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The unrecognized effects of the volume and composition of the resuscitation fluid used during the administration of blood products

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Abstract

Background—Recent publications have reported the severe adverse events associated with blood products but have not considered the effect of the volume and composition of the resuscitative fluids infused with the blood products.

Methods—Injury leads to cellular reaction characterized by insulin resistance during which glucose cannot enter muscle and fat cells. In all cells, mitochondrial pyruvate dehydrogenase activity is decreased during insulin deficiency leaving cells deficient in substrates needed to power the Krebs cycle and make ATP.

Results—D- -Hydroxybutyrate, a normal ketone body metabolite, enters cells on the monocarboxylate transport mimicking the action of insulin and bypassing the enzymatic block at PDH. Metabolism of ketone bodies increases efficiency of mitochondrial energy production and cellular ATP level.

Conclusion—Infusion of 250 ml of 600 mM Na D- -hydroxybutyrate solution, with the same osmotic strength as the hypertonic NaCl solution currently being used, would correct insulin resistance, provide energy substrates for cells to produce ATP, correct the tendency of injured tissue to swell due to decreased energy of ionic gradients and correct acidosis observed in hemorrhage.

In recent months, several articles have appeared in the literature reporting the effects of storage of blood products on the outcome of the treatment of patients [1–3]. In none of these articles was the composition and volume and potential untoward effects of the resuscitation fluid used prior to or during the administration of blood products considered or discussed. The potential toxicity of parenteral fluids was recently emphasized when a trial of 3000 children with shock and infection treated with either 0.9% saline, 5% albumin or nothing was stopped because of the increased mortality of the two groups receiving intravenous fluid therapy [4]. This has led to the call for a reappraisal of the basics of currently used resuscitation fluids [5]. The use of parenteral fluids prior to or in conjunction with blood products is rarely reported and the toxicity of these fluids used prior to or during transfusion not discussed.

History and toxicity of fluids

The most commonly used parenteral fluids with transfusion are: normal or hypertonic saline, Ringer's D,L -lactate or Ringer's L -lactate and albumin or other artificial colloids. The toxicity of existing parenteral fluids was extensively reviewed in 1986 [6]. The first parenteral fluid made by Thomas Latta [7] was physiological saline with a small amount of $NaHCO_3$ to simulate normal plasma. This bicarbonate saline was curative when administered to a prostitute in shock from cholera in the north of England in 1832. Ringer's solution was essentially saline to which a small amount of Ca^{2+} was added and found to increase the cardiac output of frog hearts perfused in Sidney Ringer's back garden [8].

Artificial solutions which mimic the inorganic composition of plasma were first made by Hans Krebs in 1932 [9]. It became the basis for most subsequent tissue culture fluids. This Krebs Henseleit solution was also used in the first US hemodialysis procedures [10]. Although this solution most closely mimics plasma composition, it is not suitable for correcting the metabolic abnormalities which accompany cell injury.

Normal saline was recognized to be toxic to nerve and muscle preparations by Harvey Cushing in 1901 [11]. Administration of large amounts of normal saline during episodes of infantile diarrhea caused death in children from hyperchloremic acidosis and in 1934 lead Hartmann to formulate Ringer's lactate [12]. Notwithstanding the known toxicities of $NaCl$, both 0.9%, 155 mM, and hypertonic, 603 mM $NaCl$, are two major resuscitation fluids in current use, even though acidosis is a known accompaniment of hemorrhage shock. In a prospective study of the use of either Ringer's lactate or hypertonic saline in treatment of burns, hypertonic saline was found to increase the incidence of renal failure and death (Table 1) [13].

However the use of D,L -lactate containing fluids has been shown to induce cardiac arrhythmias and death in experimental animals and to induce arrhythmias in burn patients where large amount of D,L -lactate fluids, up to 25 l, were infused in the first 24 h [14]. During the Viet Nam war, large volumes of Ringer's D,L -lactate were used in the resuscitation of wounded casualties. There was also a high incidence of acute respiratory distress syndrome called Da Nang lung noted in these patients. It was later shown, that use of D,L -lactate containing fluids induced the expression of adhesion molecules in the lung of rats explaining the high incidence of Da Nang lung [15].

Without any evaluation, Ringer's lactate solutions have now been made containing 28 mM L -lactate. Although L -lactate does not have the same untoward effects as D,L -lactate, it is not without its own undesirable effects. First, blood and tissue L -lactate concentrations are already elevated in situations where resuscitation is required and contribute to the acidosis associated with hemorrhage. Further, elevated L -lactate levels block glycolysis at the glyceraldehyde 3 phosphate dehydrogenase step inhibiting a major source of ATP generation during hypoxic conditions.

The use of albumin solutions in resuscitation has not been demonstrated to improve outcome in any prospective study. Indeed, in the treatment of shock due to infection in children, infusion of either 0.9% $NaCl$ or 5% albumin have been shown to increase mortality requiring the cessation of the prospective study as noted above [4]. Further, it has been shown that albumin does not stay in the intravascular space during hemorrhage [16] and is therefore unsuitable for use as a resuscitation fluid during hemorrhage or trauma [17].

Because of the toxicities outlined above, it is not possible to evaluate the efficacy of transfusion practices without knowing and considering the volume and composition of the

resuscitation fluids administered before or during the administration of blood products. Clearly, a re-evaluation of the basics of resuscitation fluids is required [5].

Substrate resuscitation

Carl Walter in 1937, established the first blood bank in Boston. He later developed the plastic blood bag, for collection of blood thus facilitating the separation of blood components. In 1986, he wrote a succinct summary of a long paper to outline the toxicity of current parenteral fluid [6], "The prescribing of parenteral fluids has become so routine that most physicians have become oblivious to the toxic impact of current practices on the cellular metabolism of their patients. Few physicians recognize the iatrogenic threat of replacement of body fluids based solely on volumetric and caloric needs. Understanding the metabolic and ionic organization of cells can provide the physician means to use parenteral fluids to control the inherent metabolic energy of cells. Application of new insight into physical chemistry and metabolic properties of the cell can enhance the physician's therapy in critically ill patients".

Injury of any sort, leads to a cellular reaction which is characterized by insulin resistance [18]. During insulin resistance, glucose cannot enter muscle and fat cells nor can the cell metabolize the lactate given in lactated Ringer's solutions. More importantly in all cells the mitochondrial pyruvate dehydrogenase (PDH) activity is decreased during insulin deficiency leaving the cell deficient in substrates needed to power the Krebs cycle to make ATP. The normal ketone body metabolite D-β-hydroxybutyrate enters cells via the monocarboxylate transporter mimicking the action of insulin [19] and bypassing the enzymatic block at PDH. Even more importantly, the metabolism of ketone bodies, increases the efficiency of mitochondrial energy production and increases the energy contained within the ATP molecule, that is the GATP [20].

In order to prevent dilutional coagulopathy, one needs to use low volume, substrate based resuscitation fluids which are capable of correcting the metabolic and physical chemical abnormalities and the energy deficit of the injured cell. The most important metabolic defect needing correction in injured patients receiving blood products and parenteral fluids is insulin resistance [18]. Insulin resistance prevents the injured cell from metabolizing the lactate produced by glycolysis as well as the lactate administered in Ringer's lactate fluids. This metabolic defect of insulin resistance in the cells of injured patients can be overcome by the administration of Na D-β-hydroxybutyrate containing solutions which by-pass the metabolic block at PDH and increase the energy of the ATP molecule [19,20]. The six most important metabolic effects of ketone bodies can be summarized as follows [20]:

1. Increases the concentration of Krebs cycle substrates depleted by insulin resistance.
2. Production of mitochondrial NADH required as a substrate for electron transport.
3. Oxidation of Coenzyme Q thus lowering the production of free radicals.
4. Increases the energy of ATP hydrolysis, GATP.
5. Mimics the action of insulin.
6. Overcomes the blockade of insulin resistance.

Such a solution would be one comprised of 600 mM Na D-β-hydroxybutyrate which would have the same osmotic strength as the current hypertonic NaCl solutions being used. It could be provided in 250 ml volumes. Infusion of D-β-hydroxybutyrate containing solutions would correct the insulin resistance of injury [18], provide energy substrates for the cell to produce ATP [20], correct the tendency of injured tissue to swell due to the decrease in the energy of ionic gradients [21] as well as correcting the acidosis often accompanying hemorrhage.

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Table 1

Commonly used and proposed resuscitation fluids, High volume resuscitation, low volume resuscitation.

Component in mM	Ringer's lactate	Ringer's ketone	Normal saline	Hypertonic saline	Hypertonic ketone
Na ⁺	130	130	155	603	600
K ⁺	4	4			
Ca ²⁺	3	3			
Cl ⁻	109	109	155	603	
Lactate	28				
D- -hydroxybutyrate		28			600
pH	6.5	6.5	6.5	6.5	6.5
Osmolarity (mOsm/l)	275	275	310	1200	1200
Sterilization	Heat	Heat	Heat	Heat	Heat