What’s new in trauma resuscitation

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Associate Professor of Surgery, University of Melbourne, Royal Melbourne Hospital.
Choice of Fluid

Can we choose fluids that improve restoration of cellular O2 delivery without massive volume?

- Hypertonic fluids
  - Mobilise interstitial to plasma volume

- Colloids
  - Increase retention in circulation

- Blood & Hb Substitutes
  - Increase O2 carrying
Hypertonic saline vs Hartmanns
Cooper J, *JAMA*, 2004

- Hypotension + brain injury (n=229)
- HTS (7.5%) vs Hartmanns - 250 mls
- ISS 38, GCS 4

- Mortality equivalent: 45% (HTS) v 50%
  - No differences in secondary outcomes
- No differences in outcome at 6 mos
  - GOS, Return to work
Crystalloid vs colloid
Roberts, Cochrane Library, 2004

- Albumin or plasma protein fraction vs crystalloid
  - 19 trials, 7,576 patients
  - RR of death: 1.02 (0.93-1.11)

- Hydroxethyl starch (pentastarch/hetastarch)
  - 10 trials, 374 patients
  - RR of death: 1.16 (0.68-1.96)

- Dextran in hypertonic saline
  - 8 trials, 1,283 patients
  - RR of death: 0.88 (0.74-1.05)
Saline vs Albumin Fluid Evaluation study
ANZICS Clinical Trials Group

- Multicentre RCT fluid for intravascular volume in ICU
- Intervention: 4% Albumin vs NSaline during 1st 28 days
- Outcome death within 28 days, S/MOF, LOS, vent, renal.

  - 6997 heterogeneous ICU pts
  - RR death 0.99 (0.91-1.09), no diff other outcomes
- Albumin & NSaline equivalent

- Head Injured Pts – post hoc study (N Engl J Med. 2007;357(9):874-84.)
  - 460 pts, 69% with severe TBI
  - 24 mo. Mortality: 33% (Alb) v 20%, RR 1.63 (1.17-2.26)
- Albumin seems harmful in TBI
Comparison of Different Colloids
Bunn F, Cochrane Library, Jan 2008

- 70 trials, 4375 participants, death as outcome in 46 trials.

- Alb/PPF vs Hydroxyethyl Starch (HES): 25 trials (n=1234), RR 1.14 (0.91-1.43)
- Alb/PPF vs Gelatin: 7 trials (n=636), RR 0.97 (0.68-1.39)
- Alb/PPF vs Dextran: 4 trials (n=360), RR 3.75 (0.42-33.09)
- Gelatin vs HES: 18 trials (n=1337), RR 1.00 (0.80-1.25)
- Gelatin vs dextran and HES vs Dextran: not estimable.

- Conclusion: None safer or more effective than another.
What about Blood?

- Logical to replace what’s being lost.

But:
- Red cell transfusion strongly associated with later development of MOF/infection

- Association or causation?

Possible interventions
- More restrictive transfusion policy
- Manipulation of red cell preparation/storage
- Hemoglobin substitutes
Transfusion “Trigger” in the ICU
Hebert et al, *NEJM*, 1999

- Restrictive or Liberal transfusion policy:
  - Restrictive policy: 7 to 9 g/dl (Hct 23)
  - Liberal policy: 10 to 12 g/dl (Hct 33)
- Normovolemic, non-bleeding patients
# Transfusion Policy & Outcome

<table>
<thead>
<tr>
<th></th>
<th>Liberal</th>
<th>Restrictive</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>23.3%</td>
<td>18.7%</td>
</tr>
<tr>
<td>Age&lt;55</td>
<td>13.0%</td>
<td>5.7%*</td>
</tr>
<tr>
<td>Apache II&lt;20</td>
<td>16.1%</td>
<td>8.7%*</td>
</tr>
<tr>
<td><strong>Ventilator-free days</strong></td>
<td>Hebert et al, Chest, 2001</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>16.1 d</td>
<td>17.5</td>
</tr>
<tr>
<td>Intubated&gt;7 d</td>
<td>9.8 d</td>
<td>12.1*</td>
</tr>
</tbody>
</table>
Restrictive policy: Trauma subset analysis

McIntyre, *J Trauma*, 2004

- N=203, Mean ISS ~25
- Mortality equivalent (10% vs 9%)
- MOD scores, infection rates equivalent

**Conclusion**
- Restrictive Policy is safe
- Applicable to the resuscitated, euvolemic trauma patient
- Cannot be extrapolated to those with active bleeding
Hemoglobin-based blood substitutes

- Human
  - Diaspirin cross-linked (DCLHb) - Hemassist™
  - Polymerized Hgb - Polyheme™

- Animal (Bovine)
  - Polymerized Hgb - Hemopure™
Trauma resuscitation

- Shock
  - Clinical syndrome arising as a result of inadequate tissue perfusion
  - Discrepancy between cellular oxygen delivery and cellular oxygen demand

- Trauma resuscitation goal:
  - Optimize oxygen consumption (delivery) at the cellular level

- Resuscitation phase typically limited to the first 24 hours after injury
Diaspirin Cross-Linked Hgb in Trauma
Sloan, *JAMA*, 1999

- Multicenter, RCT
- Traumatic hemorrhagic shock: SBP<90
- DCLHb versus saline: 500 or 1000 mls: 2-4 units
- Outcome: mortality

- Trial stopped at interim analysis (n=111)
  - Mortality at 48 hrs: DCLHb: 38%, Saline: 21%
  - Mortality at 28 days: DCLHb: 47%, Saline: 25%

- Unlucky randomization?
- Hb scavenging effect of NO?
How much resuscitation is enough?

- Goal Directed Therapy
  - Simple measures:
    - BP, HR, U.O.
    - CVP
    - Base Deficit, SVO2
  - Invasive measures:
    - Pulmonary Artery Catheter
Traumatic shock

On ICU admission: art, PA catheter, baseline ABG, Hb, lactate

DO₂ goal

Yes

Monitor:
lactate, BD, PrCO₂, bladder pressure
Q 4h (reassess sooner if abnormal)

24 hours?

No

1) Hb (PRBC; Hb > 10)
2) volume (LR; PCWP > 15)

3) Optimize CI - PCWP
(Starling curve)

4) low dose Inotropes
5) vasopressor

No

Echocardiography

Yes

stop resuscitation standard ICU care
Goal-directed resuscitation using a PAC in trauma


- Randomized pts with hemorrhagic shock following trauma requiring operation
- Goals for control group
  - SBP>100, HCT>30, UO>1 cc/kg, BD<-3
  - IF PAC was inserted, DO2>450, VO2>130
- Goals for “optimal” group
  - CI>4.5, DO2>600, VO2>170
- Optimal endpoints
  - Reached in 70% of “optimal” group
  - Reached in 40% of control group
- Process of care
  - More inotrope use in “optimal” group & slightly more fluid given
Goal-directed resuscitation using a PAC in trauma

- Outcomes
  - Mortality 15% in optimal group, vs 11% in controls
  - ICU and hospital length of stay equivalent

- Comparison of patients who met optimal outcomes and those who didn’t
  - Higher mortality
  - Longer LOS
  - More organ failure
Supranormal Trauma Resuscitation Causes More Cases of Abdominal Compartment Syndrome

Zsolt Balogh, MD; Bruce A. McKinley, PhD; Christine S. Cocanour, MD; Rosemary A. Kozar, MD, PhD; Alicia Valdivia, RN; R. Matthew Sailors, PhD; Frederick A. Moore, MD

152 Resuscitation Protocol Patients

85 Patient

$\text{DO}_2\text{l} \text{ Goal} > 600$

71 Patients

$\text{DO}_2\text{l} \text{ Goal} > 500$
<table>
<thead>
<tr>
<th>Group</th>
<th>Age (years)</th>
<th>ISS</th>
<th>BD (mEq/L)</th>
<th>Pre-ICU LR (L)</th>
<th>Pre-ICU PRBC (U)</th>
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</thead>
<tbody>
<tr>
<td>DO₂I₆₀₀</td>
<td>37 ±3</td>
<td>28 ±3</td>
<td>9 ±1</td>
<td>6 ±1</td>
<td>5 ±1</td>
</tr>
<tr>
<td>DO₂I₅₀₀</td>
<td>33 ±2</td>
<td>27 ±2</td>
<td>9 ±1</td>
<td>5 ±1</td>
<td>5 ±1</td>
</tr>
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</table>
## Effect of manipulating the resuscitation goals

<table>
<thead>
<tr>
<th>Group</th>
<th>IAH %</th>
<th>ACS %</th>
<th>MOF %</th>
<th>Death %</th>
</tr>
</thead>
<tbody>
<tr>
<td>DO$<em>2$I$</em>{600}$</td>
<td>42 *</td>
<td>16 *</td>
<td>22 *</td>
<td>27 *</td>
</tr>
<tr>
<td>DO$<em>2$I$</em>{500}$</td>
<td>20</td>
<td>8</td>
<td>9</td>
<td>11</td>
</tr>
</tbody>
</table>

IAH = UBP $> 20$ mm Hg

* $p < 0.05$
Controversies

- Initial choice of resuscitation fluid
  - Massive fluid resuscitation vs controlled hypotension
  - Crystalloid vs colloid
  - Hypertonic versus isotonic

- Transfusion practices
  - Is there a role for a strict transfusion policy?
  - What is the role of blood substitutes?

- Endpoints for resuscitation
Summary so far

- Pendulum is moving away from massive volume resuscitation
  - No justification for routine use of colloids, hypertonic saline
- Hemorrhage control precedes significant volume resuscitation
- Transfusions
  - for the bleeding patient – replace what is actively being lost,
  - once bleeding stopped – restrictive policy
- PAC only for resuscitation failure & progressive hypoxaemia
  - Base deficit, urine output adequate in most

- Why is volume harmful?
  - Oedematous states
  - Pro-Inflammatory, gene activation?
- Are inotropes an alternative for promoting cellular O2 delivery without harm of volume?
Antioxidants in resuscitation phase: rationale

- Critically ill patients have an increase in circulating products of oxidative metabolism
  - Lipid peroxides (Goode, 1995)
  - Oxidation of protein thiols (Bunnell, 1993)

- Depletion of endogenous antioxidants
  - ↓ Total plasma antioxidant capacity
  - ↓ Plasma ascorbate (vitamin C)
  - ↓ α-tocopherol (vitamin E)
  - ↓ Reduced glutathione

- Parallels development of ARDS/MOF
Antioxidants in Reperfusion Injury

- Prospective RCT
- Penetrating trauma patients prior to complete resuscitation (n=18)
  - NAC 450 mg/kg/day
  - Vitamin C 300 mg/day
  - Vitamin E 1200 IU/day
  - Selenium 300 mg/day
- Groups well matched

<table>
<thead>
<tr>
<th></th>
<th>Control N=9</th>
<th>Antioxidant N=9</th>
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</thead>
<tbody>
<tr>
<td>MODS</td>
<td>3 (33%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Infections</td>
<td>8 (89%)</td>
<td>5 (56%)</td>
</tr>
<tr>
<td>ICU LOS</td>
<td>36 d</td>
<td>22 d</td>
</tr>
</tbody>
</table>
Antioxidants in the Resuscitation Phase  

- **Trauma/Surgical ICU, n=595**
- **Antioxidant arm**
  - Vitamin C (ascorbic acid) 1 gm IV q8h
  - Vitamin E (dl-α-tocopherol acetate) 1000 IU po/NG q8h
- **Control arm**
  - No antioxidant supplementation, standard care

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Antioxidant</th>
<th>Relative Risk/Decrease (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOF</td>
<td>18 (6.1%)</td>
<td>8 (2.7%)</td>
<td>0.43 (0.19-0.96)</td>
</tr>
<tr>
<td>Ventilation (d)</td>
<td>4.6 d</td>
<td>3.7 d</td>
<td>0.9 d (0.6-1.2)</td>
</tr>
<tr>
<td>ICU LOS</td>
<td>6.4 d</td>
<td>5.3 d</td>
<td>1.2 d (0.81-1.5)</td>
</tr>
<tr>
<td>28-day mortality</td>
<td>7 (2.4%)</td>
<td>4 (1.3%)</td>
<td>0.55 (0.2-1.9)</td>
</tr>
</tbody>
</table>
Inflammation and the Host Response to Injury, a Large-Scale Collaborative Project: Patient-Oriented Research Core—Standard Operating Procedures for Clinical Care

III. Guidelines for Shock Resuscitation

Frederick A. Moore, MD, Bruce A. McKinley, PhD, Ernest E. Moore, MD, Avery B. Nathens, MD, PhD, MPH, Michael West, MD, PhD, Michael B. Shapiro, MD, Paul Bankey, MD, PhD, Bradley Freeman, MD, Brian G. Harbrecht, MD, Jeffrey L. Johnson, MD, Joseph P. Minei, MD, and Ronald V. Maier, MD

- Large prospective cohort study designed to characterise the genomic and proteomic response to injury
- Protocols developed to minimize variation in care across centres
ICU Resuscitation

A

Continue CVP algorithm

B

PA catheter algorithm

C

Place arterial & PA catheters
Obtain baseline ABG & Hb
Assess need for intubation

D

Monitor

q 1 hour

24 hours?

Yes

Stop Resuscitation
Standard ICU Care

No

Cl ≥ goal
3.8 L/min - m²

E

Yes

1) Hb (PRBC; Hb ≥10)
2) Volume (LR; PCWP ≥15)

F

3) Optimize PCWP - Cl
(Starling curve)

G

4) Low-dose inotrope

H

5) Vasopressor

Echocardiography
Early Use of Vasopressors After Injury: Caution Before Constriction

Jason L. Sperry, MD, MPH, Joseph P. Minei, MD, Heidi L. Frankel, MD, Micheal A. West, MD, PhD, Brian G. Harbrecht, MD, Ernest E. Moore, MD, Ronald V. Maier, MD, and Ram Nirula, MD, MPH

- Observational study using Glue Grant Data
- Associations between Early Crystalloid Resusc & Mortality, and Early Peripheral-acting Vasopressor Use & Mortality
- 7 institutions 2003-2007
- 16-90 yo, Blunt trauma, Prehospital hypotension, Blood Tx in first 12/24, Not Isolated Brain/Spinal Cord Injury, not deemed “unsalvageable”, survived >48/24
- Cox proportional hazards model: physiologic, injury, treatment & demographic factors
921 pts, 12.3% mortality
177 ECR > 16 litres, 119 EV use
Both ECR & EV associated with older & sicker pts who had greater physiologic disturbance & more resuscitative interventions
Saline/Hartmanns & Fluid Resuscitation

- Approach largely unchanged since 1960’s
- Still using the lessons learned from Vietnam

“Fluids are good”

- Vietnam conflict
  - Aggressive use of crystalloid
  - Da Nang Lung - Shock Lung
Value of this study?

- Challenges the proposition that vasopressors are an alternative to fluid resuscitation in early treatment of haemorrhagic shock

- Able to consider a wide variety of potentially confounding factors, but there may be others.

- Prospective RCT is the next step
In the early resuscitation of most trauma patients, evidence supports giving priority to stopping bleeding, giving blood to replace what’s lost, and judicious use of crystalloids.

Mean arterial pressure >70, base deficit returning to normal & production of urine are adequate monitors in most pts, with HR, CVP and SaO2 as other important parameters to trend.
1980’s more fluid = better

- Bishop, Shoemaker et al:
  - ‘in critically ill patients ongoing ischemia is bad”
  - Treat “oxygen debt”

- Resuscitation *before* OR
  - Cut-downs
  - ATLS - emphasized IV access
  - Two litres then blood (became too many litres)
Excess mortality associated with the use of a rapid infusion system

Secondary effects of massive crystalloid resuscitation

- ALI/ARDS
- Cerebral edema
- Ocular compartment syndrome and blindness
- Abdominal compartment syndrome (ACS)
A role for controlled hypotension?

Bickell et al, NEJM, 1994

- Randomized 598 patients with shock following penetrating truncal injury in urban Houston:
  - Immediate fluid resuscitation
  - Delayed fluid resuscitation – postponed until after OR

- Transport times <30 minutes

- Fluid administration
  - Immediate group – 2500 cc given preop (2/3 in ED)
  - Delayed group – 280 cc given preop
Results

- Delayed group
  - Slightly improved survival – 62% vs 70%
  - Shorter hospital LOS
  - Less coagulopathy

- If anything, not harmful and possibly beneficial
  - Caveats: young patients, short transport times, penetrating injury

- Main Message: Stop the Bleeding First