

## Nephrotoxicity by Administration of Hyperchloremic Solutions

To the Editor:

The title of the publication by Kancir *et al.*<sup>1</sup> implies lack of nephrotoxicity associated with the use of either 6% hydroxyethyl starch 130/0.4 or 0.9% NaCl during hip arthroplasty. The primary outcome variable was urinary concentrations of neutrophil gelatinase-associated lipocalin (u-NGAL). For all observation points, u-NGAL concentrations are reported as absolute and as values adjusted for creatinine (table 3). However, at the time of the highest u-NGAL concentrations (*i.e.*, at discharge; observation point “urine 4”), values of neither creatinine clearance (table 3) nor plasma creatinine concentration (table 4) are provided.

The authors describe the postoperative u-NGAL concentrations as only “slightly increased” and remaining “well below” the threshold of 100 ng/ml, considered to reflect acute kidney injury. However, at the time of patient discharge, median u-NGAL concentrations had increased 9- to 11-fold over baseline values, and the 75% quartile values of u-NGAL at discharge were 160.5 and 116.3 ng/ml in the hydroxyethyl starch and NaCl groups, respectively (table 3). This indicates that several patients of each group had u-NGAL concentrations well above the critical concentration of 100 ng/ml, reflecting the development of some degree of nephrotoxicity.

The authors mention in a somewhat passing fashion that their use of chloride-rich solutions may have contributed to the transient increases in u-NGAL concentrations. Infusion of 2 l of 0.9% NaCl in healthy individuals was associated with a 40% decrease of renal blood flow velocity and renal cortical tissue perfusion.<sup>2</sup> This was accompanied by a mean increase in serum chloride concentrations from initially 103 to 108.5 mmol/l within 60 min of starting the infusion. Additional evidence supports the adverse renal effects of hyperchloremic solutions.<sup>3–5</sup>

Therefore, administration of hyperchloremic solutions might well have contributed to the clinically relevant increases in u-NGAL concentrations in some patients observed by Kancir *et al.*<sup>1</sup> There are no large prospective clinical studies clearly documenting an adverse effect of perioperative administration of hyperchloremic solutions on outcome. Nevertheless, intraoperative infusion of hyperchloremic 0.9% NaCl carries a high potential of inducing hyperchloremic metabolic acidosis,<sup>6</sup> and acute hyperchloremia and hyperchloremic acidosis have numerous adverse effects.<sup>7</sup> It may thus be prudent to avoid the perioperative administration of hyperchloremic solutions altogether whenever possible.

## Competing Interests

The author has received lecturing honorarium from Fresenius Kabi AG, Bad Homburg, Germany.

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## Is Hydroxyethyl Starch 130/0.4 Safe for the Kidney in Noncardiac Surgical Patients?

To the Editor:

The recent article by Kancir *et al.*<sup>1</sup> assessing nephrotoxicity of 6% hydroxyethyl starch (HES) 130/0.4 compared with 0.9% isotonic saline in the patients undergoing hip arthroplasty was of great interest. They showed no harmful effect of intraoperative infusion of 6% HES 130/0.4 on postoperative renal function. Many things of this study were well done. The authors used a prospective, double-blinded, placebo-controlled design and chose a sensitive and well-validated endpoint of acute kidney injury (AKI): neutrophil gelatinase-associated lipocalin (NGAL), which fulfills many characteristics of an appropriate “real-time” biomarker for AKI detection and is called as a troponin-like biomarker for human AKI.<sup>2,3</sup> They had a consistent operation (elective hip arthroplasty). Also, they had tried to control most of the known factors affecting perioperative AKI, such as age, body mass index, preoperative comorbidities and medications, duration of surgery, intraoperative blood loss and transfusion, uses of vasoactive drugs.<sup>4,5</sup> All these are strengths in the study design.

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.<sup>6</sup> 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.*<sup>7,8</sup> 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.<sup>9</sup> 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.<sup>10</sup> 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.*<sup>11</sup> 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.

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

### To the Editor:

Kancir *et al.*<sup>1</sup> 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