

## Journal Pre-proof

Impact of colloids or crystalloids in renal function assessed by NGAL and KIM-1 after hysterectomy: randomized controlled trial

Murillo G. Santos , João Paulo Jordão Pontes ,  
Saulo Gonçalves Filho , Rodrigo M. e Lima , Murilo M. Thom ,  
Norma Sueli P. Módolo , Daniela Ponce , Lais Helena Navarro

PII: S0104-0014(21)00408-5

DOI: <https://doi.org/10.1016/j.bjane.2021.10.009>

Reference: BJANE 744325



To appear in: *Brazilian Journal of Anesthesiology (English edition)*

Received date: 23 June 2021

Accepted date: 30 October 2021

Please cite this article as: Murillo G. Santos , João Paulo Jordão Pontes , Saulo Gonçalves Filho , Rodrigo M. e Lima , Murilo M. Thom , Norma Sueli P. Módolo , Daniela Ponce , Lais Helena Navarro , Impact of colloids or crystalloids in renal function assessed by NGAL and KIM-1 after hysterectomy: randomized controlled trial, *Brazilian Journal of Anesthesiology (English edition)* (2021), doi: <https://doi.org/10.1016/j.bjane.2021.10.009>

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2021 Published by Elsevier Editora Ltda. on behalf of Sociedade Brasileira de Anestesiologia.

This is an open access article under the CC BY-NC-ND license

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

**BJAN-D-21-00265 - Original Investigation****Impact of colloids or crystalloids in renal function assessed by NGAL and KIM-1 after hysterectomy: randomized controlled trial**

**Murillo G. Santos<sup>a,\*</sup>, João Paulo Jordão Pontes<sup>a,b</sup>, Saulo Gonçalves Filho<sup>a</sup>, Rodrigo M. e Lima<sup>a,c</sup>, Murilo M. Thom<sup>d</sup>, Norma Sueli P. Módolo<sup>d</sup>, Daniela Ponce<sup>e</sup>, Lais Helena Navarro<sup>c,d</sup>**

<sup>a</sup> Universidade Estadual Paulista (UNESP), Faculdade de Medicina de Botucatu, Botucatu, SP, Brazil

<sup>b</sup> Santa Genoveva Complexo Hospitalar, Uberlândia, MG, Brazil

<sup>c</sup> Queen's University, Department of Anesthesiology and Perioperative Medicine, Kingston, Canada

<sup>d</sup> Universidade Estadual Paulista (UNESP), Faculdade de Medicina de Botucatu, Departamento de Anestesiologia, Botucatu, SP, Brazil

<sup>e</sup> Universidade Estadual Paulista (UNESP), Faculdade de Medicina de Botucatu, Departamento de Clínica Médica, Botucatu, SP, Brazil

**\* Corresponding author.**

E-mail: murillogsantos@gmail.com (M.G. Santos).

**ORCID ID:**

Murillo G. Santos - 0000-0001-6897-1469

João Paulo Jordão Pontes - 0000-0003-3428-0664

Saulo Gonçalves Filho - 0000-0002-5033-4098

Rodrigo M. e Lima - 0000-0002-7699-8669

Murilo M. Thom - 0000-0002-2857-735X

Norma Sueli P. Módolo - 0000-0002-8549-6820

Daniela Ponce - 0000-0002-6178-6938

Lais Helena Navarro - 0000-0001-9596-7289

Received 23 June 2021; accepted 30 October 2021

**KEYWORDS**

Hydroxyethyl Starch Derivatives;

Hysterectomy;

Kidney function tests

**Abstract**

*Background:* Hydroxyethyl starches are colloids used in fluid therapy that may reduce volume infusion compared with crystalloids, but they can affect renal function in critical care patients. This study aims to assess renal effects of starches using renal biomarkers in the perioperative setting.

*Methods:* This prospective, controlled, randomized study compared Hydroxyethyl starch 6% (HES) with Ringer's lactate (RL) in hysterectomy. Each episode of mean arterial pressure (MAP) below 60 mmHg guided the fluid replacement protocol. The RL group received 300 mL bolus of RL solution while the HES group received 150 mL of HES solution. All patients received RL ( $2 \text{ mL.kg}^{-1}.\text{h}^{-1}$ ) intraoperatively to replace insensible losses. Blood and urine samples were collected at three time points (preoperatively, 24 hours, and 40 days postoperatively) to assess urinary NGAL and KIM-1, as primary outcome, and other markers of renal function.

*Results:* Seventy patients were randomized and 60 completed the study. The RL group received a higher crystalloid volume ( $1,277 \pm 812.7 \text{ mL}$  vs.  $630.4 \pm 310.2 \text{ mL}$ ;  $p = 0.0002$ ) with a higher fluid balance ( $780 \pm 720 \text{ mL}$  vs.  $430 \pm 440 \text{ mL}$ ;  $p = 0.03$ ) and fluid overload ( $11.7\% \pm 10.4\%$  vs.  $7.0\% \pm 6.3\%$ ;  $p = 0.04$ ) compared to the HES group. NGAL and KIM-1 did not differ between groups at each time point, however both biomarkers increased 24 hours postoperatively and returned to preoperative levels after 40 days in both groups.

*Conclusion:* HES did not increase renal biomarkers following open hysterectomy compared to RL. Moreover, HES provided better hemodynamic parameters using less volume, and reduced postoperative fluid balance and fluid overload.

**Introduction**

Intraoperative fluid replacement is controversial in the literature, and it is related to the clinical outcomes of patients undergoing surgical procedures.[1,2] On one hand, restrictive fluid therapy can lead to hypovolemia, tissue hypoxia, and acute kidney injury (AKI); while a liberal regimen can lead to tissue edema impairing pulmonary,

cardiac, and gastrointestinal function.[3-5] Goal-directed fluid therapy (GDT) seems to be better than previous fixed fluid regimens, and has shown reduction in complications related to hypervolemia, such as gastrointestinal dysfunction and infections, and also related to perioperative hypovolemia, such as AKI.[3-7]

Besides fluid regimen, the type of fluid is also challenging.[5] Crystalloids, such as Ringer's lactate (RL), are standard solutions for fluid replacement, but when in excess, can damage the vascular endothelium, and result in interstitial edema due to its 20% limited capacity of intravascular expansion.[4,5,7,8] Colloids are considered intravascular plasma expanders remaining longer in the intravascular compartment, and Hydroxyethyl starch 6% (HES) solution is a type of colloid with intermediate molecular weight used in major surgeries, and that may reduce hypervolemia related to crystalloids.[4-6,8] Although more efficient as a plasma expander, the safety of using HES in the surgical context has been questioned due to concerns on kidney damage.[6,7]

Perioperative acute kidney injury is related to inadequate fluid replacement and increases morbidity and mortality of surgical patients.[2,8-10] Thus, early diagnosis and immediate treatment are essential.[9,10] Normally, plasma creatinine and urine output are used to diagnose AKI according KDIGO guidelines,[10] although the first may take 48 hours to rise, and the latter can be affected by endocrine-metabolic response to surgery.[10] The advent of new renal biomarkers, such as NGAL (neutrophil gelatinase-associated lipocalin), and KIM-1 (kidney injury molecule-1), has enabled early diagnosis of kidney injury.[10-12] NGAL is absent in the urine and plasma of healthy individuals and is expressed as early as 2 hours after renal ischemia.[10] KIM-1 is a membrane glycoprotein that is upregulated after an ischemic or nephrotoxic injury and increases after 6 hours in urine.[10]

The aim of this study was to assess kidney effects of either HES or RL solutions used for volume resuscitation, using GDT, in patients without previous renal dysfunction undergoing elective open hysterectomy. The study hypothesis was that these solutions differ in terms of kidney damage assessed by urinary NGAL, and other traditional and novel markers of renal function.

## Methods

This randomized, prospective, controlled, double-blind clinical study was conducted at the Hospital das Clínicas da Faculdade de Medicina de Botucatu – UNESP and

approved by the Research Ethics Committee (registry number: 1246806) of the same institution. The study was registered in the Brazilian Clinical Trials Registry (REBEC): RBR-7J75Q5, and described in accordance with the Declaration of Helsinki and Consolidated Standards of Reporting Trials (CONSORT) statement.

All participants provided informed consent and were considered eligible if they met the following criteria: physical status I and II of the American Society of Anesthesiologists (ASA), ages between 18 and 65 years, and scheduled to undergo elective open abdominal hysterectomy under general anesthesia. We did not include patients who declined to participate in the study, those with any previous kidney dysfunction (glomerular filtration rate  $< 60 \text{ mL}\cdot\text{min}^{-1}\cdot 1.73\text{m}^2$  according to the CKD-EPI formula, or urinary protein/creatinine ratio  $> 0.3$ ), [13] uncontrolled hypertension (SBP  $> 180 \text{ mmHg}$  or DBP  $> 120 \text{ mmHg}$ ), uncontrolled diabetes mellitus (fasting blood glucose  $> 200 \text{ mg}\cdot\text{dL}^{-1}$ ), chronic use of nonsteroidal anti-inflammatory drugs or diuretics, preoperative anemia (Hb  $< 7 \text{ g}\cdot\text{dL}^{-1}$ ), or obesity II (BMI  $> 35 \text{ kg}\cdot\text{m}^{-2}$ ). Exclusion criteria were: patients with severe intraoperative bleeding in the operating room or in the first 24 hours after the surgical procedure, requiring blood transfusion; perioperative diuretic use; and patients who did not return 40 days after the surgery for medical consultation.

Patients were randomized into two groups (HES group and RL group) according to the fluid replacement protocol with codes generated by computer software (random.org) and allocated at a proportion of 1:1. The protocols were stored in opaque envelopes that were only opened by the medical team immediately prior to anesthesia administration. The patients and the physician responsible for the evaluation of laboratory test results and possible complications presented by the study patients, were blinded to patient grouping.

Patients were monitored via continuous 5-lead cardioscopy, pulse oximetry, capnography with a gas analyzer, noninvasive blood pressure (NIBP), neuromuscular blockade monitor (TOF-Watch<sup>®</sup> SX, Organon, Swords Co., Dublin, Ireland), and urinary output (UO) by a bladder indwelling catheter. Induction of general anesthesia used propofol  $2 \text{ mg}\cdot\text{kg}^{-1}$ , sufentanil  $0.5\text{--}0.7 \text{ }\mu\text{g}\cdot\text{kg}^{-1}$ , and rocuronium  $0.6 \text{ mg}\cdot\text{kg}^{-1}$ . After tracheal intubation, anesthesia was maintained with isoflurane 1–1.5% combined with continuous infusion of remifentanil ( $0.1\text{--}0.3 \text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ).

Additionally, all patients received intravenous 5 mg of methadone and 8 mg of dexamethasone after induction of anesthesia, and 2 g of dipyrene, 100 mg of tramadol

and 8 mg of ondansetron at the end of surgery. Neuromuscular blockade was reversed using neostigmine and atropine, guided according to neuromuscular blockade depth. Possible pain in the postanesthesia care unit (PACU) was treated with intravenous morphine as rescue medication, with a dose titrated according to the verbal Numeric Rating Scale (NRS), and pain scores ranged from 0 to 10.

Both groups received 300 mL of RL during the induction of anesthesia and a standard baseline RL infusion of  $2 \text{ mL.kg}^{-1}.\text{h}^{-1}$  through a continuous infusion pump (Samtronic® ST550 T2, São Paulo/SP, Brazil) in order to maintain mean arterial pressure (MAP) between 60–80 mmHg and replace insensible losses and diuresis. For every episode of  $\text{MAP} < 60 \text{ mmHg}$ , volume expansion was performed according to the patient group: 150 mL of Hydroxyethyl starch 6% (Voluven®, Fresenius Kabi, Bad Homburg, Germany) in the HES group, or 300 mL of Ringer's lactate solution in the RL group, both infused over 5 minutes and repeated one time if necessary. If the  $\text{MAP} < 60 \text{ mmHg}$  after two solution boluses in each group, ephedrine 5 mg was administered to restore  $\text{MAP} > 60 \text{ mmHg}$ . The fluid protocol above mentioned is outlined in Fig. 1. The same protocol was also used during the stay in the PACU. For the HES group, dose of HES was limited to  $20 \text{ mL.kg}^{-1}$  intraoperatively and in PACU (below that stipulated as safe: up to  $50 \text{ mL.kg}^{-1}.\text{day}^{-1}$ ), [14] when the solution for resuscitation was switched to RL.

Hemodynamic data were recorded electronically throughout surgery and at the PACU each five and fifteen minutes, respectively, and stored for later analysis. The absolute number of episodes of hypotension, as determined through mean arterial pressure ( $\text{MAP} < 60 \text{ mmHg}$ ) and systolic blood pressure ( $\text{SBP} < 90 \text{ mmHg}$ ), was recorded. We also analyzed vital signs at 0, 30, 60, 90, and 120 minutes during surgery, and upon awakening. Time-point 0 corresponded to general anesthesia induction and the “upon awakening” time corresponded to the moment when the orotracheal tube was removed.

Intraoperative bleeding was estimated by the difference in the weight of the surgical pads used during surgery (the dry weight of each small pad was 10 g and of each large pad 20 g). Blood loss was also assessed by the blood volume present in the surgical aspirator prior to peritoneal irrigation at the end of surgery. Total blood loss was recorded in milliliters.

Urine output was calculated by the relationship between the total urine volume preoperative weight from each patient and period during intraoperatively, and PACU.

The perioperative fluid balance was calculated by the difference between the volume of solution infused and the volume of losses (bleeding and diuresis). Fluid overload was calculated as the ratio between fluid balance and the preoperative weight of each patient multiplied by 100, considering volume overload when greater than 10%. [15]

Blood samples (4 mL) were collected for hemoglobin (Hb), hematocrit (Ht), plasma creatinine (CrP), and plasma urea (Ur) analyses in the preoperative and 24 hours after surgery. Urine samples (2 mL) were also collected for urinary creatinine (CrU), proteinuria, NGAL and KIM-1 analyses. Measurements of biomarkers NGAL and KIM-1 were performed for a single time-point at a specific laboratory of the Experimental Research Unit – UNESP Botucatu by a trained professional who did not have any contact with the patients or study protocols. The measurements were performed using enzyme-linked immunosorbent assay (ELISA) kits from Elabscience (Wuhan, Hubei, China) according to the manufacturer's instructions. Forty days after surgery, only urine samples were collected to compare to previous samples. The measurements of CrU and proteinuria were used to calculate the urine protein/creatinine (P/CrU) ratio, which relates the loss of protein in urine in an isolated sample (equivalent to 24-hour proteinuria), to a normal range between 0.03–0.3. [16] Thus, values above 0.3 indicate renal injury.

As primary outcome, we used the comparison between groups in urinary NGAL. As secondary outcomes, in order to also assess perioperative renal function, we collected other urinary biochemical data (urinary KIM-1 and P/CrU), serum biochemical data (CrP and Ur), and urine output changes. Other secondary outcomes assessed were: fluid balance, fluid overload, intraoperative hemodynamic data, total surgical bleeding, postoperative Hb and Ht, volumes of administered fluids, and vasopressor requirement. Other perioperative data collected included: age; BMI; ASA physical status; estimated preoperative renal function; [13] duration of surgery; length of PACU stay; pain scores according to NRS; total morphine consumption at PACU; possible immediate complications (cardiac ischemia, arrhythmias, pulmonary edema, pneumonia, respiratory failure, sepsis, AKI, early reoperation and death); and late postoperative complications within 40 days (wound infection, wound dehiscence, reoperation and death).

For a significance level of 5% and test power of 90%, a total of 22 patients per group would be necessary to detect a  $100 \text{ ng.mL}^{-1}$  difference in urinary NGAL levels, with a standard deviation of  $100 \text{ ng.mL}^{-1}$ , according to previous investigations. [17,18]

We estimated that at least 66 patients should be enrolled in the study due to the possibility of losing 50% of the sample in a 40-day follow-up, as we have already observed in our institution.

The Shapiro-Wilk test was used to determine normality of data. Continuous variables with normal distribution were expressed as mean  $\pm$  SD and tested with the Student's t-test with equal or different variances. Continuous variables with asymmetrical distribution comparisons were made by fitting a gamma distribution model. Categorical variables were expressed as absolute counts (%) and analyzed using Pearson's Chi-square test.

In order to compare variables of the tests at three time points, a repeated measurement design was used to evaluate group *versus* time interaction. In the case of data with symmetrical distribution, repeated measurement ANOVA followed by Tukey's multiple comparison test were used. If the data had an asymmetric distribution, a gamma distribution was fitted, followed by the Wald test for multiple comparisons. All analyses were performed considering a significance level of 5% or the corresponding p-value, and using SAS<sup>®</sup> 9.4 for Windows.

## Results

Fig. 2 illustrates details of the study. Patients were recruited between November 1, 2015, and March 28, 2018. Seventy patients were randomized, and 60 patients completed the study. The demographic characteristics of patients and intraoperative data are shown in Table 1. Except for total volume of crystalloid administered, which was lower in the HES group, the other variables did not differ between groups.

Regarding hemodynamic parameters, participants in the HES group showed higher systolic blood pressure at 30 minutes and MAP at 30 and 60 minutes after induction of anesthesia compared to the RL group. Mean heart rate values did not differ between groups at the time points studied, as shown in Fig. 3. Vasopressor requirement was similar between groups, ranging from 5 to 30 mg in both groups (Table 1).

During PACU assessment, the volume of crystalloid, fluid balance and fluid overload were significantly higher in the RL group than in the HES group, as shown on Table 2. There were no differences in urine output, length of stay, pain scores, and morphine consumption between groups.

All patients were discharged 48 hours after surgery, and immediate complications were not observed. Although not significant, within 40 days after the



procedure, late complications were more common in the RL group compared to the HES group (13.3% vs. 3.3%;  $p = 0.16$ ). There was surgical wound infection in 2 patients in the RL group, and in 1 patient in the HES group, and suture dehiscence requiring reoperation in 2 patients in the RL group.

Preoperative serum laboratory analysis did not differ between the groups. In both groups, urea values in the postoperative period increased when compared to the preoperative period, whereas plasma creatinine levels decreased comparing these time points. Evaluating NGAL and KIM-1 mean values, comparing both groups within each time point, no significant differences were found between the groups; however, the mean of these biomarkers increased in both groups 24 hours after surgery, followed by a return to preoperative levels 40 days after surgery. The urine protein/creatinine ratio increased in the RL group and decreased in the HES groups at different time points within each group. When comparing the groups within each time point, there was a statistically significant difference between groups in the preoperative period and 40 days after surgery. These results are shown in Table 3.

## Discussion

The main finding of the present study is that HES when compared to Ringer's lactate did not cause renal impairment, reflected by urinary NGAL elevation, when using goal-directed fluid therapy in patients with normal renal function undergoing open abdominal hysterectomy under general anesthesia. In addition, other markers of renal function such as plasma creatinine, urinary output, urea, and KIM-1 were similar between groups. This finding is in accordance with previous investigations in which RL was compared to HES in orthopedic and urological surgery, and did not show any differences in postoperative urinary NGAL between groups.[17-20]

In both groups, urinary NGAL and KIM-1 measurements increased postoperatively compared to baseline values, but not plasma creatinine. The same finding was observed by Kancir et al regarding urinary NGAL, and the explanations for this phenomenon probably are surgical and hemodynamic stress leading to transient worsening in renal function. This corroborates the usefulness of these biomarkers on early diagnosis and intervention in AKI compared to traditional plasma creatinine levels.[10,12] Moreover, this was the first trial to include urinary KIM-1 measurements alongside NGAL to detect absence of early kidney damage with intraoperative HES administration.

We also assessed late renal function after 40 days as secondary outcome using P/Cr ratio and, like late urinary NGAL and KIM-1 measurements, there was no difference between groups, showing that patients who received HES intraoperatively did not have their renal function affected in the long term. This result is in line with Feldheiser et al, who showed that even after HES doses of  $50 \text{ mL.kg}^{-1}$  in patients undergoing cytoreductive cancer surgery, there was no difference in NGAL, creatinine and urine output after 3 months compared to balanced crystalloids.[21] Using standard renal function tests, Joosten et al also showed that even after 12 months, HES did not cause renal dysfunction compared to crystalloids in abdominal surgery.[22] Interestingly, when compared to baseline values, late P/Cr ratio was increased in the RL group, but not in the HES group. The higher volume of solution administered in the RL group might be the reason for this, since the relationship between hypervolemia and glomerular damage, expressed by proteinuria, has been discussed.[23] However, we do underline that our study was not powered to detect differences in late outcomes.

In critically ill patients under intensive care, Hydroxyethyl starches were more likely to cause AKI compared to crystalloids for fluid resuscitation.[24,25] However, it is well known that intravascular fluid dynamics and behavior depend on the integrity of endothelial glycocalyx that make up the barrier between intravascular and interstice.[4] In the studies in intensive care units,[24,25] most of the patients evaluated were in sepsis and this severe clinical condition is naturally related to glycocalyx damage and increased capillary permeability.[4] In these patients, intravascular fluids shift rapidly to the interstice and tissue edema ensues, which can be worse with osmotically active solutions such as starches.[4] Conversely, in elective surgical patients, otherwise healthy, endothelial glycocalyx is intact and, in accordance with other studies, HES can be used for fluid resuscitation without increasing morbidity and mortality.[17-20,26-28]

As expected by the design of the study's protocol, the RL group received higher volumes of fluids, once every episode of hypotension was treated with twice the volume of crystalloids compared to colloids. This became necessary because of the dynamics of crystalloids staying shorter time and in lower volumes in the intravascular compartment compared to colloids.[4] Thus, using the same volume of both solutions could have delayed hypotension treatment in the RL group. However, even receiving less volume, the HES group had the same incidence of hypotension episodes and showed a better hemodynamic profile, expressed by higher MAPs at almost every moment assessed after anesthetic induction. This is in accordance with Joosten et al, who showed that a

HES group had better volume expansion reflected by higher hemodynamic variables using less volume of fluid.[28] Kancir et al confirmed this greater intravascular expansion effect of HES measuring vasoactive plasmatic hormones such as renin, angiotensin II and aldosterone, which were lower compared to crystalloids in the perioperative period.[18]

In order to achieve the hemodynamic goals of our study, the RL group had significantly greater perioperative fluid balance and fluid overload than the HES group. Although we used MAP < 60 mmHg as our target for fluid resuscitation, this excess of fluid was also observed in other studies using perioperative GDT with either stroke volume variation[19,28] or esophageal doppler[21] in the balanced crystalloid group compared to the HES group. Fluid overload during surgery decreases tissue oxygen tension, delays recovery of gastrointestinal function and is associated with postoperative complications.[28] It is well known that fluid overload > 10% is associated with increased adverse events in critical patients[15] and, in our study, the RL group overcame this limit, whereas the HES group did not.

Although the new HES solutions, such as Hydroxyethyl starch 6%, were designed to minimize adverse effects in coagulation,[7] they can still impair thrombin generation and platelet function.[1,29] Kancir et al used up to 2,500 mL of HES for fluid resuscitation in prostatectomy and showed significant increased bleeding compared to the crystalloid group.[17] Rasmussen et al used up to 3,500 mL of HES and found both increase in blood loss and coagulation impairment on thromboelastography after cystectomy when compared to crystalloids.[29] Due to bleeding and coagulopathy concerns, recently, the European Medicines Agency (EMA) banned the use of HES in the European Union.[30] Our study, however, did not find increased bleeding in the HES group, probably due to the lower mean HES volume used and the lower risk of blood loss associated with elective abdominal hysterectomy, when compared to those trials.[17,29] Other trials using up to 1,500 mL of HES intraoperatively, such as ours, also did not find increased bleeding using HES 6% showing that coagulation impairment is dose dependent.[18-20,28]

Our findings should be interpreted in the context of study limitations. Firstly, open hysterectomy is not frequently associated with postoperative AKI, and none of the patients had this complication postoperatively. Thus, a larger sample size would be necessary to detect any difference in such outcome between groups. Since our primary outcome was to detect differences in urine biomarkers of kidney damage due to type of

fluid administered, we chose a procedure without great hemodynamic stress that would add minimal bias over kidney function. Secondly, following the fluid replacement protocol, we used different volumes of fluid between groups, and, therefore, the anesthesiology attending staff was not blinded to the intervention both in the operating room and in the PACU, what may be considered a performance bias. However, the researcher responsible for analyzing the results was blinded regarding the groups and the variables in the study. Thirdly, we used only MAP values in order to guide fluid administration in our GDT protocol, and this choice could be criticized since dynamic parameters may predict fluid responsiveness more reliably. Finally, our study was not powered to examine the effects of intravenous solutions on hospital length of stay, bleeding events or postoperative complication rates, probably due to the reduced sample size, although adequate to analyze the main outcomes.

### **Conclusion**

In conclusion, this study did not find a harmful effect of intraoperative infusion of HES on kidney function using renal biomarkers following open hysterectomy compared to Ringer's lactate solution. We also found that colloidal solutions can achieve better hemodynamic parameters using less volume and reduce postoperative fluid balance and fluid overload.

### **Funding**

This study was financed by CAPES-DS (funding code 1764506) and FAPESP (funding code 16713-3/2015) and departmental sources.

### **Conflicts of interest**

The authors declare no conflicts of interest.

### **Acknowledgments**

We thank Maria Regina Moretto from the laboratory of the Experimental Research Unit of UNESP – Botucatu Campus/SP for measuring the NGAL and KIM-1 urinary biomarkers. We thank Professor José Eduardo Corrente for the statistical analysis and sample size calculation.

### **References**

1. Boer C, Bossers SM, Koning NJ. Choice of fluid type: physiological concepts and perioperative indications. *Br J Anaesth.* 2018;120:384-96.
2. Plumb B, Brown J. Fluid therapy for anaesthetists and intensivists. *Anaesth Intensive Care Med.* 2015;16:439-42.
3. Calvo-Vecino JM, Ripollés-Melchor J, Mythen MG, et al. Effect of goal-directed haemodynamic therapy on postoperative complications in low–moderate risk surgical patients: a multicentre randomised controlled trial (FEDORA trial). *Br J Anaesth.* 2018;120:734-44.
4. Doherty M, Buggy DJ. Intraoperative fluids: how much is too much? *Br J Anaesth.* 2012;109:69-79.
5. Navarro LHC, Bloomstone JA, Auler JOC, et al. Perioperative fluid therapy: a statement from the international Fluid Optimization Group. *Perioper Med.* 2015;4:3.
6. Schol PBB, Terink IM, Lancé MD, et al. Liberal or restrictive fluid management during elective surgery: a systematic review and meta-analysis. *J Clin Anesth.* 2016;35:26-39.
7. Strunden MS, Tank S, Kerner T. Perioperative fluid therapy: defining a clinical algorithm between insufficient and excessive. *J Clin Anesth.* 2016;35:384-91.
8. McCahon R, Hardman J. Pharmacology of plasma expanders. *Anaesth Intensive Care Med.* 2017;18:418-20.
9. Drury N, Lewington A. Prevention and management of acute kidney injury in the perioperative patient. *Surgery.* 2018;36:705-9.
10. Gumbert SD, Kork F, Jackson ML, et al. Perioperative acute kidney injury. *Anesthesiology.* 2020;132:180-204.
11. Teo SH, Endre ZH. Biomarkers in acute kidney injury (AKI). *Best Pract Res Clin Anaesthesiol.* 2017;31:331-44.
12. Vanmassenhove J, Vanholder R, Nagler E, et al. Urinary and serum biomarkers for the diagnosis of acute kidney injury: An in-depth review of the literature. *Nephrol Dial Transplant.* 2013;28:254-73.
13. Michels WM, Grootendorst DC, Verduijn M, et al. Performance of the Cockcroft-Gault, MDRD, and new CKD-EPI formulas in relation to GFR, age, and body size. *Clin J Am Soc Nephrol.* 2010;5:1003-9.
14. Lewis SR, Pritchard MW, Evans DJW, et al. Colloids versus crystalloids for fluid resuscitation in critically ill people. *Cochrane Database Syst Rev.* 2018;8(8):CD000567.

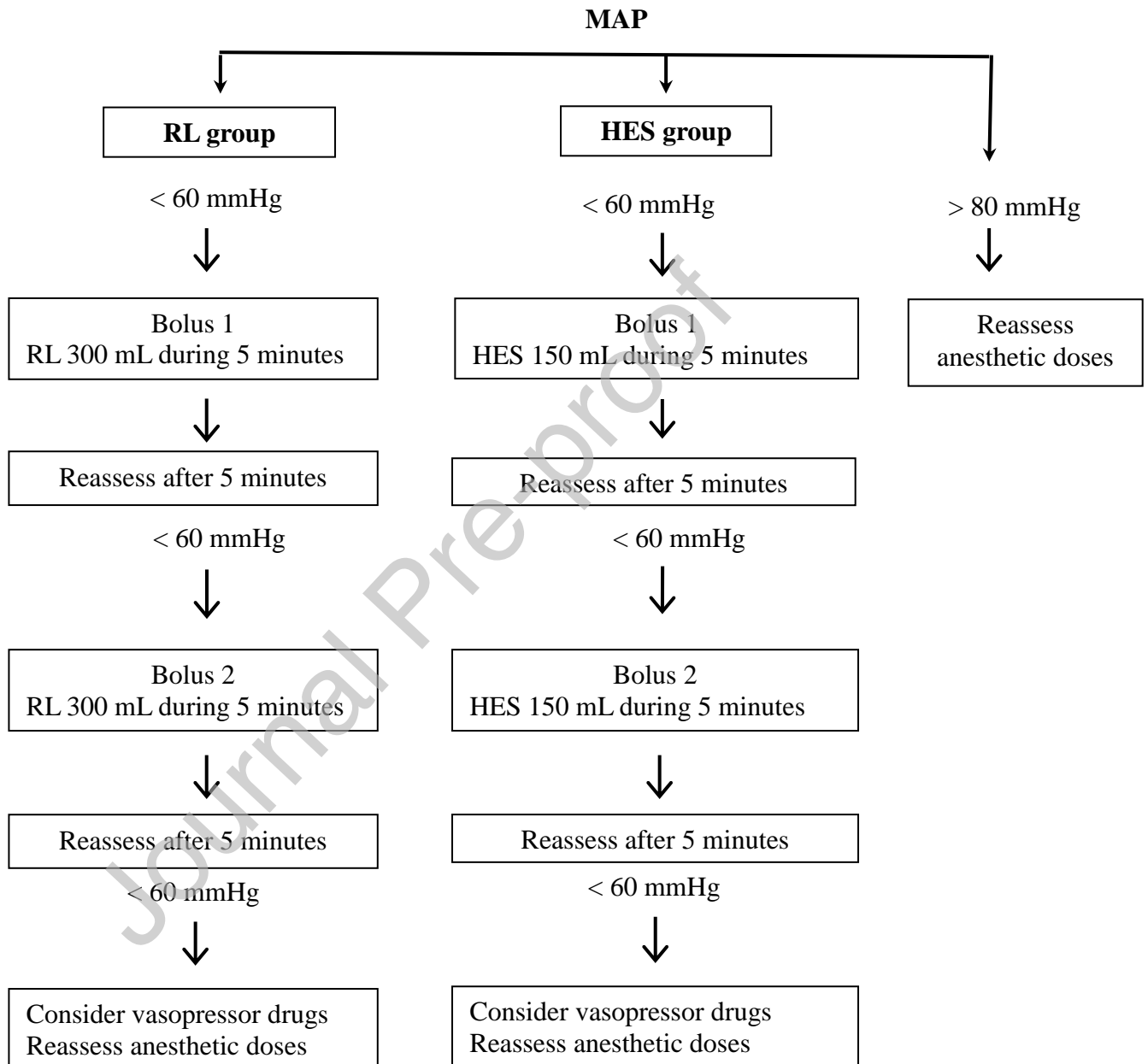
15. Claire-Del Granado R, Mehta RL. Fluid overload in the ICU: evaluation and management. *BMC Nephrology*. 2016;17:1-9.
16. Lane C, Brown M, Dunsmuir W, Kelly J, Mangos G. Can spot urine protein/creatinine ratio replace 24 h urine protein in usual clinical nephrology? *Nephrology*. 2006;11:245-9.
17. Kancir ASP, Johansen JK, Ekeloef NP, et al. The effect of 6% hydroxyethyl starch 130/0.4 on renal function, arterial blood pressure, and vasoactive hormones during radical prostatectomy: a randomized controlled trial. *Anesth Analg*. 2015;120:608-18.
18. Kancir ASP, Pleckaitiene L, Hansen TB, et al. Lack of nephrotoxicity by 6% hydroxyethyl starch 130/0.4 during hip arthroplasty: a randomized controlled trial. *Anesthesiology*. 2014;121:948-58.
19. Tyagi A, Verma G, Luthra A, et al. Risk of early postoperative acute kidney injury with stroke volume variation-guided tetrastarch versus Ringer's lactate. *Saudi J Anaesth*. 2019;13:9-15.
20. Zhang Y, Yu Y, Jia J, et al. Administration of HES in elderly patients undergoing hip arthroplasty under spinal anesthesia is not associated with an increase in renal injury. *BMC Anesthesiol*. 2017;17:29.
21. Feldheiser A, Pavlova V, Bonomo T, et al. Balanced crystalloid compared with balanced colloid solution using a goal-directed haemodynamic algorithm. *Br J Anaesth*. 2013;110:231-40.
22. Joosten A, Delaporte A, Mortier J, et al. Long-term impact of crystalloid versus colloid solutions on renal function and disability-free survival after major abdominal surgery. *Anesthesiology*. 2019;130:227-36.
23. Nishimoto M, Murashima M, Kokubu M, et al. Positive association between intra-operative fluid balance and post-operative acute kidney injury in non-cardiac surgery: the NARA-AKI cohort study. *J Nephrol*. 2020 ;33:561-8.
24. Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med*. 2012;367:1901-11.
25. Perner A, Haase N, Guttormsen AB, et al. Hydroxyethyl starch 130/0.42 versus ringer's acetate in severe sepsis. *N Engl J Med*. 2012;367:124-34.
26. Kabon B, Sessler DI, Kurz A, et al. Effect of intraoperative goal-directed balanced crystalloid versus colloid administration on major postoperative morbidity. *Anesthesiology*. 2019;130:728-44.

28. Joosten A, Delaporte A, Mortier J, et al. Long-term impact of crystalloid versus colloid solutions on renal function and disability-free survival after major abdominal surgery. *Anesthesiology*. 2019;130:227-36.
29. Rasmussen KC, Johansson PI, Højskov M, et al. Hydroxyethyl starch reduces coagulation competence and increases blood loss during major surgery: results from a randomized controlled trial. *Ann Surg*. 2014;259:249-54.
30. Roberts I, Shakur H, Bellomo R, et al. Hydroxyethyl starch solutions and patient harm. *Lancet*. 2018;391:736.

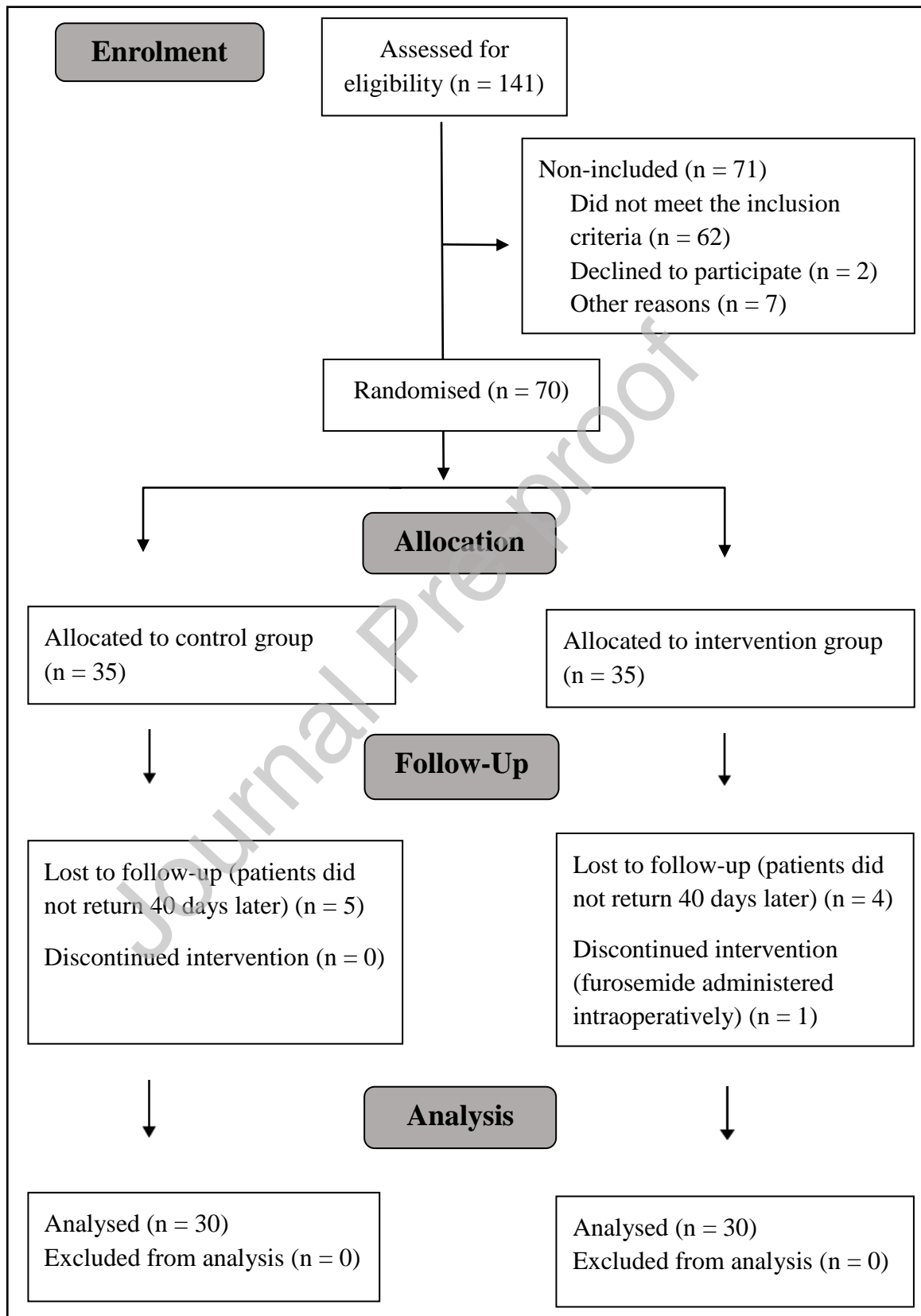
Journal Pre-proof

**Figure 1** Algorithm for fluid replacement protocol. HES, Hydroxyethyl starch 6%; MAP, mean arterial pressure; RL, Ringer's lactate.

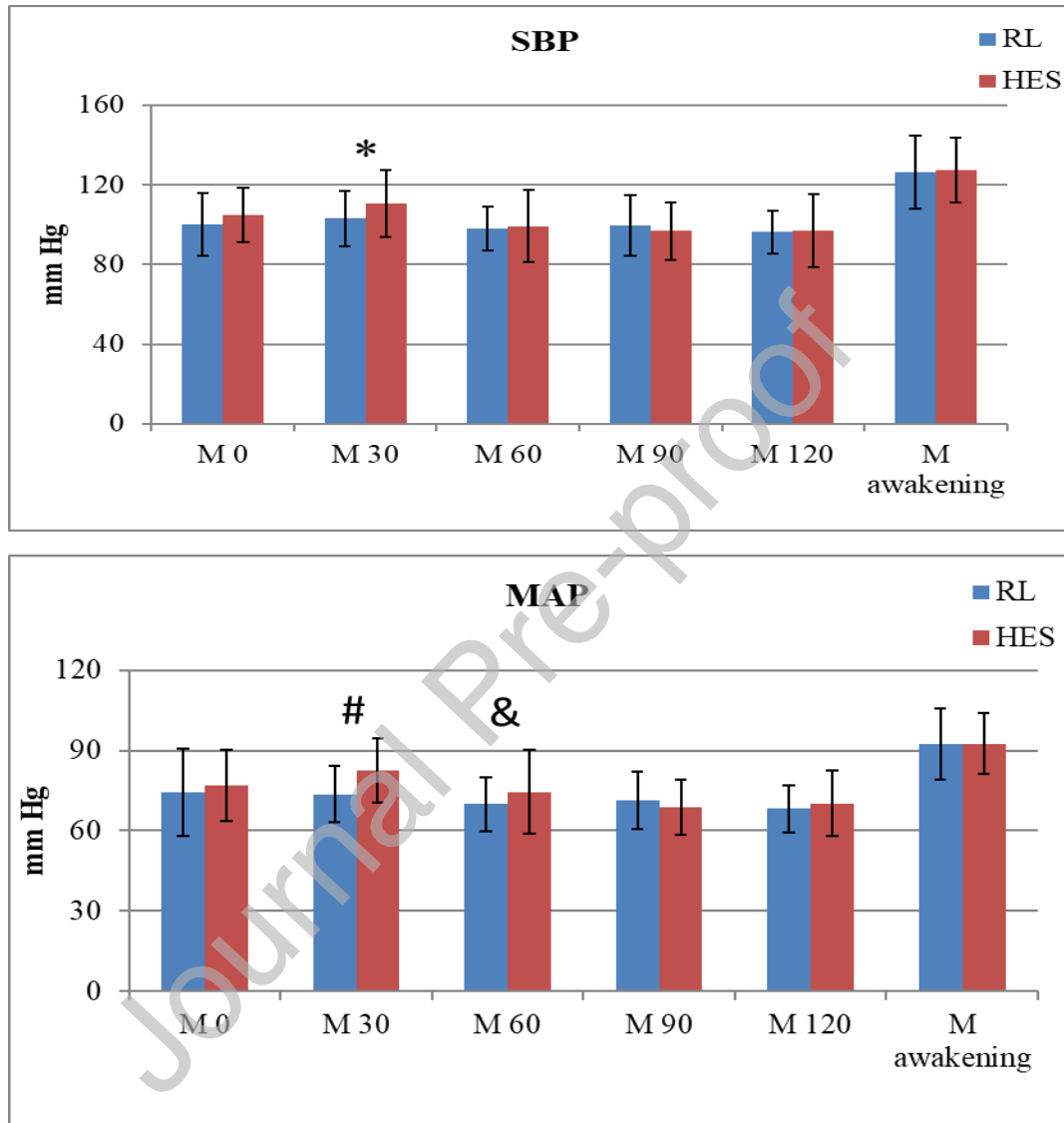
**Goal: MAP 60 - 80 mmHg with RL 2 mL.kg<sup>-1</sup>.h<sup>-1</sup>**

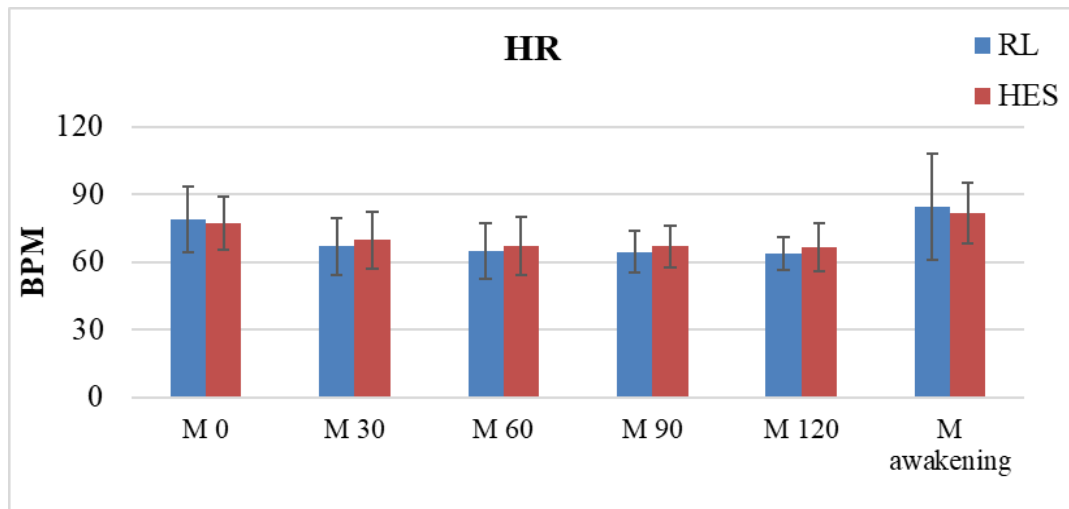




**Figure 2** CONSORT flow diagram. n, number of patients.

**Figure 3** Behavior of hemodynamic parameters at the different moment studied. Student's t-test; \*  $p < 0.05$ , 95% CI; #  $p < 0.05$ , 95% CI; &  $p < 0.05$ , 95% CI. BPM, beats per minute; HES, Hydroxyethyl starch 6% group; HR, heart rate; M, moments studied after anesthetic induction, in minutes; MAP, mean arterial pressure; RL, Ringer's lactate group; SBP, systolic blood pressure.





**Table 1** Characteristics of the patients and intraoperative data of the studied groups (mean  $\pm$  standard deviation).

Variables	RL (n = 30)	HES (n = 30)	p-value
Age (years)	43.7 $\pm$ 5.4	46 $\pm$ 5.5	0.11
Weight (kg)	75.0 $\pm$ 11.8	72.6 $\pm$ 12.3	0.43
ASA physical status (n)			0.41
1	12 (40%)	9 (30%)	
2	18 (60%)	21 (70%)	
Height (cm)	160.2 $\pm$ 6.2	160.5 $\pm$ 6.1	0.85
BMI (kg.cm <sup>-2</sup> )	29.2 $\pm$ 3.8	28.2 $\pm$ 4.7	0.38
GFR (mL.min <sup>-1</sup> /1.73m <sup>2</sup> )	103 $\pm$ 11.9	104.8 $\pm$ 11.9	0.56
RL volume (mL)	1277.4 $\pm$ 812.7	630.4 $\pm$ 310.2	0.0002
HES volume (mL)	-	439.6 $\pm$ 243	-
Bleeding (mL)	495.5 $\pm$ 338.2	439.8 $\pm$ 286.9	0.49
SBP < 90 mmHg	8.3 $\pm$ 8.5	7.87 $\pm$ 6.2	0.55
MAP < 60 mmHg	3.87 $\pm$ 4.9	3.5 $\pm$ 4.1	0.46
Vasopressor requirement (n)	8 (27%)	8 (27%)	1.0
Surgical time (min)	150 $\pm$ 40.6	149.67 $\pm$ 41.6	0.97

Student's t-test,  $p < 0.05$ , 95% CI.

n, number of patients; BMI, body mass index; GFR, glomerular filtration rate estimated by CKD-EPI (*Chronic Kidney Disease Epidemiology Collaboration*) formula; HES, hydroxyethyl starch 6% group; MAP, mean arterial pressure; SBP, systolic blood pressure; RL, Ringer's lactate group.

**Table 2** Variables evaluated in the post-anesthesia recovery period in the PACU (mean  $\pm$  standard deviation).

Variables	RL	HES	<i>p</i> -value
Length of stay in the PACU (min)	101.7 $\pm$ 65.7	84.7 $\pm$ 41	0.23
RL volume (mL)	294.2 $\pm$ 176.7	214.6 $\pm$ 125.4	0.049
Pain (NRS)	5.03 $\pm$ 3.26	4.47 $\pm$ 4.06	0.55
Morphine dose (mg)	4.1 $\pm$ 4.2	3.9 $\pm$ 4.3	0.85
Fluid balance (mL)	780 $\pm$ 720	430 $\pm$ 440	0.03
Fluid overload (%)	11.7 $\pm$ 10.4	7.0 $\pm$ 6.3	0.04
Urine output (mL.kg <sup>-1</sup> .h <sup>-1</sup> )	1.05 $\pm$ 0.60	1.4 $\pm$ 0.97	0.09

Student's t-test,  $p < 0.05$ , 95% CI.

HES, hydroxyethyl starch 6% group; PACU, post-anesthesia care unit; RL, Ringer's lactate group; NRS, numeric rating scale.

**Table 3** Mean of the laboratorial analysis between the groups and moments studied.

Variables	Groups	Preoperative	Postoperative	40 days after surgery	<i>p</i> -value
		Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	
Hemoglobin (g.dL <sup>-1</sup> )	RL	13.21 $\pm$ 2.1 <sup>aA</sup>	11.82 $\pm$ 2.0 <sup>bA</sup>	.	0.48
	HES	12.13 $\pm$ 1.9 <sup>aA</sup>	11.26 $\pm$ 1.9 <sup>aA</sup>	.	
Hematocrit (%)	RL	40.60 $\pm$ 5.6 <sup>aA</sup>	36.18 $\pm$ 5.5 <sup>bA</sup>	.	0.42
	HES	37.64 $\pm$ 5.1 <sup>aA</sup>	34.83 $\pm$ 5.7 <sup>aA</sup>	.	
Urea (mg)	RL	25.73 $\pm$ 7.3 <sup>aA</sup>	32.86 $\pm$ 10.1 <sup>bA</sup>	.	0.49
	HES	27.72 $\pm$ 6.8 <sup>aA</sup>	32.73 $\pm$ 8.8 <sup>aA</sup>	.	
Plasma Cr (mg.dL <sup>-1</sup> )	RL	0.69 $\pm$ 0.1 <sup>aA</sup>	0.58 $\pm$ 0.1 <sup>bA</sup>	.	0.72
	HES	0.67 $\pm$ 0.1 <sup>aA</sup>	0.54 $\pm$ 0.1 <sup>bA</sup>	.	
Urine P/Cr	RL	0.07 $\pm$ 0.1 <sup>aA</sup>	0.21 $\pm$ 0.4 <sup>bA</sup>	0.36 $\pm$ 1.3 <sup>bA</sup>	0.04
	HES	0.15 $\pm$ 0.2 <sup>aB</sup>	0.12 $\pm$ 0.1 <sup>aA</sup>	0.10 $\pm$ 0.1 <sup>aB</sup>	
Urine NGAL (ng.mL <sup>-1</sup> )	RL	55.27 $\pm$ 27.3 <sup>aA</sup>	73.85 $\pm$ 41.4 <sup>bA</sup>	42.08 $\pm$ 24.1 <sup>cA</sup>	0.64
	HES	51.13 $\pm$ 22.7 <sup>aA</sup>	75.74 $\pm$ 48.2 <sup>bA</sup>	38.10 $\pm$ 19.1 <sup>cA</sup>	
Urine KIM-1 (ng.mL <sup>-1</sup> )	RL	0.09 $\pm$ 0.3 <sup>aA</sup>	0.26 $\pm$ 0.4 <sup>aA</sup>	0.03 $\pm$ 0.1 <sup>aA</sup>	0.12
	HES	0.17 $\pm$ 0.6 <sup>aA</sup>	0.46 $\pm$ 1.0 <sup>aA</sup>	0.15 $\pm$ 0.4 <sup>aA</sup>	

Mean values followed by the same lowercase letter (setting groups and testing moments) do not differ significantly at the 5% level.

Mean values followed by the same capital letter (setting moments and testing groups) do not differ significantly at the 5% level.

ANOVA repeated measures,  $p < 0.05$ , 95% CI.

ANOVA, analysis of variance; Cr, creatinine; HES, hydroxyethyl starch 6% group; P/Cr, protein creatinine ratio; RL, Ringer's lactate group.

Journal Pre-proof