Literature Update

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No Conflict of Interest
140 mmol/L of sodium versus 77 mmol/L of sodium in maintenance intravenous fluid therapy for children in hospital (PIMS): a randomised controlled double-blind trial

Sarah McNab, Trevor Duke, Mike South, Franz E Babl, Katherine J Lee, Sarah J Arnup, Simon Young, Hannah Turner, Andrew Davidson

SPICO
Study style: Prospective RCT
Population: hospitalised children: age 3 months to 18 years
Intervention: Plasmalyte (+ glucose)
Comparator: 0.45% saline (+ glucose)
Outcome: Incidence of hyponatremia: <135 mmol/L + decrease > 3 mmol/L
Inclusion:
Patients requiring maintenance fluids (>50% daily requirements)

Exclusions:
Long list of medical (eg cirrhosis), Na<130, + surgical eg neuro

Method
Randomised to 0.45% saline or Plasmalyte
Study fluid was continued 72 h or until < 50% maintenance rate.
Early stop:
< 130 mmol/L or > 150 mmol/L, change at least 3 mmol/L
withdraw consent,
treating clinician

Measures:
U+Es: 6, 24, 48, and 72 hrs + treatment bloods
<table>
<thead>
<tr>
<th></th>
<th>0.45% Saline</th>
<th>Hartmann’s</th>
<th>Plasmalyte</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osmolality</td>
<td>150</td>
<td>274</td>
<td>294</td>
</tr>
<tr>
<td>Sodium</td>
<td>77</td>
<td>129</td>
<td>140</td>
</tr>
<tr>
<td>Chloride</td>
<td>77</td>
<td>109</td>
<td>98</td>
</tr>
<tr>
<td>Potassium</td>
<td>0</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Calcium</td>
<td>0</td>
<td>2.5</td>
<td>3</td>
</tr>
<tr>
<td>Magnesium</td>
<td>0</td>
<td>0</td>
<td>1.5</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>29(lactate)</td>
<td>27(acetate)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>23(gluconate)</td>
</tr>
</tbody>
</table>
Incidence of hyponatremia: <135 mmol/L + decrease > 3 mmol/L
Plasmalyte: 12 / 319 (3.8%) 0.45% Saline 35 / 322 35 (10.9%)
Difference: 7% (95% CI: 3 to 11%, P = 0.001)
The statistical significance of randomized controlled trial results is frequently fragile: a case for a Fragility Index


- **The Fragility Index**: number of events required to change statistically significant results to non-significant: $P > 0.05$, 95% CI includes 0
  - Fragility index 3 or less = *bad*
- 400 RCTs high impact journals: *NEJM, JAMA, Annals, Lancet, BMJ*
- Median FI = 8, 25% FI 3 or less
• Fragility index = 5
• Isotonic fluid protective against hyponatraemia compared to hypotonic
• Large heterogeneous population of children in hospital.
• Findings consistent across medical and surgical.
• Tended to exclude very sick and unusual
• Little evidence of increased adverse outcomes.
• Hospital-wide guidelines for maintenance IV fluids:
  • “isotonic fluid containing similar Na concentration to plasma”.
• Generalisability?: single centre, specialist hospital
• Anecdotally – game changer
Hypothesized that hydroxyethyl starch (HES) and albumin might be associated with increased odds for perioperative complications.

SPICO
Study style: Retrospective cohort study of population based data
Population: Patients for elective joint replacement
Interest: HES or Albumin
Comparator: Other fluids
Outcome: Acute renal failure, thromboembolic, cardiac, pulmonary comps
• Data from 510 US hospitals in the Premier Perspective database
• “We defined perioperative use of hydroxyethyl starch or albumin as use on the day of surgery and the day after surgery and excluded patients who were billed for either hydroxyethyl starch or albumin before or after this period”
• ICD-9 codes complications, less prescriptive than KDIGO
<table>
<thead>
<tr>
<th>Primary outcome variables</th>
<th>Hydroxyethyl starch (n=43732)</th>
<th>Albumin (n=8022)</th>
<th>Neither (n=999687)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute renal failure</td>
<td>764 (1.7)</td>
<td>273 (3.4)</td>
<td>13857 (1.4)</td>
</tr>
<tr>
<td>Thromboembolic complications</td>
<td>182 (0.4)</td>
<td>73 (0.9)</td>
<td>6631 (0.7)</td>
</tr>
<tr>
<td>Cardiac complications</td>
<td>1087 (2.5)</td>
<td>238 (3.0)</td>
<td>21619 (2.2)</td>
</tr>
<tr>
<td>Pulmonary complications</td>
<td>642 (1.5)</td>
<td>221 (2.8)</td>
<td>13193 (1.3)</td>
</tr>
<tr>
<td>Combined complications*</td>
<td>3289 (7.5)</td>
<td>916 (11.4)</td>
<td>67125 (6.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Hydroxyethyl starch v neither</th>
<th>Albumin v neither</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Odds ratio (95% CI)</strong></td>
<td><strong>P value</strong></td>
<td><strong>Odds ratio (95% CI)</strong></td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>1.23 (1.13 to 1.34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thromboembolic complications</td>
<td>0.89 (0.76 to 1.05)</td>
<td>0.153</td>
</tr>
<tr>
<td>Cardiac complications</td>
<td>1.22 (1.13 to 1.31)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulmonary complications</td>
<td>1.22 (1.11 to 1.33)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Combined complications*</td>
<td>1.20 (1.15 to 1.25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intensive care unit admission</td>
<td>1.53 (1.45 to 1.60)</td>
<td>&lt;0.001</td>
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</table>
Conclusions

HES 6% and albumin 5% associated with a higher risk of acute renal failure and of other complications after Elective total hip and knee arthroplasties – but composite

In US HES 6% in elective orthopedic surgery decreased and albumin 5% increased

These results question the widespread perioperative use of hydroxyethyl starch 6% and albumin 5%
-Balance of probabilities
The Effect of Adding Functional Classification to ASA Status for Predicting 30-Day Mortality

Ognjen Visnjevac, MD,*† Sina Davari-Farid, MD,*† Jun Lee, MSc,*† Leili Pourafkari, MD,*† Pradeep Arora, MBBS,*† Hasan H. Dosluoglu, MD,*† and Nader D. Nader, MD, PhD*†

SPICO
Study style: Retrospective cohort study
Interest: ASA + assistance ≥1 ADL
Comparator: ASA alone
Outcome: 30 Day mortality.
<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 10,533</td>
<td>N = 1791</td>
</tr>
<tr>
<td>ASA II</td>
<td>3624 (34.3%)</td>
<td>81 (4.6%)</td>
</tr>
<tr>
<td>ASA III</td>
<td>5587 (52.8%)</td>
<td>926 (53.1%)</td>
</tr>
<tr>
<td>ASA IV</td>
<td>941 (8.9%)</td>
<td>691 (39.6%)</td>
</tr>
<tr>
<td>Emergency surgery</td>
<td>661 (6.3%)</td>
<td>349 (19.5%)</td>
</tr>
<tr>
<td>Sex (Male %)</td>
<td>10361 (94.8%)</td>
<td>1390 (98.5%)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>63 (63–63)</td>
<td>74 (73–75)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28.7 (28.4–28.8)</td>
<td>26.7 (26.1–27.3)</td>
</tr>
<tr>
<td>Serum albumin (g/dL)</td>
<td>3.8 (3.8–3.8)</td>
<td>2.9 (2.9–3)</td>
</tr>
</tbody>
</table>
Recent paper: ASA + ADLs

>12,000 patients
30 day mortality
≥1 ADL (15%): OR 4.6
Albumin: OR 1.8
Emerg: OR 2.5

ROC: 0.71 vs 0.74
ROC: 0.81 vs 0.85
## Secondary outcomes

### Table 3. Early (30-Day) Postoperative Complications

| Complication                             | Group A  
|                                        | N = 10,533 | Group B  
|                                        | N = 1791 |
|-----------------------------------------|-----------|-----------|
| Stroke (%)                              | 40 (0.4) | 13 (0.7) |
| Myocardial infarction (%)               | 65 (0.6) | 27 (1.5) |
| Cardiac arrest (%)                      | 74 (0.7) | 65 (3.7) |
| Pulmonary embolization (%)              | 26 (0.2) | 8 (0.5)  |
| Pneumonia (%)                           | 235 (2.2) | 140 (8.0) |
| Failure to wean from mechanical ventilation (%) | 257 (2.4) | 192 (11.0) |
| Urinary tract infection (%)             | 221 (2.1) | 107 (6.1) |
| Renal insufficiency (%)                 | 117 (1.1) | 54 (3.1)  |
| Wound infection (%)                     | 465 (4.4) | 98 (5.6)  |
| Death within 30 days (%)                | 194 (1.8) | 226 (12.9) |
| Return to operating room               | 997 (9.4) | 376 (21.5) |
| Hospital length of stay (days)          | 5 (4–5)   | 8 (7–8)   |
“Functional dependence proved to be a reliable independent predictor of postoperative mortality within each ASA class.”

EDITORIAL

Is “Ol’ Reliable” Still Reliable?

Sorin J. Brull, MD, FCARCSI (Hon),* and Paul G. Barash, MD†

“It seems that >7 decades after the introduction of the “simple” ASA physical status classification system, we can improve the prediction in the quality of care. This will take a significant amount of time, resources, and proof of improvement in the patients’ clinical outcome. Until then, “ol’ reliable” seems to remain the only game in town.”
Time lag publication and PubMed updates…

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation

James D. Douketis, M.D., Alex C. Spyropoulos, M.D., Scott Kaatz, D.O.,

SPICO
Study style: Non-inferiority RCT
Population: AF + Warfarin for non-cardiac surgery, US + Canada
Intervention: Dalteparin (fragmin) bridging
Comparator: Placebo
Outcome: 30-day arterial thromboembolism.
“We hypothesized that forgoing bridging anticoagulation would be non-inferior to bridging with low-molecular weight heparin for the prevention of perioperative arterial thromboembolism and would be superior to bridging with respect to major bleeding.”

Non-inferiority <1% worse
**5 criteria:**

1) adult
2) warfarin (> 3 months), INR 2.0-3.0
3) temporary interruption of warfarin for elective surgery
4) chronic (permanent or paroxysmal) atrial fibrillation
   +/- mitral valve disease
5) have *at least one* major stroke risk factors:
   (a) Age >75 years;
   (b) hypertension;
   (c) diabetes mellitus;
   (d) congestive heart failure or left ventricular dysfunction;
   (e) previous ischemic stroke, TIA, systemic embolism
Exclusions

- Mechanical heart valve
- Stroke, systemic embolism or TIA within 12 weeks
- Major bleeding within past 6 weeks
- Calculated creatinine clearance <30mL/min
- Platelet count <100 × 10⁹/L
- Heparin allergy or HITS
- Patient is having: cardiac, neurosurgery (c) high-risk nonsurgical
- Surgeon precludes LMWH
Types of surgery

Minor surgery
- Endoscopy (with or without biopsy)
- Cardiac catheterization (+/-PCI)
- Dental surgery or other dental procedure
- Dermatologic procedure
- Ophthalmologic procedure

Major surgery
- Intraabdominal + thoracic surgery
- Major orthopaedic
- Vascular arterial
- Urology
- Any other surgery lasting ≥1 hour
Warfarin discontinued 5 days before
Dalteparin (bridging) 100 units/kg or placebo (no bridging) BD SC
Study drug started 3 days before
INR 1 day before:
    INR > 1.8, oral Vit K
    INR was 1.5 to 1.8, oral Vit K was optional
Study drug discontinued 24 hours before

Warfarin restarted evening or day after
Study drug restarted
- 12 to 24 hours after a minor (or low-bleeding-risk) surgery
- 48 to 72 hours after a major (or high-bleeding-risk) surgery
- Continue study drug until the INR > 2.0
1) **Symptomatic or clinically overt bleeding associated with 1+:**
   a. Transfusion $\geq 2$ units RBCs, and/or
   b. Decrease in hemoglobin $>20$ g/L, and/or
   c. Need for reoperation or invasive intervention

2) **Symptomatic or clinically overt bleeding at a critical site:**
   - intracranial, intraspinal, intraocular, retroperitoneal,
     intraarticular, pericardial, compartment syndrome

3) **Fatal bleeding**
   - Directly or causes clinical deterioration leading to death

Expected bleeding rates: 1.0% no-bridging vs 3.0% bridging
<table>
<thead>
<tr>
<th>Outcome</th>
<th>No Bridging (N=918)</th>
<th>Bridging (N=895)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial thromboembolism</td>
<td>4 (0.4)</td>
<td>3 (0.3)</td>
<td>0.01*</td>
</tr>
<tr>
<td>Stroke</td>
<td>2 (0.2)</td>
<td>3 (0.3)</td>
<td>0.73†</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>2 (0.2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>12 (1.3)</td>
<td>29 (3.2)</td>
<td>0.005†</td>
</tr>
</tbody>
</table>

Minor bleeding: 12% 21% P<0.001

Emboli: difference, 0.1 %; 95% CI: −0.6 to 0.8%
Conclusions

BRIDGE trial
Patients with atrial fibrillation who require temporary warfarin interruption for elective operation:

1. forgoing bridging anticoagulation was non-inferior to bridging for preventing arterial thromboembolism.

2. Forgoing bridging treatment also decreased the risk of major bleeding.

Few events overall
Not-bridging clinically effective
Assume cost effective
Cost-effectiveness plane

Difference in Cost

-  DOMINATED
  Higher costs, worse outcome
  +  Higher costs, improved outcome
-  Lower costs, worse outcome
  +  DOMINANT

Difference in Effectiveness
Reality is more subtle
Perioperative Medicine


Collaboratively managing patient and operative risks before, during, and after surgery to provide patient-centred, clinically effective and cost effective care

Anaesthesia-led perioperative medicine

“We need to increase our footprint in the pre-op and post-op period more, or we are going to go the way of the dinosaurs” – Mark Warner, past president, American Society of Anesthesiologists
Thanks!

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