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Original Article

The effects of tranexamic acid and 6% hydroxyethyl starch (HES) solution (130/0.4) on postoperative bleeding in coronary artery bypass graft (CABG) surgery

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Abstract: Background: The addition of 6% hydroxyethyl starch (HES) into Ringer lactate priming solution may have adverse effects on hemostasis in patients undergoing coronary artery bypass grafting (CABG) with cardiopulmonary bypass (CPB) with or without the use of tranexamic acid. Methods: In a prospective, randomized clinical trial, 132 patients were assigned to receive 20 ml/kg of Ringer priming solution with or without tranexamic acid (TA) (Group RS-TA, n=34 and Group RS-noTA, n=32) or 10 ml/kg of 6% HES plus 10 ml/kg of RS priming solution with or without intravenous tranexamic acid (Group HES-TA, n=35 and Group HES-noTA, n=31). Estimated blood loss, chest tube drainage, amount of blood products, hemoglobin, hematocrit, platelet and coagulation parameters were examined before and 24 hour after surgery. Results: For Group HES with tranexamic acid, when compared to other groups, estimated blood loss, postoperative 24 hour drainage loss and blood product transfusions were less (P=0.023; P=0.003; P=0.001; respectively) and hemoglobin, hematocrit values at 12 and 24 hours after surgery increased in comparison to other groups (P=0.041, P=0.034, P=0.004, P=0.001; respectively). Platelet concentrations were similar between groups (P>0.05). Conclusions: In CABG, the administration of tranexamic acid in HES 130/0.4 prime solution study group decreased estimated blood loss and chest tube drainage in comparison to patients receving Ringer prime solution with or without tranexamic acid postoperatively however, no effects on renal functions or postoperative complications were shown.

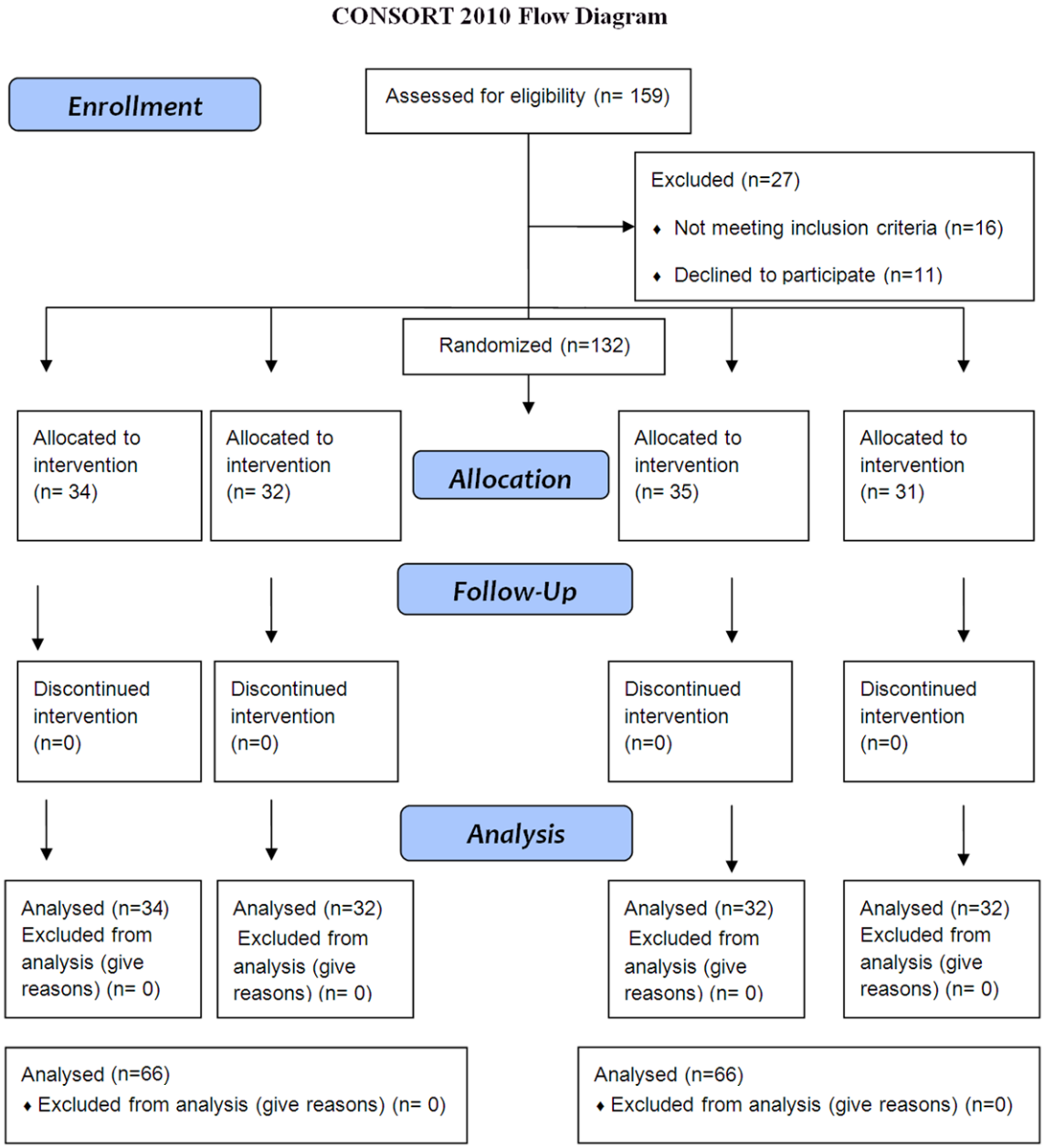
Keywords: Hetastarch, tranexamic acid, cardiac surgery, crystalloid, colloid, cardiopulmonary bypass, hemostasis, renal

Introduction

During coronary artery bypass surgery (CABG) with cardiopulmonary bypass (CPB) a recently introduced low molecular weight hydroxyethyl starch (HES) 6% 130/0.4 solution showed less amount of tissue accumulation, a faster renal excretion and reduced impact on hemostasis and coagulation in comparison to crytalloids and other colloids [1-6]. The rationale for adding HES 6% solution into CPB prime is preservation of colloid osmotic pressure that will result in a diminished amount of fluid retention [7]. Also, there are studies showing that hemostasis and renal function is well preserved with this solution [4, 7, 8]. The importance of the diluent solution of HES 6% 130/0.4 has recently been emphasized [9]. The Ringer's solution (RS) is a crystalloid solution that has sodium ion of 130 mmol/L, chloride ion of 109 mmol/L with an osmolality of 273 mOsm/kg. Most colloids including albumin are diluted in 0.9% normal saline and because of this hyperchloremic acidosis may occur [10].

Tranexamic acid (TA) is a synthetic antifibrinolytic drug that reduces fibrinolysis and plasmin mediated platelet dysfunction. The overall clini-

Table 1. Consort 2010 Flow Diagram of groups



cal effect of TA is to reduce blood loss and administration of blood products after CPB [11]. There is a debate on dosing of TA and an increased incidence of seizures with a total dose of more than one gram has been reported. In general, while the total intravenous dose of TA ranges between one gram to 20 gram, the total duration of administration is a period between 20 min to 12 hours [12].

In this study, we hypothetized to compare the effects of CPB priming on osmolality, fluid balance, hemostatic variables and postoperative blood loss in four patient groups having RS or HES 6% 130/0.4 as a prime solution in addition to the presence or absence of administration of tranexamic acid during surgery.

Methods

Patients

From a total of 149 patients, 132 patients undergoing elective coronary artery bypass grafting (CABG) with cardiopulmonary bypass (CPB) were included into a prospective, randomized clinical trial study. Seventeen patients

Table 2. CONSORT 2010 checklist of information

Section/Topic	Item No	Checklist item	Reported Page No
Title and abstract			
	1a	Identification as a randomised trial in the title	4
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	4
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4, 5
	2b	Specific objectives or hypotheses	3-5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5, 9
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	5
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	4, 9
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	9
Sample size	7a	How sample size was determined	10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	4
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	4
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	4, 20
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	4, 20
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	4
	11b	If relevant, description of the similarity of interventions	4
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	4
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	4

Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	4
	13b	For each group, losses and exclusions after randomisation, together with reasons	4
Recruitment	14a	Dates defining the periods of recruitment and follow-up	4
	14b	Why the trial ended or was stopped	4
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	4
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	4
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	9
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	9
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	4-6
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	4
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	13
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	4
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	4
Other information			
Registration	23	Registration number and name of trial registry	
Protocol	24	Where the full trial protocol can be accessed, if available	4
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	1

Table 3. The demographic data and the preoperative characteristics of four groups

	Group RS-TA (n=34)	Group RS-noTA (n=32)	Group HES-TA (n=35)	Group HES-noTA (n=31)	P*
Age	60.1 ± 9.2	62.5 ± 9.6	61.8 ± 7.9	63.2 ± 11.4	0.218
Gender (M/F)* (n,%)	15/19	7/25	18/15	10/23	0.312
Height (cm)	163.2 ± 11.9	164 ± 9.3	163.2 ± 11.9	164 ± 9.3	0.518
Weight (kg)	77.5 ± 13	79.1 ± 19.8	77.5 ± 13	79.1 ± 19.8	0.220
Euroscore	5.7 ± 2.3	6.2 ± 2.3	5.7 ± 2.3	6.2 ± 2.3	0.832
Preoperative EF* (%)	35.0 (20-50)	38 (25-50)	35.0 (20-50)	38 (25-50)	0.781
Number of vessels	3.0 (1.0-5.0)	3.0 (1.0-5.0)	3.0 (1.0-5.0)	3.0 (1.05.0)	0.935
Preoperative risk factors for CAD*					
Diabetes mellitus	8 (23.5)	11 (24.2)	9 (26.5)	2 (6.5)	0.062
Hypertension	20 (58.8)	12 (37.5)	12 (34.3)	12 (38.7)	0.159
COPD	9 (26.5)	6 (18.8)	6 (17.1)	5 (16.1)	0.706
Use of smoke	9 (26.5)	6 (18.8)	8 (22.9)	9 (29)	0.791
Obesity	4 (11.8)	1 (3.1)	3 (8.6)	4 (12.9)	0.525
Hypercholesterolemia	7 (20.6)	8 (25)	10 (28.6)	13 (41.9)	0.267

*P<0.05: statistical significance; M ± SD: mean and standard deviation; M/F: male/female; n, %: number, percentage; EF: ejection fraction; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease.

refused to participate into the study. The approval of the Hospital Ethical Commitee and informed consent of the patients were obtained prior to enrollment of the patients into the study.

Study population

The patients were randomized into four groups depending on sealed envelope method that provides a group number to each specific patient. The observers who collect the data were blinded to the protocol. An information of the method was not provided to the observers. Caregivers (nurses and doctors) were not blinded, but they did not participate in data collection or interpretation. Thus, the study protocol is considered single-blinded, masked to observers.

From 159 patients, 27 were excluded as 16 of them did not meet the inclusion criteria and 11 of them declined to participate. A total of 132 patients were randomized into four groups. All patients received allocated intervention. A consort diagram is presented in **Tables 1** and **2**.

The patients randomly assigned to four different groups depending on the use of either one of a prime solution with or without the use of intravenous TA and these include; 1500 ml of RS or 10 ml/kg of 6% HES in addition to RS to have a total of 1500 ml as a priming solution of the CPB circuit together with or without TA during surgery.

Inclusion and exclusion criterias.

Inclusion criterias include; 18 to 75 years of age, body mass index between 25 and 31, with normal ejection fraction (≥50%), initial hematocrit value within the boundaries of the normal for adult male and female patients (31 to 40% for women and 34 to 45% for men).

Exclusion criterias include; repeat cardiac surgery, emergent surgery, preoperative coagulation disorder, preoperative use of clopidogrel, coumarin anticoagulants, heparin, or acetylsalisylic acid within the previous 5 days before operation, preoperative congestive heart failure, ejection fraction <49%, preoperative renal dysfunction (serum creatinine > 1.3 mg/dL), chronic oliguria/anuria requiring dialysis, preoperative hepatic dysfunction (serum aspartate/alanine amino transferase > 40 U/L), preoperative electrolyte imbalance, history of pancreatitis or current corticosteroid treatment.

The groups were divided into four groups depending on the use of tranexamic acid or not. The extracorporeal circuit was primed with Ringer's solution at a dose of (20 mL/kg), mannitol 20% at a dose of 0.5 g/kg, sodium bicar-

Table 4. The comparison of operative and postoperative parameters in four groups

	Group RS-TA (n=34)	Group RS-noTA (n=32)	Group HES-TA (n=35)	Group HES-noTA (n=31)	P*
ACC* (minute)	71.5 (45.0-104.0)	66.0 (40.0-123.0)	71.5 (45.0-104.0)	66.0 (40.0-123.0)	0.218
CPB* (minute)	82.0 (60.0-166.0)	66.0 (42.0-156.0)	82.0 (60.0-166.0)	66.0 (42.0-156.0)	0.312
Postoperative EF* (%)	55.0 (50.0-65.0)	50.0 (50.0-65.0)	55.0 (50.0-65.0)	50.0 (50.0-65.0)	0.518
Extubation time (hours)	8.0 (3.0-17.0)	10 (4.0-29.0)	8.0 (3.0-17.0)	10 (4.0-29.0)	0.220
Intensive care unit stay (day)	2.0 (1.0-9.0)	2.0 (1.0-12.0)	2.0 (1.0-9.0)	2.0 (1.0-12.0)	0.832
Estimated blood loss (postoperative 24 hour) (ml)	1100 (700-1350)	1200 (850-1650)	900 (700-1100)	1100 (750-1500)	0.023*
Prime solution amount (ml)	1500	1500	1500	1500	NS
Fluid added to the pump during CPB (ml)	1300 (600-2200)	1100 (500-2000)	900 (650-1800)	1000 (550-2100)	0.019*
Net balance at the pump outlet (ml)	1500 ± 260	1700 ± 350	600 ± 150	700 ± 200	0.0001*
Intraoperative PRBC transfusion (units)	0 (0-2)	1 (0-2)	0 (0-2)	1 (0-2)	0.159
Postoperative 24 hour PRBC transfusion (units)	1 (0-6)	1 (0-8)	1 (0-7)	1 (0-8)	0.003*
Intraoperative FFP transfusion (units)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	0.791
Postoperative 24 hour FFP transfusion (units)	2 (0-5)	2 (0-5)	2 (0-5)	2 (0-5)	0.525
Postoperative 24 hour balance (ml)	410 (-500-2900)	350 (-600-2600)	450 (-700-1800)	400 (-800-2000)	0.267
Postoperative 24 hour chest tube drainage (ml)	350 (100-1200)	400 (50-1350)	300 (150-1250)	400 (100-1400)	0.001*

*$P<0.05$ statistical significance, Mann Whitney U test for not equally distributed data (median (range; minimum-maximum) and independent student's t test for equally distributed data (mean ± standard deviation); ACC: aortic cross-clamp time; CPB: cardiopulmonary bypass time; EF: ejection fraction; FFP: fresh frozen plasma; PRBC: packed red blood cell.

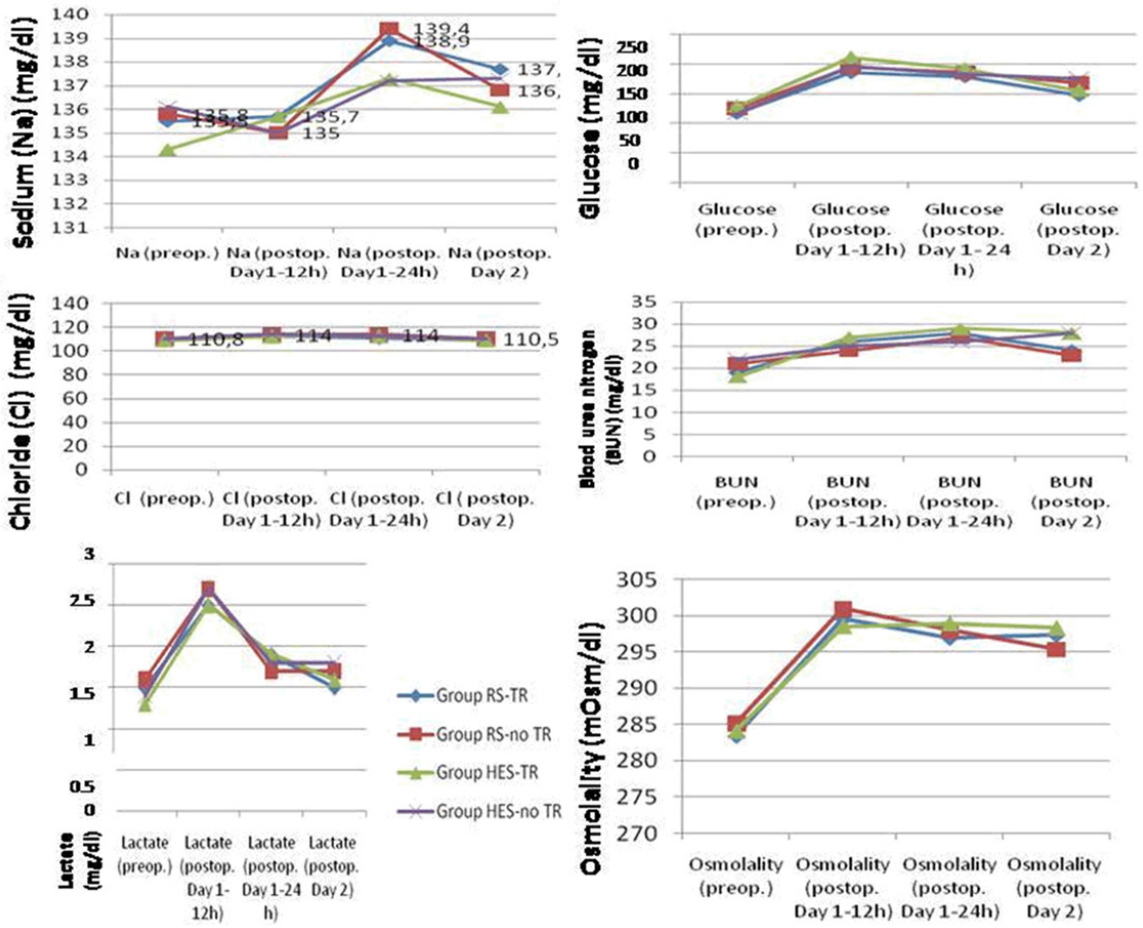


Figure 1. The comparison of serum creatinine, electrolyte, osmolality and lactate levels between Ringer and HES groups with or without tranexamic acid preoperatively and postoperatively.

bonate 7.5% 1 ml/kg, 150 IU/kg heparin (Group RS-TA, n=34 and Group RS-noTA, n=32). The priming solution consisted of 6% 130/0.4 HES solution at a dose of 10 ml/kg (Voluven® %, Fresenius Kabi, Bad Homburg, Germany) + Ringer solution at a dose of 10 ml/ kg, mannitol 20% at a dose of 0.5 g/kg, sodium bicarbonate 7.5% 1 ml/kg, 150 IU/kg heparin (Group HES-TA, n=35 and Group HES-noTA, n=31). In TA groups, TA was given as an intravenous loading dose of 10 mg/kg, before the skin incision, followed by a continuous infusion of 1 mg/kg/h for five hours. The other two groups received a bolus of normal saline solution and a continuous infusion of normal saline for five hours.

Anesthesia procedure

Routine monitoring for cardiac anesthesia was established prior to induction of anesthesia. Anesthesia induction was administered to all patients with intravenous doses of midazolam (Roche, Basel, Switzerland) at a dose of 0.2 mg/kg, fentanyl (Janssen-Cilag, Beerse, Belgium) at a dose of 5 to 10 μg/kg and rocuronium bromide (Organon, Netherlands) at a dose of 0.1 mg/kg were administered. For maintenance, all patients received sevoflurane at an end-tidal concentration of 0.5% to 2% and intravenous maintanance doses of midazolam and fentanyl every half an hour.

Surgical procedure

Median sternotomy was performed on all patients. Before the beginning of the CPB, heparin at a dose of 300 IU/kg plus additional doses if necessary was administered intravenously to keep the ACT (Active Clotting Time) greater than 450 second. Mild hypothermia at

Table 5. The comparison of postoperative complications between Ringer and HES groups

Parameters	Ringer Group (n=66)	HES Group (n=66)	*P**
Exploration for hemorrhage (n%)*	3 (4.5)	2 (3.0)	0.376
Atrial arrhythmia	4 (6.3)	7 (10.6)	0.532
Ventricular arrhytmia	4 (6.1)	2 (3.0)	0.680
Temporary neurologic deficit	2 (3)	3 (4.5)	0.897
Permanent neurologic deficit	0	1 (1.5)	0.896
Renal dysfunction*	5 (7.6)	7 (10.6)	0.613
Seizure (tonic-clonic)	0	1 (1.5)	0.896
Reintubation	0	2 (3)	0.496
Prolonged mechanical ventilation(>48 h)	3 (4.5)	7 (10.8)	0.206
Pneumonia	1 (1.5)	2 (3.0)	0.789

**P*<0.05: statistically significant; n (%): number, percentage; median (range; minimum-maximum); IABP: intra-aortic baloon pump; renal dysfunction is defined when peak creatinine value was 1.5 or greater times the preoperative value; ICU: intensive care unit; AF: atrial fibrillation.

a level of 28 to 32°C was established during all cases. Antegrade and retrograde blood cardioplegia were supplied to each patient through appropriate cannulation. Before CPB, each patient received Ringer's lactate solution at a dose of 10 ml/hr. In Group RS-TA and RS-noTA; the bypass circuit was primed with Ringer's lactate solution 20 ml/kg, sodium bicarbonate 7.5% 1 ml/kg, and heparin 150 IU/kg. Mannitol 20% at a dose of 0.5 g/kg was added to the CPB prime solution. In Group HES-TA and HES-noTA; the use of 6% hydroxyethyl starch 130/0.4 (Voluven) (Fresenius Kabi, Bad Hamburg, Germany) was restricted at a dose of 10 ml/kg during CPB. In all patients HES solution was not used during other parts of the operative procedure or in the postoperative period.

Central venous pressure (CVP) was maintained between 8 and 14 mmHg by infusion of ringer of isotonic sodium chloride solutions after CPB. Cardiopulmonary bypass circulation was provided by a roller Biomedicus pump (Biomedicus, Germany) in all patients. Systemic blood flow during CPB was maintained between 2 to 2.5 l/min/m^2 and systemic blood pressure was kept between 50 to 80 mmHg. Arterial blood gas values were followed every 60 minutes to keep the levels as; PO_2 greater than 250 mmHg, PCO_2 between 35 to 45 mmHg, pH between 7.35 to 7.40, hematocrit between 22 to 28%, blood glucose between 100 to 180 mg/dl. After rewarming with a 37°C maximal heat-exchanger temperature, CPB was discontinued. Intraoperative ventricular tachyarrhythmias were treated with internal cardioversion or lidocaine at a dose of 1 to 1.5 mg/kg. Reversal of heparin was achieved with 1.0 to 1.5 mg protamine per 100 IU heparin. Inotropic support, initially with dobutamine (5-10 μg/kg/min) then if necessary with addition of adrenaline (0.02-0.15 μg/kg/min) and/or noradrenaline (0.2 to 1.3 μg/kg/min) was commenced if the mean arterial pressure (MAP) was <65 mm Hg as well as depending on other clinical monitoring parameters such as CVP >14 mmHg, heart rate <70 beats/minute. Dopamine at a dose of 2 to 3 μg/kg/min was provided at the end of CPB if the urine output was less than 2 ml/kg in every half an hour during surgery. Intravenous bolus dose of furosemide at a dose of 0.2 mg/kg was added and repeated if necessary. After surgery, the hematocrit was maintained at approximately 30% by giving packed red blood cells (PRBCs) or Ringer's lactate solution in both group of patients. If postoperative bleeding through the mediastinal tubes exceeded 200 mL/h, ACT (activated clotting time), platelet count, activated partial thromboplastin time and prothrombin time were determined. If the ACT was prolonged more than 10 s as compared with the value obtained five minutes after protamine administration, a supplemental dose of protamine of either 25 mg or 50 mg was given. If the platelet count decreased to more than 100 to 109/mm^3, 8 units of platelets were transfused and repeated if necessary. If the activated partial thromboplastin time or prothrombin time was prolonged more than 1.5 times the preoperative values, 2 units of fresh frozen plasma (FFP) were transfused and repeated if necessary.

All patients were transferred to the intensive care unit (ICU) where their lungs were mechanically ventilated. Tracheal extubation was performed when hemodynamics were stable, temperature was 36°C, and there was adequate

Table 6. The comparison of hemostasis related parameters between four groups

Parameters	Group RS-TA (n=34)	Group RS-noTA (n=32)	Group HES-TA (n=35)	Group HES-noTA (n=31)	P*
Hgb (preop.) (mg dL^{-1})	12.5 ± 1.9	12.4 ± 1.6	12.6 ± 1.8	11.6 ± 1.6	0.330
Hgb (postop. day 1-12 h)	10.9 ± 1.4	10.3 ± 1.5	11.3 ± 1.5	10.5 ± 1.6	0.041*
Hgb (postop. day 1-24 h)	10.1 ± 1.5	10.4 ± 1.6	10.9 ± 1.2	10.5 ± 1.5	0.034*
*P**	0.001*	0.001*	0.001*	0.001*	
Hct (preop.) (%)	38.7 ± 5.5	37.8 ± 5.6	37.4 ± 5.2	38.2 ± 5.3	0.184
Hct (postop. day 1-12 h)	32.8 ± 4.2	31.4 ± 3.2	33.4 ± 3.8	31.9 ± 3.9	0.004*
Hct (postop. day 1-24 h)	32.6 ± 3.6	32.8 ± 3.4	34.3± 3.3	32.9 ± 3.8	0.001*
*P**	0.001*	0.001*	0.001*	0.001*	
Platelet count (preop.) (x10^9/mm^3)	236 (108-459)	212 (98-398)	192 (98-398)	212 (110-398)	0.413
Platelet count (postop. day 1-12 h)	154 (105-270)	159 (129-308)	160 (129-278)	164 (141-269)	0.233
Platelet count (postop. day 1-24 h)	153 (105-310)	162 (84-293)	157 (91-259)	162 (84-313)	0.478
*P**	0.001*	0.001*	0.001*	0.001*	

**P*<0.05 statistical significance; Hgb: Hemoglobin; Hct: Hematocrit.

spontaneous breathing (PaO_2 (partial arterial oxygen saturation) greater than 80 mmHg with FiO_2 (Fraction of inspired oxygen) equals to 0.4 and breathing frequency of 14/min). After surgery, blood products including PRBCs were given when the hemoglobin was <9 g/dL, hematocrit level was <25%. FFP transfusion was considered when there was excessive bleeding (>400 mL/h) in the presence of an activated partial thromboplastin time (APTT) >60s. Platelet concentrates were given when bleeding continued (>400 ml/h) despite a normal ACT value. The decision for re-exploration for hemorrhage was made when 200 ml/h of drainage was documented on two consecutive hours despite measures taken or more than 300 ml/h drainage. FFP and platelet concentrates were administered in cases of documented postoperative coagulation abnormalities (international normalized ratio (INR) > 1.5, prothrombin time (PT) >12s, APTT >60 s and platelet count < 80.000/mm^3) or suspected postoperative platelet dysfunction and factor deficiency. "Estimated blood loss" was defined as the sum of objective losses, e.g., via drainage and swabs plus clinically estimated additional losses.

Primary and secondary end points

As a primary end point, we analyzed and compared the values of hemoglobin, hematocrit, platelet, protrombin time, activated protrombin time, international normalized ratio (INR), blood urea nitrogen (BUN), creatinine, sodium, potassium, chloride, lactate, pH, base excess between four groups. Also, estimated blood loss, drainage amount, transfused blood products and coagulation variables before surgery, 12, 24 and 48 hour after surgery were compared between groups.

The postoperative complications were evaluated between Ringer and HES group of patients (n=66 of each group). Secondary end point was the effect of priming solution on clinical outcomes such as; 1-Aortic cross-clamp time, 2-Cardiopulmonary bypass time, 3-The use of inotropic support, 4-Intra-aortic balloon pump, 5-Prolonged mechanical ventilation, 6-Development of pneumonia, 7-Perioperative myocardial infarction, 8-Cerebrovascular event (stroke, transient ischemic attack), seizure, 9-Atrial fibrillation and other rythm disturbances, 10-Need for renal replacement therapy (RRT), 11-Reoperation secondary to bleeding, 12-Intensive care unit stay, 13-Hospital stay and, 14-Thirty-day mortality [12, 13]. The need for RRT is defined as; 1-Urine output was less than 100 mL within the last 8 hours, 2-No response to 50 mg intravenous dose of furosemide, 3-Urine sodium concentration greater than 40 mEq/L before administration of furosemide, 4-Blood urea nitrogen level >50 mg/dl 5-Additional presence of one or more of the following factors such as; a- An increase in serum creatinine level >50% from preoperative value, b-Presence of metabolic acidosis, c-Presence of hypervolemia, d-Presence of hyperkalemia (potassium ion level >5 mEq/L) [13]. Blood samples were obtained before heparinization, 12, 24 and 48 hour after CPB. Samples for

coagulation factor analyses were immediately cooled on ice and plasma was stored at -70°C. The hemoglobin and platelet counts in the whole blood were determined by using a Cell-Dyn 610 hematology analyzer (Sequoia-Turner Corp., Mountain View, CA, USA).

Statistical analysis

The statistical analyses were performed using SPSS software for Windows version 17.0 (Statistical Package for the Social Sciences Inc, Chicago, IL, USA). The continuous variables were expressed as median or mean values ± standard deviation (SD). The categorical variables were expressed as number and percentages. The data of the four groups were compared using analysis of variance and Kruskal Wallis tests. The statistical significance was shown as P<0.05. Depending on previous studies; a sample size including 30 patients per group was sufficient to detect a 300 ml difference in chest tube drainage between groups (with a 90% power and a significance level of 0.05) [4, 14]. Hemodynamic and laboratory data were compared using a two-way analysis of variance for repeated measurements followed by a post-hoc Tukey test.

Results

There were no differences in regard to demographics and preoperative risk factor distribution between groups (P>0.05) (**Table 3**). The intraoperative and postoperative data are presented in **Table 4**. For Group HES with TA, when compared to other groups, estimated postoperative 24 hour blood loss, postoperative 24 hour transfused unit of packed red blood cell and postoperative 24 hour chest tube drainage loss were less than other groups (P=0.023, P=0.003, P=0.001; respectively). Regarding fluid added to the pump during CPB and net balance at the pump outlet, the Group HES with or without TA showed similar values (P>0.05) however, these group values were significantly lower than Group Ringer with or without TA (P=0.019, P=0.0001; respectively) (**Table 4**). In comparison of the four groups, there was no significant differences regarding serum creatinine values preoperatively, (1.0 (0.6-1.6 vs 1.0 (0.5-1.6) vs 1.3 (0.6-1.8) vs 1.1 (0.5-2.1) mg/dl, P=0.046), postoperative day one (12 hour) (1.1 (0.6-2.6) vs 1.25 (0.5-2.5) vs 1.3 (0.6-2.9) vs 1.65 (0.5-3.1) mg/dl, P=0.327), postoperative day one (24 hour); (1.0 (0.5-2.4) vs 1.15 (0.40-2.6) vs 1.3 (0.5-2.7) vs 1.4 (0.40-2.9) mg/dl, P=0.511) and postoperative day two (48 hour) levels; (1.1 (0.6-2.4) vs 1.0 (0.5-2.7) vs 1.1 (0.6-2.3) vs 1.0 (0.5-2.8) mg/dl, P=0.651). However, within group evaluations revealed that, in all groups, serum creatinine values differ significantly at different time points (P<0.001). The comparison of sodium, chloride, blood urea nitrogen, osmolality and lactate levels between groups revealed no significant differences (P>0.05) (**Figure 1**). The postoperative complications between Ringer and HES group of patients ashowed no significant differences (P >0.05) (**Table 5**). For patients in either Ringer or HES with TA, when compared to groups without TA, hemoglobin, hematocrit on postoperative day one at 12 and 24 hours showed higher values in comparison to groups without TA (P=0.041, P=0.034, P=0.004, P=0.001; respectively). The other hemostasis parameters were similar between groups (P>0.05) (**Table 6**).

Discussion

Our findings demonstrate that the use of 6% HES 130/0.4 at a dose of 10 ml/kg during CPB is not associated with clinical signs of bleeding depending on; 1-Estimated blood loss, 2-Amount of blood product transfusion, 3-Amount of 24 hour chest tube drainage, 4-Coagulation related labaratory data including PT, PTT and INR. Our main finding is that; in comparison between HES and Ringer with or without TA groups, the values of estimated blood loss, postoperative 24 hour chest tube drainage and transfused unit of PRBCs were less in Group HES with TA than other groups.

Recently, in a total of 200 patients Gurbuz and his colleagues demonstrated similar findings showing that 6% hydroxyethyl starch 130/0.4 when used as a prime solution did not adversely affect postoperative outcomes following coronary bypass surgery [15]. In another study by Choi et al., HES and albumin were used as priming solutions during CPB and this study did not show difference on coagulation variables, postoperative blood loss, transfusion requirements and inflammatory response were demonstrated between groups [16-18]. In our study, we showed that the changes in coagulation vari-

ables in groups were similar between groups however, HES with TA provides less amount of estimated blood loss, postoperative 24 hour chest tube drainage and transfused unit of PRBCs in comparison to the other groups.

TA was recommended to diminish blood loss postoperatively during cardiac surgery [19]. In our study, we evaluated the effects of TA in group of patients that had either Ringer or HES in the prime solution. The results show that; in both group of patients TA decreased estimated blood loss, 24 hour drainage postoperatively with an increase of hemoglobin and hematocrit values in 12 and 24 hour time periods postoperatively. In recent studies, it has been pointed out clearly that TA reduces postoperative blood loss after cardiac surgery however, the most important issue is to decide on the appropriate dose of tranexamic acid to prevent postoperative seizure related disorders [11, 12]. For this purpose, we used a low dose of tranexamic acid in our study and observed no tonic clonic seizures in our patients. Our finding is similar to other reported findings in the literature that tranexamic acid related seizures are observed in patients that received higher total doses of tranexamic acid [12].

Previously, it has been shown that HES 120 and HES 400 when used as the main component of the CPB prime, impair hemostasis after cardiac surgery by decreased clot formation rate, the strength of the fibrin clot in the thromboelastographic studies [20]. Recently, it has been demonstrated that a short time infusion (70-240 min) of HES solutions at a dose of 15 ml/kg (either 6% HES 200/0.5 or 6% HES 130/0.4) after cardiac surgery produces impairment in fibrin formation and clot strength in thromboelastometry tracings in comparison to 4% human albumin solution [5]. However, in a recent meta-analysis, the use of HES as a prime solution did not increase the risk of complications, reoperation and mortality [2]. Recently, it was shown that although the addition of small amounts of HES 130/0.4 or gelatin into prime solutions impaired clot strength after cardiac surgery in a dose-dependent fashion, neither colloid increased blood loss [21].

Regarding adverse effects of HES 130/0.4 on renal functions, a previous study by Tiryakioglu et al showed no unfavorable effects of HES on renal functions and we found similar results in our study [3]. Also, in previous studies, in cardiac and aortic surgery patients with or without renal dysfunction, HES 6% 130/0.4 showed no increase in serum creatinine values or increased incidence of RRT [22, 23]. However, a recent study showed that gelatin impairs renal function more than HES 130/0.4 solution when used as a prime solution [7].

Regarding effects of HES 130/0.4 on platelet function, a better preserved platelet function is found in comparison to a group of patients receiving other colloids as a prime solution [18-20]. In addition to albumin, gelatins impair blood coagulation in vitro and influence platelet aggregation after cardiac surgery [7]. Our observation in this study is that there is no significant differences for the level of serum platelet concentration in comparison between groups of Ringer's and HES with or without the use of TA. This finding is similar to the reported findings of previous studies [3, 15, 20].

It is important to decide on the optimal quantity of hydroxyethyl starch in the cardiopulmonary bypass prime and this has been related to the effects of HES on oncotic pressure by diminishing the transition of the fluid to the interstitium [16, 17, 24, 25]. In our study, the net balance at the pump outlet was higher in Ringer groups with or without TA in comparison to HES groups with or without TA. The extubation times and intensive care durations were compared in the postoperativ complications section and these showed no significant differences in comparison between Group Ringer and Group HES. Also in previous studies, differences in osmolality between colloid and crystalloid solutions were investigated however, as there is addition of Ringer's solution in preparation of our prime solution, a significant difference between our study groups was not demonstrated [24, 26]. In a recent meta-analysis it has been summarized that as crystalloids produced a more significant positive fluid balance, their use as a single prime solution is not recommended [18].

Although, there is Ringer's solution added to the prime solution, we did not observe differences in lactate concentrations between groups and this finding is similar to the previous studies [25]. In a recent study by Damar et al., a difference in lactate values were not demonstrated however, they observed decreasing

demand for inotropic support and shortening time to extubation and duration of ICU stay in HES 130/0.4 group of patients in comparison to Ringer solution group of patients [27]. In our study, we were not able to show a difference regarding extubation times and ICU stay.

The limitations of this study include; the study groups are relatively small although it was calculated to be sufficient to detect difference between groups for postoperative 24 hour chest tube drainage. Although there are several factors that can effect perioperative hemostasis and coagulation, these factors may not be eliminated prior to the enrollment into the study.

Conclusions

This study shows that in patients undergoing CABG with CPB, the choice of the priming solution for the CPB circuit during CABG can affect hemostasis however, no effect on renal function is demonstrated in patients receiving either only Ringer's solution or HES 130/0.4 in addition to Ringer's solution as priming fluids with or without addition of TA. Overall, it is remarkable to observe that the addition of TA in either only Ringer's or both Ringer and HES 130/0.4 added prime solutions causes a decrease in estimated blood loss and 24 hour chest tube drainage after operation.

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Disclosure of conflict of interest

None.

Abbreviations

ACC, aortic cross-clamp time; AF, atrial fibrillation; ACT, activated clotting time; BUN, blood urea nitrogen; PT, protrombin time; APTT, activated protrombin time; INR, international normalized ratio; RRT, renal replacement therapy; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CPB, Cardiopulmonary bypass; CVP, central venous pressure; CABG, coronary artery bypass grafting; EF, ejection fraction; FFP, fresh frozen plasma; HES, hydroxyethyl starch; Hgb, hemoglobin; Hct, hematocrit; IABP, intra-aortic baloon pump; MAP, mean arterial pressure; ICU, intensive care unit; PRBC, packed red blood cell; RS, ringer's solution; S.D., standard deviation; TA, tranexamic acid.

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