ARC SAC SCIENTIFIC REVIEW
Traumatic Brain Injury
Osmotic Agents

Questions to be addressed:

For adults with an acute major traumatic brain injury, does mannitol or hypertonic saline (HTS), compared to each other or neither, result in different outcomes?

Introduction/Overview:

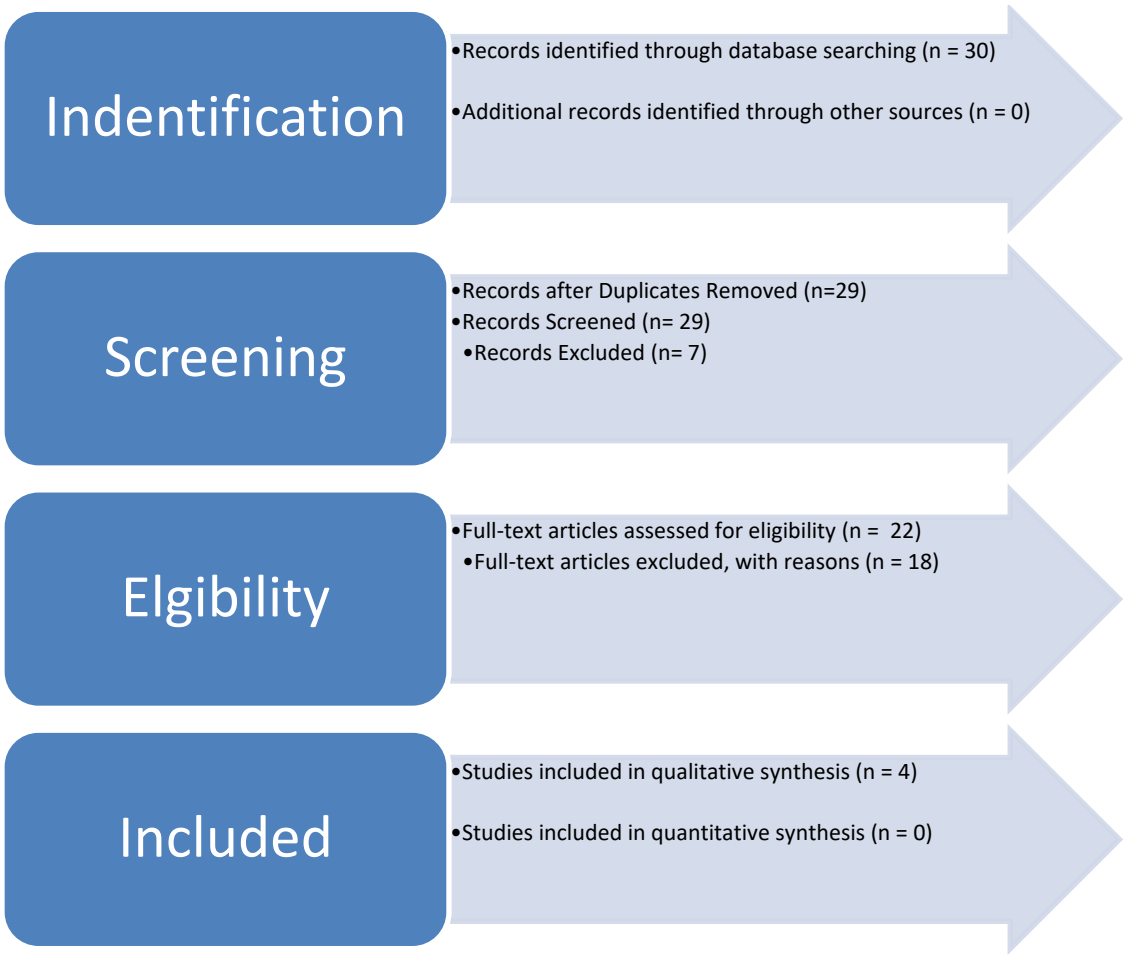
TBI is the leading cause of death following blunt trauma, and survivors often sustain severe disability. TBI is responsible for the greatest number of potential years of life lost from any cause and carries the highest burden on loss of quality-adjusted life-years among survivors. Current therapy following severe TBI is focused on minimizing secondary injury by supporting systemic perfusion and reducing intracranial pressure. Hypertonic fluids have been shown to decrease ICP and improve cerebral perfusion pressure in animal models and patients with severe TBI. Hypertonic saline has also been shown to have beneficial vasoregulatory, imunomodulatory, and neurochemical effects on the injured brain. Trials have suggested that early administration of hypertonic fluids to patients with severe TBI may improve outcomes.

Search Strategy and Literature Search Performed

Answer all questions and complete PRISMA flow sheet below
Key Words Used

Inclusion Criteria (time, type of articles and journals, language, methodology)
English only
Exclusion Criteria (only human studies, foreign language, etc…)
Human Studies only

Databases Searched and Additional Methods Used (references of articles, texts, contact with authors, etc...)


Indentification
•Records identified through database searching (n = 30)
•Additional records identified through other sources (n = 0)
Screening
•Records after Duplicates Removed (n=29)
•Records Screened (n= 29)
•Records Excluded (n= 7)
Elgibility
•Full-text articles assessed for eligibility (n = 22)
•Full-text articles excluded, with reasons (n = 18)
Included
•Studies included in qualitative synthesis (n = 4)
•Studies included in quantitative synthesis (n = 0)

Scientific Foundation:

Several studies have shown that Mannitol and Hypertonic Saline have decreased intracranial pressure (ICP). Hypertonic saline has been shown to decrease pressure more than Mannitol in some studies. However, there were two studies showing no effect in decreasing ICP with either agent. It is significant that a structure literature review showed that there were no studies that were able to identify an improvement in neurological outcomes based on the administration of Mannitol or Hypertonic Saline vs Normal Saline.

Recommendations and Strength (using table below):

Standard:

None

Options:

Some studies show that the use of Mannitol or Hypertonic Saline do not result in an improvement in outcomes. The use of either can be an option in the treatment of Traumatic Brain Injury.

Knowledge Gaps and Future Research:

Future studies that demonstrate a definitive improvement in outcomes may result in a change in recommendations.

Implications for ARC Programs:

No change

Attach Any Lists, Tables of List of Recommendations Created as Part of This Review

None

ARC SAC SCIENTIFIC REVIEW
Traumatic Brain Injury
Osmotic Agents

Summary of Key Articles/Literature Found and Level of Evidence/Bibliography:

Author(s)	Full Citation	Summary of Article (provide a brief summary of what the article adds to this review including which question(s) it supports, refutes or is neutral)	Methodology	Bias Assessment	Indirectness/ Imprecision/ Inconsistency	Key results and magnitude of results	Support, Neutral or Oppose Question	Level of Evidence (Using table below)	Quality of study (excellent, good, fair or poor) and why
Bulgar	Out-of-Hospital Hypertonic Resuscitation Following Severe Traumatic Brain Injury JAMA, October 6, 2010—Vol 304, No. 13	Refutes: Among patients with severe TBI not in hypovolemic shock, initial resuscitation with either hypertonic saline or hypertonic saline/dextran, compared with normal saline did not result in superior 6-	Multicenter, double-blind, randomized, placebo controlled clinical trial involving 114 North American emergency medical services agencies within the Resuscitation Outcomes Consortium,	Retrospective observational study		Among the 1087 patients with data available, there was no improvement in those with Hypertonic Saline w/wo Dextran vs NS	Oppose	2b	Excellent

		month neurologic outcome or survival.	conducted between May 2006 and May 2009 among patients 15 years or older with blunt trauma and a prehospital Glasgow Coma Scale score of 8 or less who did not meet criteria for hypovolemic shock.						
Boone	Mannitol or Hypertonic saline in the setting of TBI: What have we learned? Surgical Neurology International 10.4103/2152-7806.170248 2015 Nov 23	Refutes: No improvement in outcomes were reported.	The PubMed database was used to systematically search for articles comparing mannitol to HTS in severe TBI.	Out of 45 articles, seven articles were included in our review: 5 were prospective, randomized trials; one was a prospective, nonrandomized trial; and one was a retrospective, cohort study.		There was heterogeneity about which agent was most efficacious for reducing ICP. None showed a reduction in outcomes.	Oppose	Varied	Excellent

Burgess	A Systematic Review of Randomized Controlled Trials Comparing Hypertonic Sodium Solutions and Mannitol for Traumatic Brain Injury: Implications for ED Management Ann Pharmacother. 2016 Apr;50(4):291-300. doi: 10.1177/1060028016628893. Epub 2016 Jan 29	Refutes: Important differences in neurologic outcomes were not observed.	Prospective, randomized trials comparing HTS and mannitol in adults (≥16 years) with severe TBI (Glasgow Coma Scale score ≤8) and elevated ICP were included. ICP elevation, ICP reduction, and treatment failure were defined using study definitions.	Studies were underpowered to detect a significant difference in neurologic outcomes.		Based on limited data, clinically important differences in mortality, neurological outcomes, and ICP reduction were not observed between HTS or mannitol in the management of severe TBI. HTS appears to lead to fewer ICP treatment failures.	Oppose	2b	Good

Jagannatha	An equiosmolar study on early intracranial physiology and long term outcome in severe traumatic brain injury comparing mannitol and hypertonic saline. J Clin Neurosci. 2016 May;27:68-73. doi: 10.1016/j.jocn.2015.08.035. Epub 2016 Feb 28	Refutes: No physiological advantages were seen in either group or differences seen in long term mortality.	Over 450 episodes of refractory ICH were treated with equiosmolar boluses of 20% mannitol in 20 patients and 3.0% HTS in 18 subjects	Sample size was small – 38 patients		Immediate physiological advantages seen with HTS over mannitol did not translate into long term benefit on ICP/CPP control or mortality of patients with TBI.	Oppose	2a	Good

Level of Evidence	Definitions (See manuscript for full details)
Level 1a	**Experimental and Population based studies -** population based, randomized prospective studies or meta-analyses of multiple higher evidence studies with substantial effects
Level 1b	**Smaller Experimental and Epidemiological studies -** Large non-population based epidemiological studies or randomized prospective studies with smaller or less significant effects
Level 2a	**Prospective Observational Analytical** - Controlled, non-randomized, cohort studies
Level 2b	**Retrospective/Historical Observational Analytical** - non-randomized, cohort or case-control studies
Level 3a	**Large Descriptive studies** – Cross-section, Ecological, Case series, Case reports
Level 3b	**Small Descriptive studies** – Cross-section, Ecological, Case series, Case reports
Level 4	**Animal studies or mechanical model studies**

Level 5	**Peer-reviewed Articles** - state of the art articles, review articles, organizational statements or guidelines, editorials, or consensus statements
Level 6	**Non-peer reviewed published opinions -** such as textbook statements, official organizational publications, guidelines and policy statements which are not peer reviewed and consensus statements
Level 7	**Rational conjecture** (common sense); common practices accepted before evidence-based guidelines
Level 1-6E	**Extrapolations** from existing data collected for other purposes, theoretical analyses which is on-point with question being asked. Modifier E applied because extrapolated but ranked based on type of study.