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.

Morelli, A. et al. Continuous terlipressin versus vasopressin infusion in septic shock (TERLIVAP): a randomised, controlled pilot study. Critical care. 2009. 13:R130.

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

1) A comparison of terlipressin and vasopressin in sepsis and their influence on noradrenalin requirement and reversal of arterial hypotension.

2) Investigation of the effects of both agents on global and regional haemodynamic parameters and 'organ function'

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

Yes

Give a concise explanation of their rationale.

The basis seems to be that subgroup analysis in the VASST Trial suggested a survival analysis in patients treated with vasopressin over low dose noradrenaline. However, vasopressin is not universally available, and terlipressin has been used instead (in bolus doses). The authors wanted to discover if terlipressin and vasopressin were equally effective at reducing noradrenaline requirements when used first-line, (this is not known) and if there was any evidence of deleterious haemodynamics, or end organ dysfunction in either group. This was based on the premise that earlier use of effective agents improves efficacy, (as on early goal-directed therapy), whilst noting that common practice is to use terlipressin as a last resort therapy in late sepsis.

There is animal evidence that terlipressin as a continuous infusion as compared with vasopressin improves survival and may increase mesenteric perfusion.

Is the case well presented / argued?

Not really. I had to read it several times before I got a clear idea of the rationale.

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

Prospective RCT. Described as a pilot study.

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?

18 bed single centre general ICU in Europe (Italy). University hospital. Casemix not specified. Presumably generalisable to a UK teaching hospital ICU.

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?

119 patients were said to have met the inclusion criteria (ie fulfilled criteria for septic shock as defined in the Surviving Sepsis literature, and had a MAP<65mmHg despite appropriate fluid resuscitation to achieve a PAOP 12-18mmHg, and a CVP of 8-12mmHg), but 74 of these met exclusion criteria (Prev vasopressors: 64, CRF: 4, severe liver dysfunction: 1, low cardiac index (<2.2l/min): 7), and so 45 were enrolled. CRF was not defined.

It is unclear why only 119 patients were screened in an 18 bed unit over a year.

Patients were randomly enrolled into one of 3 groups of 15. (does not specify how this was done, other than 'by computer')

The sample sizes were calculated to detect a 30% difference in noradrenaline requirements between the 2 groups.

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?

All patients had a PAC, a radial arterial line, air tonometer in stomach, and a femoral arterial line.

Patients received either terlipressin at 1.3mcg/kg/hr, vasopressin at 0.3U/min, or noradrenaline at 15mcg/min, (this equates to 0.7mcg/kg/min for the average study patient) AND then all groups received open label noradrenaline until a MAP of 65-75 was obtained.

All patients received fluid to a CVP of 8-12, and a PAOP of 12-18. Blood if Hb <8, and, and dobutamine if SvO2 <65%.

I think the biggest flaw in this study is the use of a per kilogram dose of terlipressin, but fixed doses of study drugs in the vasopressin and noradrenaline groups. This would tend to favour a reduction in the noradrenaline requirements in the heavier patients in the terlipressin group, and hence confirm the study hypothesis. It is not explained why this protocol was followed.

There is no data presented to measure the degree to which protocols were followed.

At 6 hours terlipressin patients received more dobutamine (15mcg/kg/min compared with

9mcg/kg/min). This is not controlled for.

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?

Primary outcomes were blood pressure and open label noradrenaline requirements, and these seem reasonable.

The secondary end points are a collection of haemodynamic and biochemical parameters that are easily measure, and that the authors chose to try and detect changes between groups and infer from this that one agent was superior to the other with regard to renal perfusion, or mesenteric perfusion, and so on. Those chosen variables are reasonable, but the nature of the study means that the results are only going to suggest areas for further study.

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

Yes. Yes.

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

Study period 48 hours. 54 and 60 hour follow up to look for rebound hypotension.

Consider the validity of this study

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

Method of randomisation described as 'computer based' No further information offered.

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?

Yes. Broadly similar in terms of age, weight, SAPS II score, mortality and length of stay. Most patients were male (80% in the noradrenaline group, 67% in the vasopressin group). Just over half the patients in each group had surgical as opposed to medical pathologies. Equal numbers in each group received APC.

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

Yes. All 45. No deaths and no withdrawals.

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

Yes

Were patients and / or clinicians blinded to treatment?

The implication is that clinicians were blinded, as the manuscript refers to additional 'open-label' noradrenaline, but this is not explicitly stated, and nor is the method of blinding. Similarly, patients were not explicitly stated to have been blinded, but on the other hand they were sedated with sufentanil and midazolam.

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?

More or less. APC and renal support was similar between groups. The terlipressin group got least fluid (4.3l) compared with the noradenaline group (4.8l; a 17% difference). The terlipressin group also received more dobutamine, and at 6 hours were on approximately 15mcg.kg/min as opposed to close to 19 in the other groups.

Consider the reported results

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

Partly. The data on the secondary outcomes is presented in tables and is relatively clear. However, the primary outcome measure of noradrenaline requirement is presented as a single 10x10cm table which is poorly labelled (table 2).

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

Low dose terlipressin reduced noradrenaline requirements and reversed sepsis induced hypotension.

It may be justified if the additional use of dobutamine in the terlipressin group had been controlled for, and if we knew if the study drug dose of noradrenaline had been accounted for in the total noradrenaline requirement in the noradrenaline group.

That said, the conclusion seems reasonable.

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

The secondary outcome (is a little wolley ('effect of drugs on systemic and regional haemodynamics as well as organ function)

The result:

Haemodynamics. Heart rate lower in the terlipressin group. Other variables not significantly different. (ie CI, SVI, MAP, MPAP, PAOP, RAP, PVRI, RVSWI, LVSWI). New onset tachyarrhthmias. Trend to towards more in the noradrenaline group. Not statistically significant.

Acid Base & Oxygen transport. No significant differences except lower arterial pH and higher lactate in the noradrenaline group at 48hours. Range of lactates 3.6-4.4mmol/l. ? clinically significant? The difference in pH does seem important. (7.28 and 7.37).

Regional haemodynamics. No difference.

Variables of organ function. Similar between groups except bilirubin was significantly lower in the terlipressin group at 48hours. Also creatinine significantly higher at 48 hours compared to baseline in the noradrenaline group. There was also a trend towards more renal support 53% vv 26% and 33% in the noradrenaline group. Clotting was unchanged in the groups with the exception of a decrease in platelet count in the terlipressin group.

Inflammation. IL-6 significantly decreased in the vasopressin group, and there was a trend towards a decrease in the terlipressin group.

Length of stay. No difference.

What was the measured adherence to treatment protocols?

Not stated

Where there any adverse events / effects reported?

No deaths. No other adverse events reported that were clearly directly attributable to the study drugs as opposed to the underlying disease process. (for example, renal support)

Consider the discussion

What were the strengths and weaknesses of this study?

Small numbers. Uncertainty over blinding, particularly the clinicians. Single centre study. Failure to define chronic renal failure (an exclusion criteria) makes application of results to a standard ICU population difficult. The use of fixed doses of vasopressin and noradrenaline but a per kilogram of bodyweight dose of terlipressin means that the heavier patients in the terlipressin group will have been more adequately treated than the other two groups.

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

Yes. With VASST.

Describe the authors' conclusions. Are they reasonable?

The main conclusion that terlipressin reduced noradrenaline requirements and reversed hypotension may be reasonable. Terlipressin patients were on approximately 0.2mcg/kg/min of noradrenaline compared with 1 or 1.2mcg.kg/min in the other 2 groups. However, this data is presented in graph with an unclear title (presumably the average requirements are plotted), and it is unclear if total noradrenaline requirement or additional noradrenaline requirement (ie open label noradrenaline above study drug noradrenaline) is being plotted in the noradrenaline group. To plot the former would favour terlipresin and vasopressin over noradrenaline.

The authors have not explicitly come to a conclusion regarding their secondary outcomes, but this is unsurprising as this was really a trawl through a number of measured parameters in a very small study with the hope of finding some differences and with no prospective power calculation

What conclusions do you draw from this study?

Terlipressin probably reduces noradrenaline requirements in SEVERE sepsis, and it may be worth further study to examine if terlipressin has fewer deleterious side effects than noradrenaline.

How should this study affect our clinical practice?

I'm not sure that it should. This study has not shown change in mortality or in length of stay, and given that patients were on 1mcg/kg/min of noradrenaline, it isn't applicable to most of our patients.

The authors imply that they have chosen a population to examine the use of terlipressin early, but they seem to have selected a group of patients who went on to have severe disease, as measured by their noradrenaline and dodutamine requirements. SAPS II scores of 65 equate to a mortality of 75%, which is not typical for our ICU based on the original study inclusion criteria. In fact, the 60 hour mortality in the study was 0%.

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

Prospect RCT comparing vasopressin with terlipressin and noradrenaline in septic shock, and powered to demonstrate improvement in length of stay or mortality, and perhaps without the use of open label noradrenaline.

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?

The VASST Study (Vasopressin versus Norepinephrine Infusion in Patients with Septic Shock; NEJM Feb 2008)

Any additional comments / information / points for discussion.
