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Hypertonic saline in the traumatic hypovolemic shock: meta-analysis

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ABSTRACT

Background: A wealth of evidence from animal experiments has indicated that hypertonic saline (HS) maybe a better choice for fluid resuscitation in traumatic hypovolemic shock in comparison with conventional isotonic saline. However, the results of several clinical trials raised controversies on the superiority of fluid resuscitation with HS. This meta-analysis was performed to better understand the efficacy of HS in patients with traumatic hypovolemic shock comparing with isotonic saline.

Materials and methods: According to the search strategy, we searched the PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials, which was completed on October 2013. After literature searching, two investigators independently performed the literature screening, assessment of quality of the included trials, and data extraction. Disagreements were resolved by consensus or by a third investigator if needed. The outcomes included mortality, blood pressure, fluid requirement, and serum sodium.

Results: Six randomized controlled trials were included in the meta-analysis. The pooled risk ratio for mortality at discharge was 0.96 (95% confidence interval [CI], 0.82–1.14), whereas the pooled mean difference for the change in systolic blood pressure from baseline and the level of serum sodium after infusion was 6.47 (95% CI, 1.31–11.63) and 7.94 (95% CI, 7.38–8.51), respectively. Current data were insufficient to evaluate the effect of HS on the fluid requirement for the resuscitation.

Conclusions: The present meta-analysis was unable to demonstrate a clinically important improvement in mortality after the HS administration. Moreover, we observed HS administration maybe accompanied with significant increase in blood pressure and serum sodium.

1. Introduction

As a leading cause of death and morbidity worldwide, hypovolemic shock resulting from traumatic injury has received considerable attention in the clinical practice [1]. Unfortunately, although the deleterious effects of traumatic hypovolemic shock have long been recognized and intensive researches have been carried out in the area, the strategies of fluid resuscitation in the patients with traumatic hypovolemic shock remain controversial [2].

It is well known that conventional fluid resuscitation protocols posit an important role of isotonic saline such as

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normal saline and lactated ringers in the treatment of patients with traumatic hypovolemic shock [3]. According to the Advanced Trauma Life Support guidelines, aggressive fluid resuscitation with up to two or more liters of isotonic saline is suggested [4]. However, the side effects of large-volume isotonic saline are also concerned. Since the intravascular fluid can leak into the interstitial space because of the increased capillary permeability in the setting of trauma, large-volume resuscitation may cause "water-logging" effects and cell swelling, which can result in organ dysfunction and ultimate death [5]. Furthermore, it is reported that the administration of large-volume isotonic saline is associated with significantly increased inflammatory response [6], whereas the latter also can exaggerate the "water-logging" effects. These issues have led to increasing enthusiasm about the development of alternative approaches in fluid resuscitation [7].

In recent years, hypertonic saline (HS) has emerged as an attractive alternative in fluid management in a variety of clinical practices including traumatic hypovolemic shock [8]. A wealth of evidence from animal experiments has indicated that treatment with small volume of HS is able to effectively restore the hemodynamic stability and decrease the mortality in the models of traumatic hypovolemic shock [9]. The protective mechanism of HS may mainly involve its ability to shift fluid from interstitial and intracellular space to intravascular space by establishing the osmotic gradient across the vessel and cell [10]. Moreover, HS can modulate the overwhelming inflammatory response after trauma, which contributes to disturb the vicious inflammation cascades [11]. Previous several clinical trials have also shown that small-volume resuscitation with HS maybe superior to conventional fluid resuscitation with isotonic saline [8,9]. However, the impact of these trials on clinical practices has been limited because of various reasons such as small sample size and different research endpoints. Therefore, to better understand the efficacy of HS in patients with traumatic hypovolemic shock, we performed this meta-analysis of randomized controlled trials (RCTs) in the area.

2. Materials and methods

2.1. Study identification

We performed a systematic review of the published literature to identify all randomized controlled clinical trials in which HS has been used for the treatment of patients with traumatic hypovolemic shock in comparison with isotonic saline. Studies that were either not RCTs or that did not directly involve the effects of HS on the treatment of patients with traumatic hypovolemic shock were eliminated.

2.2. Search strategy

Based on the text words or MeSH terms such as "saline solution, hypertonic," "hypertonic saline," "wounds and injuries," "trauma," "hypovolemia," and "shock," an electronic search for relevant articles was conducted on PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) without language limitation. We also complemented this by using the *Related Articles* function on PubMed and searching the reference lists of relevant articles. For full details of the search strategy, see Supplementary Data File 1. The search was performed independently by two investigators and was completed on October 2013.

2.3. Literature screening

After literature search, two investigators independently reviewed the titles and abstracts of all studies identified and excluded those that were obviously irrelevant. The trials that totally did not involve the clinical practice of HS alone were excluded in the final analysis. The full articles of the remaining studies were then retrieved and independently reviewed by them using a structured form to determine eligibility and extract data. When the trials included multiple arms of patients with the treatment of HS alone or HS with colloids, the data from the patients with the treatment of HS alone without colloids were extracted. Disagreements were resolved by consensus or by a third investigator if needed. We contacted study authors for clarifications and further information as necessary.

2.4. Quality assessment

The quality of eligible studies was formally evaluated by using the Cochrane Collaboration's tool for assessing the risk of bias in RCTs. Specifically, studies were judged on (1) the adequacy of the random sequence generation, allocation concealment, and blinding; (2) the completeness of outcome data; (3) the possibility of selective outcome reporting; and (4) the existence of other potential sources of bias.

2.5. Data extraction

We extracted the following data from each study: its design, objective, number of patients, method of delivery, timing of measurements, main results of the study, and follow-up results. The primary outcome assessed was mortality at discharge. The secondary outcomes included changes of the systolic blood pressure after the HS administration from baseline, fluid requirements in the research period scheduled for each trial, and the level of serum sodium after the administration of HS.

2.6. Statistical analysis

A homogeneity-based method of meta-analysis was performed using Review Manager for Windows(version 5.2, The Cochrane Collaboration and Update Software) for prospective RCTs. Homogeneity between studies was assessed by means of standard Cochran Q and I^2 statistics. Homogeneity was prespecified as $P > 0.10$ or $I^2 < 50\%$. A fixed-effect model was used to merge the values of relative risk and mean difference and to estimate the overall effect size when the homogeneity between studies was reached. Otherwise, a random-effect model was used in the statistics. Overall effect, risk ratio, mean difference, and 95% confidence interval (CI) were presented in the present systematic review.