Mannitol in TBI

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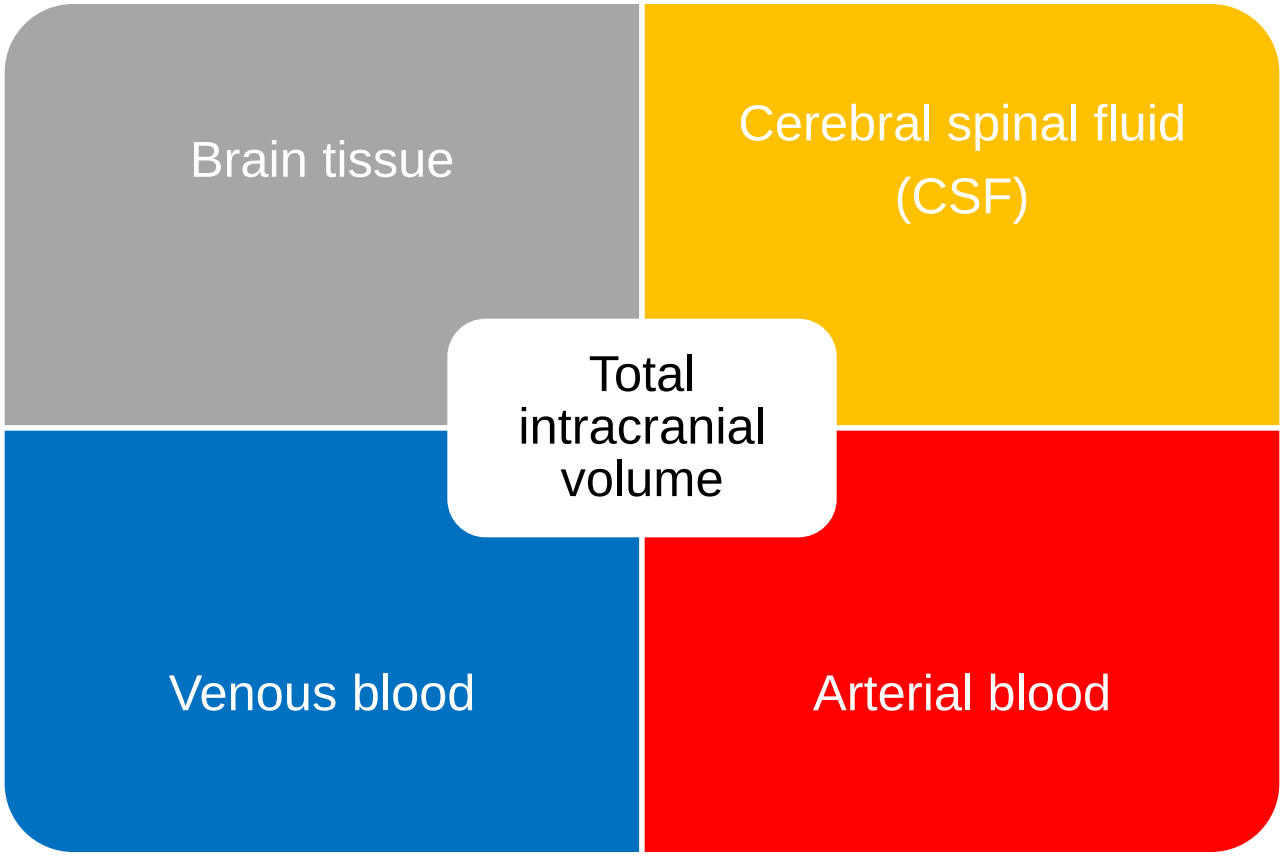
The Monro-Kellie hypothesis



CPP ↓

CBF ↓

İschemia and hypoxia

Worsening the initial brain injury

Traumatic Brain Injury Pathway, GCS <9

ADMISSION TO TRAUMA ICU

- Consult neurosurgery service
- Begin 7 d seizure prophylaxis
- CBC, BMP, PT/INR, PTT, ABG, Serum Osm

↓

- Intubation (if not already performed)
- Keep $PaCO_2$ 35–40 mm Hg, PaO_2>60 mm Hg
- HOB >30 degrees or reverse Trendelenberg
- SBP >90 mm Hg
- If IPC, SDH, EDH → FFP/Platelets for INR<2.0, Platelet > 100K
- Establish central access; arterial line
- Maintain euvolemia
- Optimize sedation and analgesia
- Consider DHT for early enteral nutrition

↓

ICP Monitor
Note: TICU attending may request with direct discussion with NSU attending

CPP<60 →

1st line: Phenylephrine
2nd line: Norepinephrine

ICP >20 ↓

If EVD, then drain CSF

ICP >20 →

ICP >20 ↓ ↑ *CPP<60*

Hyperosmolar Therapy

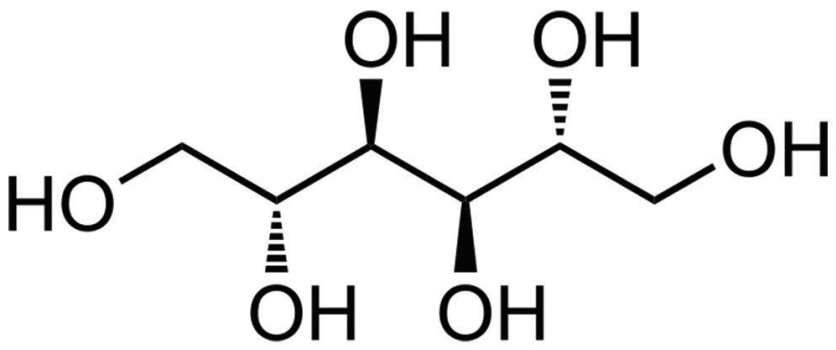
- 3% NaCl @ 30–50 mL/h
- CVP High: Mannitol bolus q6h
- CVP Low: 3% NaCl bolus q6h
- Q6h BMP, Osm
- Max: Na 160, Osm 320

Persistent ICP >20 and/or CPP <60 →

- **Contact TICU attending or fellow**
- **Contact neurosurgery (consider decompressive craniectomy)**
- **Monitor intra-abdominal pressures**
- **Consider pentobarbital coma with neurology consult (continuous EEG)**
- **Consider palliative care consult**

Mannitol

Chemical structure of mannitol



Physical and pharmacokinetic properties of mannitol

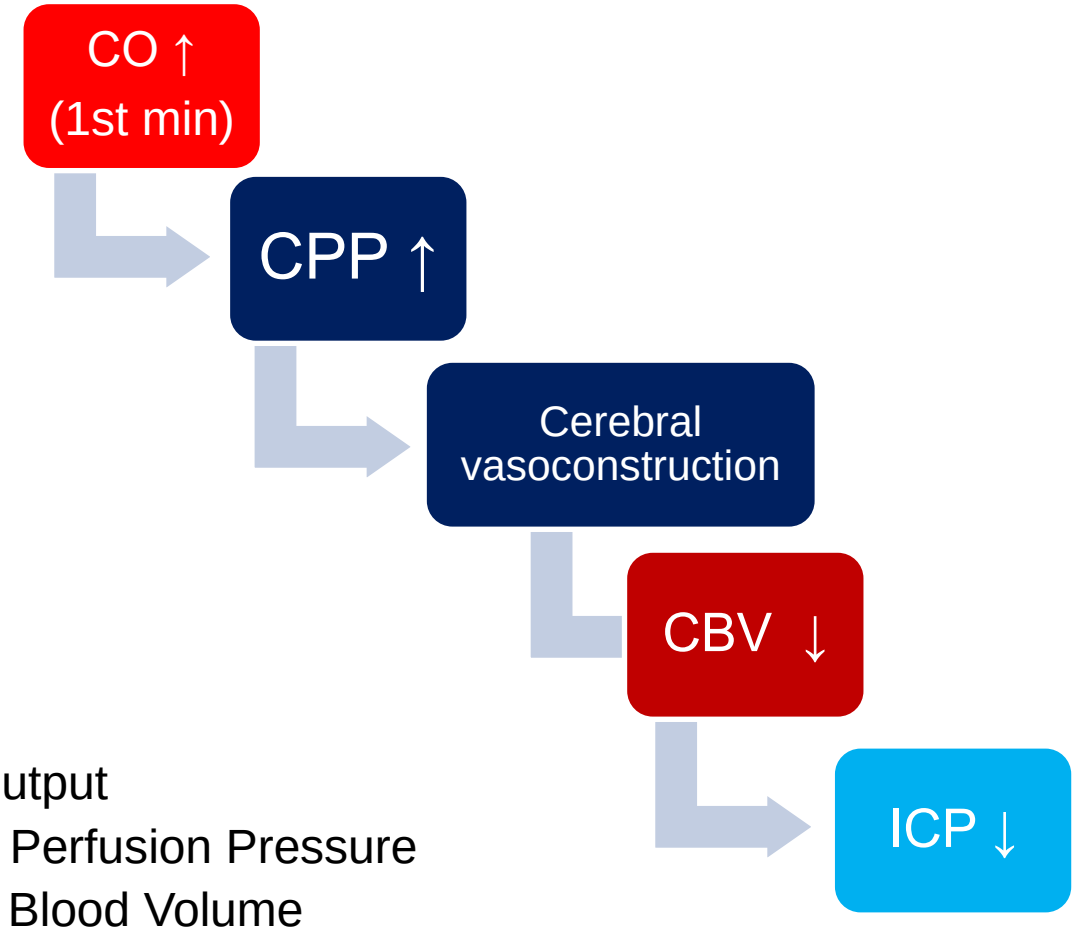
Characteristic	Description
Molecular weight	182 Daltons
Osmolarity (20%)	1098 mOsm/L
Volume of distribution	0.471 L/kg
Onset	≈15 min
Maximal effect	≈45 min
Duration	≈6 h
Half-life	70-100 min
Biotransformation	None
Excretion	Renal
Reabsorption	7%

Mannitol

- 6 carbon polyol, isomer of sorbitol
- Produced by several mo and plants
- At room temperature it may cristallise
- Hypertonic mannitol (20%)≈ 3,2% hypertonic saline
- Hypertonic mannitol=>1960 by Scharfetter for ICP
- Low dose =>20% mannitol 0,15-0,20 g/kg 30-60 min
- Or 2 g/kg in a single administration

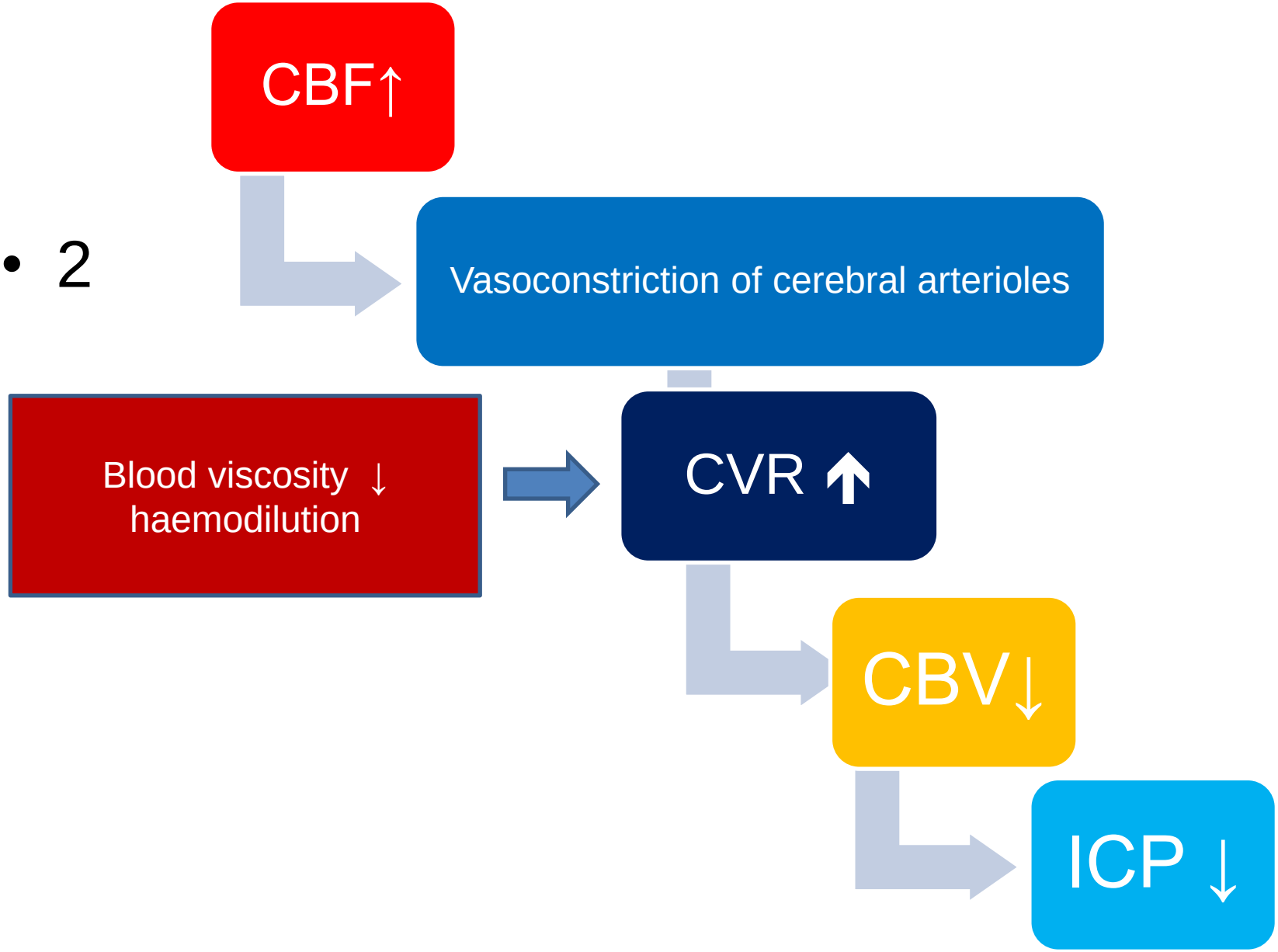
How does the mannitol decrease the ICP?

- 1-



CO:Cardiac Output
CPP:Cerebral Perfusion Pressure
CBV:Cerebral Blood Volume

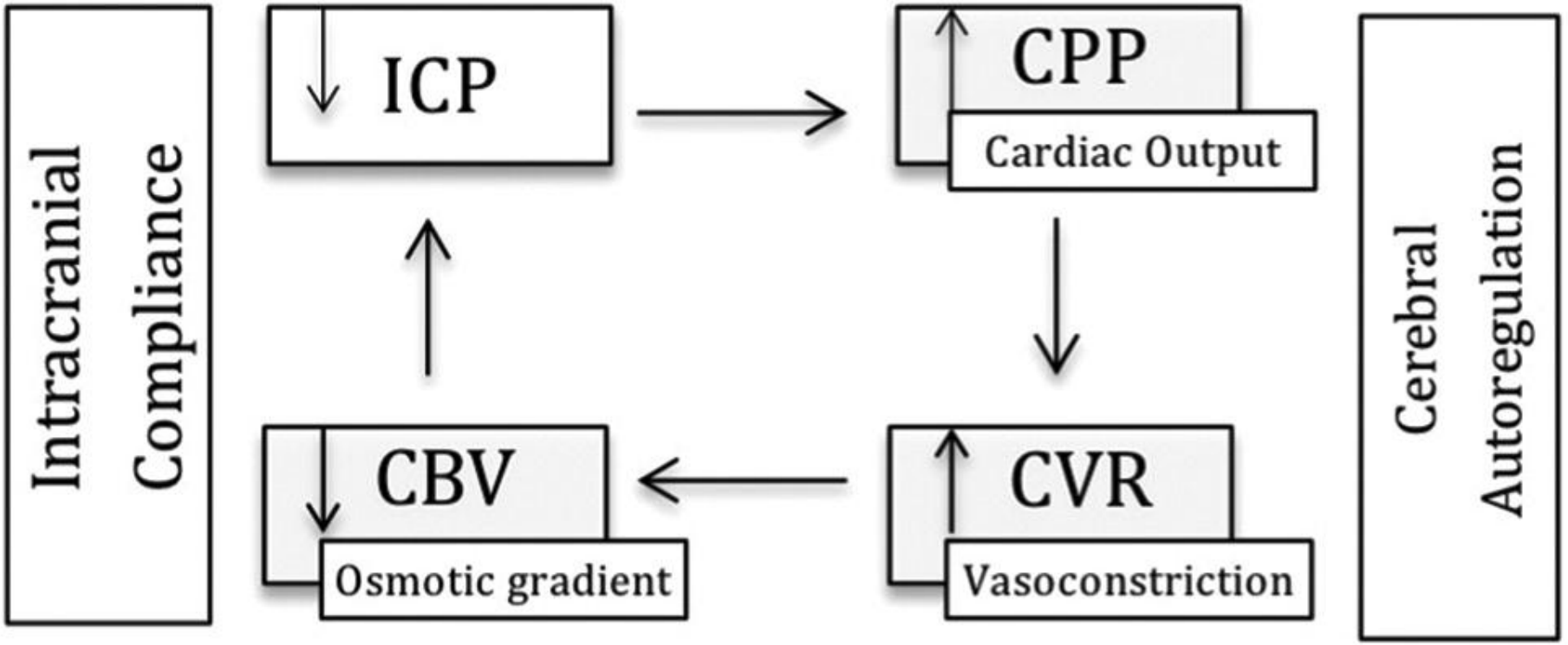
- 2


CBF↑
Vasoconstriction of cerebral arterioles
Blood viscosity ↓
haemodilution
CVR ↑
CBV↓
ICP ↓

- 3 Switch the shift of water
İntracelluar =>extracellularcompartment

Cerebral oedema ↓

ICP ↓


Intracranial Compliance
ICP
CPP
Cardiac Output
Cerebral Autoregulation
CBV
Osmotic gradient
CVR
Vasoconstriction

- If it ıs administered in fast boluses
- CBV↑=>dose related in Grey matter and large venous sinuses
- ICP get worses.

Brain Trauma FOUNDATION

Guidelines for the Management of Severe Traumatic Brain Injury
4th Edition

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Reviewed for evidence-based integrity and endorsed by the American Association of Neurological Surgeons and the Congress of Neurological Surgeons.

September 2016

According to this guidelines

- Mannitol doses
- **0,25-1 g/kg** in a *single* dose over **20-30 min**
- Insufficient data for regular administration over several days
- Lack of evidence for intermittent boluses or continous infusion

J Neurosurg 59:945–950, 1983

Effect of mannitol and furosemide on blood-brain osmotic gradient and intracranial pressure

MICHAEL POLLAY, M.D., CHARLES FULLENWIDER, M.D., P. ALEX ROBERTS, PH.D., AND F. ALAN STEVENS, B.S.

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✔ The effect of mannitol (1.0 gm/kg) and furosemide (0.7 mg/kg), alone and in combination, on the blood-brain extracellular fluid and cerebrospinal fluid (CSF) osmotic gradient, elevated intracranial pressure (ICP), CSF and serum osmolality, and urine output was studied in 26 mongrel dogs. Mannitol and furosemide, when used together, produced a greater (62.4% versus 56.6%) and more sustained (5 hours versus 2 hours) fall in ICP than mannitol alone. This correlated with a prolongation of the reversal of the blood-brain osmotic gradient (−3.4 to +38.5 mOsm/kg) and a rate of urine formation 15 times control values. There was a transient but not significant fall in serum Na^+ with the combined treatment, but the arterial pressure did not vary from pretreatment levels. The results from this present study suggest that the distal loop diuretics in a dose of less than 1.0 mg/kg act synergistically with mannitol by causing preferential excretion of water over solute in the renal distal tubule, and thereby sustaining the osmotic gradient initially established by the mannitol infusion. It is possible, but unlikely in the doses used, that the additive effect of furosemide on reducing ICP in the presence of mannitol is due to interference with CSF formation or Na^+ and H_2O movement across the blood-brain barrier.

Annals of Pharmacotherapy
2016, Vol. 50(4) 291–300

DOI: 10.1177/1060028016628893
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A Systematic Review of Randomized Controlled Trials Comparing Hypertonic Sodium Solutions and Mannitol for Traumatic Brain Injury: Implications for Emergency Department Management

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Abstract

Objective: To comparatively evaluate hypertonic sodium (HTS) and mannitol in patients following acute traumatic brain injury (TBI) on the outcomes of all-cause mortality, neurological disability, intracranial pressure (ICP) change from baseline, ICP treatment failure, and serious adverse events. **Data Sources:** PubMed, EMBASE, CENTRAL, Cochrane Database of Systematic Reviews, ClinicalTrials.gov, and WHO ICTRP (World Health Organization International Clinical Trials Registry Platform) were searched (inception to November 2015) using *hypertonic saline solutions, sodium chloride, mannitol, osmotic diuretic, traumatic brain injury, brain injuries*, and *head injury*. Searches were limited to humans. Clinical practice guidelines and bibliographies were reviewed. **Study Selection and Data Extraction:** 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. **Data Synthesis:** Of 326 articles screened, 7 trials enrolling a total of 191 patients met inclusion criteria. Studies were underpowered to detect a significant difference in mortality or neurological outcomes. Due to significant heterogeneity and differences in reporting ICP change from baseline, this outcome was not meta-analyzed. No difference between HTS and mannitol was observed for mean ICP reduction; however, risk of ICP treatment failure favored HTS (risk ratio [RR] = 0.39; 95% CI = 0.18-0.81). Serious adverse events were not reported. **Conclusions:** 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.

Neurosurgical Review
https://doi.org/10.1007/s10143-018-0991-8

ORIGINAL ARTICLE

Hypertonic saline or mannitol for treating elevated intracranial pressure in traumatic brain injury: a meta-analysis of randomized controlled trials

Jiajie Gu[1] · Haoping Huang[1] · Yuejun Huang[2] · Haitao Sun[3] · Hongwu Xu[4]

Received: 18 March 2018 / Revised: 5 May 2018 / Accepted: 4 June 2018

Abstract

Hyperosmolar therapy is regarded as the mainstay for treatment of elevated intracranial pressure (ICP) in traumatic brain injury (TBI). This still has been disputed as application of hypertonic saline (HS) or mannitol for treating patients with severe TBI. Thus, this meta-analysis was performed to further compare the advantages and disadvantages of mannitol with HS for treating elevated ICP after TBI. We conducted a systematic search on PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Wan Fang Data, VIP Data, SinoMed, and China National Knowledge Infrastructure (CNKI) databases. Studies were included or not based on the quality assessment by the Jadad scale and selection criteria. Twelve RCTs with 438 patients were enrolled for the meta-analysis. The comparison of HS and mannitol indicated that they were close in field of improving function outcome (RR = 1.17, 95% CI 0.89 to 1.54, $p = 0.258$) and reducing intracranial pressure (MD = − 0.16, 95% CI: − 0.59 to 0.27, $p = 0.473$) and mortality (RR = 0.78, 95% CI 0.53 to 1.16, $p = 0.216$). The pooled relative risk of successful ICP control was 1.06 (95% CI: 1.00 to 1.13, $p = 0.044$), demonstrating that HS was more effective than mannitol in ICP management. Both serum sodium (WMD = 5.30, 95% CI: 4.37 to 6.22, $p < 0.001$) and osmolality (WMD = 3.03, 95% CI: 0.18 to 5.88, $p = 0.037$) were increased after injection of hypertonic saline. The results do not lend a specific recommendation to select hypertonic saline or mannitol as a first-line for the patients with elevated ICP caused by TBI. However, for the refractory intracranial hypertension, hypertonic saline seems to be preferred.

A Comparison of Pharmacologic Therapeutic Agents Used for the Reduction of Intracranial Pressure After Traumatic Brain Injury

Ahmed M. Alnemari, Brianna M. Krafcik, Tarek R. Mansour, Daniel Gaudin

Key words
- Cerebral perfusion pressure
- Intracranial hypertension
- Management
- Traumatic brain injury

Abbreviations and Acronyms
HTS: Hypertonic saline
ICP: Intracranial pressure
TBI: Traumatic brain injury

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Citation: World Neurosurg. (2017) 106:509-528. http://dx.doi.org/10.1016/j.wneu.2017.07.009

Journal homepage: www.WORLDNEUROSURGERY.org

Available online: www.sciencedirect.com

1878-8750/$ - see front matter

OBJECTIVE: In neurotrauma care, a better understanding of treatments after traumatic brain injury (TBI) has led to a significant decrease in morbidity and mortality in this population. TBI represents a significant medical problem, and complications after TBI are associated with the initial injury and postevent intracranial processes such as increased intracranial pressure and brain edema. Consequently, appropriate therapeutic interventions are required to reduce brain tissue damage and improve cerebral perfusion. We present a contemporary review of literature on the use of pharmacologic therapies to reduce intracranial pressure after TBI and a comparison of their efficacy.

METHODS: This review was conducted by PubMed query. Only studies discussing pharmacologic management of patients after TBI were included. This review includes prospective and retrospective studies and includes randomized controlled trials as well as cohort, case-control, observational, and database studies. Systematic literature reviews, meta-analyses, and studies that considered conditions other than TBI or pediatric populations were not included.

RESULTS: Review of the literature describing the current pharmacologic treatment for intracranial hypertension after TBI most often discussed the use of hyperosmolar agents such as hypertonic saline and mannitol, sedatives such as fentanyl and propofol, benzodiazepines, and barbiturates. Hypertonic saline is associated with faster resolution of intracranial hypertension and restoration of optimal cerebral hemodynamics, although these advantages did not translate into long-term benefits in morbidity or mortality. In patients refractory to treatment with hyperosmolar therapy, induction of a barbiturate coma can reduce intracranial pressure, although requires close monitoring to prevent adverse events.

CONCLUSIONS: Current research suggests that the use of hypertonic saline after TBI is the best option for immediate decrease in intracranial pressure. A better understanding of the efficacy of each treatment option can help to direct treatment algorithms during the critical early hours of trauma care and continue to improve morbidity and mortality after TBI.

INTRODUCTION

The paradigm of evidence-based practice largely measures quality of care by improved patient outcomes. In neurotrauma care, a better understanding of treatments after traumatic brain injury (TBI) has led to a significant decrease in morbidity and mortality in this population; however, new research in this area continues to be produced. TBI represents a significant medical problem, affecting more than 10 million people in the global population annually.[1] Morbidity and mortality after TBI are associated with the complications of the initial injury, in addition to

A Comparative Study of Bolus Dose of Hypertonic Saline, Mannitol, and Mannitol Plus Glycerol Combination in Patients with Severe Traumatic Brain Injury

Harshad Patil[1] *and Rakesh Gupta*[2]

BACKGROUND: This prospective randomized controlled study compared the efficacy of an equiosmolar and isovolumetric dose of 3% hypertonic saline, 20% mannitol, and 10% mannitol plus 10% glycerol combination in reducing the raised intracranial pressure (ICP) in patients with severe traumatic brain injury (TBI).

METHODS: A total of 120 patients of severe TBI with increased ICP were randomized to receive an equiosmolar and isovolumetric dose of 3% hypertonic saline, 20% mannitol, and 10% mannitol plus 10% glycerol combination at a defined infusion rate, which was stopped when ICP was <15 mm Hg.

RESULTS: A total of 120 patients with severe TBI (aged >18 years, Glasgow Coma Scale ≤8, and had sustained elevated ICP of >20 mm Hg for more than 5 minutes) were randomized during the study. All data were presented as mean (minimum-maximum). A one-way analysis of variance test was used to analyze the effect across the treatment group, and Tukey's method was used for multiple comparisons. A paired *t*-test was employed to analyze the effect of the medication within each group. All 3 drugs decreased ICP below 15 mm Hg ($P < 0.0001$). The maximum change in ICP occurred after a bolus dose of 3% hypertonic saline followed by 10% mannitol plus 10% glycerol combination and then 20% mannitol (60% vs. 57% vs. 55%, respectively). Mean arterial pressure and cerebral perfusion pressure were increased after the bolus dose of study medications. Maximum changes occurred after infusion of 3% hypertonic saline followed by 10% mannitol plus 10% glycerol combination and 20% mannitol ($P < 0.0349$ and <0.0013, respectively). There was no statistically significant change in the hematocrit value noted after the bolus dose of any of the study medications. Serum sodium and osmolarity were raised significantly after the bolus dose of study medications. Maximum changes in serum sodium and osmolarity occurred after the bolus dose of 3% hypertonic saline. The mean dose required to reduce ICP below 15 mm Hg for 3% hypertonic saline: 1.4 mL/kg, for 10% mannitol plus 10% glycerine: 1.7 mL/kg, and for 20% mannitol: 2.0 mL/kg. The mean time required to reduce ICP below 15 mm Hg for 3% hypertonic saline: 16 minutes, for 10% mannitol plus 10% glycerine: 19 minutes, and for 20% mannitol: 23 minutes. The maximum change in the Glasgow Coma Scale occurred after the bolus dose of 3% hypertonic saline, followed by 10% mannitol plus 10% glycerol combination and then 20% mannitol.

CONCLUSIONS: All 3 osmotic compounds exhibit comparable effectiveness in reducing ICP when a similar osmotic load is administrated, but 3% hypertonic saline appeared to be more effective followed by 10% mannitol plus 10% glycerol combination and 20% mannitol. A dose of 1.4 mL/kg can be recommended as an initial bolus dose for 3% hypertonic saline. Hypertonic saline can be recommended to treat patients with pretreatment hypovolemia, hyponatremia, or renal failure. There is no clear benefit compared with 20% mannitol in regard to neurologic outcome, even though there is a minor positive trend for 3% hypertonic saline and 10% mannitol plus 10% glycerol combination.

Citation: World Neurosurg. (2019).
https://doi.org/10.1016/j.wneu.2019.01.051

Acta Neurochir (2017) 159:1553–1559
DOI 10.1007/s00701-017-3190-4

ORIGINAL ARTICLE - BRAIN INJURY

Aggressive medical management of acute traumatic subdural hematomas before emergency craniotomy in patients presenting with bilateral unreactive pupils. A cohort study

Arturo Chieregato[1] · Alessandra Venditto[2] · Emanuele Russo[2] · Costanza Martino[2] · Giovanni Bini[2]

Received: 26 October 2016 / Accepted: 13 April 2017 / Published online: 24 April 2017

Abstract

Background The outcome of patients with severe traumatic brain injury (TBI) and acute traumatic subdural hematoma (aSDH) admitted to the emergency room with bilaterally dilated, unreactive pupils (bilateral mydriasis) is notoriously poor.

Methods Of 2074 TBI patients consecutively admitted to our facility between 1997 and 2012, 115 had a first CT scan with aSDH, unreactive bilateral mydriasis, and a Glasgow Coma Score of 3 or 4. Sixty-two patients were unoperated and died within hours or a few days. The remaining 53 patients (2.5% of the 2074 consecutive patients) were scheduled for emergent evacuation of the aSDH. We compared three different dosages of mannitol to landmark different comprehensive levels of treatment: (1) a "*basic*" level of treatment characterized by a single conventional dose (18 to 36 g), (2) "*reinforced*" treatment landmarked by a single high dose (54 to 72 g), and (3) "*aggressive*" treatment landmarked by a single high dose (90 to 106 g). Doses above 36 g were administered intravenously over a period of 5 min.

Results Of the 53 selected patients, 7 were aggressively managed (13.2%) and 24 (45.3%) received reinforced treatment. Rates of hyperventilation and barbiturate bolus administration were appropriately associated with increasing doses of mannitol. After adjustment for age, aggressive management was significantly associated with a lower risk of death and persistent vegetative state [adjusted OR 0.016 (95% 0.001–0.405)]. Patients surviving after aggressive management suffered more severe disability at 1 year.

Conclusion The study shows an association between reduced mortality and persistent vegetative state, albeit at the cost of increased long-term severe disability in survivors, and aggressive medical preoperative management of mydriatic patients with aSDH following TBI.

Effect of Mannitol Infusion on Optic Nerve Injury After Acute Traumatic Subarachnoid Hemorrhage and Brain Injury

Gonul Guvenc, MD, Ceren Kizmazoglu, MD,† and Hasan Emre Aydin, PhD, MD‡*

Abstract: The primary aim of this paper is to investigate the neuroprotective and antiinflammatory effects of mannitol on optic nerve injury after acute traumatic subarachnoid hemorrhage and brain injury in rat models. Traumatic brain injury (TBI) and traumatic subarachnoid hemorrhage (tSAH) were produced by a custom-made weight-drop impact acceleration device. Thirty male Wistar rats were divided into 3 groups. Group I (n = 10) was the sham group, group II (n = 10) received TBI, and group III (n = 10) received TBI + mannitol (1 mg/kg intravenously). Optic nerve tissue glutathione peroxidase (GPx) and interleukin 1 beta (IL-1β) levels were measured 4 hours after the trauma. The authors used Kruskal–Wallis variance analysis and Mann–Whitney *U* tests for statistical analysis. Optic nerve tissue GPx levels were significantly higher in group III than in groups I and II ($P < 0.05$). Optic nerve tissue IL-1β levels were significantly lower in group III than in group II ($P < 0.05$) and higher than in group I ($P < 0.05$).

Mannitol increased the antioxidant GPx levels and decreased the IL-1β levels, which can protect the optic nerve from secondary injury after severe acute trauma. Mannitol plays an important role in the treatment of acute severe indirect optic nerve injury after TBI and tSAH.

Key Words: Glutathione peroxidase, interleukin-1 beta, mannitol, optic nerve, trauma

(*J Craniofac Surg* 2018;29: 1772–1775)

A Retrospective Study of Intracranial Pressure in Head-Injured Patients Undergoing Decompressive Craniectomy: A Comparison of Hypertonic Saline and Mannitol

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Objective: The impact of hypertonic saline (HTS) on the control of increased intracranial pressure (ICP) in head-injured patients undergoing decompressive craniectomy (DC) has yet to be established. The current retrospective study was conducted to compare the effect of HTS and mannitol on lowering the ICP burden of these patients.

Methods: We reviewed data on patients who had sustained a traumatic brain injury (TBI) and were admitted to the First People's Hospital of Kunshan between January 1, 2012, and August 31, 2017. Patients who received only one type of hyperosmotic agent, 3% HTS or 20% mannitol, after DC were included. The daily ICP burden (h/day) and response to the hyperosmolar agent were used as primary outcome measures. The numbers of days in the intensive care unit and in the hospital, and the 2-weeks mortality rates were also compared between the groups.

Results: The 30 patients who received 3% HTS only and the 30 who received 20% mannitol only were identified for approximate matching and additional data analyses. The demographic characteristics of the patients in the two groups were comparable, but the daily ICP burden was significantly lower in the HTS group than in the mannitol group (0.89 ± 1.02 h/day vs. 2.11 ± 2.95 h/day, respectively; $P = 0.038$). The slope of the reduction in ICP in response to a bolus dose at baseline was higher with HTS than with mannitol ($P = 0.001$). However, the between-group difference in the 2-weeks mortality rates was not statistically significant (2 [HTS] vs. 1 [mannitol]; $P = 0.554$).

Conclusion: When used in equiosmolar doses, the reduction in the ICP of TBI patients achieved with 3% HTS was superior to that achieved with 20% mannitol after DC. However, this advantage did not seem to confer any additional benefit terms of short-term mortality.

Keywords: traumatic brain injury, intracranial pressure, decompressive craniectomy, hypertonic saline, mannitol

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Specialty section:
This article was submitted to Neuro-Otology, a section of the journal Frontiers in Neurology

Received: *05 January 2018*
Accepted: *12 July 2018*
Published: *31 July 2018*

Citation:
Cheng F, Xu M, Liu H, Wang W and Wang Z (2018) A Retrospective Study of Intracranial Pressure in Head-Injured Patients Undergoing Decompressive Craniectomy: A Comparison of Hypertonic Saline and Mannitol. Front. Neurol. 9:631. doi: 10.3389/fneur.2018.00631

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