ORIGINAL ARTICLE

Assessment of hemostatic changes after crystalloid and colloid fluid preloading in trauma patients using standard coagulation parameters and thromboelastography

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ABSTRACT

Background: The choice of an ideal fluid administered post trauma and its subsequent influence on coagulation still poses a clinical dilemma. Hence, this study was designed to assess the influence of *in vivo* hemodilution with various fluid preparations (4% gelatin, 6% hydoxyethyl starch (HES), Ringer's lactate, 0.9% normal saline) on coagulation using standard coagulation parameters and real-time thromboelastography (TEG) in patients undergoing elective surgery post trauma. **Methods:** In a randomized, double-blind study, 100 patients of either sex and age, belonging to ASA Grades I and II, scheduled for elective surgeries were allocated into four groups of 25 each according to the type of fluid infused. Group G (4% gelatin), Group N (0.9% normal saline), Group R (Ringer's lactate), and Group H (6% HES) received preloading with 1 L of fluid according to the group. The coagulation status of the patients was assessed during perioperative period (before surgery, after fluid preloading, and at the end of the surgery) using both conventional coagulation analysis and TEG. **Statistical Analysis:** Analysis of variance (ANOVA), *post hoc* and Pearson Chi-square test were used. **Results:** In all the patients preloaded with gelatin, there was a significant increase in prothrombin time index (PTI; 14.88±0.90 vs. 13.78±3.01, $P<0.001$) and international normalized ratio (INR; 1.12±0.09 vs. 1.09±0.19, $P<0.05$) compared to the baseline value. An increase was observed in these parameters in the postoperative period also. In the HES group, there was statistically significant increase in PT time (15.70±1.51 vs. 13.74±0.75, $P=0.01$) and INR (1.20±0.15 vs. 1.03±0.17, $P<0.001$) as compared to the baseline. In the intergroup comparisons, the patients preloaded with HES had a significant increase in INR (1.20±0.15 vs. 1.12±0.09, $P=0.04$) and reaction time (R time; 6.84±2.55 min vs. 4.79±1.77 min, $P=0.02$) as compared to the gelatin group. The fall in coagulation time (k time; 2.16±0.98 vs. 3.94±2.6, $P=0.02$), rise in maximum amplitude (MA; 61.94±14.08 vs. 50.11±14.10, $P=0.04$), and rise in A20 (56.17±14.66 vs. 43.11±14.24, $P=0.05$) were more in patients preloaded with RL as compared to the HES group. 100% patients in the gelatin group, 84.2% patients in the NS group, 94.4% patients in the RL group, and 66.7% patients in the HES group had hypocoagulable (R time > 14 min) state in the postoperative period. **Conclusion:** Crystalloids are optimal volume expanders in trauma, with RL having beneficial effects on coagulation system (decrease in k time and increase in MA and A20). Among the colloids, HES 6% (130/0.4) affects coagulation parameters (increase in PTI, INR, R time, k time) more than gelatin. Trial registration (protocol number-IEC/NP-189/2011).

Key words: *Colloids, crystalloids, thromboelastography, trauma*

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INTRODUCTION

Trauma patients are known to develop dilutional coagulopathy attributable to blood loss, consumption of coagulation factors and platelets, and intravascular volume replacement.[1] Incidence of coagulopathy in trauma patients on admission is 25-35%.[2] The choice of an ideal fluid

administered post trauma and its subsequent influence on coagulation still poses a clinical dilemma. Hence, this study was designed to assess the influence of *in vivo* hemodilution with various fluid preparations (4% gelatin, 6% hydoxyethyl starch (HES), Ringer's lactate (RL), 0.9% normal saline (NS)) on coagulation using standard coagulation parameters and real-time thromboelastography (TEG) in patients undergoing elective surgery post trauma. In view of the large number of retracted papers by Professor Boldt,[3] there is a need for renewed studies of the effects of HES solutions on coagulation, which is otherwise well-traveled ground.

METHODS

Ethical approval for this study (protocol number IEC/NP-189/2011) was provided by the Ethical Committee of AIIMS (Chairperson Prof. J. P. Wali) on 8 August 2011. Written and informed consent was taken from the patients prior to surgery. The study was a prospective randomized, comparative, double-blind study conducted in 100 trauma patients above 20 years of age, posted for elective surgery in a referral tertiary trauma center. Patients on anticoagulants or antiplatelets were excluded from the study. All the blood samples which were not in proper proportions to the anticoagulant, hemolyzed samples, or samples collected by venipuncture taking more than 30 seconds were also excluded.

Study groups

Patients were randomly divided based on computer-generated randomization list into four groups according to the type of fluid infused. Group G (4% gelatin), Group N (0.9% NS), Group R (RL), and Group H (6% HES) received preloading with 1 L of fluid within 45 min according to the group after induction of anesthesia. Anesthesiologist preloading the fluid was also blinded to the type of fluid being infused. The following fluids were investigated:

- 4% succinylated gelatin solution, Gelofusine®, B. Braun Co., Penang, Malaysia
- 0.9% normal saline, Viaflex, Baxter, Gurgaon, India
- Ringer's lactate, Viaflex, Baxter, Gurgaon, India
- 6% HES 130/0.4, Voluven, Fresenius kabi, Germany.

The coagulation status of the patients was assessed during perioperative period (before surgery, after fluid preloading, and at the end of the surgery in the recovery room) using both conventional coagulation analysis and TEG. Conventional coagulation parameters measured included prothrombin time index (PTI), activated prothrombin time (APTT), and international normalized ratio (INR). TEG parameters being measured were reaction time (R time), coagulation time (k time), alpha angle (α angle), maximum amplitude (MA), A10, and A20. The baseline characteristics (age, sex, diagnosis, mode of injury, type of anesthesia, Injury Severity Score (ISS), hemogram, and intraoperative blood loss) of all trauma patients undergoing elective surgery were recorded.

4.5 ml blood sample was collected by venipuncture into vacutainer tubes containing citrate (0.129 M trisodium citrate) for standard coagulation parameters and thromboelastogram, 2 ml collected in ethylenediaminetetraacetic acid (EDTA) vacutainer tubes for hemogram and platelet counts, and 0.36 ml (360 μl) whole blood was taken in automated thromboelastometer (TEM-A vacutainer). Blood samples were drawn before surgery, after fluid preloading, and at the end of the surgery. For PT, APTT and INR, the fully automated coagulation analyzer STA-COMPACT and STA reagents were used. R time, k time, α angle, MA, A10, and A20 were obtained using TEM-A automated thromboelastometer (Framar Biomedica, Rome, Italy) within 4 min of venipuncture. Analysis was performed in a standardized way and assessed for R time (normal range 9-14 min), k time (normal range 4-6.5 min), α angle (normal range 29°-43°), and MA (normal range 48-60 mm). Automatic calibration before every test and calibration for the end scale of 100 ensured the same linearity of the signal throughout its range, i.e., in TEM-A, it is sufficient to run a single quality control test that verifies the zero.

To study the correlation between TEG parameters and standard coagulation assays, we pooled together all the samples taken for TEM-A analyzer and compared these with standard coagulation assays.

Statistical analysis

A sample size of 60 is required to be within 5 units of the true A10 (amplitude at 10 min) with 95% Confidence Interval and allowing multiple comparisons. The sample size was calculated based on the pilot study results; the Standard Deviation in A10 was estimated at 21.9. The formula used to estimate the sample size was:

$$Z^2_{1-\alpha/2} = 1.96$$

where σ = Standard deviation

$$n = \frac{Z^2_{1-\alpha/2}\sigma^2}{d^2}$$

A power analysis of the study using R time as the variable showed a power of 99. Demographic profile, baseline hemogram, and coagulation parameters at different time intervals and in relation to different fluids administered were analyzed using analysis of variance (ANOVA) and *post hoc* comparison with the Bonferroni correction applied to adjust the level of significance. Log transformation was applied for the skewed data and

P value was adjusted for ISS, platelets, and intraoperative blood loss. Categorical data of inhomogeneous distribution (sex, diagnosis, mode of injury, type of anesthesia, hemoglobin, TEG parameters during different time intervals with normal and abnormal values) were analyzed using Pearson Chi-square and expressed as frequency (%). Multiple comparisons (within a group and between groups) of each coagulation parameter were performed using ANOVA and data were expressed as Mean±SD. Statistical analysis of postoperative sample adjustment for duration of surgery, intraoperative blood loss, and fluids transfused was done using analysis of covariance (ANCOVA) and data expressed as Mean±SD. Pairwise comparisons with 95% confidence interval for difference and Bonferroni adjustment for multiple comparisons was used. *P* values of less than 0.05 were considered statistically significant. All statistical tests were performed using commercially available statistical software (SPSS for windows version 15.0 Chicago, IL, USA) and graphs were produced using Microsoft Excel for MAC 2011(version 14.1.2).

RESULTS

All 100 trauma patients completed the study according to protocol and were included in the analysis. Distribution of subjects according to the demographic profile, baseline hemogram, and coagulation parameters is summarized in Table 1. Statistically significant difference was observed in sex distribution, diagnosis of patients, and type of anesthesia administered. Statistical analysis of postoperative sample adjustment for duration of surgery, intraoperative blood loss, and fluid transfused showed non-significant pairwise comparisons of all the TEG values [Table 2].

Baseline preoperative routine coagulation and TEG parameters amongst surgical trauma patients were similar among the four groups [Figure 1]. Crystalloid (NS/RL) preloading did not influence the coagulation parameters (conventional and TEG). In all the patients preloaded with gelatin, there was a highly significant increase in PTI (14.88±0.90 vs. 13.78±3.01, *P*<0.001) and a

Table 1: Distribution of subjects according to demographic profile, baseline hemogram and coagulation parameters

Group (no. of patients)	Group G (*n*=25)	Group N (*n*=25)	Group R (*n*=25)	Group H (*n*=25)	*P* value
Age (years)	31.31±10.00	32.71±1011	33.90±14.12	33.41±12.80	0.64
Sex					
M	19 (73.1)	24 (100)	24 (88.9)	20 (95.2)	0.01*
F	7 (26.9)	0 (0)	3 (11.1)	1 (4.8)	
Weight	33.67±9.76	38.30±11.50	34.77±9.55	36.34±9.72	0.23
Diagnosis					0.002*
Long bone fracture	8 (30.8)	9 (37.5)	24 (88.9)	6 (28.6)	
Spinal injury	11 (42.3)	13 (54.2)	2 (7.4)	11 (52.4)	
Abdominal surgery	2 (7.7)	0 (0)	1 (3.7)	1 (4.8)	
Skin grafting	3 (11.5)	2 (8.3)	0 (0)	2 (9.5)	
Maxillofacial injury	2 (7.7)	0 (0)	0 (0)	1 (4.8)	
Mode of injury					0.24
Fall	11 (42.3)	7 (30.4)	7 (29.6)	4 (20)	
Road traffic accident	11 (42.3)	11 (47.8)	18 (69.2)	14 (70)	
Others	4 (15.4)	5 (21.7)	1 (3.8)	2 (10)	
Type of anesthesia					0.01
GA	20 (76.9)	18 (75)	12 (44.4)	20 (95.2)	
Spinal	5 (19.2)	5 (20.8)	10 (37)	1 (4.8)	
Others	1 (3.8)	1 (4.2)	5 (18.5)	0 (0)	
ISS (Injury severity score)	15.27±8.55	14.96±6.62	13.74±7.78	15.43±5.98	0.58
Days after trauma	6.67±3.30	4.75±2.48	5.42±2.20	5.66±2.294	0.66
Hb on admission	12.12±1.77	12.19±1.80	12.29±1.56	12.31±2.18	0.98
Platelets on admission	247.38±113.64	297.96±143.44	268.88±162.60	302.00±186.12	0.56
PT on admission	13.78±3.01	14.05±1.00	14.31±1.84	13.74±0.75	0.08
INR on admission	1.09±0.19	1.02±0.0.10	1.06±0.14	1.03±0.17	0.08
APTT on admission	28.83±5.98	27.95±6.63	30.00±13.42	27.77±6.27	0.81
Intraoperative blood loss	525.50±396.05	538.96±391.11	394.23±340.68	544.44±421.094	0.33

Age, ISS, baseline Hb, platelets, INR, APTT, Intraoperative blood loss was expressed as Mean±SD using one-way ANOVA for overall comparison. Log transformation was applied for the skewed data and *P* value was adjusted for ISS, platelets and intraoperative blood loss. Categorical data-Sex, diagnosis, mode of injury, type of anesthesia expressed as frequency (%) using Pearson Chi-square analysis. **P* value<0.05 – Statistically significant

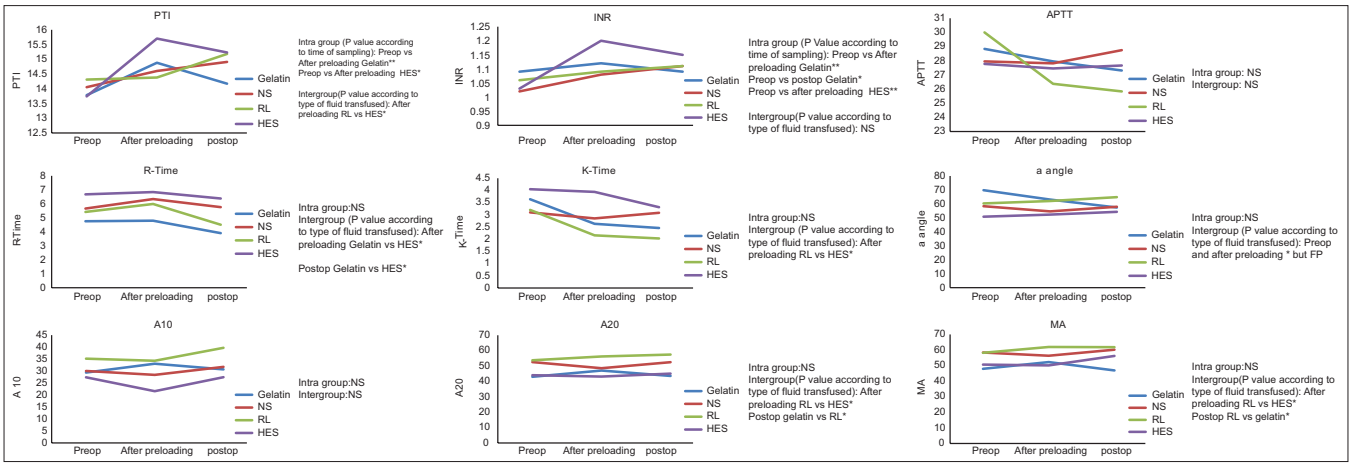

Figure 1: Various coagulation parameters among trauma surgical patients according to the period of sample withdrawn and according to the type of fluid given

Table 2: Statistical analysis of post operative sample adjusting for duration of surgery, intraoperative blood loss and fluid transfused

Group (no. of patients)	Group G (*n*=25)	Group N (*n*=25)	Group R (*n*=25)	Group H (*n*=25)	Pairwise comparison
R- time	4.75±2.48	5.66±2.29	5.42±2.20	6.67±3.30	NS
K-time	2.48±2.5	2.96±1.7	2.03±1.0	3.78±2.1	NS
α angle	57.24±19.0	59.0±12.11	64.84±12.56	64.83±12.56	NS
MA	46.42±19.0	59.5±16.73	61.83±16.58	49.28±10.34	NS
A10	31.63±3.50	34.15±3.9	37.8±4.0	26.0±8.4	–
A20	43.14±17.58	53.6±17.11	57.44±17.0	42.6±14.46	NS

Sample adjustment using analysis of covariance (ANCOVA) with covariates appearing in the model being evaluated as: duration of surgery , intraoperative blood loss and fluid transfused. Pairwise comparisons with 95% confidence interval for difference and bonferroni adjustment for multiple comparisons. **P* value <0.05: Statistically significant

significant increase in INR (1.12±0.09 vs. 1.09±0.19, *P*<0.05) compared to the baseline value. An increase was observed in the parameters, namely, PTI (14.17±1.14, *P*<0.001) and INR (1.09±0.11, *P*<0.05) in the postoperative period also. In the HES group, there was statistically significant increase in prothrombin time (PT) (15.70±1.51 vs. 13.74±0.75, *P*=0.01) and INR (1.20±0.15 vs. 1.03±0.17, *P*<0.001) as compared to the baseline. Rest of the variables, i.e., APTT, R time, k time, α time, A10, A20, and MA, were not influenced in any group after preloading or at the end of the surgery.

In the intergroup comparisons [Figure 1], the patients preloaded with HES had a significant increase in INR (1.20±0.15 vs. 1.12±0.09, *P*=0.04) and R time (6.84±2.55 min vs. 4.79±1.77 min, *P*=0.02) as compared to the gelatin group. At the end of the surgery, the same group (HES) had significantly more R time (6.38±3.56 min, *P*=0.02) as compared to the gelatin group (3.9±2.1 min). After preloading with RL, the increase in PTI (14.38±1.66 vs. 15.70±1.51, *P*=0.02) was statistically less as compared to the HES group. Between these two groups, the fall in k time (2.16±0.98 vs. 3.94±2.6, *P*=0.02), rise in MA (61.94±14.08 vs. 50.11±14.10, *P*=0.04), and rise in A20 (56.17±14.66 vs. 43.11±14.24, *P*=0.05) were more in patients preloaded with RL as compared to the HES group. At the end of the surgery, the patients who had received RL had significantly higher value of MA (61.83±16.58 vs. 46.85±18.61, *P*=0.02) and more increase in A20 (57.43±17.00 vs. 43.54±17.31, *P*=0.04) as compared to the gelatin group.

Table 3 depicts the distribution of TEG parameters during different time intervals (preoperative, intraoperative, and at the end of the surgery). In all the four groups, preoperatively a statistically significant number of patients were hypercoagulable (R time <9 min (rapid initial fibrin formation), *P*=0.04), (k time <4 min (rapid fixed level of clot strength), *P*=0.02), (α time >43 (rapid rate of fibrin buildup and cross-linking, i.e., clot formation rate), *P*=0.03), but had MA <48 mm (poor clot strength) (*P*=0.05) values. These results were observed maximum in the RL group, which had the maximum frequency of patients showing rapid clot formation, propagation, and cross-linking but poor clot strength preoperatively. However, during intraoperative period, the number of patients with abnormal TEG parameters was not significant. 100% patients in the gelatin group, 84.2% patients in the NS group, 94.4% patients in the RL group, and 66.7% patients in the HES group had hypocoagulable (R time >14 min) state in the postoperative period.

Table 3: Statistical evaluation and distribution of thromboelastography parameters during different time interval

TEG	Parameter	Group G	Group *N*	Group R	Group H	*P* value
Preoperative						
R Time	Normal: 9-14	2 (7.7)	2 (8.3)	1 (3.7)	4 (28.6)	0.04*
	<9	24 (92.3)	22 (91.7)	26 (96.3)	15 (71.4)	
	>14	0 (0)	0 (0)	0 (0)	0 (0)	
K-time	Normal 4-6.5	2 (7.7)	4 (16.7)	2 (7.4)	7 (33.3)	0.02*
	<4	18 (69.2)	19 (79.2)	24 (88.9)	10 (47.6)	
	>6.5s	6 (23.1)	1 (4.2	1 (3.7)	4 (19.0)	
α angle	Normal 29-43	2 (7.7)	3 (12.5)	0 (0)	7 (33.3)	0.03*
	<29	1 (3.8)	0 (0)	1 (3.7)	1 (4.8)	
	>43	23 (88.5)	21 (87.6)	26 (96.3)	13 (61.9)	
MA	Normal 48-60	9 (34.6)	6 (25.0)	8 (29.6)	8 (38.1)	0.05*
	<48	13 (50.0)	7 (29.2)	5 (18.5)	9 (42.9)	
Intraoperative						
R Time	Normal values: 9-14	0 (0)	5 (21.7)	4 (18.2)	4 (21.1)	0.2
	<9	0 (0)	0 (0)	0 (0)	5	
	>14	24 (100)	18 (78.3)	18 (81.8)	15 (71.4)	
K-time	Normal 4-6.5	5 (20.8)	5 (21.7)	1 (4.5)	4 (21.1)	0.07
	<4	0 (0)	1 (4.3)	0 (0)	3 (15.8)	
	>6.5	19 (79.2)	17 (73.9	21 (95.5)	12 (63.2)	
α angle	Normal 29-43	0 (0)	3 (13)	0 (0)	3 (15.8)	0.2
	<29	0 (0)	1 (4.3)	1 (4.5)	1 (5.3)	
	>43	24 (100)	19 (82.6)	21 (95.5)	15 (78.9)	
MA	Normal 48-60	11 (45.8)	11 (47.8)	9 (40.9)	6 (31.6)	0.4
	<48	7 (29.2)	3 (13)	4 (18.2)	8 (42.1)	
	>60	6 (25.0)	9 (39.1)	9 (40.9)	5 (26.3)	
Postoperative						
R Time	Normal values: 9-14	0 (0)	3 (15.8)	1 (3.7)	5 (33.3)	0.04*
	(Hypercoagulable)<9	0 (0)	0 (0)	0 (0)	0 (0)	
	(Hypocoagulable)>14	24 (100)	16 (84.2)	17 (94.4)	10 (66.7)	
K-time	Normal 4-6.5	3 (12.5)	5 (26.3)	1 (5.6)	3 (20)	0.33
	Hypercoagulable)<4	1 (4.2)	1 (5.3)	0 (0)	2 (13.3)	
	(Hypocoagulable)>6.5	20 (83.3)	13 (68.4	1 (3.7)	17 (94.4)	
α angle	Normal 29-43	7 (29.2)	3 (15.8)	3 (16.7)	5 (33.3)	0.14
	<29	3 (12.5)	0 (0)	0 (0)	0 (0)	
	>43	14 (58.3)	16 (84.2)	15 (83.3)	10 (66.7)	
MA	Normal 48-60	9 (37.5)	5 (26.3)	6 (33.3)	5 (33.3)	0.5
	<48	10 (41.7)	4 (21.1)	4 (22.2)	5 (33.3)	
	>60	5 (20.8)	10 (52.6)	8 (44.4)	5 (33.3)	
	>60	5 (20.8)	10 (52.6)	8 (44.4)	5 (33.3)	

Data expressed as frequency (%) using Pearson Chi-square analysis; *P<0.05: Statistically significant

DISCUSSION

Perioperative coagulation assessment is important in the clinical setting of trauma to diagnose the cause of bleeding, guide hemostatic therapies, and predict bleeding risk in surgical interventions.[4] Different fluids have different effects on hemostasis, attributable to either dilution of clotting factors or the substance-specific effects of the plasma substitute. Both *in vivo* and *in vitro* studies have demonstrated that crystalloids have lesser effect on coagulation system than colloids.[5-8] Among the colloids, gelatin shows lesser effect than HES.[1,9,10] However, none of the studies compares all the commonly used fluids (NS, RL, HES, and gelatin) in trauma patients who are prone to develop coagulopathy. We selected trauma patients undergoing elective surgery to have a homogenous group of population. Though the four solutions studied do not have similar effects on plasma volume expansion, we decided to use the same volume of each to remove the confounding factor of different fluid volumes infused.

Various contrasting results regarding use of different fluids have been obtained in both *in vivo* and *in vitro* studies, which have been discussed in Table 4.

Hypothermia, acidosis, and dilution from standard resuscitation can worsen the presenting coagulopathy in a trauma victim. Hence, judicious use of resuscitation fluids becomes a challenge for the treating anesthesiologist.[11] As viscoelastic techniques have been used for coagulation assessment in multiple clinical settings but their experience in trauma is limited, we undertook this study to assess the influence of various fluid preparations (gelatin, HES, RL, and NS) on coagulation using standard coagulation parameters and real-time TEG in patients undergoing elective surgery post trauma.

There is a marked male preponderance in all communities of the world among trauma victims,[12] which was statistically significant in our study as well [Table 1]. Weights of patients were statistically similar, and hence the estimated blood volumes of patients were similar across the groups [Table 1]. Viscoelastic hemostatic assays (VHA) in majority of patients with minor trauma, moderate trauma (ISS: 10-20), severe injury (ISS: 20-35), and massive tissue injury (ISS >30) showed normal, hypercoagulability, hypocoagulability, and hyperfibrinolysis, respectively.[13] In our study, preoperative ISS (Mean±SD) fell between 10 and 20, i.e., moderate injury in all the four groups, and the frequency of patients that were hypercoagulable was statistically significant, which was consistent with the report of Johannson *et al*.[13] Effect of individual anesthesia technique on hemostasis and coagulation parameters is controversial. The study by Huang *et al*. failed to demonstrate any enhancement of hemostasis or fibrinolysis postoperatively in patients undergoing arthroscopy under either general anesthesia or spinal anesthesia.[14] However, stress induced by tracheal intubation may result in catecholamine surge resulting in enhanced platelet aggregation and hence accelerated blood coagulation in other studies.[15]

Preloading with gelatin and HES caused increase in PTI and INR compared to the baseline [Figure 1], and this influence could be observed in postoperative period also in the gelatin group but not in the HES group. However, no significant effect of preloading on TEG parameters indicates that interaction of hemostatic components *in vivo* is not affected by the time of sampling. This observation can be explained by the fact that the dose we used for *in vivo* hemodilution (<40% and <28 ml/kg) was low as compared to some other studies.[16]

On intergroup comparison [Figure 1], preloading with HES delayed clot formation (increased R time and k time) and resulted in weaker clot (decreased MA) but slower clot lysis at 20 min after attaining MA, as compared with crystalloids. These results are consistent with the previous studies which state that HES 6% causes weaker clot with less stable fibrin network and less firm aggregation of platelets.[1,3,6,17-19] Preloading with RL when compared to HES, on the other hand, resulted in statistically significant decrease in k time and increase in MA and A20, indicating rapid clot propagation and strong clot, but rapid fibrinolysis. Ansari *et al*.[20] observed that *in vitro* dilution of blood to 60% using lactated Ringer's/HES (130/0.4) combination produced significantly more derangement in all parameters compared with RL alone (increased clotting time and clot formation time, and decrease in maximum clot formation). A statistically significant rise in PTI after HES preloading compared to RL does not represent clot dynamics or quality. Postoperatively; gelatin caused more rapid clot formation (R time minimum) compared to HES, with weaker clot strength (lesser MA) and slower fibrinolysis (lesser A20) compared to RL. Konrad *et al*.[21] compared *in vitro* coagulation in gelatin, 6% HES (450/0.7), and RL in 33% and 66% dilutions, measuring routines laboratory and SONOCLOT (viscoelastic) variables. Hemodilution with RL tended to increase *in vitro* coagulability. Amongst the tested colloids, gelatin had the least impact on markers of coagulation. HES had the largest impact on markers of coagulation compared with gelatin and RL, which is similar to the results obtained by Neimi *et al*.[22] and Mittermayr *et al*.[1]

Our study demonstrates that crystalloids effect coagulation much lesser than colloids as they mainly exhibit diluting effect on coagulation system. RL is better than NS as it promotes rapid clot propagation, strong clot, and rapid fibrinolysis. Previous studies demonstrate resuscitation with RL reduces tissue hypoxia indices but does not effect the changes in fibrinogen metabolism resulting from hemorrhage.[33] In our study, HES delayed clot formation and resulted in weaker clot but slow clot lysis. Such hypocoagulability may be detrimental in patients having increased bleeding risk, e.g., severe trauma (ISS >20), who are already hypocoagulable.[13] Such an effect might be because HES is a highly branched and hydroxyethylated glucose polymer that can reduce von Willebrand (vWB) factor and interferes with fibrinogen function and polymerization.[3,4,34] We chose HES 130/0.4, which is known to effect coagulation to the least because of its low molecular weight and low degree of substitution, amongst other starches.[35] Gelatin caused more rapid clot formation, but weakest clot strength and slowest fibrinolysis that might be due to the dilutional effect, and gelatin solutions might influence the weight and reticular network of fibrin strands and platelet function with decreased vWB factor.[34,36]

One limitation of the study was that numbers in each group were relatively small, which led to inequities in sex

Table 4: Characteristic studies comparing different fluid admistration effect on thromboelastography values

Study group	Viscoelastic device used	Patient group	Fluids compared	Conclusion drawn
In vitro studies				
Jamnicki *et al*. (1998)[7]	TEG	80 patients for elective surgery	HES 130/0.4 vs. HES 200/0.5 vs. NS	Both HES solutions affected *in vitro* coagulation to the same degree (r and k increased; MA and angle decreased progressively) There was hypercoagulability with 30% hemodilution with 0.9% NS (decrease in r and an increase in the α angle but MA decreased slightly, and CI increased)
Entholzner *et al*. (2000)[23]	ROTEM	30 healthy volunteers	HES 130/0.4 vs. Ringer's acetate vs. HES 200/0.5 vs. HES 450/0.7 vs. 4% gelatin	HES 130/0.4 has no significant effect on platelet variables, shows a faster clot formation process and a better clot retraction as compared with the other HES solutions. HES 130/0.4 compared with HES 200/0.5 or gelatin-based volume replacement 168 fluid affects coagulation to the same extent resulting in 169 similar degree of blood loss
Lidgard E *et al*. (2000)[24]	Sonoclast	8 intensive care patient	NS, Ringer's acetate, 5% albumin, 6 % dextran 70, starch 140/0.3, buffered starch 140/03 and gelatin	Synthetic colloid fluids are more detrimental to coagulation than albumin and crystalloid alternatives Dextran had a significantly higher impact on platelet function compared to other fluids
Fries D *et al*. (2002)[15]	ROTEM	10 healthy volunteer males	RL vs. gelatin vs. 6% HES 130/0.4 vs. 6% HES 200/0.5 vs. combinations of these solutions at a ratio of 1:1 (gelatin/RL, 6% HES 130/0.4:RL, 6% HES 200/0.5:RL, 6% HES 130/0.4:gelatin, 6% HES 200/0.5:gelatin)	Compared with the administration of 6% HES 130/0.4 alone, the combination of 6% HES 130/0.4 and gelatin produced a advantage concerning the impairment of hemostasis
Niemi TT *et al*. (2005)[22]	ROTEM	12 healthy volunteers	6% HES 120/0.7, vs. 6% HES 140/0.4, vs. 4% Gelatin, vs.4% albumin	Haemodilution with gelatin and albumin induced fewer coagulation abnormalities than HES. The haemodilution with gelatin impaired coagulation more than albumin solution
DeLorenzo *et al*. (2006)[18]	ROTEM	8 healthy volunteers	HES 6% vs. 0.9% NS	Clot firmness became critical after 40% dilution with HES 6% but not until 60% dilution with NS 0.9%. HES molecules interfere with fibrin polymerization and, thus, administration of fibrinogen after dilution with HES 6% failed to significantly improve clot firmness
Niemi TT *et al*. (2006)[8]	TEG	45 cardiac patients	4% albumin, 4% succinylated gelatin, or 6% HES (200/0.5)	Fibrin formation (clot formation time, a-angle) and fibrinogen-dependent clot strength (maximum clot firmness and shear elastic modulus) were more disturbed in the HES group than in the gelatin group
Bang *et al*. (2010)[6]	TEG	95 End stage liver disease patients for liver transplant	HES (130/0.4) vs. 0.9% NS	33% dilution with NS, only the reaction time (*r*) was increased.11% dilution with 6% HES (130/0.4), maximum amplitude (MA) decreased. At 33% dilution, the *r* and *K* increased, and the MA, alpha angle, and coagulation index decreased
Ansari T *et al*. (2010)[20]	ROTEM	8 pregnant females for caesarean section	RL vs. RL+6% HES	Dilution of blood to 60% using RL/HES (130/0.4) combination produced significantly more derangement in all parameters compared with lactated Ringer's alone
Casutt *et al*. (2010)[7]	ROTEM sonoclast	10 healthy volunteers	Balanced 6% HES 130/0.42 vs. saline-based 6% HES 130/0.4 vs. RL vs. 4% gelatin	There are fewer effects on blood coagulation using crystalloids compared with colloids. (Increase in CT and CFT and decrease in Alpha and MCF). The effects of GEL and HES are similar
In vivo studies				
Gann TJ *et al*. (1999)[25]	TEG	120 patients for major surgeries	Hextend vs. 6% HES	Patients receiving HES had significant prolongation of time to onset of clot formation but not seen in the Hextend patients
Felfernig M *et al*. (2003)[26]	TEG	50 patients for minor surgeries	NS HES 70/0.5/4 vs. HES 130/0.4/9 vs. HES 200/0.6/9.4, vs. HES 450/0.7/4.6	Infusion of HES 450/0.7/4.6 compromises TEG parameters more than the other solutions tested, whereas HES 130/0.4/9 has the smallest effect

(Contd...)

Table 4: Condt...

Study group	Viscoelastic device used	Patient group	Fluids compared	Conclusion drawn
Haas T *et al*. (2007)[27]	ROTEM	42 children for minor surgeries	albumin 5% vs 4% gelatine vs 6% HES 130/0.4	After gelatine and after albumin the median clot firmness decreased significantly but remained within the normal range. Following HES, coagulation time increased significantly, and clot formation time, α angle, clot firmness, and fibrinogen/fibrin polymerisation were significantly more impaired than for albumin or gelatine
Haas T *et al*. (2007)[28]	ROTEM	30 pigs	7.2% HS vs. 6% HES 200/0.62 vs. 9 or 6% HES 130/0.4 vs. 4% gelatin	Fibrinogen polymerization was significantly higher after HS-HES when compared with 4% gelatin or HES 130/0.4
Mittermayr M *et al*. (2007)[1]	ROTEM	61 spine surgery patients	Gelatin vs.HES 130/0.4, vs. RL	The a angle, clot firmness, and fibrinogen polymerization significantly decreased in the patients receiving HES followed by gelatin with the least reductions for RL
Butwick *et al*. (2007)[29]	TEG	30 patients undergoing elective caesarean	6% HES vs. RL	Group HES had longer reaction times (r) and clot formation times (k) after fluid loading compared to baseline values but within normal reference range
Schramko *et al*. (2009)[30]	ROTEM	45 cardiac patients	6% HES (130/0.4) vs. 4% gelatin vs. Ringer's acetate	Clot formation time was prolonged, and the alpha-angle as well as maximum clot firmness (MCF) decreased similarly after infusion of 7 ml/kg both colloid solutions In contrast, after infusion of 14 ml/kg and 21 ml/kg Ringer's acetate MCF increased slightly but significantly
Choi YS *et al*. (2010)[31]	TEG	36 patients for cardiac surgeries	5% albumen vs. 6% HES 130/0.4	Similar effects on coagulation variables, blood loss and proinflammatory activities
Jin SL *et al*. (2010)[32]	TEG	36 patients for gastric carcinoma surgeries		
Zdolsek HJ *et al*.[19]	ROTEM	84 hip replacement surgery	HES 130/0.42/vs. HES 30/0.4/vs. HES 200/0.5 vs. 6% dextran 70	All tested colloid fluids induced a mild hypercoagulable state with faster clotting, but with weaker clot strength

distribution between groups and in the kinds of operations and anesthesia. Larger groups would be necessary to correct this problem. Another pitfall of our study was that our study population included patients of ISS 10-20 (moderately injured patients) undergoing elective surgeries. However, in patients with severe or life-threatening injury, high volume of fluids will be infused that would result in more pronounced hemoalterations. Besides, our study was an *in vivo* study; the effect of extreme hemodilution with larger volumes of fluid was not investigated upon, which might occur in patients of trauma during resuscitation. Type of surgery and type of anesthesia were the uncontrolled variables in our study. TEG may not detect platelet adhesion abnormalities such as vWB factor deficiency or drug-induced platelet inhibition.[37]

In conclusion, the choice of fluid for elective surgery does not matter, as the coagulation abnormalities observed are clinically irrelevant. However, the results might me more readily explained by observing that gelatin and HES expand the circulation more than NS or LR. Our study demonstrates that crystalloids are optimal volume expanders in trauma, with RL having beneficial effects on coagulation system (decrease in k time, increase in MA and A20), however, which is clinically irrelevant. Among the colloids, HES 6% (130/0.4) affects coagulation parameters (increase in PTI, INR, R time, k time) more than gelatin.

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