OSMOLAR THERAPY
WITH A SIDE OF FLUIDS

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DISCLOSURE

• NO CONFLICT OF INTEREST
EPIDEMIOLOGY OF TBI

• US statistics
  • Leading cause of death in pts <45 years old
  • ~90,000 severely disabled
  • Cost > $100 billion/ year
EPIDEMIOLOGY OF TBI

- 75% have another organ system involved
- 25-50% mortality based on severity
  - GCS ↓ : morality ↑
- 40-50% EtOH involvement
PRIMARY INJURY
Physiologic response to primary insult
• Definitively pathologic

**PREVENTION IS WHERE WE SAVE LIVES**

**SECONDARY INJURY**

• Neuroprotective measures
  • MAP >80
  • Fever control/prevention
  • Avoid hypoxia/hyperoxia
  • pCO2 35-45
  • Na⁺ 135-145
  • Blood sugar 150-180
  • Prevention of seizure
MUNROE-KELLIE DOCTRINE

- Cranial Volume = Brain + CSF + Blood
CEREBRAL PERFUSION PRESSURE

- Intracranial pressure → equally distributed in all directions
  - Normal ICP: 0-10
  - Pathogenic: >22 for more than 5min
- MAP maintains blood vessel patency in face of pressure
- CPP = MAP – ICP
  - *Normal* CPP: 70-100
  - *Target* CPP: 60-70
WHY IS CPP IMPORTANT?

• “Blood pressure” of the brain → cerebral blood flow (CBF)
• Remember CPP = MAP – ICP
  • Can manipulate BOTH numbers in equation to manage CPP
    • MAP augmentation vs ICP reduction
  • Mortality ↑ 20% for every 10mmHg↓ CPP below 60
CAUSES OF ICP ELEVATION

• Increase in one or more component of intracranial contents
  • Blood $\rightarrow$ Intracranial bleeding
    • Blood gets in, can’t get out
  • CSF $\rightarrow$ Acute obstruction of cisterns
    • CSF is produced, flow is clogged?
  • Brain $\rightarrow$ Increase cell size or tumor
CEREBRAL EDEMA

- Vasogenic
- Breakdown in BBB
  - Proteins and fluid penetrate parenchymal extracellular space → rapid and extensive
CEREBRAL EDEMA

- Cytotoxic
  - BBB remains intact
  - Disruption of cellular metabolism
  - Impaired Na+/K+ pump
  - Retention of intracellular sodium and water
By increasing plasma osmolarity, edema (water) will move from the neuron into the bloodstream in order to normalize the concentration gradients.
<table>
<thead>
<tr>
<th></th>
<th>Mannitol 20%</th>
<th>Sodium Chloride 23.4%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equi-osmolar dose</td>
<td>0.5-1 gm/kg</td>
<td>0.687 mL/kg (30mL)</td>
</tr>
<tr>
<td>Osmolarity</td>
<td>1098 mOsm/L</td>
<td>7987 mOsm/L</td>
</tr>
<tr>
<td>Infusion</td>
<td>IVPB over 5-15min</td>
<td>IV push over 10-20min</td>
</tr>
<tr>
<td>Line</td>
<td>Central preferred</td>
<td>Central</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Osmolar Gap - trough BMP and serum osmolality Strict fluid ins/outs Electrolytes</td>
<td>Trough sodium levels</td>
</tr>
<tr>
<td>Holding Parameters</td>
<td>Serum osmolality&gt;320? Osmolar Gap &gt;10-15</td>
<td>Serum sodium &gt;155</td>
</tr>
</tbody>
</table>
MANNITOL

• Natural sugar found in fruits and vegetables
• Dual mechanism
  • Lowering blood viscosity (almost immediately)
    • Occurs very quickly → transiently increases cerebral blood flow and oxygen transport
    • *Increases venous drainage through compressed vessels*
  • Produces an osmotic diuresis
    • Increasing the solute concentration of the urine, increasing urinary output
• Reflection co-efficient of 0.9
• Requires in-line filter (precipitates-crystal formation)
• May be given via peripheral access
• Duration of effect 90 min – 6 hr
• Monitor trough osmotic gap → Rarely rely on sOsm cut-off of >320
  • Goal < 15-20 mOsm/L
  • Osmolar gap = Measured osmolality – Calculated osmolality
  • Osmolar gap = Measured osmolality – [(2 x Na) + (BUN/2.8) + (glucose/18)]
HYPERTONIC SALINE

- 23.4% HTS typically used "bullets"
  - 30mL push
- Inhibition of inflammation
- Increased cardiac output
  **Can be used if hemodynamically unstable
- Reflection co-efficient of 1.0

Increased ICP... well, I think that we need some more Salt! This should do nicely.
PICKING THE RIGHT THERAPY

- Mannitol = hypertonic saline
- Mannitol:
  - Avoid in acute kidney injury/ renal failure
  - Caution in hypovolemia or acute resuscitation
- Hypertonic saline
  - Avoid in chronic hyponatremia
  - Caution in respiratory failure/ acute chest trauma
  - Caution in heart failure
- There are times when alternating therapies is appropriate
CASE

- 25 YO male post TBI, sustained ICP 25-30 mmHg x 5 minutes
- Has received 3 doses of 23.4% NaCl and 2 doses of mannitol in last 24 hours
- Lab findings:
  - Na 154 mEq/L
  - K 4.5 mEq/L
  - Cl 119 mEq/L
  - HCO3 18 mEq/L
  - BUN 29 mg/dL (10.4 mmol/L)
  - Cr 1.1 mg/dL (97.3 umol/L)
  - Gluc 188 mg/dL (10.4 mmol/L)
  - Osm 341 mOsm/L

What is the best osmotic therapy for this patient for ICP control?

A. 30 ml of 23.4% NaCl
B. Mannitol at 1 gm/kg
OSMOLARITY CALCULATOR (EPIC)

Measured Osm: 341
Calculated Osm: 329
Osm Gap: 341 - 329 → 12 → Mannitol OK!
DISCONTINUING OSMOLAR THERAPY

The patient has been receiving osmolar therapy for several days with mannitol. As noted, ICP is now controlled and exam has significantly improved. In what manner should mannitol be discontinued?

A) Discontinue today and monitor closely for MS changes
B) Taper both dose and frequency over the next week
C) Defer to hospitalist upon transfer to step-down
DISCONTINUING OSMOLAR THERAPY

• Prolonged administration of osmolar therapy is associated with formation of idiopathic osmoles
  • Cellular response to extended “dehydration” and cytoskeleton stress

• Abrupt discontinuation of osmolar therapy results in significant plasma/neuronal osmolar gradient imbalance → profound and rapid rebound cerebral edema
DISCONTINUING OSMOLAR THERAPY

- No “recipe” for discontinuation, but should be tapered in both frequency and dose over several days to a week

<table>
<thead>
<tr>
<th>Day</th>
<th>Mannitol Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50g Q6hr</td>
</tr>
<tr>
<td>2</td>
<td>50g Q8hr</td>
</tr>
<tr>
<td>3</td>
<td>50g Q12hr</td>
</tr>
<tr>
<td>4</td>
<td>25g Q12hr</td>
</tr>
<tr>
<td>5</td>
<td>12.5g q12hr</td>
</tr>
<tr>
<td>6</td>
<td>12.5g x1</td>
</tr>
</tbody>
</table>
OSMOLAR THERAPY QUESTIONS
WHAT IS SHOCK?

Cardiogenic
Hypovolemic
Neurogenic
Obstructive
Septic
Hemorrhagic
Distributive
Anaphylactic
WHAT IS SHOCK?

Oxygen Supply

Oxygen Demand
WHAT IS SHOCK?
MANAGING PATIENT IN SHOCK

- Blood Pressure
- Cardiac Output
- Systemic Vascular Resistance
- Stroke Volume
- Heart Rate
- Preload
- Afterload
- Contractility
WHAT IS PRELOAD?

- Left ventricular end diastolic volume (LVEDV)
  - At the end of diastole, amount of *blood volume* in the left ventricle
  - Measure of stretch of the left ventricle
- Why does it matter?? → Stretch = Force
OPTIMIZING PRELOAD

- IV Fluids (crystalloids)
  - Normal saline
  - LR
- Colloids
  - Albumin
- Blood

↑SV
OK, SO WHICH FLUID?

- Crystalloid = Colloid
- Pro’s and con’s of each strategy

- Replace **blood** with **blood**
- Replace **plasma** with **colloid (albumin)**
  - Burns
- **Resuscitate** with **colloid and/or crystalloid**
- Replace **ECF depletion** with **saline** (Loss of water and salt)
  - Dehydration
## WHAT’S NORMAL ABOUT NORMAL SALINE?

<table>
<thead>
<tr>
<th></th>
<th>0.9% Saline</th>
<th>Blood Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺ (mEq/L)</td>
<td>154</td>
<td>134-145</td>
</tr>
<tr>
<td>Cl⁻ (mEq/L)</td>
<td>154</td>
<td>95-105</td>
</tr>
<tr>
<td>K⁺ (mEq/L)</td>
<td>0</td>
<td>3.6-5.0</td>
</tr>
<tr>
<td>Mg²⁺ (mg/dL)</td>
<td>0</td>
<td>1.5-2.5</td>
</tr>
<tr>
<td>Ca²⁺ (mg/dL)</td>
<td>0</td>
<td>8.5-10</td>
</tr>
<tr>
<td>HCO₃⁻ (mEq/L)</td>
<td>0</td>
<td>22-26</td>
</tr>
<tr>
<td>Osmolarity</td>
<td>308 (mOsm/L)</td>
<td>285-295 (mOsm/L)</td>
</tr>
<tr>
<td>pH</td>
<td>5.8 (4.5-7.0)</td>
<td>7.35-7.45</td>
</tr>
</tbody>
</table>
OK, SO HOW MUCH SODIUM IS THAT?

- 0.9% Saline → Means that there are 0.9g NaCl / 100mL
- So… in 1L of NS there are 9g of NaCl
OK, SO HOW MUCH SODIUM IS THAT?

52 Small bags of chips in 1 liter!!!!
SALINE PEARLS

- Most widely used IVF (200 million liters sold in US!)
- Not “normal” from chemical or physiologic standpoint
- Only 25-35% stays within the blood vessel
- Administration of large volumes may lead to interstitial edema and acidosis

<table>
<thead>
<tr>
<th>Volume Given</th>
<th>% That stays in vasculature</th>
<th>Volume that stays in vasculature</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000mL</td>
<td>~25%</td>
<td>250mL</td>
</tr>
</tbody>
</table>
### LACTATED RINGERS

<table>
<thead>
<tr>
<th></th>
<th>0.9% Saline</th>
<th>Lactated Ringers</th>
<th>Blood Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Na⁺ (mEq/L)</strong></td>
<td>154</td>
<td>130</td>
<td>134-145</td>
</tr>
<tr>
<td><strong>Cl⁻ (mEq/L)</strong></td>
<td>154</td>
<td>109</td>
<td>95-105</td>
</tr>
<tr>
<td><strong>K⁺ (mEq/L)</strong></td>
<td>0</td>
<td>4</td>
<td>3.6-5.0</td>
</tr>
<tr>
<td><strong>Mg²⁺ (mg/dL)</strong></td>
<td>0</td>
<td>0</td>
<td>1.5-2.5</td>
</tr>
<tr>
<td><strong>Ca²⁺ (mg/dL)</strong></td>
<td>0</td>
<td>3</td>
<td>8.5-10</td>
</tr>
<tr>
<td><strong>HCO₃⁻ (mEq/L)</strong></td>
<td>0</td>
<td>0</td>
<td>22-26</td>
</tr>
<tr>
<td><strong>Osmolarity</strong></td>
<td>308 (mOsm/L)</td>
<td>273 (mOsm/L)</td>
<td>285-295 (mOsm/kg)</td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td>5.8 (4.5-7.0)</td>
<td>6.5 (6-7.5)</td>
<td>7.35-7.45</td>
</tr>
<tr>
<td><strong>Lactate</strong></td>
<td></td>
<td>28mmol/L</td>
<td></td>
</tr>
</tbody>
</table>
LACTATED RINGERS PEARLS

• Developed in 1930’s → Hartmann’s solution
• Benefit is lack of impact on acid-base status…. BUT….
• Trend toward LR utilization over NS in most cases of resuscitation
  • Hypotonic → not good in TBI patients
  • Potassium → not good in renal patients??
    • ACTUALLY MAY BE BETTER
• AND it has lactate and we check lactic acid levels on EVERYONE???
WHAT HAPPENS TO LACTATE?

- Lactate and lactic acid are different entities

- Lactate $\rightarrow$ pyruvate $\text{OR CO}_2 + \text{H}_2\text{O}$
- $\text{H}_2\text{O} \rightarrow \text{H}^+ + \text{OH}^-$
- $\text{OH}^- + \text{CO}_2 \rightarrow \text{HCO}_3^-$

May PREVENT acidosis
### ARE BALANCED FLUIDS “BETTER”?

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Balanced Crystalloids (N=7942)</th>
<th>Saline (N=7860)</th>
<th>Adjusted Odds Ratio (95% CI)†</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major adverse kidney event within 30 days — no. (%)‡</td>
<td>1139 (14.3)</td>
<td>1211 (15.4)</td>
<td>0.90 (0.82 to 0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Components of primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-hospital death before 30 days — no. (%)</td>
<td>818 (10.3)</td>
<td>875 (11.1)</td>
<td>0.90 (0.80 to 1.01)</td>
<td>0.06</td>
</tr>
<tr>
<td>Receipt of new renal-replacement therapy — no./total no. (%)§</td>
<td>189/7558 (2.5)</td>
<td>220/7458 (2.9)</td>
<td>0.84 (0.68 to 1.02)</td>
<td>0.08</td>
</tr>
<tr>
<td>Among survivors</td>
<td>106/6787 (1.6)</td>
<td>117/6657 (1.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final creatinine level ≥200% of baseline — no./total no. (%)§</td>
<td>487/7558 (6.4)</td>
<td>494/7458 (6.6)</td>
<td>0.96 (0.84 to 1.11)</td>
<td>0.60</td>
</tr>
<tr>
<td>Sepsis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>744/6775 (11.0)</td>
<td>756/6691 (11.3)</td>
<td></td>
<td>0.96 (0.86–1.07)</td>
</tr>
<tr>
<td>Yes</td>
<td>395/1167 (33.8)</td>
<td>455/1169 (38.9)</td>
<td></td>
<td>0.80 (0.67–0.94)</td>
</tr>
</tbody>
</table>
Cerebral perfusion pressure can be manipulated by changing MAP, ICP, or both.

ICP reduction is generally achieved via osmolar therapy.

HTS and mannitol are equivalent in efficacy but each has caveats for use.

Osmolar therapy should be tapered.

IV Fluids are an important component of shock resuscitation.

“Normal” saline is a medication.

“Normal” saline does not resemble human plasma.

Balanced fluids MAY provide some protection against resuscitation related adverse events.
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