SCCTG Copenhagen 080403-04

The meeting was held in the excellent facilities at DGI-byen close to Copenhagen Grand Central Station. The meeting started as usual with coffe and informal discussions. Four projects were presented during the first evening.

INCUBATOR SESSION 20080403

TEMS (Transcutaneous Electrical Muscle Stimulation) to prevent muscle wasting in ICU patients. Jesper Poulsen, Rigshositalet Copenhagen

Causes of muscle wasting in ICU patients

- Immobilization
- Inflammation
- Steroids

(Septic shock patients exposed to all 3 factors)

Follow up studies show

- Poor physical function attributed to poor muscle function by patients
- 18% loss of body weight
- Normalised respiratory function after 6 months

Study: TEMS to prevent muscle wasting.
Hypothesis: Septic Shock and immobilization associated with significant reduction of physical function which may be prevented with TEMS. May result in improved physical capacity thus improving rehabilitation

Method: Interview HRQoL (Health Related Quality of Life), CT midfemur, Protein degradation/synthesis levels. Discussions about the influence of fluids on CT exams.

Mitocondrial function in platelets in patients with severe sepsis. Fredrik Sjövall, Rigshospitalet CPH/Lund University

Temporal changes in platelet mitochondrial function in patients with

- Sepsis
- Longstanding MOF
- Elective CABG

- In septic shock impaired mitochondrial function and thus impaired oxygen extraction (Levy RJ CCM 2007)
- Non-survivors of septic shock have lower ATP levels
- Mitocondrial activity measured with Oxygraph-2k (The Bull from Schröcken)
- O2-consumption as a function of mitochondrial function, loss of O2-consumption means loss of mitochondrial function
- Controls in blood from blodd bank
- Endpoints: SOFA, mortality, PCT, inotropes

Problems

- "Stimulation with ADP"
- Longstanding MOF very heterogenous group
- Analysis in platelets + other tissues should show same results to be clearly interpretable
- 48h not early Septic Shock
- Why do mitochondria not work in Septic Shock? Is it lack of substrate (ADP)? Other?
- How else can mitochondria be stimulated?
- Are the time points correct to detect mitochondrial dysfunction?

Luminal lactate in the rectum in patients with septic shock. M Ibsen, Rigshospitalet, Copenhagen

- Systemic hyperlactatemia is a late sign of splanchnic ischaemia (Jakobs, Shock 2000)
- Luminal rectal lactate on the other hand is less affected by systemic hyperlactatemia (Anesthesiology, Tenunen 1999)
- Rectal luminal lactate can be elevated in gut ischaemia despite normal systemic lactate
- The study could not detect high luminal or systemic lactate in patients with early septic shock

Effect of Levosimendan in early Endotoxic Shock in a porcine experimental model. Michelle Chew, UMAS, Lund University

Levosimendan

- Sensitizes TroponinC to Ca^{2+}
- Inotropic effect without increased myocardial O2-consumption
- Lusitropic effects
- Rigt ventricular effects (Morelli CCM 2006)
- Vascular effects on ATP sensitive K^{+} channels, vasodilatation
- Rescue therapy or drug of choice in septic shock?
- Pros: Full cardiac cycle support, no increase in O2-consumption
- Cons: Shunting in pulmonary circulation? Refractory hypotension in an already vasodilated situation?

Michelle Chew found with Levosimendan

- Increased CI
- Increased lactate (surprisingly)
- Increased pro-inflammatory cytokines (surprisingly)
- No evidence of improved myocardial contractility
- No great difference in haemodynamics (surprisingly)
- Bleeding and oedema in the myocardium (in properly resuscitated animals)

However, problems with timing of study drug to represent clinical situation.

This presentation ended the first day.

Dinner at the restaurant in DGI byen

BUSINESS MATTERS 20080404

The SCCTG board suggests yearly meetings instead of twice yearly. Next meeting in Oslo, 2009. Information about home page and Expert maker software for SSAI related research. SCCTG has been contacted by the Canadian CTG regarding potential common meetings for all critical care trial groups. We will support such an initiative.

Ongoing Studies in SCCTG

Hypothermia Network Study. Niklas Nielsen, Helsingborg

Mild therapeutic hypothermia for cardiac arrest. 2002 NEJM + ILCOR 2003. Included in AHA and ERC guidelines.
Hypothermia Network Registry with data from 7 countries and 35 hospitals.
1100 patients analysed with 6 month data.
CPC (1-5): Good, moderate, severe, coma, death. At 6 months 47% dead, 36% CPC 1 (of patients who received hypothermia). Complications and utilisation of resources acceptable. Surprisingly high survival with good outcome among patients with primary asystole. High survival for patients with time to restoration of circulation longer than 40 minutes. Multivariate analysis under way.

The Scandinavian Glutamine Study. Jan Wernerman, Huddinge

n = 1000. Largest study so far on glutamine for ICU population. End point SOFA. Study closed, data not analyzed.

FLUIDS Study, Anders Perner, Rigshospitalet CPH

Web-based survey: Most units used both natural and synthetic colloids. HES 130 by far the prefered colloid with few contraindications. Article in press in ACTA.
SAFE TRIPS I Scandinavia: Inception cohort study by ANZICS CTG. Preliminary results: 400 Scandinavian patients included in 63 ICUs, 200 patients received 450 volume boluses, 30% crystalloids, 30% synthetic and natural colloids (most frequently HES 130 and HA) and 30% blood products. Data are being analysed by ANZICS CTG.

Study Proposals

Scandinavian Starch for Severe Sepsis/Septic Shock Study (6S). A Perner, Rigshospitalet

Starch may cause renal failure in sepsis

- Effects of hydroxyethyl starch and gelatin on renal function in severe sepsis: a multicentre randomised study HES 200. Schortgren, Lancet 2001
- Brunkhorst NEJM 2008 HES 200 (VISEP)

Proposed study n = 600. 6% HES 130 (Tetraspan) 50 ml/kg/d vs. crystalloid (Ringer acetate)

Inclusion criteria: Resuscitation in ICU due to severe sepsis/septic shock
Exclusion criteria

- Allergy to HES
- >100 ml of synthetic colloid within current septic episode
- ARF/CRF
- DNR
- Renal or liver transplant
- Other trial in same patient

Primary Endpoint: ARF (RIFLE)
Secondary Endpoints: 30d, 90d and 1 year mortality, SOFA score at d5, transfusions, Surviving sepsis campaign protocol followed for resuscitation

Electrographic Status Epilepticus and Outcome after Cardiac Arrest. Evaluation of Aggressive Treatment of SE when monitoring cerebral status with aEEG. M Rundgren, Lund

- 10-37% SE in comatose patients after CA
- High Mortality
- Electrical SE, flat EEG and spontaneous Burst suppression patterns predict bad outcome
- No randomized trial but a pilot with aggressive treatment with propofol/pentothal? to flat EEG when ESE after cardiac arrest. Hypothesis: no benefit of treatment.

Hypothermia for Cardiac Arrest, Niklas Nielsen Helsingborg
Two randomized studies where only one are of adequate quality. Selected population. Trend that data are extrapolated quite liberally. Further studies warranted
Problems if clinical equipoise still exists in the clinical community. Many centres would regard normothermia as unethical.
Proposed study

- Hypothermia vs normothermia in asystole/PEA
- Hypothermia vs controlled normothermia in all patients (patients in the previous studies did not control for fever)

Other studies of importance

- Duration of treatment
- Timing of hypothermia
- Depth, what temperature is the optimum?

<u>Large Clinical Trials in the ICU – Why and How</u>
Why are high quality RCTs important? Jörn Wetterslev, Copenhagen Trial Unit
Interventions in human disease best tested on humans, humans are not magnified cell cultures and are very different from other species. Discussion on meta analyses and trial sequential analysis (TSA). The history of perioperative beta blockade.
Info on TSA on CTU:s homepage www.ctu.rh.dk

GCP. Karen Friis Bach, GCP Unit of Univeristy of Copenhagen
2001 EEC GCP legislation: all studies with medical products must follow

- Protocol
- GCP
- Other national legislations

Proper monitoring mandatory, Danish GCP unit offers 200h of monitoring free of charge

PASS. Jens-Ulrik Jensen, PASS study coordinator

- Hypothesis: Research Question
- Possible RCT design
- Candidate ICUs

- Inner circle 3-5 people (Scientific, high work capacity, moral, leadership, hierarchial position with strong mental health and is likeable)
- Steering Committee
- PI
- Ethics Board Appl
- Data Surveillance Board Application
- Funding: Company, independent

BaSES Study. Martin Siegemund, Basel, Switzerland
Starches after VISEP
Legendre Lancet 1993 Osmotic lesions in the kidneys
Described 1940 with sucrose, edema in the kidneys
Higher MW HES increased toxicity
Effects of hydroxyethyl starch administration on renal function in critically ill patients (SOAP study) Y Sakr BJA 2007

BaSES study HES 130 (Voluven) vs NS

- Primary endpoints: ICU + Hospital length of stay
- Secondary endpoints: Creatinine, Creatinine clearance, BUN excretion, RRT, vasocatives
- So far no increase in RRT with HES

VISEP

- Tight glucose control arm stopped early due to hypoglycaemia
- HES arm stopped early due to 35 vs 23% ARF with HES
- HES 200, hyperoncotic HES and 50 ml/kg given first day (33 ml/kg recommended)
- Tubular hyperosmolarity the proposed mechanism for ARF (after degradation below the renal threshold)

The meeting was closed with a special thanks to Anders Perner for excellent work with the meeting.

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