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Original Contribution

Does the infusion rate of fluid affect rapidity of mean arterial pressure restoration during controlled hemorrhage☆

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ABSTRACT

Objective: This study aimed to compare 2 fluid infusion rates of lactated Ringer (LR) and hydroxyethyl starch (HES) 130/0.4 on hemodynamic restoration at the early phase of controlled hemorrhagic shock.
Methods: Fifty-six anesthetized and ventilated piglets were bled until mean arterial pressure (MAP) reached 40 mm Hg. Controlled hemorrhage was maintained for 30 minutes. After this period, 4 resuscitation groups were studied (n = 14 for each group): HES infused at 1 or 4 mL/kg per minute or LR1 infused at 1 or 4 mL/kg per minute until baseline MAP was restored. Hemodynamic assessment using PiCCO monitoring and biological data were collected.
Results: Time to restore baseline MAP ± 10% was significantly lower in LR4 group (11 ± 11 minutes) compared to LR1 group (41 ± 25 minutes) ($P = .0004$). Time to restore baseline MAP ± 10% was significantly lower in HES4 group (4 ± 3 minutes) compared to HES1 (11 ± 4 minutes) ($P = .0003$). Time to restore baseline MAP ± 10% was significantly lower with HES vs LR whatever the infusion rate.
No statistically significant difference was observed in cardiac output, central venous saturation, extravascular lung water, and arterial lactate between 4 and 1 mL/kg per minute groups.
Conclusions: In this controlled hemorrhagic shock model, a faster infusion rate (4 vs 1 mL/kg per minute) significantly decreased the time for restoring baseline MAP, regardless of the type of infused fluid. The time for MAP restoration was significantly shorter for HES as compared to LR whatever the fluid infusion rate.

1. Introduction

Despite large prevention programs around the world, severe injuries remain a major cause of death, greater than large pandemic infectious diseases [1]. Massive hemorrhage and neurologic injuries are the 2 main causes of death [2,3]. Even if early aggressive transfusion strategies are a key issue of severe bleeding management [4,5], fluid infusion remains the first therapeutic step, especially in prehospital settings [6]. However, infusion of large crystalloids volumes was shown to be associated with increased complications and mortality rates [4,7,8]. Damage control resuscitation is an emerging concept based on early transfusion and reduction of crystalloids [9–11]. If the link between the use of high fluid infusion rate, hemodynamic instability and need for emergent surgery was demonstrated, the optimal fluid infusion rate remains unclear [12]. In recent guidelines, no precise recommendation on fluid infusion rate during severe hemorrhage was mentioned [13]. Previous studies have reported the effects of fluid administration rates on plasma dilution in volunteers by applying principles similar to those used in pharmacokinetics [14–16]. Mathematical models suggested that high infusion rates (>80 mL/kg per hour) of crystalloids may not increase effectiveness of fluid resuscitation in acute hemorrhage model and could induce a higher transfer of fluid from plasma to interstitium [17]. Interstitial edema due to high crystalloid infused volume is associated with poor outcomes [8,9,18]. Some studies suggested that high infusion rates could be deleterious as compared to low infusion rates [19–21], whereas other study did not show any benefit of different infusion rates [22]. In controlled hemorrhage, the infusion rate used could also have a different impact. Such conflicting results suggest that additional studies are needed to investigate the impact of fluid infusion rate on resuscitation target, especially arterial pressure restoration and global hemodynamics. The role of the type of fluid is also debated. Arterial colloids are no longer recommended in critically ill patients with septic shock because of lack of superiority over crystalloids, increased renal toxicity, and increased mortality [23,24]. These deleterious effects of

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colloids are not demonstrated in nonseptic patients, and some studies suggest a better hemodynamic efficacy of artificial colloids over crystalloids during hemorrhage [25–28].

The primary objective of the present study was to compare the time needed to restore mean arterial pressure (MAP) at 2 different infusion rates (1 vs 4 mL/kg per minute) in a model of controlled hemorrhage in anesthetized piglets. The second objective was to assess if infusion rates could differently affect the ability of lactated Ringer (LR) and hydroxyethyl starch 130/0.4 (HES) to restore MAP.

2. Materials and methods

This study was conducted as a prospective trial in a piglet model. The Animal Care and Use Committee approved the protocol, and all experiments were performed in an authorized animal research laboratory. All facilities and transport comply with current legal requirements.

2.1. Animal preparation

Fifty-six male 3-month-old piglets weighing 25 to 30 kg were included in the study. Animals were fasted overnight with free access to water. The animals were prepared as previously reported. Briefly, the piglets were premedicated with intramuscular injection of ketamine 10 mg/kg, atropine 0.05 mg/kg, and midazolam 1 mg/kg. Anesthesia was induced with a bolus dose of propofol (4 mg/kg) and cisatracurium (0.25 mg/kg) via an ear vein. Anesthesia was maintained with propofol (8 mg/kg per hour), and neuromuscular blockade was achieved with cisatracurium (0.5 mg/kg per hour). Animals were ventilated after surgical tracheotomy (6.5 endotracheal tube Tyco) with an inspired fraction of oxygen of 0.21, a tidal volume of 8 mL/kg, and a positive end-expiratory pressure of 5 cm H_2O (Servo 900C ventilator; Siemens, Solna, Sweden).

Once the piglets were anesthetized, a left cervical downward cut was performed, and a 7F double-lumen catheter was inserted through the internal jugular vein into the right atrium. The central venous line was used for central venous pressure (CVP) monitoring, venous blood gazes sampling, and cold bolus injections for cardiac output (CO) measurement by transpulmonary thermodilution method. A 5F 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 blood pressure monitoring, arterial blood sampling, and CO measurement. The femoral vein was also cannulated with an 8.5F catheter (Arrow; Arrow international, Inc) 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.

2.2. Experimental protocol and times of measurements

The protocol was divided into 4 phases (Fig. 1).

At baseline (T_0), measurements of hemodynamic and biological parameters were performed. Hemorrhage was initiated by withdrawing venous blood through the femoral venous catheter at 2 mL/kg per minute until a MAP of 40 mm Hg was reached (~45% total blood volume or ~30 mL/kg). At the time of a 40 mm Hg MAP value could be read on the monitor (T_1), CO was measured by transpulmonary thermodilution. Withdrawn blood was collected in a bag containing a solution of sodium citrate to prevent coagulation and to allow an autotransfusion if necessary for the following phase. During the following 30 minutes, MAP was maintained between 35 and 45 mm Hg by additional blood withdrawal or reinfusion of the shed blood. At the end of this phase (T_2), hemodynamic parameters were measured, and blood samples were collected. Fifty-six piglets were divided into 4 groups based on the administration rate of infused fluid: LR1 group ($n = 14$) was resuscitated with LR at a 1 mL/kg per minute infusion rate; LR4 group ($n = 14$), with LR at a 4 mL/kg per minute infusion rate; HES1 group ($n = 14$), with 6% HES 130/0.4 (Voluven; Fresenius Kabi, France) at a 1 mL/kg per minute infusion rate; and HES4 group ($n = 14$), with 6% HES 130/0.4 at a 4 mL/kg per minute infusion rate. The choice between LR and HES was randomized. To respect the 3Rs rule of the use of animals in research and to reduce the number of animals, we used collected data of the piglets resuscitated at 1 mL/kg per minute in our previous study, and we added 2 groups: HES4 and LR4 submitted to the strict similar protocol. The overall experiment for the 4 groups was performed during the same and short period (from April 2011 to June 2012) and under strictly same experimental conditions. The allocated fluid was infused until MAP reached the baseline value ± 10%. At this point (T_3), hemodynamic parameters including CO by thermodilution were measured. During the following hour, MAP was maintained at its baseline value ± 10% by additional fluid infusion according to the allocated group when necessary.

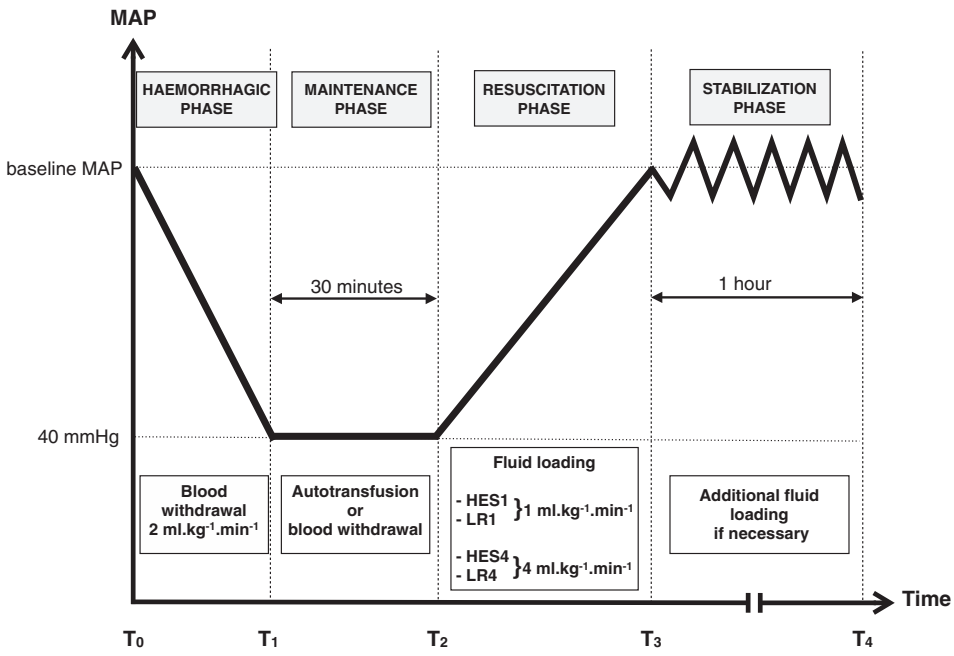

Fig. 1. Study design.