Effect of Hydroxyethyl Starch (HES) 130/0.4 on renal function and mortality one year after adult cardiac surgery : a single center retrospective study

Ph. Amabili (*), E. Servais (**), M. Senard (*), L. Roediger (*), B. Hubert (*), J.-F. Brichant (*) and G. A. Hans (*)

Summary : Hydroxyethyl starch (HES) adversely affect short-term survival and renal function of intensive care unit and possibly of surgical patients. We retrospectively investigated whether using HES as a pump prime and for intraoperative fluid therapy is associated with mortality and end-stage renal failure one year after adult cardiac surgery. Multivariable logistic regression was used to adjust for imbalanced characteristics between the two study groups. The primary outcome, a composite of end-stage renal failure or mortality during the first postoperative year was observed in 9.7% of patients who received HES and in 6.2% of patients treated with crystalloids only (Adjusted OR 1.05; 95%CI, 0.5-2; P = 0.9). These results suggest that using HES or balanced crystalloids as a pump prime and for intraoperative fluid therapy results in similar one-year outcomes but must be considered as preliminary given the limited statistical power of the study.

Key words: Cardiac surgery, Hydroxyethyl Starch, Renal Insufficiency, Long-term effects, Mortality.

In critically ill patients, fluid resuscitation with hydroxyethyl starches (HES) results in a higher risk of renal failure than fluid resuscitation with crystalloids alone (1,2). Accordingly, a renal toxicity of HES has been observed experimentally (3). Moreover, in the subgroup of patients suffering sepsis, HES is also associated with a higher rate of mortality after 90 days (2). As a result, the Pharmacovigilance Risk Assessment Committee (PRAC), a part of the European Medicines Agency (EMA), recommended against the use of HES in cases of sepsis, severe burn injuries and more generally in critically ill patients (4).

Whether a similar toxicity of HES also exists in surgical patients remains debated. Four meta-analyses found no association between the use of HES and postoperative acute kidney injury (AKI) or death (5–8). The interpretation of the results of these meta-analyses is, however, hindered by the fact that different generations of HES and different comparators were used. On the other hand, several recent studies, admittedly retrospective, have shown that the use of HES was associated with a greater risk of postoperative AKI after cardiac, thoracic and vascular surgery (9–11). All these studies used crystalloids as a comparator and focused on short-term postoperative outcomes such as early postoperative AKI and 30-day mortality.

Postoperative AKI is associated with a higher long-term mortality, at least after cardiac surgery (12,13). In addition, patients who experience an episode of AKI are at increased risk of developing chronic kidney disease (CKD) on the long-term (14). The long-term consequences of exposure to HES during the perioperative period has, however, never been investigated.

The aim of the present work is to determine whether using HES as a pump prime and for intraoperative fluid therapy increases the risk of chronic kidney disease or death one year after adult cardiac surgery.

Methods

Our institutional ethics committee approved the study and waived informed consent (Chairperson : Prof. V. Seutin, Ref 2014/139 ; amendment from the

Philippe Amabili[1], Emilie Servais[1], Marc Senard, Laurence Roediger, Bernard Hubert, Jean François Brichant and Gregory A. Hans

(*) Department of Anesthesia and ICM, CHU of Liege, Liege, Belgium
(**) Department of Anesthesia, University of Louvain, St. Luc Hospital, Brussels, Belgium.
Corresponding author : Dr. Gregory Hans, Department of Anesthesia and ICM, CHU of Liege, Avenue de l'Hôpital, Bat B35, Domaine Universitaire du Sart Tilman. 4000 Liege, Belgium. Tel : +3243667180. Fax : +3243667636. Email : G.Hans@chu.ulg.ac.be

[1] These two authors equally contributed to this work.

22th of October 2015). The study consisted in a one-year follow-up of patients previously included in a retrospective observational study about the effect of HES on early postoperative AKI after cardiac surgery (NCT02445820). (9)

Patients and Groups

All patients underwent on-pump cardiac surgery at the CHU of Liege between April 2013 and June 2014. Exclusion criteria were age less than 18 years, preoperative dialysis, and addition of blood or albumin to the cardiopulmonary bypass (CPB) prime solution.

The primary exposure of interest was the type of fluid used to prime the CPB circuit and for intraoperative infusions. Data were obtained from the perfusion charts and the anesthetic records. Before August 2013, the CPB circuit was primed with 1500 mL of 6% HES 130/0.4 in a balanced salt solution (Volulyte®, Fresenius Kabi AG, Bad Homburg, Germany). In addition, up to 1000 mL of HES were given intravenously. Overall, patients received 2000-2500 mL of HES during the surgical procedure. From August 2013 and onwards, HES was entirely replaced by an equal amount of a balanced crystalloid solution (Plasma-Lyte A®, Baxter SA, Lessines, Belgium).

Clinical Management

Except for the type of fluid used, the clinical management remained unchanged throughout the study period and was described previously (9). Briefly, patients were anesthetized using continuous infusions of propofol and remifentanil. Full muscle relaxation was achieved using 0.9 mg/kg of rocuronium. Protective ventilation (tidal volume of 8 ml/kg and positive end-expiratory pressure of 5 cmH$_2$O) was used before and after CPB. A pulmonary artery catheter was used in all patients and a transoesophageal echocardiography was performed in case of valve surgery or when considered necessary by the attending anesthetist. A 1.5-g bolus of cefuroxime followed by an infusion of 3 g over 21 hours was used for antibiotic prophylaxis. A 2.5-g bolus of tranexamic acid was given before and repeated after separation from CPB.

Full anticoagulation was achieved with 300 UI/kg of unfractionated heparin before the initiation of CPB. Additional boluses of heparin were given when necessary to keep the activated clotting time (ACT, Hemochron® Signature Elite, International Technidyne Corporation, Edision, NJ) above 420 sec. Roller pumps (Stöckert SIII, Munich, Germany) and circuits with integrated reservoirs and hollow fibers oxygenators (Quadrox-i®, Maquet Getinge Group, Rastatt, Germany or Sorin Inspire 8F®, Sorin Group, Milano, Italy) were used for CPB. The pump flow was initially set at 3L/min/m². When necessary, vasoactive drugs were used to keep the mean arterial pressure between 45 mmHg and 75 mmHg. The mixed venous oxygen saturation was kept above 65%. In case of hematocrit lower than 20%, transfusion of red blood cells or hemofiltration was used according to the blood volume available. A cell saver was used in all cases.

After separation from CPB, persistent hypovolemia was primarily corrected by transfusing the cell saver blood. Balanced crystalloids (Plasma-Lyte A®) were added when necessary. No synthetic colloid was used postoperatively. Transfusion of blood and blood products was strictly guided by our institutional transfusion protocol that was established before and remained unchanged throughout the study (15).

Outcome

The primary outcome was a composite of end-stage renal failure requiring dialysis or death during the first postoperative year. Data were retrieved from our institutional electronic patient records or by contacting general practitioners.

Secondary outcome measures included the estimated glomerular filtration rate (eGFR) one year after surgery and mortality within the first postoperative year. The estimation of the glomerular filtration rate was based on the serum creatinine level using the CKD-EPI equation (16). Serum creatinine levels obtained anytime between 10 and 14 months after surgery were considered. The eGFR was categorized using the five-stage classification of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative : Stage I, GFR≥90 ml/min; Stage II, GFR 60-89 ml/min ; Stage III, GFR 30-59 ml/min ; Stage IV, GFR 15-29 ml/min ; Stage V, GFR < 15 ml/min or dialysis (17).

Statistics

Shapiro-Wilk test was used to assess the distribution of the data. Continuous variables are presented as mean (SD) and median [p25-p75] for normally and non-normally distributed data, respectively. Categorical data are presented as count (percent).

Assuming a 10% incidence of the primary outcome (i.e. a mortality rate of 6% and a 4% rate of dependence on dialysis) and a low correlation between exposure to HES and other covariates ($R^2 = 0.05$), we had a power of 0.8 at the 0.05 alpha level to detect an odds ratio of 2.0 or stronger with a sample size of 526 patients. This sample size of 526 patients accounted for a follow-up rate of 85%.

Baseline characteristics of patients were compared between the two groups using Student's *t*-test, the Mann-Whitney U-test, or the chi-square test as appropriate. Crude association between the type of fluid used and the primary outcome was assessed using binomial logistic regression. Adjusted association between the primary outcome and the type of fluid used was assessed by entering the type of fluid used and imbalanced characteristics between the HES and the crystalloid groups into a multivariable binary logistic regression model. Multinomial logistic regression was used to assess the adjusted association between the use of HES and the stage of CKD one year after surgery. Results are reported as adjusted odds ratio (OR) with 95% confidence interval (CI). One-year survival was described using the Kaplan-Meier method. A multi-variable Cox regression model was used to assess the association between one-year survival and the type of fluid used after adjusting for the EuroSCORE II.

A sensitivity analysis was also conducted by matching patients treated with crystalloids only to patients given colloids. The propensity score (i.e. probability of colloid treatment) of each patient was determined in a multivariable logistic regression including potential confounders as covariates. Patients were matched 1:1 using the nearest neighbor within a caliper distance of 0.2 SD of the propensity score and without replacement. The balance of covariates between groups before and after matching was assessed using the standardized mean difference (SMD). SMD > 0.1 in absolute value was considered potentially indicative of a residual confounding effect. On the matched sample, the proportion of patients who required dialysis or died during the first postoperative year was compared using the McNemar's test. The proportion of patients in each stage of the chronic kidney disease classification was compared between the group by performing asymptotic symmetry and marginal homogeneity tests. Finally, the paired Student's t-test was used to compare the eGFR one
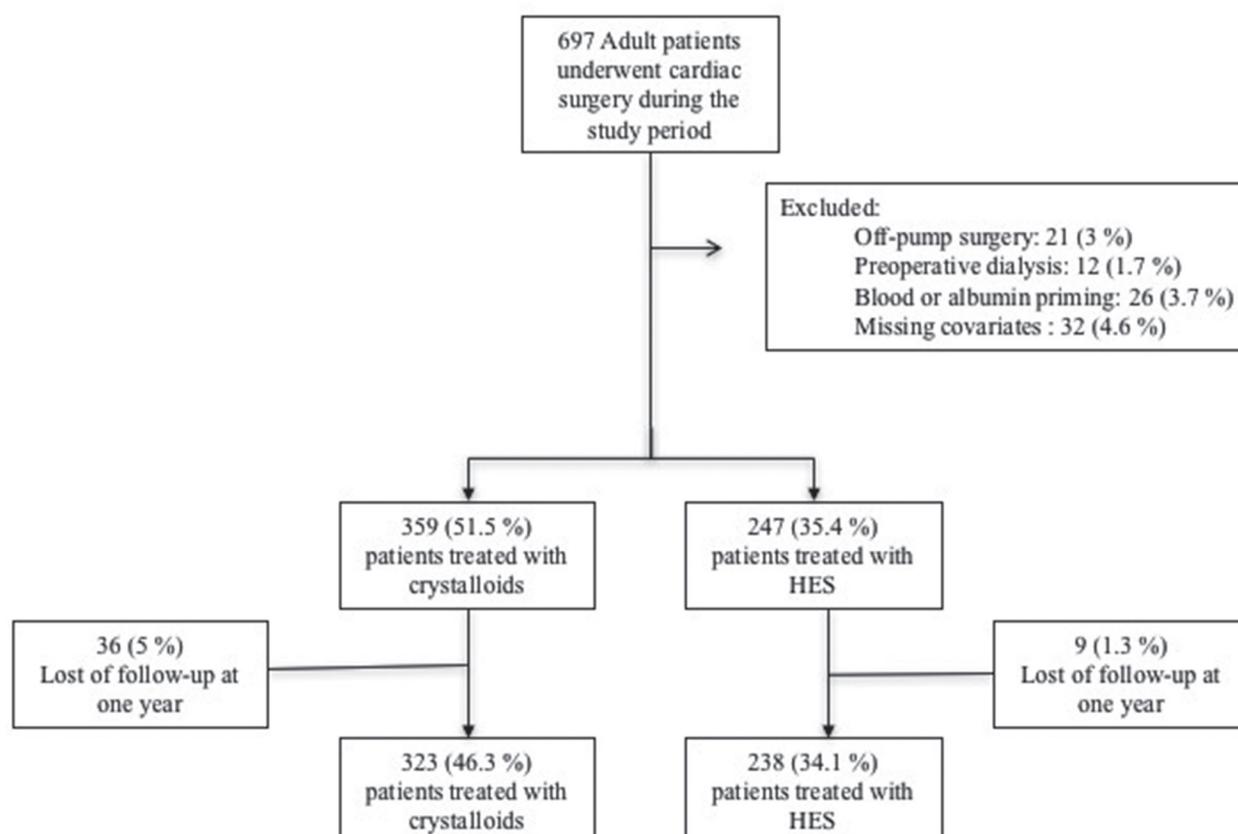

Fig. 1. — Flow chart of patient selection.

year after surgery between the groups. A two-tailed P value ≤ 0.05 was considered statistically significant. Statistical analyses were performed with Stata 13.1 (StatCorp LP, Texas).

Results

A total of 697 patients underwent cardiac surgery during the study period. Fifty-nine (8.4%) patients did not meet inclusion criteria. Thirty-two patients (4.6%) had to be excluded because of missing data on covariates and 45 (6.5%) were lost to follow-up. A total of 561 patients were thus retained for final analyses of whom 323 (46.5%) were treated with crystalloids only and 238 (34%) received HES (Fig. 1). Patients and operative characteristics are summarized in Table 1. Patients treated with HES were older (P = 0.03), had slightly higher preoperative creatinine level (P = 0.01), and had lower preoperative hemoglobin levels (P <0.01) than patients who received crystalloids only. In the HES group, the proportion of female was also higher (P = 0.01) and patients were more likely to be transfused (P <0.01) than in the crystalloid group.

Primary Outcome

During the first post-operative year, death or end-stage renal failure requiring dialysis occurred in 23 (9.7%) patients of the HES group and in 20 (6.2%) patients of the crystalloid group (OR 1.6 ; 95%CI, 0.9-3.0; P = 0.129). No association was found between the use of HES and the primary outcome after adjustment for age, sex, preoperative levels of creatinine and hemoglobin, and transfusion (Adjusted OR 1.05 ; 95%CI, 0.5-2; P = 0.9).

Secondary Outcomes

Serum creatinine levels one year after surgery were obtained in 207 patients of the crystalloid group and 154 patients of the HES group. We found no association between the use of HES and any stage of CKD one year after surgery (Table 2). Thirteen patients (4.0%) of the crystalloid group and 17 patients of the colloid group (7.1%) died within the first post-operative year (P = 0.1). After adjusting for the EuroSCORE II, mortality during the first post-operative year was unaffected by the use of HES (HR 1.5; 95%CI, 0.7-3.2 ; P = 0.25 ; Fig. 2).

Sensitivity Analyses

Two hundred and four patients treated with HES were successfully matched with 204 patients of the crystalloid group. All covariates had a SMD ≤ 0.1
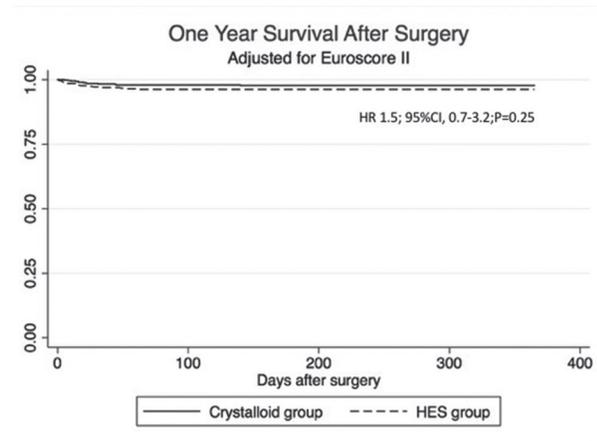

Fig. 2. — Kaplan Meier estimates comparing survival between the HES and the crystalloid group during the first post-operative year. After Adjusting for the predicted mortality by the EuroSCORE II, no effect of HES was on mortality during the first postoperative year was observed (Hazard Ratio = 1.5; 95%CI, 0.7-3.2 ; P = 0.25).

in absolute value after matching (Table 3). On the matched sample, death or end-stage renal failure requiring dialysis occurred in 16 patients (7.8%) of the colloid group and in 16 patients (7.8%) of the crystalloid group (P = 1.0). On the matched sample, the serum creatinine one year after surgery was available in 142 patients of the colloid group and 137 patients of the crystalloid group. The mean eGFR of non-dialyzed patients one year after surgery was 68.8 ± 11 ml·min⁻¹ in the crystalloid group and 69.7 ± 11 ml·min⁻¹ in the HES group (P = 0.6). Finally, one year after surgery, the proportion of patients in each stage of the classification of chronic kidney disease did not differ between the groups (Asymptotic symmetry test : P = 0.34 ; Marginal homogeneity test : P = 0.17).

Discussion

These data suggest that using HES 130/0.4 or crystalloids as a pump prime and for intraoperative fluid therapy results in similar one-year outcomes in adult patients undergoing cardiac surgery.

Cardiac surgery involving the use of cardio-pulmonary bypass is associated with a systemic inflammatory response somewhat similar to what happens in sepsis. (18, 19). In addition to hemodynamic instability and embolic events, inflammation contributes to AKI associated with cardiac surgery and explains that the incidence of AKI after cardiac surgery is higher than after any other type of surgery (20). This could place cardiac surgery patients at high risk of HES-induced nephrotoxicity. Accordingly, in a retrospective

Table 1
Patient and procedure characteristics according to the type of fluid used. Data are mean ± sd or median [P25-P75] unless otherwise stated.

	Crystalloid (n=323)	HES (n=238)	P Value
Age, y	69[59-77]	72[63-78]	0.03
BMI (kg m^{-2})	26.5[23.5-29.6]	26.2[23.5-30.2]	0.79
Creatinine (mg dl^{-1})	10[8.7-11.6]	10.6[8.9-12.8]	0.01
Hemoglobin (g dl^{-1})	13.9[12.6-15.2]	13.5[12.2-14.4]	<0.01
CPB duration (min)	88[71-115]	86[67-113]	0.23
Female gender, %	31	41	0.01
IDD, %	6.8	8.0	0.60
NYHA class IV, %	5.3	7.0	0.19
PVD, %	26.3	24.4	0.60
LVEF < 30 %, %	4.3	2.9	0.39
Critical State, %	1.3	3.4	0.09
Previous cardiac surgery, %	4.6	6.3	0.39
Urgent or emergent surgery, %	25.7	27.3	0.67
Pulmonary Hypertension, %	6.8	7.6	0.73
MI ≤ 30 days, %	16.4	17.6	0.70
Blood product transfusion, %	22.9	41.6	<0.01
Type of surgery, %			
CABG	59.4	52.9	0.13
AVR	38.1	43.3	0.22
MVR	12.7	11.8	0.74
Major Aortic	9.0	7.1	0.43
Other	8.4	11.8	0.18
Predicted mortality according to EuroscoreII	2.3[1.3-4.8]	2.4[1.2-6.1]	0.47
Postop AKI	9.6	22.7	<0.01

CPB = cardiopulmonary bypass. IDD= Insulin-dependent diabetes mellitus. PVD = Peripheral vascular disease. LVEF = Left ventricular ejection fraction. Critical state = patients receiving mechanical ventilation, inotropes or having and intra-aortic balloon pump before coming to the theatre. MI=myocardial infarction. CABG=Coronary artery bypass grafts. AVR = Aortic valve replacement. MVR = Mitral valve replacement or repair. Pulmonary hypertension was defined as a systolic pulmonary artery pressure ≥ 55 mmHg. BMI = Body Mass Index

Table 2
Crude and adjusted risk ratios between the use of HES and the CKD stage one year after surgery

GFR	Crystalloid (n=222)	HES (n=171)	Crude RR (95 % CI)	P Value	Adjusted* RR (95 % CI)	P Value
≥90 ml/min, n(%)	15(6.8)	11(6.4)	-	-	-	-
60-89 ml/min, n(%)	169(76.1)	134(78.4)	1.1(0.5-2.4)	0.9	1.0 (0.4-2.7)	1
30-59 ml/min, n(%)	29(13.1)	15(8.8)	0.7(0.3-1.9)	0.5	0.4(0.1-1.5)	0.2
15-29 ml/min, n(%)	0(0)	0(0)	-	-	-	-
<15 ml/min or dialyzed, n(%)†	9(4.0)	11(6.4)	1.7(0.5-5.4)	0.4	0.8(0.2-3.3)	0.8

CKD = Chronic Kidney Disease. GFR = Glomerular Filtration Rate. RR= Risk Ratio. † All patients in this category were actually dialysis-dependent.
* Adjusted for preoperative values of serum creatinine and hemoglobin, age, gender, and transfusion.

study, we found an association between the intraoperative use of HES and early postoperative AKI(9). These findings led us to investigate the long-term consequences of exposure to HES during the perioperative period for two reasons. Firstly, postoperative AKI is associated with reduced survival after cardiac surgery (13). Secondly, patients suffering transient acute renal failure are at increased risk of developing progressive CKD in the long term. (21)

The present results do not support the hypothesis that HES is associated with a higher mortality or

the development of chronic kidney disease during the first postoperative year. The absence of an association between the use of HES and subsequent development of CKD during follow-up is consistent with the transient nature of HES-associated AKI that we reported previously (9). Indeed, we found that HES was associated with a greater incidence of AKI during the first 48 postoperative hours but the effect was no longer observed one week after surgery. Moreover, the vast majority of patients who suffered postoperative AKI had a stage one AKI according to the Acute Kidney Injury Network classification (22). Such a mild and transient AKI may not increase the risk of developing CKD on the long-term to the same extent as more severe degrees of AKI(23). A higher risk of death has also consistently been reported in patients suffering AKI after cardiac surgery (12, 24). However, different causes of AKI may have different prognosis. Specifically, toxic AKI to which HES-associated AKI can be related, seems to carry a better prognosis than ischemic or septic AKI. (25) In addition, AKI episodes of short duration are less likely to result in long-term consequences than AKI of extended duration (23).

The first and most important limitation of this study is its retrospective design, which exposes to the risk of bias and confounders. The fact that it was a departmental decision to withdraw HES from cardiac surgery theaters from August 2013 limits the risk of a spurious association. Indeed, the type of fluid used was completely unrelated to the characteristics of the patient or the procedure but only determined by when surgery happened. In addition, we used multivariable logistic regression to adjust for imbalances in patient characteristics between the groups. The possibility that other perioperative variables contributed to the outcome nevertheless remains and our ability to adjust for confounders was limited by the sample size and the available data. The analysis of one-year mortality was only adjusted for the EuroSCORE II given the low number of events. Although the EuroSCORE II cannot be used to predict the long-term risk of death after cardiac surgery, it is associated with one-year mortality (26). We also have to deplore unequal dropout rates between the groups, which is another potential source of bias. The small sample size of the study is its second major limitation. This study consisted in a one-year follow-up of patients previously included in another research protocol (9). According to our power calculation, the minimal detectable odds ratio for the primary outcome was 2.0. This corresponds to a risk ratio

of 1.9 given the 6% prevalence of the outcome, which is higher than the reported toxicity of HES in septic patients (2). We nevertheless decided to undertake the work because we thought that long-term data about the consequences of exposure to HES during the perioperative period were urgently needed. Because this study is not adequately powered to rule out a smaller effect, its results should be regarded as preliminary. In a sensitivity analysis, we used propensity-score matching instead of multivariable logistic regression to adjust for potential confounders. The results obtained on the propensity-matched sample support the primary analysis. In addition, on the propensity-matched sample, the eGFR one year after surgery did not differ between the groups. Again, this is in favor of the absence of renal toxicity of HES on the long term. However, because they involve the selection of a subpopulation of patients, propensity-score matching analyses have reduced applicability and lower statistical power.

In conclusion, this is the first report on the long-term effects of exposure to HES in patients undergoing cardiac surgery with CPB. The results suggest that, in our patient population, using HES 130/0.4 did not affect survival or the development of CKD during the first postoperative year. The study has, however, a limited statistical power.

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