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Randomised Controlled Trial

The effects of hydroxyethyl starch 130/0.4 on perioperative renal function in patients undergoing cardiac surgery: A randomised controlled trial

Kei Nagaya [a,*], Akiko Yoshida [a], Yosuke Ito [a], Suguru Watanabe [b], Tadanori Minagawa [c], Yoshifumi Saijo [d]

[a] Department of Anesthesia, Tohoku Medical and Pharmaceutical University Hospital, Sendai, Japan
[b] Department of Cardiovascular Surgery, Sendai Medical Center, Sendai, Japan
[c] Department of Cardiovascular Surgery, Tohoku Medical and Pharmaceutical University Hospital, Sendai, Japan
[d] Biomedical Imaging Laboratory, Graduate School of Biomedical Engineering, Tohoku University, Sendai, Japan

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ABSTRACT

Background: Acute kidney injury (AKI) after cardiac surgery increases the risk of morbidity and mortality. Hydroxyethyl starch (HES) is often used during surgery due to its plasma-volume expanding effect, but the impact of HES 130/0.4 on renal function in patients undergoing cardiac surgery remains unclear. The aim of our study is to investigate the impact of HES 130/0.4 on postoperative renal function in patients undergoing cardiac surgery using cardiopulmonary bypass.

Methods: Our study was a randomised, single-center, single-blind study conducted on 60 adult patients who underwent cardiac surgery using cardiopulmonary bypass: 30 patients were intraoperatively administered with HES 130/0.4; the other 30 with Ringer's bicarbonate. The primary endpoints were occurrence of AKI within 30 days of surgery and the disease stages.

Results: The mean dose of 6% HES 130/0.4 was 28 ml/kg. AKI occurred within 30 days of the operation in 8 cases (28.6%) in the HES group and 6 cases (21.4%) in the crystalloid group (no significance: $p = 0.5371$). Disease stages were as follows: "no AKI", "stage 1", "stage 2″ and "stage 3″, accounting for 20 cases (71.5%), 6 cases (21,4%), 2 cases (7.1%), and 0 cases, respectively, in the HES group, and 22 cases (78.6%), 6 cases (21.4%), 0 cases, and 0 cases, respectively, in the crystalloid group (no significance: $p = 0.3508$).

Conclusion: There was no significant difference in the occurrences or stages of AKI during the 30 days following cardiac surgery with cardiopulmonary bypass between patients administered with HES 130/0.4 or Ringer's bicarbonate.

1. Introduction

Acute kidney injury (AKI) is a relatively frequent complication after cardiac surgery, leading to higher morbidity and mortality [1–4]. AKI after cardiac surgery can be caused by preoperative heart failure and renal dysfunction, embolism, hemodilution, hypothermia, and hypoperfusion due to cardiopulmonary bypass (CPB), systemic inflammatory response to operative stress, and side effects of various drugs.

Hydroxyethyl starch (HES) has a plasma-volume expanding effect and has consequently been widely used in emergency, intensive, and perioperative care. However, recent large-scale clinical trials have shown that the incidence of AKI increased when HES was used in critically ill patients suffering from conditions such as sepsis [5,6]; these critically ill patients received long-term treatment with high doses of HES. However, the risk involved in treating critically ill patients with HES for short periods at relatively low doses is unknown. Numerous studies have shown that in non-cardiac surgery, the use of HES has no impact on renal function [7–9], but there is little research on how the intraoperative administration of HES affects the postoperative onset of AKI after cardiac surgery [10–12]. HES remains in the blood vessels for longer periods due to its high molecular weight and high degree of substitution, and its plasma-volume expanding effect also persists longer; furthermore, for patients undergoing surgery, there is a higher risk of bleeding and of developing postoperative AKI [13,14]. HES

* Corresponding author. Department of Anesthesia, Tohoku Medical and Pharmaceutical University Hospital1-12-1, Fukumuro, Miyagino-ku, Sendai, Miyagi, Japan.
E-mail address: k-nagaya@hosp.tohoku-mpu.ac.jp (K. Nagaya).

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130/0.4 has a low molecular weight of 130,000 Da and a low degree of substitution (0.4). Its plasma-volume expanding effect persists for a relatively long time, and it is believed to be rapidly excreted with limited accumulation in the plasma [15]; therefore, it is expected to be safe.

The purpose of this study was to investigate the impact of intraoperative administration of HES 130/0.4 on perioperative renal function in patients undergoing cardiac surgery with CPB.

2. Methods

2.1. Subjects

Our study was a single-institution, single-blinded study that was registered as a clinical trial after being approved by the Independent Ethics Committee of Tohoku Medical and Pharmaceutical University Hospital (Sendai, Japan) (approval number 2013-1-007). Our study was registered at the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) as a clinical trial (Unique Identifying Number: UMIN000025055 -Link https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000028833). Our study followed the Consolidated Standards of Reporting Trials (CONSORT) guidelines [16]. Among adult patients (age ≥20 years) undergoing cardiac surgery with CPB at the Tohoku Medical and Pharmaceutical University Hospital, we excluded those on chronic dialysis or with severe renal dysfunction (estimated glomerular filtration rate: eGFR <45 ml/min/1.73 m^2), and those undergoing emergency surgery or repeat surgery. All participants provided written informed consent.

The study was conducted by random allocation of patients into the HES group (30 individuals), in which 6% HES 130/0.4 (Voluven, Fresenius Kabi, Germany) was administered intraoperatively, or the crystalloid group (30 individuals), in which Ringer's bicarbonate (Bicanate, Otsuka Pharmaceutical Factory, Japan) was administered. A computer-generated list of random numbers (Microsoft Excel, Redmond, Washington) was allocated to the participants.

2.2. Patient management

In both groups, general anesthesia was induced using midazolam, remifentanil, and rocuronium, and was maintained using propofol, remifentanil, fentanyl, and rocuronium.

In both groups, Ringer's bicarbonate was used as a crystalloid solution from the beginning to the end of the general anesthesia. Ringer's bicarbonate was also used as a priming solution for the CPB; however, in the HES group, 1,000 mL of HES 130/0.4 was also administered. In the HES group, HES 130/0.4 was administered as an intravenous fluid after the termination of CPB. The maximum dose of HES 130/0.4 was set at 50 mL/kg. Additionally, in both groups, a 5% albumin solution and blood transfusions were used when needed.

2.3. Primary endpoints

Occurrence and stages of AKI during the 30-day postoperative period:

We used the creatinine-based criteria according to the "*Kidney Disease: Improving Global Outcomes*" (KDIGO) [17] for the diagnosis and staging of AKI (Table 1).

2.4. Statistical analysis

The authors were unable to define a valid sample size before conducting the study. The sample size was determined based on resources available in our institution.

The results were expressed as mean ± SD or median [interquartile range] for continuous variables and as number (percentage) for categorical variables. The normality of the data distribution was assessed using the Kolmogorov-Smirnov test. Student's *t*-test or Mann-Whitney *U* test were used to compare continuous variables and the chi-square test was used to compare categorical variables between groups. A $p < 0.05$ was considered statistically significant. BellCurve for Excel (Social Survey Research Information Co., Ltd.) was used for all statistical analyses.

Table 1
KDIGO definition and classification of AKI (serum creatinine criteria).

Difinition	AKI is diagnosed if serum creatinine ≥0.3 mg/dl for ≤48 hours, or rises to ≥1.5-fold from baseline, which is known or presumed to have occurred within the prior 7 days.
Classification	
Stage 1	Increase in serum creatinine by ≥ 0.3 mg/dl, or increase to 1.5–1.9 times from baseline
Stage 2	Increase in serum creatinine to 2.0–2.9 times from baseline
Stage 3	Increase in serum creatinine to 3 times from baseline, or increase in serum creatinine to ≥4 mg/dl, or initiation of RRT

KDIGO kidney disease: improving global outcomes, *AKI* acute kidney injury, *RRT* renal replacement therapy.

3. Results

Of the 119 adult patients who underwent cardiac surgery at the Tohoku Medical and Pharmaceutical University Hospital between April 2014 and May 2016, 60 patients were enrolled in the study and were randomly allocated to the HES group (30 patients) and the crystalloid group (30 patients). The other patients were excluded for the following reasons: 24 patients had severe renal dysfunction, 9 patients had undergone emergency surgery, 5 patients had undergone repeat surgery, and 21 patients did not provide consent to participate in the study. Furthermore, a patient in the HES group and two patients in the crystalloid group were excluded from the study due to changes in the surgical procedure, and another patient in the HES group was excluded because of a postoperative acute exacerbation of interstitial pneumonia, which required the use of an extracorporeal membrane oxygenator; thus, the study was eventually conducted on 28 patients in the HES group and 28 patients in the crystalloid group (Fig. 1).

Despite the random allocation, those in the HES group were younger than those in the crystalloid group. In addition, the left ventricular end-diastolic and end-systolic diameters of patients in the HES group were larger than in those in the crystalloid group. There were no significant differences in the other patient characteristics between the two groups (Table 2).

Compared to patients in the crystalloid group, those in the HES group experienced a longer surgery time and CPB time and bled more. Furthermore, the fluid balance during CBP, the amount of crystalloid solutions infused, and the intraoperative total fluid balance were lower in the HES group. A smaller amount of 5% albumin solution was used in the HES group, but there was no significant difference between the two groups in terms of blood transfusion volume or urine output. The amount of HES 130/0.4 administered was 1,600 mL [1,500–1,800] (28 mL/kg) (Table 3).

Eight cases in the HES group and six cases in the crystalloid group developed AKI within the 30-day postoperative period, with no difference between the two groups ($p = 0.5371$). The AKI stage showed no significant difference between the two groups ($p = 0.3508$) (Table 4).

4. Discussion

The exact mechanism of hydroxyethyl starch-induced kidney damage is unknown, but HES is believed to be captured by renal tubular epithelial cells in which it accumulates and causes disorders. This leads to osmotic nephrosis, which is morphologically characterized by vacuolation and swelling of the renal proximal tubular epithelial cells [18–20]. HES accumulates in the skin, liver, kidneys, and bone marrow, causing various side effects; however, it accumulates in particularly high

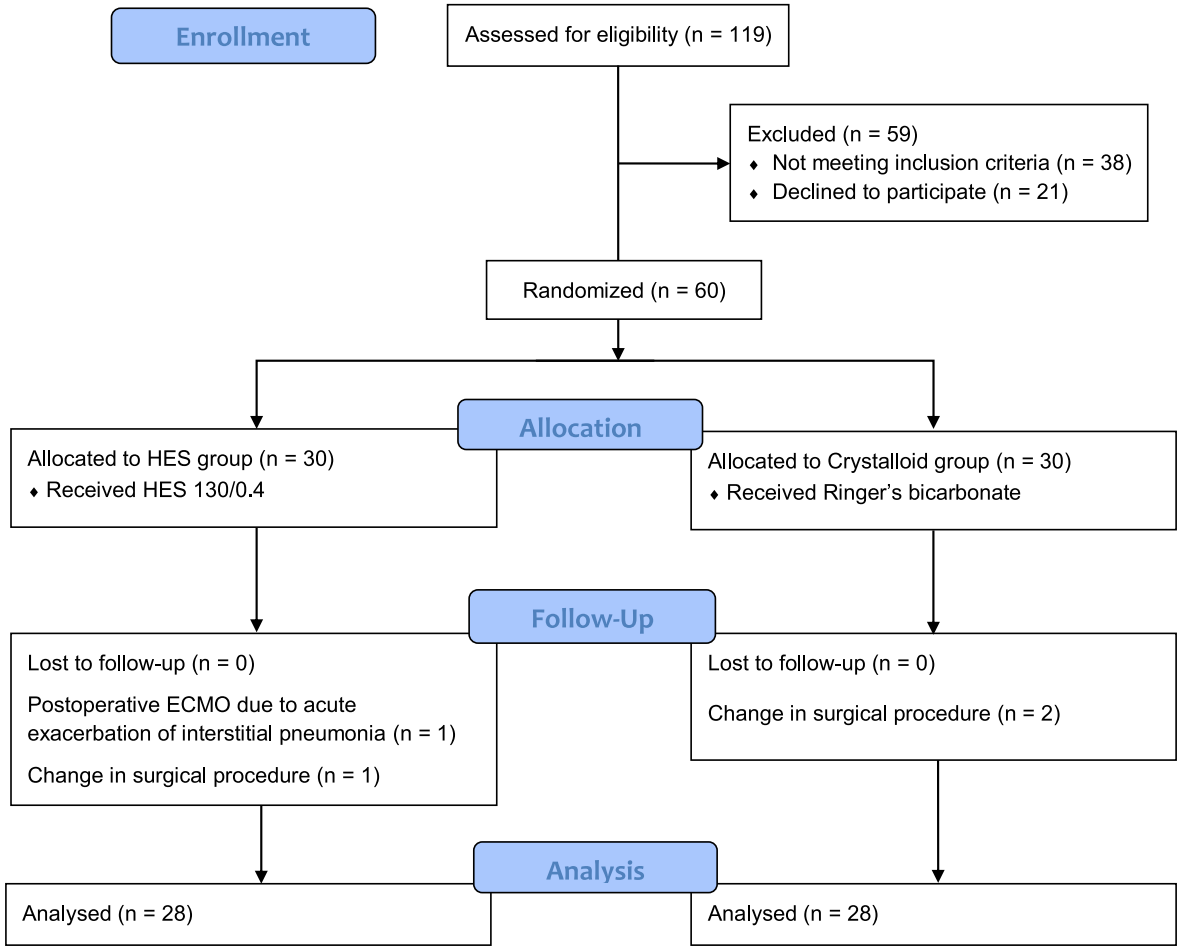

Fig. 1. Flow diagram of participants. *HES* hydroxyethyl starch, *ECMO* extra-corporeal membrane oxygenation.

concentrations in the kidneys, and in some cases, remains there for up to 10 years [21]. Furthermore, an increase in colloid osmotic pressure causes a reduction in the effective glomerular filtration pressure, and as a result, GFR decreases, and high concentrations of HES may lead to further loss of kidney function [22].

The incidence of postoperative AKI is 1–7% [8,13] in non-cardiac surgery and is as high as 15–40% in cardiac surgery [1–4]. This high incidence in cardiac surgery could be because the patients already have risk factors for postoperative AKI [3] prior to surgery, including heart failure, chronic kidney disease (CKD), and arrhythmia. Other causes include various impacts of CPB, such as hypoperfusion, hypothermia, hemodilution, and embolism. The CPB-induced hemodilution itself may reduce kidney injury caused by HES, but the relationship between the use of HES as a priming solution for CBP and kidney injury remains unclear.

In our study, HES 130/0.4 was used as a priming solution for CPB and after the termination of CPB; however, the occurrence of AKI within the 30-day postoperative period did not differ between HES and Ringer's bicarbonate. In addition, no difference in AKI stages was observed between the two groups. This may be because the study was conducted on patients with a relatively well-preserved preoperative renal function (eGFR $\geq$45 ml/min/1.73 m^2). CKD is one of the risk factors for postoperative AKI [3], and the KDIGO guidelines on CKD also mention that renal dysfunction is more likely to progress in CKD patients at an eGFR $<$45 ml/min/1.73 m^2 [23]. Additionally, the total amount of HES 130/0.4 used in our study was relatively small (28 mL/kg), and the preoperative and postoperative urine output was sufficient, indicating that HES 130/0.4 was rapidly excreted and that it may have had little impact on the renal function.

Using HES as intravenous fluid resuscitation in critically ill patients leads to an increase in the rate of renal replacement therapy [5,6,24] and in the mortality rate [6,24]. This could be because most patients had hypotension and a decreased circulating blood volume, which caused a decrease in GFR. When HES is used under such conditions, the plasma concentration of HES will be high, and renal tubular cells will be exposed to high concentrations of HES, causing even greater damage.

Meanwhile, using HES in patients undergoing surgery decreases the risk of developing postoperative AKI [7–9]. This is because of a low total administered dose and a short administration period. This may also be because the circulating blood volume is relatively well preserved when HES is used.

HES-induced impairment of coagulation is due to a dilution-induced decrease in the concentration of coagulation factors, mainly factor VIII and von Willebrand factor (VWF), and an inhibition of platelet aggregation due to a decrease in the levels of VWF [25,26]. This impact is greater in the HES types that have larger molecular weights and remain in the blood vessels for longer periods. The association between the use of HES 130/0.4 in cardiac surgery and the amount of intraoperative and postoperative bleeding is still unclear [9,11,14,27,28]. However, in our study, the amount of intraoperative bleeding was significantly greater in the HES group. Although CPB causes impairment of hemostatic function through various mechanisms, the CPB time was significantly longer in the HES group. Therefore, our findings could not elucidate whether HES 130/0.4 had an impact on the amount of intraoperative bleeding.

Our study had several limitations. Despite the random allocation, the patients in the HES group were younger, had poor preoperative cardiac functions, and longer CPB times. Younger patients are believed to have a reduced risk of postoperative AKI. A low cardiac function and longer

Table 2
Baseline characteristics.

	HES Group (n = 28)	Crystalloid Group (n = 28)	*p* value
Age, yr	65 ± 11	71 ± 11	0.0487
Gender, male/female	20/8	14/14	0.1007
Height, m	1.63 ± 0.11	1.57 ± 0.13	0.0683
Weight, kg	59.7 ± 9.6	57.0 ± 13.0	0.3778
Body mass index, kg/m^2	21.3 [20.2–24.0]	22.8 [20.5–24.1]	0.6820
Preoperative lab			
Albumin, g/dl	4.0 [3.9–4.2]	4.0 [3.8–4.2]	0.7352
Creatinine, mg/dl	0.90 ± 0.20	0.80 ± 0.19	0.1352
eGFR, ml/min/1.73m^2	63 [50–74]	61 [54–75]	0.7616
Hemoglobin, g/dl	12.9 ± 1.9	12.8 ± 2.0	0.8485
Platelet counts, × 103/μl	151 [133–208]	156 [128–185]	0.8058
APTT, s	31.5 [29.7–35.7]	34.0 [30.6–35.3]	0.3630
PT, s	13.7 [13.0–13.9]	13.8 [13.1–14.5]	0.2974
Fibrinogen, mg/dl	320 [286−367]	351 [312–411]	0.1516
Cystatin C, mg/l	1.11 ± 0.30	1.18 ± 0.31	0.3691
Urine β2 microglobulin, μg/l	83 [68–153]	109 [78–153]	0.2445
L-FABP, μg/g·Cr	1.9 [0.4–2.6]	1.4 [0.0–2.3]	0.4106
Preoperative echocardiographic data			
LVDd, mm	59 ± 9	54 ± 8	0.0272
LVDs, mm	42 ± 9	36 ± 7	0.0072
LVEF, %	60 [38–65]	64 [56–66]	0.1157
Medical history			
Hypertension, no. (%)	14 (50)	15 (53.6)	0.7891
Diabetes mellitus, no. (%)	7 (25)	5 (17.9)	0.5148
Chronic obstructive pulmonary disease, no. (%)	4 (14.3)	4 (14.3)	1.0000
Peripheral artery disease, no. (%)	3 (10.7)	2 (7.1)	0.6393
Preoperative medications			
ACEI or ARB, no. (%)	15 (53.6)	13 (46.4)	0.5930
NSAID, no. (%)	6 (21.4)	3 (10.7)	0.2750

HES hydroxyethyl starch, *eGFR* estimated glomerular filtration rate, *APTT* activated partial thromboplastin time, *PT* prothrombin time, *L-FABP* Liver type fatty acid-binding protein, *LVDd* left ventricular end-diastolic diameter, *LVDs* left ventricular end-systolic diameter, *LVEF* left ventricular ejection fraction, *ACEI* angiotensin converting enzyme inhibitor, *ARB* angiotensin II receptor blocker, *NSAID* nonsteroidal anti-inflammatory drug.

CPB time are believed to increase the risk of postoperative AKI. Although HES group has a higher risk of AKI than the crystalloid group, there was no difference of occurrence of AKI between two groups. It remains unclear, however, as to how these limitations may have affected the results of our study, and therefore, more unbiased case studies are needed in the future.

5. Conclusion

Intraoperative administration of HES 130/0.4 in patients with relatively normal renal functions did not differ in terms of the occurrence and stage of AKI within 30-days of cardiac surgery with CBP compared to the administration of Ringer's bicarbonate.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Availability of data and material

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Table 3
Intraoperative characteristics.

	HES Group (n = 28)	Crystalloid Group (n = 28)	*p* value
Surgical procedure			0.1005
CABG, no. (%)	4 (14.3)	1 (3.6)	
Valve surgery, no. (%)	17 (60.7)	24 (85.7)	
Combined CABG and valve surgery, no. (%)	7 (25)	3 (10.7)	
Intraoperative variables			
Duration of anesthesia, min	354 [308–424]	285 [272–335]	0.0026
Duration of surgery, min	268 [219–322]	192 [180–247]	0.0068
Duration of CPB, min	157 [131–184]	114 [99–170]	0.0191
Duration of aortic crossclamping, min	100 ± 60	88 ± 44	0.4331
Lowest temperature during CPB, °C	33.9 [33.4–34.3]	34.2 [33.3–34.4]	0.5715
Lowest hematocrit during CPB, %	22 [20–25]	23 [20–26]	0.4356
Fluid balance during CPB, ml	−277 [-750–597]	1660 [847–2252]	<0.0001
Crystalloid, ml	1577 ± 603	2264 ± 605	0.0001
HES130/0.4, ml	1600 [1500–1800]	0	
HES130/0.4, ml/kg	28 ± 5	0	
5% albumin, ml	0 [0–0]	0 [0–250]	0.0183
Erythrocyte, U	2 [0–4]	0 [0–3]	0.2477
Fresh-frozen plasma, ml	0 [0–0]	0 [0–0]	0.6190
Platelet, U	0 [0–0]	0 [0–0]	0.1535
Blood loss, ml	404 [280–766]	243 [194–290]	0.0001
Urine output, ml	568 [349–846]	520 [366–746]	0.7062
Total fluid balance, ml	2316 ± 1593	3385 ± 1867	0.0251

HES hydroxyethyl starch, *CABG* coronary artery bypass grafting, *CPB* cardiopulmonary bypass.

Table 4
Incidence of AKI and KDIGO stage.

	HES Group (n = 28)	Crystalloid Group (n = 28)	*p* value
Incidence of AKI until POD 30, no. (%)	8 (28.6)	6 (21.4)	0.5371
KDIGO stage			0.3508
No AKI, no. (%)	20 (71.5)	22 (78.6)	
Stage 1, no. (%)	6 (21.4)	6 (21.4)	
Stage 2, no. (%)	2 (7.1)	0 (0)	
Stage 3, no. (%)	0 (0)	0 (0)	

AKI acute kidney injury, *KDIGO* kidney disease: improving global outcomes, *POD* postoperative day.

Please state any sources of funding for your research

This study did not receive any extramural funding.

Ethical Approval

This study was approved by the Independent Ethics Committee of Tohoku Medical and Pharmaceutical University Hospital (Sendai, Japan) (approval number 2013-1-007).

Consent

All the patients signed the institutional informed consent form.

Authors contribution

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Kei Nagaya, Akiko Yoshida, and Yosuke Ito. The first draft of the manuscript was written by Kei Nagaya, and all authors commented on previous

versions of the manuscript. All authors have read and approved the final manuscript.

Registration of Research Studies

1. Name of the registry:
University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR)
2. Unique Identifying number or registration ID:
UMIN000025055
3. Hyperlink to your specific registration (must be publicly accessible and will be checked):
https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000028833

Guarantor

Yoshifumi Saijo

Declaration of competing interest

The authors declare no conflict of interest.

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