An evaluation of 6% hydroxyethyl starch 130/0.4 use in fluid therapy following coronary artery surgery

Koroner arter cerrahisi sonrası sıvı tedavisinde %6 hidroksietil nişasta 130/0.4 kullanımının değerlendirilmesi

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Background: This study aims to compare the effects of 6% hydroxyethylstarch 130/0.4 with a commonly used balanced electrolyte solution in patients undergoing coronary artery bypass surgery.

Methods: One hundred and fifty seven patients who underwent coronary artery bypass surgery were randomized into two groups. The first group received 6% hydroxyethyl starch 130/0.4, while the second group received a commonly used balanced electrolyte solution. The effects of both solutions on postoperative outcomes were studied.

Results: Six percent hydroxyethyl starch 130/0.4 did not increase postoperative blood loss and the amount of blood and blood products (p>0.05). No adverse effect was observed on renal and pulmonary functions. Intubation time, intensive care unit stay and postoperative duration of hospital stay did not differ between the groups (p>0.05). Hydroxyethyl starch had no effect on the occurrence of postoperative atrial fibrillation (p>0.05).

Conclusion: Six percent hyroxyethyl starch 130/0.4 may be considered safe in fluid therapy following coronary bypass surgery.

Key words: Cardiac surgery; crystalloid solutions; hydroxyethyl starch.

Amaç: Bu çalışmada koroner arter baypas cerrahisi yapılan hastalarda %6 hidroksietil nişasta 130/0.4'ün etkileri, sıklıkla kullanılan dengeli bir elektrolit solüsyonu ile karşılaştırıldı.

Çalışma planı: Koroner arter baypas cerrahisi yapılan 157 hasta iki gruba randomize edildi. İlk gruba %6 hidroksietil nişasta 130/0.4, ikinci gruba ise sıklıkla kullanılmakta olan dengeli bir elektrolit solüsyonu verildi. Her iki solüsyonun da ameliyat sonrası sonuçlar üzerine olan etkileri araştırıldı.

Bulgular: Yüze altı hidroksietil nişasta 130/0.4 ameliyat sonrası kan kaybı ve kullanılan kan ve kan ürünü miktarını artırmadı (p>0.05). Renal ve pulmoner fonksiyonlar üzerine olumsuz etkisi saptanmadı. Entübasyon zamanı, yoğun bakım kalış süresi ve ameliyat sonrası hastane kalış süresi açısından gruplar arasında fark görülmedi (p>0.05). Hidroksietil nişastanın ameliyat sonrası atriyal fibrilasyon oluşumu üzerine herhangi bir etkisi saptanmadı (p>0.05).

Sonuç: Yüze altı hidroksietil nişasta 130/0.4 koroner baypas cerrahisi sonrası sıvı tedavisinde güvenli olarak kullanılabilir.

Anahtar sözcükler: Kalp cerrahisi; kristalloid solüsyonlar; hidroksietil nişasta.

Postoperative fluid therapy following cardiac surgery is still a matter of debate in clinical settings. The amount of fluid administered is influenced by the presence of hypovolemia, the underlying cardiac and non-cardiac diseases, the preoperative status of the patient, and the cardiac surgical procedure itself. Cardiopulmonary bypass (CPB) is the major factor related to the surgery since it causes derangements in capillary permeability as a consequence of the systemic inflammatory response. Regional and systemic vasodilation, which occurs due to the production of vasoactive amines, together with hemodilution leads to intercompartmental shifts.[1,2] These unwanted major fluid shifts may then lead to hypotension.[3] In addition, anesthetics, perioperative bleeding, and postoperative diuresis along with increased insensible loss cause a hypovolemic state.[4] Replacement is the main goal of fluid therapy, but there is still an ongoing debate between the choice of 'colloid-crystalloid' and 'colloid-colloid' as the fluid preference.[4,5]

The aim of this study was to compare the effects of 6% hydroxyethyl starch (HES) 130/0.4 with a crystalloid (balanced multi-electrolyte solution) with regard to postoperative bleeding, blood transfusion requirements, and renal and pulmonary functions and to document the risks related to the administration of HES in patients with coronary artery bypass grafting (CABG). We hypothesized that fluid resuscitation with this colloid solution would be considered safe and effective.

PATIENTS AND METHODS

A prospective, controlled, randomized study was carried out. The study was approved by the local ethics committee, and written informed consent was obtained from every patient. Between July 2011 and December 2011, 226 CABG operations were performed, either in isolation or with additional procedures. Off-pump procedures and CABG concomitant with other procedures, such as valvular interventions, left ventricular aneurysm repair, and the Maze procedure, were discarded, leaving 178 isolated CABG patients in the study. All patients were operated on by the same surgeon.

The only inclusion criterion was that the surgery had to be an isolated on-pump CABG procedure. Both genders were accepted, and there were no age or weight restrictions. Exclusion criteria were the following: repeat cardiac surgery, emergent surgery, preoperative coagulation disorder, preoperative clopidogrel use, preoperative congestive heart failure, preoperative renal dysfunction (serum creatinine >1.3 mg/dl), preoperative hepatic dysfunction (serum aspartate/alanine amino

transferase >40U/l), preoperative electrolyte imbalance, a history of pancreatitis, or a known hypersensitivity to HES. After the inclusion and exclusion criteria were employed, 157 patients remained in the study (Figure 1). The patients were then randomized by giving each patient a number in chronological order beginning with 1. The odd-numbered patients (n=79) were administered 6% HES 130/0.4 in 0.9% sodium chloride (Voluven® %, Fresenius Kabi, Bad Homburg, Germany) and the even-numbered patients (n=78) were administered a balanced multi-electrolyte solution (Isolyte-M®, Eczacıbaşı-Baxter Hospital Supply Inc., İstanbul, Turkey) which contained dextrose monohydrate, 40 mEq/l sodium, 40 mEq/l chloride, 35 mEq/l potassium, 15 mEq/l phosphate, 20 mEq/l acetate; 400 mOsm/l, 170 kCal/l).

The participants were evaluated preoperatively, and inclusion and exclusion criteria were applied by the same physician. If the patients were deemed suitable, they were numbered chronologically from the beginning of the study by the same physician in the operating room. They were then enrolled by this same surgeon and assigned the intervention. A blind study was not possible since the same surgical team also performed the follow-up and performance evaluation. The same type of fluid administered to the patients in the first 24 hours was given until discharge, and there were no crossovers between the groups.

Preoperative acetylsalicylic acid 100 mg/day was given to all patients prior to the day of surgery, and all patients were also premedicated with 10 mg of oral diazepam. Anesthesia was induced with etomidate 2 mg/kg, fentanyl 1μg/kg and vecuronium 1 mg/kg, and isofluorane 1 MAC was used for anesthesia maintainance. In addition, intraoperative arterial and central venous pressure monitorization also took place.

The CPB circuit was primed with 1500 ml of the Isolyte-S® (Eczacıbaşı-Baxter Hospital Supply Inc., İstanbul, Turkey), and heparin (5000 units) was added. After anticoagulation with heparin (300 U/kg), CPB was established using a roller pump with a membrane oxygenator (Dideco Compactflo Evo, Sorin Group Italia S.R.L., Mirandola, Italy). The average flow rate varied from 2.3 to 2.4 l/min/m². Surgery was performed under mild hypothermia (33°C), and the mean arterial pressure was kept between 45 to 70 mmHg. All patients were rewarmed to 37 °C (nasopharyngeal temperature) before weaning from CPB. The heparin was then neutralized with 1:1 protamine sulfate.

After aortic cross-clamping, 1000 ml of cold (4-8 °C) blood cardioplegia (25 mEq/l potassium) was administered, and 500 ml repeat doses were given
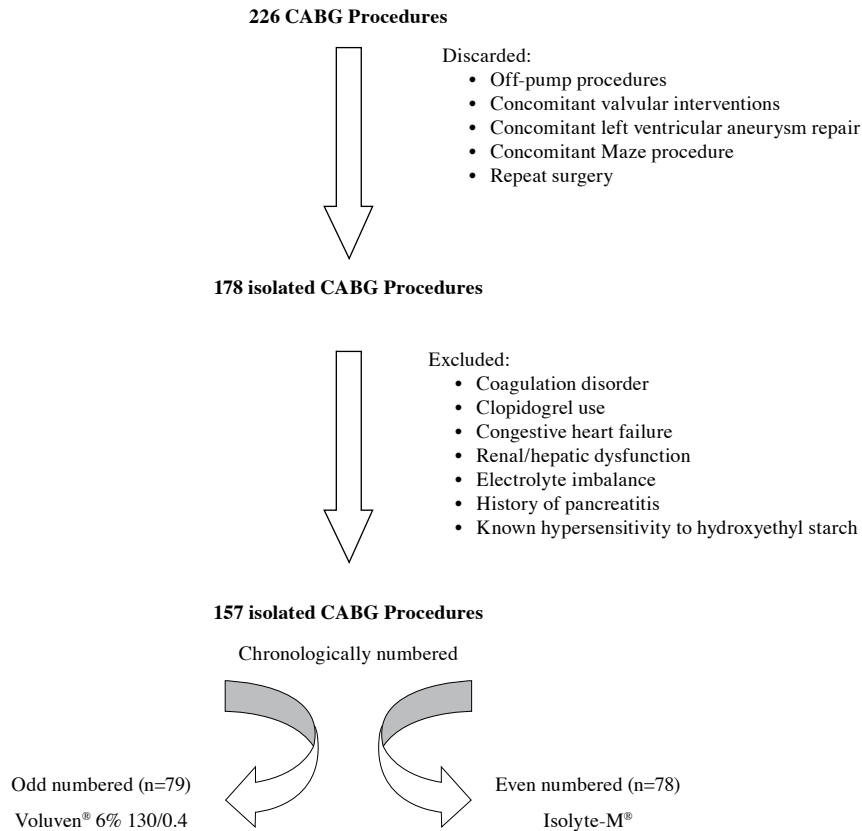
226 CABG Procedures

Discarded:
- Off-pump procedures
- Concomitant valvular interventions
- Concomitant left ventricular aneurysm repair
- Concomitant Maze procedure
- Repeat surgery

178 isolated CABG Procedures

Excluded:
- Coagulation disorder
- Clopidogrel use
- Congestive heart failure
- Renal/hepatic dysfunction
- Electrolyte imbalance
- History of pancreatitis
- Known hypersensitivity to hydroxyethyl starch

157 isolated CABG Procedures

Chronologically numbered

Odd numbered (n=79)

Voluven® 6% 130/0.4

Even numbered (n=78)

Isolyte-M®

Figure 1. Study design. CABG: Coronary artery bypass grafting.

every 15 to 20 minutes (antegrade and from venous bypass grafts; retrograde in cases of left main stenosis). Terminal warm blood cardioplegia (36-37 °C) was then given prior to aortic clamp release.

The operation room temperature was kept at 20-21 °C during the entire operation. Following surgery, the patients were taken to the intensive care unit (ICU) where they were intubated, and intravenous propofol (1-2 mg/kg/hour) and morphine (0.01-0.02 mg/kg/hour) were given for maintainance of analgesia and sedation.

Postoperative fluid infusion rates were adjusted according to hemodynamic measurements. Central venous pressure was maintained between 8-12 mmHg, and packed red blood cells (RBCs) were given if the hematocrit level fell below 25%. Fresh frozen plasma (FFP) and platelet concentrates (PCs) were administered in cases of newly documented postoperative coagulation abnormalities [international normalized ratio (INR) >1.5, activated partial thromboplastin time >60 seconds, and platelet count <80,000/mm^3] or when postoperative platelet dysfunction and factor deficiency were suspected.

The decision for re-exploration due to hemorrhage was made when 200 ml/hour of drainage was documented over two consecutive hours, despite measures taken to slow the drainage rate, or if there was more than 300 ml/hour of drainage.

The amount of fluid administered in the postoperative period was noted on an hourly basis. Furthermore, the postoperative total amount of blood loss, the number of used packed RBCs, FFP, and PCs, the mean time to extubation, ICU and postoperative hospital length of stay, and renal dysfunction (defined when the peak creatinine value was greater than or equal to 1.5 times the preoperative value) were documented. The occurence of atrial fibrillation (AF) was also studied.

Statistical analysis

Statistical analysis was performed using SPSS software for Windows version 17.0 (SPSS Inc, Chicago, Illinois, USA). Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables were expressed as numbers and percentages. Demographic characteristics and group outcomes were compared using an independent samples t-test for continuous variables, and a chi-square test and Fisher's exact test for categorical variables. Statistical significance was set as $p < 0.05$.

RESULTS

One hundred and fifty-seven patients were included in this study. Balanced crystalloid solution Isolyte-M® was used to treat 78 patients and the colloid solution Voluven® 6% was used to treat the other 79. The two treatment groups were comparable according to age, gender, and body surface area (kg/m²), and the demographic characteristics along with the preoperative and operative data of the patients are given in Table 1 and 2.

When postoperative variables for the two groups were compared (Table 3 and 4), the mean time to extubation, length of stay in the ICU, postoperative hospital length of stay, total amount of chest tube drainage, postoperative hemorrhage requiring exploration, and the mean numbers of FFP, packed RBC, and PC that were transfused were not statistically significant (p>0.05). No foci of bleeding were found in any of the re-explored cases. In the first 24 hours, the total amount of crystalloid solution administered (2542.2±502.9 ml) was lower than the colloid solution (2737.3±591.3 ml) (p<0.05). Following discharge, pericardial tube drainage was not performed for any of the patients.

Postoperative renal dysfunction was observed in three patients (3.8%) in the crystalloid group and five patients (6.3%) in the colloid group, but this difference was not statistically significant (p=0.719). Renal dysfunction requiring hemodialysis was not seen in either group, and all of the patients with this issue recovered fully.

No mortality was seen in the study, and no allergic reactions were observed during the study in the colloid group.

We also studied the incidence of postoperative AF and the effect of HES therapy on its occurence and found that nine patients (11.5%) in the crystalloid group and 13 (16.5%) in the colloid group developed postoperative AF (p=0.375). The left atrial diameters were comparable between the groups (3.6±0.5 cm for the colloid group and 3.62±0.4 cm for the crystalloid

Table 1. Comparison of the colloid and crystalloid groups by preoperative and intraoperative characteristics

Factor	Voluven® 6% group (n=79) Mean±SD	Isolyte-M® group (n=78) Mean±SD	p*
Age	62.1±7.9	61.8±10.5	0.844
Body surface area (kg/m²)	1.9±0.2	1.9±0.2	0.727
Left ventricular ejection fraction (%)	56.1±11.2	53.3±10.7	0.108
Cross-clamp time (min)	56.7±19.0	51.6±19.9	0.104
Euroscore (standard)	2.1±1.7	2.1±2.1	0.364
Cardiopulmonary bypass time (min)	82.7±28.4	78.1±29.3	0.322
Graft #	3.1±0.9	3.2±1.1	0.572

SD: Standard deviation; * Independent samples t-test.

Table 2. Comparison of the colloid and crystalloid groups by preoperative demographic characteristics

Factor	Voluven® 6% group (n=79)		Isolyte-M® group (n=78)		p**
	n	%	n	%	
Patient total	79	100	78	100	
Male gender	68	86.1	59	75.6	0.096
Current/ex-smoker	67	84.8	52	66.7	0.008
Diabetes mellitus	34	43.0	35	44.9	0.817
Hypertension	49	62.0	52	66.7	0.544
Dyslipidemia	65	82.3	64	82.1	0.970
Preoperative β-blocker use	32	40.5	28	35.9	0.552
Peripheral arterial disease[a]	2	2.5	1	1.3	1.000[b]
Stroke	2	2.5	–	–	0.497[b]
Carotid disease[c]	3	3.8	6	7.7	0.328[b]
COPD/asthma	6	7.6	8	10.3	0.559

** Chi-square test; [a] History of therapeutic vascular intervention, history of claudication, angiography/non-invasive proven peripheral arterial disease; [b] Fisher's exact test; [c] History of carotid intervention or angiographic/non-invasive proven >40% stenosis of either carotid artery; COPD: Chronic obstructive pulmonary disease.

Table 3. Comparison of the colloid and crystalloid groups by postoperative variables

	Voluven® 6% group (n=79)	Isolyte-M® group (n=78)	Effect size (r)	p*
	Mean±SD	Mean±SD		
Amount of fluid administered				
in the first 24 hours (ml)	2737.3±591.3	2542.2±502.8	0.17	0.028
ICU intubation time (hours)	10.2±4.4	10.5±10.1	0.01	0.799
Length of stay				
ICU, hours	46.0±9.1	47.9±13.1	0.08	0.286
Postoperative (days)	5.5±1.3	6.1±2.5	0.30	0.108
Drainage tubes removed, hours	38.4±12.8	35.5±8.2	0.19	0.083
Total amount of drainage (ml)	760.5±590.5	723.4±317.0	0.04	0.625
Number of FFPs used	1.1±1.8	1.0±1.2	0.0	0.841
Number of packed RBCs used	1.8±1.9	1.9±1.6	0.0	0.654
Number of PCs used	0.7±2.2	0.4±1.5	0.0	0.290

SD: Standard deviation; * Independent samples t-test; FFP: Fresh frozen plasma; RBC: Red blood cell; PC: Platelet concentrate.

group, p=0.333). All patients were treated with amiodarone therapy, and normal sinus rhythm was maintained.

DISCUSSION

Physiologically, colloid solutions should be preferable for the management of intravascular hypovolemic states in cases of extravascular dehydration.[4] However, it is not always possible to determine whether colloid or crystalloid solutions should be used in post-cardiac surgical patients. Only 20% of isotonic crystalloid solutions remain in the intravascular compartment. This leads to higher volumes of fluid administration, which causes volume overload, edema formation, and possible adverse outcomes.[4,6,7] The initial volume effect varies from 70% to over 100% among the different colloid solutions.[4] These generally increase plasma oncotic pressure and keep the intravascular fluid in place, resulting in faster and greater plasma volume expansion. This contrasts with crystalloid solutions which dilute plasma proteins and decrease oncotic pressure.[3,6,8]

The debate continues over the ideal postoperative fluid therapy following cardiac surgery. Unfortunately, in 2010, Boldt, who along with his colleagues[9] had made substantial contributions to the debate in favor of colloids, especially HES, was suspended and was charged for scientific misconduct including failure to acquire ethical approval and fabrication of study data in 88 of 102 studies all of which are now withdrawn from medical literature.[10] Unfortunately, the charges against Boldt have multiplied the skeptical view regarding HES; hence, more clinical studies should be undertaken to find reliable answers related to the efficacy of this solution.

The ideal colloid administered for volume resuscitation should neither adversely affect the coagulation system nor impair the renal and other systems. Commercially available colloid solutions that are used today include albumin, gelatin, and HES preparates. Storage difficulties and the strict payment policies of health insurance companies limit the use of albumin, and gelatin leads to a high incidence of anaphylactoid reactions and has a limited volume effect of only two to three hours due to rapid renal excretion.[4,6]

Hydroxyethyl starch is a multi-branched glucose polymer amylopectin derived from waxy maize or potato starch in which glucose residues are linked by α-1-4- and α-1-6- glycosidation.[11] Pharmacokinetic

Table 4. Comparison of the colloid and crystalloid groups by postoperative adverse events

	Voluven® 6% group (n=79)		Isolyte-M® group (n=78)		OR (95% CI)*	p**
	n	%	n	%		
Postoperative exploration for						
hemorrhage	2	2.5	1	1.3	2.0 (1.1-119.5)	1.000
Renal dysfunction[a]	5	6.3	3	3.8	1.7 (0.3-11.2)	0.719
Postoperative stroke	1	1.3	1	1.3	1.0 (0.0-80.5)	1.000

* Isolyte-M® group is the reference group; ** Fisher's exact test; [a] Defined when the peak creatinine value was ≤1.5 times the preoperative value; ICU: Intensive care unit.

properties and safety profiles have improved with the use of 6% HES 130/0.4, but in spite of higher clearance rates, equivalent volume efficacy of this solution has not improved compared with the first and second generation HES products.[12,13]

In post-cardiac surgery patients, the hemodynamic deleterious effects of the resultant state are managed by providing optimal tissue perfusion, which mainly depends on the cardiac index. This is optimized by adjusting the preload, which necessitates an additional adjustment in the infusion therapy.[14] Verheij et al.[3] studied the hemodynamic performance of colloid solutions versus crystalloids after cardiac or vascular surgery and discovered that colloid fluid loading increased the cardiac index, but the crystalloids did not have this effect. This difference was attributed to the greater plasma volume expanding effect caused by increased colloid osmotic pressure rather than by the affected cardiac functions. In contrast, we found that the total amount of fluid administered in the colloid group in our study was higher than the crystalloid group. However, since our patients received either only the crystalloid fluid or only the colloid solution, this contrast might not be relevant. Therefore, not only did the hemodynamic status of the patient possibly influence the total amount of fluid that was administered, but the daily amount of fluid requirement could have also had an effect, and this may have caused some amount of bias.

The use of CPB, which causes a non-physiological state, and the invasive nature of cardiac surgery are both associated with increased perioperative blood loss and blood transfusion requirements.[15] When investigating the effects of HES on hemostasis and total postoperative blood loss, Raja et al.[16] searched Medline and compared nine in vivo studies. Their research revealed that HES has the same effects as other colloids. Ooi et al.[17] studied the effects of starch solutions on coagulation, and no negative effects were found. In addition, there was no increase in transfusion requirements. Similarly, Schramko et al.[18] found no difference in blood loss and postoperative chest tube drainage in two separate studies that compared different colloids and discovered no differences in the amount of blood and blood products that were used. Our study revealed similar results. The total amount of blood loss and chest tube drainage was similar in the crystalloid and colloid groups. Furthermore, we found that the amount of blood and blood products given after cardiac surgery did not increase with 6% HES therapy.

In a meta-analysis by Navickis et al.[19] comprised of 18 trials and 970 patients, HES 450/0.7 and 200/0.5

solutions were compared with albumin, and these solutions were reported to increase postoperative blood loss by 33.3%, packed RBC use by 28.4%, FFP use by 30.6%, and PC use by 29.8%. The authors also demonstrated that the rate of reoperation was 2.24-fold higher with the HES solutions. Even though 6% HES 130/0.4 was not administered in their study, it was assumed that the effects of HES 130/0.4 were equal to 200/0.5 based on the available head-to-head comparisons. We had contrasting results, but we compared a crystalloid solution rather than albumin to 6% HES 130/0.4. As previously outlined, a number of contrary reports exist. For instance, Wilkes et al.[20] in their meta-analysis composed of 653 patients and 16 clinical trials revealed that HES 200/0.5 did not increase blood loss or the use of blood and its products compared with albumin, but high molecular weight HES did. They also declared that albumin possesses positive effects on coagulation via its anti-oxidative and protective effects on platelet morphology and function, which are disturbed by CPB. Similarly, Lange et al.[4] in their recent review concluded that HES 130/0.4 did not increase blood loss or the use of blood and its products compared with albumin solutions. Therefore, we think that the discussion regarding the effects of HES solutions on coagulation will continue and studies with larger sample sizes studies are needed to obtain more definitive results.

Postoperative renal dysfunction related to the use of HES is still under discussion. There is controversy regarding renal impairment with HES, but recently it has been shown repeatedly that there is no difference in renal function when the different colloid solutions are used.[17,21] In their report, Lange et al.[4] reviewed the use of 6% HES and revealed that this solution was very safe to be used with different patient populations, including those on high-dose therapy, the elderly, and those with pre-existing renal impairment. Additionally, they found that urine output, serum creatinine levels, and creatinine clearance rates were similar when a comparison was made between different colloid solutions, including albumin, gelatin, and various HES preparations. Wang et al.[22] arrived at a similar conclusion when they reported a decreased inflammatory response and well-maintained endothelial integrity with modern HES preperations, which they also discovered had beneficial effects on kidneys in an animal study. In our study, it was clearly shown that 6% HES 130/0.4 had no deleterious effects on renal function.

The incidence of AF after CABG surgery was reported to be as high as 30% in a meta-analysis comprised of 24 studies.[23] Furthermore, AF leads

to an increased length of hospital stay, high resource utilization, and greater healthcare costs.[24] A vast number of studies have been published regarding the etiology of post-CABG AF. To our knowledge, however, no data exists regarding the effects of the type of fluid administered on postoperative arrhythmias in CABG patients. Concerning the effects of HES on cardiac rhythm, Harutjunyan et al.[25] studied a group of patients with high intracranial pressure who were administered 7.2% HES and observed no changes in heart rate and rhythm. Prior to our study, we hypothesized that the incidence of post-CABG AF would be lower in the colloid group due to the attenuated inflammatory response after CPB that occurs with HES.[22,25] However, our results revealed no change in the incidence of AF with this solution.

The postoperative variables, including intubation time, ICU stay, and postoperative hospital length of stay, were similar between the two groups in our study. These clinical parameters reflect the fact that 6% HES 130/0.4 does not adversely affect the variables outlined above and that it is efficacious and reliable when used with post-CABG surgery patients. Demirok et al.[26] reported similar results in 60 patients who underwent coronary or valve surgery. The authors expressed that low molecular weight HES was safe and suggested that it could be used for hemodynamic stabilization following cardiac surgery.

No mortality was noted during this study. We think that is because all of the patients with preoperative risk factors were excluded. In addition, patients requiring concomitant procedures which would have increased the likelihood of mortality, for example valvular interventions and ventricular aneurysm repair, were also not included.

Our study was not without limitations. No hemodynamic measurements, such as the cardiac index, pulmonary and systemic vascular resistance, and cardiac filling pressures, were taken during the study. Had these measurements been available, a more objective reflection of the hemodynamic effects of the administered fluid could have been obtained.

In summary, our study involved considerably more patients than have been included in previous studies that have examined the effects of HES on various outcomes following cardiac surgery. Thus, we believe our data is reliable. We showed that 6% HES 130/0.4 does not interfere with renal and pulmonary functions following cardiac surgery when administered alone or in high doses as postoperative fluid therapy. We also discovered that this solution does not increase the total amount of blood loss, postoperative hemorrhage necessitating exploration, or the amount of blood and blood products used. Another important finding was that in spite of its attenuating effects on inflammatory response, 6% HES 130/0.4 did not decrease post-CABG AF.

Declaration of conflicting interests

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