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Trauma to the Brain? Osmotics are the Game: An Update on Traumatic Brain Injury & Hyperosmolar Therapy

A presentation for HealthTrust members

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Speaker Disclosures

- The presenter has no real or perceived conflicts of interest related to this presentation

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Learning Objectives

- Describe the literature evaluating the use of hyperosmolar agents in the treatment of traumatic brain injury and identify areas for future research
- Identify patients with traumatic brain injury for which treatment with hyperosmolar agents would be appropriate
- List the potential risks and benefits of using hyperosmolar agents in the treatment of severe traumatic brain injury

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Background

According to the Centers for Disease Control and Prevention, traumatic brain injury (TBI) is defined as:

"A disruption in the normal function of the brain that can be caused by a bump, blow, or jolt to the head or a penetrating head injury."

Sources: Centers for Disease Control and Prevention. (2015). Report to Congress on Traumatic Brain Injury in the United States: Epidemiology and Rehabilitation. National Center for Injury Prevention and Control; Division of Unintentional Injury Prevention. Atlanta, GA.

Background

Alteration in brain function defined as one of the following:

- Any period of loss or decreased consciousness
- Any loss of memory for events immediately before or after the injury
- Neurological deficits such as muscle weakness, loss of balance or coordination, disruption of vision, change of speech or memory loss
- Altered mental status

Sources: Centers for Disease Control and Prevention. (2015). Report to Congress on Traumatic Brain Injury in the United States: Epidemiology and Rehabilitation. National Center for Injury Prevention and Control; Division of Unintentional Injury Prevention. Atlanta, GA.

Epidemiology

- Approximately 1.5 million visits to the emergency department annually are from TBI
- About 50,000 of these patients die from TBI
- Intentional self-harm, falls and motor vehicle collisions account for the majority of civilian TBI deaths
- Some characteristics of patients:
  - Higher rates in older adults (age >75) and young adults (age 15-24)
  - Males

Sources: Centers for Disease Control and Prevention (2019). Surveillance Report of Traumatic Brain Injury-related Emergency Department Visits, Hospitalizations, and Deaths—United States, 2014. Centers for Disease Control and Prevention, U.S. Department of Health and Human Services.

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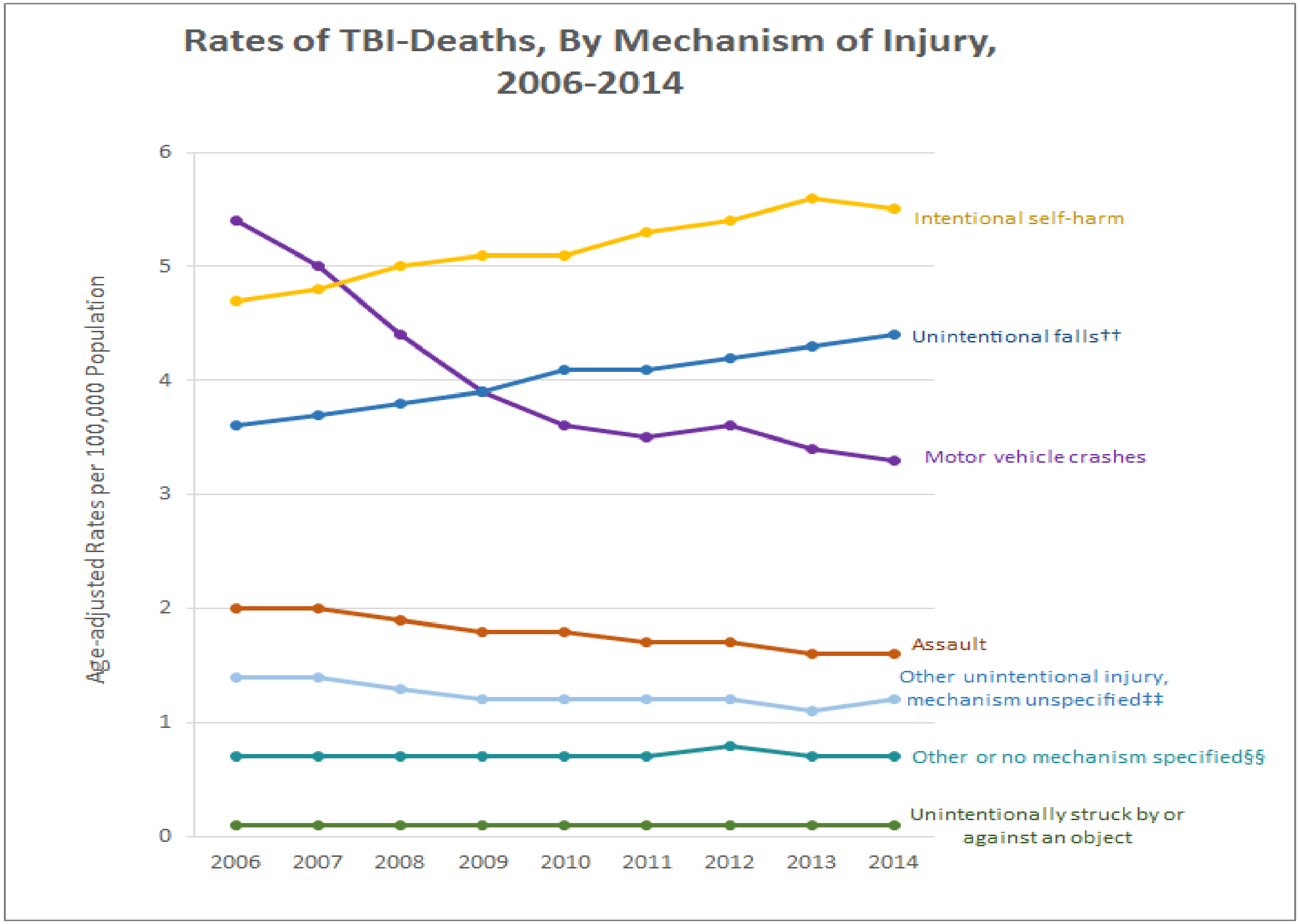
Epidemiology



Sources: Centers for Disease Control and Prevention (2019). Surveillance Report of Traumatic Brain Injury-related Emergency Department Visits, Hospitalizations, and Deaths—United States, 2014. Centers for Disease Control and Prevention, U.S. Department of Health and Human Services.

Conditions

- Subdural Hematoma
  - Buildup of blood in the subdural space
  - Symptomatic w/in 24 hours after trauma & usually have a loss of consciousness (LOC) & a Glasgow Coma Scale (GCS) less than 8
- Traumatic Subarachnoid hemorrhage
  - Outcome and mortality directly related to amount of blood in subarachnoid space & GCS
- Intracerebral hematoma (ICH)
  - 50% of patients with ICH will have LOC at time of impact

Sources: Advanced Trauma Life Support, Tenth Edition. 2018

Pathophysiology

- Primary Injury: Injury that occurs directly from the traumatic event
  - Direct impact, rapid acceleration and deceleration, penetrating injuries and blasts
- Secondary Injury: Injury to the brain due to other factors such as hypoperfusion, hypoxia or electrolyte disturbances

Sources: Advanced Trauma Life Support, Tenth Edition. 2018

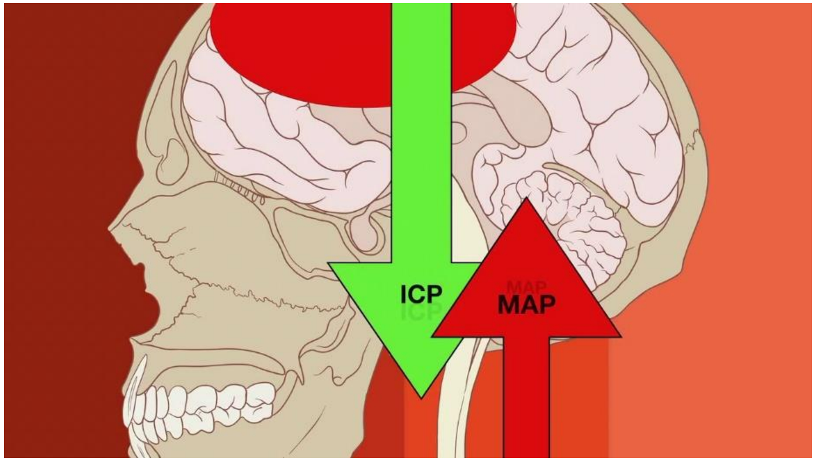
Cerebral Hemodynamics & Increased Intracranial Pressure

- Cerebral blood flow (CBF) or amount of blood flow to the brain, is dependent on varying **blood pressure, blood pH and oxygen/CO_2**
- Hypertension/alkalosis/hypocarbia promotes cerebral vasoconstriction
- When O_2 declines, vessels dilate to optimize oxygen supply to the brain

Sources: Advanced Trauma Life Support, Tenth Edition. 2018

Cerebral Hemodynamics & Increased Intracranial Pressure

- Cerebral blood flow dependent on pressure gradient across the blood brain barrier, also known as the cerebral perfusion pressure (CPP)
- Cerebral perfusion pressure decreases as intracranial pressure (ICP) increases
- Avoiding decreases in mean arterial pressure (MAP) are crucial
- Intracranial pressure considered **elevated** above 15 mmHg and **increased risk of mortality** in >22 mmHg



CPP = MAP – ICP

Sources: Advanced Trauma Life Support, Tenth Edition. 2018
Relationship between ICP, MAP and CPP. (2020). [Image]. Retrieved from https://i.ytimg.com/vi/I21hyLHP3Y0/maxresdefault.jpg

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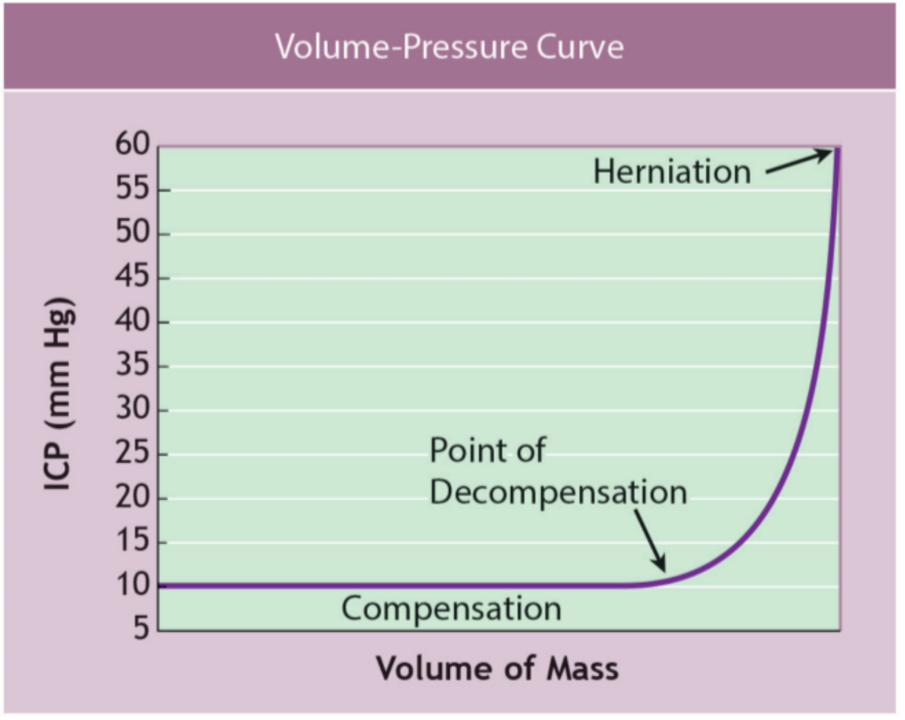
Monro-Kellie Doctrine

- Volume in intracranial space remains constant as skull is rigid
- Venous blood and CSF can be displaced to compensate for increase in the volume of mass



Sources: Advanced Trauma Life Support, Tenth Edition. 2018

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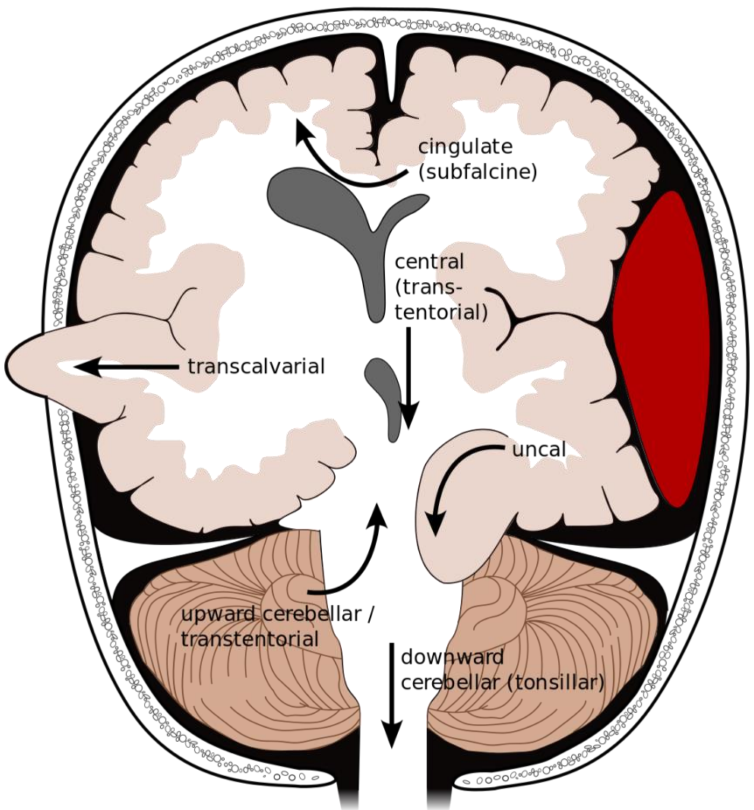
Complication of Increased ICP



- When the body is unable to compensate for the increased pressure in the skull, cerebral herniation is imminent
- Cerebral herniation is when the brain is displaced within the skull

Sources: Advanced Trauma Life Support, Tenth Edition. 2018

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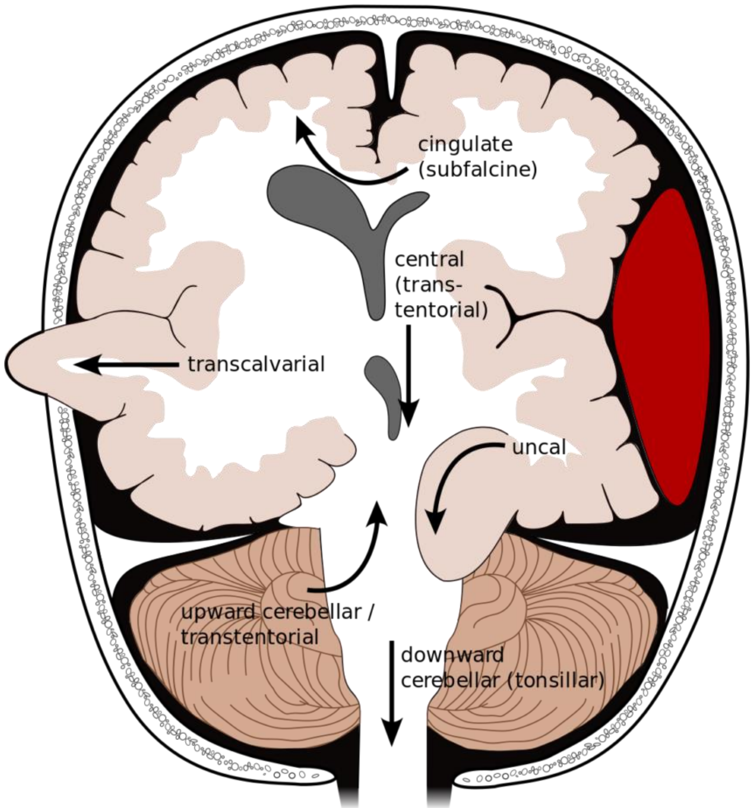
Types of Herniation



- Uncal herniation
  - Most common type
  - Due to hematomas in the lateral medial fossa & push brain matter into the uncus
- Cerebellotonsilar herniation
  - Occurs when a mass extends downwards and herniates through the foramen magnum
  - Respiratory & cardiovascular failure due to cerebellar dysfunction
- Central transtentorial herniation
  - Lesion or mass at the vertex of the brain pushing downwards

Sources: Advanced Trauma Life Support, Tenth Edition. 2018

Cushing's Reflex or Triad

- The Cushing's reflex or triad is a set of manifestations that result due to a life-threatening increase in ICP
- The three manifestations are:
  - Progressive hypertension
  - Bradycardia
  - Respiratory irregularity
- Approximately one-third of patients with life-threatening increases in ICP will exhibit the Cushing's Triad

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Neurological Examination

Pupillary Exam

- Pupil asymmetry, inability to react to light and/or dilated pupils indicative of pressure on Cranial Nerve III (CNIII)
- CN III has effects on parasympathetic fibers & pupil dilation due to unopposed sympathetic activity

Sources: Advanced Trauma Life Support, Tenth Edition. 2018

Neurology Exam

- Glasgow-Coma Scale after resuscitation and stabilization
  - Objective means of quantifying level of consciousness
  - Mild TBI (GCS 13-15)
  - Moderate TBI (GCS 9-12)
  - Severe TBI (GCS <9)

TABLE 6-2 GLASGOW COMA SCALE (GCS)

ORIGINAL SCALE	REVISED SCALE	SCORE
Eye Opening (E)	Eye Opening (E)	
Spontaneous	Spontaneous	4
To speech	To sound	3
To pain	To pressure	2
None	None	1
	Non-testable	NT
Verbal Response (V)	Verbal Response (V)	
Oriented	Oriented	5
Confused conversation	Confused	4
Inappropriate words	Words	3
Incomprehensible sounds	Sounds	2
None	None	1
	Non-testable	NT
Best Motor Response (M)	Best Motor Response (M)	
Obeys commands	Obeys commands	6
Localizes pain	Localizing	5
Flexion withdrawal to pain	Normal flexion	4
Abnormal flexion (decorticate)	Abnormal flexion	3
Extension (decerebrate)	Extension	2
None (flaccid)	None	1
	Non-testable	NT

Sources: Advanced Trauma Life Support, Tenth Edition. 2018

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Management

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General Management

Prevent secondary brain injury from hypoxia and hypotension

Airway management of Hypoxia/Hypercarbia

○Maintain SpO_2 above 90%	Intubation if: - GCS <9 - Possible risk of airway compromise - SPO_2 less than 90% despite supplemental O_2	Hyperventilation in life-threatening increases in ICP

Sources: (Carney, 2016)
(Advanced Trauma Life Support, Tenth Edition. 2018)

General Management

Prevent secondary brain injury from hypoxia and hypotension

Circulatory management of Hypotension

○Administer isotonic fluids (NS) or blood products	Maintain SBP >110 for patients age 15-49 and SBP >100 for patients age 50-69

Sources: (Carney, 2016)
(Advanced Trauma Life Support, Tenth Edition. 2018)

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Hyperosmolar Therapy

Hyperosmolar Therapy

- Since ICP is increased, CPP is decreased; therefore, blood flow into the brain is also decreased
- Hyperosmolar therapy is used to increase CPP by decreasing ICP instead of increasing MAP with vasopressors

CPP= MAP – ICP

Sources: Advanced Trauma Life Support, Tenth Edition. 2018

Hyperosmolar Therapy

- If the growing hematoma or mass extends beyond the capacity of the body's compensatory mechanisms, therapy beyond hyperosmolar therapy is needed (i.e., neurosurgical intervention)
- Hyperosmolar therapy is a temporizing measure & may bridge therapy for transport to the operating room for emergent decompression of the cranial space

Sources: (Carney, 2016)
(Advanced Trauma Life Support, Tenth Edition. 2018)

Brain Trauma Foundation Severe Traumatic Brain Injury Guidelines

- The most up to date edition of the Brain Trauma Foundation's (BTF) Severe Traumatic Brain Injury Guidelines provide recommendations on use of hyperosmolar agents for severe TBI
- These guidelines sought to compare the effectiveness of different hyperosmolar agents

Sources: (Carney, 2016)

Hyperosmolar Therapy

- Indication for use of Hyperosmolar Therapy
  - The current BTF Severe TBI Guidelines recommend restricting hyperosmolar therapy “prior to ICP monitoring to patients with signs of transtentorial herniation or progressive neurological deterioration not attributable to extracranial causes”
  - The 10th edition of the Advanced Trauma Life Support (ATLS) Guidelines mentions neurological deterioration as evident by development of “a dilated pupil, hemiparesis, or loss of consciousness”

Sources: (Carney, 2016)
(Advanced Trauma Life Support, Tenth Edition. 2018)

A Tale of Two Therapies

- Mannitol
  - Mainstay therapy according to current BTF Traumatic Brain Injury Guidelines
  - Postulated to reduce blood viscosity thereby increasing CBF & oxygen transport
  - Due to hyperosmotic properties, draws fluid out from brain
- Hypertonic Saline (HTS)
  - Alternative hyperosmotic agent with increasing use for TBI
  - Hypertonic solution to draw fluid from the brain

Sources: (Carney, 2016)
(Advanced Trauma Life Support, Tenth Edition. 2018)

Mannitol

- Mannitol has been used historically for traumatic brain injuries & is still the current recommendation by BTF for the control of raised ICP
- As per the ATLS 10th edition guidelines, the recommended dosing is as follows:
  - Impending herniation: 1 g/kg over 5–10 min.
  - Control elevated ICP: 0.25-1 g/kg over 30–60 min.

Sources: (Carney, 2016)
(Advanced Trauma Life Support, Tenth Edition. 2018)

Mannitol

- Available as a 20% solution IV bag or vial
- Warning & precautions
  - Can cause renal failure
  - Hypotension in large doses from action as an osmotic diuretic
  - Possible rebound cerebral edema due to leakage of mannitol into brain, reversing gradient
  - Can crystallize; therefore, needs to be warmed to prevent occurrence

Monitoring for Mannitol

- Mannitol should be monitored for serum osmolality. An osmolality of less than 320 mOsm should be maintained
- Fluid status
- Renal function
- Blood pressure
- Intracranial pressure (maintain below 20 mmHg)

Hypertonic Saline

- Available as a 3% or 23.4% solution
- Dosing
  - Impending herniation
    - **23.4% NaCl**: 30 to 60 mL over 5–10 minutes
    - **3% NaCl:** 250 mL over 15–30 minutes
  - Control elevated ICP
    - **3% NaCl:** 30 mL to 50 mL/hour

Sources: (Alnemari, Krafcik, Mansour & Gaudin, 2017)
(Maguigan, Dennis, Hamblin & Guillamondegui, 2017)

Hypertonic Saline

- Potential benefits
  - Is not an osmotic diuretic as mannitol is, therefore, hypotension less of a concern
  - Endothelium of blood-brain-barrier is less permeable to sodium and therefore more osmotically active
  - Less risk of adverse effects such as rebound ICP elevation and renal failure
  - Less volume required if using the 23.4%, which is beneficial in the hemorrhagic trauma patient

Sources: (Major, O'Connor & Mullan, 2014)

Hypertonic Saline

- Potential Risks
  - Central pontine myelinolysis
    - State in which there is programmed death of myelin-producing oligodendrocytes
    - Results in acute paralysis, dysphagia, and other neurological symptoms
    - Occurs when serum sodium is rapidly corrected during a hyponatremic state
    - Risk is greatest in those who have an initial sodium concentration ≤ 105 mEq/L, hypokalemia, alcoholism, malnutrition & liver disease

Sources: (Sterns, Hix & Silver, 2013)

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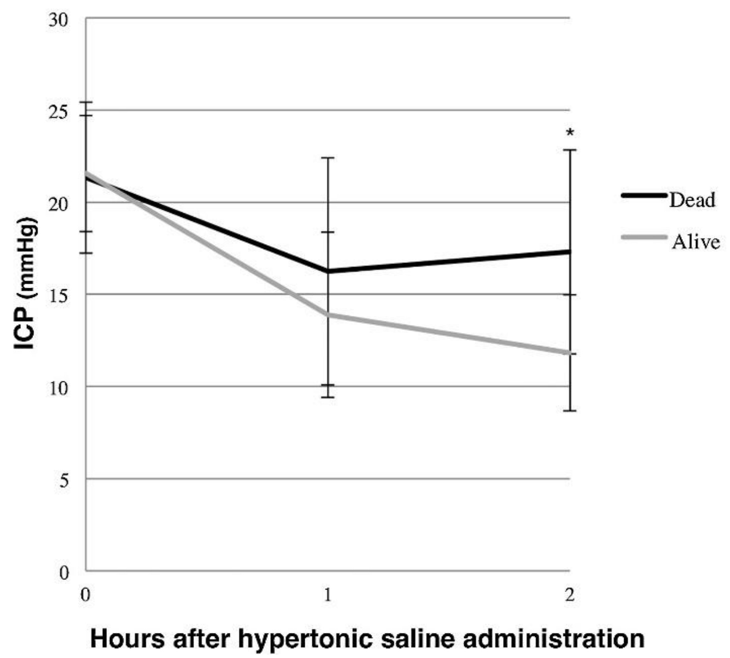
Hypertonic Saline

- Potential Risks
  - Rebound increase in ICP
    - One study noticed a rebound in ICP in non-survivors 2 hours after receiving HTS when compared to survivors
    - This finding was also consistent when the authors stratified for good vs. poor neurological outcome



Sources: (Colton et al., 2014)

Monitoring for Hypertonic Saline

- Hypertonic saline should be monitored for serum sodium levels. Maximum sodium level tolerable is 160 mEq/L
  - Maintain a gradual increase in sodium as rapid correction may result in central pontine myelinolysis
- Blood pressure
- Intracranial pressure (maintain below 20 mmHg)

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Clinical Studies

Cottenceau et al., 2011: Hypertonic Saline vs. Mannitol

- Randomized control trial
- Purpose of the study: to evaluate average time above an ICP of 20 mmHg
- Number of patients: 47 total
  - 22 patients in the HTS 7.5% group and 25 patients in the mannitol 20% group
- Results:
  - Average time of ICP >20 (11.1 ± 7.9 h) vs (8.4 ± +5.9 h)
  - HTS and mannitol both equally reduced ICP and increased CPP and cerebral blood flow
  - No difference in neurological outcomes
- Conclusion:
  - Mannitol was as effective as HTS in decreasing ICP in TBI

Sources: (Cottenceau et al., 2011)

Mangat et al., 2014: Hypertonic Saline vs. Mannitol

Design	A retrospective cohort study. (n=73)
Purpose	Compare the effects of mannitol and HTS on the cumulative and daily ICP burdens

Methods	• Inclusion: Age ≥ 16 and suffered a severe TBI in which they were hospitalized for at least 5 days
	• Interventions: Mannitol or hypertonic saline
	• Primary Outcomes: Cumulative ICP burden (%) and daily ICP burden (hours/day)
	  ◦ Cumulative ICP burden defined as percentage of days a patient had an ICP spike >25 mmHg
	  ◦ Daily ICP burden defined as average hours per day with an ICP >25 mmHg

Results	• Significant decrease in cumulative ICP burden and daily ICP burden with HTS vs mannitol • ICU length of stay was significantly lower for HTS • 2-week mortality was not significant
Conclusion	HTS given as bolus therapy was more effective than mannitol in lowering the cumulative and daily ICP burdens after severe TBI. HTS was able to lower number of ICU days but unable to show significant difference in 2-week mortality

	Mannitol (n= 25)	HTS (n=25)	P-value
Cumulative ICP burden (%)	36.5%	15.2%	0.003
Daily ICP burden (hours/day ± standard deviation)	1.3 ± 1.3	0.3 ± 0.6	0.001
ICU length of stay (days ± standard deviation)	9.8 ± 0.6	8.5 ± 2.1	0.004
2- week mortality	1:1 matched odds ratio 0.50 [95% CI 0.05-5.51]		0.56

Source: (Mangat et al., 2014)

Mangat et al., 2019: Hypertonic Saline vs. Mannitol

Design	A case-control study. (n=73)
Purpose	Compare the effects of mannitol and HTS on the combined burden of high ICP and low CPP in patients with severe TBI

Methods	• Inclusion: Age ≥ 16 and suffered a severe TBI in which they were hospitalized for at least 5 days
	• Interventions: Mannitol or hypertonic saline
	• Primary Outcomes: Combined cumulative and total ICP_{high} burden and CPP_{low} burden (%)
	  ◦ ICP_{high} burden defined as percentage of days a patient had an ICP spike >25 mmHg
	  ◦ CPP_{low} burden defined as percentage of days with a CPP <60 mmHg

Results	• Significant decrease in cumulative and total ICP_{high} + CPP_{low} for HTS compared to mannitol • Significant decrease in total CPP_{low} for HTS vs Mannitol • No difference in MAP <80 mmHg or vasopressor use
Conclusion	HTS given as bolus therapy was more effective than mannitol in lowering the incidence and duration of the combination of raised ICP and reduced CPP in patients with severe TBI. HTS also lowered in the incidence and duration of reduced CPP

Source: (Mangat et al., 2019)

	Mannitol (n= 25)	HTS (n=25)	P-value
Cumulative ICP_{high} + CPP_{low} (% days ±standard deviation)	28.1 ± 26.9	8.8 ± 10.6	<0.01
Total ICP_{high} + CPP_{low} (days ±standard deviation)	2.4 ± 2.3	0.6 ± 0.8	<0.01
Total CPP_{low} (days ±standard deviation)	3.6 ± 2.8	2.0 ± 1.7	0.03
Duration of MAP <80 mmHg (h [IQR]	32 [10-52]	28 [13-46]	>0.99

Clinical Scenarios

- Clinical scenarios in which mannitol may have benefit
  - Hypervolemic patients in which diuresis effects from mannitol may benefit patient
  - Patient with concern for central pontine myelinolysis (e.g. severely low sodium levels)
- Clinical scenarios in which hypertonic saline may have benefit
  - Hypotensive patient as it can be used as a resuscitative fluid
  - Settings in which mannitol warmer is unavailable

Summary

- In patients with traumatic brain injury, preventing secondary injury through ICP control is one of the main focuses
- Cerebral hemodynamics are largely based on a fixed intracranial volume in which our body can compensate for after TBI
- Hyperosmolar agents, such as mannitol & HTS, are used to control ICP and both agents have their respective risks and benefits
- According to the most recent data, HTS may have an advantage over mannitol in terms of reduction of ICP & increase in CPP

Patient Case

A 58-year-old male arrives in the emergency department as a trauma due to motor vehicle collision. The patient is hypotensive with a blood pressure of 93/52 mmHg and is tachycardic at 105 beats per minute. On physical exam, the patient’s pupils are asymmetric with his right pupil at 8 mm and the trauma team suspects impending herniation of the brain.

Assessment Question #1

- The team asks for your recommendation for a hyperosmolar agent for this patient. What is your recommended hyperosmolar agent and dosing for this patient?
  a. 1 g/kg IV bolus of mannitol over 5-10 minutes
  b. 30 to 60 mL bolus of 23.4% hypertonic saline over 10 minutes
  c. 15 mL bolus of 3% hypertonic saline over 30 minutes
  d. 10 mL bolus of 7.5% hypertonic saline over 10 minutes
  e. Patient does not require a hyperosmolar agent

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  d. 10 mL bolus of 7.5% hypertonic saline over 10 minutes
  e. Patient does not require a hyperosmolar agent

Assessment Question #2

- According to Mangat et al., 2014, which of the following was **not** a statistically significant finding regarding hyperosmolar therapy?
  a. Cumulative ICP burden
  b. Two-week mortality
  c. Daily ICP burden
  d. None of the above were statistically significant
  e. All the above were statistically significant

Assessment Question #2

- According to Mangat et al., 2014, which of the following was **not** a statistically significant finding regarding hyperosmolar therapy?
  a. Cumulative ICP burden
  b. Two-week mortality
  c. Daily ICP burden
  d. None of the above were statistically significant
  e. All the above were statistically significant

Assessment Question #3

- According to Mangat et al., 2019, which of the following was a notable result regarding hypertonic saline when compared to mannitol?
  a. Significant decrease in cumulative and total ICP_{high} + CPP_{low}
  b. Significant decrease in total CPP_{low}
  c. No difference in MAP <80 mmHg or vasopressor use
  d. All of the above
  e. None of the above

Assessment Question #3

- According to Mangat et al., 2019, which of the following was a notable result regarding hypertonic saline when compared to mannitol?
  a. Significant decrease in cumulative and total ICP_{high} + CPP_{low}
  b. Significant decrease in total CPP_{low}
  c. No difference in MAP <80 mmHg or vasopressor use
  d. **All of the above**
  e. None of the above

Assessment Question #4

- Which of the following may be indications for use of hyperosmolar therapy?
  a. Dilated/asymmetric pupils
  b. Hemiparesis
  c. Decorticate/decerebrate positioning
  d. “Cushing’s Triad”
  e. All the above

Assessment Question #4

- Which of the following may be indications for use of hyperosmolar therapy?
  a. Dilated/asymmetric pupils
  b. Hemiparesis
  c. Decorticate/decerebrate positioning
  d. "Cushing's Triad"
  e. **All the above**

Assessment Question #5

- Each of the following risks are associated with the correct hyperosmotic agent except?
  a. Mannitol: Severe hypotension due to osmotic diuretic properties
  b. Mannitol: Crystal precipitation
  c. Mannitol: Rebound increased ICP due to leakage into brain
  d. Hypertonic Saline: Central Pontine Myelinolysis
  e. Hypertonic Saline: Severe hypotension due to osmotic diuretic properties

Assessment Question #5

- Each of the following risks are associated with the correct hyperosmotic agent except?
  a. Mannitol: Severe hypotension due to osmotic diuretic properties
  b. Mannitol: Crystal precipitation
  c. Mannitol: Rebound increased ICP due to leakage into brain
  d. Hypertonic Saline: Central Pontine Myelinolysis
  e. **Hypertonic Saline: Severe hypotension due to osmotic diuretic properties**

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Thank you!

Additional questions may be directed to e-mail below.

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