St George's GICU Journal Club Template

DIRECTIONS
Please answer all of the questions in the boxes provided. Wherever possible, use your own words. Cut and paste tables / illustrations or refer to specific locations within the paper concerned. Be thorough but concise. Be critical but realistic.

Reference of paper:
Please use the following format: 1st author et al. Title. Journal. Date. Volume: page range. Please also give details of any accompanying editorial.

SAFE study investigators. Saline or Albumin for Fluid Resuscitation in Patients with traumatic Brain Injury. NEJM 2007; 357:874-84

Introduction:
What question(s) are the authors trying to answer?

Which resuscitation fluid should be used (albumin vs saline) in patients with traumatic brain injury? Is resuscitation with albumin associated with a higher mortality rate?

Do the authors provide a rationale to support their investigation / hypothesis?

The initial SAFE study (Saline vs Albumin Fluid Evaluation Study) suggested patients with traumatic brain injury resuscitated with albumin had a higher mortality rate than those resuscitated with saline. Prior to this there had been a lack of adequately powered RCTs to investigate this.

Give a concise explanation of their rationale.

See above

Is the case well presented / argued?

Yes – clear and concise

Consider the methods used:
What design was used – randomised control trial / controlled not randomised / cohort / case series / case report / prospective vs. retrospective / review / systematic review / consensus guideline

Post hoc follow up study of patients from the SAFE study, who had traumatic brain injury.

SAFE was double blind randomized controlled trial.

From what population were the patients recruited – single centre (type & location) / multi-centre (types and locations) / multinational (types & locations). Given this population, how generalisable is this study?

Multidisciplinary ICUs of 16 hospitals in Australia and New Zealand.

Likely to be a similar population to ours (health care set-up not wildly different from NHS, multidisciplinary units)

Describe patient numbers / important inclusion criteria / important exclusion criteria / screening & enrolment methods / number screened vs. number enrolled. Was the sample size estimated by performing a power calculation, if so, was this reasonable? Was the estimated sample size achieved? If not, why?

Data on 420 was analysed (515 patients initially identified, but 55 were excluded – usually as they were misclassified as TBI on SAFE database, and 40 were lost to follow up)

Inclusion: history of trauma, head trauma on CT, GCS< or = 13

No power calculation as retrospective.

Briefly describe control and intervention protocols. Any good ideas? Any concerns? Where all reasonable methods used to minimise the effects of confounding variables? Did the authors measure to what extent their protocols were adhered to? Was there a clinically meaningful difference in intervention actually delivered to the 2 (or more) groups?

Patients randomised to receive either 4% albumin or normal saline for all fluid resuscitation in the ICU until death, discharge or 28 days after randomization.

Not recorded which fluids received prior to ICU admission (eg in A+E or theatres). No comment about adherence to protocol, but given it's simplicity, hopefully good compliance.

Authors looked at a number of potentially confounding variables e.g. systemic hypotension, episodes of raised ICP, severity of brain injury on CT score and GCS. Found the 2 groups well matched.

Baseline covariates known to be assoc with increased mortality from traumatic brain injury (age >60yrs, GCS</=8, systolic BP <90 and traumatic SAH) were fitted into a multivariate logistic regression model, and the odds ratio at 24 months was adjusted accordingly.

What outcome measures were employed (primary and secondary)? How well defined were the chosen endpoints. How reliable were any measurements taken? Would alternative endpoints have been better and if so, how?

Endpoints:

1. mortality rate,

2. functional neurological outcome at 24 months (by telephone interview by a single assessor – extended Glasgow outcome scale 1-8) and

3. if died within 28 days – primary and secondary cause of death (determined by blinded investigator, reviewing trial report forms, hospital notes and death certificates).

Endpoints are well defined but some are dependent on retrospective review of notes etc (notoriously unreliable source of info). Functional outcome is likely to be influenced by type of rehab received, so I would like to know whether this is universally available and of similar quality in different regions. Telephone interview may also be unreliable as patients / families do not always tell the "whole truth", particularly if they may be speaking to someone who cared for them in the ICU.

Was the method of analysis decided upon during the design and described? Where any subgroup analyses included in the study design?

The whole study is essentially a sub-group analysis of the original trial. The analysis was described clearly and seems appropriate.

What follow-up, if any was performed? If so duration / completeness?

Patients were contacted by phone at 24 months to assess their functional neurological outcome. Data seems quite complete (neuro outcome known in 203 of 214 patients in albumin group and 198 of 206 patients in saline group).

Consider the validity of this study

If randomised, was the method sound? Was the list concealed?

In the original SAFE study, randomisation was stratified by a diagnosis of trauma, hence similar numbers in each treatment group in this analysis. The do not comment on method of randomisation (although being a multicentre trial – it was likely to be centralised and therefore concealed).

Where the treatment groups similar at baseline? How was this assessed? Was this assessment adequate? If not, what additional / alternative methods would have enhanced this assessment?

Groups were well matched at baseline (age, gender, injury severity by APACHE II and abrieviated injury score, MAP, HR, CVP, serum albumin, GCS (stratified into 3-8, 9-12 and 13+), score on motor component of GCS, severity of brain injury (CT score) neurosurgical intervention, traumatic SAH, pre-randomisation hypotension, ICP and pre-randomisation raised ICP.)

This appears to be a comprehensive list and includes sensible variables including physiological variables, nature of brain injury and its severity and other organ / system failures.

Are all the patients enrolled in the study accounted for at conclusion?

Yes (all those with traumatic brain injury in the SAFE study)

Are patients analysed in the groups to which they were randomised?

Yes – analysis was on intention to treat basis, but there is no comment of any patients "crossing over"

.

Were patients and / or clinicians blinded to treatment?

Yes

Were the groups treated similarly outside of the study intervention? Was there anything about their non-study treatment which was notable? Is there insufficient detail to draw a conclusion?

This is difficult to assess form the study. Some treatment / interventions were commented on e.g. ICP monitoring, neurosurgical intervention, and these were similar in each group.

You would expect the interests / speciality of the ICU (e.g. neurosurgery on-site, trauma centre etc) would also influence outcomes – the paper states that the participating units were "multidisciplinary ICUs".

Rehab is also likely to strongly influence neurological recovery, and we do not know if this was similar. However, neurological outcome was similar in each group of survivors, the difference in outcomes in the 2 treatment groups were due to greater mortality rate.

Consider the reported results

Are the results well presented? Are any / all statistical analyses properly performed, reported and interpreted?

I feel the results are clear and well presented – tables, Kaplan-Meier plots and text.

Little info about statistical analyses, but the tests applied seem appropriate for the type of data.

For primary outcome(s) what was the result concluded by authors? Is this justified?

Mortality: at 24 months 33.2 % patients in the albumin group and 20.4% of those in saline group had died. (Relative risk 1.63 95% Confidence interval 1.17-2.26 P=0.003).

Neurological Outcome: favourable neuro outcome 47.3% in albumin group vs 60.6% in saline group. (Relative risk 0.78, 95% confidence interval 0.65 – 0.94 P=0.007). Smaller number of favourable outcomes in albumin group was due to greater mortality rate, since functional outcome in the survivors was similar (RR 0.95, 95% CI 0.83-1.08 P=0.42)

Traumatic brain injury was identified as primary cause of death at 28 days in 75.4% of deaths in the albumin group and 83.3% of deaths in saline group.

These results are justified conclusions

For secondary outcome(s) was the result concluded by authors? Is this justified?

See above

What was the measured adherence to treatment protocols?

No

Where there any adverse events / effects reported?

N/A

Consider the discussion

What were the strengths and weaknesses of this study?

Post hoc analysis and retrospective collection of some data are the study's main weaknesses, however this was an important analysis of a sub-group of the SAFE study who appeared to have worse outcomes in the treatment group.

Large number of patients and clinically useful end-points. 2 year follow up complete data in >90% patients.

Despite retrospective analysis, patients with traumatic brain injury were identified a priori in SAFE study. They maintained blinding throughout study period.

Are the results compared to the literature on this topic and / or the current standard of' care?

Mortality rate in albumin group was similar to international epidemiological studies.

Crystalloid based fluid resuscitation is recommended in trauma resus protocols, although evidence to support this is scant. Colloid based resuscitation has been promoted by some groups, with the aim of maintaining oncotic pressure to minimise extravasation of fluid into brain interstitium.

A single centre longitudinal case series has suggested a lower mortality rate after introduction of albumin based fluid resus strategy, but worse neurological outcome.

Describe the authors' conclusions. Are they reasonable?

Higher mortality rate in patients with severe traumatic brain injury who received 4% albumin compared to those who received saline. These are reasonable.

What conclusions do you draw from this study?

Albumin should not be used in the early fluid resuscitation phase of a patient's care if they have traumatic brain injury

How should this study affect our clinical practice?

Continue current practice of using crystalloid

What should be the next steps for further study of this area?

Comparison of saline / other colloid (e.g. gelofusin) which we use a lot

Comparison of normal saline with hypertonic saline

Consider the references
Where all statements of fact appropriately referenced?

Yes

Did you read any of the references (please give details)? If so, did you gain any additional insights and what were they?

Original SAFE study – largely to get a better feel for their study protocol. Albumin appears to have similar outcome to saline in general resuscitation of ICU patients

Any additional comments / information / points for discussion.
