Lack of Nephrotoxicity by 6% Hydroxyethyl Starch 130/0.4 during Hip Arthroplasty

A Randomized Controlled Trial

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ABSTRACT

Background: Hydroxyethyl starch (HES) is commonly used as plasma expander during surgery but may be nephrotoxic as seen in studies in patients with sepsis. The authors hypothesized that the possible nephrotoxicity of 6% HES 130/0.4 could be revealed by measurements of urinary excretion of neutrophil gelatinase–associated lipocalin (u-NGAL) in patients with normal renal function during hip arthroplasty.

Methods: In this randomized, double-blinded, placebo-controlled study, 40 patients referred for hip arthroplasty received either 6% HES 130/0.4 or isotonic saline 0.9%; 7.5 ml/kg during the first hour of surgery and 5 ml/kg during the following hours; 38 patients completed the study. U-NGAL, urine albumin, blood pressure, and plasma concentrations of creatinine, renin, NGAL, albumin, angiotensin-II, and aldosterone were measured before, during, and after surgery. U-NGAL was defined as primary outcome.

Results: There were no significant differences in U-NGAL (mean difference and 95% CI), plasma creatinine, and urine albumin during the study. U-NGAL and urine albumin increased significantly in both groups the morning after surgery but was normalized at follow-up after 10 to 12 days. Mean arterial pressure was significantly higher during the recovery period in the HES group compared with that in the control group (91 [13] and 83 [6] mmHg, mean [SD], $P < 0.03$). Plasma renin and angiotensin-II were nonsignificantly different in both groups, whereas plasma aldosterone was significantly lower in the HES group. Plasma albumin was reduced in both groups, but to a significantly lower level in the HES group.

Conclusion: The study showed no evidence of a harmful effect of intraoperative infusion of 6% HES 130/0.4 on renal function in patients during hip arthroplasty. **(Anesthesiology 2014; 121:948-58)**

HYDROXYETHYL starch (HES) is widely used as volume expander to maintain circulation in patients during surgery, trauma, and in critical disease, where a rapid and sustained volume expansion is the goal.[1–3] However, acute kidney injury (AKI) is sometimes a complication in these patients and HES might be a contributing factor.

Acute kidney injury is often diagnosed using a sudden rise in plasma creatinine (p-crea) or an abrupt decrease in urine output (UO).[4,5] P-crea depends on sex, nutrition, medication, muscle mass, and age and it increases 24 to 48 h after renal injury, so the diagnosis of AKI is delayed when using p-crea alone as an indicator for renal damage.[6,7] New technology allows for earlier diagnosis of AKI using measurements of biomarkers in urine.[8,9] Neutrophil gelatinase–associated lipocalin (NGAL) is a small protein, which is filtered *via* the glomeruli and reabsorbed in the proximal tubules, and thus low concentrations of NGAL can be measured in the blood and urine.[6,7] Approximately 6 h after a renal injury, NGAL increases rapidly due to an up-regulated expression and secretion in the epithelial cells of the thick ascending limb of Henle's loop, the distal tubules, and the collecting ducts.[6,7] Thus, NGAL can be used as a marker of renal damage. However, infections and malignancies can give falsely increased levels.[7,10]

Intravenously administrated HES is excreted in urine but is also partly accumulated in the tissues.[11,12] Studies in animals

What We Already Know about This Topic

- Acute kidney injury is sometimes observed in patients in whom hydroxyethyl starch has been used to produce a rapid and sustained expansion of intravascular volume

What This Article Tells Us That Is New

- Thirty-eight patients with normal renal function were randomly assigned to receive intraoperative infusions of 6% hydroxyethyl starch 130/0.4 or 0.9% saline during hip arthroplasty
- Measurement of urinary excretion of neutrophil gelatinase–associated lipocalin and albumin as well as plasma creatinine concentrations and creatinine clearance before, during, and after surgery revealed no evidence of a harmful nephrotoxic effect of 6% hydroxyethyl starch 130/0.4 in patients with previous normal renal function

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and humans showed that HES molecules were accumulated in the proximal tubule cells with subsequent vacuolization and swelling—a condition known as osmotic nephrosis.[13–19] New HES solutions, tetrastarches, were developed to reduce the plasma persistence time and the harmful side effects of the older types of HES. A lower molecular weight and molar substitution decreased the tissue accumulation and the impact on coagulation, whereas the pharmacokinetic properties regarding the hemodynamic were sustained due to the nature of colloid solutions.[11,19–21] However, recent studies, primarily conducted in patients with sepsis, found impaired renal function even when using tetrastarches.[22–24] In contrast, perioperative studies found no evidence of AKI after infusion of tetrastarches.[25–30]

We hypothesized that 6% HES 130/0.4 had a nephrotoxic effect, which could be revealed by measurements of urinary NGAL (u-NGAL); that 6% HES 130/0.4 influenced kidney function differently than crystalloids due to the different pharmacokinetic properties of colloids compared with that of crystalloids; that subsequent changes in vasoactive hormones also could influence renal function. In the current consecutive, randomized, placebo-controlled, double-blinded study, the purposes were to measure (1) renal function, that is, urine and plasma NGAL (p-NGAL), p-Crea, creatinine clearance (C_{crea}), urine albumin (u-Alb), UO, urine aquaporin2 (u-AQP2), and free water clearance (C_{H2O}); (2) blood pressure; (3) plasma concentrations of renin (PRC), angiotensin-II (p-AngII), aldosterone (p-Aldo), vasopressin (p-AVP), and albumin (p-Alb) before, during, and after surgery in patients with normal renal function during and after hip arthroplasty.

Materials and Methods

Ethics

The study was approved by the Danish Medicines Agency, Copenhagen, Denmark (EudraCT: 2011-004906-12), the Regional Committee of Health Research Ethics, Viborg, Denmark (J. No. M-20110250), and registered at ClinicalTrialsGov (NCT01486576) before recruitment started. The study was carried out in accordance with the Declaration of Helsinki and monitored by the Good Clinical Practice committee, University of Aarhus, Aarhus, Denmark. Written informed consent was obtained from each patient.

Patients

Inclusion Criteria. Inclusion criteria were as follows: both sexes, older than 18 yr, diagnosed with primary osteoarthritis, and scheduled for cement-less hip-replacement done with spinal anesthesia.

Exclusion Criteria. Exclusion criteria were as follows: estimated glomerular filtration rate less than 15 ml/min, pregnancy or breast feeding, need of nonsteroid antiinflammatory drugs, blood donation within a month before the surgery, anamnestic, or clinical findings, which excluded surgery according to the general procedures in Departments of Anesthesiology or Orthopedics.

Withdrawal Criteria. Withdrawal criteria were as follows: development of exclusion criteria, change from spinal anesthesia to general anesthesia, complications during surgery such as severe bleeding with blood transfusion, prolonged postoperative course due to resurgery, infection or withdrawal of consent, and unexpected increased levels of u-NGAL before intervention.

Recruitment

All patients were recruited from the Department of Orthopedics, Holstebro Hospital, Holstebro, Denmark.

Design

The study was a randomized, placebo-controlled, double-blinded study in 40 patients undergoing elective hip arthroplasty.

Intervention

The patients were randomized consecutively to receive either 6% HES 130/0.4 (Voluven®) as active treatment or 0.9% isotonic saline as placebo. Both fluids were manufactured by Fresenius Kabi (Bad Homburg, Germany) and produced in 500 ml freeflex® bags (Fresenius Kabi). Each bag was concealed in identical black plastic and sealed and marked 1 to 40. Five bags (same fluid) were packed in cardboard boxes corresponding to each randomization number. All packing and blinding was performed by the Hospital Pharmacy.

The infusion rate was 7.5 ml/kg in the first hour and 5 ml/kg in the following hours until the end of recovery. If an episode of excess bleeding occurred or if mean arterial pressure (MAP) decreased below 60 mmHg, more fluid could be given until hemodynamic stability was obtained. According to the manufacturer and the Danish Medicines Agency (Copenhagen, Denmark), the maximum dose was 50 $mlkg^{-1}$ d^{-1}. No supplemental fluid was given intravenously during the surgery and in the recovery period.

Randomization

Staff from the hospital pharmacy generated the randomization list in blocks of eight using a Web page.* Treatment assignment was concealed from patients, clinicians, and research staff until after the last visit of the last patient.

Outcomes

Primary outcome: u-NGAL.

Secondary outcomes: P-NGAL, UO, PRC, p-ANGII, p-Aldo, p-AVP, C_{crea}, P-crea, C_{H2O}, u-Alb, u-AQP2, p-alb, systolic blood pressure, diastolic blood pressure (DBP), MAP, and heart rate (HR).

Number of Patients

With a significance level of 5% and a power of 80%, a total of 32 patients were needed to detect a 100 ng/ml difference

* Available at: www.randomization.com. Accessed March 18, 2014.

in u-NGAL with an SD of 100 ng/ml. We estimated that 40 patients should be included in the trial, 20 patients in each intervention group (HES/saline), because of possible drop-outs and complications during surgery.

Experimental Procedures

Anesthetic Procedures before, during, and after Surgery. All patients received paracetamol 1,000 mg before surgery. On the operating table, a venous cannula was placed in a cubital vein for blood sampling and medication. After the first blood sampling, the fluid infusion was started together with monitoring of systolic blood pressure, DBP, HR, and arterial saturation. All patients then received prophylactic doses of cefuroxime 1.5 g and tranexamic acid 15 mg/kg (maximum 1 g) and a urinary catheter. Spinal anesthesia was performed with the patient in the lateral decubitus position, side of surgery upwards, spine column horizontal, lumbar puncture preferably midline at L3 to L4 with a pencil point 25-gauge needle. Marcaine 5 mg/ml, 3 ml was injected in the subdural space. If MAP decreased below 60 mmHg, intermittent doses of phenylephrine 0.1 mg or supplemental intervention fluid were given intravenously. Supplemental oxygen was provided *via* a nasal cannula if arterial saturation decreased below 96%. The patients were not allowed to receive ephedrine, dexamethasone, or nonsteroid antiinflammatory drug during the entire study period due to a possible false-negative influence on the results in the blood or urine samples

Urine and Blood Sampling. The patients collected 24-h urine the day before surgery (urine 1, baseline). Urine was collected from start of surgery and during 4 h (urine 2, surgery). Afterward, urine was collected till the next morning at 8.00 AM (urine 3, postsurgery). Urine bags were emptied every 4 h, and urine was stored at 5°C. When the patient was discharged, one further urine sample was obtained. This was collected after the urine catheter had been removed (urine 4, discharge). The patients collected 24-h urine at home 10 or 12 days after surgery on the day before the follow-up visit at the hospital (urine 5, follow-up). Blood samples were drawn through the venous cannula just before anesthesia and intervention. In the recovery room after surgery, blood samples were drawn within the first 2 h after arrival. In total, 140 ml blood was drawn from each patient.

Biochemical Analyses. All urine and blood samples were centrifuged for 10 min at 3,500*g* and 4°C. Then plasma was separated from blood cells. All samples were then kept frozen at −80° or −20°C until assayed and were centrifuged again just before the assays were performed to minimize any impurities in the samples. Every analysis was done at the same time by the same laboratory technician to minimize variability in the results.

A commercial enzyme-linked immunosorbent assay (ELISA) from Bioporto (Hellerup, Denmark) was used to determine the NGAL in urine and plasma. Minimal detection level was 1.6 pg/ml. Variations were interassay max 7.2% in urine and max 4.6% in plasma and intraassay max 4.9 % in urine and max 4.5% in plasma. All samples were analyzed with kits from the same batch.[31] *U-AQP2* was measured by radioimmunoassay. Antibodies were raised in rabbits to a synthetic peptide corresponding to the 15 COOH-terminal amino acids in human AQP2 to which was added an NH_2-terminal cysteine for conjugation and affinity purification. Minimal detection level was 34 pg per tube. Coefficients of variation were 11.7% (interassay) and 5.9% (intraassay).[32,33] *PRC* was determined by radioimmunoassay from CIS Bio International (Gif-Sur-Yvette Cedex, France). Minimal detection level was 1 pg/ml. Coefficients of variation were 0.9 to 3.6% (intraassay) and 3.7 to 5.0% (interassay) in the range of 4 to 263 pg/ml. *P-Aldo* was determined by radioimmunoassay, using a commercial kit from Demeditec Diagnostics GmbH (Kiel, Germany). Minimal detection level was 25 pmol/l. Coefficients of variation were 9.0% (interassay) and 8.5% (intraassay). *P-AngII* and *p-AVP* were extracted from plasma with C18 Sep-Pak (Water Associates, Milford, MA) and subsequently determined by radioimmunoassay. The antibody against AngII was obtained from the Department of Clinical Physiology, Glostrup Hospital, Glostrup, Denmark. Minimal detection level was 2 pmol/l. Coefficients of variation were 12% (interassay) and 8% (intraassay). The antibody against vasopressin was a gift from Professor Jacques Dürr, M.D., H. Lee Moffitt Cancer Center, Memorial Hospital of Tampa, Saint Joseph's Hospital, Tampa General Hospital, Tampa, Florida. Minimal detection level was 0.2 pmol/l. Coefficients of variation were 13% (interassay) and 9% (intraassay).[34,35] *P-Alb* was analyzed with a photometric method using Architect C16.000 from Abbott (Abbott Park, IL), with a coefficient of variation of 2.6% (interassay) as a part of routine analyses done at the Department of Clinical Biochemistry.

Hemodynamic Data. Systolic blood pressure, DBP, and HR were recorded continuously throughout the surgery with Infinity Delta, XL® (Dräger, Lübeck, Germany). All values during surgery were noted in 5-min intervals on paper forms following normal hospital protocol. In the recovery period, values were noted in 15-min intervals and S/5 Compact Anesthesia Monitor (Datex-Ohmeda; GE Healthcare Finland Oy, Helsinki, Finland) was used. All values were divided into five different time periods (baseline, preincision, incision, postincision, and recovery period), and the average of those periods was calculated and used for analyses.

Calculations. Clearance (C) of substance X was calculated as $C_X = U_X/(P_X \times UO)$, where U_X denotes concentration of x in urine, P_X denotes concentration of x in plasma, and UO is urine excretion rate

Mean arterial pressure was calculated according to the formula: MAP = (systolic blood pressure − DBP)/3 + DBP.

Statistic Analysis

Parametric data are presented as means with SDs and nonparametric data as medians with 25 and 75 quartiles. Normality was assessed by Shapiro–Wilk test ($P > 0.05$). *P* values were reported as two-tailed values and statistical significance was defined at a *P* value of less than 0.05.

When data were found to be parametric, homogeneity of variances was assessed by Levene test for equality of variance

to minimize the risk of type-I statistical errors. An unpaired *t* test was used for comparison between the groups, and if homogeneity was violated, a Welch *t* test was used, respectively. ANOVA with repeated measures were used for comparisons within each group. The assumption of sphericity was assessed by Mauchly test of sphericity, and if violated, a Greenhouse–Geisser correction was applied. If ANOVA was significant, a *post hoc* analysis with a Bonferroni adjustment was performed. Parametric data of plasma samples were compared within each group with a paired *t* test.

If data were found to be nonparametric, by the Shapiro–Wilk test, similar distribution of the groups was assessed by visual inspection and hereafter a Mann–Whitney U test was used to compare the groups. The Friedman test was used for comparisons within each group, and if statistically significant, a *post hoc* analysis with pairwise comparisons was performed with a Bonferroni correction for multiple comparisons. Nonparametric data of plasma samples were compared within each group by a Wilcoxon signed-rank test.

A mean difference with a 95% CI was calculated using bootstrapping for the nonparametric data. Comparison of two frequencies was done by Fisher exact test. Statistics were performed using PASW version 20.0.0 (SPSS Inc., Chicago, IL).

Results

Demographics

Patients referred for elective hip arthroplasty were consecutively screened between February 2012 and January 2013 (fig. 1). Letters with trial information were sent to 185 patients and 54 of those requested further information. Twelve patients were noneligible due to: use of nonsteroid antiinflammatory drugs (three patients), not possible to anesthetize with spinal anesthesia (three patients), not willing to receive spinal anesthesia (two patients), and not willing to participate (four patients). A total of 42 patients were included. Two patients were excluded *before* intervention due to a change from spinal anesthesia to general anesthesia because of a spinal scoliosis (one patient) and due to an intake of nonsteroid antiinflammatory drug just before surgery (one patient). Thus, 20 patients received HES and 20 received saline. One patient in the HES group was excluded during intervention due to an ineffective spinal anesthesia and one patient in the saline group due to practical problems with the blood and urine sampling, and thus, 38 patients were included in the analysis. The trial ended after the last visit of the last patient in March 2013.

The two groups were comparable regarding age, sex, body mass index, comorbidities, antihypertensive medication, office blood pressure, and screening biochemistry (table 1). During the entire trial, there were no serious adverse reactions related to the intervention and no protocol violations.

Two patients (one in each group) had very high u-NGAL and u-Alb values at baseline, and u-NGAL and u-Alb values of these two patients were not included in these calculations.

Operative Procedures

The two groups were comparable regarding duration of anesthesia, surgery and recovery, and length of hospital stay (table 2). Furthermore, the loss of blood (HES 250 ml *vs.* saline 200 ml, $P = 0.2$) and the amount of intravenous fluid given (HES 1,475 ml *vs.* saline 1,500 ml, $P = 0.9$) were the same in both groups. There was no significant difference between the groups regarding the number of patients receiving phenylephrine (6 *vs.* 10, $P = 0.33$) or the used average dose per patient (0.15 mg *vs.* 0. 30 mg, $P = 0.26$) even though more patients in the saline group received higher doses of phenylephrine.

Urine Neutrophil Gelatinase–associated Lipocalin, Urine Albumin Excretion, and Urine Albumin/Creatinine Ratio

Table 3 shows that u-NGALs were nonsignificantly higher in the HES group after the intervention—both when expressed as a concentration and when adjusted for creatinine. However, the differences between the groups were modest and nonsignificant throughout the study period. All CIs were wide and ranged from negative to positive values and were thus nonsignificant. Within each group, significant differences were found when the urines were compared with baseline, but at follow-up, u-NGAL was normalized. Urine albumin/creatinine ratio increased to the same extent in both groups after intervention and was normalized at follow-up (table 3).

Creatinine Clearance, Urine Aquaporine2, Free Water Clearance, and Urine Output

Table 3 shows the results of C_{crea}, u-AQP2, C_{H2O}, and UO. C_{crea} was numerically higher in the HES group at baseline and during the study, but no significant differences were found between the groups at any time. U-AQP2$_{CR}$ was numerically higher in the HES group except at postsurgery. U-AQP2$_{CR}$ increased during surgery in both groups, decreased in postsurgery, and increased again at discharge. The differences were nonsignificant between the groups during the entire period. C_{H2O} decreased during surgery and postsurgery in the HES group, whereas in the saline group, C_{H2O} increased during surgery and afterward decreased. The differences in C_{H2O} were nonsignificant between the groups at all times. At baseline, UO was significantly lower in the HES group ($P < 0.05$), whereas increased during surgery. During surgery and postsurgery, UO decreased in the saline group. However, except at baseline, the differences were nonsignificant between the groups.

Plasma Neutrophil Gelatinase–associated Lipocalin, Plasma Albumin, and Plasma Creatinine

Plasma NGAL was decreased significantly in the HES group after intervention ($P < 0.001$) but was almost unchanged in the saline group. P-Alb was significantly lower in the HES group after intervention ($P < 0.001$) compared with that in the saline group. There was no significant difference in p-crea between the groups at baseline or after intervention (table 4).

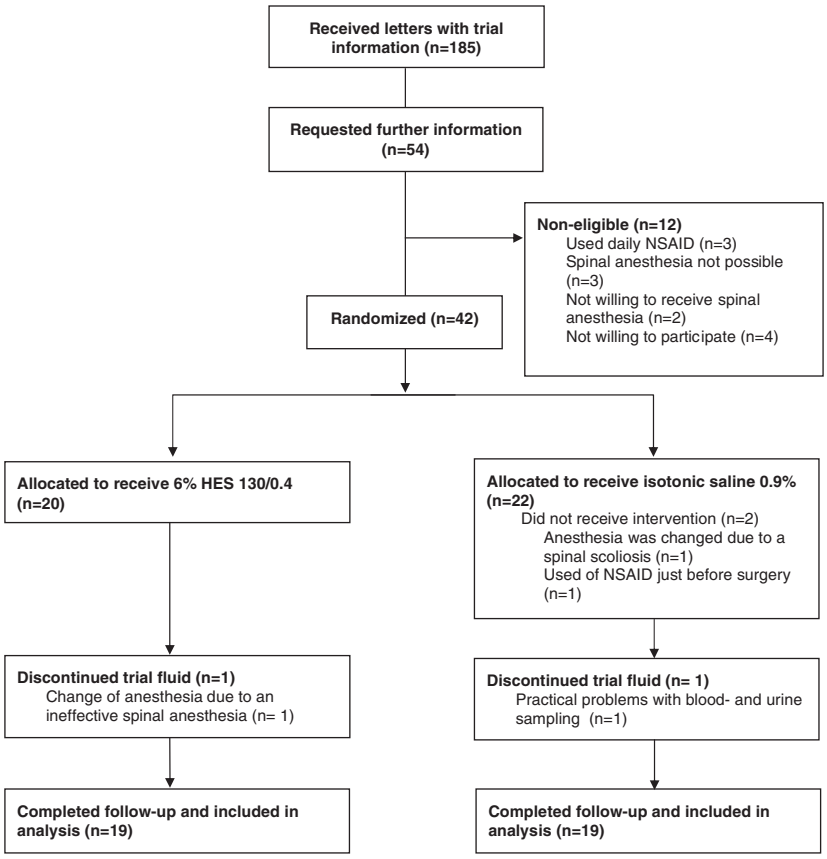

Fig. 1. Flow chart of assessment, randomization, and completion. HES = hydroxyethyl starch; NSAID = nonsteroid antiinflammatory drug.

Vasoactive Hormones in Plasma

Table 4 shows the concentration of vasoactive hormones before and after intervention. PRC and p-ANGII were significantly decreased in the HES group after intervention (PRC, $P = 0.007$; p-ANGII, $P < 0.05$). P-Aldo was lower in both groups after intervention, but only to a significantly lower level in the HES group ($P < 0.003$). In each group, p-AVP was increased to a significantly higher level after intervention (HES, $P < 0.01$; saline, $P = 0.01$).

Blood Pressure and HR

During baseline, preincision, incision, and postincision periods, HR, systolic blood pressure, DBP, and MAP were numerically higher in the HES group, but no significant differences existed between the groups. In the recovery period, DBP (72 ± 14 *vs.* 63 ± 7, $P < 0.03$) and MAP (91 ± 14 *vs.* 83 ± 6, $P < 0.03$) were significantly higher in the HES group (table 5).

Discussion

In this randomized, placebo-controlled, double-blinded study, we compared the effect of intraoperative infusion of 6% HES 130/0.4 *versus* 0.9% saline in patients with normal renal function. The aim was to clarify whether 6% HES 130/0.4 had a nephrotoxic effect by measuring u-NGAL, C_{crea}, u-Alb, and p-crea before, during, and after surgery. None of these outcomes indicated any sign of nephrotoxicity during the study. Thus, we found no evidence of a harmful nephrotoxic effect of 6% HES 130/0.4 in patients with previous normal renal function during hip arthroplasty.

In our study, we did find slightly increased levels of u-NGAL in urine samples in both groups in the postoperative period, highest before discharge from the hospital, but u-NGAL was normalized again at follow-up after 10 to 12 days. It is possible that these transient increased values in both groups could be explained by the hemodynamic stress during surgery. In addition, we used chloride-rich solutions as intervention and placebo, which may increase the risk of AKI.[36] The 95% CI for the discharge urine was very wide, which limits our conclusion that no difference in u-NGAL was measured between the groups. This shows that the study is too small to have a sufficient power to detect a difference between the groups. However, as all the measured values of u-NGAL are well below the threshold of 100 ng/ml, which is stated by the manufacturer of the ELISA kit to indicate the sign of AKI, it would properly be a clinically irrelevant difference even if we had found a significant one. Two other randomized controlled trials did not find any differences between tetrastarch and crystalloid in severe sepsis and in surgery regarding u-NGAL either.[1,23]

Our trial was not designed to evaluate the long-term influence on renal function as it would be unlikely to find a

Table 1. Baseline Characteristics

	HES (n = 19)	NaCl (n = 19)
Age, yr	63 (10)	66 (10)
Male sex, no. (%)	15 (79)	14 (74)
Body mass index	28.8 (4.9)	28.5 (2.9)
Comorbidities, no. (%)		
Hypertension	9 (47.4)	12 (63.2)
Heart disease		
PCI	1 (5.3)	2 (10.5)
CABG	1 (5.3)	0
Heart failure	1 (5.3)	1 (5.3)
COPD	2 (10.5)	2 (10.5)
Diabetes mellitus		
Type I	0	0
Type II	1 (5.3)	0
Stroke	0	1 (5.3)
Other	7 (36.8)	8 (42.1)
Antihypertensive treatment, no. (%)		
ACE inhibitors/ ATIIrb	6 (31.6)	8 (42.1)
Calcium channel blockers	5 (26.3)	4 (21.1)
β-blockers	3 (15.8)	3 (15.8)
Diuretics	4 (21.1)	8 (42.1)
Office blood pressure, mmHg		
SBP	149 (16.3)	148 (17.6)
DBP	89 (6.4)	87 (11.7)
Pulse	69 (9.1)	69 (14.0)
Screening biochemistry		
p-K, mmol/l	4.0 (0.3)	4.1 (0.3)
p-Na, mmol/l	141 (2.2)	141 (1.4)
p-Alb (g/l)	44 (2.8)	43 (2.4)
p-Crea, μmol/l	81 (13.0)	87 (32.3)
eGFR, ml/min	82 (14.2)	80 (21.1)
p-Hgb, mmol/l	9.1 (0.7)	9.2 (0.6)
Volume of baseline urine (ml/24 h)	2,140 (1,881:2,598)	2,609 (2,257:3,020)

Values are no. (%) or means (SD).

ACE = angiotensin-converting enzyme; ATIIrb = angiotensin-II receptor blockers; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HES = 6% hydroxyethyl starch 130/0.4; NaCl = saline 0.9%; p-Alb = plasma albumin; p-crea = plasma creatinine; p-Hgb = plasma hemoglobin; p-K = plasma potassium; p-Na = plasma sodium; PCI = percutaneous cardiovascular intervention; SBP = systolic blood pressure.

nephrotoxic effect of HES after a longer observation period, when no signs of renal impairment were seen within a period of a fortnight after the intervention. This is in agreement with another surgical trial that had a follow-up period of 28 days and did not find any sign of adverse renal effects.[37] However, this trial was different from ours as it had a pediatric population and compared 6% HES 130/0.4 with 5% human serum albumin. Several studies have evaluated renal function in surgical patients, who received intraoperative infusions of tetrastarch. Comparisons of tetrastarch to crystalloids showed no evidence of renal impairment.[3,25,26,28,38,39] One study measured transiently higher levels of p-crea and p-carbamide in patients after cardiac surgery receiving colloids, but the changes were modest and within normal ranges, and no differences existed between the groups after 72 h.[27] This is supported by two recently published articles that found no indications of a harmful effect of intraoperative infusions of tetrastarch.[29,30] These articles based their evaluation on incidence of renal replacement therapy or changes in creatinine concentrations. Throughout our study, the patients in the 6% HES 130/0.4 group had a numerically, slightly higher C_{crea} compared with the saline 0.9% group, but no significant differences existed at any time.

Recently, increased mortality or increased use of renal replacement therapy was reported in critically ill patients with septicemia, who received tetrastarch as fluid resuscitation compared with crystalloids.[22–24] However, a recently published study found a nonsignificant increase in renal replacement therapy and an increased 90-day mortality in the crystalloid group.[40] But due to the open-label design and free use of different types of colloids and crystalloids, this study design make direct conclusions regarding HES difficult. The effect of fluid therapy depends deeply on an intact endothelial glycocalyx layer, which is severely compromised in patients with septicemia. Thus, the degraded glycocalyx results in immediate tissue edema, less effect of the administered fluid therapy and increased harm.[21,41] Hereby in 2013, new recommendations from the European Medicines Agency comprised a restriction of use of products containing HES in patients with septicemia, renal impairment, and burns, but not in patients with acute hypovolemia due to blood loss. In our study, we included patients with previous normal renal function, who were scheduled for elective

Table 2. Perioperative Management

	HES (n = 19)	NaCl (n = 19)	*P* Value
Time periods (hh:mm)			
Duration of anesthesia	1:48 (1:45–2:00)	1:50 (1:40–2:00)	0.99
Duration of the surgery	0:40 (0:36–0:49)	0:40 (0:38–0:42)	0.44
Duration of the recovery period	2:30 (1:57–2:55)	2:45 (2:05–3:20)	0.33
Length of hospital stay, days	1.5 (1.5; 2.5)	1.5 (1.5; 2.5)	0.90
Intervention fluid iv, ml	1,475 (1,000:1,500)	1,500 (1,000:1,500)	0.93
Blood loss, ml	250 (200:500)	200 (150:296)	0.23
Patients needing phenylephrine, no. (%)	6 (32)	10 (53)	0.33
Phenylephrine dose per patient, mg	0.15 (0.1:0.4)	0.30 (0.2:0.5)	0.26

Values are medians (25%; 75% quartiles) or no (%).

HES = 6% hydroxyethyl starch 130/0.4; iv = intravenous; NaCl = saline 0.9%.

Table 3. Renal Function

	Urine 1 Baseline	Urine 2 Surgery	Urine 3 Postsurgery	Urine 4 Discharge	Urine 5 Follow-up	*P* Value
U-NGAL (ng/ml) (primary outcome)						
HES	9.5 (5.3:15.3)	6.0 (3.0:12.0)	16.0 (13.5:33.5)	85.0 (41.5:160.5)***	9.0 (7.0:16.5)	<0.001
NaCl	7.0 (5.0:10.0)	5.5 (4.8:8.5)	14.0 (6.8:24.5)	78.0 (49.8:116.3)***	10.0 (6.0:16.0)	<0.001
Mean difference (95% CI)	2.5 (–1.5 to 6.3)	1.5 (–3.0 to 6.5)	3.7 (–7.3 to 14.4)	3.8 (–32.9 to 41.1)	0.5 (–3.3 to 4.4)	
P value	0.35	0.93	0.12	0.26	0.57	
$U\text{-}NGAL_{CR}$ (ng/μmol)						
HES	1.3 (0.9:2.4)	1.0 (0.5:2.3)	2.1 (1.4:2.6)	6.6 (4.9:7.7)***	1.7 (1.0:2.6)	<0.001
NaCl	1.2 (0.8:2.2)	1.1 (0.6:1.7)	1.5 (1.0:2.5)	5.5 (3.7:8.9)***	1.6 (1.0:2.9)	<0.001
Mean difference (95% CI)	–0.01 (–0.8 to 0.7)	0.2 (–0.4 to 0.9)	0.1 (–0.8 to 0.9)	–2.3 (–6.4 to 1.3)	–0.4 (–1.1 to 0.4)	
P value	0.70	0.76	0.31	0.70	0.97	
U-Alb (mg/l)						
HES	6.0 (3.3:11.8)	15.0 (8.3:22.5)	26.0 (11.8:49.3)*	41.5 (12.5:73.5)**	4.0 (2.0:5.5)	<0.001
NaCl	6.0 (3.0:15.3)	16.0 (10.0:30.0)*	20.0 (10.0:42.0)***	27.0 (15.0:63.0)***	3.5 (1.0:6.5)	<0.001
Mean difference (95% CI)	–8.2 (–49.4 to 31.0)	–0.1 (–31.7 to 34.4)	–36.0 (–114.1 to 18.7)	–2.6 (–58.1 to 51.3)	–26.4 (–90.3 to 12.5)	
P value	0.88	0.48	0.67	0.92	0.85	
$U\text{-}Alb_{CR}$ (mg/mmol)						
HES	1.0 (0.5:1.7)	2.4 (1.5:4.1)**	2.3 (1.3:3.4)	2.4 (1.0:3.7)	0.5 (0.3:0.8)	<0.001
NaCl	0.8 (0.6:2.7)	2.4 (1.7:4.5)*	2.3 (1.7:3.3)	3.3 (1.7:4.3)	0.7 (0.2:1.1)	<0.001
Mean difference (95% CI)	–4.1 (–13.6 to 2.5)	–5.3 (–17.9 to 2.9)	–4.5 (–13.1 to 0.9)	–2.4 (–6.7 to 1.5)	–5.8 (–17.5 to 0.5)	
P value	0.90	0.58	0.78	0.48	0.73	
C_{crea} (ml/min)						
HES	115.6 (83.8:141.3)	118.7 (91.8:129.9)	122.7 (84.2:153.1)	—	126.0 (89.2:160.8)	0.31
NaCl	104.6 (83.4:129.6)	109.2 (73.1:137.1)	106.3 (85.2:129.9)	—	104.9 (81.9:125.9)	0.82
Mean difference (95% CI)	–0.4 (–23.8 to 23.2)	4.6 (–26.3 to 33.0)	2.9 (–25.0 to 32.4)	—	19.5 (–6.8 to 44.5)	
P value	0.32	0.48	0.63	—	0.08	
$U\text{-}AQP2_{CR}$ (ng/mmol)						
HES	171.5 (125.9:204.0)	182.2 (125.0:216.3)	151.5 (113.0:207.8)	294.3 (187.8:455.2)***	181.3 (135.7:200.2)	<0.01
NaCl	157.5 (132.5:183.8)	182.5 (150.7:223.5)	178.0 (150.0:230.6)	210.2 (178.9:334.4)**	182.8 (166.8:191.5)	<0.01
Mean difference (95% CI)	0.6 (–27.4 to 27.8)	–65.3 (–123.1 to –16.4)	–13.1 (–53.6 to 28.2)	31.1 (–70.4 to 132.6)	–7.7 (–30.3 to 12.9)	
P value	0.47	0.20	0.27	0.20	0.81	
C_{H2O} (ml/min)						
HES	1.1 (0.3:1.5)	0.3 (–1.1:2.4)	–0.7 (–2.8:0.2)*	—	—	<0.05
NaCl	0.3 (–0.2:0.9)	1.2 (–1.5:3.5)	–2.5 (–3.8: –0.4)*	—	—	0.03
Mean difference (95% CI)	0.5 (–0.6 to 1.5)	–0.3 (–3.1 to 2.5)	1.2 (–0.3 to 2.7)	—	—	
P value	>0.05	0.66	0.11	—	—	
UO (ml/min)						
HES	1.4 (1.3:1.8)	2.1 (1.0:3.8)	0.7 (0.5:1.3)**	—	1.4 (1.1:1.9)	0.03
NaCl	1.7 (1.6:2.1)	1.2 (1.0:2.6)	1.1 (0.7:1.5)***	—	1.8 (1.4:2.1)	0.02
Mean difference (95% CI)	–0.4 (–0.7 to 0.0)	0.01 (–0.8 to 0.8)	–0.2 (–0.5 to 0.1)	—	–0.2 (–0.6 to 0.2)	
P value	<0.05	0.43	0.11	—	0.25	

Values are medians (25% and 75% quartiles).

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

C_{crea} = Creatinine Clearance; C_{H2O} = free water clearance; HES = 6% hydroxyethyl starch 130/0.4; NaCl = saline 0.9%; u-Alb = urine albumin; $u\text{-}Alb_{CR}$ = urine albumin adjusted for creatinine; $u\text{-}AQP2_{CR}$ = urine aquaporine2 adjusted for creatinine; u-NGAL = urine neutrophil gelatinase–associated lipocalin; $u\text{-}NGAL_{CR}$ = urine neutrophil gelatinase–associated lipocalin adjusted for creatinine; UO = urine output.

Table 4. Vasoactive Hormones, p-NGAL, p-Alb, and p-crea

	Presurgery	Postsurgery	*P* Value Within
P-NGAL (ng/ml)			
HES	88.0 (78.0:103.0)	79.0 (73.0:94.0)	<0.001
NaCl	78.0 (71.0:105.3)	80.5 (66.5:95.8)	0.18
P value	0.48	0.92	
P-Alb (g/l)			
HES	42.0 (41.0:43.0)	31.0 (30.0:34.0)	<0.001
NaCl	42.0 (39.0:43.3)	37.0 (35.0:38.3)	<0.001
P value	0.77	<0.001	
P-crea (μmol/l)			
HES	81.0 (72.0:91.0)	80.0 (69.0:95.0)	0.17
NaCl	77.0 (66.0:87.3)	75.0 (67.3:87.0)	0.30
P value	0.35	0.53	
PRC (pg/ml)			
HES	9.5 (5.3:14.2)	7.4 (4.9:13.6)	0.01
NaCl	6.9 (4.0:12.2)	6.9 (4.3:20.5)	0.11
P value	0.16	0.92	
P-ANGII (pg/ml)			
HES	9.0 (6.0:15.0)	6.0 (5.0:11.0)	<0.05
NaCl	6.5 (5.0:11.0)	7.5 (5.0:12.5)	0.31
P value	0.31	0.31	
P-Aldo (pmol/l)			
HES	132.0 (104.0:169.0)	57.0 (37.0:82.0)	<0.01
NaCl	125.0 (101.3:184.8)	104.0 (49.0:219.8)	0.29
P value	0.82	0.03	
P-AVP (pg/ml)			
HES	0.3 (0.2:0.4)	0.7 (0.3:0.8)	<0.01
NaCl	0.2 (0.1:0.3)	0.4 (0.2:0.7)	0.01
P value	0.14	0.14	

Values are medians (25% and 75% quartiles).

HES = 6% HES 130/0.4; NaCl = saline 0.9%; p-Alb = plasma albumin; p-Aldo = plasma aldosterone; p-AngII = plasma angiotensin II; p-AVP = plasma vasopressin; p-Crea = plasma creatinine; p-NGAL = plasma neutrophil gelatinase–associated lipocalin; PRC = plasma renin.

hip arthroplasty, who were healthy except for primary osteoarthritis and well-treated hypertension. Our group of surgical patients with an intact endothelial glycocalyx barrier cannot be compared with the severely ill patients in the intensive care unit mentioned above, which is also stated in the review article about tetrastarches and surgery.[30] Our results do not indicate that 6% HES 130/0.4 have a nephrotoxic effect on renal function in surgical patients with a previous normal renal function.

Mean arterial pressure and DBP were significantly higher in the recovery period after HES infusion compared with saline infusion. The amount of intravenous fluid and blood loss during surgery were the same in the two groups and the number of patients, who received phenylephrine, and the total dose of phenylephrine did not deviate significantly. But the sample size was small. It was, however, most unexpected that MAP and DBP only deviated in the recovery period and not during anesthesia, as theoretically, the hemodynamic properties of colloid should exceed that of crystalloid by up to three times due to the different pharmacokinetic properties of the fluids, with a higher intravascular persistence time of the colloid due to the colloid osmotic forces.[11] Hereby, significantly less volume should be used in the colloid group to obtain a hemodynamic goal.[1,2] An equal amount of 6% HES 130/0.4 and saline 0.9% have only been used in one previous randomized, controlled trial and no differences in hemodynamic values were found.[3] An older study found an effective hemodynamic response to infusion of hetastarch in healthy volunteers, which have contributed to the general opinion that all types of HES are more effective to obtain a hemodynamic goal than crystalloids.[2] However, one cannot extrapolate these results to the tetrastarches, as hetastarch is known to have other pharmacokinetic properties.[20] Most likely, the increase in MAP and DBP found in the recovery period in the 6% HES 130/0.4–treated patients in this study should be attributed to an expansion of the plasma fluid volume to a greater extent than after saline infusion even though this is properly minor. This is supported by the more pronounced reduction of p-Alb found in the HES group.[42] In conclusion, our results surprisingly found only a minor efficiency of HES compared with saline, which can be explained by the different pharmacokinetic properties of the fluids. However, it is important to remember that our study was not adequately powered to analyze hemodynamic differences between HES and saline in detail.

In this study, volume expansion with HES resulted in a significant reduction in PRC, p-AngII, and p-Aldo, whereas the three hormones remained unchanged in the control group. P-Aldo was significantly lower after 6% HES 130/0.4 infusion, which is in accordance with a more expanded extracellular fluid volume in this group. This is supported by the low p-Alb in the HES group as mentioned above. P-AVP increased after surgery to the same extent in both groups. This effect could be attributed to the decrease in blood pressure and stimulation *via* baroreceptors during surgery. The increase in p-AVP can explain the increase in u-AQP2 in both groups after surgery compared with baseline.[32] Increased u-AQP2 reflects increased water transport from the tubular lumen to the intracellular space *via* the aquaporin2 water channels in the principal cells in the distal part of the nephron.[32,33,43] This increase in water absorption fits in very well with the decrease in C_{H2O} measured after both HES and saline. Thus, our study did not reveal any difference in water absorption between 6% HES 130/0.4 and saline 0.9% regarding transport in the aquaporin 2 water channels during spinal anesthesia and orthopedic surgery.

The major strengths of this study are the exactly defined test conditions regarding operative procedures, anesthesia, and recovery period. In addition, we included an examination both before operation and at follow-up 10 to 12 days after surgery. Furthermore, we used a fixed rate of infusion and no supplemental fluid to minimize the risk of bias and confounders. We found that justified because the aim of the study was to test a possible nephrotoxicity of 6% HES 130/0.4 in patients referred for elective hip arthroplasty with a normal renal function. There are several limitations for this study. It cannot be excluded that we could have obtained further information about the renal tubular function, if we had measured several other biomarkers in urine. In addition, our study has a small sample size and

Table 5. Hemodynamic Values

	Baseline	Preincision	Incision	Postincision	Recovery	*P* Value Within
HR (beat/min)						
HES	79 (9)	74 (8)*	70 (14)	67 (12)**	73 (11)	<0.01
NaCl	74 (12)	72 (13)	64 (11)	62 (11)	63 (9)	<0.01
P value	0.37	0.94	0.57	0.60	0.06	
SBP (mmHg)						
HES	160 (18)	133 (17)***	124 (10)***	126 (12)***	129 (18)***	<0.001
NaCl	157 (17)	139 (25)***	119 (18)***	116 (18)***	122 (8)***	<0.001
P value	0.89	0.42	0.19	0.17	0.09	
DBP (mmHg)						
HES	93 (11)	78 (13)***	74 (11)***	71 (10)***	72 (14)***	<0.001
NaCl	87 (11)	75 (13)**	68 (11)***	65 (11)***	63 (7)***	<0.001
P value	0.76	0.95	0.18	0.25	0.03	
MAP (mmHg)						
HES	115 (13)	97 (14)***	90 (10)***	89 (10)***	91 (14)***	<0.001
NaCl	110 (12)	96 (16)***	85 (13)***	82 (12)***	83 (6)***	<0.001
P value	0.79	0.73	0.16	0.18	0.03	

Values are means (SD).

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

Baseline = just before anesthesia; DBP= diastolic blood pressure; HES = 6% hydroxyethyl starch 130/0.4; HR = heart rate; incision = during surgery; MAP = mean arterial pressure; NaCl = saline 0.9%; postincision = time after surgery, but before recovery; preincision = just after anesthesia, but before surgery; recovery = during recovery; SBP =systolic blood pressure.

addressed hypotension related to spinal anesthesia, so our result may not be comparable with all perioperative situations.

In conclusion, this randomized, controlled, double-blinded trial did not find any evidence of a harmful effect of intraoperative infusion of 6% HES 130/0.4 on renal function in patients during hip arthroplasty. Furthermore, we found only significant differences in MAP and DBP during the recovery period and not, as expected, during the surgery. The higher MAP, lower p-Alb, and lower p-Aldo in the HES group in the recovery period could be attributed to a higher degree of plasma fluid volume expansion during treatment with HES 6% 130/0.4 compared with 0.9% saline even though this was only minor.

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Competing Interests

The authors declare no competing interests.

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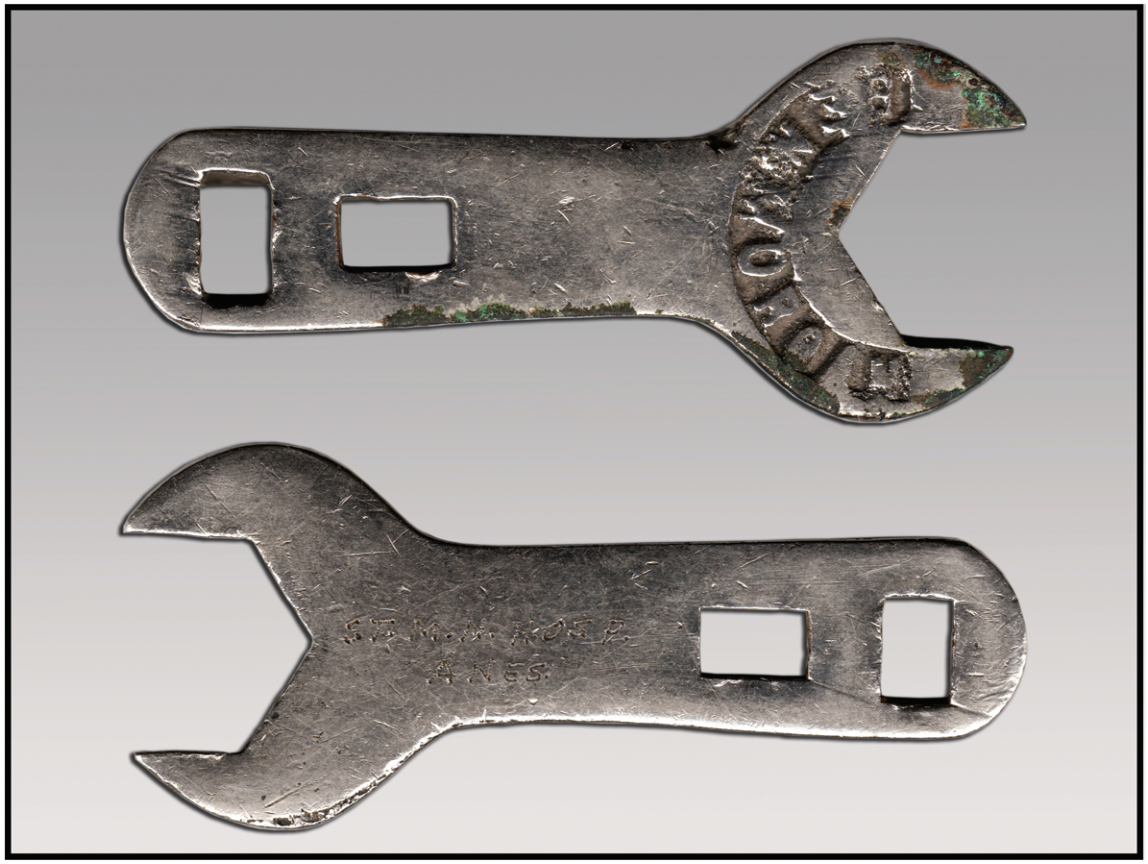
Wrenching Clues from a Key: "Morgan" & "M. N."



One face (*top*) of this compressed gas cylinder wrench ("key") bears the mold mark "Morgan." Chicago's Ben Morgan, M.D., was an early manufacturer of ether machines who by 1945 had shifted his interests away from obstetric anesthesia and toward the general practice of gynecology. On the back of this Ben Morgan cylinder wrench the letters "M. N." are engraved. Closer inspection reveals additional rough scratching which seems to read (*bottom*): "ST. M. N. HOSP./ ANES." Established to treat large waves of immigrants from Poland to Chicagoland, Saint Mary of Nazareth Hospital (our wrench's "ST. M. N. HOSP.") was founded by the Sisters of the Holy Family of Nazareth in 1894. So "Morgan" on one side and "M.N." on the other are clues to the interesting provenance behind this piece of anesthesia history.

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