Special Issue: Anesthesia & Critical Care

Effects of Resuscitation Fluids: The HBOC Excipients, And Length of Storage of RBC at 4°c on the Toxicity of Hemoglobin Based Oxygen Carriers (HBOC)

C. Robert Valeri[1]*, Gina Ragno Giorgio[1], Paul Looney[2] and Richard L. Veech[3]

[1]Naval Blood Research Lab Inc, 195 Bournehurst Drive, Plymouth, MA 02360, United States
[2]Naval Blood Research Lab Inc, 195 Bournehurst Drive, Plymouth, MA, Non-paid consultant, United States
[3]National Institutes of Health, Washington, D.C

Abstract

Severe adverse events have been observed following the infusion of Hemoglobin Based Oxygen Carriers (HBOCs) in patients subjected to elective orthopedic procedures, cardiopulmonary bypass surgery, and vascular surgical procedures. Along with all three of the hemoglobin based oxygen carriers, the patients received Ringer's D,L-lactate as the resuscitation fluid, Ringer's D,L lactate in the excipient medium for the stroma-free hemoglobin, and liquid preserved red blood cells that has been stored at 4°C for longer than 2 weeks. The Ringer's D,L lactate solution has been shown to be toxic in both animals and patients. In a recent publication morbidity and mortality have been reported and associated with the length of storage of red blood cells at 4°C for longer than 2 weeks in patients subjected to re-operative cardiac surgery. Current clinical adverse events with HBOCs may be associated with the composition of the resuscitation solution (Ringer's lactate), the composition of the excipient medium (Ringer's lactate) for the hemoglobin based oxygen carrier, and the length of storage of the liquid preserved red blood cells infused with the hemoglobin based oxygen carrier.

Two billion dollars have been spent on attempts to develop Food and Drug Administration (FDA)-approved safe and therapeutically effective hemoglobin based oxygen carriers. Despite the significant investment, the clinical studies performed in elective orthopedic surgical patients; in patients subjected to cardiopulmonary bypass surgery; and in patients subjected to major vascular surgical procedures have all been associated with severe adverse events. The combination of the Ringer's D,L lactate resuscitation fluids administered to these patients, the Ringer's D,L lactate excipient medium for the HBOC, and the length of storage at 4°C of the liquid preserved RBC infused into these patients who received HBOC may be responsible for severe adverse events that have been observed.

Objective

The objective of this review is to identify the factors that affect the toxicity of HBOCs.

Hemoglobin based oxygen carriers (HBOCs) are resuspended in media referred to as excipients. The primary excipient for HBOC has been Ringer's D,L lactate solution supplemented with antioxidants to prevent the formation of methemoglobin during the storage period. Investigators have reported cardiac arrhythmias in animals and patients infused with Ringer's D,L lactate solution. Studies have also shown that D-lactate stimulates human granulocytes to generate oxygen free radicals [1,2]. These studies led the manufacturers to modify the Ringer's D,L-lactate solution so that it now contains only the L isomer of lactate. However, a publication by Cross HR and associates has shown that L-lactate inhibits glycolysis impairing resuscitation of the isolated rat hearts [3].

Based on several studies, Veech RL has recommended replacing the 28 mM Ringer's D,L lactate with 28 mM Na-D-beta hydroxybutyrate (NaD BHB). NaD BHB has been shown to reduce the generation of oxygen free radicals by mitochondria and human granulocytes. The original Ringer's ketone solution suggested by RL Veech contained a physiological concentration of glucose (5 mM) [4].

Alam HB and associates, Koustova E and associates, Jaskille A and associates, and Ayuste EC and associates demonstrated that Ringer's ketone-glucose solution administered to rats and swine subjected to hemorrhagic shock, produced significantly less apoptosis in the lung than Ringer's D,L lactate solutions [5-8].

Ringer's D,L lactate has been the principle resuscitation fluid used in clinical medicine and the excipient for HBOC for more than 30 years [9]. Ringer's D,L lactate solution causes neutrophil activation which produce reactive oxygen intermediates which are inhibited by ketones [10-12].

Both Ringer's D,L lactate and HBOC produce oxygen free radicals and the presence of both may be responsible for severe adverse events reported with the use of HBOC in patients subjected to elective orthopedic and cardiopulmonary bypass

Effects of Resuscitation Fluids: The HBOC Excipients, And Length of Storage of RBC at 4˚c on the Toxicity of Hemoglobin Based Oxygen Carriers (HBOC)

Copyright:
© 2015 Valeri et al.

surgical procedures. Orthopedic and cardiopulmonary bypass patients who received HBOC in Ringer's D,L lactate excipient have also been resuscitated with Ringer's D,L lactate solution. Oxygen free radicals generated by Ringers D,L lactate and HBOC may oxidize nitric oxide in endothelial cells, causing the vasoconstrictor effects reported following the infusion of HBOC. In addition, generation of oxygen free radicals activate Nuclear Fragment-Kappa Beta (NF-Kb) and the apoptotic cascade. The combination of Ringer's D,L lactate resuscitation fluid and the HBOC in the Ringer's D,L lactate excipient may be responsible for the severe adverse events observed in the clinical studies of HBOC [13].

Scientific rational for use of Ringer's ketone solution include the maintenance of ATP production which is essential for cell survival and function. NaD BHB (NaD beta hydroxybutyrate) produces ATP by mitochondria and prevents oxygen free radical damage. By acting as a substrate during acute and chronic stress NaD BHB maintain cell survival and function and modifies disease progression [2].

Studies done by our laboratory demonstrated that final heat sterilization or irradiation could not be used to sterilize the Ringer's ketone solution containing 5 mM glucose without adversely affecting beta hydroxybutyrate and glucose levels. The large volume (1L) Ringer's ketone-glucose solution was prepared by a commercial company using final filter sterilization [13].

Recent studies have demonstrated that removal of 5 mM glucose allowed for heat sterilization of the solution with no adverse effects on beta hydroxybutyrate levels. Ringer's ketone solution is now prepared without glucose to allow for heat sterilization.

Insulin Resistance and Therapeutic Effect of NaD Beta Hydroxybutyrate Solution

Severe injury, infection and hemorrhage all cause insulin resistance. Insulin resistance blocks glucose entry into cells and conversion of pyruvate to acetyl CoA impairing cellular energy production. Na-DB-hydroxybutyrate containing fluids, increase metabolic efficiency and bypass blocks caused by insulin resistance and lactate. D-lactate containing fluids can cause neurological dysfunction, cardiac arrhythmias and death [1,4,14,15]. Ringer's D,L lactate solution was a major cause of DaNang lung in Vietnam wounded casualties. Ringer's D,L lactate was used to prevent hyperchloremic acidosis [16] and Ringer's D,L lactate became the standard for treatment of hemorrhagic shock [17]. After publication of several papers in 1986 on the toxicity of Ringer's D,L lactate solution, Baxter Laboratories provided Ringer's L lactate solution in 1987.

Acute respiratory distress syndrome observed in wounded casualties by administration of Ringer's D,L lactate can be prevented by the use of Ringer's ketone solution.. The ketone body Na D-B-hydroxybutyrate improves cardiac efficiency, maintains brain function and can be incorporated into improved resuscitation fluids [18].

Sato K and associates reported that Ringer's ketone solution

increased myocardial function of isolated perfused rat heart by 28% while decreasing oxygen consumption compared to Ringer's D,L lactate solution [19]. Clarke K and associates have reported that feeding ketone esters to rats increased physiological and cognitive performance. Masuda R and associates have reported Na-D-B-hydroxybutyrate was neuroprotective against hypoxia in serum free hippocampal cultures [20]. Hu ZG and associates have reported that ketogenic diet reduced apoptosis in traumatic brain injury [21]. Effective therapy of traumatic brain injury can be achieved by closure of the mitochondrial permeability transitional pore by administration of cyclosporine A or by oral administration of ketone body esters [22]. Prins ML has reported on cerebral metabolic adaptation and ketone metabolism after brain injury [23].

Longnecker DE et al [24] recommended investigation of NaD-B-hydroxybutyrate resuscitation fluids at the Institute of Medicine Committee on Fluid Resuscitation for Combat Casualties and Civilian Injuries in 1999. Methods for the production of Na-D-B-hydroxybutyrate parenteral fluids have been developed at NIH by Veech RL and associates. In collaboration with Dr. Richard Veech Ringer's ketone solutions were prepared by NBRL, Boston, MA which are stable following storage at room temperature for 2 years.

Severe Adverse Events Associated with Hemoglobin Based Oxygen Carriers: Role of Resuscitation Fluids and Liquid Preserved RBC

At an Institute of Medicine meeting held in September 1998 in Washington, DC on resuscitation fluids, the toxicity of Ringer's D,L lactate was discussed. Veech RL has reported the cardiac arrhythmias observed in experimental animals and patients infused with Ringer's D,L lactate solution [4]. Veech also reported that D- lactate generated oxygen free radicals and that the metabolism of L-lactate inhibited glycolysis and recommended the use of Ringer's ketone solution which contains 28mM D beta hydroxybutyrate instead of the 28 mM of D,L-lactate. Subsequent studies by Alam, Koustova, Jaskille, Ayuste and associates have reported that Ringer's D,L-lactate resuscitation solution produced pulmonary apoptosis and intracellular adhesion molecule-1 expression in rats and swine and that those adverse effects were attenuated by the use of Ringer's ketone solution and Ringer's pyruvate solution [5-8]. Ringer's ketone solution is stable at room temperature for at least 2 years, but Ringer's sodium pyruvate and Ringer's ethyl pyruvate solutions are not stable at room temperature.

In studies conducted during the Vietnam war, young wounded servicemen who were resuscitated with large volumes of crystalloid solutions consisting of Ringer's D,L lactate developed acute respiratory distress syndrome referred to as "Danang Lung" In recent studies in which rats subjected to hemorrhagic shock were resuscitated with Ringer's D,L lactate, the toxic effects of this solution were observed in the production of pulmonary, liver and intestinal apoptosis. Rhee and associates have reported that Ringer's D,L lactate stimulates human granulocytes to produce oxygen free radicals but that Ringer's L-lactate is less effective [10,11].

Citation: Valeri CR, Giorgio GR, Looney P, Veech RL (2015) Effects of Resuscitation Fluids: The HBOC Excipients, And Length of Storage of RBC at 4˚c on the Toxicity of Hemoglobin Based Oxygen Carriers (HBOC). SOJ Anesthesiol Pain Manag, 2(3): 1-6.

Page 2 of 6

Effects of Resuscitation Fluids: The HBOC Excipients, And Length of Storage of RBC at 4˚c on the Toxicity of Hemoglobin Based Oxygen Carriers (HBOC)

Copyright:
© 2015 Valeri et al.

A study was performed at the NBRL with the collaboration of Dr. Carl S. Apstein and his associates to assess the therapeutic effect of Ringer's ketone solution or Ringer's D,L lactate solution on myocardial function in rats. The cardiac output was reduced from 60 ml/min to 5-7 ml/minute and then the rats were resuscitated with Ringer's ketone solution or Ringer's D,L lactate solution for 2 hours followed by stimulation with dobutamine. Both mortality and cardiac output were measured.

The data shows that treatment with Ringer's ketone solution produced significant improvement in survival in rodents at one hour and two hours following hemorrhage and resuscitation. Cardiac output was significantly improved at one hour and two hours in rats resuscitated with Ringer's ketone solution compared to Ringer's D,L lactate solution [25].

In another study at the NBRL, the therapeutic effect of resuscitative solutions to treat hypovolemic anemic rats subjected to renal ischemia was studied in collaboration with Dr.W.Lieberthal and his associates. A protocol was developed in rats subjected to hypovolemic anemia and renal ischemia to assess the therapeutic effects of blood, Ringer's D,L-lactate, and Ringer's ketone solution.

The left kidney of the rat was removed and the right renal artery was clamped for 30 minutes. During the period of renal ischemia, 8 ml of blood was removed in l0 minutes for the three groups except for the sham-treated rats. The 8 ml of heparinized blood was reinfused over a 10-minute period or 15 ml of solution of Ringer's ketone or Ringer's D,L lactate. The renal artery clamp was removed after 30 minutes of renal ischemia. Twenty-four (24) hours and 2 days following the resuscitation of the hypovolemic anemic rats with renal ischemia, the Glomerular Filtration Rate (GFR), the hematocrit, the weight and ratio of insulin in the urine and plasma were measured.

The glomerular filtration rate and the insulin urine to plasma ratio 48 hours following resuscitation were the highest for rats treated with Ringer's ketone solution. The weight loss in the rats treated with Ringer's ketone was similar to the sham treated rats. Greater weight loss was observed in the rats treated with blood and Ringer's D,L-lactate. The Ringer's ketone solution improved renal function 48 hours after resuscitation when compared to the Ringer's D,L lactate solution. The observation on the improvement of renal function in hypovolemic anemic rats subjected to renal ischemia by the use of Ringer's ketone solution supports the preparation of ketone containing resuscitation solutions [25].

Following the documentation of Ringer's D,L-lactate's toxicity and the demonstration that the D-isomer of lactate was primarily responsible for its toxicity, Ringer's DL-lactate solution was modified and the solution now contains only the L-isomer of lactate, i.e. Ringer's L-lactate. However, there has been no clinical testing of the modified solution. Cross and associates have reported that L-lactate inhibited glycolysis and impaired resuscitation of isolated rat hearts [3]. Recent studies in rodents and swine subjected to hemorrhagic shock showed that resuscitation with Ringer's L-lactate solution reduced the hepatic

and pulmonary apoptosis observed with Ringer's D,L-lactate solution [3].

Any resuscitation fluid and excipient medium used in the HBOC should minimize the oxygen free radicals that may be formed by the HBOC. Beta hydroxybutyrate, when substituted for D,L lactate in the Ringer's ketone solution, has been shown to attenuate the pulmonary apoptosis in rat lungs following hemorrhagic shock and resuscitation. Moreover, beta hydroxybutyrate reduces the generation of oxygen free radicals by mitochondria and by human granulocytes [4,12].

Data have shown that Ringer's D,L-lactate resuscitation fluid combined with a HBOC that contains Ringer's D,L-lactate in the excipient may be responsible for reported severe adverse events observed in clinical studies of HBOC. Diabetic patients have a higher incidence of severe adverse events than non-diabetic patients following cardiopulmonary bypass surgery when they received HBOC in the Ringer's D,L-lactate excipient. In these patients, Ringer's D,L-lactate was used as hemodilution solution and it was infused as the resuscitation solution. Ringer's D,L-lactate is toxic and it should not be used as the excipient for HBOC. Ringer's L-lactate should be more extensively evaluated, both as a resuscitation fluid and as an excipient medium for the HBOC. The therapeutic effectiveness of Ringer's ketone solution in resuscitation has been demonstrated in animals and it appears to be an ideal resuscitative fluid and excipient medium for HBOC [18].

The Effects of Preserved Red Blood Cells on the Severe Adverse Events Observed in Patients Infused with Hemoglobin Based Oxygen Carriers

The severe adverse events observed in patients who received hemoglobin based oxygen carriers (HBOCs) were associated with the Ringer's D,L-lactate resuscitation solution administered and in the excipient used in the HBOCs containing Ringer's D,L-lactate and the length of storage of the preserved RBC administered to the patient at the time that the HBOCs were infused. The quality of the red blood cells preserved in the liquid state at 4°C and that of previously frozen RBCs stored at 4°C with regard to their survival, function, therapeutic effectiveness and safety need to be assessed. Severe adverse events have been observed related to the length of storage of the liquid preserved RBC at 4°C for longer than 2 weeks prior to transfusion [26]. The current methods to preserve RBC in the liquid state in additive solutions at 4°C is to maintain their survival and function for only 2 weeks. The freezing of red blood cells with 40% W/V glycerol and storage at -80°C allows for storage at -80°C for 10 years and following thawing, deglycerolization and storage at 4°C in the additive solution (AS-3 Nutricel) for 2 weeks with acceptable 24 hour post transfusion survival, less than 1% hemolysis, and moderately impaired oxygen transport function with no associated adverse events. Frozen deglycerolized RBCs are leukoreduced and contain less than 5% of residual plasma and non-plasma substances. Frozen deglycerolized RBCs are the ideal RBC product to transfuse patients receiving HBOCs [27].

Citation: Valeri CR, Giorgio GR, Looney P, Veech RL (2015) Effects of Resuscitation Fluids: The HBOC Excipients, And Length of Storage of RBC at 4˚c on the Toxicity of Hemoglobin Based Oxygen Carriers (HBOC). SOJ Anesthesiol Pain Manag, 2(3): 1-6.

Page 3 of 6

Effects of Resuscitation Fluids: The HBOC Excipients, And Length of Storage of RBC at 4°c on the Toxicity of Hemoglobin Based Oxygen Carriers (HBOC)

Copyright:
© 2015 Valeri et al.

Role of Nitric Oxide in the Prevention of Severe Adverse Events Associated with Blood Products

The reduction in vitro of nitric oxide binding to the globin portion of hemoglobin (SNoHb) in fresh and liquid preserved red blood cells has been reported to be responsible for the Severe Adverse Events (SAEs) associated with red blood cell transfusion. No in vivo data were reported that the reduction in SNoHb in red blood cells produced severe adverse events (SAEs) in recipients.

Several articles have reported severe adverse events associated with the transfusion of FDA-approved RBC blood products. The recent article published in the Proceedings of the National Academy of Sciences Journal by Bennett-Guerrero E and associates [28] reported on the possible relationship between the decrease in nitric oxide occurring in fresh and liquid preserved RBC in AS-3 additive solution (Nutricel) during storage at 4°C for 42 days and the mortality and morbidity associated with the transfusion of FDA approved RBC products. Since this article received extensive coverage in the lay press, we felt that it was important to comment on our experiences at the NBRL in human and baboon studies which suggest that the reduction in S-nitrosohemoglobin is a reversible defect that is corrected following transfusion. The preservation of red blood cell, platelets, and plasma using freeze preservative procedures has not been associated with the severe adverse events that are currently observed with the transfusion of FDA-approved blood products.

The recent publication by Bennett-Guerrero B and associates suggests that nitric oxide bound to the cysteine of the globin portion of hemoglobin (S-N0Hb) within red blood cells is rapidly lost in fresh CPD whole blood and in CP2D RBC stored in the additive solution AS-3 (Nutricel) at 4°C for 42 days. The authors speculate that this depletion of S-nitrosohemoglobin (S-NOHb) produces severe adverse events in recipients related to vasoconstriction of the microcirculation. They report no data to document that this in vitro decrease in S-NOHb is irreversible and is not corrected following the transfusion of the red blood cells [29].

Valeri CR and RL Veech have reported on the unrecognized effects of the volume and composition of the resuscitation fluid used during the administration of blood products [30]. 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.

Injury leads to cellular reaction characterized by insulin resistance during which glucose cannot enter muscle and fat cells. In all cells, mitochondrial Pyruvate Dehydrogenase (PDH) activity is decreased during insulin resistance leaving cells deficient in substrates needed to power the Krebs cycle and make ATP.

D-B-hydroxybutyrate, a normal ketone body metabolite, enters cells on the monocarboxylate transport channel 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.

Infusion of 250 ml of 600 mM Na-D-B-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 (Table 1). Table 1 reports the composition of isotonic Ringer's lactate solution, isotonic Ringer's ketone solution, and isotonic sodium chloride solution used for high volume resuscitation and hypertonic sodium chloride solution and hypertonic ketone solution used for low volume resuscitation that are available for evaluation.

Substrate Resuscitation

Carl W. Walter in l937estab1ished the first blood bank in Boston. He later developed the plastic bag for collection of blood thus facilitating the separation of blood components. In 1986, he wrote a succinct summary of a paper which outlined the toxicity of current parenteral fluid published by RL Veech [4]. "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 [31]. 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 resistance leaving the cell deficient in substrates needed to power the Krebs cycle to make ATP [32]. The normal ketone body metabolite D-B-hydroxybutyrate enters cells via the monocarboxylate transport channel mimicking the action of insulin [33] 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 delta G ATP [19].

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 [31]. 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

Citation: Valeri CR, Giorgio GR, Looney P, Veech RL (2015) Effects of Resuscitation Fluids: The HBOC Excipients, And Length of Storage of RBC at 4°c on the Toxicity of Hemoglobin Based Oxygen Carriers (HBOC). SOJ Anesthesiol Pain Manag, 2(3): 1-6.

Page 4 of 6

Effects of Resuscitation Fluids: The HBOC Excipients, And Length of Storage of RBC at 4˚c on the Toxicity of Hemoglobin Based Oxygen Carriers (HBOC)

Copyright:
© 2015 Valeri et al.

Table 1: High volume resuscitation and low volume resuscitation fluids.

Component (mM)	Ringer's lactate	Ringer's ketone	Normal saline	Hypertonic saline	Hypertonic ketone
Na+	130	130	155	603	600
K+	4	4	-	-	-
Ca++	3	3	-	-	-
Cl-	109	109	155	603	-
Lactate	28	-	-	-	-
D-B-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

With permission (Elsevier, Inc., 360 Park Avenue South, New York, NY 10010-1710 USA)

be overcome by the administration of Na-D-B-hydroxybutyrate containing solutions which bypass the metabolic block at PDH and increase the energy of the ATP molecule [19,33]. The six most important metabolic effects of ketone bodies can be summarized as follows [19]:

- Increases the concentration of Krebs cycle substrates depleted by insulin resistance
- Production of mitochondrial NADH required as a substrate for electron transport
- Oxidation of coenzyme Q thus lowering the production of free radicals
- Increases the energy of ATP hydrolysis, delta G ATP
- Mimics the action of insulin
- Overcomes the blockade of insulin resistance

Such a solution would be compromised of 600 mM Na-D-B-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-B-hydroxybutyrate containing solutions would correct the insulin resistance of injury [31] provide energy substrates for the cell to produce ATP [19] correct the tendency of injured tissue to swell due to the decrease in the energy of ionic gradients [34] as well as correcting the acidosis often accompanying hemorrhage.

Summary

This review reports the interactions of hemoglobin based oxygen carriers (HBOCs), the Ringer's D,L lactate resuscitation fluid and excipient in which the HBOCs are resuspended and the length of storage of the liquid preserved RBC administered with the HBOCs to produce the severe adverse events (SAEs) observed in these patients. The trifecta of the HBOCs, the Ringer's D,L lactate solution, and the length of storage of RBCs at 4˚C prior to transfusion with the HBOCs needs to be investigated.

References

1. Chan L, Slater J, Hasbargen J, Herndon ON, Veech, RL, Wolf S. Neurocardiac toxicity of racemic D,L-lactate fluids. Integr Physiol Behav Sci. 1994; 29(4): 383-94.

2. Veech RL. The therapeutic implications of ketone bodies: the effects of ketone bodies in pathological conditions, ketosis, ketogenic diet, redox states, insulin resistance, and mitochondrial metabolism. Prostaglandins Leukot Essent Fatty Acids. 2004; 70(3): 309-19.

3. Cross HR, Clarke K, Opie LH, Radda GK. Is lactate induced myocardial ischemic injury mediated by decreased pH or increased intracellular lactate? J Mol Cell Cardiol. 1995; 27(7): 1369-81.

4. Veech RL. The toxic impact of parenteral solutions on the metabolism of cell: a hypothesis for physiological parenteral therapy. Am J Clin Nutr. 1986; 44(4): 519-51.

5. Alam HB, Austin B, Koustova E, Rhee P. Resuscitation induced pulmonary apoptosis and intracellular adhesion molecule-1 expression in rats are attenuated by the use of ketone Ringer's solution. J Am Coll Surg. 2001; 193(3): 255-63.

6. Koustova E, Rhee P, Hancock T, Chen H, Inocencio R, Jaskille A, et al. Ketone and pyruvic Ringer's solution decreases pulmonary apoptosis in a rat model of severe hemorrhagic shock and resuscitation. Surgery. 2003; 134(2): 267-74.

7. Jaskille A, Koustova E, Rhee P, Britten-Webb J, Chen H, Valeri CR, et al. Hepatic apoptosis following hemorrhagic shock in rats can be reduced through modification of conventional Ringer's solution. J Am Coll Surg. 2006; 202(1): 25-35.

8. Ayuste EC, Chen H, Koustova E, Rhee P, Ahuja N, Chen Z, et al. Hepatic and pulmonary apoptosis after hemorrhagic shock in swine can be reduced through modifications of conventional Ringer's solution. J Trauma. 2006; 60(1): 52-63.

9. Pope A, French 0, Longnecker DF. Fluid resuscitation: state of the science for treating combat casualties and civilian injuries. National Academy Press: Washington, DC 1999.

Citation: Valeri CR, Giorgio GR, Looney P, Veech RL (2015) Effects of Resuscitation Fluids: The HBOC Excipients, And Length of Storage of RBC at 4˚c on the Toxicity of Hemoglobin Based Oxygen Carriers (HBOC). SOJ Anesthesiol Pain Manag, 2(3): 1-6.

Page 5 of 6

Effects of Resuscitation Fluids: The HBOC Excipients, And Length of Storage of RBC at 4°c on the Toxicity of Hemoglobin Based Oxygen Carriers (HBOC)

Copyright:
© 2015 Valeri et al.

10. Rhee P, Burris D, Kaufmann C, Pikoulis M, Austin B, Ling G, et al. Lactated Ringer's solution resuscitation causes neutrophils activation after hemorrhagic shock. J Trauma. 1998; 44(2): 313-9.

11. Rhee P, Wang D, Ruff P, Austin B, DeBraux S, Wolcott K, et al. Human neutrophils activation arid increased adhesion by various resuscitation fluids. Crit Care Med. 2000; 28(1): 74-8.

12. Sato N, Shimizu H, Shimomura Y, Suwa K, Mort M, Kobayashi L. Mechanism of inhibitory action of ketone bodies on the production of reactive oxygen intermediates (ROIS) by polymorphonuclear leukocytes. Life Sci. 1992; 51(2): 113-8.

13. Valeri CR, Ragno G, Veech RL. Effects of the resuscitation fluid and the HBOC excipient on the toxicity of the HBOC Ringer's D, L-Lactate, Ringer's L-Lactate, and Ringer's ketone solutions. Artif Cells Blood Substit Immobil Biotechnol. 2006; 34(6): 601-6.

14. DeCosta JM. On irritable heart. Am J Med Sci. 1971; 61:18-52.

15. Carr DB, Shih VE, Richter JM, Martin JB. D-lactate acidosis stimulating hypothalamic syndrome. Ann Neurol. 1982; 11(2): 195-7.

16. Hartmann AF. D-L lactate was used to prevent hyperchoremic acidosis. JAMA. 1934; 103: 1349-54.

17. Shires T. Ringer's D-L lactate became standard treatment of hemorrhagic shock. Arch Surg. 1964; 88: 688-93.

18. Veech RL, Chance B, Kashiwaya Y, Lardy HA, Cahill GFJ. Ketone bodies, potential therapeutic uses. IUBMB Life. 2001; 51(4): 241-7.

19. Sato K, Kashiwaya Y, Keon CA, Tsucbiya N, King MT, Radda GK, et al. Insulin, ketone bodies, and mitochondrial energy transduction. FASEB J. 1995; 9(8): 651-8.

20. Masuda R, Monahan JW, Kashiwaya Y. D-B-hydroxybutyrate is neuroprotective against hypoxia in serum free hippocampal primary cultures. J Neurosci Res. 2005; 80(4): 501-9.

21. Hu ZG, Wang HD, Jin W, Yin HX. Ketogenic diet reduces cytochrome c release and cellular apoptosis following traumatic brain injury in juvenile rats. Ann Clin Lab Sci. 2009 Winter; 39(1): 76-83.

22. Veech RL, Valeri CR, VanItalie TB. The mitochondrial permeability transition pore provides a key to the diagnosis and treatment of traumatic brain injury. IUBMB Life. 2012; 64(2): 203-7. doi: 10.1002/iub.590.

23. Prins ML. Cerebral metabolic adaptation and ketone metabolism after brain injury. J Cereb Blood Flow Metab. 2008; 28(1): 1-16.

24. Longnecker DE et al. Recommend investigation of Na-D-B-hydroxybutyrate resuscitation fluids. Institute of Medicine Committee on Fluid Resuscitation for Combat Casualties and Civilian Injuries. National Academy Press, 1999.

25. Valeri CR, Ragno G, Veech RL. Severe adverse events associated with hemoglobin based oxygen carriers: role of resuscitative fluids and liquid preserved RBC. Transfus Apher Sci. 2008; 39(3): 205-11. doi: 10.1016/j.transci.2008.09.008.

26. Koch CG, Li L, Sessler DI, Figueroa P, Hoeltge GA, Mihaljevic T, et al. Duration of red cell storage and complications after cardiac surgery. N Engl J Med. 2008; 358(12): 1229-39. doi: 10.1056/NEJMoa070403.

27. Valeri CR, Ragno G. The effects of preserved red blood cells on the severe adverse events observed in patients infused with hemoglobin based oxygen carriers. Artif Cells Blood Substit Immobil Biotechnol. 2008; 36(1): 3-18. doi: 10.1080/10731190701857736.

28. Bennett-Guerrrero E, Veldman TH, Doctor A, Telep MS, Otel TL, Beld TS, et al. Evolution of adverse changes in stored RBCs. Proc Natl Acad Sci U S A. 2007; 104(43): 17063-8.

29. Valeri CR, Ragno G. Role of nitric oxide in the prevention of severe adverse events associated with blood products. Transfus Apher Sci. 2008; 39(3): 241-5. doi: 10.1016/j.transci.2008.09.011.

30. Valeri CR, Veech RL. The unrecognized effects of the volume and composition of the resuscitation fluid used during the administration of blood products. Transfus Apher Sci. 2012; 46(2): 121-3. doi: 10.1016/j.transci.2012.01.010.

31. Li L, Messina JL. Acute insulin resistance following injury. Trends Endocrinol Metab. 2009; 20(9): 429-35. doi: 10.1016/j.tem.2009.06.004.

32. Sharma P, Benford B, Li ZZ, Ling GS. Role of pyruvate dehydrogenase complex in traumatic brain injury and measurement of pyruvate dehydrogenase enzyme by dipstick test. J Emerg Trauma Shock. 2009; 2(2): 67-72. doi: 10.4103/0974-2700.50739.

33. Kashiwaya Y, King MT and Veech RL. Substrate signaling by insulin: a ketone bodies ratio mimic insulin action in heart. Am J Cardiol. 1997; 80(3A): 50A-64A.

34. Veech RL, Kashiwaya Y, Gates DN, King MT, Clarke K. The energetic of ion distribution: the origin of the resting electric potential of cells. IUBMB Life. 2002; 54(5): 241-52.

Citation: Valeri CR, Giorgio GR, Looney P, Veech RL (2015) Effects of Resuscitation Fluids: The HBOC Excipients, And Length of Storage of RBC at 4°c on the Toxicity of Hemoglobin Based Oxygen Carriers (HBOC). SOJ Anesthesiol Pain Manag, 2(3): 1-6.

Page 6 of 6