Hypertonic saline for treatment of shock: have we looked for everything?

Mauricio Rocha e Silva, dedicated to Luiz Poli de Figueiredo

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This review is dedicated to the memory of Luis Poli de Figueiredo, who is responsible for much of what we know about small volume resuscitation. Hypertonic salt solutions (osmolality > 300 mOsm/L) have been viewed with interest since 1919, when Penfield reported that a small volume of 1.8% NaCl (600 mOsm/L) induced a transient recovery of the hypotension caused by blood loss in dogs. Fifty years later, Baue et al. and Messmer et al. reported equally transient effects of 5% NaCl in severely hypotensive animals. Gazitua et al. from Arthur Baue’s laboratory, showed that these same formulations induced vasodilation when selectively infused into the renal, coronary, and limb circulations. Enhanced interest in the field was induced when Velasco et al demonstrated that 4 ml/kg of a 7.5% NaCl solution induced a highly significant hemodynamic recovery and a high percentage of long term survival compared to no treatment. By the end of 2013, this paper had been cited 433 times in journals in the Thomson Reuters Journal of Citation Reports. Over the past 20 years, i.e., 14 to 34 years after publication, it collected 253 citations (12.5 per year) and apparently counting. Second generation citations total 12,444.

A preliminary human study by de Felippe et al showed that 7.5% NaCl solutions given in successive 50 ml aliquots to patients in hemorrhagic shock induced beneficial hemodynamic effects. Soon afterwards, in the laboratory of George Kramer, it was shown that the association of dextran to hypertonic saline combined the hyperosmotic effects of NaCl to the hyperoncotic effects of dextran and added new conceptual and practical possibilities. This review is a follow-up of our previously published coverage of the subject and endeavors to follow developments over the past eight years.

KEYWORDS: Shock; Hemorrhage; Sepsis Hypertonic saline; Immune circulation.


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INTRODUCTION

This review is dedicated to the memory of Luis Poli de Figueiredo, who is responsible for much of what we know about small volume resuscitation. Hypertonic salt solutions (osmolality > 300 mOsm/L) have been viewed with interest since 1919, when Penfield reported that a small volume of 1.8% NaCl (600 mOsm/L) induced a transient recovery of the hypotension caused by blood loss in dogs. Fifty years later, Baue et al. and Messmer et al. reported equally transient effects of 5% NaCl in severely hypotensive animals. Gazitua et al. from Arthur Baue’s laboratory, showed that these same formulations induced vasodilation when selectively infused into the renal, coronary, and limb circulations. Enhanced interest in the field was induced when Velasco et al demonstrated that 4 ml/kg of a 7.5% NaCl solution induced a highly significant hemodynamic recovery and a high percentage of long term survival compared to no treatment. By the end of 2013, this paper had been cited 433 times in journals in the Thomson Reuters Journal of Citation Reports. Over the past 20 years, i.e., 14 to 34 years after publication, it collected 253 citations (12.5 per year) and apparently counting. Second generation citations total 12,444.

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METHOD

This review is based upon a systematic search performed in the Medline databases using the following search parameters: ((hypertonic saline) AND (NaCl)) AND ((shock) OR (hemorrhage) OR (sepsis) OR (Traumatic brain injury)). A publication date [2005-2013] was added as a filter. The search brought up 114 articles. They were then manually short listed to 59 based on pertinence. Thirteen references relating to the previous history of the topic were added. This study is designed as a sequel to a previously published review on the same topic.

PHYSICAL PROPERTIES OF HS AND HSD

The initial effect of hypertonic saline is significant plasma volume expansion. Performing a very simple set of experiments, it was possible to work out the theoretical distribution of space evolving through the first minutes following its intravenous administration. Given that 4 mL of 7.5% NaCl contains 5.12 mEq. Na⁺, its simple dilution into 40 mL of water produces a concentration of 128 mEq. Na⁺/L. In theory, if added instantaneously to the plasma volume of a normovolemic dog (approximately equal to 40 mL/kg), this Na⁺ load should increase plasma Na⁺ to

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**PHYSIOLOGICAL PROPERTIES OF HS/HSD**

**Cardiovascular system**

Work reported before 2006 and reviewed in our previous publication\(^1\) showed that hypertonic resuscitation induced cardiovascular improvement consisting of a partial recovery of mean arterial pressure and cardiac output. This was variously attributed to plasma volume expansion, vasodilation in arterial and systemic vascular beds, and to a direct cardiac inotropic effect. Vasodilation of the renal and mesenteric territories was also reported. An early development suggested that the central nervous system was important in the development of the cardiovascular response to hypertonic saline,\(^2\) but this concept has been revised. Two papers from the laboratory of Sergio Cravo indicate (i) that the effect of hypertonic saline in the restoration of cardiovascular function is attenuated by denervation of the carotid sinus, but not of the aortic arch,\(^3\) and (ii) that this response is virtually suppressed by selectively knocking out the carotid chemoreceptor bodies.\(^4\)

Hypertonic saline has been reported to act directly or indirectly on cardiac function. Frithiof et al.\(^5\) showed that increased Na\(^+\) concentration at the Paraventricular Nucleus combined with its effects on the cerebral angiotensin receptor AT(1) contribute to induce a positive inotropic effect, thus enhancing cardiac performance. Letson et al.\(^6\) reported an interesting difference between the effects of simple hypertonic saline (HS), on one hand, and the same combined with either dextran (HSD) or hetastarch (HSHES). In a rat model with 40% blood loss, none of the treatments induced arrhythmias or led to mortality. Simple HS suppressed arrhythmias and mortality; HSD had no effect on arrhythmias but suppressed mortality; HSHES had no effect on arrhythmias or mortality.

Microcirculation was the object of a number of reports. In a pig model of severe hemorrhage, an evaluation of hypertonic saline-hespan, hespan alone and Gelatin by Maier et al.\(^7\) revealed restoration of baseline parameters in all three groups, with significantly higher filling pressures and cardiac output after the isotonic colloids. Sublingual microcirculation blood flow and flow quality were also equivalent with the three treatments, but again, only the isotonic colloid improved microvascular hemoglobin oxygen content. The use of polymerized hemoglobin to enhance O\(_2\) carrying capacity as an adjunct to small volume resuscitation has been revisited by Cabrales et al.\(^8\) in a hamster dorsal window chamber model. Severe hemorrhagic shock was resuscitated by hypertonic saline plus polymerized bovine hemoglobin, 4 or 23 g/dL. Interestingly, only the smaller dose restored perfusion, functional capillary density, and tissue PO\(_2\). In a sequel study using the same model, Palmer et al.\(^9\) claimed that hypertonic saline resuscitation followed by the administration of high molecular weight tense-state polymerized human or bovine hemoglobin. Human...
hemoglobin induced vasoconstriction and decreased perfusion when compared to bovine hemoglobin or albumin. Bovine hemoglobin produced a pronounced recovery in blood gas parameters and tissue PO₂ vs. albumin or human hemoglobin. The authors of this study suggested that appropriately engineered polymerized hemoglobin may enhance/reinstate oxygenation, without hypertension or vasoconstriction, and could be useful in situations where blood transfusion is not logistically feasible. Gong et al. examined the microcirculation of the piamater and found that hypertonic saline does not inhibit neutrophil – endothelial interactions induced by severe blood loss. This is an interesting observation in that it sharply contrasts with many reports indicating that this inhibition effectively occurs in the systemic circulation. Apparently the piamater has another specific property not shared by other blood – tissue barriers.

The immune system

A series of papers added to previously established facts about the interaction of hypertonicity with the immune system. For convenience, this discussion will separate its effects on lymphocytes and polymorphonuclear neutrophils.

Lymphocyte Function

In vitro hypertonic saline interferes beneficially with lymphocyte function after severe blood loss. It has been shown to restore T cell function. Two mechanisms have been proposed. (a) The Migratory Inhibitory Factor (MIF) has been reported by Yoon et al. to be depressed in response to hemorrhagic shock, but restored by hypertonic saline treatment. (b) The release of lymphocyte cell ATP is induced by hypertonicity, and, thus, restores its function. This effect appears to be mediated through pannexin-1 hemichannels and P2X receptors, as reported by Woerhle et al. This same report suggests that hypertonic saline could be used to improve T cell function in trauma patients. These concepts have been confirmed in vivo by Lu et al. in a rat model of severe hemorrhagic shock, where resuscitation with hypertonic saline attenuated the rise of CD4 T lymphocytes, and CD4/CD8 induced by the previous blood loss. In a separate report, the same protocol showed that hemorrhage induced intense apoptosis in the intestinal mucosa; and that this is partially reduced by hypertonic saline resuscitation, but not by resuscitation with normal saline.

Neutrophil function

It has been previously established that neutrophil function is enhanced by hemorrhage leading to organ and tissue damage, but attenuated by hypertonic saline resuscitation. Lee et al. have shown that in shock, neutrophils are primed for an increased production of superoxide, which is implicated in acute lung injury. Neutrophils were isolated from healthy donors, primed with arachidonic acid and incubated with hypertonic saline. The well established activation of neutrophils by arachidonic acid was inhibited. Neutrophil degranulation and proinflammatory mediator synthesis, also implicated in pulmonary inflammation, is likewise enhanced by hemorrhage as shown by Deree et al. in a murine model of severe hemorrhagic shock. Resuscitation with a combination of hypertonic saline and pentoxifylline drastically reduced this response; whereas, lactated Ringer’s was ineffective. As described above, hypertonic saline effectively decreases the interaction of neutrophils with endothelial cells in the systemic circulation, but not in the blood brain microcirculation. In spite of an inhibitory effect on neutrophil function, Bahrami et al. report that in a murine model of very severe hemorrhagic shock, with arterial blood pressure reduced to and kept at 30-35 mm Hg for two hours, no reduction in mortality was observed following hypertonic saline, or hypertonic saline plus hydroxyl ethyl starch. Theobaldo et al. employed a mouse model of cecal ligation and puncture and showed that hypertonic saline drives neutrophils from bystander organs to an infectious site in polymicrobial sepsis: a cecal ligation and puncture model.

Other immune effects

In a rat model of severe hemorrhage over-resuscitated with either 81 ml/kg isotonic or 9.7 ml/kg hypertonic saline, H. Chen et al. found that toll-like receptors were activated by hypertonic resuscitation. More recently, L.W. Chen et al. report that in rats submitted to burns and resuscitated as described above, hypertonic saline enhances host defenses and reduces apoptosis by increasing the level of toll-like receptors. Fernandes et al. reported that hypertonic saline solution increases the expression of heat shock protein 70 and improves lung inflammation early after reperfusion in a rodent model of controlled hemorrhage.

The Central Nervous System

The importance of the central nervous system in the resuscitative properties of systemically infused hypertonic saline had been suggested soon after the Velasco paper, however, during the period under study, this observation was once again revised this time by Frithiof et al. Using a sheep model of hemorrhage, with or without anesthesia, they report that an intact autonomic cardiovascular control system is crucial for the effect of intracerebralventricular hypertonic saline and indicate that intravenous hypertonic saline exerts some of its action through the central nervous system. Xiao et al. used 7.5% NaCl (alone or in combination with hydroxyethyl starch-40) to treat a two hit condition (acute intracranial hypertension plus hemorrhage). The hypertonic starch combination exhibited the fastest mean arterial pressure recovery. Cerebral perfusion pressure was increased after resuscitation with both solutions, but intracranial pressure was decreased only by the simple hypertonic saline solution. Other reports used the 3% NaCl solution to treat subdural hematoma, traumatic brain injury, or subdural hematoma with beneficial results. Balbino et al. in a canine model of traumatic brain injury associated with hemorrhage, report hypertonic saline prevents intraneural calcium influx. Noppens et al. employed a rat model of global cerebral ischemia. Treatment with a single bolus of 7.5% NaCl + 6% hydroxyethyl starch resulted in an important restoration of regional cerebral blood flow, reduced post-ischemic mortality, and ameliorated neurologic symptoms 10 days after insult, Nout et al. employed repeated injections of 5% NaCl to successfully attenuate cord swelling and edema in experimental spinal cord injury animal model.

ANIMAL CLINICAL TRIAL MODELING

In this section, an animal clinical trial modeling is defined as any trial performed in a live animal model, in which a
realistic human clinical condition is simulated. I will restrict myself to discussing experiments in which a reasonable approximation to standard of care was used as a control, with two exceptions, both of which are included as Sepsis trials.41,42 This discussion shall be divided into two sections, namely hemorrhage and sepsis trials.

Hemorrhage trials
We shall subdivide reports on these hemorrhage trials into groups showing (a) superiority or (b) equivalence of small volume resuscitation vs. conventional isotonic treatment. Table 1 summarizes the distribution.

Table 1 - Summary of animal clinical trials for hypertonic saline

<table>
<thead>
<tr>
<th>Author (ref)</th>
<th>Species</th>
<th>Test Agent</th>
<th>CTR</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Superiority</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coimbra43</td>
<td>rat</td>
<td>HS, PTX;</td>
<td>NS</td>
<td>Immune function</td>
</tr>
<tr>
<td>Constantini44</td>
<td>rat</td>
<td>HS, PTX;</td>
<td>NS</td>
<td>Immune function</td>
</tr>
<tr>
<td>Cruz45</td>
<td>rat</td>
<td>HS, PTX;</td>
<td>NS</td>
<td>Immune function</td>
</tr>
<tr>
<td>Lu23</td>
<td>rat</td>
<td>HS, NS</td>
<td></td>
<td>Apoptosis; Organ damage</td>
</tr>
<tr>
<td>Lu46</td>
<td>rat</td>
<td>HS, NS</td>
<td></td>
<td>Liver function</td>
</tr>
<tr>
<td>Hoppen47</td>
<td>rat</td>
<td>HS, NS</td>
<td></td>
<td>Liver function</td>
</tr>
<tr>
<td>Sharma48</td>
<td>rat</td>
<td>HS, LR</td>
<td></td>
<td>renal function</td>
</tr>
<tr>
<td><strong>Equivalence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Younes49</td>
<td>dog</td>
<td>HS, NS</td>
<td></td>
<td>Survival</td>
</tr>
<tr>
<td>Nascimento50</td>
<td>dog</td>
<td>HS, LR</td>
<td></td>
<td>liver function</td>
</tr>
<tr>
<td>Watters51</td>
<td>swine</td>
<td>HS, NS</td>
<td></td>
<td>renal function</td>
</tr>
<tr>
<td>Legrand52</td>
<td>dog</td>
<td>HS, NS</td>
<td></td>
<td>renal function</td>
</tr>
<tr>
<td>Garcia-Martinez53</td>
<td>dog</td>
<td>HS, H2O2</td>
<td></td>
<td>Hemodynamics</td>
</tr>
</tbody>
</table>

*: Hypertonic Saline; †: Pentoxiphylline; ‡: Normal saline; §: Lactated Ringer’s.

In a simple hemorrhage/resuscitation model, Coimbra et al43 report that a combination of small volume hypertonic saline combined with pentoxifylline, compared with conventional lactated Ringers resuscitation, decreases organ injury. They conclude that this strategy with marked immunomodulatory potential may be an attractive alternative to conventional hemorrhagic shock resuscitation. They later showed that the hypertonic saline-pentoxifylline (vs. conventional lactated Ringers resuscitation) modulates pulmonary transcription factor activation and reduces lung injury.44 An equivalent conclusion, including superiority of the hypertonic saline-pentoxifylline strategy, was reached by Cruz et al,45 regarding cardiovascular performance and gastric mucosal oxygenation. As previously noted, Lu et al46 examined the effects of small volume resuscitation and report that it showed itself to be more effective than normal saline in reducing immunologic disorders and promoting a more balanced profile of T-lymphocyte subpopulations regulating networks. More recently, they reported on the effects of standard isotonic saline vs. small volume hypertonic resuscitation on the expression of heme oxygenase-1 mRNA and apoptosis in various organs of rats submitted to hemorrhagic shock. They found a significant up-regulation of heme oxygenase-1 in the small intestinal mucosa, liver and kidney following small volume vs. normal saline resuscitation, and conclude that this may be one of the mechanisms alleviating organ damage.46 Liver function and integrity was the object of a report by Hoppen et al47 in a rat model of hemorrhage and resuscitation, hypertonic saline restored bile secretion and liver integrity better than conventional lactated Ringer’s up to 6 hours after resuscitation. Sharma et al48 report that rats submitted to a hemorrhagic shock procedure with 100% lethality if untreated, were effectively resuscitated by normal saline, lactated Ringers solution, or small volume. However, they claim that hypertonic saline was more effective in preventing kidney damage than isotonic fluid administration. This contrast with equivalence reports on renal function, as described below.

Equivalence
Younes et al49 performed a very extensive study with a rat model of hemorrhage, including 180 animals. Standard of care isotonic saline was compared to hypertonic saline and total blood retransfusion in a hemodilution model: they report that hypertonic saline is an effective and safe initial therapy for hemodiluted rats undergoing hemorrhagic shock, with an overall outcome comparable to blood replacement or high volume isotonic saline administration. Nascimento et al50 submitted anesthetized dogs to a 40% blood volume hemorrhage and treated them with lactated Ringers, hypertonic saline, hypertonic saline-dextran or hydroxyethyl starch. In spite of initial differences in hemodynamic responses, all treatments were equally effective in restoring renal performance 120 min after treatment. A similar equivalence of response with regard to systemic hemodynamics and renal function was described for a swine model by Watters et al.51 In a rat model, Legrand et al52 also reported an equivalence of response between isotonic vs. hypertonic saline vs. blood retransfusion: none of the regimens restored renal O2 delivery or PO2. In a canine model of severe hemorrhage, Garcia-Martinez53 reported that the addition of naloxone to small volume hypertonic-hyperoncotic resuscitation (vs. retransfusion of shed blood) does not alter the vascular response or the acid-base equilibrium.

In a diagnostic-oriented protocol, Reynolds et al54 evaluated lactate profiles as a resuscitation assessment tool in a rat model of battlefield hemorrhage resuscitation. A comparison was made between 7.5% hypertonic saline and 6% hetastarch for low volume resuscitation. They conclude that survivors exhibited a decline in lactate levels following resuscitation.

Sepsis trials
Reports on animal sepsis trials will likewise be divided into a group showing (a) superiority or (b) equivalence of small volume resuscitation vs. conventional treatment. A total of nine such reports were found, eight of which indicate superiority in the use of small volume vs. conventional treatment with respect to surrogate endpoints. It must be noted that in only one of these studies was survival shown to be improved. A single report showed equivalence. Table 2 summarizes these findings.

Superiority
In a rat model of cecal ligation puncture, Shih et al55 reported that hypertonic saline prevented circulatory failure and alleviated multiple organ dysfunction syndrome when compared to conventional Lactated Ringer’s treatment. These effects were attributed to decreased lung neutrophil
Table 2 - Summary of animal trials for hypertonic saline in sepsis

<table>
<thead>
<tr>
<th>Author (ref)</th>
<th>Species</th>
<th>Test Agent</th>
<th>CTR</th>
<th>Model/Target</th>
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<tbody>
<tr>
<td>Superiority</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shih et al.</td>
<td>rat</td>
<td>HS or HSH</td>
<td>-</td>
<td>CLP/immune response</td>
</tr>
<tr>
<td>Shih et al.</td>
<td>rat</td>
<td>HS</td>
<td>-</td>
<td>CLP/immune/ survival</td>
</tr>
<tr>
<td>Yu et al.</td>
<td>swine</td>
<td>HS + tezosantan</td>
<td>-</td>
<td>Endotoxin/Cardiac function</td>
</tr>
<tr>
<td>Somell et al.</td>
<td>rat</td>
<td>HS + PTX</td>
<td>LR</td>
<td>CLP/immune/lung injury</td>
</tr>
<tr>
<td>Liu et al.</td>
<td>rat</td>
<td>HS</td>
<td>-</td>
<td>CLP/lung injury</td>
</tr>
<tr>
<td>Gao et al.</td>
<td>rat</td>
<td>HS or HSS</td>
<td>LR</td>
<td>Hemorrhage/+sepsis/lung injury</td>
</tr>
<tr>
<td>Luiz et al.</td>
<td>rat</td>
<td>HS</td>
<td>LR</td>
<td>Intestinal obstruction/immune &amp; gut damage</td>
</tr>
<tr>
<td>Equivalence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wan et al.</td>
<td>sheep</td>
<td>HS</td>
<td>NS</td>
<td>Gram-negative sepsis/renal function</td>
</tr>
</tbody>
</table>

Infiltration and liver necrosis. Mortality rate was not improved. However, in a sequel report, the authors report that a two-dose hypertonic saline administration (3 and 9 hr after cecal ligation) significantly reduced mortality and improved hyponatremia, hypocalcemia, metabolic acidosis, and electrolyte imbalance. In a rat model of endotoxin administration, Yu et al. report that small volume resuscitation with hypertonic saline or hypertonic sodium chloride + hydroxyethyl starch 40 reduced lung damage when compared to isotonic saline. In a porcine model of endotoxemic sepsis, Somell et al. claim that the combination of tezosantan and hypertonic saline-dextran improved cardiac index and arterial oxygenation. In a two hit model (hemorrhage + cecal ligation puncture), Kim et al. showed that the combination of hypertonic saline and pentoxifylline when compared to lactated Ringers reduced lung injury score and neutrophil count. The combination of hypertonic saline with valproic acid worked synergistically to attenuate inflammation and improve survival. In this report, by Liu et al., no control standard of care treatment was used. In a hemorrhage + lipopolysaccharide model, Gao et al. report that hypertonic saline alone, and especially when combined with hydroxyethylstarch, reduces lung tissue damage and pulmonary edema. In rats subjected to intestinal obstruction and ischemia, lactated Ringer’s reduced intestinal obstruction/immune & gut damage when compared to lactated Ringer’s.

Table 3 - Summary of human clinical trials for hypertonic saline

<table>
<thead>
<tr>
<th>Author (ref)</th>
<th>patients</th>
<th>Test Agent</th>
<th>CTR</th>
<th>Model/Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superiority</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rizoli et al.</td>
<td>27</td>
<td>HSD</td>
<td>NS</td>
<td>Hemorrhage/immune response</td>
</tr>
<tr>
<td>Junger et al.</td>
<td>34</td>
<td>HSS/HSD</td>
<td>NS</td>
<td>Hemorrhage/immune response</td>
</tr>
<tr>
<td>Bulger et al.</td>
<td>62</td>
<td>HSD</td>
<td>NS</td>
<td>Hemorrhage/immune response</td>
</tr>
<tr>
<td>Yildiz et al.</td>
<td>67</td>
<td>HS mannitol</td>
<td></td>
<td>Pediatric cerebral edema/intracranial pressure</td>
</tr>
<tr>
<td>Schroth et al.</td>
<td>50</td>
<td>HSH</td>
<td>NS</td>
<td>Pediatric open heart surgery</td>
</tr>
<tr>
<td>Equivalence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bulger et al.</td>
<td>209</td>
<td>HSD</td>
<td>LR</td>
<td>Blunt trauma &amp; hypotension/ARDS-free at 28 days</td>
</tr>
<tr>
<td>Bulger et al.</td>
<td>1331</td>
<td>HSS/HSD</td>
<td>NS</td>
<td>Head Injury/Brain deficit at 6 months</td>
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<tr>
<td>Bulger et al.</td>
<td>853</td>
<td>HSS/HSD</td>
<td>NS</td>
<td>Hemorrhage/Survival at 28 days</td>
</tr>
<tr>
<td>Fang et al.</td>
<td>94</td>
<td>HSHCO₃</td>
<td>NS</td>
<td>Sepsis &amp; Hypotension/Survival</td>
</tr>
</tbody>
</table>

In clinical trials, it is impossible to attain the tight homogeneity normally present in animal experiments. Also, in contrast to animal experiments, human clinical trials necessarily aim for survival as a primary endpoint. All of the reports to be discussed below targeted superiority of small volume resuscitation as compared to standard of care as the trial objective. It a well known fact that none of the standard of care procedures used today have ever been put to the formal test of efficacy or safety, but the extensive medical experience attached to their use warrants the view that they are generally effective and usually safe. Over the period covered by this review, we found nine reports in which small volume resuscitation was compared to standard of care in double blinded prospective trials. Five of them report superiority of small volume resuscitation over standard of care in surrogate or secondary objectives, but none showed survival superiority. In terms of survival, all trials pointed toward equivalence, even though they did not have sufficient statistical power to warrant the conclusion. Table 3 summarizes the main points of these reports.

Superiority
Rizoli et al. compared hypertonic saline dextran to normal saline in a study including 27 traumatic hemorrhage patients. They found no differences in clinical measurements, but report that small volumes resuscitation blunted neutrophil activation by abolishing shock-induced CD11b up-regulation. Consequently, it altered the shock-induced monocyte redistribution pattern by reducing the drop in “classic” CD14 and the expansion of the hemorrhage or sepsis in tightly controlled animal experiments, the described pharmacological actions of hypertonic saline appear to be mainly beneficial as treatment of shock.
“pro-inflammatory” CD14/CD16 subsets. In parallel, HSD significantly reduced pro-inflammatory tumor necrosis factor (TNF)-alpha production while increasing anti-inflammatory IL-1ra and IL-10. HSD prevented shock-induced norepinephrine surge with no effect on adrenal steroids. More recently, the same group, headed by Junger et al.,\textsuperscript{63} studied a different group of traumatic hemorrhage patients and reported that initial resuscitation with hypertonic saline, but not normal saline or hypertonic saline dextran, attenuate posttraumatic neutrophil and endothelial cell activation. A report by Bulger et al.,\textsuperscript{64} on 62 patients with traumatic hemorrhage, claims that CD11b expression, 12 hours after injury, was increased 1.5-fold in patients resuscitated with lactated Ringer’s compared with controls. In contrast, those resuscitated with hypertonic saline dextran had a significant reduction in CD11b expression compared with Ringer’s.

Two studies were reported on pediatric patients. Yildizdas et al.\textsuperscript{65} claim that hypertonic saline is superior to mannitol in reducing cerebral edema and increasing cerebral blood flow. Schroth et al.\textsuperscript{66} reported on the use of hypertonic saline dextran in the immediate post-operative phase of pediatric open heart cardiac surgery and concluded that it might be a useful and safe treatment and the amelioration of contractility, inotropy, and the possible treatment of early-onset capillary leakage.

Equivalence

Four studies report equivalence. A prospective double blind prospective trial was conducted by Bulger et al.\textsuperscript{67} with 209 blunt trauma hypotensive patients. No significant difference in ARDS-free survival at 28 days was demonstrated overall, but the use of hypertonic saline dextran may have offered maximum benefit in patients at highest risk for ARDS. A recent large scale multicenter trial produced two reports. (a) In a population of 1,282 traumatic brain injury patients with no hemorrhage, Bulger et al.\textsuperscript{68} reported that a three arm study (with a planned enrollment of 2,122 patients) was interrupted for futility. The conclusion was that initial resuscitation with either hypertonic saline or hypertonic saline dextran, compared with normal saline, did not result in superior 6-month neurologic outcome or survival. (b) In a population of 853 traumatic hypovolemic shock patients, a similarly planned study by Bulger et al.\textsuperscript{69} was also interrupted very early (after 23% of the planned population had been included) for futility, but also because of a potential safety concern. There was no difference in 28-day survival between the three arms, but a higher mortality for the post-randomization subgroup of patients who did not receive blood transfusions in the first 24 hours. They received instead hypertonic fluids as compared to normal saline. Fang et al.\textsuperscript{70} investigated the effects of normal saline, hypertonic saline, and hypertonic bicarbonate on 94 severe sepsis patients with hypotension. No differences were detected among the three groups in cardiopulmonary parameters during the 120 min trial or the 8 hour follow-up, or in the observed mortality rate after 28 days. Authors conclude that all three crystalloid solutions may be used for initial volume loading in severe sepsis, but that sodium bicarbonate confers a limited benefit in humans with severe sepsis.

Some comments on the trials resulting in equivalence are warranted.

1. In a feasibility study for a pre-hospital hypertonic resuscitation-head injury and multi organ dysfunction, Morrison et al.\textsuperscript{71} noted that although previous clinical trials suggest no survival superiority of small volume over normal saline, subgroup analyses suggest there may be a reduction in the inflammatory response and multi-organ failure which may lead to better survival and enhanced neurocognitive function with small volume resuscitation.

2. In a recently published review, Dubick et al.\textsuperscript{72} note that in spite of a huge body of literature showing that HSD and HS improve hemodynamic and metabolic responses, modulate immune function, and reduce brain edema, translating these results into improved survival in clinical trials in hemorrhagic shock and traumatic brain injury has been difficult. This is not altogether surprising because clinical trials have several limitations, such as being too underpowered to show improved survival, or not having been focused on the trauma population most likely to benefit. When compared to animal experiments, patients may have received significantly less than 4 ml/kg; the total volume of coded solution, 250 ml/kg, corresponds to giving 4 ml/kg to a person with a body weight of 62.5 kg, which is far less than the average weight of the predominantly male young adult population included in the trials.

3. This reviewer will add a third point, namely that in all previously conducted clinical trials, a poor strategy regarding objective may have been systematically embarked upon: all trials focused on a quest for superiority of small volume vs. standard of care resuscitation. However, the demonstration of medical equivalence would have brought out a truly significant logistical advantage, especially in military and mass civilian injury scenarios: the volume of pre-hospital administration employing small volume would be reduced by nearly 90%; the simplicity of ministration would likewise be enhanced. Accessory advantages might include the facts that simple hypertonic saline is sterile per se and only freezes below -4°C. Not surprisingly, the single segment of the population receiving initial small volume resuscitation is to found in military scenarios, where civilian restrictions may be overlooked and where the logistic advantages would be maximal.

4. Another point that should be made concerns the concept of diluting NaCl to 3% or 5% using a larger infused volume. This would partly defeat the main logistic advantage and might not trigger the beneficial immune responses described for 7.5% NaCl.

In conclusion, it is the contention of one of its discoverers, that proving equivalence is the most viable future for the use of simple 7.5% NaCl as a clinically useful tool, even if this has had to wait for more than 30 years after its discovery.\textsuperscript{5}

**RESUMO**

O procedimento de ressuscitação hipertônica a pequeno volume foi originalmente baseado no conceito de que uma expansão fisiologicamente significativa de volume sanguíneo resulta da administração de um pequeno volume de fluido hipertônico. A hipertonia é reconhecidamente um vasodilatador fisiológico, de modo que seu uso após uma importante perda
de sangue induz reperfusão. Pesquisas anteriormente divulgadas descreveram uma série de propriedades da solução hipertônica de NaCl, entre eles (i) a correção de endotelial e edema de células vermelhas com consequências significativas em termos de fluxo sanguíneo capilar, (ii) a modulação do sistema imunológico. Esta avaliação abrange a evolução neste campo entre 2005 e 2013. Como conclusão, discutimos a discrepância entre ações experimentais e clínicas, argumentando que em suas essências, as possivelmente faltos os objetivos dos ensaios clínicos multicêntricos recentemente realizados.

**REFERENCES**

16. Letson HL, Dobson GP. Small volume 7.5% NaCl with 6% Dextran-70 or 130/0.4% hydroxyethyl starch 40 injections. J Trauma. 2006;60(1):41-51.