

Hydroxyethyl Starch for Fluid Resuscitation

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Conflicts of Interest

- Bristol Myers Squibb
- Baxter Inc
- CSL Behring
- Plasma Protein Therapeutics Association

What are hydroxyethyl starch (HES) fluids?

How do the hydroxyethyl starches differ?

- **Size (Molecular weight)**
- **Concentration (6% versus 10%)**
- **Amount of substitution**
- **Ratio of substitution**
- **Carrier fluid**

HES fluids: different physiochemical properties

10% Pentastarch

6% Tetrastarch

**What do these differences mean
clinically?**

Crystalloid

Jungheinrich & Neff, Clin Pharmacokinet, 2005; Package Insert Voluven:

<http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/NewDrugApplicationsNDA/UCM083138.pdf>

Why do we use hydroxyethyl starch fluids for fluid resuscitation?

Other potential reasons.....

- **Microvascular perfusion**
- **Endothelial cell function and permeability**
- **Modulation of inflammation**

Are colloids better maintained in the intravascular space compared to crystalloids?

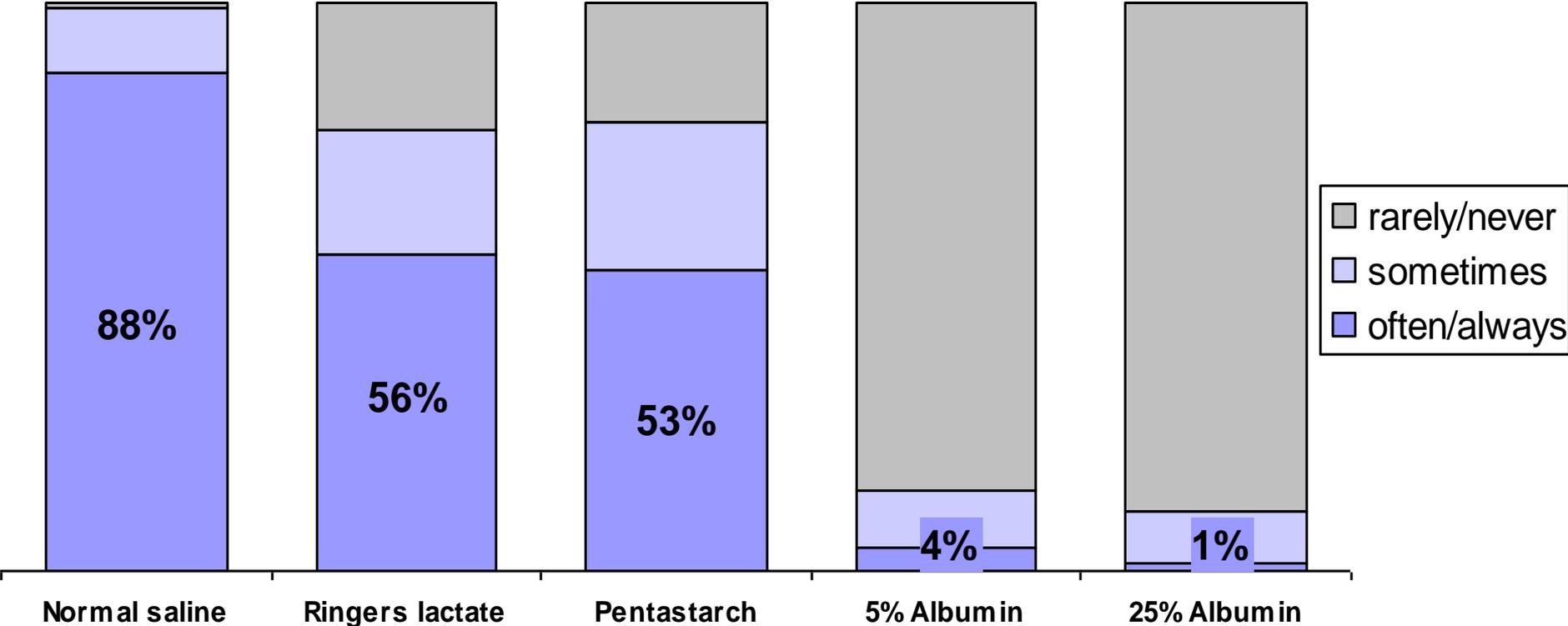
RCT/Yr	Population	Fluid Comparators	Ratio Colloid:Crystalloid
SAFE/04	Critically ill N = 6997	4% albumin vs normal saline	1:1.4
WISEP/08	Severe Sepsis/Septic Shock N = 537	10% ringer's vs normal saline	1:1.4
McIntyre/08	Septic shock	4% albumin vs 0.9% saline	1:1.1
McIntyre/12	Septic shock	5% albumin vs 0.9% saline	1:1.4
Perne...	Severe Sepsis and shock N = 800	6% HES (130/0.42) vs ringers acetate	1:1.1

Endothelial Cell Dysfunction and Leak

International Cross Sectional Study of Resuscitation Fluid Episodes in 391 ICUs

Fluid Type	
Crystalloid	33%
Colloid	48%
Type of Colloid	
HES	44%
Albumin	30%
Gelatin	25%
Dextran	3%

Canadian ICU physicians stated fluid resuscitation choices in early septic shock? (N=210)



The “HES for fluid resuscitation question” has been heightened

Editors-in-Chief Statement Regarding Published Clinical Trials
Conducted without IRB Approval by Joachim Boldt

ORIGINAL ARTICLE

Hydroxyethyl Starch 130/0.42 versus
Hydroxyethyl Starch or Saline for Fluid
Resuscitation in Intensive Care

Myburgh, J.2012, NEJM, October, 2012

Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care

Myburgh, J NEJM, October, 2012

- Double blind multi-centre RCT 7000 adult patients who required bolus fluid resuscitation in ICU
- 6% HES (140/0.4) versus normal saline for duration of ICU stay
- Requirement for fluid resuscitation inclusion criteria:
 - Heart rate > 90 beats per minute
 - SBP < 100 mm Hg or MAP < 75 mm Hg or ≥ 40 mm Hg decrease in SBP or MAP from baseline recording
 - Central venous pressure < 10 mm Hg
 - PAWP < 12 mm Hg
 - Respiratory variation in SBP or MAP > 5 mm Hg
 - Capillary refill time > 1 second
 - Urine output < 0.5 ml/kg for 1 hour

CHEST exclusion criteria

- Any previous fluid resuscitation in study ICU
- Patients receiving renal replacement therapy
- Impending dialysis (following 6 hours)
- Creatinine > 350 $\mu\text{mol/L}$ or urine output < 10 mls/hr over previous 12 hours
- > 1 L of HES in previous 24 hours
- Primary non – traumatic intracranial hemorrhage or severe traumatic intracranial hemorrhage
- ICU admission post cardiac surgery, or post liver transplantation

CHEST Outcome measures

- Primary outcome:
 - Death within 90 days
- Secondary outcomes within 90 day follow up:
 - Acute kidney injury (RIFLE)
 - Treatment with RRT
 - New organ failures
 - Duration of ventilation
 - Cause specific mortality

CHEST Baseline Characteristics

Baseline Characteristics	HES (n = 3358)	Saline (n = 3384)
Age <i>Median (IQR)</i>	63.1 (17)	62.9 (16.9)
Male <i>No (%)</i>	60.5	60.3
APACHE II <i>Median (IQR)</i>	17.0 (12.0 – 22.0)	17.0 (12.0 – 23.0)
APACHE II ≥ 25 <i>No %</i>	17.9	18.6
Diagnosis on Admission %		
Surgical	42.5	42.9
Non - surgical	57.3	57.0
Time from ICU admission to randomization <i>Mean (SD)</i>	10.9 +/- 156.5	11.4 +/- 165.4
Vasopressors <i>No (%)</i>	45.5	46.1
Acute Kidney Injury <i>No (%)</i>	36	36
Mechanical Ventilation <i>No (%)</i>	64.1	64.9

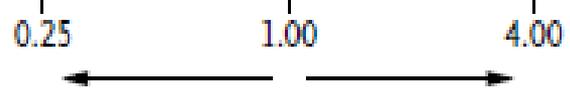
CHEST Results

	HES (n = 3358)	Saline (n = 3384)	P value
Study Fluid (mls) first 4 days Mean (SD)	526 (425)	616 (488)	<0.001
Blood Products (mls) first 4 days Mean (SD)	78 (250)	60 (190)	<0.001
CVP (mm Hg) first 4 days	11.3 (4.8)	10.4 (4.4)	<0.001

Variable	HES	Saline	Relative Risk (95% CI)	P Value
Outcome				
Primary outcome of death at day 90 — no./total no. (%)	597/3315 (18.0)	566/3336 (17.0)	1.06 (0.96 to 1.18)	0.26
Secondary outcomes — no./total no. (%)				
Renal outcomes				
RIFLE-R	1788/3309 (54.0)	1912/3335 (57.3)	0.94 (0.90 to 0.98)	0.007
RIFLE-I	1130/3265 (34.6)	1253/3300 (38.0)	0.91 (0.85 to 0.97)	0.005
RIFLE-F	336/3243 (10.4)	301/3263 (9.2)	1.12 (0.97 to 1.30)	0.12
Use of renal-replacement therapy	235/3352 (7.0)	196/3375 (5.8)	1.21 (1.00 to 1.45)	0.04
New organ failure†				
Respiratory	540/2062 (26.2)	524/2094 (25.0)	1.05 (0.94 to 1.16)	0.39
Cardiovascular	663/1815 (36.5)	722/1808 (39.9)	0.91 (0.84 to 0.99)	0.03
Coagulation	142/2987 (4.8)	119/3010 (4.0)	1.20 (0.95 to 1.53)	0.13
Hepatic	55/2830 (1.9)	36/2887 (1.2)	1.56 (1.03 to 2.36)	0.03
Tertiary outcomes — no./total no. (%)				
Death in ICU	364/3313 (11.0)	360/3331 (10.8)	1.02 (0.89 to 1.17)	0.81
Death within 28 days	458/3313 (13.8)	437/3331 (13.1)	1.05 (0.93 to 1.19)	0.40
Death in hospital	483/3307 (14.6)	456/3324 (13.7)	1.06 (0.95 to 1.20)	0.30
Mean Difference (95% CI)				
Service utilization — no.				
Days in ICU	7.3±0.2	6.9±0.2	0.4 (0.0 to 0.9)	0.07 ←
Days in hospital	19.3±0.3	19.1±0.3	0.2 (-0.8 to 1.1)	0.72 ←
Days receiving mechanical ventilation	6.0±0.2	5.7±0.2	0.4 (-0.1 to 0.8)	0.12 ←
Days receiving renal-replacement therapy	5.6±0.4	5.5±0.4	0.1 (-0.1 to 1.2)	0.86

B Subgroup Analyses

Subgroup	HES <i>no. of events/total no. (%)</i>	Saline <i>no. of events/total no. (%)</i>	Risk Ratio (95% CI)	P Value
Death from any cause at 90 days	597/3315 (18.0)	566/3336 (17.0)	1.06 (0.96–1.18)	0.26
RIFLE criteria at randomization				0.66
Presence of acute renal injury	99/519 (19.1)	95/503 (18.9)	1.01 (0.78–1.30)	0.94
Absence of acute renal injury	132/919 (14.4)	118/896 (13.2)	1.09 (0.87–1.37)	0.46
Sepsis at randomization				0.78
Diagnosis on admission	248/976 (25.4)	224/945 (23.7)	1.07 (0.92–1.25)	0.38
No diagnosis on admission	349/2337 (14.9)	342/2383 (14.4)	1.04 (0.91–1.19)	0.57
Trauma				0.90
Yes	18/258 (7.0)	18/263 (6.8)	1.02 (0.54–1.91)	0.95
No	579/3057 (18.9)	548/3073 (17.8)	1.06 (0.96–1.18)	0.26
Traumatic brain injury				0.31
Yes	1/27 (3.7)	3/30 (10.0)	0.37 (0.04–3.35)	0.35
No	594/3269 (18.2)	560/3287 (17.0)	1.07 (0.96–1.18)	0.23
APACHE II score before randomization				0.60
≥25	217/590 (36.8)	221/616 (35.9)	1.03 (0.88–1.19)	0.74
<25	372/2702 (13.8)	342/2690 (12.7)	1.08 (0.94–1.24)	0.25
Receipt of HES before randomization				0.78
Yes	48/508 (9.4)	42/499 (8.4)	1.12 (0.76–1.67)	0.57
No	547/2798 (19.5)	522/2825 (18.5)	1.06 (0.95–1.18)	0.31



CHEST conclusions

- No benefit of HES over saline for the treatment of hypovolemia
 - Potential small harm risk with HES (renal replacement therapy)
 - HES \$\$\$ compared to crystalloid

Should we generalize CHEST findings for...

- Patients who present with septic shock?
- Patients who present with shock from trauma?
- Which post – operative patients may we apply the CHEST results?

FIRST Trial: hypovolemic shock

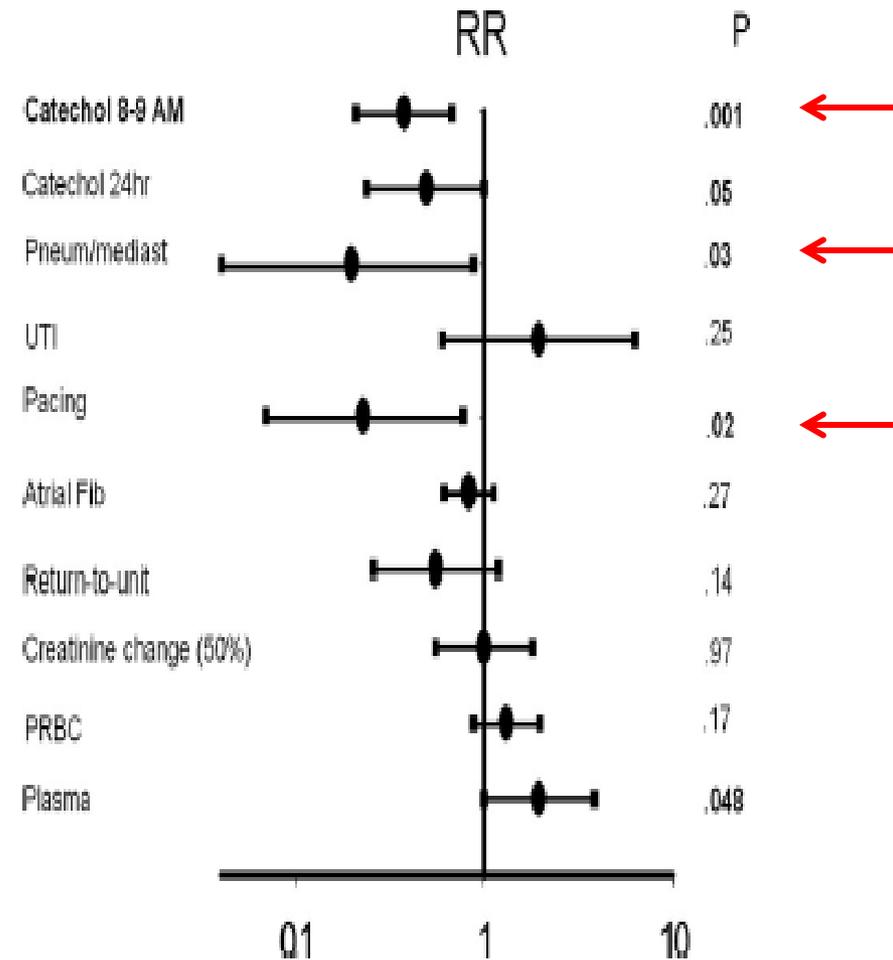
- Single centre double blind RCT 115 patients age 18 – 60 yrs with severe blunt and penetrating trauma who had received at least 2 litres of crystalloid fluid
- HES (130/0.4) versus saline according to algorithmic care
- Primary outcome: volume of study fluid in first 24 hours and return of normal gastrointestinal function by day 5

FIRST Trial: hypovolemic shock from trauma

- Return to gastrointestinal function similar
- 5 patients required dialysis: 2 in HES group and 3 in Saline group
- Penetrating group – lower plasma lactate level lower first 4 hours and on day 1 in the HES compared to saline group
- 18 (16.5%) deaths

Fluids after cardiac surgery: A pilot study of the use of colloids versus crystalloids*

- Single centre double blind RCT
- 237 cardiac surgical patients
- Post –operative study boluses of 0.9% saline vs. 10% pentastarch
- Nurse run flow directed algorithm
- Maximum study fluid 1 litre
- **Primary Outcome:** requirement for catecholamines the following post – operative morning



In Summary

- Generation of new and rigorous HES evidence over the last several months
- For the treatment of hypovolemia – no benefit for HES over saline
- Severe sepsis and septic shock....for Dr. Myburgh
- Other shock types like trauma, or higher risk peri-operative populations like cardiac surgery are populations that deserve further study

Thank you!