

In this study, the urine and plasma NGAL levels were determined by a commercial enzyme-linked immunosorbent assay, with a minimal detection level of 1.6 pg/ml. We noted that median levels of urine NGAL at hospital discharge (urine 4) for two groups were about between 9 and 10 times of baseline values. Furthermore, measured values of urine NGAL at every observed time point had the highly variable ranges. In such a small sample study, therefore, only comparing median urine NGAL levels may have of limited clinical value. Most importantly, we were not provided with the cutoff value of urine or plasma NGAL with their enzyme-linked immunosorbent assay for diagnosis of postoperative AKI. Furthermore, we were very interested in knowing how many patients in each group had a higher NGAL level than the cutoff value. As a general rule, a level of more than 150 ng/ml can identify patients at high risk for AKI, and a level greater than 350 ng/ml, those at high risk for renal replacement therapy.⁶ Were the number of patients with a risk of AKI by NGAL measurement in the two groups comparable?

In fact, AKI is a low incidence event after noncardiac surgery. Kheterpal *et al.*^{7,8} demonstrate that in patients undergoing major noncardiac surgery with preoperatively normal renal function, incidence of AKI is approximately 1%, with AKI defined as an absolute level of estimated glomerular filtration rate less than 50 ml/min during the postoperative period. Assuming that this is a real incidence of AKI after noncardiac surgery and 6% HES 130/0.4 can result in a 100% increased risk of AKI, namely, a 2% incidence of AKI, 2,351 patients per group would have been required to have an 80% chance of finding a significant difference. Evidently, the study by Kancir *et al.* is not powered to show this difference.

Finally, follow-up period of this study only was 10 to 12 days. The median reported time to HES-induced acute renal failure is 16 days.⁹ According to the accumulated evidences, the U.S. Food and Drug Administration recently released a Safety Communication-Boxed Warning for HES solutions to increase mortality, severe renal injury, and risk of bleeding. Its recommendations include that need for renal replacement therapy has been reported up to 90 days after HES administration, and renal function monitor should last for at least 90 days in all patients.¹⁰ A short follow-up period in this study would have missed some of the adverse renal events. In addition, this study was also not designed to assess patient-relevant safety outcomes. Thus, this study fails to provide the robust evidence that HES 130/0.4 is safe for the kidney in noncardiac surgical patients. Here, we would like to echo the conclusion of a recent systematic review by Gattas *et al.*¹¹ that there is no convincing evidence that third generation HES 130/0.4 is safe in surgical, emergency, or intensive care patients despite publication of numerous clinical studies.

Competing Interests

The authors declare no competing interests.

Fu-Shan Xue, M.D., Xin-Long Cui, M.D., Shi-Yu Wang, M.D. Plastic Surgery Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, People's Republic of China (F.-S.X.). xuefushan@aliyun.com

References

1. Kancir AS, Pleckaitiene L, Hansen TB, Ekeløf NP, Pedersen EB: Lack of nephrotoxicity by 6% hydroxyethyl starch 130/0.4 during hip arthroplasty: A randomized controlled trial. *ANESTHESIOLOGY* 2014; 121:948–58
2. Haase M, Bellomo R, Haase-Fielitz A: Neutrophil gelatinase-associated lipocalin. *Curr Opin Crit Care* 2010; 16:526–32
3. Devarajan P: Review: Neutrophil gelatinase-associated lipocalin: A troponin-like biomarker for human acute kidney injury. *Nephrology (Carlton)* 2010; 15:419–28
4. Thakar CV: Perioperative acute kidney injury. *Adv Chronic Kidney Dis* 2013; 20:67–75
5. Calvert S, Shaw A: Perioperative acute kidney injury. *Perioper Med (Lond)* 2012; 1:6
6. Moore E, Bellomo R, Nichol A: Biomarkers of acute kidney injury in anesthesia, intensive care and major surgery: From the bench to clinical research to clinical practice. *Minerva Anestesiol* 2010; 76:425–40
7. Kheterpal S, Tremper KK, Englesbe MJ, O'Reilly M, Shanks AM, Fetterman DM, Rosenberg AL, Swartz RD: Predictors of postoperative acute renal failure after noncardiac surgery in patients with previously normal renal function. *ANESTHESIOLOGY* 2007; 107:892–902
8. Kheterpal S, Tremper KK, Heung M, Rosenberg AL, Englesbe M, Shanks AM, Campbell DA: Development and validation of an acute kidney injury risk index for patients undergoing general surgery. *ANESTHESIOLOGY* 2009; 110:505–15
9. Schortgen F, Lacherade JC, Bruneel F, Cattaneo I, Hemery F, Lemaire F, Brochard L: Effects of hydroxyethylstarch and gelatin on renal function in severe sepsis: A multicentre randomised study. *Lancet* 2001; 357:911–6
10. FDA: Hydroxyethyl starch solutions: FDA safety communication—Boxed warning on increased mortality and severe renal injury and risk of bleeding. Available at: <http://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm358349.htm>. Accessed October 31, 2014
11. Gattas DJ, Dan A, Myburgh J, Billot L, Lo S, Finfer S; CHEST Management Committee: Fluid resuscitation with 6% hydroxyethyl starch (130/0.4) in acutely ill patients: An updated systematic review and meta-analysis. *Anesth Analg* 2012; 114:159–69

(Accepted for publication March 9, 2015.)

Lack of Nephrotoxicity of Hydroxyethyl Starch 130/0.4 When Used in Surgery

To the Editor:

Kancir *et al.*¹ are to be commended for conducting a properly powered double-blind trial examining the renal effects of hydroxyethyl starch 130/0.4 in orthopedic surgery. The presented data and analyses are very instructive. An additional edifying analysis (it could have been the primary analysis) would be a comparison of the two groups (hydroxyethyl starch and NaCl) for the *changes* from baseline to the last data point (“follow-up”) for urine neutrophil gelatinase-associated lipocalin activity and creatinine

clearance. Although there were no differences between the groups for the absolute values at these time points, the relative changes from baseline are of greater clinical interest, and for urinary neutrophil gelatinase-associated lipocalin (the primary outcome measure), the groups moved in opposite directions.

Competing Interests

The author has a relationship with or consults for the following companies and organizations that have an interest in intravenous fluid therapy: U.S. Food and Drug Administration (Bethesda, Maryland); U.S. National Heart, Lung, and Blood Institute/National Institutes of Health (Bethesda, Maryland); U.S. Department of Defense (Frederick, Maryland); TerumoBCT (Lakewood, Colorado); HbO₂ Therapeutics (Souderton, Pennsylvania); and Octapharma USA (Hoboken, New Jersey). The author helped design a multicenter clinical trial (Gandhi SD, Weiskopf RB, Jungheinrich C, Koorn R, Miller D, Shangraw RE, Prough DS, Baus D, Bepperling F, Warltier DC: Volume replacement therapy during major orthopedic surgery using Voluven (hydroxyethyl starch 130/0.4) or a hetastarch. *ANESTHESIOLOGY* 2007; 106:1120–7) sponsored by Fresenius-Kabi (Bad Homburg, Germany), participated in a review of tetraastarches (Van Der Linden P, James M, Mythen M, Weiskopf RB: Safety of modern starches used during surgery. *Anesth Analg* 2013; 116:35–48), and has received reimbursements for travel expenses and honoraria from Fresenius-Kabi for presentations. In the past, the author has consulted for the following companies that had an interest in development of hemoglobin-based oxygen carriers: Somatogen (Boulder, Colorado), Hemosol (Mississauga, Ontario, Canada), Sangart (San Diego, California), and OPK Biotech (Cambridge, Massachusetts). The author was project/corporate Vice-President, Chief Medical Officer Biopharmaceuticals, and Executive Scientific Advisor at Novo Nordisk A/S (Bagsvaerd, Denmark) 2005–2007. No one from any of these organizations had knowledge of, influenced, or participated in the writing of this letter.

Richard B. Weiskopf, M.D., University of California, San Francisco, California. rbw@theweiskopfgroup.com

Reference

1. Kancir AS, Pleckaitiene L, Hansen TB, Ekeløf NP, Pedersen EB: Lack of nephrotoxicity by 6% hydroxyethyl starch 130/0.4 during hip arthroplasty: A randomized controlled trial. *ANESTHESIOLOGY* 2014; 121:948–58

(Accepted for publication March 9, 2015.)

In Reply:

We are grateful to Drs. Priebe, Xue, and Weiskopf for their interest regarding our manuscript entitled Lack of Nephrotoxicity by 6% Hydroxyethyl Starch 130/0.4 during Hip Arthroplasty: A Randomized Controlled Trial,¹ which appeared in the November 2014 issue of *ANESTHESIOLOGY*. Further, we thank for their complimentary words and remarks. We will answer the queries starting with Dr. Priebe, then Dr. Xue and finally Dr. Weiskopf.

Dear Dr. Priebe, you request additional information regarding urine 4 in terms of plasma creatinine and creatinine clearance. However, urine 4 was obtained just before discharge and was a “spot urine,” *i.e.*, not a urine collection over time. Thus, creatinine clearance could not be calculated. Additional analyses of urine and blood samples could have contributed with further information in the postoperative period and during follow-up, but this was not included in the protocol.

The study design allowed us to compare the effect 6% hydroxyethyl starch (HES) 130/0.4 and isotonic saline 0.9% on urinary neutrophil gelatinase-associated lipocalin (u-NGAL) during hip arthroplasty. We can conclude that no difference existed between the two solutions, but an increase was seen in u-NGAL in both infusion groups in urine 4. We used isotonic saline 0.9% as control fluid, because it had the same chloride content of 154 mmol similar to the intervention fluid. We agree that a possible nephrotoxic effect of the chloride component in isotonic saline 0.9% is interesting, and further studies are necessary to clarify this aspect. However, other studies that were comparing a balanced solution, *i.e.*, lactated Ringer's solution or similar to a chloride-rich solution, found no differences in u-NGAL in the groups.^{2,3}

Dear Dr. Xue, we used a cutoff value of 100 ng/ml for u-NGAL. We wanted to see whether 6% HES 130/0.4 inflicted none, mild, or severe renal injury compared with isotonic saline 0.9%. There were nine *versus* seven patients in the HES *versus* saline group with a u-NGAL value more than 100 ng/ml at discharge. Thus, no difference existed between the groups.

The study was not designed to compare the occurrence of acute kidney injury (AKI) between HES 6% 130/0.4 and isotonic saline 0.9%. It goes without saying that a huge number of subjects had to be included, if AKI should be the primary effect variable. We agree that fulminant AKI is a seldom event after noncardiac surgery, but the outcome in our study was differences in renal markers specific for renal injury, *i.e.*, u-NGAL, plasma creatinine, urine output, and creatinine clearance. So, our study was powered to find a difference in these markers and not to find a difference in the incidence of AKI. When evaluating HES-induced renal failure, it is important to differentiate between a surgical population and a septic one. The findings in severe sepsis are not applicable to surgical patients.⁴ Further, there are numerous pharmacokinetic differences between the generations of starches and the findings of side effects. The elder generations of starches cannot be compared with the latest generations of starch.⁵ Until now, no evidence exists of a perioperative renal impairment after tetraastarch infusion in subjects with normal renal function before surgery.^{6–8}

In a previous study, the follow-up was 28 days after HES infusion, and no signs were detected of HES-induced renal impairment.⁹ We are convinced that we would have seen signs suggestive of renal injury within the 14 days of follow-up in the present study, if there had been any.

Dear Dr. Weiskopf, thank you for the complementary words. Due to space limitations, we did not publish the absolute or relative changes from baseline to the follow-up.