Cytokine xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Cytokine

journal homepage: www.journals.elsevier.com/cytokine

Review Article

Immune and inflammatory role of hydroxyethyl starch 130/0.4 and fluid gelatin in patients undergoing coronary surgery

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ARTICLE INFO

Article history:
Received 24 August 2014
Received in revised form 1 October 2014
Accepted 4 October 2014
Available online xxxx

Keywords:
Hydroxyethyl starch
Gelatin
Cytokine
Inflammation
Coronary surgery

ABSTRACT

Objectives: Compare the effects on inflammatory (TNF-α, IL-6, IL-8 and IL-10) and immunologic ($CD3^+$, $CD4^+$, $CD8^+$, $CD11b^+$, $CD16^+/56^+$ T cells and total lymphocyte concentration) variables of hydroxyethyl starch 130/0.4, 4% modified fluid gelatin, or crystalloid when used as volume replacement fluids for acute normovolemic hemodilution (a blood conservation technique) in coronary artery bypass graft patients.
Methods: Thirty patients undergoing coronary artery bypass graft surgery were randomized to receive Isolyte S® (Group ISO), 6% hydroxyethyl starch 130/0.4 (Group HES) or 4% modified gelatin solution (Group GEL) for acute normovolemic hemodilution. Blood samples were taken immediately after induction of anaesthesia (T0), and 2 h (T1), 12 h (T2), 24 h (T3), and 48 h (T4) after separation from cardiopulmonary bypass. TNF-α, IL-6, IL-8 and IL-10 levels were determined with commercially available ELISA kits. $CD3^+$ (mature T cells), $CD4^+$ (T helper cells), $CD8^+$ (suppressor cytotoxic T cells), $CD16^+/56^+$ (natural killer lymphocytes), and $CD11b^+$ (Mac-1, adhesion receptor) levels were measured using flow-cytometry reagents. The $CD4^+$:$CD8^+$ ratio was calculated.
Results: Between-group comparisons showed significantly higher levels of TNF-α at T1 (2 h after weaning from cardiopulmonary bypass) in Group HES compared to Group ISO ($p = 0.003$). IL-8 was significantly lower in Group HES than Group GEL at T1 ($p = 0.0005$). IL-10 was significantly higher in Group HES than in Group GEL at T1 ($p = 0.0001$). The $CD4^+$:$CD8^+$ ratio in Group ISO was significantly lower than that in Group HES at T2 ($p = 0.003$). $CD11b^+$ levels in Group HES were also higher than those in Group GEL and group ISO at T2, but not significantly. $CD16/56^+$ levels in Group HES were higher than those in Group GEL at T2 ($p < 0.003$). No excessive hemorrhage occurred in any patient. Mediastinal drainage during the first 24 h after surgery in Group HES (347 ± 207 mL) was not significantly different from that of Group GEL (272 ± 177 mL) or Group ISO (247 ± 109) ($p > 0.05$).
Conclusion: Hydroxyethyl starch 130/0.4 reduced pro-inflammatory responses and increased anti-inflammatory responses to a greater degree than gelatin solution and isolyte S®. The use of hydroxyethyl starch, compared to gelatin solution and isolyte S®, resulted in less decrease in the $CD4^+$:$CD8^+$ ratio, suggesting less immunosuppression.

1. Introduction

Hydroxyethyl starch (HES) and gelatin colloids (GEL) are frequently used for volume expansion and as priming fluids during cardiovascular surgery [1–3]. Immunosuppressive and inflammatory effects of cardiac surgery on lymphocyte populations are associated with enhanced risk of post-operative hemorrhage, multiorgan dysfunction, and infectious complications [4–6]. Cardiopulmonary bypass (CPB)-derived inflammation includes activation of complement proteins, endothelial cells, and white blood cells, as well as the generation of pro-inflammatory cytokines, endothelins, thrombin, and proteases [7–9].

To date, the effects of hydroxyethyl starch 130/0.4 and fluid gelatin on inflammation (as measured by serum markers or clinical scores) in patients undergoing coronary surgery have been limited.

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[1] The authors contributed equally to this work. This work was supported by the Scientific Research Council of Celal Bayar University (2009072).

http://dx.doi.org/10.1016/j.cyto.2014.10.002
1043-4666/

Hydroxyethyl starch, when used as a priming solution in patients undergoing CPB, showed that the immediate post-operative increases in TNF-α, IL-6 and IL8 were similar to the increases elicited by human albumin [1,2]. However, on post-op day 2, the TNF-α, IL-10, and C-reactive protein (CRP) levels in the HES group were significantly lower than in the albumin and Ringer's lactate groups [1]. In Tamayo's study of priming with gelatin or Ringer lactate solutions in coronary surgery patients, plasma levels of IL-6, IL-8, TNF-α, and CRP increased to the same degree in both groups [3]. In another study of colloids vs saline in a pig model of acute normovolemic hemodilution, GEL and saline elicited a more intense systemic and lung inflammatory response than HES [10].

Specific immune system changes after cardiac surgery with CPB may be due to haemodilution effects or to preceding activation of lymphocytes immediate after cardiac surgery with CPB [11–13]. The activity of T helper (TH) cells was reduced after cardiac surgery. This decrease was followed by an increase in TH2 cell activity and a delayed recovery of TH1 cell function (the 'TH1/TH2 shift'). This shift was primarily caused by a decrease in cytokine (IFN-gamma) synthesis in TH1 lymphocytes and not by an increase in TH2 lymphocyte activity [14,15]. In the immediate postoperative period, the specific immune system (lymphocyte) and non-specific immune system (leukocytes, neutrophil granulocytes) cell levels are not reduced but are significantly elevated, because of the mobilization of a sufficient number of cells of the specific immune system that are able to compensate for the effects of haemodilution; the cell levels then decrease to lower than pre-op levels on post-op day 1. Similarly, the function of specific immune cells, especially those of T helper lymphocytes, was also severely impaired for during the first day after cardiac surgery with CPB [13–15].

However, little is known about the individual T-cell subsets and polymorphonuclear neutrophil (PMN) profile during cardiac surgery when colloid was used for replacement or priming. Mac-1 are adhesion molecules on the cell surface that play an important role in the adhesion, extravasation, and migration of neutrophils [16]. Previous in vitro investigations and ischemia–reperfusion models found that HES increased $CD11b^+$ (Mac-1, adhesion receptor) expression on the surface of polymorphonuclear neutrophils [17,18]. Whereas one non-cardiac surgery study found that GEL or HES did not show any effect on granulocytes ($CD11b^+$, $CD16^+$) [19], another study showed that PMN activation was reduced by low molecular weight HES, but not by GEL [20].

We used acute normovolemic hemodilution, a blood conservation technique, so that allogenic blood transfusion would not be necessary in our patients – in this way, we prevented confounding when measuring markers of inflammation and immune response [21–23].

The aim of this study was to compare the effects of HES 130/0.4 in a saline-based solution vs 4% modified fluid gelatin when used as volume replacement fluids for acute normovolemic hemodilution in patients undergoing coronary artery surgery on immunologic [$CD4^+$ (helper T cell), $CD8^+$ (suppressor cytotoxic T cells), $CD11b^+$ (Mac-1, adhesion receptor), $CD16^+/56^+$ (natural killer cells)], pro- (TNF-α, IL-6, IL-8) and anti-inflammatory (IL-10) cytokines during the early postoperative period.

2. Materials and methods

2.1. Patients

The protocol for this prospective, randomized study was approved by our university's clinical research ethics committee. Over a one-year period, all patients between 18 and 70-years-old scheduled for elective primary CABG with CPB who had a haemoglobin over 13 g/dL and had not had an acute myocardial infarction within the previous six weeks were approached for inclusion in the study. In addition, those with any of the following were not approached for participation: immune or hypothalamic-pituitary adrenal axis dysfunction, exogenous hormone therapy, malnutrition, diabetes, malignancy, infection or inflammation, abnormal coagulation profile, preoperative left ventricular ejection fraction <40%, creatinine >1.5 mg/dL, abnormal liver function, allergy to study fluids, continued use of anticoagulation medications or ε-aminocaproic acid, immune, renal, or central nervous system dysfunction. Those giving written informed consent were enrolled in the study. Aspirin and clopidogrel were discontinued one week before surgery. The patient's usual medications were administered on the morning of the procedure.

2.2. Randomization, fluids, and operative procedure

Patients preparing for elective CABG surgery were randomly assigned using a closed envelope method to one of three groups for ANH before anesthesia: Group HES received 6% HES 130/0.4 (HES Steril®, 6%, average molecule weight of 130,000 daltons, molar substitution ratio of 0.4; Fresenius Kabi, Bad Homburg, Germany), Group GEL received 4% modified gelatin solution (Gelofusine®, MW 30,000 daltons, B. Braun, Melsungen, Germany) and Group ISO received a balanced electrolyte solution (Isolyte S®, Eczacıbaşı, Istanbul, Turkey). In the HES and GEL groups, blood for ANH was withdrawn through a central venous line after induction of anesthesia. The target hematocrit level after withdrawal was 35% [24]. The same volume was simultaneously replaced by HES, GEL, or ISO. The withdrawn blood was preserved at room temperature and re-transfused immediately after weaning from CPB and heparin neutralization.

In the perioperative period, crystalloid (Isolyte S®) was infused (8 mL/kg/h during surgery and 2 mL/kg/h after surgery) to all patients. All patients were induced with etomidate (0.2 mg/kg), fentanyl (3 μg/kg), and rocuronium (0.6 mg/kg), followed by maintenance with sevoflurane and continuous fentanyl infusion (3–5 μg/kg/h) for general anesthesia. The rest of the operation was completed in a standard fashion. Study fluids and norepinephrine were given to maintain mean arterial pressure above 60 mmHg during CPB. Leukocyte-depleted packed red blood cells (PRBCs) were perfused during CPB if the hematocrit level decreased to less than 18% perioperatively and to less than 25% postoperatively.

The priming solution included Ringeŕs lactate and mannitol without colloids. Moderate hypothermia (32–34 °C) and non-pulsatile flow were maintained throughout CPB. Perioperative anticoagulation was achieved with 300 U/kg IV standard heparin and was monitored with repeated analyses of activated clotting time, which was kept over 450 s during CPB. The perfusion circuit was primed with Ringeŕs solution and mannitol only. Hematocrit level was maintained above 20% during CPB. An additional 5000 units of heparin were given whenever the activated clotting time (ACT) fell to less than 480 s. As the patient was weaned from CPB, heparin was reversed with protamine sulfate at a ratio of 1 mg per 100 units of initial heparin dose and ACT was measured.

Upon arrival to the cardiac surgical ICU, all patients were routinely given an additional 500 mL of their study fluid (HES, GEL or ISO) over 30 min. Volume replacement was performed according to routine intra- and postoperative care guidelines aimed at maintaining adequate filling pressures (CVP near baseline values) and diuresis of >0.5 mL/kg/h. Excessive postoperative blood loss was defined as blood loss of over 400 mL within the first hour after surgery or over 100 mL/h for 4 consecutive hours from mediastinal and pleural drains. Durations of CPB and aortic cross-clamping, and the amount of mediastinal chest drainage intraoperatively and in the first 24 h postoperatively were recorded. Homologous erythrocyte, fresh frozen plasma, platelet or cryoprecipitate transfusion

Please cite this article in press as: Öztürk T et al. Immune and inflammatory role of hydroxyethyl starch 130/0.4 and fluid gelatin in patients undergoing coronary surgery. Cytokine (2014), http://dx.doi.org/10.1016/j.cyto.2014.10.002