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Laboratory Investigation

LABORATORY INVESTIGATION

Effects of resuscitation with human albumin 5%, hydroxyethyl starch 130/0.4 6%, or crystalloid on kidney damage in an ovine model of septic shock

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Abstract

Background: Colloid solutions have been associated with kidney dysfunction in septic animals and humans. The present study investigated the influence of resuscitation with human albumin (HA) 5%, hydroxyethyl starch (HES) 130/0.4 6%, and balanced crystalloids on ultrastructural kidney damage, kidney function, and survival in a model of ovine septic shock.
Methods: After induction of peritoneal septic shock, animals were randomised to one of the following groups: (1) HA 5%, (2) HES 130/0.4 6%, (3) balanced crystalloid, and (4) control (each n=10). Causal therapy included re-laparotomy, peritoneal lavage, and antimicrobial therapy. Sequential kidney biopsies were obtained for the assessment of the electron microscopic tubular injury (EMTI) score.
Results: Serum creatinine and urea were highest in the control group, and there were no differences between the intervention groups. Cumulative diuresis was significantly higher in the HA group [1.0 ml kg^{-1} h^{-1} (0.6; 1.2)] compared with control [0.7 ml kg^{-1} h^{-1} (0.6; 0.9), P<0.05]. Creatinine clearance was highest in the HA and crystalloid groups. Ultrastructural kidney damage was highest in the control group [EMTI score 7.8 (6.7; 9.0)] without differences between intervention groups. Survival was 100% in the colloid groups *vs* 90% (crystalloid) and 60% (control, all P<0.05).
Conclusion: In an ovine model of septic shock, kidney function and cumulative diuresis were preserved in the 5% albumin and crystalloid resuscitation groups, whereas HES 130/0.4 6% resulted in diminished creatinine clearance. Differences in kidney function between resuscitation fluids could not be explained by differences in ultrastructural kidney damage.
Clinical trial registration: 84-02.04.2011.A300.

Keywords: acute kidney injury; HES 130–0.4; fluid therapy; septic shock; serum albumin

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Editor's key points

- Use of hydroxyethyl starch (HES) to resuscitate patients with septic shock is controversial because of an increased risk of acute kidney injury.
- In a clinically relevant ovine model for septic shock, changes in renal function were more profound with colloid resuscitation compared with a balanced crystalloid.
- HES resuscitation was associated with a lower creatinine clearance than albumin or crystalloid resuscitation, but this could not be explained by a difference in ultrastructural kidney damage.
- Further studies are necessary to unravel the mechanism of HES-induced decreases in renal function in experimental septic shock.

Sepsis and septic shock remain among the most common causes of death worldwide.[1,2] One of the most discussed topics in sepsis therapy over the past years is fluid therapy and its association with acute kidney injury.[3,4] Based on the results from several randomised controlled trials (RCTs), the Surviving Sepsis Campaign (SSC) guidelines 2016 and the European Medicines Agency recommended against the use of hydroxyethyl starches (HES) for fluid resuscitation in critically ill and septic patients, respectively. According to the SSC guidelines, fluid resuscitation in septic shock should be performed with crystalloid solutions as first choice and human albumin (HA) in case of large fluid requirements.[1] The recommendation against starch-based colloids was based mostly on the results from three large RCTs, which reported no benefit (CRYSTMAS),[5] an increase in mortality (6S),[6] or an increased need for renal replacement therapy (CHEST)[7] in septic patients receiving HES for fluid resuscitation. However, it is still unclear whether surrogates of colloid-associated kidney dysfunction correlate with structural kidney damage.

The aim of the present investigation was to compare the effects of fluid resuscitation with crystalloid or colloids (HES 130/0.4 6% or HA 5%) on kidney function, ultrastructural kidney damage, and survival in an established model of septic shock with causal and supportive therapy in sheep. We hypothesise that the use of colloids for fluid resuscitation in septic shock is not associated with increased ultrastructural kidney damage despite increased surrogates of kidney dysfunction.

Methods

Animal care

Care and handling of the animals and all methods were performed in accordance with the National Institutes of Health's Guide, the American Physiologic Society's Guide for the Care and Use of Laboratory Animals, and the ARRIVE (Animal Research: Reporting of *In Vivo* Experiments) guidelines for animal research using established protocols.[8]

Instrumentation

After approval of the local authorities (ref. no. 84-02.04.2011.A300), 43 healthy ewes were anaesthetised with an i.m. injection of S-ketamine (Ketanest® S, 10 mg kg^{-1}; Parke-Davis, Berlin, Freiburg, Germany) and midazolam (0.3 mg kg^{-1}; Hoffmann-La Roche AG, Grenzach-Wyhlen, Germany). After tracheal intubation with a 9.0 tracheal tube (Rüsch, Rüschelit©; Teleflex Medical GmbH, Kernen, Germany), anaesthesia was maintained via inhalation of isoflurane with an inspiratory fraction of 1.0–1.5% (Forene®; Abbott GmbH & Co. KG, Wiesbaden, Germany). A central venous catheter (6 Fr. Quadlumen Catheter Set; PVB Medizintechnik GmbH, Kirchseeon, Germany) was placed in Seldinger's technique via the right jugular vein through which anaesthesia was supplemented with continuous infusion of S-ketamine (1 mg kg^{-1} h^{-1}), midazolam (0.3 mg kg^{-1} h^{-1}), and lidocaine (1.5 mg kg^{-1} h^{-1}).[9] Adequate pain relief was ensured by missing increase in heart rate (HR) and mean arterial pressure (MAP) in response to painful stimuli and missing movements of the animals in the absence of any neuromuscular blocking agents during the interventional period. For continuous haemodynamic surveillance, a pulse contour cardiac output catheter was placed in the right femoral artery (5 Fr.; Pulsion Medical Systems, Munich, Germany) and connected to a transpulmonary thermodilution and pulse contour cardiac output computer (Pulsion Medical Systems). A Foley catheter (12 Fr. urinary catheter; Porgès S.A., Le Plessis Robinson-Cedex, France) was inserted to determine diuresis.

Inclusion criteria

To prevent inclusion of sick animals, the following criteria had to be fulfilled:

- HR <100 beats min^{-1}
- MAP 70–120 mm Hg
- Cardiac index (CI) 2.5–6.0 L min^{-1} m^{-2}
- Serum lactate $\leq$1.2 mmol L^{-1}
- Temperature 38.0–39.8°C
- Arterial pH: 7.30–7.50
- Pa_{CO_2}: 4.7–7.3 kPa

The inclusion criteria were based on reference values for healthy sheep.[10] From the 43 initially instrumented animals, three ewes had to be excluded from the study because they did not meet the inclusion criteria.

Surgical preparation

After a median laparotomy, the caecum of the animal was incised to withdraw 1.5 g kg^{-1} faeces and closed by suture afterwards. One 16 Fr. drain was placed near the mesentery, and the abdomen was closed with continuous suture. After a 2 h phase of recovery, the healthy baseline (BL) data were measured.

Induction of septic shock

After BL measurements, the autologous faeces were injected into the peritoneal cavity via the drain. Onset of septic shock was defined as

- MAP <60 mm Hg
- Serum lactate concentration $\geq$1.8 mmol L^{-1} (i.e. 1.5 times the upper normal limit of sheep[10])
- At least 4 h from instillation of faeces

As soon as septic shock criteria were fulfilled, the 'shock time' measurements were performed.