ANESTHESIOLOGY

Long-term Impact of Crystalloid *versus* Colloid Solutions on Renal Function and Disability-free Survival after Major Abdominal Surgery

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ABSTRACT

Background: The authors recently demonstrated that administration of balanced hydroxyethyl starch solution as part of intraoperative goal-directed fluid therapy was associated with better short-term outcomes than administration of a balanced crystalloid solution in patients having major open abdominal surgery. In the present study, a 1-yr follow-up of renal and disability outcomes in these patients was performed.

Methods: All patients enrolled in the earlier study were followed up 1 yr after surgery for renal function and disability using the World Health Organization Disability Assessment Schedule 2.0 (WHODAS). The main outcome measure was the estimated glomerular filtration rate. Other outcomes were serum creatinine, urea, pruritus, and WHODAS score. Groups were compared on a complete-case analysis basis, and modern imputation methods were then used in mixed-model regressions to assess the stability of the findings taking into account the missing data.

Results: Of the 160 patients enrolled in the original study, follow-up data were obtained for renal function in 129 and for WHODAS score in 114. There were no statistically significant differences in estimated glomerular filtration rate at 1 yr (ml min^{-1} 1.73 m^{-2}): 80 [65 to 92] for crystalloids *versus* 74 [64 to 94] for colloids; 95% CI [–10 to 7], $P = 0.624$. However, the WHODAS score (%) was statistically significantly lower in the colloid than in the crystalloid group (2.7 [0 to 12] *vs.* 7.6 [1.3 to 18]; $P = 0.015$), and disability-free survival was higher (79% *vs.* 60%; 95% CI [2 to 39]; $P = 0.024$).

Conclusions: In patients undergoing major open abdominal surgery, there was no evidence of a statistically significant difference in long-term renal function between a balanced hydroxyethyl starch and a balanced crystalloid solution used as part of intraoperative goal-directed fluid therapy, although there was only limited power to rule out a clinically significant difference. However, disability-free survival was significantly higher in the colloid than in the crystalloid group.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Balanced hydroxyethyl starch solution, as part of intraoperative goal-directed fluid therapy, is associated with better short-term outcomes than administration of a balanced crystalloid solution in patients having major open abdominal surgery
- The safety of modern hydroxyethyl starch solutions remains debated, with some studies in the intensive care setting have reported potential nephrotoxic effects, while others, performed in a surgical context, have not

What This Article Tells Us That Is New

- In a long-term follow-up of a previous trial comparing hydroxyethyl starch solution and balanced crystalloid used as part of intraoperative goal directed fluid therapy in patients undergoing major open abdominal surgery, there was no evidence that one therapy had superior renal function; however, limited power tempers any ability to completely rule out a difference
- Disability-free survival was higher in the colloid than in the crystalloid group

Colloids, including hydroxyethyl starch solutions, represent a potential option to optimize hemodynamics in high-risk surgical patients and to prevent excessive positive fluid balance with its harmful consequences.[1–5] The safety of modern hydroxyethyl starch solutions remains debated, even though these solutions have been used in many goal-directed fluid therapy studies.[6–10] Although some studies in the intensive care setting have reported potential nephrotoxic effects,[11–13] others, performed in a surgical context, have not.[14–17] However, the quality and size of surgical studies, in contrast with those performed in intensive care, is a matter of concern. In addition, the short follow-up periods represent a major limitation of these studies. Therefore, there is an urgent need for longer-term safety evaluation of such solutions.

We recently conducted a prospective, double-blind randomized controlled trial comparing a balanced hydroxyethyl starch solution to a balanced crystalloid solution for intraoperative goal-directed fluid therapy in patients undergoing elective major open abdominal surgery.[18] Our results showed that when fluid resuscitation was standardized and guided by a closed-loop system to limit the risk of investigator bias, use of a balanced hydroxyethyl starch solution was associated with fewer postoperative complications at 30-days postsurgery than was use of a balanced crystalloid solution. These results were associated with a lower intraoperative fluid balance, mainly related to a lower intraoperative fluid administration in the

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incidence of either acute kidney injury using the Kidney Disease Improving Global Outcomes classification or the need for renal replacement therapy revealed no evidence of a difference between groups at postoperative day 30. Two of our secondary registered outcomes (ClinicalTrials.gov registry number NCT02312999) were the 1-yr evaluation of the renal function based on serum creatinine and estimated glomerular filtration rate and the disability score at 1-yr after surgery using the World Health Organization Disability Assessment Schedule 2.0 (WHODAS).

The present study aimed to perform 1-yr follow-up of the patients included in this trial regarding renal and disability outcomes. Our hypothesis was that there would be no significant difference between groups in estimated glomerular filtration rate at 1 yr postdischarge between the original study groups.

Materials and Methods

The original study[18] was conducted in two academic institutions in Brussels (Brugmann and Erasme hospitals) from April 2015 through November 2016. The trial was approved by the ethics committees of Brugmann and Erasme hospitals and registered on ClinicalTrials.gov on December 5, 2014 (NCT02312999). Ethics committee approval of the original study also allowed us to follow patients after surgery to evaluate long-term renal outcomes and disability. All patients provided written informed consent before surgery.

Study Procedures

Detailed inclusion and exclusion criteria, as well as anesthesia management, were described extensively in the original manuscript.[18] In summary, 160 patients having elective major open abdominal surgery were enrolled. All patients received a maintenance infusion of balanced crystalloid at $3\,ml \cdot kg^{-1} \cdot h^{-1}$ (Plasmalyte, Baxter, Belgium). An automated closed-loop system[19–21] delivered additional 100-ml fluid boluses according to a predefined goal-directed strategy using the uncalibrated pulse contour EV1000 monitor (Edwards Lifesciences, USA). Patients were randomized to receive boluses of either a balanced crystalloid solution (Plasmalyte) or a balanced colloid (hydroxyethyl starch) solution (Volulyte, Fresenius Kabi GmbH, Germany). The primary outcome of the study was the postoperative morbidity survey score at day 2 after surgery. Secondary outcomes included all postoperative complications at 30 days after surgery. Lower postoperative morbidity survey scores and lower postoperative complications were observed in the colloid bolus group.

For the present study, we followed up with all patients for 1 yr after surgery. We used our hospitals' databases (Mediview and Mediweb software) to collect results of estimated glomerular filtration rate, Scr, and urea measures taken during postoperative outpatient follow-up appointments. The estimated glomerular filtration rate was calculated by the laboratory using the Chronic Kidney Disease Epidemiology Collaboration (CKD – EPI) formula in both hospitals.[22] Results of renal function were collected at five time points for each patient: T0, preoperative; T1, postoperative day 2; T2, last lab results before hospital discharge (may have occurred day 3 or later); T3, renal function test closest to 6 months postoperatively; and T4, renal function closest to 1 yr postoperatively. If there were no results in our database at any time point, the patient's general practitioner was contacted by telephone to obtain the renal function variables.

We also assessed disability at 1 yr after surgery using the WHODAS, which has been shown to be a clinically acceptable, valid, and reliable instrument for measuring postoperative disability across different surgical populations.[23,24] The WHODAS questionnaire was completed by telephone with the patient (patient's self-assessment). The WHODAS evaluates limitations in six domains (cognition, mobility, self-care, interpersonal relationships, work and household roles, and participation in society) over the 30 days before testing. Numerical values are attributed to each item (none = 0; mild = 1; moderate = 2; severe = 3; and extreme = 4). The total score is between 0 and 144 (36 questions on a 4-point scale) and is then divided by 144 and multiplied by 100 to convert it to a percentage of the maximum disability score. We classified disability based on the WHODAS and World Health Organization International Classification of Functioning, Disability and Health: none (0 to 4%); mild (5 to 24%); moderate (25 to 49%); severe (50 to 95%); and complete (96 to 100%) disability.[23] We calculated disability-free survival as 100% − dead (%) − moderate disability (%), where moderate disability is a WHODAS score of more than 25%. The presence of pruritus was collected during the same phone call at 1 yr after surgery. Data were collected by J.M., who was not involved in the earlier publication and was blinded to study group allocation at the time of follow-up.

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Statistical Methods

Main outcomes measures were estimated glomerular filtration rate using the CKD – EPI formula in both hospitals,[22] serum creatinine, urea, pruritus, and WHODAS score, all of which are secondary outcomes according to our original study registration. We chose a statistical approach that accounts for missing data because of patient deaths and patients lost to follow-up. First, data were tabulated and compared directly on a complete-case-analysis basis, using chi-square tests for tabular/binary outcomes and Mann–Whitney U tests for scalar data, because there is a rationale for complete-case-analysis reporting even when other imputation methods are used, particularly when binary outcome measures (like death) are involved.[25,26]

Then to account for missing data from patients lost to follow-up, missing data were first assessed for being missing completely at random *versus* missing at random or missing not at random,[27] using the methodology of Jamshidian and Jalal.[28] If the data were missing completely at random, then complete-case-analysis would likely be relatively unbiased and sufficient for analysis; if they were not missing completely at random, then the data would be assumed to be missing at random, and multiple imputation has been shown to provide more unbiased effect estimates than complete-case-analysis in this setting.[29,30]

When indicated, multiple imputation was performed by chained equations,[31,32] and the effect of fluid type was assessed using mixed-model regression and raw time-to-follow-up data for the assessment time points for each patient, with log transformation of the dependent variables (because the target outcome variables were heavily skewed). The mixed-model effects included were chosen *a priori* by the authors as those likely to be associated with long-term renal and disability outcomes: group, age, body mass index, baseline renal labs, surgery type, surgery duration, estimated blood loss, Physiological and Operative Severity Score for Enumeration of Mortality and Morbidity (POSSUM) physiology score, POSSUM morbidity score, and total intraoperative fluid volume. To test the stability of the imputed missing data in the final model, additional models were run using the same multiple imputations replacement, maximum likelihood estimation imputation, complete-case-analysis, and last observation carry-forward imputation with the times of observations discretized into preoperative, postoperative day 2, last-before-discharge, 6 months, and 12 months.

The ideal means of handling of missing data caused by patient death is still debated and likely depends on the nature of the measure in the context of the overall study.[33,34] For the present follow-up study in high-risk abdominal surgery, 71% of the original cohort had had cancer operations (more than half of these procedures were for pancreatic or biliary cancer) and another 10% had had high-risk vascular procedures, all of which carry a high year-on-year risk of death. For the present analysis, it was presumed that deaths that occurred were a result of the original presenting indication for surgery and were therefore missing at random relative to the intraoperative fluid-therapy groupings. These cases were thus included in the same process as the "missing due to lost follow-up" patients for the principal analyses. This assumption may introduce bias if deaths are attributable to group assignment. Therefore, a secondary sensitivity analysis was performed imputing all missing data for deceased patients using the worst observed value in the cohort as the replacement value to assess the possible impact of this assumption on the conclusions of the analysis.

No specific power analysis was performed because this was a secondary analysis of a parent trial.[18] According to the primary outcome of the parent trial, which was a 1-point difference in the postoperative morbidity survey score at postoperative day 2, 80 patients in each group were enrolled. All of them were included in the present analysis. Statistical analyses were performed using R (www.r-project.org) and SPSS (IBM Corp., USA). Scalar data are reported as median and [25th to 75th] percentiles. Differences in groups are described by location difference (the median of the difference between two samples). Significance testing was two-tailed, and CIs are reported at the 95th percentile. Outliers were evaluated, but no action was found to be necessary.

Results

Of the 160 patients enrolled in the original study, follow-up data were obtained for 129 (81%) for long-term renal function. Sixteen (10%) patients died before the 12-month follow-up, and 15 (9%) were completely lost to follow-up (no data obtained after discharge, no hospital or provider visits, and no response at any phone number despite repeated attempts). Complete data for WHODAS score at 12 months were obtained for 114 patients (71%). (Some patients had documented lab results from primary care during the follow-up period but did not respond on available contact numbers or addresses to obtain WHODAS results.) The study flow chart is shown in figure 1.

Of the confirmed deaths in the 12-month follow-up period, 10 occurred in the crystalloid group, and 6 occurred in the colloid group ($P = 0.429$; table 1). Eight additional patients were completely lost to follow-up in the crystalloid group, and seven were lost in the colloid group ($P > 0.999$). Pairwise testing of group differences in serum creatinine, urea, and estimated glomerular filtration rate showed no significant differences at both the 6- and 12-month follow-ups (table 1). Figures 2 and 3 show the estimated glomerular filtration rate and serum creatinine values in the two groups at the five time points. Appendix 1 provides the incidence of chronic kidney disease (and stages) at 12 months in the two groups. At 1 yr, disability as assessed by the WHODAS

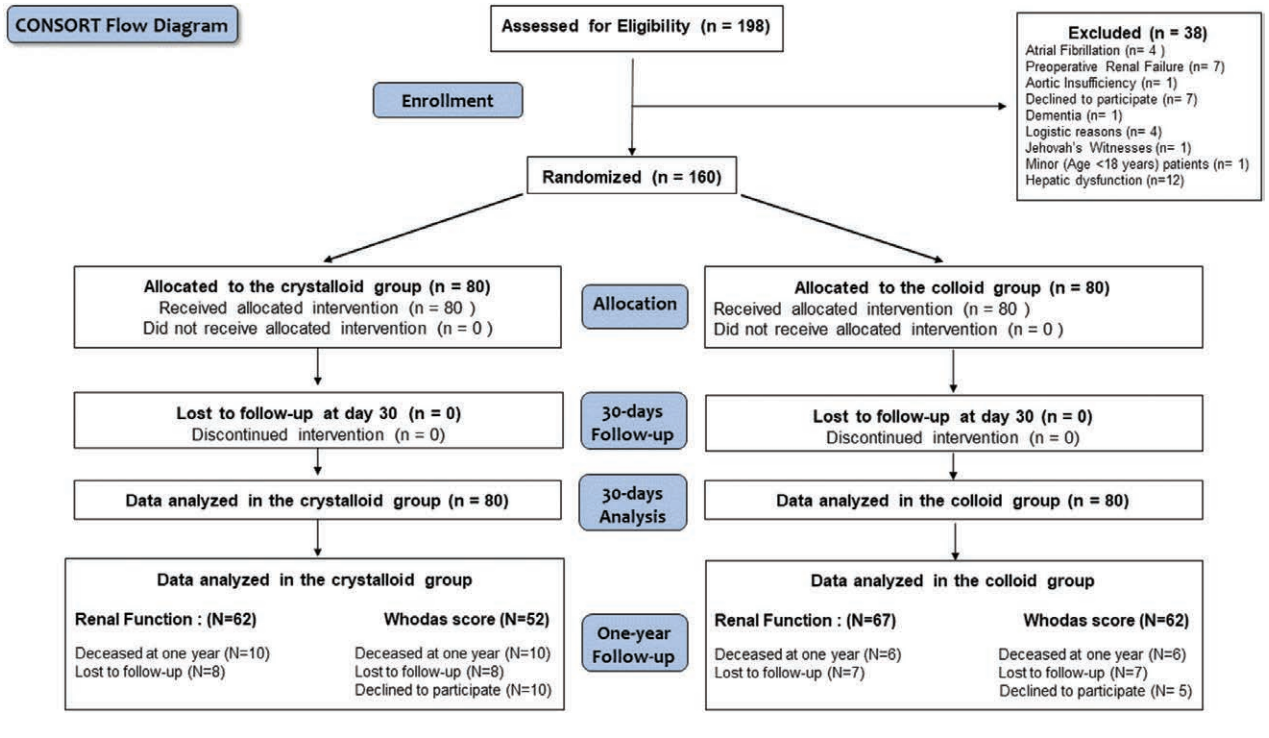

Fig. 1. Consort flow diagram of the study. Whodas, World Health Organization Disability Assessment Schedule 2.0.

score was statistically significantly lower in the colloid than in the crystalloid group (2.7 [0 to 12%] *vs.* 7.6 [1.3 to 18%]; $P = 0.015$). Disability-free survival (table 1) was significantly higher in the colloid group (79%) than in the crystalloid group (60%) at 1 yr as well ($P = 0.024$; 95% CI, 2 to 39%).

Analysis of the pattern of the missing data using Hawkins test revealed a P value of less than 0.001, and the nonparametric test of homoscedasticity revealed a P value of 0.027. Data missing completely at random were thus rejected, and the data were treated as missing at random, and multiple imputation by chained equations was performed to impute the missing values. The results for main effect of group on 6- and 12-month follow-up labs in the models using different approaches to the missing data are shown in table 2 along with the 95% CI for group effect at 12-month follow-up. Testing using exact time to follow-up showed a nonsignificant effect of fluid group on long-term estimated glomerular filtration rate, urea, and serum creatinine values (table 2). Sensitivity analysis showed that these results were stable across alternate imputation/analysis methods using discretized time handling (table 2) and under replacement of deceased patients with worst observed measurement (table 2). With the multiply imputed data set, there was a nonstatistically significant difference in WHODAS scores in the crystalloid group compared with the colloid group ($P = 0.059$; 95% CI, 0 to 8). This effect was statistically significant under maximum likelihood estimation imputation ($P = 0.016$; 95% CI, 5 to 9). Complete-case analysis ($P = 0.317$; 95% CI, −3 to 10) and replacement of deceased patients with worst-observed value ($P = 0.185$; 95% CI, −3 to 15) did not show a statistically significant effect.

Discussion

In the long-term follow-up of a double-blind, randomized controlled trial of fluid resuscitation in patients undergoing major open abdominal surgery, we found no evidence for a difference in renal function at 1 yr in patients who received a balanced crystalloid and those who received a balanced hydroxyethyl starch solution. However, patients in the hydroxyethyl starch group had a statistically significantly lower disability score after surgery and a significantly higher rate of disability-free survival. To the best of our knowledge, this study is the first to report long-term (at least 1 yr) effects of balanced hydroxyethyl starch *versus* balanced crystalloid administration in patients undergoing major abdominal surgery. Another recent study reported no change in 1-yr renal function in patients undergoing cardiac surgery who had received balanced hydroxyethyl starch for fluid resuscitation,[35] but there was no control group. In the intensive care setting, some studies have suggested a higher incidence of renal failure in critically ill patients resuscitated with hydroxyethyl starch compared

Table 1. Post-Operative Long-term Follow-up Data

	Crystalloid Group (n = 80)	Colloid Group (n = 80)	Direct Comparison *P* value	Location Difference* [95% CI]
Patients, n				
Completely lost to follow-up	8	7	> 0.999	
Deceased at 1 yr	10	6	0.429	
Long-term renal data collected	62	67	0.424	
Days to 6-month follow-up	177 [144 to 197]	163 [146 to 196]	0.467	
Days to 12-month follow-up	369 [353 to 402]	382 [362 to 428]	0.748	
Serum creatinine, mg/dl				
Preoperative	0.9 [0.8 to 1.1]	0.9 [0.8 to 1.0]	0.811	0.0 [–0.1 to 0.1]
Postoperative day 2	0.9 [0.7 to 1.1]	0.8 [0.6 to 1.1]	0.475	0.0 [–0.1 to 0.1]
Predischarge	0.8 [0.7 to 1.0]	0.9 [0.7 to 1.1]	0.752	0.0 [–0.1 to 0.1]
6 months postdischarge	0.9 [0.8 to 1.2]	1.0 [0.8 to 1.1]	0.789	0.0 [–0.1 to 0.1]
12 months postdischarge	0.9 [0.8 to 1.1]	1.0 [0.8 to 1.1]	0.704	0.0 [–0.1 to 0.1]
Serum urea, mg/dl				
Preoperative	30 [25 to 40]	33 [28 to 42]	0.149	2 [–1 to 6]
Postoperative day 2	29 [22 to 39]	29 [24 to 37]	0.615	1 [–3 to 4]
Predischarge	25 [17 to 32]	26 [20 to 36]	0.150	3 [–1 to 7]
6 months postdischarge	40 [25 to 46]	38 [28 to 47]	0.447	2 [–4 to 7]
12 months postdischarge	37 [28 to 46]	37 [28 to 46]	0.865	0 [–5 to 6]
Estimated glomerular filtration rate, ml · min^{-1} · 1.73 m^{-2}				
Preoperative	84 [69 to 102]	82 [66 to 93]	0.267	–3 [–11 to 3]
Postoperative day 2	89 [66 to 102]	90 [70 to 101]	0.924	0 [–8 to 8]
Before discharge	90 [75 to 106]	89 [67 to 96]	0.186	–4 [–12 to 2]
6 months after discharge	82 [71 to 94]	77 [59 to 91]	0.302	–4 [–14 to 4]
12 months after discharge	80 [65 to 92]	74 [64 to 94]	0.624	–2 [–10 to 7]
Pruritus (12-month follow-up)	1	6	0.175	
WHODAS score				
Patients contacted (n)	52	62		
WHODAS score (%)	7.6 [1.3 to 18]	2.7 [0 to 12]	0.015	–4.0 [–0.2 to –10]
WHODAS disability category			0.074	
None (0–4%)	17	33		
Mild (5–24%)	20	21		
Moderate (25–49%)	11	7		
Severe (50–95%)	4	1		
Complete (96–100%)	0	0		
Disability-free survival†	60%	79%	0.024	19 [2 to 39]

Counts or median with [25th to 75th] interquartile range are shown for each group. The *P* values are by chi-square test for counts and by Mann–Whitney U test for creatinine, glomerular filtration rate, and World Health Organization Disability Assessment Schedule 2.0 (WHODAS) score.

*Defined as the median of the difference between samples from each group. †Disability-free survival = 100% – deceased (%) – (≥ moderate disability = 25%).

with those resuscitated with crystalloids,[11,12] but renal function was not assessed beyond 90 days.

Our results support several recent systematic reviews and meta-analyses showing no evidence for a deleterious effect of hydroxyethyl starch solutions on short-term renal function in surgical patients.[36–39] Recently, Kammerer *et al.*[14] reported comparable renal safety profiles of hydroxyethyl starch and 5% albumin in more than 100 patients undergoing major urologic surgery, including the ratio of serum cystatin C, estimated glomerular filtration rate, and neutrophil gelatinase-associated lipocalin up to 90-days postoperatively.

The raw disability score assessed by the WHODAS questionnaire was significantly lower at 1 yr in the hydroxyethyl starch group compared with the crystalloid group, and more relevant to patients themselves, there was a higher rate of disability-free survival in the colloid group. These results were persistent in the maximum likelihood estimation imputation but not in the complete-case-analysis model or when deceased patients were replaced with the worst-observed score (the multiple imputation model is equivocal). Thus, caution is advisable in interpretation of a benefit to patients in the colloid group, but our results show no evidence at all of worsened outcomes in the colloid group. Using the MacNew questionnaire[40,41] we recently reported no deleterious effect of hydroxyethyl starch solution on quality of life in cardiac patients.[35] In the present study, we chose the WHODAS questionnaire, because the MacNew questionnaire was only designed to assess quality of life in cardiac patients. The impact of

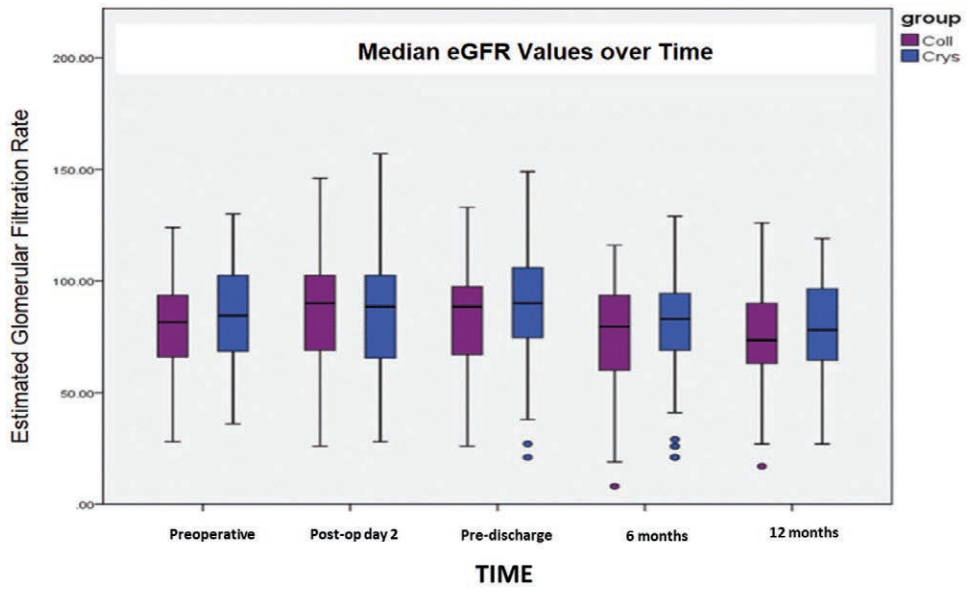

Fig. 2. Box plots of estimated glomerular filtration rate (eGFR) at each measurement time point between groups. Coll, colloid; Crys, crystalloid; Post-op, postoperative.

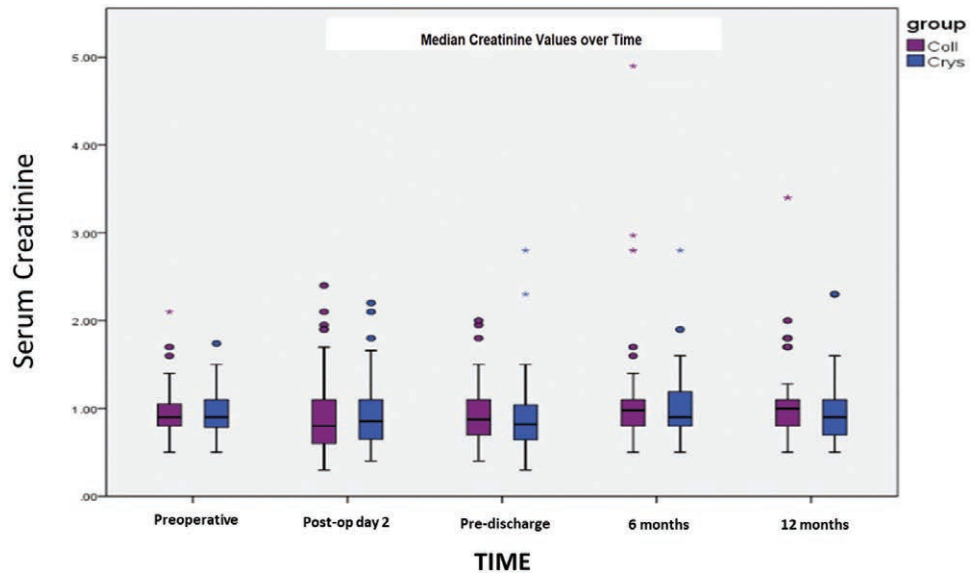

Fig. 3. Box plots of serum creatinine concentration at each measurement time point between groups. The *asterisks* represent *Extreme outliers (greater than three times interquartile range from nearest box edge). Coll, colloid; Crys, crystalloid; Post-op, postoperative.

administration of hydroxyethyl starch solution on quality of life in the critically ill population appears more controversial. Wittbrodt *et al.*[42] reported a worse self-perceived quality of life in hydroxyethyl starch–treated patients compared with crystalloid-treated patients, but Taylor *et al.*[43] observed no difference in long-term quality of life between hydroxyethyl starch– and saline-resuscitated critically ill patients. The reasons for these differences are not clear; one possible explanation might be related to the degree of inflammatory response in these different populations, with its known effects on the glycocalyx and capillary permeability.[44] The lower long-term disability score observed in our hydroxyethyl starch group is in accordance with the lower incidence of 30-day postoperative complications reported

Table 2. Statistical Significance for Group Differences in Long-term Outcomes under Different Missing-data Imputation Methods and Repeated Measures Mixed-effect Models

	Raw Time		Discretized Time						Deceased Replacement	
	Multiple Imputation		Multiple Imputation		Maximum Likelihood Estimation Imputation		Complete Case Analysis		Last-observation Carry-forward Imputation		Multiple Imputation	
	P Value	Point Estimate [95% CI]	*P* Value	Point Estimate [95% CI]	*P* Value	Point Estimate [95% CI]	*P* Value	Point Estimate [95% CI]	*P* Value	Point Estimate [95% CI]	*P* Value	Point Estimate [95% CI]
Creatinine	0.786	0 [−0.2 to 0.1]	0.150	0.0 [−0.2 to 0.1]	0.554	0.0 [−0.1 to 0.1]	0.475	0.0 [−0.3 to 0.2]	0.347	0.1 [−0.1 to 0.3]	0.221	0.3 [−0.2 to 0.9]
Estimated glomerular filtration rate	0.836	1 [−5 to 6]	0.287	1 [−3 to 7]	0.823	1 [−3 to 5]	0.641	2 [−6 to 10]	0.168	−5 [−14 to 4]	0.308	−6 [−17 to 5]
Urea	0.266	−4 [−10 to 3]	0.297	−3 [−10 to 3]	0.591	4 [−5 to 13]	0.434	4 [−7 to 16]	0.298	−5 [−15 to 5]	0.255	16 [−12 to 44]
WHODAS	*	*	0.0589	4 [0 to 8]	0.0165	5 [1 to 9]	0.317	3 [−3 to 10]	†	†	0.185	6 [−3 to 15]

P values are for group effect in repeated measures mixed-effects linear model using group, age, body mass index, baseline renal labs, surgery type, surgery duration, POSSUM physiology and morbidity scores, and total intraoperative fluid volume as factors/covariates. Point estimate and 95% CIs reported for group difference at 1 yr using the colloid group as the reference.

*All WHODAS data were collected by phone call at 1 yr, so no correction for raw time is necessary. †Last-observation carry-forward imputation was not possible with WHODAS because no previous observations are present to carry forward.

POSSUM, Physiological and Operative Severity Score for Enumeration of Mortality and Morbidity; WHODAS, World Health Organization Disability Assessment Schedule 2.0.

in our initial publication.[18] An association between the incidence of immediate postoperative complications and the development of worse long-term outcomes has been previously reported by Khuri *et al.*[45] and Moonesinghe *et al.*[46]

The double-blind design represents the main strength of this study. However, the study also has some limitations. First, the population was relatively small, and renal function was assessed only by estimated glomerular filtration rate and serum creatinine. The present study was not powered to detect differences in long-term renal function, because this was a secondary analysis of a parent trial with the postoperative morbidity survey score at postoperative day 2 as primary objective. The relatively small sample size may therefore lead to inconclusive 95% CIs. Second, because patients with preexisting elevated serum creatinine (more than 2 mg/dl) were excluded from the study, our results may not be generalizable to patients with mild preoperative renal insufficiency. Third, we did not have a baseline preoperative WHODAS score that could be considered as a significant limitation. Rates of disability (or more specifically changes in disability) might be underestimated or misinterpreted, although age, American Society of Anesthesiologists physical status, and POSSUM scores were well balanced between both groups. We also acknowledge that differences in the WHODAS score and disability-free survival may not be directly attributable to the different solutions used in our study. Finally, we considered a 10 ml min^{-1} 1.74 m^{-2} difference in estimated glomerular filtration rate to be clinically significant. The 95% CIs for estimated glomerular filtration rate difference at 6- and 12-month follow-up (table 1) include differences of 10 or greater, so we cannot completely exclude the possibility that the colloid group may have had worse long-term renal function by this measure.

Conclusions

In patients undergoing major open abdominal surgery, there was no evidence of a statistically significant difference in long-term renal function between a balanced hydroxyethyl starch and a balanced crystalloid solution used as part of intraoperative goal directed fluid therapy, although there was only limited power to rule out a clinically significant difference. However, disability-free survival was significantly higher in the colloid than in the crystalloid group.

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Competing Interests

Dr. Joosten is a consultant for Edwards LifeSciences, Irvine, California. Dr. Van der Linden has received, within the past 5 yr, fees for lectures and consultancies from Fresenius Kabi GmbH, Bad Homburg, Germany, and Janssen-Cilag SA, Beerse, Belgium. Dr. Cannesson and Dr. Rinehart both have ownership interest in Sironis, Newport Beach, California, a company developing closed-loop systems, and have consulted for Edwards Lifesciences, Irvine, CA. The other authors declare that they have no conflicts of interest concerning this article.

Reproducible Science

Full protocol available at: Alexandre.Joosten@erasme.ulb.ac.be. Raw data available at: Alexandre.Joosten@erasme.ulb.ac.be.

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Appendix 1. Incidence of Chronic Kidney Disease and Stages

Estimated Glomerular Filtration Rate Category ($ml \cdot min^{-1} \cdot 1.73\ m^{-2}$)	Description	Range	Crystalloid	Colloid
G1	Normal or high	≥ 90	11 (26)	16 (37)
G2	Mildly decreased	60–89	26 (60)	27 (63)
G3a	Mildly to moderately decreased	45–59	5 (12)	6 (14)
G3b	Moderately to severely decreased	30–44	0 (0)	3 (7)
G4	Severely decreased	15–29	1 (2.3)	2 (4.7)
G5	Kidney failure	< 15	0 (0)	0 (0)

Values indicate number of patients (%). The *P* value is 0.279.