Hyperosmolar Therapy for Traumatic Brain Injury: A Systematic Review

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Introduction

Background

- Hyperosmolar therapy is a cornerstone of neurocritical care for traumatic brain injury (TBI), reducing intracranial pressure and preventing herniation.
- Mannitol and hypertonic saline (HTS) raise serum osmolarity but can cause iatrogenic hypernatremia (HRN), a complication linked to increased mortality.
- Hospital-acquired HRN may serve as a marker of care quality, with renal injury through vasoconstriction, tubular hypoxia, oxidative stress, and inflammation implicated in adverse outcomes.

Clinical Uncertainty

- The **safe upper sodium limit** during hyperosmolar therapy remains **undefined**.
- Guidelines cite approximately **160 mmol/L** as an upper reference, but this value lacks robust evidence.
- Clinical practice varies, with some maintaining **normonatremia** and others inducing **"therapeutic" hypernatremia (≥150–160 mmol/L)** to control intracranial pressure.
- This heterogeneity reflects the **absence of clear data** linking sodium thresholds to outcomes.

Study Objectives

- Synthesize existing evidence on hypernatremia in TBI patients treated with HTS or mannitol.
- Identify sodium thresholds associated with benefit or harm.
- Compare HTS and mannitol strategies across studies.
- Define knowledge gaps to guide future randomized trials and inform clinical guidelines.

Methods

Database-Agnostic Search Items:

"TBI" OR "traumatic brain injury" AND "hypernatremia"

4 Databases:

PubMed, Web of Science, Scopus, Cochrane

Full-Text Screen:

Inclusion Criteria

- Adults with moderate-to-severe TBI
- Received hyperosmolar therapy (mannitol, hypertonic saline, or both)
- Study types: RCTs, observational (prospective/retrospective), or case series (≥10 patients)
- Reports serum sodium thresholds (e.g., Na < 150 vs ≥ 150 mmol/L) or dose–response analyses

Exclusion Criteria

- Non-TBI or pediatric-only populations
- No hyperosmolar therapy administered
- Reviews, editorials, or letters
- Animal or in vitro studies
- No serum sodium data reported
- Not in English

PRISMA Flow Diagram

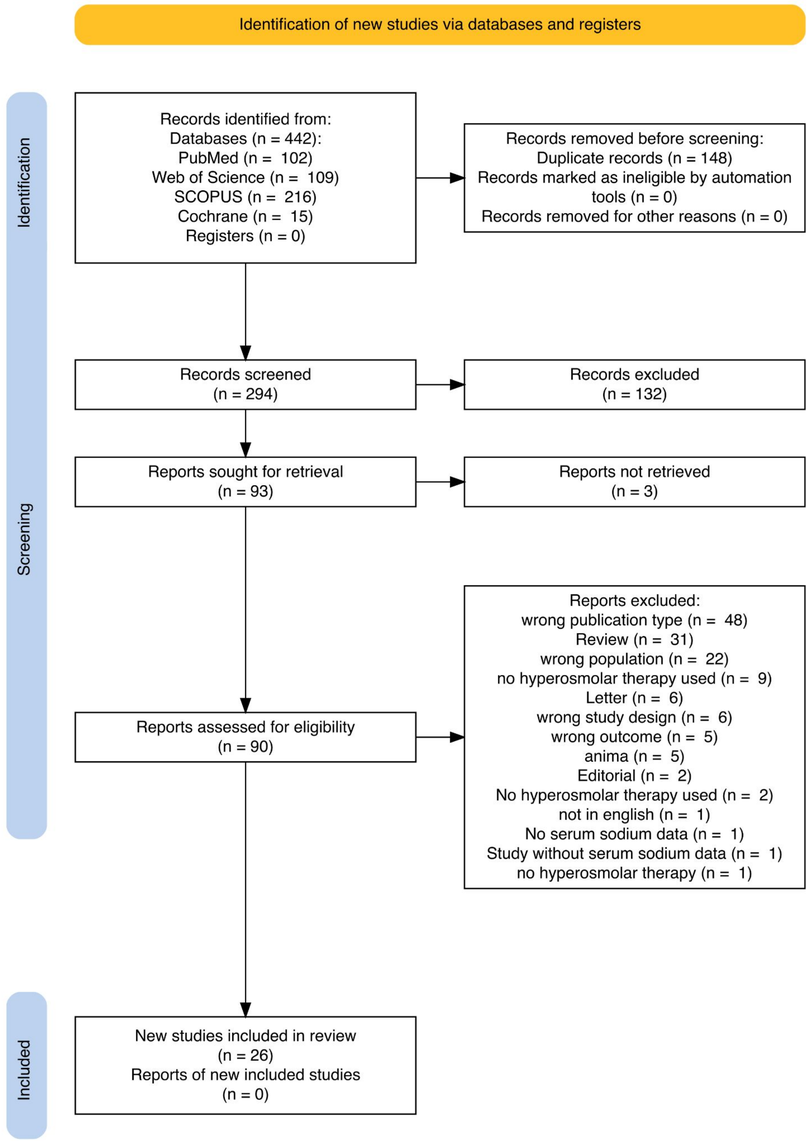

Figure 1. PRISMA Flow Diagram for Study Selection.
Flowchart summarizing the identification, screening, eligibility, and inclusion of studies evaluating hyperosmolar therapy for moderate-to-severe traumatic brain injury. A total of 442 records were identified across PubMed, Web of Science, Scopus, and Cochrane. Two independent reviewers performed full-text screening with a third for adjudicating discrepancies. After duplicate removal and screening, 26 studies met inclusion criteria for full-text review and were included in the final analysis.

Results

Study (Year)	Country	N	Therapy Type	Hypernatremia Definition	Peak Na (mmol/L)	Intentionality	Mortality / Outcomes
Hypernatremia severity and the risk of death after TBI (2012)	China	881	Mannitol	Mild 150–155, Mod 155–160, Sev >160	N/A	Incidental	21.8% mortality
Morbidity and mortality associated with hypernatremia in severe TBI (2017)	USA	588	Mannitol	Mild 151–155, Mod 156–160, Sev >160	—	Incidental	Regression-based, not directly reported
Relationship between sodium level and in-hospital mortality (2014)	China	1,749	Unclear	>145 mmol/L	—	Incidental	11.5% in-hospital
Relation between incidence of hypernatremia and outcome (2009)	Italy	130	3%/5% saline or mannitol	>145 mmol/L ×2	165	Incidental	34 deaths within 14 days
Continuous HTS infusion in severe TBI (2016)	Canada	231	HTS & Mannitol (HTS primary)	>145 mmol/L	~170	Incidental	59 deaths
Hyperchloremia, not hypernatremia, predicts mortality (2020)	USA	458	Mannitol	>140 mmol/L	>170	Incidental	44% mortality
Serum electrolyte imbalance and outcomes (2018)	Thailand	145	Mannitol (8 pts)	>146 mmol/L	—	Incidental	17.2% mortality
Method of HTS administration and outcomes (2017)	USA	162	HTS ± Mannitol	>160 mmol/L	—	Mixed	45.5% (continuous) vs 36.8% (bolus)
Natremia and clinical outcome after TBI (2025)	USA	999	HTS	145–160 mmol/L; extreme >160	—	Incidental	Not directly stated
Sodium abnormalities in moderate-to-severe TBI (2019)	S. Africa	184	HTS	>145 mmol/L	—	Incidental	18.5% mortality

Table 1. Selected studies evaluating hypernatremia during hyperosmolar therapy for traumatic brain injury (TBI).
Included studies report patient populations treated with hypertonic saline (HTS), mannitol, or both. Hypernatremia thresholds varied across studies, ranging from >140 to >160 mmol/L, with most cases occurring incidentally during therapy rather than by design. Mortality increased with rising sodium levels in several cohorts, though intentional "therapeutic" hypernatremia lacked consistent outcome benefit.

Conclusions & Future Steps

Conclusions

- Across studies, hypernatremia was predominantly incidental rather than intentionally induced.
- Higher serum sodium levels (>155–160 mmol/L) were consistently associated with increased mortality and acute kidney injury.
- No clear evidence supports therapeutic hypernatremia as beneficial for intracranial pressure control or neurologic outcomes.
- Findings highlight the need for cautious titration of osmotherapy to balance cerebral protection with systemic safety.

Future Steps

- Standardize sodium targets in TBI management through prospective, randomized trials.
- Differentiate outcomes between hypertonic saline and mannitol, including renal and hemodynamic endpoints.
- Integrate physiologic monitoring and AI-based modeling to individualize osmotherapy thresholds.
- Establish consensus guidelines to define the upper limit of safe serum sodium during hyperosmolar therapy.

References

1. Hawryluk GW. Sodium values and the use of hyperosmolar therapy following traumatic brain injury. Neurosurgical Focus. 2017 Nov 1;43(5):E3.
2. Vedantam A, Robertson CS, Gopinath SP. Morbidity and mortality associated with hypernatremia in patients with severe traumatic brain injury. Neurosurgical focus. 2017 Nov 1;43(5):E2.