Hypertonic saline versus mannitol for the treatment of elevated intracranial pressure: A meta-analysis of randomized clinical trials*

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Objectives: Randomized trials have suggested that hypertonic saline solutions may be superior to mannitol for the treatment of elevated intracranial pressure, but their impact on clinical practice has been limited, partly by their small size. We therefore combined their findings in a meta-analysis.

Data Sources: We searched for relevant studies in MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, and ISI Web of Knowledge.

Study Selection: Randomized trials were included if they directly compared equiosmolar doses of hypertonic sodium solutions to mannitol for the treatment of elevated intracranial pressure in human subjects undergoing quantitative intracranial pressure measurement.

Data Extraction: Two investigators independently reviewed potentially eligible trials and extracted data using a preformed data collection sheet. Disagreements were resolved by consensus or by a third investigator if needed. We collected data on patient demographics, type of intracranial pathology, baseline intracranial pressure, osms per treatment dose, quantitative change in intracranial pressure, and prespecified adverse events. Our primary outcome was the proportion of successfully treated episodes of elevated intracranial pressure.

Mannitol is recommended as the first-line osmotic agent for the treatment of intracranial hypertension attributable to traumatic brain injury (TBI) (1), intracerebral hemorrhage (2), malignant cerebral infarction (3), subarachnoid hemorrhage (4), and acute liver failure (5). Numerous studies have shown that mannitol is effective in decreasing intracranial pressure (ICP) (6), and at least one randomized clinical trial has shown that mannitol reduces mortality compared to barbiturates in patients with elevated ICP from TBI (7). However, mannitol has many clinically important adverse effects, such as renal failure and hypovolemia (6, 8).

These adverse effects of mannitol have led to increasing enthusiasm about the use of hypertonic saline formulations, which can reduce ICP without causing volume contraction and with less risk of nephrotoxicity (9–12). Several randomized clinical trials have suggested that sodium-based hypertonic solutions may be superior to mannitol in reducing ICP (13–17), but the impact of these studies on clinical practice has been limited, partly because of the different specific formulations used and partly because of the small size of these studies (18).

Therefore, to better understand the relative efficacy of these two forms of osmotic therapy, we performed a meta-analysis of randomized clinical trials comparing hypertonic sodium solutions and mannitol for the treatment of elevated ICP. This report of our study conforms to the recommendations of the QUORUM statement on the quality of reporting for meta-analyses of randomized clinical trials (19).

Data Synthesis: Five trials comprising 112 patients with 184 episodes of elevated intracranial pressure met our inclusion criteria. In random-effects models, the relative risk of intracranial pressure control was 1.16 (95% confidence interval, 1.00–1.33), and the difference in mean intracranial pressure reduction was 2.0 mm Hg (95% confidence interval, −1.6 to 5.7), with both favoring hypertonic saline over mannitol. A mild degree of heterogeneity was present among the included trials. There were no significant adverse events reported.

Conclusions: We found that hypertonic saline is more effective than mannitol for the treatment of elevated intracranial pressure. Our meta-analysis is limited by the small number and size of eligible trials, but our findings suggest that hypertonic saline may be superior to the current standard of care and argue for a large, multicenter, randomized trial to definitively establish the first-line medical therapy for intracranial hypertension. (Crit Care Med 2011; 39:554–559)

Key Words: intracranial hypertension; intracranial pressure; mannitol; hypertonic saline; meta-analysis; randomized controlled trial

MATERIALS AND METHODS

Inclusion Criteria. We included randomized clinical trials involving human subjects (without exclusions based on age, sex, or race) undergoing some method of quantitative ICP measurement (e.g., intraparenchymal monitor, external ventricular drain, lumbar drain, and others) and displaying evidence of ele-
vated ICP, without regard for the underlying cause. Eligible trials directly compared the effect on ICP of equiosmolar doses (within \( \pm 20\% \)) of hypertonic sodium and mannitol solutions. We included trials using any formulation containing at least 3\% sodium chloride or equivalent (e.g., hypertonic sodium plus lactate, starch, etc.). We included trials involving an unblinded or crossover design, as long as the treatment allocation was randomized. We excluded trials using varying doses or varying infusion times (e.g., titrating drug to effect), because this would have precluded standardized comparison of the two drugs.

Data Sources. We performed an electronic search of MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, and ISI Web of Knowledge for relevant studies published in any language between January 1967 and April 2010. We complemented this by using the Related Articles function on PubMed and searching the reference lists of relevant articles. To assess for possible publication bias, we searched for unpublished abstracts in Scopus and unreported studies in the http://clinicaltrials.gov registry, but we did not plan to include such studies in our analysis because of concerns about methodological limitations of unpublished trials (20).

Search Strategy. We used text words and medical subject heading terms to identify studies involving the study population and intervention of interest (i.e., a comparison of mannitol and hypertonic saline in patients with elevated ICP; for full details of the search strategy, see Supplementary Data File 1 [Supplemental Digital Content 1, http://links.lww.com/CCM/A199]). To ensure the inclusion of studies not specifically indexed to terms related to ICP, we included search terms for common causes of elevated ICP (e.g., subarachnoid hemorrhage, intracerebral hemorrhage, and subarachnoid hemorrhage). To limit our search to randomized clinical trials, we used the Cochrane highly sensitive search strategy for MEDLINE and a similar strategy for EMBASE (21). One investigator (H.K.) reviewed the titles and abstracts of all studies identified in this way and excluded those that were obviously irrelevant. The full articles of the remaining studies were retrieved and independently reviewed by two investigators (H.K. and B.N.) using a structured form to determine eligibility and extract data. Disagreements were resolved by consensus or by a third investigator (K.N.) if needed. We contacted study authors for clarifications and further information as necessary.

Quality Assessment. We formally evaluated the quality of eligible studies using the Cochrane Collaboration’s tool for assessing the risk of bias in randomized trials (22). Specifically, studies were judged on the adequacy of the random sequence generation, allocation concealment, and blinding; the completeness of outcome data; the possibility of selective outcome reporting; and the existence of other potential sources of bias.

Data Extraction. For each trial, we recorded the number, age, and sex of patients; number of episodes of elevated ICP treated with a randomized allocation of a study drug; total osms per treatment dose; mean baseline ICP in each group; and the lowest mean ICP or the maximum mean change in ICP in each group within 60 mins of treatment. Our primary outcome was the proportion of cases in which randomized drug administration resulted in control of ICP, as defined in each study. We recorded the reported frequency of the following prespecified adverse events, as defined in each study: acute renal failure, pulmonary edema, hypotension, coagulopathy, and compartment syndrome from extravasation. We expected to include trials with crossover designs and multiple treatments per patient, so all data were extracted from intention-to-treat analyses only, with the unit of analysis being each randomized dose of study drug administered to treat a new episode of elevated ICP. In other words, crossover treatments for episodes of elevated ICP not responsive to the initial therapy were not included, but crossover treatments for new recurrent episodes of elevated ICP in the same patient were allowed as long as randomization was maintained.

Statistical Analysis. In our primary analysis, we calculated the pooled relative risk of ICP control with hypertonic saline compared to mannitol. We expected heterogeneity among the trials from differences in hypertonic sodium formulations and subject populations; therefore, we used a random-effects model based on the method of DerSimonian and Laird. Because we expected a small number of eligible studies, and because random-effects models may not perform as well with few studies, we also performed an analysis using a fixed-effects model for comparison. In this analysis, we did not apply the same strategy to calculate the weighted difference between the two treatment groups in mean ICP reduction. If the mean change in ICP was not reported, we calculated it by subtracting the mean posttreatment ICP from the mean pretreatment ICP, and we then calculated the SD of the mean difference using the reported \( p \) value. If the change in ICP was not reported in terms of mean and SD, we used the median to represent the mean, because this has been shown to be reasonably accurate when the sample size is approximately 25 (23), and then calculated the SD from the \( p \) value of the difference in means within the study (24). To examine the effects of this statistical assumption regarding the mean and median, we performed sensitivity analyses by excluding such studies altogether or alternatively imputing the SD based on those of the other studies (25).

RESULTS

Five studies enrolling a total of 112 adult patients met our eligibility criteria (13, 14, 17, 18, 27) (see Supplemental Fig. 1, which describes the flow diagram of search results and study selection [Supplemental Digital Content 2, http://links.lww.com/CCM/A200]). We did not find any potentially eligible unpublished abstracts or unreported trials, and a funnel plot did not reveal visual evidence of publication bias. All studies were limited by the absence of blinding, but otherwise the overall methodological quality of the included studies was fairly high, especially because the main outcomes were quantified objective ICP readings. All the trials were small (the largest enrolled 40 patients), but several amplified their sample size by including multiple episodes of elevated ICP per patient (13, 14, 17). Afifi et al (27) and Francony et al (18) compared mannitol to hypertonic sodium chloride, Battison et al (14) and Schwarz et al (13) used hypertonic sodium chloride plus starch, and Ichai et al (17) used hypertonic sodium lactate. Most studies included a mix of patients with TBI, stroke, intracerebral hemorrhage, and subarachnoid hemorrhage (13, 14, 18); one study exclusively consisted of patients with TBI (17) and one exclusively consisted of patients with recently resected supratentorial tumors (27) (Table 1). The average age of patients was 38 yrs (\( \pm 13 \) yrs), and 64\% were men. None of the studies reported the occurrence of any of our prespecified adverse events.

Among the 112 patients in the eligible trials, a total of 184 episodes of intracranial hypertension were randomly treated with mannitol or a hypertonic sodium solution. Mannitol was effective in controlling elevated ICP in 69 of 89 episodes (78\%; 95\% confidence interval [CI], 67\%–86\%), whereas hypertonic sodium solutions were effective in 88 of 95 episodes (93\%; 95\% CI, 85\%–97\%). The pooled relative risk of ICP control using
hypertonic saline compared to mannitol was 1.16 (95% CI, 1.00–1.33, \( p = .046 \); Fig. 1). The weighted mean difference in ICP reduction using hypertonic saline compared to mannitol was 2.0 mm Hg (95% CI, −1.6 to 5.7 mm Hg, \( p = .276 \); Fig. 2). In comparison, when a fixed-effects model was applied, our point estimates did not substantially change but the confidence intervals narrowed; the relative risk of ICP control favoring hypertonic saline was 1.20 (95% CI, 1.05–1.36, \( p = .007 \)), and the weighted mean difference in ICP reduction using hypertonic saline compared to mannitol was 2.0 mm Hg (95% CI, 0.1–3.8 mm Hg, \( p = .036 \)).

Our prespecified tests indicated a mild degree of heterogeneity among trials (\( p = .26, I^2 = 24\% \) in our primary analysis). We did not find any eligible pediatric trials, and we did not have sufficient data to perform subgroup analysis based on the type of intracranial pathology. In our other prespecified subgroup analyses, there were no clear differences in effect size among subgroups based on the type of hypertonic saline formulation, dose per treatment, or baseline mean ICP. There were too few eligible studies to perform meta-regression.

DISCUSSION

In this meta-analysis of five randomized clinical trials, we found that hypertonic sodium solutions are more effective than mannitol in controlling episodes of elevated ICP. We also found a trend toward greater quantitative ICP reduction in the hypertonic sodium group. Individually, two of the five trials reported statistically greater quantitative ICP reduction using hypertonic sodium compared to mannitol, one showed a trend favoring hypertonic sodium, one showed equivalence, and one showed a statistically sig-

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<td>Stroke (n = 1)</td>
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<tr>
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<td>7.5% sodium chloride</td>
<td>7.45% sodium chloride</td>
<td>Sodium lactate</td>
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<td>Mannitol dose</td>
<td>5.49 mosm/kg</td>
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<td>255 mosm</td>
<td>1.74 mosm/kg</td>
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<td>1.65 mosm/kg</td>
<td>257 mosm</td>
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<td>Baseline ICP (mm Hg)</td>
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<td>31 (4)</td>
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<td>31 (6)</td>
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<td>22.0 (20.1–26.3)</td>
<td>27 (3)</td>
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<td>&gt;20% below</td>
<td>&lt;20 mm Hg or</td>
<td>&gt;10% below baseline</td>
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<td>Control</td>
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<td>16 of 20 (80%)</td>
<td>14 of 18 (78%)</td>
<td>10 of 10 (100%)</td>
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<td>9 of 10 (90%)</td>
<td>28 of 31 (90%)</td>
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<td>Mannitol</td>
<td>13 (5)</td>
<td>7.5 (5.8–11.8)</td>
<td>14 (8)</td>
<td>5 (2)</td>
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<tr>
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<td>Sodium</td>
<td>12 (5)</td>
<td>13.0 (11.5–17.3)</td>
<td>10 (5)</td>
<td>8 (2)</td>
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ICP, intracranial pressure; TBI, traumatic brain injury.

Continuous measures are expressed as mean (SD), except ICP measurements from Battison et al, which are expressed as median (interquartile range).

ICP control denotes the proportion of episodes of elevated ICP successfully treated with a randomized dose of study medication. ICP decrease denotes the maximum decrease in mean ICP (mm Hg) within 60 mins of study drug administration.
significant advantage to mannitol. None individually were sufficiently powered to show a difference in the proportion of episodes of elevated ICP that were successfully treated, but the pooled results indicate that hypertonic sodium solutions are, on average, more effective.

In selecting our primary outcome, we chose each study's clinical definition of ICP control, because this is a more clinically relevant end point than the mean quantitative decrease in ICP, which can mask significant intragroup heterogeneity of treatment effect. Regardless, in our secondary analysis, there was a strong trend toward greater quantitative ICP reduction in patients treated with hypertonic saline compared to mannitol; this became statistically significant when a fixed-effects model was used.

The lack of a uniform treatment effect among all the trials is not surprising; we expected heterogeneity from methodological differences among the trials, specifically in terms of study population, treatment thresholds, and types of hypertonic sodium formulation. Our meta-analysis revealed only a mild degree of heterogeneity, and our prespecified subgroup analyses did not reveal an explanation for differences in effect size. Only one of the five trials (by Francony et al [18]) failed to show a trend favoring hypertonic sodium formulations, and we noted no obvious methodological differences between this trial and the others that would explain this disparity. However, this study was the smallest of the five included trials, and its discordant results may be attributable to the effect of chance.

This explanation is supported by the results of seven observational studies demonstrating the effectiveness of hypertonic saline in lowering ICP after failure of standard mannitol therapy (28–34). Another observational study found no significant difference between the efficacy of mannitol and hypertonic saline, but the latter had a longer-lasting effect (35). Furthermore, two randomized trials that did not meet our inclusion criteria support the superiority of hypertonic saline therapy. A trial by Vialet et al (15) was not eligible because different osms per dose were used in the two treatment groups (361 osms for hypertonic saline vs. 175 osms for mannitol); nevertheless, they found that 7.5% sodium chloride was more effective in treating refractory intracranial hypertension. A trial by Harutjunyan et al (16) did not qualify because study drugs were titrated to effect, making a standardized comparison difficult; nevertheless, they found that 7.2% sodium chloride plus hydroxyethyl starch was superior to mannitol in reducing ICP.

In addition to the clinical evidence reviewed, there are also numerous biochemical and physiologic considerations when choosing between hypertonic saline and mannitol for the treatment of elevated ICP. For example, hypertonic saline solutions result in significant volume expansion, improved cardiac output, improved regional blood flow, improved cerebrospinal fluid absorption (36), and beneficial immunomodulation (11). In addition, hypertonic saline may be superior to mannitol in regard to brain oxygenation and cerebral hemodynamics (33). However, mannitol may improve microvascular cerebral blood flow (37), reduce blood viscosity (38), improve blood rheology (6, 39), reduce cerebrospinal fluid production (40), promote free-radical scavenging (41), and inhibit apoptosis (42). Overall, the conflicting nature of these basic science considerations suggests that the preferred agent for the treatment of intracranial hypertension ultimately must be established through large, well-performed, randomized human trials.

CONCLUSIONS

The need for more rigorous clinical data prompted us to perform this meta-analysis of existing randomized trials. Our study is limited by the small number and size of eligible trials, as well as their methodological differences, lack of rigorous adverse event reporting, and failure to control for clustering among patients receiving multiple doses of study drug. These limitations preclude a firm recommendation to preferentially use hypertonic saline as first-line therapy, but our findings indicate that hypertonic sodium solutions are, on average, superior to mannitol for the treatment of elevated ICP and argue for a large multicenter study comparing these two therapies. Our results suggest an absolute effect size of approximately 15% in favor of hypertonic saline, and a trial would require approximately 100 patients in each arm to have 80% power to detect this difference in the rate of ICP control between the two groups. Ideally, such a trial would incorporate a uniform hypertonic sodium solution and, more importantly, also include assessment of long-term neurologic outcomes. While we await such a trial, the balance of evidence indicates that hypertonic saline is more effective than mannitol for the treatment of intracranial hypertension.

REFERENCES


