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Vasopressor Effects on Cerebral Microcirculation: Reply

In Reply:

We thank Bombardieri and Tsui[1] for their excellent comments and interest in our study.[2] We agree with Bombardieri and Tsui that the deterioration of microperfusion and possibly tissue oxygenation after phenylephrine administration in the "healthy" brain hemisphere[2] indicates that different vasopressors may also have a different influence on microperfusion and tissue oxygenation in the healthy anesthetized brain and should be further explored.[3] In our opinion, future studies on the effects of different vasopressors on the cerebral macro- and microcirculation should be considered in the context of their different effects on the systemic circulation to provide a fully integrated picture of their influence on organ perfusion and oxygenation.[4] Due to current difficulties in monitoring brain microcirculation and cerebral tissue oxygenation, we tend to rely on systemic parameters such as heart rate and blood pressure when treating patients with inotropes/vasopressors. However, a recent publication suggests that brain tissue oxygen saturation, as measured by near-infrared spectroscopy, may reflect cerebral metabolic supply–demand balance during vasopressor therapy.[4] Although the use of near-infrared spectroscopy is associated with limitations, such as extracranial signal contamination, it may currently be the only way to provide a continuous indicium of brain microperfusion and tissue oxygenation.

Competing Interests

Dr. Rasmussen declares a financial relationship with the Health Research Foundation of the Central Denmark Region (Aarhus, Denmark). Dr. Koch declares no competing interests.

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Recent U.S. Food and Drug Administration Labeling Changes for Hydroxyethyl Starch Products Due to Concerns about Mortality, Kidney Injury, and Excess Bleeding

To the Editor:

The U.S. Food and Drug Administration (Silver Spring, Maryland) is requiring safety labeling changes to the

prescribing information for hydroxyethyl starch products to warn about the risk of mortality, acute kidney injury (AKI), and coagulopathy in all patient populations. The changes contraindicate use of hydroxyethyl starch products for treatment of hypovolemia unless adequate alternative treatment is unavailable and update the Boxed Warning, Indications and Usage, Warnings and Precautions, and Adverse Reactions sections of the prescribing information to reflect new safety information (note: the indication for leukocytapheresis using Hespan [B. Braun Medical, Inc., USA] remains unchanged).

The Food and Drug Administration first mandated a safety labeling change for hydroxyethyl starch products in 2013. Changes made at that time included the addition of a Boxed Warning to the prescribing information and contraindications to their use in critically ill patients, including patients with sepsis. This action was prompted by publication of clinical studies, including randomized controlled trials, which showed that infusion of hydroxyethyl starch products increased mortality, AKI, and coagulopathy in the intensive care unit population. An increasing number of studies published subsequently have shown a similar safety risk profile in the surgery and blunt trauma populations.

In early 2017, the Food and Drug Administration received a citizen petition from the watchdog organization Public Citizen (Washington, D.C.) requesting that hydroxyethyl starch products be removed from the market. Public Citizen argued that all patient populations were at risk from hydroxyethyl starch products and that safer alternative resuscitation fluids were widely available.

The Food and Drug Administration assembled an internal, multidisciplinary review team to evaluate the available scientific literature, with special attention directed at clinical studies performed in surgery and trauma patients published after 2012. Prespecified clinical and statistical criteria were used to assess whether each study was "informative" or "less informative" for the purposes of addressing this issue.

A statistical threshold of $P < 0.05$, usually reserved for evaluating efficacy, was prespecified to define hydroxyethyl starch safety signals (*i.e.*, an adverse event possibly or definitely related to product administration). "Informative" studies were defined as those that (1) found a statistically significant (lower bound of the 95% CI ≥ 1.0) change in the relative risk of one or more clinical safety signals associated with hydroxyethyl starch products—death, AKI including need for renal replacement therapy, and coagulopathy; and (2) did not have major methodologic limitations. "Less informative" studies were defined as those that either (1) failed to find a statistically significant change in the incidence of one or more clinical safety signals described above or (2) were determined to have major methodologic limitations.

Failure to achieve statistical significance for an hydroxyethyl starch–associated safety signal was often due to weaknesses in study design or execution. These included a study size too small to detect a safety signal had one been present (*i.e.*, inadequate power); inappropriately low control event rates; limited exposure to the product; presence of heterogeneity (I^2) that could confound the analysis (*e.g.*, data from elective surgery and critically ill surgery patients enrolled in the same study without a prespecified subgroup analysis); a comparator whose safety profile overlapped with that of the hydroxyethyl starch product under review (*e.g.*, a different hydroxyethyl starch product); changes in comparator/adjunctive therapy once the study already had begun; an incomplete description of the randomization and allocation concealment procedure, where applicable; and short duration of follow-up (typically 7 to 10 days). Less informative studies did not permit the Food and Drug Administration to draw any conclusions about product safety.

Of 37 post-2012 studies identified by the Food and Drug Administration review team, 10 were classified as informative. Results of these studies provided the basis for requiring the labeling changes.

1. In a meta-analysis of 15 randomized controlled trials and 6 observational studies in patients undergoing elective surgery, hydroxyethyl starch was associated with increased risk of mortality and AKI. The study populations included both noncardiac surgery (hepatic, renal transplant, vascular, thoracic, gastrointestinal) and cardiac surgery in association with cardiopulmonary bypass.[1–7]
2. In two observational trauma studies, hydroxyethyl starch was associated with increased mortality and AKI in patients with blunt[8,9] (but not penetrating) trauma.
3. In a randomized controlled trial and an observational study among patients undergoing elective surgery, hydroxyethyl starch was associated with excess bleeding.[5,10]

In many cases, demonstration of a dose–response and/or temporal relationship between exposure to hydroxyethyl starch and excess risk provided additional support for implementing the labeling changes, which, along with additional information about the studies, were posted online at https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/labeling-changes-mortality-kidney-injury-and-excess-bleeding-hydroxyethyl-starch-products on July 7, 2021.

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Competing Interests

The authors declare no competing interests. This free-standing letter is an informal communication that reflects the views of the authors. It should not be construed to represent U.S. Food and Drug Administration (Silver Spring, Maryland) views or policies.

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