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Pyruvate as a novel carrier of hydroxyethyl starch 130/0.4 may protect kidney in rats subjected to severe burns

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ABSTRACT

Background: The carrier of hydroxyethyl starch (HES) may play a critical role in kidney injury in fluid resuscitation. This study aimed mainly to compare effects of pyruvate-enriched saline with normal saline (NS) and acetate Ringer's (AR) solution as a carrier in HES130/0.4 on kidney function in rats subjected to severe burns.

Methods: Using a lethal burn model, 140 rats were randomly allocated in seven groups ($n = 20$): sham group (group S); no fluid after burn (group N); burn resuscitated with NS (group NS); burn resuscitated with pyruvate saline (group PS); burn resuscitated with AR plus pyruvate-HES (group SP); burn resuscitated with AR plus acetate-HES (group SA), and burn resuscitated with AR plus NS-HES (group SN). A low volume (18.75 $mL \cdot kg^{-1}$ during 12 h) of HES130/0.4 was infused with the ratio of 1:1 to crystalloids. Renal surface blood flow, blood creatinine and blood urea nitrogen, early sensitive indicators of kidney function: alpha-1 microglobulin, cystatin-C, and neutrophil gelatinase–associated lipocalin in blood and urine, and kidney tissue water contents were determined. Renal histopathological alterations with Paller scores were also measured at 8 h and 24 h after burn ($n = 10$), respectively.

Results: The results showed in a comparable manner that group SP was the best in three HES groups and group PS was superior to group NS in renal preservation; group SP appeared significantly beneficial compared with group PS in renal surface blood flow, cystatin-C, neutrophil gelatinase-associated lipocalin, water contents, and Paller scores at 8-h or both time points after burn, respectively (all $P < 0.05$).

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Conclusions: The carrier of HES130/0.4 played a crucial role in kidney injury in fluid resuscitation of rats subjected to severe burns. Pyruvate-enriched HES130/0.4 was superior and HES130/0.4, *per se*, might be not renocytotoxic, but renoprotective. Further studies are warranted.

Introduction

There has been a curious paradox whether the modern generation of hydroxyethyl starch (HES), HES130/0.4 (MW/substitution ratio), is beneficial or harmful to organ function, particularly kidney, in treatment of critically ill patients, more specifically in sepsis patients. Some emphasized its detrimental effects on renal function,[1-5] whereas others argued its favorable renoprotection or no renocytotoxicity,[6-10] even in patients subjected with severe sepsis.[11] Currently, there is a lack of clinical data from either meta-analyses or a single-center review regarding the carrier impact of HES130/0.4 on the acute kidney injury (AKI) in fluid resuscitation. The doubt that presumed HES adverse effect is resulted from either HES, *per se*, the vehicle, or both remains ignored or unverified in clinical settings.[12-14] Clinical reports in major surgery have documented that normal saline (NS, 0.9% NaCl) is not physiological, i.e., abnormal saline and even transient hyperchloremic acidosis induced by NS is destructive in intensive care unit (ICU) patients originally complicated with severe acid–base disturbances and/or high risks of organ dysfunction, contributing to further renal injury.[15,16] Although Hartmann's solution, lactated Ringer's solution, and lactated HES like Hextand can mostly prevent patients from hyperchloremia, lactate may exacerbate glycolytic inhibition, inflammation, and metabolic acidosis in ICU patients.[17,18] To avoid untoward effects, that is, Resuscitation Injury, by traditional fluids, acetate-based fluids, such as acetated Ringer's (AR) solution and acetate-based HES130/0.4 (Tetraspan), showed their rising prominence in the clinical fluid management in past decades. However, it is noteworthy that acetate has no obvious protection of cell/organ function, rather, is a proinflammatory agent.[19] In particular, acetate cannot be oxidized under anaerobic conditions and does not enable to correct lethal lactic acidosis (type A), either. It even provokes lactic acidosis.[20] Pyruvate has long been demonstrated to facilitate multiorgan function, including heart, brain, liver, kidney, intestine, eye, and blood cell, and to correct lactic acidosis in animal studies and/or clinical trials, illustrating its superior biological properties.[21-24] Of its multiorgan protection, the kidney is significantly benefited from the pyruvate administration.[25,26] Accordingly, the present study was conducted to compare pyruvate-enriched HES130/0.4 with AR- and NS-enriched counterparts together with crystalloids: pyruvate saline (PS) and NS, aiming to address the impacts of pyruvate and/or HES on the kidney in resuscitation of rats subjected to severe burns.

Materials and methods

Ethics approval

The Committee of Scientific Research of the First Hospital Affiliated to the General Hospital of People's Liberation Army, China, approved all the research protocols. The study was conducted in compliance with the Guide for Care and Use of Laboratory Animals of the National Research Council, China.

Animals and burn surgical procedures

To stand against critical illness and conception, all male Sprague–Dawley rats, aging 12 wk and weighing 250 ± 20 g, obtained from the Institute of Laboratory Animal Sciences, Chinese Academy of Medical Science, Beijing, China, were used in the experiments. Rats were acclimatized for 1 wk with the standard diet and exposure to light and dark per 12 h (a 12L:12D pattern) each day and fasted overnight, but allowed free access to water until 4 h before experiments. The rats were instrumented and anesthetized with inhalation of 3% isoflurane, and then 0.7% isoflurane was used to maintain anesthesia during the experiments. Rats were allowed to breathe spontaneously under a nose cone scavenging system using a veterinary anesthesia delivery system (Kent Scientific TOPO, Torrington, CT). After removing the hair on the back and abdomen, the rats were placed in a rectangular prefabricated frame, the bare skin with protection of the remaining part was immersed in boiling water (100°C) on the back for 15 s and abdomen for 8 s in six scald groups, resulting in about 50% total body surface area (TBSA) of full-thickness burn. In the sham group, warm water (37°C) was applied. Following the scald injury, the rats received a subcutaneous injection of 0.5 mL NS with 500 μL buprenorphine (Sigma–Aldrich, St Louis, MO) per 6-8 h for pain control. The depth of the burn was verified by pathological examinations. With aseptic technique, a polyethylene catheter (PE-50) was inserted into the right external jugular vein. The catheter was led out through a subcutaneous tunnel and fixed to the skin exit for fluid infusion during a period of 12 h after burn injury. By using a specific vest, the infusion catheter connected to intravenous fluids was fixed in the back of rats' neck, so that the universal shaft device ensured continuous fluid infusion, while rats were moving freely in the cage after recovery from anesthesia.

Grouping and treatments

One hundred forty rats were randomly divided into seven groups ($n = 20$): 1) sham control without fluid resuscitation (Group S); 2) burn with no fluid resuscitation (Group N); 3) burn resuscitated with NS (Group NS); 4) burn resuscitated with PS (Group PS); 5) burn resuscitated with AR plus pyruvate-based HES (Group SP); 6) burn resuscitated with AR plus acetate-based HES (Group SA), and 7) burn resuscitated with AR plus NS-based HES (Group SN). Each group was subdivided into two groups ($n = 10$) at each time point: 8 h and 24 h after burn. Fluid infusion was carried out through the jugular vein catheter in five resuscitation groups, using a trace infusion pump