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To evaluate the Low-volume resuscitation based on cell impermeant in hemorrhagic shock

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***Abstract*---**To see what function cell swelling played in severe hemorrhagic shock and resuscitation injury. This study was done in the department of General surgery after ethical permission from December 2019 to September 2021. Adult rats were administered a low volume resuscitation (LVR) (10–20 percent blood volume) with saline or several cell impermeants (sorbitol, raffinose, trehalose, gluconate, and Polyethylene glycol-20k) after being haemorrhaged to a pressure of 30–35 mm Hg and kept there until plasma lactate reached 10 mM. (PEG-20k). When lactate returned to 10 mM after LVR, complete resuscitation using crystalloid and red cells was initiated. The rats were euthanized one hour after complete resuscitation. The colourful microsphere technique was used to measure capillary blood flow. Impermeants significantly enhanced LVR outcomes in shocked rats by preventing ischemia-induced cell swelling in liver tissue. In comparison to saline, small cell impermeants and PEG-20k in LVR solutions increased tolerance to the low flow condition by 2 and 5 fold, normalised arterial pressure during LVR, and reduced plasma lactate after full resuscitation. With cell impermeants, this was accompanied by increased capillary blood flow. Ischemia-induced deadly cell swelling during hemorrhagic shock is a critical facilitator of resuscitation harm, and cell impermeants in low volume resuscitation solutions can help prevent it.

***Keywords*---**hemorrhagic shock, Ischemia, cell swelling.

Introduction

Traumatic and non-traumatic factors produce acute bleeding in small animals. While overall patient care varies based on the cause of acute blood loss, systemic

consequences linked with blood loss volume are predictable. The amount of blood volume lost and the compensatory reserve of the individual patient are connected to co-morbidities associated with acute loss of intravascular volume and oxygen transport capacity.[1,2] While the physiologic response is predictable, the resuscitation of the critically haemorrhaging patient has changed considerably throughout time, often as a result of medical efforts during wartime.

In 2010, approximately 171,000 people died as a result of injuries in the United States, costing over $400 billion in health-care expenses and lost productivity.[3] Trauma is the greatest cause of death for those under 44 years old in the United States, and the third leading cause of death for all age categories. In the United States, trauma accounts for over 30% of all lost life years, compared to cancer (16%), heart disease (12%), and HIV (1%). (2 percent).[4] Hemorrhagic shock is responsible for approximately 35% of pre-hospital mortality and over 40% of all deaths within the first 24 hours for all severe injuries. Trauma deaths caused by severe CNS injury are second only to trauma deaths caused by severe CNS injury.[5] Finally, hemorrhagic hypotension exposes the patient to life-threatening infections, coagulopathies, and multiple organ failure in the short term. [6]

Low amounts of intravenous blood products are used in early resuscitation procedures to enhance oxygen delivery and replenish lost coagulation and clotting components (coagulation proteins and platelets). While this strategy works well in hospital emergency rooms, it is currently impractical in pre-hospital settings, where early intervention may be the key to avoiding difficulties after more definitive resuscitation. Pre-hospital crystalloids are available because they can be securely transported and kept, although their usefulness is often restricted. Adding hypertonic NaCl or starch (Hextend) as a volume expander to basic intravenous crystalloids for pre-hospital resuscitation has yielded poor results[7].

Because they replace chemical coagulation precursors and factors, spray dried blood products will be a valuable tool in pre-hospital settings in the future. Fresh frozen plasma, which is now being evaluated in a number of institutions, will also be beneficial in the field, although it will be limited by the necessity for refrigeration. A better crystalloid is still needed to revive patients with severe hemorrhagic shock, particularly in the pre-hospital environment. Understanding the pathophysiological pathways that contribute to harm during hemorrhagic hypotension and subsequent resuscitation is critical to the design of such a remedy.The best answer will most likely be a new stable crystalloid that targets these mechanisms and is utilised in conjunction with reconstituted dry plasma products for coagulation potential replacement and reconstitution.

This basic mechanism of ischemia injury in cells has been well documented in the context of organ preservation and transplantation. [8-10] this principle has led to the development of effective modern organ preservation solutions that contain large concentrations of cell impermeants. [11] These are non-toxic molecules, generally saccharides and tiny organic cations and anions that are small enough to readily exit the microcirculation's capillary space but too large or too charged to penetrate the cell membrane. As a result, when sodium concentrations rise during ischemia, they preferentially load into the interstitial space, where they create an osmotic

tension that inhibits water from entering the cell. They keep fatal cell swelling at bay. As a class of agents, cell impermeants are one of the most effective components of today's organ preservation solutions.[12] These are non-toxic molecules, generally saccharides and small organic cations and anions, that are small enough to pass through the capillary gap in the microcirculation but too large or too charged to pass through the cell membrane. As a result, they preferentially load into the interstitial space, forming an osmotic force that prevents water from entering the cell as sodium concentrations rise during ischemia. They keep cells from ballooning up to the point where they can kill you. One of the most effective components of today's organ preservation methods is cell impermeant agents. Because cell swelling occurs during ischemia caused by hemorrhagic hypotension[13], and at a much faster rate than during organ preservation due to the warmer temperatures, it was hypothesised that loading the interstitial space with nontoxic cell impermeants during the low volume period would prevent lethal cell swelling, increase the patient's tolerance to the low volume state, and improve resuscitation outcomes.

Material and Methods

This study was done in the department of General surgery after ethical permission from December 2019 to September 2021. Warm ischemia-induced cell swelling, as well as the effects of cell impermeants on this response, were studied in mouse liver slices for the first time. Because they are simple to make and have enough bulk for multiple groups per organ, liver slices have previously been used to describe cell impermeants. The livers of adult mice (C57BL/6) were separated, immediately removed, and submerged in cold saline on ice after being sedated with isoflurane. A Staddie-Riggs microtome was used to cut liver slices (3–4 per condition) to a consistent thickness of 0.5 mm. In a Dubanoff style metabolic shaking water bath, 150 mg of liver slices were incubated in 1.5 ml Krebs buffer in 25-ml Erlenmeyer flasks in a Dubanoff style metabolic shaking water bath under an environment of oxygen or nitrogen, always containing 5% CO2. Ischemia was achieved by incubating tissue slices in a 95 percent nitrogen and 5% CO2 environment for 1 hour, followed by reperfusion in a 95 percent oxygen and 5% CO2 atmosphere for another hour. During ischemia, some tissue slice conditions had impermeants in the Krebs buffer, whereas others did not (controls). Impermeants were utilised at final concentrations of 0, 25, 50, 100, and 150 mM. Sorbitol, gluconate, trehalose, raffinose, and an equal molar combination of raffinose and trehalose were used as impermeants. Tissue slices in the untreated and impermeant treated groups were sampled after preparation (Fresh), after ischemia, and after reperfusion for analysis of total tissue water (TTW) content by calculating [wet-dry]/dry weight ratios. After drying the tissue slices in a 65° C oven, dry weights were calculated for 48 hours.

The impermeant-based LVR solution utilised for pre-hospital resuscitation of patients with severe hemorrhagic shock was developed using a low volume resuscitation (LVR) model in adult rats to test both the cell swelling theory and the impermeant-based LVR solution. During the investigation, adult Sprague Dawley rats were sedated with isofluorane and kept in a light surgical plane of anaesthesia. For blood pressure monitoring and blood sample, polyethylene catheters were inserted in both femoral arteries, and a catheter was put in one

femoral vein for fluid delivery. To achieve normal arterial blood gas (ABG) readings, the animals were permitted to ventilate on their own. To cause soft tissue injury and insert a temperature probe in the abdomen, a 1-cm midline incision was made. A PowerLab was used to continually record arterial blood pressure, heart rate, and temperature (ADInstruments, Boston, MA). Heparin (500 U/kg) was given after a 35-minute stabilisation period, and arterial blood was gently withdrawn at 1 ml/min into a syringe to keep blood pressure at 30–35 mm Hg. This hypotension was maintained until the plasma lactate level reached 9–10 mM, as assessed by a hand-held lactate analyzer (Lactate Plus, Nova Biomedical, Waltham, MA) and a blood gas analyzer, respectively (Radiometer 800). A low volume resuscitation equal to 10–20 percent of the calculated blood volume of saline was supplied I.V. during a 20-minute period using a syringe infusion pump once the goal lactate was reached. When the blood lactate levels returned to 9–10 mM, complete resuscitation was initiated, consisting of a volume of saline equal to the blood loss plus 30% of the removed red blood cells (washed) given over 15 minutes. The animals were terminated by an anaesthetic overdose after 60 minutes of full resuscitation, and terminal blood was taken for analysis. The LVR time is the amount of time between the start of the LVR period and the start of full resuscitation. It represents the animal's tolerance to the low volume state or the maximum amount of time that a shocked subject can safely remain in the low volume state until more definitive resuscitation is required. This was a significant outcome in the study.

Methodology

The following groups of animals were treated after being startled:
Controls for saline: As the LVR solution, the participants were given saline (n=10).
Gluconate: Recipients were given a 15 percent gluconate in saline LVR solution, which was a prototype cell impermeant (n=10).
Gluconate + PEG-20k: A LVR solution containing 15% gluconate and 10% polyethylene glycol with a molecular weight of 20 kDa was given (PEG-20k). PEG-20k has anti-oncotic properties (n=10).
PEG-20k: Participants were given a 10% PEG-20k LVR solution (n=10).
BSA: Patients were given an LVR solution containing 10% Bovine Serum Albumin (BSA, a prototypical oncotic substance, n=10).
LVR time, plasma lactate, mean arterial blood pressure, and regional tissue blood flow rates were the study's outcome variables.

Statistical analysis

Statistical significance was defined as a P value of less than 0.05.

Results

Blood gas data during the shock and LVR protocol in rats receiving saline, Gluconate (Glu), or Gluconte + PEG20k LVR solutions

Group	ABG Parameter	Baseline	Hemorrhagic Shock	LVR

Saline (20% BW)	Lactate (mM)	1.34 (0.22)	9.42 (0.81)	9.17 (1.91)
	HCO_3 (mM)	23.1 (2.4)	14.1 (2.67)	13.9 (1.63)
	pO_2 (mm Hg)	430 (29)	379 (62.1)	367 (35.7)
	pH	7.37 (0.04)	7.37 (0.04)	7.36 (0.05)
	pCO_2 (mm Hg)	38.2 (3.08)	25.1 (3.42)	21.7 (3.13)
Glu (20% BW)	Lactate (mM)	1.05 (0.26)	9.34 (0.37)	10.5 (1.67)
	HCO3− (mM)	25.1 (1.42)	16.3 (1.55)	13.0 (2.92)
	pO2 (mm Hg)	402 (46.3)	398 (38.1)	379 (62.6)
	pH	7.39 (0.05)	7.39 (0.05)	7.30 (0.15)
	pCO2 (mm Hg)	40.3 (3.02)	25.7 (2.09)	21.3 (2.06)
Glu + PEG20k (10% BW)	Lactate (mM)	1.13 (0.31)	8.37 (0.19)	2.51 (1.04) *
	HCO3− (mM)	24.1 (1.12)	15.7 (0.82)	30.8 (2.41) *
	pO2 (mm Hg)	432 (37.1)	407 (17.3)	408 (29.8)
	pH	7.40 (0.03)	7.34 (0.03)	7.48 (0.02) *
	pCO2 (mm Hg)	35.2 (2.71)	24.1 (1.73)	37.8 (5.21) *

Values are mean ± (SD), n=6 per group,

*P< 0.05 relative to the corresponding value in the other LVR groups, BW = volume based on calculated body weight. In the in-vitro tissue slice model, the impermeant effects of a variety of common cell impermeants. Total tissue water measurements show that after 65 minutes of hypoxia ischemia to murine liver slices, tissue water accumulation increased nearly twofold compared to ischemia alone and 1 hour of normoxic reperfusion. During ischemia, all molecular types of cell impermeants were added to the incubation media, preventing water accumulation after reperfusion. Both the impermeant's molecular weight and the media's molar concentration (50–160 mM) were found to be directly proportional to the magnitude of the response. Raffinose and combinations of raffinose and trehalose were utilised at concentrations of 50–100 mM to achieve the best results.

In this experiment, the LVR time is used to determine how long a shocked individual can safely remain in the low volume state. These are the times for the several groups of shocked rats who were given different treatments. The lactate increasing back up to 9–10 mM was the trigger for ending the LVR phase after the LVR solutions were delivered. LVR time was enhanced by 100% when gluconate (15%) was added to the saline control LVR solution, from roughly 40 minutes to over 90 minutes for the gluconate solution. The addition of 10% PEG-20k to the gluconate LVR solution enhanced the LVR time to 245 minutes, a 5.1-fold increase over the saline control. This LVR period was cut short due to anaesthetic effects, although it might have gone on much longer because the target lactate concentration of 10 mM was never reached, even after 245 minutes of LVR. After 245 minutes, the lactate in the gluconate + PEG-20k group was only 2.5 mM. Similarly, with a lactate of just 2.2 mM, the LVR duration in the group with only PEG-20k was likewise halted after 245 minutes. We don't know if there is a difference in LVR time between these two groups because the time restrictions of these two groups were never met because the target lactates were never met. Finally, LVR solutions containing 10% BSA were effective in lengthening the LVR

period (130 minutes), although not as much as LVR solutions including PEG-20k. It's also worth noting that the volume of PEG-20k-containing LVR solution used in this study was half that utilised in the other groups (10%). (20 percent : saline control, gluconate, and BSA). When compared to saline, PEG-20k-based LVR solutions were nearly 5 times more effective at extending LVR time at half the dose.

After shock and administration of the LVR solution, rats' mean arterial blood pressure increased (for as long as the LVR period lasted). According to the model, the blood pressure in the saline controls after the shock phase was 30–35 mm Hg. The MAP initially climbed to around 55 mm Hg after 10 minutes of saline LVR injection, but quickly plummeted below 50 mm Hg when the LVR phase terminated after 40 minutes, due to lactate exceeding 10 mM. Similar results were seen in the gluconate group. Although the MAP did not rise above that of the control group, it did last longer since the LVR time was increased with the addition of gluconate. The groups resuscitated with PEG-20k in the LVR solution, on the other hand, had normal MAP throughout the 245-minute LVR time, although using just 51% of the LVR resuscitation volume used in the controls. The BSA-treated oncotic controls had normal blood pressure just after the LVR solution was given, but it dropped to around 70 mm Hg at the conclusion of the LVR time. This was much greater than the control MAP, but significantly lower than the MAP in the groups resuscitated with PEG-20k-containing LVR solutions. After LVR and one hour after full resuscitation, the final plasma lactate levels in shocked rats. In comparison to the saline control group, animals administered an LVR solution with an impermeant (gluconate, PEG-20k, or both) had considerably lower lactate levels. After full resuscitation, lactate levels in the BSA group were considerably greater than in the other groups, including the saline controls.

Shocked rats treated with gluconate or saline had regional capillary blood flow in main organs and tissues. When an impermeant-based LVR solution was utilised instead of saline, local blood flow in the skeletal muscle, left ventricle, and brain (medulla) was considerably higher during the LVR time. Other tissue beds had higher trends as well. Regional blood flow in the left ventricle was considerably higher after impermeant-based resuscitation compared to saline after full resuscitation. There were big trends in other beds as well. The ABG results for rats administered saline, saline with gluconate, or saline with gluconate + PEG20k during the low volume resuscitation period are displayed in the table. After the baseline time before shock, the hemorrhagic shock period, and the low volume resuscitation period, ABG parameters are presented for each group (immediately before full resuscitation). The changes in ABG data from baseline to shock are predicted in all groups and are not different across them. Because the quantity of shock that was caused was titrated and controlled to that level of oxygen debt, lactate climbed to 10 mM in each group (lactate). In addition, while the pH stayed constant, the HCO3- and pCO2 values decreased. However, after LVR, there were some ABG differences between the group that received PEG20k in the LVR solution and the other groups. PEG20k LVR, in particular, prevented lactate levels from climbing significantly above baseline. In comparison to the other LVR groups, PEG-20k resuscitation caused a considerable metabolic alkalosis with increased HCO3- and pH. All of the LVR solutions had a pH of 7.2.

Discussion

In the field, severe hemorrhagic shock can be fatal because blood pressure lowers and microcirculatory exchange capacity deteriorates, resulting in decreased oxygen supply to tissues (DO2). What first responders can do to stabilise the DO2 is extremely limited. Pre-hospital treatment currently consists of giving low volume resuscitation solutions, as high volume crystalloid resuscitation, which was originally utilised to raise perfusion pressure, has been proven to be hazardous. Given these limits, low-volume resuscitation (less than 500 mL) should be viewed as a vehicle for delivering medicines that build tolerance to the low-volume condition rather than as a transient volume expander to raise blood pressure. This is best accomplished by focusing on the key mechanisms and pathways that cause global ischemia and resuscitation harm. Cell swelling is a very specific and underappreciated process that contributes to the phenotypic changes associated with hemorrhagic shock and global ischemia, according to this study.

Hemorrhagic shock is defined by changes in cellular energetics as a result of the loss or reduction of these energies. Because of the limited oxygen delivery, the cell's ATP levels drop, and ATP-dependent functions, such as the active volume control mechanisms powered by the Na/K ATPase pump, begin to fail. Cell and organelle membrane malfunction results from hydropic cellular degeneration, which can result in aberrant cell homeostasis, lysis, and death. In a vicious cycle, enlarged parenchymal cells compress capillary exchange channels, reducing capillary blood flow and causing additional ischemia and swelling. Although this mechanism is well understood in organ preservation injury for transplantation, it is mysteriously underappreciated in global warm ischemia associated with shock, stroke, or infarction injury. The major goal of this work was to see if cell impermeants, which are known to limit cell swelling but have few other biological effects, could reverse this shock mechanism. The findings are clear and dramatic, and they could be a major step forward in treating severe hemorrhagic shock using low-volume crystalloid-based resuscitation, especially in a pre-hospital setting.

Cell swelling is a key factor in organ preservation injury, and it may also play a role in circulatory shock following trauma. Because of the depletion of ATP during cold ischemia and the disruption of the usual ATP-dependent cell volume control systems, organ preservation promotes cell swelling. Because cell swelling may be greatly minimised by utilising cell impermeants in organ preservation solutions, it is a primary contributor to preservation injury in recovered donor organs. Cell impermeants are, in fact, one of the most significant and successful components of today's organ preservation techniques.[12] The idea is simple: fill the interstitial space with molecules that can't pass through the capillary but are impervious to the cell membrane. When the intracellular sodium concentration rises due to ischemia-induced pump failure, this preferentially increases extracellular osmolarity and inhibits water from migrating into the cell, which is the cell's natural proclivity. Since most cell impermeants are very harmless and may be provided in high enough quantities to theoretically prevent ischemic cell swelling, a similar method was tried in ischemic shock. Impermeant effects on liver cell swelling after warm ischemia, as well as impermeant effects on LVR durations,

blood lactate levels after shock, and capillary blood flow to major organs after shock, provide evidence for this parallel mechanism. Because gluconate in LVR solutions prevents cell swelling, microcirculatory exchange improves, lowering plasma lactate levels in treated people. With impermeant treatment during the low volume period, this manifests as longer LVR durations and increased capillary blood flow to important organs. Reduced swelling compression on microcirculatory exchange channels and obstructive swelling of endothelial cells forming the capillary lumen are consistent with this. [14,15], This provides for greater capillary perfusion and cellular metabolism efficiency (lower lactates). All of these findings support the theory that circulatory shock promotes cell swelling, which is a major cause of tissue, organ, and system injury and is mediated in part by a microvascular mechanism.

A model of a microcirculatory osmotic gradient was constructed and tested in order to further investigate the cell swelling theory and make impermeant treatment more successful. In a startled patient, the osmotic gradient model identifies three microvascular compartments: intracellular, interstitial (I.S.), and capillary. An osmotic gradient could be established between the intracellular and extracellular spaces by using conventional cell impermeants (like gluconate), which occupy both capillary and interstitial spaces, and between the interstitial and capillary spaces by adding an oncotic agent to the circulation, which only occupy the capillary space. This twofold gradient would be created by combining impermeant and oncotic agents, which might inhibit cell enlargement while also keeping water flowing out of the interstitial region and into the capillary area, where it belongs. Water that would have otherwise reached the ischemia cells in the tissue expands the circulatory volume and promotes capillary blood flow and oxygen exchange, reducing shock by enhancing oxygen delivery efficiency during low flow. When gluconate (an impermeant) was combined with PEG-20k, an oncotic drug, a massive potentiation impact on LVR timings was seen. Furthermore, PEG20k LVR solutions completely corrected blood pressure during the low volume resuscitation period. In comparison to the saline control, gluconate doubled the LVR time, while gluconate with PEG-20k increased the LVR time by 5 to 6 times. The upper limits of this effect are unknown because the PEG-Gluconate investigations were stopped by the experimenter 5 hours after the LVR period began. Lactate levels were only approximately 2.5 mM at the time, well below the 10 mM threshold required in our model to initiate complete resuscitation. In addition, the amount of PEG-20k or gluconate required for this effect was half that required for the saline control LVR group. This backs up the theory that PEG-20k helped to transfer water into the capillary area, where it helps to maintain intravascular volume, blood pressure, and microcirculation.

Low plasma lactate levels during the LVR period support the latter, implying adequate microcirculatory flow due to strong capillary driving pressures (fluid expansion). In clinical terms, this means that a severely shocked patient (MAP in the 40's with 50% blood loss) can receive half the volume of an impermeant-based low volume resuscitation solution (I.V.) and safely remain in the low volume state for at least 6 times longer than if conventional saline resuscitation was used, before definitive full resuscitation is required. Even 245 minutes after the initial 55 percent blood volume bleeding, LVR treatments containing PEG20k significantly prevent the buildup of lactate in the blood. A somewhat higher pH

and a substantially higher bicarbonate concentration accompanied the low lactate (double that of the other LVR groups). Because the pCO2 remained normal and the pH of the LVR solutions was kept at 7.2, this metabolic alkalosis served to repair the lactacidosis of the low volume state. We usually observed a brief diuresis after administering the LVR solution in these tests, which was due to osmotic retention of water in the renal tubules as a result of PEG20k filtration across Bowman's gap and trapping in the tubular lumen. This diuresis (and possibly a concomitant naturesis) may result in significant hydrogen ion excretion into the urine, resulting in a pH normalisation and even a slight alkalosis. Metabolic research is required to identify this potential mechanism. In any case, maintaining adequate pH during shock and limited volume resuscitation may contribute to the PEG20k LVR group's normal blood pressure.

We conducted research utilising albumin and PEG-20k alone in the LVR solution to further test the oncotic-impermeant model. We chose the physiological prototype oncotic drug albumin as an oncotic control because high molecular weight PEG molecules are known to have additional biological features besides their oncotic ones. Albumin was not as effective as PEG-20k alone in controlling oncotic effects, although it was better than saline. This suggests that PEG-20k is a one-of-a-kind product. PEG-20k's effects in LVR shock models can be attributed to more than only oncotic features. There are two plausible scenarios to consider: 1.) non-oncotic PEG effects, such as PEG's known effects on cell membranes, protein binding and hydration properties, or immunocamouflage effects, or 2.) oncotic-impermeant hybrid effects, in which PEG-20k can act as both a cell impermeant and an oncotic agent due to its unique molecular weight and properties.

There is evidence that PEG-20k serves as a cell impermeant agent by exiting the capillary space while remaining impermeable to the cell, as well as an oncotic agent by trapping a substantial amount of the material in the capillary space. Based on its size and other characteristics, this property could be induced by a long equilibration period to penetrate the capillary barrier into the interstitial area. PEG-20k has been shown in rats and pigeons[16] to efficiently enlarge the vascular space and transfer water out of the interstitial space to increase thirst, demonstrating its oncotic actions. After I.V. treatment, it has been found immunohisochemically in renal tubule epithelium as well as monocytes in the liver and lung, indicating that it leaves glomerular capillaries and hepatic sinusoids, demonstrating its partial impermeant effects. Since a large but brief diuresis is detected in rats following severe shock after receiving PEG-20k in the LVR solution, our own research and observations show that it departs Bowman's space. This diuresis could have been caused by PEG-20k-induced arterial pressure restoration during the LVR phase, or by an osmotic diuresis caused by PEG being filtered and stuck in the renal tubules, analogous to mannitol. We don't notice a diuresis in stunned rats when their blood pressure is regulated with traditional resuscitation solutions, but we do with PEG-20k solutions, therefore the latter is more feasible. During a shock condition, normalisation of renal perfusion pressure and modest filtration may be helpful, as long as the diuresis does not threaten the newly corrected blood pressure. In our research, we found no proof that this occurs. After resuscitation, the renal effects should help to prevent the development of ATN. Because a 10% blood volume LVR dose of

PEG-20k generates significantly weaker diuresis than a 20% blood volume LVR dose, the diuresis observed in this investigation with PEG-20k is transitory and dose dependent. As a result, the dose of the LVR solutions containing PEG-20k was reduced from 20% to 10%. Higher molecular weights approaching 30 kDa do not penetrate capillary gaps, including Bowman's space[17], so PEG-20k appears to be right on the size limit for partial capillary permeability. The fact that PEG-20k was as effective alone as it was in conjunction with gluconate is also consistent with a suggested hybrid oncotic-impermeant feature of PEG-20k. In other words, PEG-20k's partial capillary permeability properties may allow enough osmotically active material to escape into the interstitial space to imitate the impermeant effect of gluconate, while the bulk of material remains in the capillary to function oncotically. As a result, gluconate or other impermeants may not be required in LVR solutions containing only PEG-20k, but more research in survival experiments is required.

Conclusions

Ischemia-induced deadly cell swelling during hemorrhagic shock is a critical facilitator of resuscitation harm, and cell impermeants in low volume resuscitation solutions can help prevent it.

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