Journal update monthly top five

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This month's update is by the South East Scotland team. We used a multimodal search strategy, drawing on free open-access medical education resources and literature searches. We identified the five most interesting and relevant papers (decided by consensus) and highlight the main findings, key limitations and clinical bottom line for each paper.

The papers are ranked as:

- Worth a peek—interesting, but not yet ready for prime time.
- Head turner—new concepts.
- Game changer—this paper could/should change practice.

1. Early Restrictive or Liberal Fluid Management for Sepsis-Induced Hypotension by Shapiro *et al (1)*

Topic: Sepsis

Outcome Rating: Head turner

Several studies (FEAST, CLASSIC) have challenged the benefit of large volumes of fluid for septic shock. The Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (CLOVERS) is an unblinded, randomized multicentre trial conducted at 60 US EDs aiming to establish whether a restrictive fluid strategy outperformed a liberal fluid strategy in patients presenting with sepsis-induced hypotension.

1563 adults with sepsis-induced hypotension (defined as SBP<100mmHg or MAP<65mmHg after 1000ml crystalloid plus suspected/confirmed infection) were enrolled and randomly assigned to either a restrictive (prioritising early vasopressors) or liberal (prioritising fluid boluses) fluid strategy. The primary outcome was death before discharge at 90 days. Exclusion criteria included inability to obtain informed consent, >4hrs since meeting inclusion criteria for sepsis-induced hypotension, >3L IV fluid pre-enrolment or the presence of fluid overload or severe volume depletion.

The trial was halted after a planned interim analysis due to futility. 90-day in-hospital mortality was 14.0% in the restrictive arm and 14.9% in the liberal arm (difference –0.9% [95% CIs -4.4 to 2.6]). There were no significant differences in secondary outcomes. There was clear separation in IV fluid administered over the first 24hrs (median 1267ml in restrictive strategy vs 3400ml in liberal strategy)

This was a multicentre study with broad inclusion criteria for patients presenting in an undifferentiated manner. 3303 eligible patients were not enrolled (due to inability to consent, refused consent, clinician refusal and unspecified reasons) raising concerns about potential selection bias and generalisability. Baseline observations and lactate suggest that those enrolled may not, on the whole, have been very unwell. Other aspects of management were based on physician discretion. Further studies are ongoing and may add more information (EVIS, ARISE-FLUIDS, ANDROMEDA-SHOCK2).

Bottom line: No difference in patient-centred outcomes were observed between a liberal- and restrictive-fluid strategy for sepsis-induced hypotension.

2. Rule-out of non-ST-segment elevation acute coronary syndrome by a single, pre-hospital troponin measurement: a randomized trial by Camaro *et al* (3)

Topic: ACS

Outcome Rating: Head Turner

In low-risk patients, a single high-sensitivity troponin has been sufficient for 'rule-out' of ACS in the ED. This multicentre, open-label, RCT across five ambulance regions in the Netherlands assessed if the use of a pre-hospital point-of-care (POC) troponin in low-risk chest pain patients could significantly reduce 30-day healthcare costs.

863 patients attended by paramedics with suspected non-ST-elevation ACS starting >2 hours ago and with a HEAR (History, ECG, Age, Risk Factors) score ≤3 were randomised to either standard care or to pre-hospital 'rule-out' testing with a POC troponin (with care returned to their GP if negative) . Healthcare costs were lower in the pre-hospital group (mean difference €611; 95% CI €353 to €869]). 30 day MACE was low both in those who had ACS ruled out pre-hospital and in the ED (0.5% versus 1%, risk difference -0.5%; 95% CI -1.6% to 0.7%) although the study was not powered for this outcome.

The pre-hospital POC assay has a lower sensitivity than the ED assay, raising questions about its safety especially as the study did not have a sufficient number of patients to assess a significant difference in the incidence of MACE (the authors estimate >17,000 patients would be required for a non-inferiority study). It is unclear if this study is generalisable to systems outside of the Netherlands. However similar UK-based observational data may soon be available (PRESTO study).

Bottom line: Pre-hospital rule out of non-ST elevation ACS may have significant healthcare cost benefits but questions remain around safety of this approach.

3. Tenecteplase versus alteplase in acute ischaemic cerebrovascular events (TRACE-2): a phase 3, multicentre, open-label, randomised controlled, non-inferiority trial by Wang *et al* (4)

Topic: Acute ischaemic stroke

Outcome Rating: Game Changer

Standard of care for disabling ischaemic stroke presenting within 4.5 hours is thrombolysis with alteplase. Tenecteplase is a similar drug which takes less time to prepare and administer but has not been compared to alteplase for functional outcomes. The TRACE-2 study, an open-label non-inferiority study, recruited patients with suspected ischaemic stroke (NIHSS 5-25) and excellent functional baseline (modified Rankin score; mRS 0-1) and randomized them to receive either

tenecteplase (0.25mg/kg) or alteplase (0.9mg/kg). The primary outcome was the proportion of patients at 90 days with excellent functional outcomes (mRS = 0 or 1). A non-inferiority margin of 3.74% absolute risk difference was chosen (relative risk [RR]=0.937).

1430 patients were recruited across 53 centres in China. 62% of patients in the tenecteplase group and 58% in the alteplase group had excellent functional outcomes (RR 1.07; 95% CI 0.98 to 1.16). Safety outcomes appeared similar between groups albeit with wide 95% confidence intervals around the RR for symptomatic intracranial haemorrhage within 36 hours (95% CI of 0.56 to 2.5), and for death (95% CI 0.86 to 2.01).

Using the author's non-inferiority margin, tenecteplase was non-inferior to alteplase for functional outcome, but this analysis cannot be used to support its superiority. Moreover, the study was not powered to compare safety outcomes.

Bottom line: Tenecteplase is non-inferior to alteplase for functional outcome following acute ischaemic stroke.

4. Effects of an Immersive Virtual Reality Intervention on Pain and Anxiety Among Pediatric Patients Undergoing Venipuncture: A Randomized Clinical Trial by Wong & Choi (5)

Topic: Paediatric analgesia

Outcome Rating: Head Turner

Venepuncture is a painful and distressing procedure for children. The use of various distraction techniques (e.g. music, cartoons) tends to decrease pain and anxiety. In this RCT at a single hospital in Hong Kong, 149 children aged 4-12 undergoing venepuncture were randomized to Immediate Virtual Reality (IVR) vs standard practice. The IVR arm provided visual and auditory stimuli alongside procedural information tailored to age via a head-mounted display. Pain and anxiety were assessed using reliable and validated self-scoring systems: Faces Pain Scale–Revised (FPS-R) and Visual Analogue Scale (VAS).

IVR was associated with less procedural pain and anxiety, (although not statistically significant for all time points), shorter mean procedure duration (4.43 [SD 3.47] versus 6.56 [SD 7.39] minutes p=.03) and greater staff satisfaction with the procedure.

There were a number of measured outcomes and no pre-specified primary outcome, suggesting that the results should be interpreted with caution. Issues around infection control, device availability and staff training may also limit the adoption of the intervention into practice beyond this site.

Bottom line: Using IVR may reduce length of procedure, pain and anxiety for children during venepuncture.

5. Emergency Department Versus Operating Room Intubation of Patients Undergoing Immediate Hemorrhage Control Surgery by Dunton *et al.* (6)

Topic: Trauma

Outcome Rating: Head turner

In trauma patients requiring urgent haemorrhage control surgery (HCS), intubation in the ED can result in haemodynamic collapse; deferring intubation, and rapid resuscitation and transport to the operating theatre may be preferable**.** This retrospective cohort study utilising the US National Trauma Data Bank identified adult patients transferred to the operating theatre for HCS within 60 minutes of hospital arrival and compared in-hospital mortality among those intubated in the ED versus in theatre. The authors also performed a hospital-level analysis comparing mortality in hospitals with high vs low tendency for ED intubation.

9,667 patients across 253 centres were included. ED intubation was associated with higher mortality after controlling for patient baseline and injury characteristics (adjusted odds ratio; aOR 1.85; 95% CI=1.54 to 2.23). Level 1 trauma centres, which saw higher levels of haemorrhage control surgery, had a lower tendency to intubate in ED. Mortality at centres with a higher ED intubation tendency was not significantly different from those with lower tendency to intubate in the ED (aOR 1.27; 95% CI 0.97 to 1.65), although these sites had higher rates of in-hospital cardiac arrest (aOR 1.46; 95% CI 1.04 to 2.03).

Despite attempts to avoid confounding, the retrospective nature of this study and the use of registry data means unmeasured confounders may account for the differences found. However, ED intubations are likely to increase ED dwell time and this may be an explanation for the overall outcomes.

Bottom line: In this retrospective study ED intubation of patients requiring haemorrhage control surgery was associated with higher in-hospital mortality

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