

The 6S Trial

Scandinavian Starch for Severe Sepsis/Septic Shock Trial

Steering committee

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Management committee

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Background

Fluid therapy is life-saving in septic patients

Colloid solutions used to obtain fast and lasting effects

Use of hydroxyethyl starch - HES - may be supported by meta-analyses

Perel et al. *Cochrane Database Syst Rev* 2007; CD000567.

Bunn

et al. *Cochrane Database Syst Rev* 2008; CD001319.

High molecular weight HES 200/0.5 may cause acute kidney failure in patients with severe sepsis

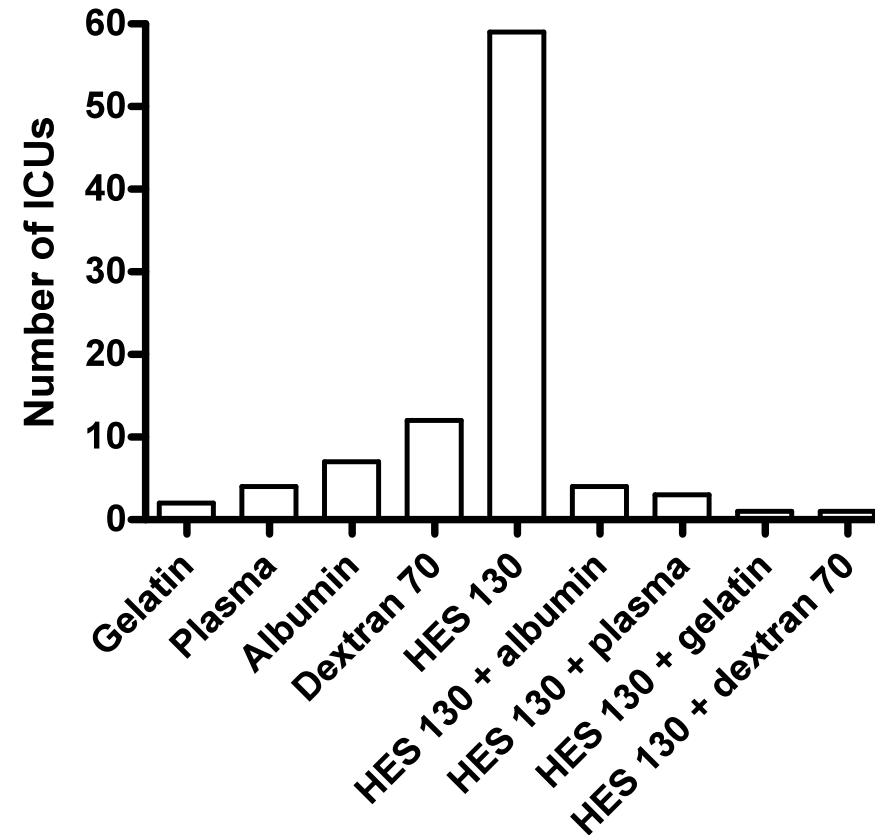
Schortgen et al. *Lancet* 2001; 357: 911-6

Brunkhorst

et al. *NEJM* 2008; 358: 125-39

Preferred colloid

Q-survey of 73 Scandinavian general ICUs in 2007



resuscitation fluid 1. day of septic shock

All septic shock pts in 3 months in 6 ICUs in DK, n=132:

Total fluid 6.265 ml (1.700 – 19.585)

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Crystalloid 109 patients – 83%

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Ringer, n=18	1000 ml (100 – 3800)

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Total fluid 6.265 ml (1.700 – 19.585)

Crystalloid 109 patients – 83%

NaCl, n=102	2000 ml (100 – 14300)
Ringer, n=18	1000 ml (100 – 3800)

Colloid 116 patients – 88%

HES 130, n=60	1500 ml (200 – 5500)
Albumin, n=51	500 ml (100 – 3300)
Dextran, n=41	1000 ml (500 – 3000)

6% HES 130/0.4

Pubmed: limits 'Human' and 'English':

- (130/0.4 or voluven) (septic or sepsis) random*:
2 studies
 - 1 ICU study: n=20, no predefined endpoints

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- (130/0.4 or voluven) (septic or sepsis) random*:
2 studies
1 ICU study: n=20, no predefined endpoints
- (130/0.4 or voluven) and shock and random*:
1 study
No ICU studies

Background

HES 130/0.4 is by far the preferred colloid in Scandinavian ICUs FLUIDS investigators. ACTA 2008; 52: 750-8

HES 130/0.4 is 1st choice colloid for severe sepsis in Scandinavian ICUs. Unpublished observations SAFE TRIPS

HES 130/0.4 given to > 50% of pts (1500 ml, 200-5500) in the East Danish Septic Shock Cohort

Very limited data on the effects of this starch in septic patients

Aim

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Design

Pragmatic, multicentre, randomised, blinded trial with concealed allocation of septic patients 1:1 to fluid resuscitation using

6% HES 130/0.42 in Ringers acetate
(Tetraspan) or Ringers acetate (Sterofundin)

Inclusion

Adult patients who

- Undergo resuscitation in the ICU AND
- Fulfil the criteria for severe sepsis/septic shock AND
- Consent obtainable

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Exclusion

- HES or malate allergy
- >1000 ml of synthetic colloid within 24 h
- Any form of renal replacement therapy
- Renal or liver Tx within current admission
- Intracranial bleeding within current admission
- Burn > 10% BSA
- P-K > 6 mM

Interventions

Trial fluid is to be used for volume expansion during the entire ICU-stay

Maximum dose of trial fluid 33 ml/kg/day followed by open treatment with Ringers acetate

Maintenance fluid and nutrition given as indicated

Initial resuscitation and blood products following the recommendations in the Surviving Sepsis Campaign



1. outcome measure

Composite endpoint of death or dialysis-dependency 90 days after randomisation

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2. outcome measures

- 28-day and ½- and 1-year mortality
- SOFA score at day 5 after randomisation
- Kidney failure (SOFA > 2) in the ICU
- Serious adverse reactions in the ICU: Severe bleeding or allergic reactions
- Hospital length of stay
- Days free of dialysis and ventilator for survivors

Safety



Trial fluid has to be stopped in case of

- Serious Adverse Reaction (SAR) – bleeding or allergy
- Suspected Unexpected Serious Adverse Reaction (SUSAR)
- Dialyse is commenced for kidney failure
- Consent is withdrawn / not granted

Saline or Ringers lactate for volume expansion during the remaining ICU-stay

Sample size

2 x 400 patients to show a 10% absolute difference in the 1. endpoint with an expected frequency of 50% in the crystalloid group, an alpha of 0.05 and a power of 80%

Interim analysis after 400 patients

Statistics

Intention-to-treat analysis comparing the 1. outcome measure in the two groups

Multiple logistic regression analysis adjusting for

Stratification variables:

shock and haematological malignancy

Age

Diabetes

Nephrotoxic drugs

Kidney failure at randomisation

SAPS II and SOFA score at randomisation



Time line

2009, Jan – Nov: Funding, Medicines agency and ethics

2009, Oct: Investigator meeting and trial site preparation

2009, 23. Dec: Randomisation of 1. patient

2010, Jan – April: Upstart of Danish and Finnish sites

2010, April – May: Upstart of sites in Swe, Nor and ICE

2011, June: Interim analysis

2012, Jan: Database closure and draft of manuscript



Budget - 900,000 Euro

Staff 300,000 Euro

Case money 200,000 Euro – 2000 DKK / pt

Monitoring 200,000 Euro

Data handling 150,000 Euro

Site visits and meetings 50,000 Euro

Funding: Danish research councils, Rigshospitalet,
ACTA foundation



Trial sites

25 - 30 sites to include 20 – 30 pts / site in a 1 – 2 yr period

Declared interest

DK: 18 sites

Swe: 5 sites

Fin: 3 sites

Nor: 3 site

Ice: 1 site

Collaboration



Phone-based randomisation and data handling
Copenhagen Trial Unit, Rigshospitalet

Monitoring

The CGP unit,

Platform for web-based data entry

Expertmaker (SSAI)

Delivery of study fluids

B Braun

Collaboration

DMSC

Clinician: D De Backer (chair)

Trialist: K Rowan

Statistician: Peter Dalgaard

Scientific Committee

Simon Finfer (Sydney), Andre Vercueil
(London), Lars Rasmussen (Copenhagen)
Frank Brunkhorst (Jena)

Individual Patient Data Meta-analysis

ANZICS CTG – John Myburgh

Septic pts from SAFE and CHEST study

Acknowledgment of contribution

All trial sites including patients will be acknowledged

All investigators will appear with their names under 'the 6S trial investigators' in an Appendix to the final manuscript.

Authorships will be granted by the SC

The Steering Committee

Trial site investigators including > 30 patients

Sites including > 60 patients: two authorships

Screening



Adult patients with severe sepsis who

Needs fluid resuscitation in the ICU




www.6S-trial.com

6s Trial Portal - Microsoft Internet Explorer er leveret af RH

Filer Rediger Vis Foretrukne Funktioner Hjælp

Tilbage Søg Mapper Foretrukne

Adresse <https://www.6s-trial.com/login.php> Gå Hyperlinks

 ExpertMaker

6S TRIAL

Username:

Password:

Login

LOGIN

Udført

Start Post - Microsoft Internet... 6s Trial Portal - Micro... Præsentationer Protocol 6S præsentation afdelin... 6S 2009-10-21-6S Trial prot... Internet

10:44

- Case View
- ▾ Screening
 - Create
- ▾ Cases
 - Select
 - Readmit

Case: Screening For assistance please call +45 3545 8415

Welcome to the 6S screening procedure

The following sequence of pages will take you through the screening procedure (inclusion and exclusion criteria) and the randomisation process. Finally you will be able to print out fluid charts for your patient. Estimated working time is less than 10 minutes.

You will need a telephone for the randomisation process.
Please answer every question throughout the procedure.

Patient identification

Patient's National Identification Number:

 [Info](#)

Samtykke



Umiddelbart

Forsøgsværge = 2 uafhængige læger:

1. Ad hoc læge (ikke ITA læge)
2. Stamafd. For-/bagvagt
3. Adm. Overlæge
4. Centrale forsøgsværger

Snarest muligt

Nærmeste pårørende + praktiserende læge
+ patienten selv

Hvad nu?



1. Væsker

Leveres fra B Braun:

80 Tetraspan + 160 Sterofundin

Pakkehold maskerer og nummerer - aflåst

2. Info materiale og inklusionsmapper

3. Undervisning ved behov

4. GCP enheden

5. Opstart