348 ± 801	281 ± 488	303 ± 518
Fresh frozen plasma (mL)	68 ± 254	58 ± 187	37 ± 149
Platelets (mL)	16 ± 86	7 ± 39	0
Cryoprecipitate (mL)	3 ± 18	0	0
Estimated blood loss (mL)	550 (175–1,250)	388 (200–1,000)	725 (350–1,700)

NOTE. Values are mean ± SD or median (25%-75%).
*$p < 0.05$ hetastarch in normal saline, hetastarch in balanced saline versus lactated Ringer's solution group.

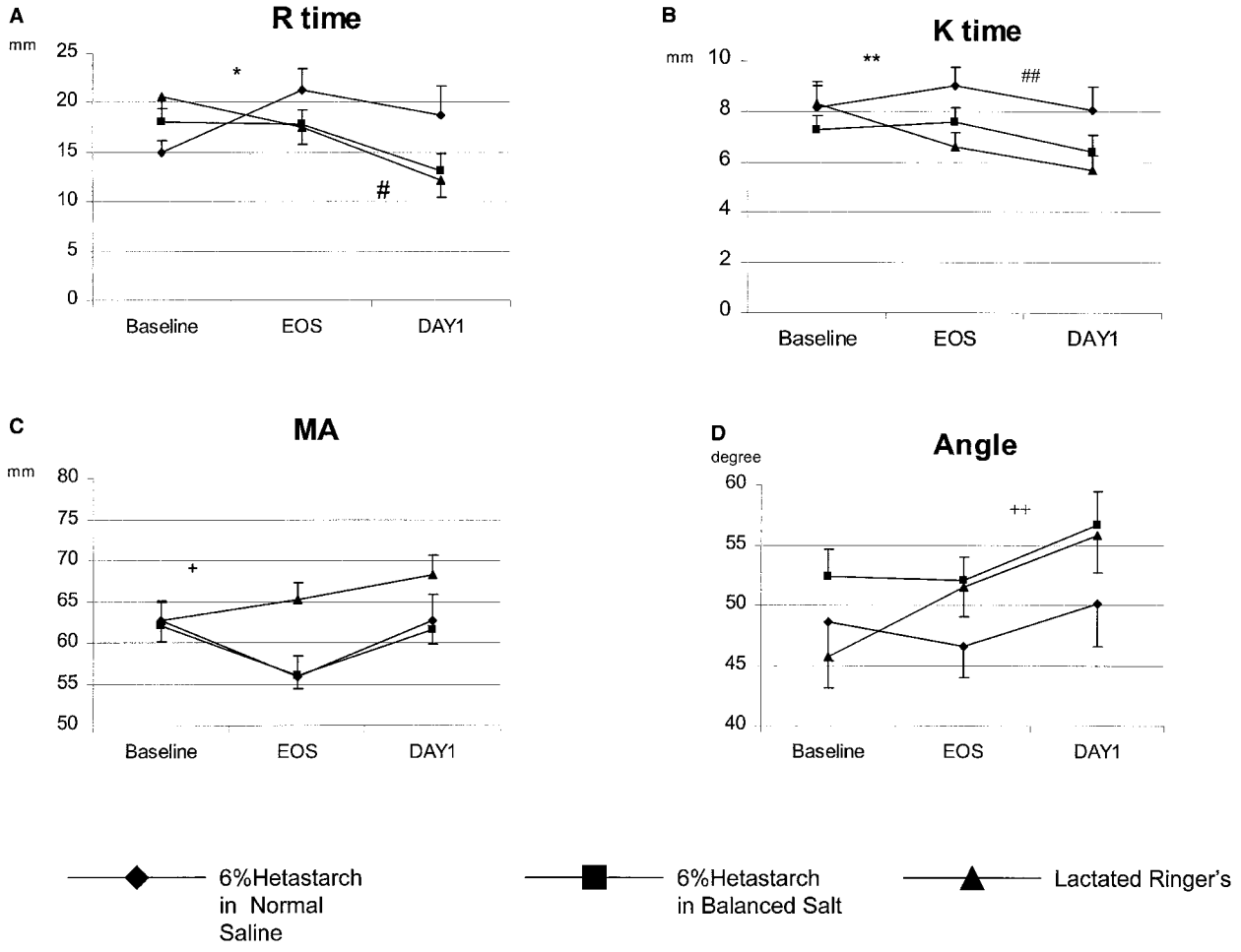

Fig 3. Changes in r time, k time, maximum amplitude and α angle for HS-BS, HS-NS, and LR at baseline, EOS (end of surgery) and day 1 (postoperative day 1). Mean ± standard error. *$p < 0.05$ between baseline and EOS, LR, and HS-NS. #$p < 0.003$ between baseline and day 1, LR and HS-BS. **$p < 0.05$ between baseline and EOS, LR, and HS-NS. ##$p < 0.003$ between baseline and day 1, LR. †$p < 0.05$ between baseline and EOS, HS-NS. ††$p < 0.003$ between baseline and day 1, LR.

In summary, LR-treated patients developed hypercoagulation, which persisted for 24 hours postoperatively. HS-NS-treated patients exhibited a state of hypocoagulation at the end of surgery that was normalized by 24 hours. HS-BS treatment has a minimal effect on hemostasis as determined by thromboelastography. Additional studies are indicated to further define the clinical relevance of these findings in this and other patient populations.

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