

# Resuscitation of Hypovolemic Emergency Department Patients: Hypertonic or Isotonic Crystalloids?

## EBEM Commentator Contact

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## SYSTEMATIC REVIEW SOURCE

This is a systematic review abstract, a regular feature of the *Annals* Evidence Based Emergency Medicine (EBEM) series. Each features an abstract of a systematic review from the Cochrane Database of Systematic Reviews and a commentary by an emergency physician knowledgeable in the subject area. The source for this systematic review abstract is: Bunn F, Roberts I, Tasker R, et al. Hypertonic versus near isotonic crystalloid for fluid resuscitation in critically ill patients.

*Cochrane Database Syst Rev.* 2004;(3):CD002045. DOI: 10.1002/14651858.CD002045.pub2. The *Annals*' EBEM editors assisted in the preparation of the abstract of this Cochrane review, as well as the Evidence-Based Medicine Teaching Points.

## OBJECTIVE

The objective of this review was to determine whether hypertonic crystalloid decreases mortality in patients with hypovolemia. This systematic review analyzes randomized trials comparing hypertonic and isotonic crystalloid fluids in hypovolemic patients with trauma or burns or in those undergoing surgery.

## DATA SOURCES

The authors searched CENTRAL, which includes the Cochrane Controlled Trials Register, the National Research Register (a specialized register of the Cochrane Injuries Group), MEDLINE (up to March 2004), and EMBASE (up to March 2004). Reference lists of all articles identified were also checked. The original search was conducted through 1999 and subsequently updated in November 2001 and March 2004.

Randomized controlled trials that compared hypertonic to isotonic and near isotonic crystalloid fluids were assessed. Trials of hypertonic crystalloid with add-on colloid were excluded. The primary outcome was all-cause mortality and disability assessed at the end of the follow-up period for each trial. The search identified 18 randomized controlled trials; however, 4 of these trials did not provide data on the outcomes specified in the review and were therefore not included.

## DATA EXTRACTION AND ANALYSIS

Two reviewers independently extracted information on study quality, number of randomized participants, type of participants, and the interventions. Mortality data expressed as the relative risk (RR) of death and 95% confidence intervals (CIs) were calculated for each trial. A  $\chi^2$  test was used to examine the statistical evidence of heterogeneity. The results obtained from the different trials were not pooled because of the clinical heterogeneity; however, relative risks of each subgroup (trauma, burn, surgery) were pooled separately, and 95% CIs were calculated with a fixed-effects model.

## MAIN RESULTS

Fourteen trials met the reviewers' inclusion criteria (Table). Of the 14, patients with burns were assessed in 3 (n=72), patients undergoing surgery in 5 (n=230), and trauma patients in 6 (n=654). Eleven trials compared hypertonic saline solution versus Ringer's lactate, with the remaining comparing hypertonic saline solution with normal saline solution. Concealment of allocation was adequate in 5, inadequate in 3, and unclear in 6 trials. Five trials reported blinding of staff to the therapy used (Table).

The use of hypertonic crystalloids did not prevent deaths for patients with burns (RR=1.49; 95% CI 0.56 to 3.95) or trauma (RR=0.84; 95% CI 0.69 to 1.04), or those undergoing surgery (RR=0.51; 95% CI 0.09 to 2.73). In one trial that provided data on disability (trauma patients; Cooper 2004), there was no difference in poor outcome (RR=1.00; 95% CI 0.82 to 1.22).

## CONCLUSIONS

According to the 14 trials included in this review, there is insufficient evidence to conclude that hypertonic saline solution is superior to isotonic crystalloid for the resuscitation of patients with trauma or burns or of those undergoing surgery.

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**Table.** Study characteristics and relative risk of death associated with the use of hypertonic crystalloids versus isotonic crystalloids in critically ill hypovolemic patients.

Study	Population	Methods	Follow-up	Mortality, Relative Risk (95% CI)
Jelenko et al, 1978	12 patients with $\geq 20\%$ BSA burns; hypertonic saline solution vs Ringer's lactate	RCT	Unclear	IT=2/7 HT=1/5 RR=0.7 (0.09-5.76)
Caldwell et al, 1979	20 children with $\geq 30\%$ BSA burns; hypertonic lactated Ringer's vs Ringer's lactate	Alt. assignments, Not blinded	Unclear	IT=1/20 HT=2/17 RR=2.35 (0.23-23.75)
Shackford et al, 1983	58 patients undergoing aortic reconstruction; hypertonic saline solution lactate vs Ringer's lactate	RCT	3 days	IT=1/28 HT=1/30 RR=0.93 (0.06-14.22)
Shackford et al, 1987	52 patients undergoing aortic reconstruction; hypertonic saline solution lactate vs Ringer's lactate	RCT	3 days	No deaths in either group
Cross, et al, 1989	20 postoperative CABG patients; 1.8% hypertonic saline solution vs normal saline solution	RCT, double blinded	24 h	No deaths in either group
Vassar et al, 1990	59 trauma patients with SBP $< 80$ ; 7.5% saline solution vs Ringer's lactate	RCT, double blinded	Until discharge	IT=7/27 HT=11/32 RR=1.33 (0.60-2.94)
Croft et al, 1992	28 patients with major intra-ab surgery; hypertonic saline solution vs Ringer's Lactate	RCT	72 h	IT=1/15 HT=0/13 RR=0.38 (0.02-8.62)
Younes et al, 1992	70 ED admissions with SBP $< 80$ ; 7.5% saline solution vs normal saline solution	RCT, double blinded	Until discharge	IT=8/35 HT=7/35 RR=0.88 (0.36-2.15)
Vassar et al, 1993a	169 out-of-hospital trauma patients with SBP $< 90$ ; 7.5% saline solution vs normal saline solution	RCT, double blinded	Until discharge	IT=14/84 HT=11/85 RR=0.78 (0.37-1.61)
Vassar et al, 1993b	95 out-of-hospital trauma patients with SBP $< 100$ and transported by helicopter to ED; 7.5% saline solution vs Ringer's lactate	RCT, double blinded	Until discharge	IT=23/45 HT=20/50 RR=0.78 (0.5-1.22)
Bortolani et al, 1996	40 patients with 30% BSA burns; hypertonic lactated saline solution vs Ringer's lactate	RCT	Unclear	IT=3/20 HT=5/20 RR=1.67 (0.46-6.06)
Simma et al, 1998	32 children ( $< 16$ y/o) with head injury and GCS $< 8$ ; hypertonic saline solution vs Ringer's lactate	RCT	Until discharge	IT=0/15 HT=2/17 RR=0.18 (0.01-3.43)
Jarvela et al, 2002	72 postoperative CABG patients; 7.5% hypertonic saline solution vs normal saline solution	RCT	First postoperative morning	No deaths in either group
Cooper et al, 2004	229 patients with TBI; 7.5% hypertonic saline solution vs Ringer's lactate	RCT, double blinded	6 mo	IT=60/113 HT=51/113 RR=0.85 (0.65-1.11)

BSA, Body surface area; RCT, randomized control trial; IT, isotonic group; HT, hypertonic group; Alt., alternating; CABG, coronary artery bypass graft; SBP, systolic blood pressure; GCS, Glasgow Coma Scale; TBI, traumatic brain injury.

## COMMENTARY: CLINICAL IMPLICATION

The cornerstone of treatment in hypovolemic patients treated in the emergency department (ED) is to replace the lost volume until the source of hypovolemia (eg, hemorrhage) is controlled. The rapid restoration of intravascular volume, tissue perfusion, and oxygen delivery is essential to patient survival and prevention of multiple organ failure. Traditionally, fluid

replacement has been accomplished by isotonic crystalloids and, if necessary, supplementation with colloids or blood transfusions. In the setting of large-volume replacement with isotonic fluid, however, rapid extravascular migration of fluid, development of interstitial edema, and inadequate efficacy in restoring blood volume has always been a concern.<sup>1</sup> An alternative approach substitutes hypertonic for isotonic fluid.

Hypertonic fluids create an osmotic gradient across the vascular space, drawing fluid from the interstitium and intracellular compartment into the vessels. Hypertonic fluids have been shown to augment cardiac output, increase myocardial contractility, reduce tissue and endothelial edema, improve microcirculation and blood viscosity, and modulate the inflammatory response.<sup>2,3</sup> Clinical ramifications of such effects include a decrease in the total amount of fluid required for resuscitation, a decrease in gut and wound edema, an increase in renal blood flow and urine output, and a lower susceptibility to sepsis in patients with hemorrhagic shock.<sup>4-7</sup>

Although hypertonic fluids have many attractive qualities, they also carry potential complications. Hypertonic saline solution can result in a rapid increase of plasma osmolality and electrolyte imbalances, specifically, hypernatremia, hypokalemia, and hyperchloridemia.<sup>8</sup> In susceptible patients, these alterations can produce fatal effects such as central pontine myelinolysis, arrhythmias, and metabolic acidosis.<sup>9,10</sup> Furthermore, in patients with a non-tamponaded injury, hypertonic saline solution can exacerbate bleeding.<sup>11</sup> Although theoretically hypertonic crystalloids have many advantages over isotonic fluids in management of hypovolemia, these advantages are only sensible if using them improves clinically relevant outcomes such as mortality.

This Cochrane review investigates the effect of hypertonic crystalloids on mortality in patients with hypovolemia in the setting of burns, surgery, and trauma. The authors used a comprehensive search strategy to avoid publication bias and independently reviewed the studies to avoid selection bias. Unfortunately, most of the trials that met the inclusion criteria for this review were small or provided wide CIs for the reported results. Review of the available trials provided insufficient evidence to support the use of hypertonic crystalloids.

Since the last update of this systematic review in March 2004, there have been few additional studies on the topic. Several of these studies have focused on hypertonic solutions with added colloids and are outside the scope of our review. One applicable randomized control trial published in 2008 failed to show any mortality benefit from using hypertonic saline solution over crystalloid fluids.<sup>12</sup> Fang et al<sup>12</sup> studied 94 severe sepsis patients with hypotension and randomized them to hypertonic saline solution, normal saline solution, or sodium bicarbonate. The mean arterial pressure and cardiac output did not differ between the 3 groups, and the study found no mortality benefit of any solutions at 8 hours or at 28 days.

## TAKE-HOME MESSAGE

Although the potential benefits of using hypertonic saline solution during resuscitation are enticing, randomized controlled trials have failed to demonstrate the superiority of hypertonic over isotonic saline solution in decreasing mortality rate in hypovolemic patients. Until further evidence becomes available, clinicians in the ED should use isotonic saline solution as the resuscitation fluid of choice.

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## EBEM TEACHING POINT

Among a variety of ways of reporting research results, the *P* value represents a commonly used measure of the significance of comparisons within studies. The *P* value is a statistical measure based on the probability that the results are due to chance. The *P* value is generated from the null hypothesis, which assumes that there are no observed differences between groups within a study (for example, between the treatment with hypertonic and isotonic saline solution). Arbitrarily, but by convention, a *P* value less than .05 is considered to be statistically significant (ie, there is less than a 1 in 20 probability that the result is due to chance alone). Small *P* values (<.05) lead us to reject the null hypothesis. By rejecting the null hypothesis, researchers claim that differences between interventions exist for the reported outcomes and these are unlikely to be due to chance alone. Therefore, the result is considered *statistically significant*.

CIs, on the other hand, are generally used to describe the precision of the point estimate of a treatment effect; however, they can also be used to reflect statistical significance. By convention, CIs are calculated at a level of 95%; however, 99% CIs are occasionally reported. For the 95% CI, the high and low values represent the values where the true value (mean, proportion, etc) would fall 95 times out of 100 if the experiment were repeated indefinitely. To determine statistical significance based on the CI, one needs to examine whether a value of “no difference” is included in the interval. For studies measuring an effect that involves subtraction, the value of “no difference” is zero. For studies measuring an effect involving a ratio, the value of “no difference” is 1. If the CI includes this “no difference” value, then the results are considered not statistically significant.

In addition to providing information on significance, CIs also inform us about the precision of the treatment effect. They provide a range of plausible results. A narrow CI has a small range of possible effect sizes, and typically this is related to large sample sizes (although with continuous outcomes, it could also be generated by small standard deviations). Wide CIs represent an imprecise range of effect sizes. This is typically related to small sample sizes (and large standard deviations in continuous outcomes). For example, in this review hypertonic crystalloids did not prevent deaths for patients with burns; however, the 95% CIs for the relative risk of death were wide (0.56 to 3.95). This represents a range from potentially *protective* (RR=0.56) to *deleterious* (RR=3.95) effect with the use of hypertonic saline solution. Clinicians would be inclined to use any treatment that reduces mortality, so these results need to be replicated to reduce the CIs around the point estimate.

Both *P* values and CIs convey information about the statistical significance of a result. CIs are now preferred, however, because they provide additional information about the precision of the results. Regardless of which method is used, it is important to remember that neither provides information on the clinical significance of the effects observed or whether the observed results are correct.<sup>13</sup>

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