

# Hypertonic Saline Dextran (HSD) and Intraosseous Vascular Access for the Treatment of Haemorrhagic Hypotension in the Far-forward Combat Arena

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## Abstract

*Battlefield statistics show that 50% of deaths are due to acute haemorrhage. Hypertonic (7.5% saline)/hyponcotic (4% Dextran-70) solution (HSD) for the treatment of haemorrhagic hypotension may have physiologic and logistic advantages over conventional fluid therapy for use in the far-forward combat arena. HSD rapidly expands plasma volume and stabilizes haemodynamic variables in various animal models of haemorrhage, at a volume dose of about 1/10 of conventional lactated Ringers solution. However, combat conditions, as well as the physiological status of the patient may result in time delays or failure to achieve vascular access. Over the past 5 years we have investigated intraosseous infusion of HSD via the sternum or tibia, as a possible means of achieving rapid vascular access and plasma volume expansion. These data in experimental animals and one clinical study show that HSD can be safely and rapidly infused via the intraosseous route achieving the same haemodynamic benefit as observed with intravenous administration.*

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**Key words:** *Experimental animals, Human, Resuscitation*

## Introduction

It is generally recognized that the major cause of battlefield deaths in conventional warfare is acute haemorrhage, accounting for 50% of fatalities.<sup>1</sup> In addition in about 30% of injured soldiers who die from wounds, haemorrhage is the primary cause of death. Current dogma dictates that early, adequate fluid resuscitation is crucial to reduce mortality and morbidity associated with haemorrhagic shock. Consequently, it is estimated that 65% of treated casualties require intravenous fluids. Bellamy<sup>2</sup> estimates that in the military setting, far-forward application of first aid and administration of resuscitation fluids could reduce battlefield deaths by 20%. It should be noted that early far-forward resuscitation of acute haemorrhage was deemed beneficial by British medical personnel during the Falkland Island War and by the Israeli Defense Force during their recent conflicts.

At present, large volumes of crystalloids, such as lactated Ringers are the standard of care for the treatment of haemorrhagic shock.<sup>2</sup> However, in the military setting logistical constraints preclude the availability of several litres of fluid per casualty on the battlefield. In

addition, combat conditions and the injured soldier's hypotensive state may lead to significant time delays or failure to gain vascular access due to collapsed veins.

In 1980, Velasco et al<sup>3</sup> reported that infusion of 7.5% NaCl at 10% of the shed blood volume restored cardiac output, blood pressure and other haemodynamic variables, and improved survival, in an otherwise lethal haemorrhage model in dogs. It was observed that this haemodynamic improvement was transient.<sup>4</sup> Consequently, other workers added a colloid, such as 6% Dextran-70, to prolong the cardiovascular improvement following haemorrhage.<sup>4,5</sup> Studies using a combined 7.5% NaCl/6% Dextran-70 solution (HSD) have shown the most promise in experimental models of haemorrhage. A single bolus infusion of 4 ml/kg HSD improved survival and rapidly expanded plasma volume 3 to 4 ml per ml infused.<sup>5</sup> It also normalized haemodynamics to baseline levels and improved metabolic and hormonal derangements associated with haemorrhage.<sup>6-10</sup> This was achieved at 1/10 to 1/12 the volume required to derive the same benefit with lactated Ringers. In the clinical trials completed to date, evaluating the pre-hospital administration of HSD,

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it improved survival in important subgroups of trauma patients, such as those with head injury or patients requiring surgery, and led to apparent reductions in 24 h fluid requirements.<sup>11,12</sup> An assessment of the efficacy and safety of HSD has been reviewed previously.<sup>13</sup>

For the military, HSD appeared to be one answer to the logistical difficulty in providing enough fluid in the far-forward combat arena to effectively resuscitate the injured soldier. However, it is recognized that combat conditions may preclude the timely ability to establish conventional venous canulations for administering these solutions. Therefore, investigations had begun to address potential useful means through which to gain vascular access more reliably and rapidly.

A likely mean of obtaining rapid vascular access is infusion directly into the bone marrow. In the 1940s, intraosseous (IO) infusion of blood, fluids and drugs into red marrow of the sternum or tibia was shown to reliably enter the circulation.<sup>14,15</sup> This approach was largely forgotten with rapid development of plastic catheters and routine venous canulations in the 1950s. A renewed interest in IO infusion, however, developed in the late 1970s, as IO infusion into the tibia became an accepted practice for emergency vascular access in children and infants.<sup>16-18</sup> In adults, since the red marrow of long bones is replaced by yellow marrow, the practicality of IO infusion was little explored. However, recent studies with human cadavers indicate that vascular access can still be achieved by injection into the yellow marrow." In adults, the sternum, distal tibia, or bones of the pelvic girdle remain sites of red marrow and are being re-examined as sites for IO infusions.<sup>20,21</sup> The sternum is attractive as an IO infusion site because it is a soft bone, has wide marrow space of relatively uniform geometry and lies under only a thin layer of skin.<sup>21</sup> The danger of using the sternum is that it overlies vital blood vessels and the heart. Therefore, any sternal IO access device must have a high margin of safety, such that complete bone puncture is not likely. The tibia has an advantage for IO access in that it has a large marrow space, but the outer cortical bone is very hard and manual IO devices cannot be placed easily in the adult tibia.

Another special consideration of IO vascular access is that infusion must be supplemented by a high pressure system to achieve reasonable flow rates.<sup>21</sup> The tortuous vascular architecture of bone marrow presents substantial hydraulic resistance to infusions. Consequently, rapid infusion of large volumes of isotonic crystalloid solutions has proven to be difficult and studies suggested that although IO infusion for the resuscitation from haemorrhagic shock in animal models and small children was achievable, in adults, it was not practical.<sup>22-24</sup>

Recently studies have begun to investigate the possible use of HSD through IO infusion. Since HSD is infused as a small volume resuscitation, it could be infused via the IO route in a timely manner. Bay et al<sup>25</sup> and Guerrero et al<sup>26</sup> reported on IO infusion of HSD through a newly developed sternal access device that automatically adjusts for variations in tissue and bone thickness to prevent the danger of puncturing underlying tissues. Using human cadavers, they reported a 93% success rate in achieving vascular access with the majority of insertions made within 30 s (12.8±7.2 s). Perron et al<sup>27</sup> showed that a 250 ml dose of HSD (the proposed adult clinical dose) could be administered intraosseously within 4 min, and Schafer et al<sup>28</sup>, employing the adult tibia as the IO injection site in human cadavers, reported a 96% and 88% success rate for needle insertion and contrast media insertion, respectively.

### Physiology of IO Infusion of HSD

Using the sternal access device employed by Bay et al,<sup>25</sup> Dubick et al<sup>28</sup> evaluated haemodynamic variables and electrolyte concentrations, as well as evidence for histological abnormalities in lung and sternum, in euvoalaemic swine infused with a 4 ml/kg bolus of HSD via either the sternal IO or IV route. They observed virtually identical responses in cardiac output, mean arterial pressure and plasma volume expansion following infusion through either route. In addition, changes in plasma protein concentrations and haematocrit were similar, as were changes in plasma sodium, potassium, chloride and dextran concentrations, when evaluated over the initial 120 min following infusion. Similarly, rapid restoration of haemodynamic variables were reported in haemorrhaged, conscious sheep, following HSD infusion into the sternum or through a central venous catheter.<sup>29</sup>

In a haemorrhaged swine model, Watson et al<sup>30</sup> reported that HSD was superior to normal saline in more rapidly returning cardiac output to prehaemorrhaged values and the volume of HSD required was less than 15% of that of normal saline (Figs. 1 & 2). Consistent with previous studies they found that delivery of an effective dose of normal saline was limited by the large volumes required and high hydraulic resistance in the marrow.

HSD was also shown to be superior to normal saline in haemorrhaged dogs infused through the medullary cavity of the tibia.<sup>31</sup> HSD improved cardiac output, mean arterial pressure, and circulating plasma volume better than normal saline over the 3 h study period.<sup>31</sup> Most recently, Runyon et al<sup>32</sup> evaluated the safety and efficacy of a highly concentrated near saturated salt (25% NaCl)/dextran (24% Dextran-70) solution (SSD), administered through the sternum, for the resuscitation of haemorrhagic hypotension in a swine model. They

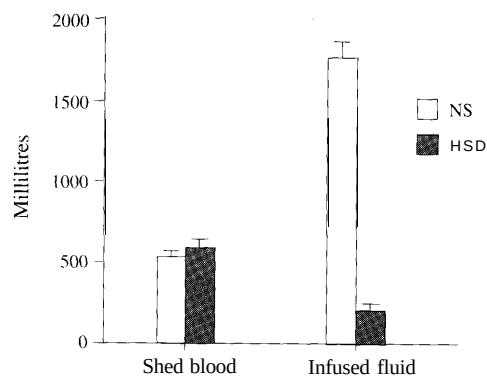


Fig. 1. Amount of shed blood to lower mean arterial pressure to 50 mm Hg and the amount of 7.5% NaCl/6% Dextran-70 (HSD) and normal saline (NS) required to restore and maintain cardiac output for 2 h in swine (Fig. 2). Data represent mean standard error. For normal saline group,  $n=5$ , and for HSD group,  $n=6$ . Volume of HSD infused was significantly less than the volume of NS ( $P<0.05$ ).

observed that SSD was as effective as normal saline in restoring cardiac output to prehaemorrhaged levels, but to maintain this endpoint for 2 h, only  $1.3 \pm 0.1$  ml/kg SSD was required compared with  $31.6 \pm 6.3$  ml/kg normal saline. In addition, SSD produced a greater expansion of blood volume and a lower systemic vascular resistance than normal saline. SSD also resulted in a longer lasting improvement in portal vein blood flow and was able to improve cardiac output without increasing pulmonary wedge pressure. The results of this study imply that for military use, a single 100 ml dose of SSD could resuscitate a 2 litre blood loss.

To date only one study has investigated IO infusion of HSD in humans. Chavez-Negrete et al<sup>33</sup> infused HSD IO and IV to patients with gastrointestinal bleeding. They found that HSD reduced the total fluid and blood requirements in these patients compared with standard of care infusions, and that IO infusion of HSD was as effective as an IV infusion. No deleterious effects of IO infusion of HSD were noted.

### Safety of IO HSD

Acceptance of the IO route as an alternative to gain vascular access in emergency situations has been somewhat limited due to lack of knowledge, training and safety concerns. These concerns include induction of epiphyseal damage, extravasation into soft tissue, compartment syndrome, osteomyelitis and fat or bone emboli.

Although adverse effects have been reported after IO infusion into both the sternum and tibia, the complication rates appear to be similar to those reported following IV infusions of the same drug.<sup>34</sup> The consequences of IO complications, such as osteomyelitis or extravasation of infused fluid into soft tissue, however, have potentially greater clinical significance than complications following IV infusion. Although some cases have been reported, significant complications are relatively

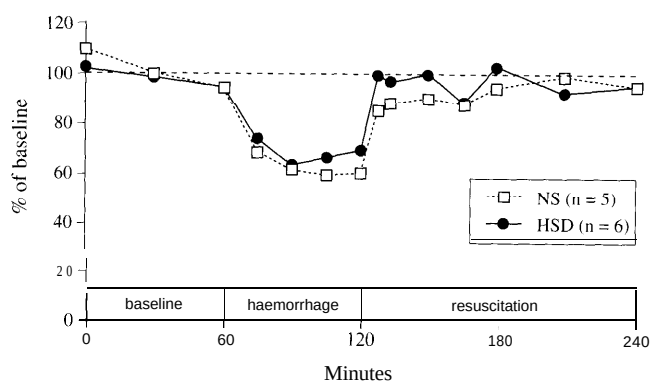


Fig. 2. Time course of cardiac output during a 1 h baseline, 1 h of hypotension and 2 h following resuscitation with HSD or normal saline (NS) in swine. Both solutions were infused as rapidly as possible to restore cardiac output to prehaemorrhage levels. Baseline cardiac output was  $4.2 \pm 0.2$  L/min.

rare,<sup>35-37</sup> suggesting that aseptic technique in the use of IO devices is both practical and effective. In addition, in children osteomyelitis was avoided if the IO needle was removed before 24 h.<sup>37</sup>

Practically, there are relative conditions where IO infusion would be avoided. These include fractures if the IO site is on the fractured bone, or the presence of sepsis or cellulitis.<sup>34,36</sup> In addition there are bone diseases, such as osteoporosis, osteopetrosis and osteogenesis imperfecta, where IO infusion would be contraindicated. However, the chances of encountering these diseases in military personnel are practically nil.

A review of IO complications by Fiser,<sup>38</sup> based almost exclusively on paediatric use, reported an 80% success rate of insertion, and a 20% failure rate due to missed landmarks, a bent needle, lack of red marrow or osteopetrosis. A 0.7% incidence (5/694) of localized cellulitis and formation of subcutaneous abscesses was observed. In addition the incidence of osteomyelitis was observed to be 0.6% (27/4270). In adults there has been little recent use of IO access and the success rate and complications await further clinical studies.

With respect to the IO infusion of HSD specifically, Dubick et al<sup>28</sup> reported that due to hydraulic resistance of the sternal red marrow, infusions were made by syringe delivery which could generate infusion pressures of 15 to 30 psi or 750 to 1500 mmHg. Histologic examination of the sternum and lungs 2 h after HSD infusion reported a similar incidence of minimal lung inflammation, whether HSD was infused IV or IO. In addition, focal haemorrhage at the IO site was observed, as well as a small 2 to 5 mm region of hypocellularity.<sup>29</sup> None of the reported lesions were rated severe. In addition, extravasation of fluid into the skin above the sternum was not observed. In another study, Kramer et al<sup>39</sup> reported no physiologic nor histologic evidence of pulmonary embolism following IO infusion of HSD into sheep. At 1 to 2 days following

infusion, haematopoietic cells exhibited a focal wash-out in the vicinity of the infusion site. Histological specimens from the infusion site at 2 to 6 weeks after infusion, showed replacement of hypocellular areas with fibrous tissue. All these changes were confined to within a 3 mm radius of the injection site. Halvorsen et al<sup>29</sup> also reported focal haemorrhage and a focal hypocellularity of marrow cells in a small area around the injection site in their sheep infused with HSD. Minimal histological changes in the lung and sternum were also observed following infusion of the saturated salt/dextran preparation (SSD).<sup>32</sup> As mentioned, because of the more concentrated nature of SSD, only 1.3 ml/kg of SSD was required in comparison to the usual 4 ml/kg dose of HSD. Therefore, these animals received similar salt and dextran loads in comparison to studies that employed HSD. Any incidences of pulmonary vasculitis (2/6) observed in the SSD group were minimal to mild. In both the SSD and normal saline groups, acute haemorrhage (5/6 versus 5/5, respectively) and cellular washout (3/6 versus 4/5, respectively) in sternum were noted around the site of needle insertion, but the incidence rate and severity appeared to be slightly higher in the normal saline group, reflecting the much greater volumes of fluid required to return cardiac output to the prehaemorrhage level. In dogs, Okrasinski et al<sup>31</sup> reported that 5% NaCl, administered IO in the proximal tibia, caused some marrow necrosis and endosteal damage, but the volumes required to induce these effects were not mentioned.

With regard to the safety of HSD itself, concerns have been raised regarding both the hypertonic saline and the dextran components. Although the prehospital clinical trials with HSD reported elevations in plasma sodium and chloride, the levels obtained were not determined to be clinically significant.<sup>11-13</sup> Historically, concerns of dextran safety have focused on interference of blood typing and crossmatching, induction of coagulopathies, induction of renal failure and potential antigenicity. Extensive toxicological evaluation of HSD in experimental animals and human blood, *in vitro*, failed to reveal any such toxicity at the recommended therapeutic dose of 4 ml/kg, and the aforementioned concerns have not been observed in over 900 patients who received HSD in the clinical trials.<sup>13</sup>

Lastly, two specific concerns of HSD resuscitation in combat situations should be addressed. The first concern is that in the presence of penetrating injury, the rapid increase in arterial pressure after HSD infusion could aggravate internal bleeding. However, in the major USA multicentre trial of HSD for the treatment of traumatic hypotension, mean survival rates were higher in patients with penetrating injury who received HSD compared with a similar group who received standard-of-care as isotonic crystalloid (88% versus 77%, respec-

tively,  $P=0.06$ ), despite HSD raising blood pressure." These results suggest that HSD did not induce significant rebleeding. Other trauma trials have also seen no evidence of increased bleeding nor greater blood requirements in patients treated with HSD in the field.<sup>12,40</sup>

The second concern is that HSD-induced hyperosmolarity / hyponatremia could be deleterious in wounded soldiers who are invariably, dehydrated. A review of 3 dehydration studies in experimental animals found HSD to improve haemodynamics, preserve renal function and improve survival in an otherwise lethal haemorrhage-dehydration swine model.<sup>41-43</sup> In addition HSD infusion did not raise plasma sodium concentrations to dangerously high levels. Most recently, a cohort analysis of patients from the HSD prehospital trials revealed 105 patients who presented with hyponatremia, and presumed to be dehydrated. In this group, those patients who received HSD had markedly improved survival compared with those patients who received standard of care (68.5% versus 39.2%, respectively).<sup>44</sup> In addition, studies in rats and pigs showed that 4 ml/kg HSD was more effective than a similar dose of normal saline in restoring plasma volume following moderate dehydration in the absence or presence of hyperthermia.<sup>45,46</sup> The implication in the military setting is that HSD could be effective in the acute treatment of hyperthermia or dehydration, until standard isotonic fluid replacement was possible. However, this area warrants further research.

## Conclusion

Current fluid resuscitation on the battlefield and other forward areas of the combat zone is limited by a number of factors, including battlefield conditions, logistical constraints in providing enough fluids, and human physiological limitations. Numerous studies with HSD have shown it to rapidly expand plasma volume, increase venous return and cardiac output, increase tissue oxygen delivery, and improve survival in experimental animals. Clinical prehospital trauma trials of HSD suggest similar physiologic responses and improved survival in patients with penetrating injury and particularly those with head injury.<sup>13</sup> The ability of HSD to be effective in small volumes, coupled with its easy preparation and excellent storage characteristics, has made it attractive for military use in the far-forward combat arena. Since multiple trauma is common on the battlefield, current studies with HSD and other hypertonic and/or hyperoncotic solutions are examining efficacy in combined models of haemorrhage and head trauma, as well as in the treatment of burns and spinal cord injury.

The potential of an effective resuscitation fluid on the battlefield has stimulated research to develop more effective means to administer HSD or future solutions

under combat conditions and in hypotensive patients where venous access is compromised. Research has focused on intraosseous infusion devices that would be simple to use, safe and rugged enough for military use. HSD can be effective when administered IO via the sternum or tibia. Studies to date in experimental animals suggest that HSD infused via the IO route is safe and as effective as an IV infusion. Safety of IO infusion may reflect maintaining aseptic technique and avoiding prolonged infusion times. Clinical experience with another IO sternal access device used by the Dutch Navy reports that the method is safe and effective, but used only rarely during peacetime (Boer, Personal Communication). However, much remains to be evaluated in the use of IO infusion in adults. For example, the use of local anaesthetics has been reported to be useful for both needle insertion and with the initial infusion,<sup>47</sup> and although anaesthetics are not necessarily used for emergency vascular access in children, it is unclear whether they would be necessary for adult trauma victims. In addition, during cardiopulmonary resuscitation (CPR), adults have been administered drugs successfully through IO needles placed in the medial malleolus.<sup>20</sup> In CPR patients the manubrium may remain an acceptable site for IO delivery and still allow cardiac compression, whereas the sternal body would not. Also, there is the issue of training. Nurses and paramedics have utilized animal bones for training and report that the technique is easily learned by observation.<sup>48</sup> Also, special manikins are available to teach pediatric IO access to paramedics. Perhaps these could be adapted for training corpmen as well. Thus, the challenges for the future are to further test IO infusion of HSD in human adults, to define its limitations, and to develop better IO infusion devices that can be easily inserted, yet rugged enough to function under the austere conditions expected in a far-forward combat environment.

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