5. Levine AI, Leibowitz AB: Flexible bronchoscopy still the definitive standard for airway management. Anesthesiology 2013; 118:461

(Accepted for publication May 24, 2013.)

In Reply:
On behalf of the American Society of Anesthesiologists (ASA) Task Force Management of the Difficult Airway and the ASA Committee on Standards and Practice Parameters, we thank Drs. Levine, DeMaria, Wilson, and Hebbas for their thoughtful Letters to the Editor regarding the Practice Guidelines published in February 2013.1 Drs. Levine and DeMaria suggest that the Difficult Airway guidelines should specifically call for a consideration of the risk of gastric aspiration. Drs. Wilson and Hebbas provide several suggestions for modifying the Difficult Airway Algorithm.

These letters exemplify the importance of the practitioners’ role in ASA Practice Parameters. The Committee on Standards and Practice Parameters listens very carefully to the clinical concerns of ASA members and leaders. These concerns guide the Committee to the selection of new practice parameters. During the process of guideline development, practitioners play a critical role by reviewing drafts, responding to on-line surveys, and providing commentary at open forums, caucuses, and reference committee hearings. After guidelines have been approved by the House of Delegates, practitioners make continuing contributions by testing the guidelines in daily practice. This real-world testing guides the focus and timing of subsequent revisions … or the occasional “retirement” of parameters that no longer provide useful guidance.

Our ASA methodologists carefully record and categorize practitioner comments. This material is studied by the Committee on an annual basis. Commentary is always welcome, and can be sent to the Chair of the Committee on Standards and Practice Parameters, to Task Force Chairs or Members, or to our Methodology Team.

These letters also provide an opportunity to review the intent of practice parameters. The ASA regards practice parameters as basic—not exhaustive—recommendations that assist both the practitioner and patient in making beneficial decisions about health care. Practice parameters are not offered as standards or absolute requirements. The recommendations found in practice parameters can be adopted, modified, or rejected according to clinical needs and constraints.

Once again, we thank our four colleagues for their insights. And we look forward to additional commentary and suggestions from ASA members.


Reference

(Accepted for publication May 24, 2013.)

Hydroxyethyl Starch 130/0.4 and Postoperative Acute Kidney Injury

To the Editor:
Martin et al.1 described a meta-analysis of 17 randomized controlled trials evaluating renal function in 1,230 total surgical patients allocated to hydroxyethyl starch (HES) 130/0.4 or control fluid. At baseline, mean serum creatinine (SCr) was lower in HES 130/0.4 recipients than the control group, and after surgery, the most extreme mean SCr values were higher in the patients receiving HES 130/0.4. However, these differences were not statistically significant. Limited data on acute renal failure and renal replacement therapy available among the trials included in the meta-analysis also showed no significant differences. The investigators concluded that there was no evidence of adverse postoperative renal effects due to HES 130/0.4.

A major weakness of this meta-analysis was short follow-up. In six of the included trials, renal function was evaluated only for 24 h or less after surgery and in two more trials only up to 48 h. SCr is neither a specific nor a sensitive marker for renal tubular injury, and threshold SCr increase for diagnosis of incipient acute kidney injury (AKI) is not typically observed until 48 h or more after surgery.2 This temporal pattern is nicely demonstrated by the Crystalloid versus Hydroxyethyl Starch Trial of HES 130/0.4, which included 2,876 surgical patients comprising 43% of the overall trial population (fig. 1).3 HES 130/0.4 significantly increased SCr in that trial but the effect was not clearly evident until after 48 h, and the SCr peak was not reached until after 4 days. Thus, in eight trials of the meta-analysis, the SCr peak is likely to have been missed because of short follow-up. In the Crystalloid versus Hydroxyethyl Starch Trial, SCr increase was accompanied by increased recourse to renal replacement therapy in the HES 130/0.4 group with a relative risk of 1.21 and 95% CI of 1.00–1.45 (P = 0.04). These

*Virginia Mason Medical Center, Seattle, Washington. anerac@vmmc.org

Dr. Groeneveld has received research grant funding from B Braun, Melsungen, Germany, and lecture fees from B Braun and Baxter, Deerfield, Illinois. Drs. Navickis and Wilkes have received research grant funding from Baxter, CSL Behring, King of Prussia, Pennsylvania, and Grifols, Los Angeles, California.
adverse renal effects were encountered despite a low average daily HES 130/0.4 dose (526 ml).

Furthermore, five of the nine trials in the meta-analysis with more than 48 h follow-up compared HES 130/0.4 with other artificial colloids known to cause renal impairment. Lack of difference in those trials would if anything suggest deleterious renal effects of HES 130/0.4.

The most extreme mean postoperative SCr value is an endpoint of convenience rather than a validated indicator of AKI in individual patients. In reality, the trials of this meta-analysis were not designed to assess HES 130/0.4-induced AKI. SCr data were often reported simply as part of a laboratory test panel. No included trial assessed AKI in accordance with a validated classification system such as risk of renal dysfunction, injury to the kidney, failure of kidney function, loss of kidney function, and end-stage kidney disease or Acute Kidney Injury Network. Only one included trial report even specified any definition for acute renal failure.

Beyond these threats to the validity of the meta-analysis, its applicability to routine clinical practice is limited. In 16 of the 17 included trials, patients with renal dysfunction at baseline were excluded. Hence, it can only be concluded that evidence was not found of adverse renal effects among surgical patients at low risk of AKI.

This meta-analysis is based on two premises that: (1) HES 130/0.4 may pose less renal risk than other HES solutions and (2) surgical patients may be less susceptible to HES-induced AKI than other critically ill patients. Neither premise was supported by a systematic review on the comparative safety of colloids encompassing 69 clinical studies, including 42 randomized trials with 10,382 total patients. Martin et al. wrongly suggest that the systematic review was incomplete. In fact, all studies fulfilling prespecified selection criteria were included in the systematic review without exception, as elsewhere detailed. Moreover, the systematic review has recently received confirmation from a new meta-analysis showing that HES increases mortality (relative risk, 1.09; 95% CI, 1.02–1.17), acute renal failure (relative risk, 1.27; 95% CI, 1.09–1.47), and renal replacement therapy (relative risk, 1.32; 95% CI, 1.15–1.50). The effects of various HES solutions were found to be similar in that meta-analysis, as were the effects of HES in assorted populations of critically ill patients.

Additional evidence also raises concern about the perioperative infusion of HES 130/0.4. In a retrospective study of 6,553 patients undergoing cardiopulmonary bypass surgery, HES 130/0.4 exposure was found to be an independent risk factor for renal replacement therapy (odds ratio, 1.70; P = 0.004).

The risk of excessive bleeding due to HES 130/0.4 also needs to be considered. A meta-analysis of randomized cardiopulmonary bypass surgery trials demonstrated increases in postoperative blood loss and blood product transfusion as well as reoperation for bleeding among patients receiving HES. There was no evidence that those risks differed among HES solutions. A systematic review of viscoelastic device studies indicated impairment of coagulation specifically by HES 130/0.4.

On the basis of available evidence, it has been recommended that clinical use of HES for acute volume resuscitation be avoided because of serious safety concerns. Whether there exist specific patient groups who might benefit from HES 130/0.4 would have to be demonstrated in future randomized trials specifically designed and adequately powered to detect differences in renal outcomes. Current data are not adequate to establish the perioperative safety of HES 130/0.4.

A. B. Johan Groeneveld, M.D., Ph.D., F.C.C.P., F.C.C.M., Roberta J. Navickis, Ph.D., Mahlon M. Wilkes, Ph.D.*
*Hygeia Associates, Grass Valley, California. mwilkes@hygeiaassociates.com

References

Anesthesiology 2013; 119:724–41

734 Correspondence

Fig. 1. Time course of serum creatinine changes in the Crystalloid versus Hydroxyethyl Starch Trial of 7,000 intensive care unit patients. HES = hydroxyethyl starch. Redrawn from Myburgh et al. and annotated.
Hydroxyethyl Starch 130/0.4: Safe for the Kidney in Surgical Patients?

To the Editor:
The safety of hydroxyethyl starch (HES), especially with regard to the kidney, has been on debate for many years.\(^1\) Newly reported meta-analyses of randomized controlled trials (RCTs), which included recent large trials of high quality, have moved the controversy much closer to consensus. HES solutions as a class have been shown to increase mortality, acute renal failure, renal replacement therapy (RRT), and erythrocyte transfusion in critically ill patients.\(^2,3\) Increased mortality and RRT have also been demonstrated specifically among critically ill patients receiving "modern" HES solutions that had been promoted as safer than their older counterparts.\(^4,5\) Among patients with sepsis, increases attributable to modern HES have been found in mortality, RRT, transfusion, and serious adverse events.\(^6,7\)

By far, the most extensively investigated modern solution is waxy maize-derived HES 130/0.4. However, similar renal effects have been observed in the 6S RCT of modern potato-derived HES 130/0.42 versus Ringer’s acetate in sepsis.\(^8\) Thus, in a meta-analysis combining the 6S trial with five RCTs of HES 130/0.4 versus saline (two in sepsis and one each in the intensive care unit, trauma, and cardiac surgery), the pooled relative risk for RRT was 1.27 with a 95% CI of 1.10–1.46.\(^9\) For the five RCTs of HES 130/0.4 alone with 6S excluded, the pooled relative risk (1.24; 95% CI, 1.05–1.47) is closely similar.

The accumulated evidence recently prompted an expert panel of the U.S. Food and Drug Administration to conclude that renal failure and bleeding are class effects of HES solutions.\(^*\) New randomized trial RRT data have been added to the Prescribing Information for HES 130/0.4 in the United States,† and the U.S. Food and Drug Administration is considering further regulatory action.\(^*\) The European Medicines Agency is currently reevaluating the marketing approvals of HES solutions.‡ Avoidance of HES has been recommended in the latest Surviving Sepsis Campaign Guidelines.\(^9\)

Therefore, is there still a place for HES in any patient group? This is the question addressed by Martin et al. in a meta-analysis of 17 RCTs evaluating the perioperative infusion of HES 130/0.4 compared with various control fluids.\(^10\) Significant differences were not observed in the most extreme postoperative mean values of serum creatinine, the incidence of acute renal failure, or the need for RRT. One interpretation is that surgical patients are not susceptible to HES 130/0.4–mediated renal injury.

An alternative explanation is that renal injury was not detected due to limitations of the meta-analysis. In almost half the included studies, the control fluid was another HES solution or gelatin. Those artificial colloids exhibit their own deleterious renal effects and hence are inappropriate comparators that confound the conclusions of the meta-analysis. In the above-described meta-analysis of six RCTs, RRT was significantly increased by modern HES compared with crystallloid, whereas no such effect was seen in three additional included RCTs with other HES solutions or gelatin as the control fluid.\(^5\)

This was a meta-analysis of small trials exclusively, the majority at single centers. The median number of patients per trial was 65 (range, 11–140). Such trials are more vulnerable to bias. Significant publication bias favoring HES 130/0.4 has recently been shown in a meta-analysis of RCTs.\(^4\) Although Martin et al. could not detect publication bias by standard statistical tests, those tests are known to be insensitive in meta-analyses with only small trials.\(^11\) Moreover, many included trials in this meta-analysis showed risk of bias due to lack of blinding and inadequate or unclear

---


---