# The use of hypertonic solutions in prehospital care in Scandinavia

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**ABSTRACT:**

**"Hypertonic solutions has recently been introduced in prehospital care in Scandinavia. Protocols were based on extensive meta-analyses showing that hypertonic saline dextran has safely been given to large numbers of trauma patients. Head trauma patients seem to specially benefit from these solutions."**

## Mechanisms of hypertonic solutions

In 1999, the Committee on Fluid Resuscitation for Combat Casualties for the United States Army recommended the use of hypertonic solutions for the treatment of combat casualties (1). Although known for a long time, renewed interest in these solutions was not widespread until 1980, when researchers in São Paulo, Brazil reported using 2400 mOsm of hypertonic saline (HS) to successfully treat severe hemorrhagic shock (2-4). Numerous studies over the last two decades have established that HS infusions promote diuresis/natriuresis, augment cardiac output, increase cardiac contractility, and directly vasodilate the peripheral vasculature. Adding a colloid can transiently (depending on the type added) expand plasma volume and can be used safely for resuscitation of hypovolemia (5).

### Volume Expansion

One of the most striking features of infusing hypertonic solutions is the rapid onset of plasma volume expansion (6). This is accomplished by mobilization of fluid from the extravascular space into the vascular space. Intracellular recruitment makes endothelial cells deflate (7), thus enhancing microvascular perfusion and restoring the function of the sodium/potassium pump, which improves both intracellular pH and $Ca^{2+}$ levels (8,9). Based on field studies with hypertonic solutions, 250 mL hypertonic saline dextran (HSD) given to a 70-kg patient who suffers a 2 L blood loss will result in a plasma volume expansion of at least 700 mL. To achieve an equivalent plasma volume expansion with lactated Ringer's, nearly 3 L would be necessary (10).

Recent kinetic studies have further shown that the volume effect is about three times higher for HS and six times higher for HSD than for an equivalent amount of 0.9% saline (11-15).

## Clinical use

### Prehospital Use

The battlefield setting is plagued by long transport times and difficult logistics. Added to these problems is the fact that medics can carry only a limited amount of fluids. The conditions are quite different, in civilian settings. Typically, transport times are much shorter and logistical preparations allow ambulances and rescue personnel to carry substantial amounts of fluids. While military medical personnel most often have to deal with penetrating trauma, civilian health care professionals encounter both penetrating and blunt trauma. The importance of early intervention has been debated (16-23), but there is now consensus on performing basic life support.

In regard to intravenous infusion therapy, the mainstay of prehospital management of postinjury hypotension has traditionally been to immediately replace the lost intravascular volume with large volumes of crystalloids (24). This concept originates from controlled hemorrhage models in the 1950s and from studies on humans in the 1960s by Shires and colleagues. There was an improvement in outcome by infusing not only blood to replace the blood lost but also by using crystalloids (in amounts two to three times that of the blood lost) to replace the extracellular deficits.

"Aggressive fluid replacement" was initiated for the wounded soldiers in Vietnam. It could be argued that success of this treatment strategy in Vietnam was confounded by improved prehospital transportation (using helicopters) and surgical field care. The concept of aggressive fluid resuscitation drew criticism from researchers who were unable to identify the large extracellular deficits and from intensivists because large amounts of fluids led to pulmonary problems. The concept was eventually transferred to the streets of the United States in the 1970s. With the advent of rapid transportation systems and trauma centers, however, the type, volume, time of initiation, and even the value of prehospital fluid resuscitation has been challenged (20,21,25-28). The reluctance of certain providers to start intravenous fluid therapy in the field has been primarily associated with the lack of sufficient education among rescue personnel, the risk of rebleeding (25,29,30), and the delay of transportation to definitive care sites (25).

Although promising, clinical trials have not provided definitive data for the efficacy of hypertonic solutions. This has been due, in part, to the limited number of enrolled patients and the diversity of the underlying trauma responsible for the injuries. Wade et al (31) in 1997 conducted an extensive meta-analysis of all randomised prospective clinical trials using hypertonic 7.5% saline solutions to determine whether hypertonic solutions improved survival in patients with hypotension associated with traumatic injury. They separated the analysis into the effects of a 250-mL bolus of HS alone or in combination with HSD. The two hypertonic groups were compared with matched groups receiving a 250-mL bolus of isotonic solution. In all cases, additional isotonic solution was administered to continue the hypertonic solution. After a meticulous search for available studies, the authors found six eligible studies using HS and eight studies using HSD. A total of 615 patients were treated with HSD and 340 patients were treated with HS. All studies were randomised, included a control group, and had, as end points, survival at discharge or after 30 days. In the meta-analysis for studies using HS, there was no difference in outcome. In the HSD group, all studies (32-38) except one showed improvement in survival, but again, these differences reached statistical significance in only one study (36) and in specific subpopulations—patients with head injuries (35) and those with penetrating injuries requiring surgery (39). The mean difference of survival calculated for all studies favoring treatment with HSD over controls was 3.5% ($p = 0.07$, one-tailed). The conclusion was that HSD might be beneficial in improving survival in patients with hypotension associated with traumatic injury. Subsequently, Wade et al (31) performed a meta-analysis using individual data from six of the eight studies containing data with HSD that showed a significantly lower mortality rate for HSD in patients for whom HSD was infused as the first fluid (compared with isotonic therapy).

The lesson to be learned from these studies is that the numbers of patients in trauma trials generally have been insufficient to establish statistically significant improvement in survival and that aggregate data from these same trials are encouraging but not fully significant. Meta-analyses can be criticized (40) because there are difficulties associated with comparing the underlying studies. Since meta-analyses are not generally considered sufficient evidence for regulatory approval, HSD has not been approved for use in the United States. Interestingly, no other IV fluid or volume expander has historically been required to improve survival in order to be used in the prehospital setting. Current fluids are used mainly because they have shown volume-expansion properties.

The interest for hypertonic solution resuscitation declined when Bickell et al (25) reported that conventional fluid therapy in an urban setting with short transport times was inferior to delayed prehospital fluid resuscitation in hypotensive and penetrating trauma patients. In other countries, however, the situation has been different. Austria and Brazil were the first countries in which this type of solution was used routinely for resuscitation from severe trauma and shock. In Austria, HS is mixed with hetastarch (Osmohes—7.2% sodium chloride + 10% hetastarch 200/0.5— now replaced by Hyperhes—7.2% sodium chloride + 6% hydroxyethyl starch 200/0.62). In the past decade, more than 50,000 units have been administered safely. Sweden was the first country to register Rescueflow ®, (7.5% sodium chloride + 6% dextran 70) in 1998 (41). Finally, Germany, in 2000, approved HyperHAES, (7.2% sodium chloride + 6% hetastarch 200/0.5). In the majority of these cases, the standard amount of hypertonic solution given was 250 mL.

**Head Trauma**

Closed-head injury is a common feature of severe blunt trauma. The outcome from closed-head injury is determined primarily by the severity of the injury and the age of the patient. Additional important factors are the presence of hypoxia and hypotension (42), which make the brain vulnerable to secondary injury. Many patients with severe head injury have hypoxemia upon arrival at the hospital, with $PaO_2$ values < 60 mm Hg or pulse oximeter saturation readings < 90% (43,44). This may be caused by direct injuries to the brain, like smashing the head into the windshield of a car, or by associated injuries to the chest or by major hemorrhage. Studies have highlighted the importance of maintaining cerebral perfusion pressure (CPP) (43), which is defined as the difference between the mean arterial pressure (MAP) and the intracranial pressure (ICP): CPP = MAP - ICP

Mean arterial pressure can be measured fairly accurately in the field by using noninvasive devices, but it is not possible to measure ICP. However, when the Glasgow Coma Score (GCS) is eight or less, the prehospital rescue team should be able to assume that ICP is elevated unless there is substantial evidence to suspect that the low level of consciousness is related to reasons other than trauma or hypoxemia (45). To reach a perfusion rate higher than the necessary 70 mm Hg, the MAP would need to be maintained in the range of 90 to 105 mm Hg (assuming an ICP of 20 to 25 mm Hg) (46). Traditional fluid therapy for head-trauma patients or multiply injured patients with head trauma has consisted of crystalloids or a combination of crystalloids and colloids (47,48). Early fluid resuscitation with crystalloid solutions after head injury worsens cerebral hemodynamics (49). Despite some conflicting evidence in animal models with regard to improved perfusion pressure but worsened oxygen delivery because of hemodilution caused by using hypertonic solutions (50-54), there is much clinical evidence that HS alone or in combination with colloids is the fluid of choice for head trauma patients (31,34,45,55-60).

## Prehospital use of hypertonic saline dextran in Scandinavia (41)

The algorithm for the use of HSD in Scandinavia is shown on the pocket card in Figure 1.

- For head trauma patients with a GSC≤8 or for multiply injured patients in severe shock with or without head trauma:
  - give 250 mL of HSD over the course of 5 to 10 minutes.
- For other types of trauma, if prehospital time (from arrival at scene to admittance to the emergency room) ≥ 30 minutes

and systolic blood pressure ≤ 90 mm Hg:
- give 250 mL of HSD over the course of 5 to 10 minutes. Do not start IV fluid earlier than 15 minutes after trauma.

- For other types of trauma, if prehospital time ≤ 30 minutes: give no fluids

In all these scenarios, one should continue treatment with the standard fluid regimen (crystalloids or colloids as needed) after the administration of the hypertonic solution. It is not recommended to give Dextran-1 to prevent immune complex formation in the trauma setting. Trauma patients are obviously more protected against anaphylaxis and no such reactions were seen in any of the clinical studies (41). If the patient deteriorates, one should suspect rebleeding, stop infusion of the hypertonic solution, and give a slow crystalloid infusion (1000 mL over the course of 30 minutes) (61). Data for two urban settings are shown in Tables 1 and 2.

## Case report

10.35: Winter in Laplandia, north of the Arctic Circle. Three young skiers were walking along the railway track toward a tourist station. With weather conditions consisting of deep snow and a freezing temperature of -5°C, the track was surrounded by 5-m-high snow walls and was being cleared by a train. The skiers were award that the train was approaching, but the 25-year-old female could not escape. She slid down the embankment, was hit by the rotary snow-plow, and was pulled under the train.

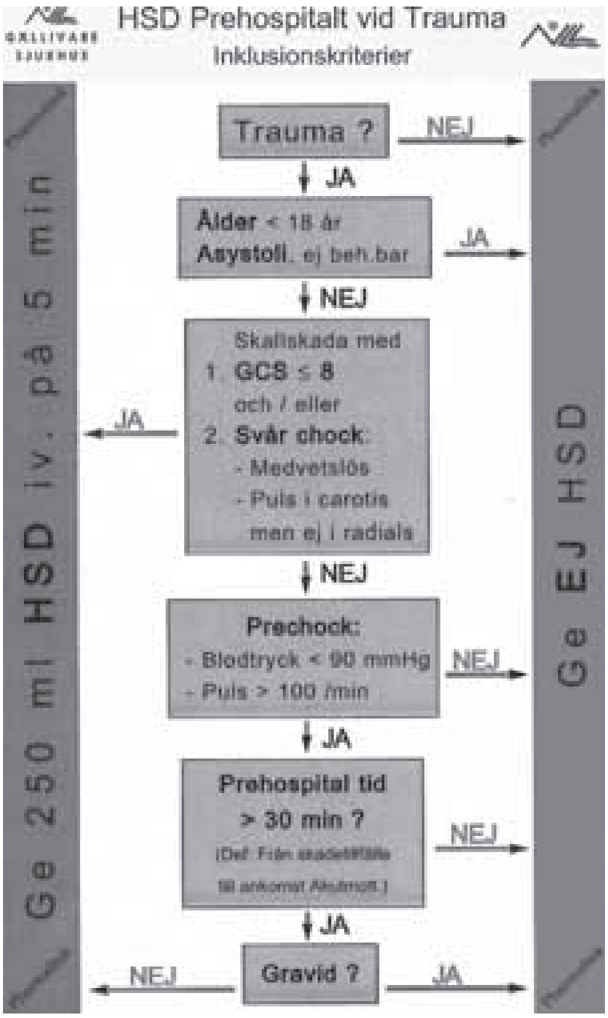


*Fig. 1. Pocket card with algorithm for the administration of hypertonic saline dextran (Rescueflow®).*

Skiing nearby was an attending anaesthesiologist/neurosurgeon. He was able to perform an initial neck stabilization and extrication with a KED device. The patient was taken on a stretcher to a nearby tourist station. She was awake but agitated, had eye deviation and possible liquorrhea. The GCS score was 10. She was hypothermic and bled profusely from wounds in the gluteus and the scalp. Systolic blood pressure (SBP) was 80 to 90 mm Hg. Heart rate (HR) was 120/minute. Respiratory rate was fairly normal. IV access was established, and an infusion of Ringer's Acetate was started (2 L) + 0.5 L Dextran 70.

11.40: The regional rescue helicopter arrived (Figure 2). At the scene, the patient deteriorated. She no longer reacted to pain stimulus and showed a flexion pattern. GCS 6, Revised Trauma Scale (RTS) 6.

12.00: An infusion of 250 mL Rescue-Flow (HSD) was started. The patient's circulation improved immediately (SBP 130, HR 60), she was intubated with ketamine, fentanyl and succinylcholine, hyperventilated, and an infusion of Propofol was started

12.45: The nearest neurosurgical facility was in Tromsö, Norway and was not reachable due to bad flying conditions to the west. Instead, the helicopter took off toward Umeå University Hospital, 1.5 hours away in a southerly direction.

*Tab. 1. Results of administering RescueFlow as the initial fluid at the scene of the accident in some trauma patients in the Stockholm area October 2000-July 2001.*

| Patient (gender-age) | Type of injury before | SBP after | SBP before | GCS after | GCS |
|---|---|---|---|---|---|
| Male-51 | Knife wound/thorax | 50 | 120 | 13 | 15 |
| Male-51 | MVA | 0 | 150 | 3 | 4 |
| Male-80 | MVA | 0 | 120 | 3 | 3 |
| Male-73 | Blunt | 80 | 90 | 15 | 15 |
| Female-65 | MVA | 50 | 80 | 8 | 13 |
| Male-82 | MVA | 50 | 100 | 9 | 13 |
| Male-45 | Fall | N/A | 160 | 14 | 14 |
| Male-55 | MVA | 0 | 90 | 3 | 3 |

SBP = systolic blood pressure; GCS = Glasgow Coma Score; MVA = motor vehicle accident. Data provided by Mona Resby, Stockholm, Sweden.

*Tab. 2. Prehospital Trauma Treatment at the Ambulance Service in Gothenburg, Sweden*

| | Patients (n) | Mean SBP (mmHg) |
|---|---|---|
| Pretreatment RescueFlow* | 25 | 84 (60-100) |
| 5 min after RescueFlow | 24 | 103 (60-150) |
| 10 min after RescueFlow | 22 | 117 (70-170) |
| 20 min after RescueFlow | 9 | 118 (70-140) |
| Arrival at Hospital | 30 | 127 (70-180) |

Results of administering RescueFlow as the initial fluid at the scene of the accident in some trauma patients in the Gothenburg area June 2000-July 2001. Of the 30 patients studied, types of injuries involved were as follows: motor vehicle accidents = 20; injuries caused by falls = 5; knife wounds = 4; and crush wounds = 1. The observed side effects noted were that 3 patients suffered from local pain at the site of the infusion.
*5 patients excluded because of immeasurable systolic blood pressure (SBP).
Data provided by Lisbeth Waagstein, Gothenburg, Sweden.

*Fig. 2. Regional Rescue Helicopter in northern Lapland, Sweden. A Sokorsky S-76 staffed by two pilots, anesthesiologist and intensive care nurse. The helicopter can transport an intubated patient with full monitoring.*

The patient's circulation during the entire 1.5-hour transport was stable with BP 130-140/65-90 mm Hg and HR 45-60/min. During one occasion, the patient displayed increased BP combined with bradycardia. On suspicion of threatening cerebral herniation, mannitol and furosemide were given.

14.20: The patient arrived at Umeå Hospital. She was pale, hypothermic (35°C) with BP 150/90 and HR 56/min. The attending emergency helicopter doctor later verified the patient's stable condition during transport despite the use of opioids, propofol infusion and positive pressure ventilation. No vasopressors were given.

At the hospital: The CT scan showed a right skull-base fracture, parietal bone fractures, bilateral frontal brain contusions, minor epidural and subdural hematomas, and advanced generalized brain edema. A stabile arch fracture on C6, compression fractures TH4-5 and fractures on transverse processes L1-2 were also noted.

Attempts were made to decrease her ICP according to the "Lund-model" – sedation, thiobarbital, metoprolol, clonidine and mild hyperventilation. As the patient's condition did not improve, she was given mannitol and taken to the OR for bilateral hemicraniectomies, hemostasis, and ventriculostomy. ICP was 40-50 mm Hg and CPP 40 mm Hg. The relatives were informed of a probable poor outcome.

Day 2: Unchanged.

Day 4: ICP 40 mm Hg. The hyperventilation treatment was discontinued. The CT scan showed an unchanged generalized edema. A minor laceration of the spleen was also seen on the CT scan, but the decision was made not to intervene.

Day 7: ICP was unchanged. The CT image of the brain was slightly better.

Day 14: A tracheostomy was performed to enhance emergence from sedation and weaning from ventilatory support.

Day 17: The patient awoke and was able to communicate fully. Her mental status and peripheral neurological status normalized.

Day 21: The patient was transported to the University Hospital in her home town—completely lucid and mentally adequate.

Some months later, plastic surgery with synthetic replacement of her large skull bones defects was performed and she was finally able to resume her education to become a teacher. Comment: This was a severe case with a very happy ending. Although the hypertonic solution was not given as the initial solution, it seems probable that it contributed to the stable transport and possibly also to the favorable outcome.

## Adverse effects

**Dose and Rate of Administration**

The reasons for using a standard dose of 4 $mL \cdot kg^{-1}$ or 250 mL of HS, HSD, or HHS seem to be based more on practicality rather than on any true physiological concept. Although it may be reasonable, even in the prehospital area, to titrate the solution toward an endpoint (62), there is still support among some clinicians for using a standard dose for reasons of simplicity. The rate of infusion should be rapid to establish the desired effects.

The greatest concern regarding rate of infusion has been derived from the hypothesis that fluid resuscitation of prehospital trauma can exacerbate uncontrolled internal hemorrhage (29,30,61,63-66). A controlled bleeding (< 1 L) is normally adequately treated by internal redistribution of fluids and thus does not require IV fluid support. A controlled bleeding > 1 L implies a situation where fluids need to be given, but if prerequisites for IV insertion are difficult and transport time is short, it is probably better to go immediately to the hospital. In the scenario where major penetrating injury to the heart or large vessels has created an uncontrolled bleeding that has not stopped, immediate transport to the proper surgical center is mandatory. Nothing else will save the patient.

Uncontrolled bleeding that has stopped is seen in some penetrating trauma cases but also occurs in cases involving blunt trauma (67). In cases like this, an increased risk of rebleeding should be considered. Since hypertonic solutions tend to increase blood pressure more than isotonic solutions, rebleeding could be a potential risk. Consequently, decreasing the rate of infusion and reducing the infused volume to patients with presumptive "uncontrolled bleeding" is recommended (62). However, this recommendation is disputed since the clinical data do not show that the administration of hypertonic solutions increases mortality in the clinical setting. It appears that internal bleeding in patients with traumatic injuries is different from that presented in animal models. Nevertheless, it seems reasonable to slow the dose from the recommended 2 to 5 minutes to 5 to 10 minutes.

Furthermore, timing of the infusion must be considered. In an urban setting with short transport times, it is most likely always best to immediately transfer the patient to the emergency room. In a longer transport scenario, it is unlikely that any IV infusion will be started earlier than 15 minutes after trauma, when the risk of rebleeding is less likely. Perhaps what can be seen from the voluminous amount of work performed on hypertonic solutions is that they seem to be very safe to give. In 35 clinical trials, over 1,400 patients received 7.5% saline (HS) with 6% dextran 70 (HSD) or hetastarch (HSS) without any complications (68-70).

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