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\textsuperscript{a,}\textsuperscript{*}, Akiko Yoshida\textsuperscript{a}, Yosuke Ito\textsuperscript{a}, Suguru Watanabe\textsuperscript{b}, Tadanori Minagawa\textsuperscript{c}, Yoshifumi Saijo\textsuperscript{d}

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

ARTICLE INFO

Keywords:  
Hydroxyethyl starch 130/0.4  
Acute kidney injury  
Cardiac surgery  
Cardiopulmonary bypass

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).

https://doi.org/10.1016/j.amsu.2022.104475
Received 12 June 2022; Received in revised form 9 August 2022; Accepted 16 August 2022
Available online 24 August 2022
2049-0801/© 2022 The Authors. Published by Elsevier Ltd on behalf of IJS Publishing Group Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
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 m²), 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 intravenously, or the crystalloid group (30 individuals), in which Ringer’s bicarbonate (Bicarbonate, 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.

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 CPB, 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

| Table 1 |
| --- |
| **KDIGO definition and classification of AKI (serum creatinine criteria).** |
| **Definition** | 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.
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 CPB 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 ≥45 mL/min/1.73 m²). 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 m² [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
Although HES group has a higher risk of AKI than the crystalloid group, ACEI, 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 CPB 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 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/m²    | 21.3              | 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/1.73m²       | 63 [50–74]        | 61 [54–75]                | 0.7616  |
| Hemoglobin, g/dl          | 12.9 ± 1.9        | 12.8 ± 2.0                | 0.8485  |
| Platelet counts, × 10³/ml | 151 [133–208]     | 156 [128–185]             | 0.8058  |
| APTT, s                   | 31.5              | 34.0 [30.6–35.3]          | 0.3630  |
| PT, s                     | 13.7              | 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 [2 microglobulin, µg/l] | 83 [68–153] | 109 [78–152] | 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 ± 9                    | 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  |

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 ± 68   | 88 ± 44                   | 0.4331  |
| Lowest temperature during CPB, °C | 33.9              | 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              | 1660 [847–2252]           | <0.0001 |
| Crystalloid, ml                  | 1577 ± 603        | 2624 ± 605                | 0.0001  |
| HES130/0.4, ml                    | 1600              | 0                         |         |

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?recptn=0000028833

Guarantor

Yoshifumi Saijo

Declaration of competing interest

The authors declare no conflict of interest.

References

[1] J.W. Pickering, M.T. James, S.C. Palmer, Acute kidney injury and prognosis after cardiopulmonary bypass: a meta-analysis of cohort studies, Am J Kidney Dis 65 (2015) 283–293.
[2] A.J. Bastin, M. Ostermann, A.J. Slack, G.P. Diller, S.J. Finney, T.W. Evans, Acute kidney injury after cardiac surgery according to risk/injury/failure/loss/end-stage, acute kidney injury Network, and kidney disease: improving global outcomes classifications, J Crit Care 28 (2013) 389–396.
[3] D. Kristovic, I. Horvatic, I. Husedzinovic, Z. Sutlic, I. Rudez, D. Baric, et al., Cardiac surgery-associated acute kidney injury: risk factors analysis and comparison of prediction models, Interact CardioVasc Thorac Surg (2015) 1–8.
[4] C. Corredor, R. Thomson, N. Alsubaie, Long-term consequences of acute kidney injury after cardiac surgery: a systematic review and meta-analysis, J Cardiothorac Vasc Anesth 30 (2016) 69–75.
[5] A. Perner, N. Haeusler, A.B. Guttormsen, J. Tenhunen, G. Klemenzson, A. Åneman, et al, 6S Trial Group, Scandinavian critical care trials group. Hydroxyethyl starch 130/0.42 versus Ringer’s acetate in severe sepsis, N Engl J Med 367 (2012) 124–134.
[6] J.A. Myburgh, S. Finfer, R. Bellomo, L. Billot, A. Cass, D. Gattas, et al., CHEST investigators; Australian and New Zealand intensive care society clinical trials group. Hydroxyethyl starch or saline for fluid resuscitation in intensive care, N Engl J Med 367 (2012) 1901–1911.
[7] A. Joosten, A. Delaporte, J. Mortier, B. Ickx, L. Van Obbergh, J.L. Vincent, et al., Long-term impact of crystalloid versus colloid solutions on renal function and disability-free survival after major abdominal surgery, Anesthesiology 130 (2019) 227–236.
[8] T. Kammerer, F. Breitner, S. Hilferink, N. Hulde, F. Klug, J. Pangel, et al., No differences in renal function between balanced 6% hydroxyethyl starch (130/0.4) and 5% albumin for volume replacement therapy in patients undergoing cystectomy: a randomized controlled trial, Anesthesiology 128 (2018) 67–78.
[9] P. Van Der Linden, M. James, M. Mythen, R.B. Weiskopf, Safety of modern starchyes used during surgery, Anesth Analg 116 (2013) 35–48.
[10] T. Datema, M. Hoenicka, H. Reinold, A. Liebold, H. Gorki, Influence of 6% hydroxyethyl starch 130/0.4 versus crystalloid solution on structural renal damage markers after coronary artery bypass grafting: a post hoc subgroup Analysis of a prospective trial, J Cardiothorac Vasc Anesth 32 (2018) 205–211.
[11] M.G. Lagery, L. Roediger, J.N. Koch, F. Dubois, M. Senard, A.F. Donneau, et al., Hydroxyethyl starch 130/0.4 and the risk of acute kidney injury after cardiopulmonary bypass: a single-center retrospective study, J Cardiothorac Vasc Anesth 30 (2016) 869–875.
[12] M.A. Gilles, M. Habicher, S. Jhanji, M. Sander, M. Mythen, M. Hamilton, et al., Incidence of postoperative death and acute kidney injury associated with i.v. 6% hydroxyethyl starch use: systematic review and meta-analysis, Br J Anaesth 112 (2014) 25–34.
[13] B.K. Kashy, A. Podolyak, N. Makarova, J.E. Dalton, D.I. Sessler, A. Kurz, Effect of hydroxyethyl starch on postoperative kidney function in patients having noncardiac surgery, Anesthesiology 121 (2014) 730–739.
[14] A. Jacob, J.L. Fellabi, D. Chappell, A. Kurz, The impact of hydroxyethyl starches in cardiac surgery: a meta-analysis, Crit Care 18 (2014) 656.
[15] C. Jungeheinrich, R. Scharpf, M. Wagenas, F. Bepperling, J.F. Baron, The pharmacokinetics and tolerability of an intravenous infusion of the new hydroxyethyl starch 130/0.4 (6%, 500 mL) in mild-to-severe renal impairment, Anesth Analg 95 (2002) 544–551.
[16] Rosin D. LauJWY, R. Agha, The CONSORT (CONsolidated standards of reporting trials) 2010 guideline, Int. J. Surg. 93 (2021) 2900565–2900566. Available online: http://www.journal-surgery.net/article/S1743-9191(11)00565-6/fulltext.
[17] Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, KDIGO clinical practice guideline for acute kidney injury, Kidney International Suppl 2 (2012) 1–138.
[18] Schortgen, L. Brochard, Colloid-induced kidney injury: experimental evidence may help to understand mechanisms, Crit Care 13 (2009) 130.
[19] L. Hüter, T.P. Simon, L. Weimann, T. Schuerholz, K. Reinhart, G. Wolf, et al., Hydroxyethylstarch impairs renal function and induces interstitial proliferation, macrophage infiltration and tubular damage in an isolated renal perfusion model, Crit Care 13 (2009) R23.
[20] M. Dickenmann, T. Oettl, M.J. Mihatsch, Osmostic nephropotic acute kidney injury with accumulation of proximal tubular lysosomes due to administration of exogenous solutes, Am J Kidney Dis 51 (2008) 491–502.
[21] C.J. Wiedermann, M. Joannidis, Accumulation of hydroxyethyl starch in human and animal tissues: a systematic review, Intensive Care Med 40 (2014) 160–170.
[22] C.J. Wiedermann, S. Dunzendorfer, Gaziou Lu, F. Zaraca, M. Joannidis, Hypersensitive colloids and acute kidney injury: a meta-analysis of randomized trials, Crit Care 14 (2010) R191.
[23] Kidney Disease: improving Global Outcomes (KDIGO) CKD Work Group, KDIGO clinical practice guideline for the evaluation and management of chronic kidney disease, Kidney Intern Suppl 3 (2013) 1–150.
[24] A. Serape Neto, D.P. Veelo, V.G. Peireira, M.S. de Assunção, L. Vasc, ˜ao, J.A. Manetta, D. C. Esposito, et al., Fluid resuscitation with hydroxyethyl starches in patients with sepsis is associated with an increased incidence of acute kidney injury and use of renal replacement therapy: a systematic review and meta-analysis of the literature, J Crit Care 29 (2014) 185, e1–7.
[25] R.G. Strauss, C. Stansfield, R.A. Henriksen, P.J. Villhauer, Pentastarch may cause fewer effects on coagulation than hetastarch, Transfusion 28 (1988) 257–260.
[26] R.G. Strauss, B.J. Pennell, D.C. Stump, A randomized, blinded trial comparing the hemostatic effects of pentastarch versus hetastarch, Transfusion 42 (2002) 27–36.
[27] S.M. Kasper, P. Meinert, S. Kampe, C. Gorg, C. Geisen, U. Meldhorn, et al., Large-dose hydroxyethyl starch 130/0.4 does not increase blood loss and transfusion requirements in coronary artery bypass surgery compared with hydroxyethyl starch 200/0.5 at recommended doses, Anesthesiology 99 (2003) 42–47.
[28] R.J. Navickis, G.R. Haynes, M.M. Wilkes, Effect of hydroxyethyl starch on bleeding after cardiopulmonary bypass: a meta-analysis of randomized trials, J Thorac Cardiovasc Surg 144 (2012) 223–230.