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Impact of balanced tetrastarch raw material on perioperative blood loss: a randomized double blind controlled trial†

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Abstract

Background: As 6% hydroxyethyl starch (HES) 130/0.40 or 130/0.42 can originate from different vegetable sources, they might have different clinical effects. The purpose of this prospective, randomized, double-blind controlled trial was to compare two balanced tetrastarch solutions, one maize-derived and one potato-derived, on perioperative blood loss in patients undergoing cardiac surgery with cardiopulmonary bypass (CPB).

Methods: We randomly assigned 118 patients undergoing elective cardiac surgery into two groups, to receive either a maize- or a potato-derived HES solution. Study fluids were administered perioperatively (including priming of CPB) until the second postoperative day (POD#2) using a goal directed algorithm. The primary outcome was calculated postoperative blood loss up to POD#2. Secondary outcomes included short-term incidence of acute kidney injury (AKI), and long-term effect (up to one yr) on renal function.

Results: Preoperative and intraoperative characteristics of the subjects were similar between groups. Similar volumes of HES were administered (1950 ml [1250–2325] for maize-HES and 2000 ml [1500–2700] for potato-HES; *P*=0.204). Calculated blood loss (504 ml [413–672] for maize-HES *vs* 530 ml [468–705] for potato-HES; *P*=0.107) and the need for blood components were not different between groups. The incidence of AKI was similar in both groups (*P*=0.111). Plasma creatinine concentration and glomerular filtration rates did vary over time, although changes were minimal.

Conclusions: Under our study conditions, HES 130/0.4 or 130/0.42 raw material did not have a significant influence on perioperative blood loss. Moreover, we did not find any effect of tetrastarch raw material composition on short and long-term renal function.

Clinical trial registration: EudraCT number: 2011-005920-16.

Key words: acute kidney injury; blood loss; cardiac surgical procedures; colloids; hydroxyethyl starch

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Editor's key points

- The influence of hydroxyethyl starch (HES) raw material on haemostasis and renal outcome in cardiac surgery is unknown.
- Patients undergoing cardiac surgery with cardiopulmonary bypass were prospectively randomized to receive balanced tetrastarch solutions derived from either maize or potato.
- Perioperative blood loss, transfusion, and kidney injury did not differ between groups in this study of 118 subjects.
- These preliminary findings suggest no significant clinical differences between balanced tetrastarch solutions derived from two different sources.

Six percent hydroxyethyl starch (HES) 130/0.40 or 130/0.42, commonly known as tetrastarch, has been routinely used to treat hypovolaemia, in patients undergoing cardiac surgery with cardiopulmonary bypass (CPB), as it is considered to be superior for volume expansion compared with crystalloid solutions.[1] This fluid consists of large branched glucose molecules substituted with hydroxyethyl groups for increased solubility and intravascular persistence. They are formulated to a concentration of 6%, a mean molecular weight of 130 kDa, and a molar substitution of 0.40 or 0.42. There is an active debate over the use of tetrastarch in high risk surgical patients. However, five recent meta-analyses failed to identify an association between surgical HES administration and postoperative morbidity or mortality.[2–6]

Newer tetrastarch solutions have been developed in an electrolyte balanced solution. Recent German guidelines recommend that if colloids are used in perioperative care, balanced solutions are preferred.[7] While previously published studies have shown that 0.9% NaCl ('unbalanced') HES solutions are associated with various clinical side-effects, balanced-HES solutions with electrolyte concentrations closer to human plasma have not been as rigorously examined. Interestingly, these newer solutions might improve postoperative acid-base status[8] and potentially decrease the incidence of AKI and use of renal replacement therapy (RRT).[9] Importantly, balanced tetrastarch solutions can be derived from two different raw materials (maize or potato). Maize and potato-derived HES differ in their molecular and chemical structures[10] and are not bioequivalent.[11] Maize starch is largely composed (98%) of highly branched amylopectin, while potato starch contains a lower degree of branching, consisting of a heterogeneous mixture of around 75% of amylopectin and 25% of linear chains of amylose. Potato starch contains several thousand esterified phosphate groups, whereas almost none can be detected in maize starch. Negatively charged phosphate-ester groups in potato-HES could impair coagulation and also metabolization in the liver. Jamnicki and colleagues[12] demonstrated that potato-HES compromises *in vitro* blood coagulation more than maize-HES. There is clinical evidence supporting the clinical use of maize-HES, while published data are lacking with regards to potato-HES.[13] Therefore, one cannot justify the clinical use of potato-HES with evidence derived from studies investigating maize-HES. The main objective of this prospective, randomized, double-blind trial was to compare two balanced tetrastarch solutions, one maize derived 6% HES 130/0.4 (Volulyte®, Fresenius Kabi GmbH, Bad Homburg, Germany) and one potato derived 6% HES 130/0.42 (Vitafusal®, Serum Werk Bernburg AG, Germany), on perioperative blood loss in patients undergoing cardiac surgery. Additionally, as the short and long-term safety profile of HES continues to fuel controversy, we secondarily examined both perioperative and long-term renal function, patient quality of life and occurrence of pruritus.

Methods

Ethics

The investigation was approved by the Ethics Committee of Brugmann's Hospital and registered under the EudraCT number: 2011-005920-16. All 118 subjects provided written informed consent the day before surgery.

Patients

Inclusion criteria were patients >18 yr undergoing elective cardiac surgery with CPB. Exclusion criteria were patients with an ASA physical status greater than III, heart failure (left ventricular ejection fraction <30%), cardiac arrhythmias, significant aortic regurgitation, coagulation disorders (platelet count <100 000 μl^{-1}, activated partial thromboplastin time >1.5 normal), preoperative renal dysfunction (serum creatinine >2 mg ml^{-1}, oliguria, anuria, or receiving haemodialysis), impaired hepatic function (aspartate amino-transferase, alanine amino-transferase >2 times normal), current pregnancy or lactation, and known allergy to HES.

Randomization and blinding

Randomization of the study was created by our hospital pharmacist in blocks of 10 using an internet-based software (http://www.randomization.com). The morning of surgery, blinded solutions were provided in identical plastic bags (500 ml) which prevented identification of the type of fluid being used. All investigators and people taking care of the patients remained blinded until the completion of the study and finalization of the statistical analysis.

Anaesthesia procedures

Premedication was standardized and consisted of 0.5 mg of alprazolam on the morning of surgery. Preoperative medications such as β-blockers, statins and calcium channel blockers were continued until the day of surgery. Preoperative antiplatelet drugs were stopped seven days before surgery, unless medical conditions required them to be maintained until the day of surgery. Angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB) and oral hypoglycaemic agents were stopped 24 to 48 h before surgery. Standard monitoring included 5-lead ECG, pulse oximetry, noninvasive blood pressure, central venous pressure, invasive radial artery catheter (using a Flotrac catheter connected to the Vigileo monitoring device, Edwards Lifesciences, Irvine, CA, USA), rectal temperature, inspiratory and expiratory gas concentrations, urine output, and depth of anaesthesia monitoring (Spectral Entropy, GE Healthcare, Helsinki, Finland). Anaesthesia was induced with lean body weight-adjusted doses of etomidate (0.2 mg kg^{-1}), sufentanil (0.2 mcg kg^{-1}), and rocuronium (0.5 mg kg^{-1}), and was maintained with sufentanil (Geps PK model: 0.7–1.2 ng ml^{-1}) and midazolam (0.05–0.1 mg kg^{-1} h^{-1}) using a target-controlled infusion pump (Alaris® PK) syringe assessment. After intubation, lungs were ventilated with a tidal volume of 8 ml kg^{-1} lean body weight, PEEPof 5 cm H_2O, and respiratory rate to achieve an end tidal carbon dioxide pressure between 4.3 and 4.8 Kpa. Prophylactic antibiotic (2 g of cefazolin), methylprednisolone (15 mg kg^{-1}) and tranexamic acid (30 mg kg^{-1} loading dose +2 mg kg^{-1} pump prime +16 mg kg^{-1} h^{-1} maintenance infusion during CPB)[14] were administered to all subjects. Anaesthetic drugs were