BJA

British Journal Of Anaesthesia, 117 (4): 521–8 (2016)

doi: 10.1093/bja/aew277
Translational Research

The role of bicarbonate precursors in balanced fluids during haemorrhagic shock with and without compromised liver function

B. Ergin[1†], A. Kapucu[2†], P. Guerci[1,3†] and C. Ince[1*†]

[1]Department of Translational Physiology, Academic Medical Centre, Amsterdam, The Netherlands, [2]Department of Biology, Science Faculty, University of Istanbul, Istanbul, Turkey and [3]University of Lorraine, Vandoeuvre-les-Nancy, INSERM U1116, Nancy, France

*Corresponding author. E-mail: c.ince@amc.uva.nl

Abstract

Background: Lactate, acetate, and gluconate are anions used in balanced resuscitation fluids, of which lactate and acetate are considered bicarbonate precursors. This study investigated the role of the liver in the ability of balanced and unbalanced solutions to correct acid–base alterations and renal haemodynamics and microvascular oxygenation in a rat model of resuscitated haemorrhagic shock.

Methods: Ringer's lactate, Ringer's acetate, PlasmaLyte, or normal saline were administered following haemorrhagic shock in the presence or absence of a 70% partial liver resection. Renal haemodynamics and microvascular oxygenation (by oxygen-dependent quenching of phosphorescence) were measured as well as concentrations of lactate, gluconate, and acetate in plasma and urine. Kidney wet and dry weight was also assessed.

Results: Partial liver resection resulted in increased liver enzymes compared with control and shock groups ($P < 0.01$). Haemorrhagic shock decreased systemic and renal perfusion and reduced microvascular kidney oxygenation with lactic acidosis ($P < 0.01$). Resuscitation with balanced fluids did not fully restore renal oxygenation ($P < 0.01$). Ringer's acetate and PlasmaLyte increased bicarbonate content and restored pH better than Ringer's lactate or saline after partial liver resection ($P < 0.01$). Liver resection caused an increase in plasma gluconate after PlasmaLyte resuscitation ($P < 0.05$).

Conclusions: Acetate-buffered balanced fluids show superior buffering effects compared with Ringer's lactate or saline. Gluconate is partially metabolized by the liver, although it does not contribute to acid–base control because of its excretion in urine. Acetate is metabolized regardless of liver function and may be the most efficient bicarbonate precursor. Lactate infusion tends to overwhelm the metabolism capacity of the residual liver.

Key words: buffered solution; gluconate; haemorrhagic shock; microcirculation; PlasmaLyte

[†]Aysegul Kapucu and Bulent Ergin contributed equally to this study.

Accepted: June 28, 2016

Editor's key points

- The composition of resuscitation fluids is important for outcome from haemorrhagic shock.
- Fluids containing acetate may be better than those containing lactate in the presence of liver dysfunction.
- In rats subjected to partial liver resection and shock, fluids containing acetate had superior buffering effects than fluids containing lactate or saline.
- Acetate metabolism does not depend on liver function, but lactate infusion overwhelms the liver.
- Saline is inappropriate for resuscitation during shock and liver failure.

Current evidence suggests that the type of fluid used for resuscitation, particularly colloids, may lead to unfavourable outcomes or have no effect compared with normal saline.[1–5] Several studies have demonstrated that balanced fluids are commonly used for volume expansion in critically ill patients.[6–8] This has led to increased attention towards the role of crystalloids and the effects of their different composition.[9 10] Fluid preparation may be based on a simple, non-buffered salt solution, such as normal saline, or be balanced with anion substitutes, such as maleate, gluconate, lactate, or acetate, of which the latter two are considered bicarbonate precursors. PlasmaLyte (Baxter Healthcare, Deerfield, IL, USA) is a crystalloid fluid containing two weak anions—acetate and gluconate—and is engineered to closely mimic the plasma electrolyte content while not altering its osmolality.[11] However, the role of gluconate in terms of acid–base control is unknown.

There is a growing body of evidence indicating that balanced fluids improve the acid–base status and preserve a strong ion difference.[12] The purpose of using these solutions is based on two principles: (i) reducing the chloride content and its detrimental effects,[13] while providing a plasma-like ionic content, and (ii) increasing bicarbonate content and pH by metabolism of bicarbonate precursors.[14] It is commonly accepted that these precursors are mainly metabolized in the liver.[15 16] To our knowledge there is little information on the contribution of liver function to acid–base control during fluid-balanced resuscitation for haemorrhagic shock. What is unclear and not well described is the metabolic fate of such components during shock states associated with compromised liver function and the degree to which other organ beds are effective in metabolizing these precursors to produce bicarbonate and correct acid–base alterations.[9] Although it is generally assumed that lactate is primarily metabolized in the liver in case of shock, the acetate is metabolized in other organs.[17] We hypothesized that acetate-based resuscitation fluids would have a superior buffering effect than non-acetate-based fluids in the presence of liver dysfunction.

To this end we assessed the buffering effect of three commonly used balanced fluids—Ringer's lactate (RL), Ringer's acetate (RA) and PlasmaLyte (RA-Glu/Mg) (**supplementary Table 1**)—in a relevant model of fixed-pressure haemorrhagic shock. In the first part of the study we aimed to determine the role of the liver in the metabolism of these buffers. To accomplish this, an ~70% partial liver resection (PLR) was performed to reduce the capacity of the liver to metabolize these precursors. In addition, we studied the fate of gluconate in these models. Second, we investigated the extent to which each type of fluid is effective in improving acid–base status and tissue oxygenation, which can be considered the primary goals of fluid resuscitation in states of shock. We focused on the kidney because it is considered to be the organ most at risk during states of shock and fluid overuse.

Material and methods

Animals

All experiments in this study were approved by the Animal Research Committee of the Academic Medical Centre of the University of Amsterdam (DFL 102919) and followed relevant aspects of the Animal Research: Reporting of In Vivo Experiments guidelines. The care and handling of the animals were in accordance with the guidelines from the Institutional and Animal Care and Use Committees. A total of 75 rats were needed in these experiments ($n = 6$ per group), including 3 animals for setting up the PLR model. Experiments were performed on male Sprague–Dawley rats (Harlan Netherlands), age 10 (SD 2) weeks with a mean body weight of 330 (SD 20) g.

Surgical preparation

The rats were anaesthetized with an intraperitoneal injection of a mixture of 100 mg kg^{-1} ketamine (Nimatek; Eurovet, Bladel, The Netherlands), 0.5 mg kg^{-1} medetomidine (Domitor; Pfizer, New York, NY, USA) and 0.05 mg kg^{-1} atropine sulphate (Centrafarm, Etten-Leur, The Netherlands) and maintained with 50 mg kg^{-1} ketamine at a dose of 5 ml kg^{-1} h^{-1}. Adequate anaesthesia was ascertained by pedal withdrawal response to a nociceptive stimulus and physiological observations. After tracheostomy, the animals were mechanically ventilated with 40% of inspired oxygen. A heating pad under the animal allowed the body temperature to be controlled and maintained at 37 (SD 0.5) °C. The end tidal P_{CO2} was maintained between 4 and 4.7 kPa.

The right carotid (pressure) and femoral (for blood shedding and samples) arteries and jugular (anaesthesia) and femoral (fluid resuscitation) veins were cannulated with polyethylene catheters (outer diameter = 0.9 mm; Braun, Melsungen, Germany). For fluid maintenance during surgery, 0.9% NaCl (Baxter, Utrecht, The Netherlands) at a rate of 10 ml kg^{-1} h^{-1} was administered. For liver resection, a 70% partial liver resection (PLR) was achieved by ligature of branches of the hepatic artery and portal vein using 3/0 silk thread and resecting two lobes of the liver after a midline laparotomy. The left kidney was exposed, decapsulated and immobilized in a Lucite kidney cup (K. Effenberger, Pfaffingen, Germany) via a 4 cm incision in the left flank. Renal vessels were carefully separated to preserve the nerves and adrenal gland. An ultrasonic flow probe was placed around the left renal artery (type 0.7 RB; Transonic Systems, Ithaca, NY, USA) and connected to a flow meter (T206; Transonic Systems) to continuously measure renal blood flow (RBF). The left ureter was isolated, ligated and cannulated with a polyethylene catheter for urine collection.

After the surgical procedure (approximately 60 min), one optical fibre was placed above the decapsulated kidney and another one above the renal vein to measure oxygenation using a phosphorescence lifetime technique.[18] A small piece of aluminium foil was placed on the dorsal side of the renal vein to prevent the contribution of the underlying tissue toward the phosphorescence signal in the venous P_{O2} measurement. Oxyphor G2