Title: Mannitol or Hypertonic Saline for Treatment of TBI? Is hypertonic saline more effective at lowering ICP?

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Clinical Scenario: Dispatched code 1: 24-year-old male with ALOC, single vehicle MVC.

Upon arrival you find a 4-door sedan has left a rural road and collided with a large tree. Posted speed limit is 80km/h and the pavement shows no signs of skid/brake marks. There is significant front-end damage with tenting of the hood, windshield starring and front airbag deployment.

The patient is located in the driver's seat, unrestrained with blood to his head/face and an odor of ETOH is noted. Pt. will moan and withdraw to painful stimulus, GCS 7 (E1, V2, M4). Pt. is immobilized, ABCs stabilized and extricated to the ambulance. After conferring with your partner, you agree upon a clinical impression of a TBI with increased ICP.

PICO (Population – Intervention – Comparison – Outcome)

P- Trauma patients with increased intracranial pressure

I – Mannitol

C- 3% Saline

O- Reduction in ICP

Question: Is hypertonic saline more effective at reducing ICP in trauma patients than mannitol?

Search Strategy: Search: ***Hypertonic saline and Mannitol and traumatic brain injury***

Search Outcome: 145 Results, 2 were included:

1) Shi et al, 2020: *Hypertonic saline and mannitol in patients with traumatic brain injury: a systematic and meta-analysis*

2) Miyoshi et al, 2020: *Effects of hypertonic saline versus mannitol in patients with traumatic brain injury in prehospital, emergency department, and intensive care unit settings: a systematic review and meta-analysis*

Summary of findings pertaining to ICP outcome: (Shi, 2020)

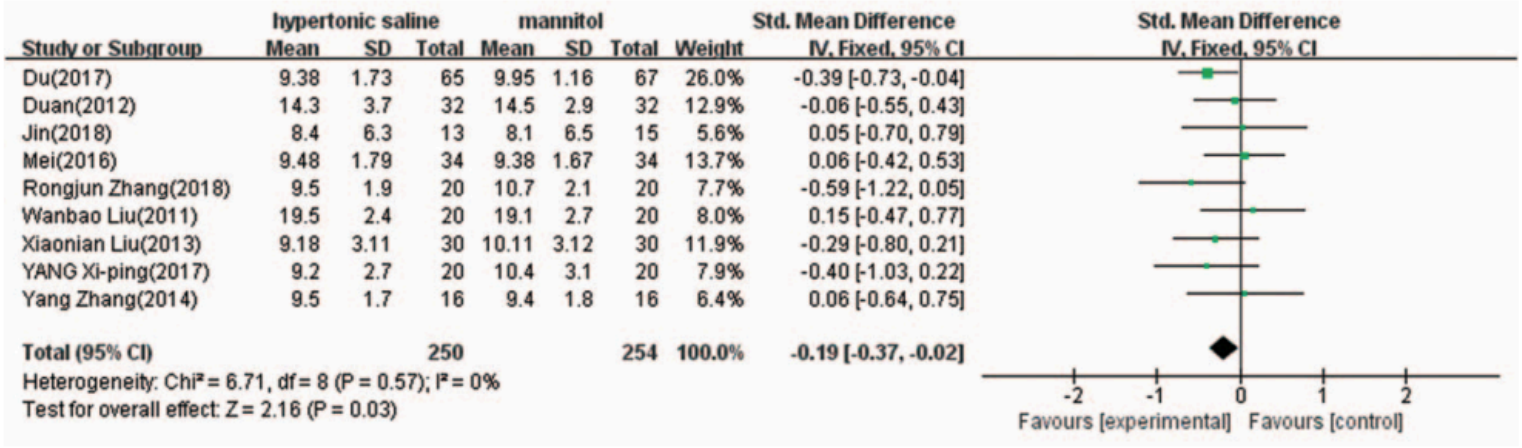

Figure 3. Comparison of intracranial pressure reduction between 3% hypertonic saline and 20% mannitol (mm Hg). CI = confidence interval.

AUTHOR, DATE	POPULATION	DESIGN (LOE)	OUTCOMES	RESULTS	STRENGTHS/ WEAKNESSES
Shi, 2020	544 trauma patients with increased ICP 270 in the hypertonic saline group 274 in the mannitol group	Systematic Review and Meta-Analysis Randomized Control Trials 3 databases were searched: WAN-FANGDATA, CNKI, CQVIP 10 articles between 2010-2019 met inclusion criteria	Compare the effects of 3% hypertonic saline and 20% Mannitol on brain injury: Compare the maximum changes of 1) ICP 2) CPP 3) Compare time of onset 4) Compare maintenance time/duration of action i.e. continuous ICP reduction time after termination of infusion	1) ICP: The pooled difference in means indicated that Mannitol reduces ICP more than hypertonic saline = -0.19 (95% CI:-0.37 to -0.02, p=.03) 2) CPP: The pooled difference in means indicated that 3% hypertonic saline is more effective than 20% Mannitol in increasing CPP = 0.54 (95% CI: 0.15-0.92, P=.007) 3) Onset: The pooled difference in means indicate no significant difference in onset time between 3% HS and 20% Mannitol.= 0.05 (95% CI: -0.14 to 0.23, P=.64) 4) Maintenance Time: The pooled difference	Strengths: Systematic Review and Meta-analysis. Inclusion criteria consisted of RCTs. The risk-of-bias assessment tool in the Cochrane Handbook for systematic reviews of interventions was used to assess the quality of studies selected. Weaknesses: Did not account for infusion rate, frequency or mode of administration when obtaining best therapeutic effects.

AUTHOR, DATE	POPULATION	DESIGN (LOE)	OUTCOMES	RESULTS	STRENGTHS/ WEAKNESSES
				in means indicated that 3% hypertonic saline lasts longer time for ICP reduction than 20% Mannitol. = 0.84 (95% CI: 0.64-1.05, P <.00001)	

AUTHOR, DATE	POPULATION	DESIGN (LOE)	OUTCOMES	RESULTS	STRENGTHS/ WEAKNESSES
Miyoshi, 2020	352 studies initially identified Inclusion criteria narrowed the sample size to 105 adult patients with TBI 50 in the hypertonic saline group 55 in the mannitol group	Systematic Review and Meta-Analysis 4 Randomized Control Trials 3 databases were searched: MEDLINE, the Cochrane Central Register of Controlled Trials, Igaku Chuo Zasshi (ICHUSHU) No date restrictions	Assess the effects of Hypertonic Saline vs. Mannitol on clinical outcomes in patients with TBI via systematic literature review and synthesizing evidence from RCTs. Primary outcome: all cause mortality comparison Secondary outcomes: 90 &180-day mortality, good neurological outcome, reduction in ICP and serum sodium level.	Primary outcome: No significant difference between the infusion groups; (95% CI 0.49-1.37, p=0.71) 16 patients - 32% mortality in the hypertonic saline group 21 patients - 38.2% mortality in the mannitol group. Secondary Outcome Results: Good neurological outcomes were higher in the mannitol group otherwise no significant difference noted in 90 &180 day mortality or ICP reduction and serum sodium levels.	Strengths: Systematic review and Meta-analysis conducted in accordance with the PRISMA guidelines. Quality of evidence was rated based on the criteria established by the GRADE working group Weakness: The certainty of the evidence was rated very low for all outcomes. Small sample size.

Miyoshi et al. summary:

Table 2 Summary of findings

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)
	Risk with mannitol	Risk with HS			
All-cause mortality	382 per 1000	**313 per 1000** (187 to 523)	**RR 0.82** (0.49 to 1.37)	105 (3 studies)	Very low
90-days mortality	500 per 1000	**270 per 1000** (115 to 635)	**RR 0.54** (0.23 to 1.27)	58 (2 studies)	Very low
180-days mortality	356 per 1000	**292 per 1000**(160 to 540)	**RR 0.82** (0.45 to 1.52)	85 (2 studies)	Very low
Good neurological outcome	709 per 1000	**752 per 1000** (546 to 1000)	**RR 1.06** (0.77 to 1.47)	105 (3 studies)	Very low
ICP	-	MD **1.9 lower** (6.9 lower to 3.1 higher)	-	58 (2 studies)	Very low
Serum sodium levels	-	MD **2.6 higher** (2.76 lower to 7.97 higher)	-	105 (3 studies)	Very low

ICP intracranial pressure, *CI* confidence interval, *HS* hypertonic saline, *MD* mean deviation, RR risk ratio

Comments:

Shi et al. indicated that mannitol was slightly more effective at reducing ICP while hypertonic saline had a more sustained reduction of ICP and also increased CPP more than mannitol. It was suggested however that the duration of action of mannitol might be related to the infusion rate. Perhaps a slower infusion rate might decrease the renal elimination rate and therefore have a more sustained reduction of ICP. To obtain the best therapeutic effect; the infusion rate, frequency, dose, concentration and route of administration should be taken into account.

Miyoshi et al. did not find a significant difference between mannitol and hypertonic saline in reducing increased ICP however found that good neurological outcomes were higher in the mannitol group. The certainty of evidence however was graded very low for all outcomes.

Consider: I would not recommend change to current clinical practice. These reviews did not conclude the same results as one another. Further research is required to include larger samples along with a risk-benefit analysis inclusive of potential side effects and their prevalence. A more refined PICO question aimed at contrasting between hypertonic saline and mannitol with respect to overall morbidity and mortality would also be beneficial.

Clinical Bottom Line: These systematic reviews and meta-analysis have not indicated that hypertonic saline is more effective at reducing ICP than mannitol. Both mannitol and 3% saline are effective treatment options for reducing ICP and managing patients with traumatic brain injuries.

References:

Shi J, Tan L, Ye J, Hu L. Hypertonic saline and mannitol in patients with traumatic brain injury: A systematic and meta-analysis. Medicine (Baltimore). 2020 Aug 28;99(35):e21655. doi: 10.1097/MD.0000000000021655. PMID: 32871879; PMCID: PMC7458171.

Miyoshi Y, Kondo Y, Suzuki H, Fukuda T, Yasuda H, Yokobori S; Japan Resuscitation Council (JRC) Neuroresuscitation Task Force and the Guidelines Editorial Committee. Effects of hypertonic saline versus mannitol in patients with traumatic brain injury in prehospital, emergency department, and intensive care unit settings: a systematic review and meta-analysis. J Intensive Care. 2020 Aug 12;8:61. doi: 10.1186/s40560-020-00476-x. PMID: 32817796; PMCID: PMC7425012.