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Pyruvate oral rehydration solution improved visceral function and survival in shock rats

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ABSTRACT

Background: Recent findings showed advantages of a novel pyruvate-enriched oral rehydration solution (Pyr-ORS) in resuscitation of burns. This study focused on effects of Pyr-ORS on the visceral blood perfusion (VBP), gastrointestinal function, and survival rate, compared with the bicarbonate-based World Health Organization-guided oral rehydration solution (WHO-ORS), during intragastric rehydration of lethal hemorrhagic shock in rats.

Methods: Sixty adult rats were subjected to 45% total blood volume loss and were randomly allocated to the following three groups ($n = 20$): group NR (no fluid resuscitation), group PORS (oral Pyr-ORS rehydration), and group BORS (oral WHO-ORS rehydration), respectively. Other 10 rats were served as group NH (the sham group). Enteral rehydration lasted for 4 h after hemorrhage. The mean arterial pressure (MAP), VBP, and plasma enzymes activities of heart, liver, and kidney, and intestinal fatty acid binding protein were measured. Liver, kidney, and ileum were harvested for the evaluation of activities of oxidative enzymes and intestinal barrier protein (ZO-1). Other 84 rats with identical procedures without sampling were observed for their 24-h survival rates.

Results: Pyr-ORS was more effective in enhancing the MAP and VBP, inhibiting tissue oxidative damage, and improving organ function, compared with WHO-ORS. Hypoxic lactic acidosis was fully corrected in group PORS in 4 h, whereas it worsened in group BORS, and the 24-h survival rate was twice higher in group PORS than in group BORS (45.8 *versus* 20.8%, $P < 0.05$).

Conclusions: A small amount of pyruvate in Pyr-ORS was more therapeutically beneficial than equivalent bicarbonate in WHO-ORS and greatly raised survival in enteral rehydration of lethal hemorrhagic shock. The Pyr-ORS may be an ideal oral fluid in resuscitation of hypovolemic shock, especially in prehospital and resource-poor settings.

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1. Introduction

Severe trauma, burn, sepsis, and hemorrhage require early intravenous fluid resuscitation, however, it is usually not feasible in prehospital or resource-poor settings. It has been demonstrated that the standard World Health Organization-guided oral rehydration solution (WHO-ORS) could improve hemodynamic parameters and survival rates in animals and humans with burn injury [1–4]. The Ceralyte 90 formula of WHO-ORS was recently suggested to be an alternative to intravenous fluids in clinical burn resuscitation [5]. However, oral rehydration is still challenged because gastrointestinal ischemia due to severe trauma and/or burn and hypovolemic shock impairs the intestinal absorption of water and sodium induced by mucosal barrier injury [6,7]. There is no optimal or "universal" ORS formula conceived and current formulas of WHO-ORS may require further modifications for clinical shock resuscitation [4]. However, as yet, little is known regarding effective drugs or agents to improve the visceral blood perfusion (VBP) and gastrointestinal function in hypovolemic shock.

Pyruvate, a metabolic intermediate of the glycolytic pathway, has been substantiated to be of protective effects on glucose metabolic pathways, super buffer capabilities, and anti-oxidative and/or inflammatory activities [8–12], greatly increasing survival rates in intravenous resuscitation from severe hemorrhagic shock (HS) in various animal models [9,11,13]. Recently, it was documented that pyruvate reversed visceral hypoperfusion in peritoneal resuscitation from HS and a novel pyruvate-enriched ORS (Pyr-ORS) also protected intestinal barrier function in enteral rehydration of scald injury in rats [14,15]. To further explore effects of the new Pyr-ORS, in which equimolar pyruvate replaced bicarbonate in the standard WHO-ORS with an isotonic osmolarity, a hypothesis was tested in this experiment that Pyr-ORS would also improve the VBP, gastrointestinal function, acidosis, and survival rate, compared with bicarbonate-based WHO-ORS, during enteral rehydration in rats subjected to severe HS.

2. Methods

2.1. Animals and surgical procedures

Adult male Sprague–Dawley rats, weighing 250–282 (263.2 ± 16.1) g, purchased from Experimental Animal Center of Academy of Military Medical Sciences of PLA, Beijing, China were used in the experiments. Rats were acclimated for 7 d at 25°C on a 12-h light–dark cycle and free access to the standard laboratory feed and water and were fasted overnight, but allowed free access to water until 4 h before surgery. All animal experiments were performed in accordance with the National Institutes of Health Guidelines under protocols approved by the Committee of Scientific Research of First Affiliated Hospital of General Hospital of PLA, Beijing, China. The rats were anesthetized by the inhalation of 3% isoflurane with a nose cone scavenging system using a veterinary multi-channel anesthesia delivery system and vaporizer (kent Scientific TOPO, Torrington, CT) and allowed to breathe room air spontaneously. Anesthesia was maintained by delivering 0.7% isoflurane during surgical procedures and lidocaine (1%) was injected subcutaneously for local anesthesia. With aseptic technique, poly-ethylene (PE50) catheters were placed in the stomach for ORS infusion, in the right carotid artery for continuous mean arterial pressure (MAP) monitoring, and in the left femoral artery for blood withdraw. The VBP was measured with a flexible probe with 0.25 mm laser rheophore, which was inserted through an abdominal incision and positioned on surfaces of liver and kidney, and on intestinal mucosa intraluminally via a small enterotomy. The body temperature was maintained at 37.5°C with a heating lamp. All animals were acclimated after surgery for 10 min and fully recovered from anesthesia before exsanguinations.

2.2. HS protocols

The volume of hemorrhage was based on each animal's estimated total blood volume (TBV), which was calculated as follows: TBV (mL) = weight (g) × 0.06 (mL/g) + 0.77 [13]. Controlled HS in rats was induced, following a simple modification of the method described previously [14], by withdrawing 45% of the calculated TBV within 30 min (30% over the first 5 min, then 15% over 10 min with an interval of 15 min) in a syringe with 0.02 mL heparin (1000 IU/mL) with an infusion or a withdrawal pump. A 2 mL blood sample was drawn from the femoral artery at the baseline, the end of hemorrhage (0 h) and at the end of resuscitation (4 h) for blood analysis, which was included in the total hemorrhage calculation. The shed blood was not reinfused.

2.3. Preparations of ORS

On the experimental day, the ORS solutions were freshly prepared by dissolving the following components in filtered distilled water, as previous described [15]. Pyr-ORS (PORS) was 1000 mL containing 59.8 mM of NaCl, 29.8 mM of NaPyr, 20.2 mM of KCl and 111.1 mM of glucose with the osmolarity of 335 mOsm L^{-1}; WHO-ORS (BORS) was 1000 mL containing 59.8 mM of NaCl, 29.8 mM of $NaHCO_3$, 20.2 mM of KCl, and 111.1 mM of glucose with the osmolarity of 331 mOsm L^{-1}. The pH value of solutions was titrated to 7.3 ± 0.2 and the solutions were preheated to 37°C before use.

2.4. Experimental groups and treatments

Sixty rats with HS were randomly divided into group NR (n = 20): no fluid rehydration, group PORS (n = 20): enteral rehydration with Pyr-ORS, and group BORS (n = 20): enteral rehydration with WHO-ORS. Intragastric infusion of ORS with 2 times volume of shed blood was immediately initiated after the hemorrhage termination and three fourths of the total calculated volume of ORS was completed in 4 h with a half of the total volume infused in the first 2 h and the rest of one fourth in the late 2 h by a micro-infusion pump. Other rats underwent the comparable surgical procedure without hemorrhage and resuscitation were served as the sham group NH