

## Review Article

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# Hypertonic Saline in the Treatment of Hemorrhagic Shock

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## Abstract

**Context:** The present review discusses different studies about the treatment of hemorrhagic shock (HS) with hypertonic saline (HTS).

**Evidence acquisition:** We have searched the title in the most popular databases containing recent meta-analysis or randomized clinical trials (RCTs).

**Results:** We introduce the hemodynamic effects and mechanisms of action of HTS in HS. Evidence in this field shows controversial results. There are some data supporting the potential benefits of HTS infusion in HS. The goal of research in this field is to identify the best therapy in HS with the least mortality.

**Conclusion:** Our conclusion shows that although HTS can decrease inflammatory response during HS, it can attenuate hypercoagulability and cause complications. There are no data supporting less mortality while treatment with HTS versus other fluids in HS.

**Key words:** Evidence-based emergency medicine; Saline solution, hypertonic; Shock, hemorrhagic; Patient care management

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## CONTEXT

Is hypertonic saline effective in the treatment of hemorrhagic shock? Is it capable of reducing mortality in hemorrhagic shock?

## EVIDENCE ACQUISITION

We searched "hypertonic saline in the treatment of hemorrhagic shock" in the most popular databases including MEDLINE, the Cochrane Collaboration Database, the Center for Research Support, TRIP Database, PubMed, Web of Science, and Google Scholar. We reviewed the most cited articles related to our study. Patient-oriented evidence that matters (POEM) was used to support key clinical recommendations rather than disease-oriented evidence (DOE), for example studies dealing with changes in morbidity, mortality, or quality of life was the main structure of our research rather than studies dealing with mechanistic explanations or surrogate end points, such as changes in laboratory tests. Studies of patients likely to be representative of those in primary care practices, rather than subspecialty referral centers were reviewed. We tried to ensure that all recommendations were based on the highest level of evidence available. In particular, we tried to find the answer in an authoritative compendium of evidence based reviews or at least tried to find a meta-analysis or

well-designed randomized controlled trial (RCT) to support it. Most of the studies used in this review are published during the last 20 years.

## RESULTS

Rapid reduction in blood volume is the main cause of hemorrhagic shock (HS). Evidence shows that circulatory shock has a high mortality rate. Especially when talking about trauma, severe hemorrhage after injury carries a mortality rate of 30-40% and almost 50% of this occurs within 24 hours of injury (1-4). HS is divided into four stages, from mild hemodynamic changes to severe multi-organ failure and acidemia. Depending on the severity of blood loss, the disease manifestations will appear (5). Neutrophils play the most significant role here, binding to tissue endothelium and causing capillary leaks that characterize acute respiratory distress syndrome, hepatic or renal failures. Inflammatory cytokines are liberated during resuscitation, causing membrane injury in many cells (6).

Standard treatment for HS has historically been consisted of rapidly infusing isotonic crystalloid. Colloids can be used as well, but they have no effect on morbidity or mortality (7). Numerous studies have suggested that small volume resuscitation with hypertonic saline (HTS) can improve

hemodynamics and oxygenation in HS (8-10). HTS (7.5% saline) has been proposed as a potential crystalloid alternative because it has omitted the tissue edema effects of isotonic crystalloid solutions. HTS has anti-inflammatory and immunomodulatory effects and it can decrease lung and intestinal injury in animal models of HS (11). Many studies have suggested the addition of dextran to HTS, aimed at sustaining the hemodynamic effect of it. The volume of HTS solution given during resuscitation should be limited due to the potential risk of hypernatremia (12).

As mentioned before, laboratory studies have suggested that small volume resuscitation with HTS may be more effective in HS in improving central hemodynamics, organ perfusion, and oxygen delivery than conventional crystalloid solutions (13-15). Furthermore, it is confirmed that HTS can limit the inflammatory response, prevent lung and liver injury, as well as improve intestinal blood flow (16-19). Shi et al. in 2002 indicated that small volume resuscitation using HTS limited lung and gut injury after traumatic HS compared to traditional crystalloid resuscitation (20). Gut ischemia induced by HS can mediate lung injury by neutrophil and cytokines activation, and the protective role of HTS appears to be related to prohibition of this neutrophil activation (18, 21). Oliveira et al. in 2002 published a clinical review introducing the main mechanisms of action of HTS: "instantaneous mobilization of fluids from intracellular to extracellular compartments by the osmotic gradient produced by HSS; increased myocardial contractility; reduced endothelial and tissue edema, improvement in microcirculation; improved blood viscosity due to hemodilution; and immunomodulation" (22). Pascual et al. in 2002 showed that HTS diminished neutrophil rolling and adherence to endothelium and thus led to less vascular leakage in HS. They suggested more usage of HTS in the resuscitation of HS in order to decrease morbidity and mortality (23). There are studies demonstrating the benefits of administering hypertonic fluid to trauma patients (24-27). In some animal studies like Bahrami et al. study of mice, it was found that resuscitation with HTS decreased the inflammatory process but not the mortality (28). Krausz et al. in 2006 compared lactated ringer's solution with HTS and said that HTS was associated with less blood loss and better survival in rats (29).

Nowadays there are large multicentric randomized human clinical trials that confirm safety and efficiency of HTS resuscitation, but they have failed

to show a definite survival advantage over standard isotonic resuscitation (30-33). A recent multicenter trial conducted in the prehospital setting showed that initial resuscitation with HTS or HTS and dextran, compared with normal saline, did not result in superior 28-day survival (34). Randomized controlled trials have not found a clinically significant difference in outcome when HTS was compared with conventional isotonic fluids (35).

Studies of humans have shown that excessive fluid therapy can lead to coagulopathy, increased acidosis, hypothermia, abdominal compartment syndrome, elevated intracranial pressure, and immunologic disorders (27, 36-38). Fluid therapy is supposed to increase the mortality rate in such conditions (39). Saeedi et al. in 2013 compared HTS treatment to normal saline and no fluid resuscitation in HS in goats. They concluded that the group with no fluid resuscitation had considerably better results for all features of uncontrolled HS, such as pH, hemoglobin level, and mean arterial pressure. They found that HTS might not be a suitable option in HS (40). Gross et al. studied the safety of HTS in HS following abdominal trauma in rats in 1988 and reported that HTS led to early mortality, severe bleeding, and low arterial blood pressure (41). In the study of Krausz et al. on rats in 1992, it was determined that early (within 15 min) treatment with HTS in traumatic HS, could result in increased bleeding, hypotension, and early death. On the other hand, this danger would not happen if the infusion was started 30 min or later (42).

## Discussion

The potential beneficial effect of small volume resuscitation with HTS has been extensively studied in HS. The anti-inflammatory effect of HTS on neutrophils, oxidative burst, and cytokine release has been established in various animal models (17-22). These effects have been said to reduce the excessive proinflammatory action thus reducing the degree of damage to multiple organs. Hemodynamic effects have been widely studied, but recent data have failed to demonstrate its efficacy in reducing mortality. There are few studies discussing against treatment with extra fluids like HTS at the accident scene in an uncontrolled HS setting, because this can lead to coagulopathy, increased acidosis, hypothermia, abdominal compartment syndrome, elevated intracranial pressure, and immunologic disorders. The evidence here says HTS therapy might increase the mortality rate in such conditions (36-39).

Further studies and larger randomized clinical trials are required to confirm either effectiveness or harmfulness of UHS in the treatment of HS, where the administration of fluids is detrimental. There is still lack of studies with high level of evidence about determining the physiologic reasons that support administrating HTS in HS. A therapy that simultaneously blocks the vicious cycle happening during the treatment phase of HS, and improves hemodynamics with greater degree as soon as possible, will probably have an enormous impact on our ability to manage this condition. HTS, in general, seems to fail being the best option here.

#### CONCLUSIONS

Our conclusion shows that although HTS can decrease inflammatory response during HS, it can attenuate hypercoagulability and cause complications. There are no data supporting less

mortality while treatment with HTS versus other fluids in HS.

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#### AUTHORS' CONTRIBUTION

All authors passed four criteria for authorship contribution based on recommendations of the International Committee of Medical Journal Editors.

#### Conflict of INTEREST

None declared.

#### FUNDING

None declared.

#### REFERENCES

1. Young PP, Cotton BA, Goodnough LT. Massive transfusion protocols for patients with substantial hemorrhage. *Transfus Med Rev.* 2011;25(4):293-303.
2. Kauvar DS, Lefering R, Wade CE. Impact of hemorrhage on trauma outcome: an overview of epidemiology, clinical presentations, and therapeutic considerations. *J Trauma.* 2006;60(6 Suppl):S3-11.
3. Paydar S, Kabiri H, Barhaghtalab M, Ghaffarpasand F, Safari S, Baratloo A. Hemodynamic Changes Following Routine Fluid Resuscitation in Patients With Blunt Trauma. *Trauma Mon.* 2016;21(4):e23682.
4. Bagheri-Hariri S, Yekesadat M, Farahmand S, Arbab M, Sedaghat M, Shahlafar N, et al. The impact of using RUSH protocol for diagnosing the type of unknown shock in the emergency department. *Emerg Radiol.* 2015;22(5):517-20.
5. Rahim-Taleghani S, Fatemi A, Alavi-Moghaddam M, Shojaee M, Abushouk AI, Forouzanfar MM, et al. Correlation of central venous pressure with venous blood gas analysis parameters; a diagnostic study. *Turk J Emerg Med.* 2017;17(1):7-11.
6. Jones AE KJ. shock. In: Marx JA, editor. *Rosen's emergency medicine.* 1: ELSEVIER; 2014. p. 67-74.
7. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med.* 2004;350(22):2247-56.
8. Wade CE, Hannon JP, Bossone CA, Hunt MM, Loveday JA, Coppes R, et al. Resuscitation of conscious pigs following hemorrhage: comparative efficacy of small-volume resuscitation. *Circ Shock.* 1989;29(3):193-204.
9. Maningas PA. Resuscitation with 7.5% NaCl in 6% dextran-70 during hemorrhagic shock in swine: effects on organ blood flow. *Crit Care Med.* 1987;15(12):1121-6.
10. Traverso LW, Bellamy RF, Hollenbach SJ, Witcher LD. Hypertonic sodium chloride solutions: effect on hemodynamics and survival after hemorrhage in swine. *J Trauma.* 1987;27(1):32-9.
11. Kobayashi L, Costantini TW, Coimbra R. Hypovolemic shock resuscitation. *Surg Clin North Am.* 2012;92(6):1403-23.
12. Somand DM WK. Fluid and blood resuscitation in traumatic shock. In: Tintinalli JE, editor. *Tintinallis emergency medicine.* 1: Mc Grow Hill; 2016. p. 69-74.
13. Nerlich M, Gunther R, Demling RH. Resuscitation from hemorrhagic shock with hypertonic saline or lactated Ringer's (effect on the pulmonary and systemic microcirculations). *Circ Shock.* 1983;10(2):179-88.

14. Gunnar W, Jonasson O, Merlotti G, Stone J, Barrett J. Head injury and hemorrhagic shock: studies of the blood brain barrier and intracranial pressure after resuscitation with normal saline solution, 3% saline solution, and dextran-40. *Surgery*. 1988;103(4):398-407.
15. Nakayama S, Sibley L, Gunther RA, Holcroft JW, Kramer GC. Small-volume resuscitation with hypertonic saline (2,400 mOsm/liter) during hemorrhagic shock. *Circ Shock*. 1984;13(2):149-59.
16. Diebel LN, Tyburski JG, Dulchavsky SA. Effect of hypertonic saline solution and dextran on ventricular blood flow and heart-lung interaction after hemorrhagic shock. *Surgery*. 1998;124(4):642-9.
17. Corso CO, Okamoto S, Leiderer R, Messmer K. Resuscitation with hypertonic saline dextran reduces endothelial cell swelling and improves hepatic microvascular perfusion and function after hemorrhagic shock. *J Surg Res*. 1998;80(2):210-20.
18. Angle N, Hoyt DB, Coimbra R, Liu F, Herdon-Remelius C, Loomis W, et al. Hypertonic saline resuscitation diminishes lung injury by suppressing neutrophil activation after hemorrhagic shock. *Shock*. 1998;9(3):164-70.
19. Coimbra R, Junger WG, Hoyt DB, Liu FC, Loomis WH, Evers MF. Hypertonic saline resuscitation restores hemorrhage-induced immunosuppression by decreasing prostaglandin E2 and interleukin-4 production. *J Surg Res*. 1996;64(2):203-9.
20. Shi HP, Deitch EA, Da Xu Z, Lu Q, Hauser CJ. Hypertonic saline improves intestinal mucosa barrier function and lung injury after trauma-hemorrhagic shock. *Shock*. 2002;17(6):496-501.
21. Koike K, Moore FA, Moore EE, Read RA, Carl VS, Banerjee A. Gut ischemia mediates lung injury by a xanthine oxidase-dependent neutrophil mechanism. *J Surg Res*. 1993;54(5):469-73.
22. Oliveira RP, Velasco I, Soriano FG, Friedman G. Clinical review: Hypertonic saline resuscitation in sepsis. *Crit Care*. 2002;6(5):418-23.
23. Pascual JL, Ferri LE, Seely AJ, Campisi G, Chaudhury P, Giannias B, et al. Hypertonic saline resuscitation of hemorrhagic shock diminishes neutrophil rolling and adherence to endothelium and reduces in vivo vascular leakage. *Ann Surg*. 2002;236(5):634-42.
24. van den Elsen MJ, Leenen LP, Kesecioglu J. Hemodynamic support of the trauma patient. *Curr Opin Anaesthesiol*. 2010;23(2):269-75.
25. Ghafari MH, Moosavizadeh SA, Moharari RS, Khashayar P. Hypertonic saline 5% vs. lactated ringer for resuscitating patients in hemorrhagic shock. *Middle East J Anaesthesiol*. 2008;19(6):1337-47.
26. Bender R, Breil M, Heister U, Dahmen A, Hoeft A, Krep H, et al. Hypertonic saline during CPR: Feasibility and safety of a new protocol of fluid management during resuscitation. *Resuscitation*. 2007;72(1):74-81.
27. Sampalis JS, Tamim H, Denis R, Boukas S, Ruest SA, Nikolis A, et al. Ineffectiveness of on-site intravenous lines: is prehospital time the culprit? *J Trauma*. 1997;43(4):608-15; discussion 15-7.
28. Bahrami S, Zimmermann K, Szelenyi Z, Hamar J, Scheiflinger F, Redl H, et al. Small-volume fluid resuscitation with hypertonic saline prevents inflammation but not mortality in a rat model of hemorrhagic shock. *Shock*. 2006;25(3):283-9.
29. Krausz MM, Semenikhina L, Hirsh M. Lactated Ringer's solution and hypertonic saline improve survival in uncontrolled hemorrhagic shock in female rats in metestrus. *J Surg Res*. 2006;132(1):23-31.
30. Mattox KL, Maningas PA, Moore EE, Mateer JR, Marx JA, Aprahamian C, et al. Prehospital hypertonic saline/dextran infusion for post-traumatic hypotension. The U.S.A. Multicenter Trial. *Ann Surg*. 1991;213(5):482-91.
31. Velasco IT, Pontieri V, Rocha e Silva M, Jr., Lopes OU. Hyperosmotic NaCl and severe hemorrhagic shock. *Am J Physiol*. 1980;239(5):H664-73.
32. Kreimeier U, Thiel M, Peter K, Messmer K. Small-volume hyperosmolar resuscitation. *Acta Anaesthesiol Scand Suppl*. 1997;111:302-6.
33. Wade CE, Kramer GC, Grady JJ, Fabian TC, Younes RN. Efficacy of hypertonic 7.5% saline and 6% dextran-70 in treating trauma: a meta-analysis of controlled clinical studies. *Surgery*. 1997;122(3):609-16.

34. Bulger EM, May S, Kerby JD, Emerson S, Stiell IG, Schreiber MA, et al. Out-of-hospital hypertonic resuscitation after traumatic hypovolemic shock: a randomized, placebo controlled trial. *Ann Surg.* 2011;253(3):431-41.
35. Wang JW, Li JP, Song YL, Tan K, Wang Y, Li T, et al. Hypertonic saline in the traumatic hypovolemic shock: meta-analysis. *J Surg Res.* 2014;191(2):448-54.
36. Turner JNJ, Webber L, Cox H, Dixon S, Yates D. A randomized controlled trial of prehospital intravenous fluid replacement therapy in serious trauma. *Health Technol Assess* 2000;4:1-57.
37. Yaghoubian A, Lewis RJ, Putnam B, De Virgilio C. Reanalysis of prehospital intravenous fluid administration in patients with penetrating truncal injury and field hypotension. *Am Surg.* 2007;73(10):1027-30.
38. Watters JM, Tieu BH, Differding JA, Muller PJ, Schreiber MA. A single bolus of 3% hypertonic saline with 6% dextran provides optimal initial resuscitation after uncontrolled hemorrhagic shock. *J Trauma.* 2006;61(1):75-81.
39. Kaweski S, Sise M, Virgilio R. The effect of prehospital fluids on survival in trauma patients. *J Trauma.* 1990;30(10):1215-8.
40. Saeedi M, HajiseyedJavadi H, Shams-Vahdati S, Eslami V, Mokhtarpour M, Momeni M, et al. Hypertonic saline, normal saline or neither: which is best for uncontrolled hemorrhagic shock? An experimental study in goats. *Ulus Travma Acil Cerr Derg* 2013;19(6):500-6.
41. Gross D, Landau E, Assalia A, Krausz M. Is hypertonic saline resuscitation safe in "Uncontrolled" hemorrhagic shock? *J Trauma.* 1988;28(6):751-6.
42. Krausz MM, Landau EH, Klin B, Gross D. Hypertonic saline treatment of uncontrolled hemorrhagic shock at different periods from bleeding. *Arch Surg.* 1992;127(1):93-6.