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Does the type of fluid affect rapidity of shock reversal in an anaesthetized-piglet model of near-fatal controlled haemorrhage? A randomized study

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Editor's key points

- Optimal fluid strategies after haemorrhage remain a debated topic.
- Using piglets the speed of shock reversal was compared using lactated Ringer's solution compared with hydroxyethyl starch (HES).
- Baseline arterial pressure was restored much faster with HES and required less fluid.

Background. The optimal resuscitation fluid for the early treatment of severe bleeding patients remains highly debated. The objective of this experimental study was to compare the rapidity of shock reversal with lactated Ringer (LR) or hydroxyethyl starch (HES) 130/0.4 at the early phase of controlled haemorrhagic shock. To assess the influence of vascular permeability in this model, we measured plasma vascular endothelial growth factor (VEGF) levels during the experiment.

Methods. Thirty-six anaesthetized and mechanically ventilated piglets were bled (<30 ml kg^{-1}) to hold mean arterial pressure (MAP) at 40 mm Hg for more than 30 min and were resuscitated in two randomized groups: LR ($n=14$) or HES ($n=14$) at 1 ml kg^{-1} min^{-1} until MAP reached its baseline value of $\pm 10\%$. MAP was maintained at its baseline value for 1 h. The time and fluid volume necessary to restore the baseline MAP value were measured.

Results. The time to restore the baseline MAP value of $\pm 10\%$ was significantly lower in the HES group ($P<0.001$). During the initial resuscitation phase, the infused volume was 279 (119) ml in the HES group and 1011 (561) ml in the LR group ($P<0.0001$). During the stabilization phase, the infused volume was 119 (124) ml in the HES group and 541 (506) ml in the LR group. Biological data and plasma VEGF levels were similar between the groups.

Conclusions. Restoration of MAP was four times faster with HES than with LR in the early phase of controlled haemorrhagic shock. However, there was no evidence of increased vascular permeability.

Keywords: bleeding; laboratory animal model; resuscitation; shock

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Rapid fluid administration is the first therapeutic step in the management of severely bleeding patients in order to restore circulatory stability.[1] Controversy remains regarding the choice of fluids for shock resuscitation.[2 3] Given that colloids such as hydroxyethyl starch (HES) are more likely to be maintained in the intravascular space, they could theoretically be more efficient at expanding the circulating volume. Therefore, physicians commonly use HES for hypovolaemia resuscitation, shock resuscitation, or both.[4–7] However, in severe sepsis, HES has been associated with renal dysfunction, increased mortality, or both.[8–10] In addition, the crystalloids to colloids required volume ratio reported in large randomized studies was close to 1:1 questioning the plasma volume expansion effect of HES.[2 11–14] During haemorrhage, the superiority of colloids compared with crystalloids remains unresolved.[15 16] In penetrating trauma, James and colleagues[17] have reported a colloid to crystalloid ratio of 1:1.5 associated with improvements in renal function and lactate clearance.

Many factors could influence the distribution of administered fluids such as the volume status of the patient, vascular tone, and capillary leak.[18 19] After i.v. infusion, a fluid is first distributed into the intravascular space before diffusing to the extravascular space.[20] This diffusion can vary under different conditions. Indeed, Drobin and Hahn[21] have shown that the worse the hypovolaemia, the greater the circulating blood volume expansion of lactated Ringer (LR) in volunteers, because of a reduction in the elimination rate constant. Anaesthetic drugs also modify fluid shifts between compartments.[22]

Finally, increased vascular permeability as a result of inflammation could influence fluid distribution and could minimize differences between crystalloids and colloids in terms of plasma volume expansion. On the contrary, in situations without increased vascular permeability, colloids could be a better plasma expander, especially in terms of the rapidity of blood volume restoration.

To the best of our knowledge, the rapidity of shock reversal with crystalloids or colloids has never been compared at the initial phase of haemorrhagic shock resuscitation. We hypothesized that initial administration of HES for rapid fluid resuscitation may provide a faster and greater plasma volume expansion effect compared with LR during the early phase of severe haemorrhage. To assess vascular permeability in this model, we measured plasma vascular endothelial growth factor (VEGF) levels during the experiment. Therefore, the aim of the present study was to compare time and volume of HES 130/0.4 needed to restore haemodynamics *vs* LR at the initial phase of a controlled haemorrhage model in anaesthetized and ventilated piglets.

Methods

This study was designed as a prospective randomized unblinded trial in a piglet model. The Animal Care and Use Committee Languedoc-Roussillon (CEEA-LR-12013) approved the protocol and all experiments were performed in an authorized animal research laboratory. All facilities and transport comply with current legal requirements.

Animal preparation

Thirty-six piglets weighing 20–31 kg were included. Animals were fasted overnight with free access to water. The piglets were pre-medicated with i.m. injection of ketamine 10 mg kg^{-1}, atropine 0.05 mg kg^{-1}, and midazolam 1 mg kg^{-1}. Anaesthesia was induced with a bolus dose of propofol (4 mg kg^{-1}) and cisatracurium (0.25 mg kg^{-1}) via an ear vein. Anaesthesia was maintained with propofol (8 mg kg^{-1} h^{-1}) and neuromuscular block was achieved with cisatracurium (0.5 mg kg^{-1} h^{-1}). Animals' lungs were ventilated after surgical tracheostomy (6.5 tracheal tube Tyco®, Atlanta, GA, USA), with an inspired fraction of oxygen of 0.21, a tidal volume of 8 ml kg^{-1}, and a positive end-expiratory pressure of 5 cm H_2O (Servo 900C® ventilator, Siemens, Solna, Sweden). A similar anaesthetic management protocol was shown to be stable over a 2-h period in piglets.[23]

Once the piglets were anaesthetized, a left cervical downward cut was performed and a 7 French double-lumen catheter was inserted through the internal jugular vein into the right atrium. The central venous line was used to monitor central venous pressure (CVP), to sample venous blood gases and to inject cold boluses for transpulmonary thermodilution. A 5 French arterial catheter with an integrated thermistor tip was inserted through the femoral artery (PiCCO®; Pulsion Medical Systems, Munich, Germany) into the descending aorta for continuous arterial pressure monitoring, arterial blood sampling, and cardiac output (CO) transpulmonary thermodilution measurement. The femoral vein was also cannulated with an 8.5 French catheter (Arrow®; Arrow International, Inc., Cleveland, OH, USA) for blood withdrawal and for the administration of resuscitation fluids. All pressure-measuring catheters were connected to transducers (PiCCO® plus, Pulsion) for continuous recording of systemic arterial pressure, heart rate (HR), and temperature.

Experimental protocol and times of measurements

The duration of the protocol was 2 h (Fig. 1). Haemorrhage was initiated by withdrawing venous blood through the femoral venous catheter at 2 ml kg^{-1} min^{-1} until a mean arterial pressure (MAP) of 40 mm Hg was reached (~35% total blood volume or ~30 ml kg^{-1}). Blood withdrawn was collected in a bag containing a solution of sodium citrate to prevent coagulation and to allow an autologous transfusion if necessary for the following phase.

During the next 30 min, MAP was maintained between 35 and 45 mm Hg by additional blood withdrawal or reinfusion of the shed blood as described in similar controlled haemorrhage models.[24] Twenty-eight piglets were randomly allocated using sealed envelopes into two groups based on the type of infused fluid: LR group (n=14) was resuscitated with LR solution and the HES group (n=14) received 6% HES 130/0.4 (Voluven®; Fresenius Kabi, Sèvres, France). Fluid was infused at 1 ml kg^{-1} min^{-1} until MAP reached the baseline value of $\pm$10%. The time needed to restore MAP $\pm$10% was recorded. We also studied two additional groups of piglets with the same protocol as the others except for the resuscitation phase: a transfusion group (n=4) received blood by autologous transfusion for shock resuscitation and a control group (n=4) received no fluid resuscitation.

MAP was maintained at its baseline value $\pm$10% by additional fluid infusion according to the allocated group for a further hour then all animals were killed using i.v. thiopental infusion (2 g).

During the experiment, the following parameters were measured:

(1) Haemodynamic parameters at T_0, T_1, T_2, T_3, and T_4: CVP, systolic, and diastolic arterial pressure, MAP, HR, CO by transpulmonary thermodilution, global end-diastolic volume (GEDV), extravascular lung water (EVLW), and pulse pressure variation (PPV) by pulse contour analysis.
(2) Biological parameters at T_0, T_2, and T_4: arterial blood gases, haemoglobin, venous oxygen saturation, Na^+, Cl^-, Ca^{2+}, lactate, creatinine, haemoglobin, and albumin.

VEGF measurements

VEGF is an endothelial cell-specific growth factor. It appears to be a key regulator of vascular permeability and has been implicated in several pathophysiological situations such as angiogenesis, retinopathy, tumour growth, and wound healing. In septic shock, high levels of VEGF were reported, correlated