Normal Saline vs PlasmaLyte in Critically Ill Patients: a multicentre randomised controlled trial

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Background

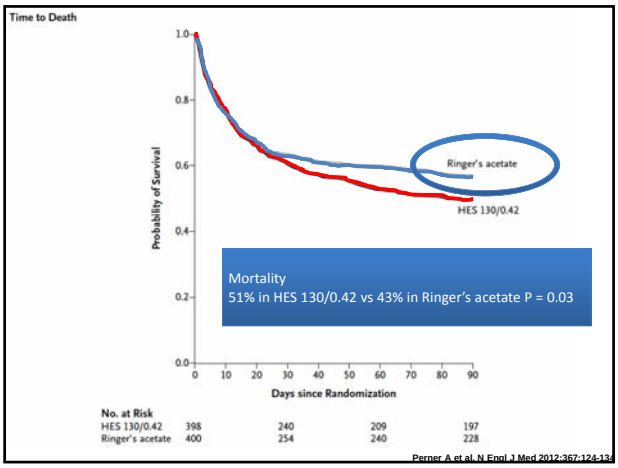
- Ongoing fluid debate in ICU
- Colloids role questioned and limited by recent studies.
- In RCT Colloids compared to balanced crystalloids or NaCl 0.9%
- High variability in use of crystalloids worldwide
- No RCT for NaCl 0.9% vs Balanced Crystalloids

ORIGINAL ARTICLE

Hydroxyethyl Starch 130/0.42 versus Ringer's Acetate in Severe Sepsis

Anders Perner, M.D., Ph.D., Nicolai Haase, M.D., Anne B. Guttormsen, M.D., Ph.D., Jyrki Tenhunen, M.D., Ph.D., Gudmundur Klemenzson, M.D., Anders Åneman, M.D., Ph.D., Kristian R. Madsen, M.D., Morten H. Møller, M.D., Ph.D., Jeanie M. Elkjær, M.D., Lone M. Poulsen, M.D., Asger Bendtsen, M.D., M.P.H., Robert Winding, M.D., Morten Steensen, M.D., Pawel Berezowicz, M.D., Ph.D., Peter Søe-Jensen, M.D., Morten Bestle, M.D., Ph.D., Kristian Strand, M.D., Ph.D., Jørgen Wiis, M.D., Jonathan O. White, M.D., Klaus J. Thornberg, M.D., Lars Quist, M.D., Jonas Nielsen, M.D., Ph.D., Lasse H. Andersen, M.D., Lars B. Holst, M.D., Katrin Thormar, M.D., Anne-Lene Kjældgaard, M.D., Maria L. Fabritius, M.D., Frederik Mondrup, M.D., Frank C. Pott, M.D., D.M.Sci., Thea P. Møller, M.D., Per Winkel, M.D., D.M.Sci., and Jørn Wetterslev, M.D., Ph.D., for the 6S Trial Group and the Scandinavian Critical Care Trials Group*

N ENGL J MED 367;2 NEJM.ORG JULY 12, 2012



Perner A et al. N Engl J Med 2012;367:124-134

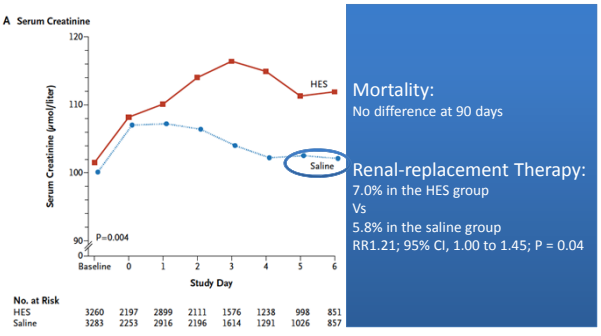
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care

John A. Myburgh, M.D., Ph.D., Simon Finfer, M.D., Rinaldo Bellomo, M.D., Laurent Billot, M.Sc., Alan Cass, M.D., Ph.D., David Gattas, M.D., Parisa Glass, Ph.D., Jeffrey Lipman, M.D., Bette Liu, Ph.D., Colin McArthur, M.D., Shay McGuinness, M.D., Dorrilyn Rajbhandari, R.N., Colman B. Taylor, M.N.D., and Steven A.R. Webb, M.D., Ph.D., for the CHEST Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group*

NEJM October 17, 2012

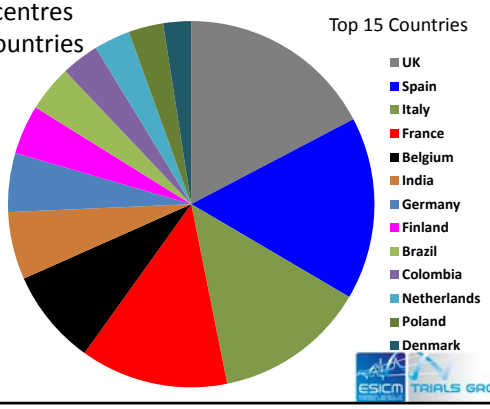


JA Myburgh et al NEJM 2012

2279 patients
311 centres
46 Countries

Fluid challENges in Intensive CarE (FENICE) Cecconi et al ICM 2015

Top 15 Countries



Fluid challENges in Intensive CarE (FENICE) Cecconi et al ICM 2015

Fluid Challenge Characteristics	
Volume ml	500 [500-999]
Rate ml/hr	1000 [500-1333]
Duration min	40 [24-60]
Crystalloids	74 %
Colloids	26 %

Variable	Human Plasma	Crystalloids		
		0.9% Saline	Compounded Sodium Lactate	Balanced Salt Solution
Trade name		Normal saline	Hartmann's or Ringer's lactate	PlasmaLyte
Colloid source				
Osmolarity (mOsm/liter)	291	308	280.6	294
Sodium (mmol/liter)	135–145	154	131	140
Potassium (mmol/liter)	4.5–5.0		5.4	5.0
Calcium (mmol/liter)	2.2–2.6		2.0	
Magnesium (mmol/liter)	0.8–1.0			3.0
Chloride (mmol/liter)	94–111	154	111	98
Acetate (mmol/liter)				27
Lactate (mmol/liter)	1–2		29	
Malate (mmol/liter)				
Gluconate (mmol/liter)				23

Differences in composition compared to Human Plasma

Main difference:
Osmolarity
Sodium
Chloride
Lactate/Acetate

JA Myburgh and M Mythen NEJM 2013

Acidosis and NaCl 0.9%

Table 1 | Trials comparing 0.9% NaCl with other crystalloid solutions

Reference	Patients	Design	Fluids	Main results
Young *et al.*[88]	46 Adult trauma	Randomized blind	0.9% NaCl vs. PL less hyperchloremia	PL less acidosis
Shaw *et al.*[20]	30,994 NS vs. 926 PL abdominal surgery	Observational retrospective	0.9% NaCl vs. PL	PL had less postop morbidity than 0.9% NaCl
Hadimioglu *et al.*[51]	30 Kidney Tx	Prospective randomized double blind	0.9% NaCl vs. PL vs. RL	0.9% NaCl raised acidosis RL rise ser Lac PL neither effect
O'Malley *et al.*[89]	52 Kidney Tx	Prospective randomized double blind	0.9% NaCl vs. RL	0.9% NaCl no adverse effect on renal function RL less hyperkalemia, acidosis
Scheingraber *et al.*[90]	24 Gynecological surgery	Randomized	0.9% NaCl vs. RL	0.9% NaCl caused acidosis but RL did not
Waters *et al.*[91]	66 Abdominal aortic aneurysm	Randomized double blind	0.9% NaCl vs. RL	0.9% NaCl caused acidosis no difference in outcome
Reid *et al.*[92]	9 Volunteers	Crossover double blind	0.9% NaCl vs. RL	Serum more acid HCO3- lower 0.9% NaCl than RL
Hasman *et al.*[93]	90 Patients emergency dept for rehydration	Prospective randomized double blind	0.9% NaCl vs. RL vs. PL	0.9% NaCl caused acidosis no other adverse effect
Zunini *et al.*[94]	122 Children undergoing craniofacial surgery	No randomization	0.9% NaCl vs. RL vs. PL	0.9% NaCl caused acidosis

Can Ince and A.B. Johan Groeneveld Kidney International 2014

NaCl and Acidosis

Handerson-Hasselbach:

- dilution of bicarbonate

SID explantion:

- increase in Chloride Ion concentration

NaCl 0.9% and acidosis:
1) very reproducible
2) Epiphenomenon or clinical problem?

Can Ince and A.B. Johan Groeneveld Kidney International 2014

Regulation of renal blood flow by plasma chloride.

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CS Wilcox J Clin Invest. 1983;71(3):726-735.

Decreased renal blood flow with high chloride infusion

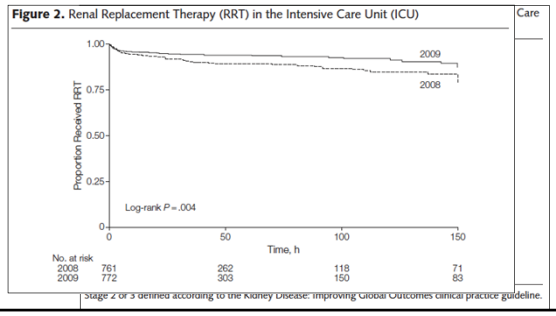
A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and Plasma-Lyte 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers.

AH Chowdhury Ann Surg. 2012;256(1):18-24.

SID reduced RBF decreased with NaCl, preserved with PlasmaLyte

Association Between a Chloride-Liberal vs Chloride-Restrictive Intravenous Fluid Administration Strategy and Kidney Injury in Critically Ill Adults

Yunos et al JAMA 2012



Major complications, mortality, and resource utilization after open abdominal surgery: 0.9% saline compared to Plasma-Lyte.

Shaw AD, et al Ann Surg. 2012

Outcome	NaCl 0.9%	PlasmaLyte	p
Mortality	5.6%	2.9%	<0.0001
Major Complications	33.7%	23%	<0.0001

Less Infections, RRT and electrolyte disturbances in the PlasmaLyte group

Fluid challENges in Intensive CarE (FENICE) Cecconi et al ICM 2015

Preliminary Data

Crystalloids use in FENICE	
NaCl 0.9%	46 %
Balanced solutions (Hartman's, Plasmalyte)	54 %

ESICM TRIALS GROUP

Study Aim and Hypothesis

- **Primary aim:**
  - To assess if the isotonic balanced solution PlasmaLyte is associated to an increased 90 days survival in critically ill patients.
- Hypothesis:
  - Ho: There is no difference in terms of 90 days survival between Normal Saline and Plasmalyte
  - H1:PlasmaLyte significantly increases the survival (decreases 90 day all cause mortality) in critically ill patients when compared to normal saline.

Study Aim and Hypothesis

- **Secondary Aim:**
  - To assess the effect of PlasmaLyte on renal function and need for RRT in patients admitted to an intensive care unit.
- Hypothesis:
  - Ho: There is no difference in terms of AKI and need for RRT between PlasmaLyte and Normal Saline
  - H1: The use of Plasma Lyte is associated to less requirement of renal replacement therapy for acute kidney injury.

Study Outcome Measures

- **Primary outcome**
  - 90 days all cause mortality.
- **Secondary outcomes**
  - AKI and need for RRT during ICU stay

  + others:
  - ICU LOS
  - Hospital LOS
  - Resource utilisation (ventilators days, vasoactive support etc)
  - Cost effectiveness analysis

Inclusion Criteria

- Emergency admissions over 18 years
- Requiring fluid resuscitation
- For active treatment
- Expected to survive more than 90 days at ICU admission

Exclusion Criteria

- Patient below 18 years old
- Expected to survive less than 90 days at ICU admission
- Patients admitted for palliation
- Patients with traumatic brain injury
- Patients considered at risk of developing cerebral oedema

For the secondary outcome (AKI and RRT) patients on RRT before ICU admission will be excluded from the analysis

Randomization

- Individual patient randomization

Initial idea:

Cluster Randomisation with cross over every 8 weeks :

Pros: efficient study design for recruitment:

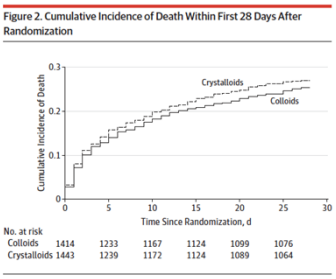
Cons: increased variability and confounders, and sample size, pharmacy logistics

Blinding vs Open Label

Open Label Study:

- Pros:
  - it allows for comparison of different use of drug
  - cheaper
- Cons: increased confounding factors and poor/no control of it

Effects of Fluid Resuscitation With Colloids vs Crystalloids on Mortality in Critically Ill Patients Presenting With Hypovolemic Shock
The CRISTAL Randomized Trial
Djillali Annane,MD et al for the CRISTAL Investigators



Mortality
- No difference at 28 days
- Lower mortality in colloid group at 90%

Blinding: not performed, considered not feasible.

Different use knowing type of fluid?

D Annane et al JAMA 2014

Interventions

- Patients randomized to NaCl or Plasmalyte will receive only the allocated fluid:
  - During the initial resuscitation phase
  - for all the duration of the ICU stay
- Dose, volume and rate of fluid administration will be at discretion of the treating physician

Sample Size

- Based on alpha level, one sided type 1 error rate of 0.05 and power of 90 % and expected 90 days mortality of 25% with difference in mortality of 2.5% between groups the sample size required will be:
- 6087 per group or 12174 in total.
- Based on drop-out rate of 2% the number of participants required is 12418.

Open Issues

- Blinding method
- Number of Units
- Clinician and Unit Equipoise
- Study Duration
- Fluids given pre and post-ICU
- Consent and Opt-out

Normal Saline vs Plasmalyte in Critically Ill Patients

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