St George's GICU Journal Club Template

Reference of paper:

Paper: Annane D et al. Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial. Lancet 2007; 370: 676–84

Editorial: Singer M, Catecholamine treatment for shock—equally good or bad? Lancet 2007; 370: 636-7

Introduction:

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

In the management of patients with septic shock, is there an advantage of norepinephrine plus dobutamine (whenever needed) over epinephrine alone?

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

Yes. International guidelines place epinephrine as second line

Give a concise explanation of their rationale.

When compared with norepinephrine in small randomised trials, epinephrine has shown deleterious effects on splanchnic blood flow and on acid–base balance. However, these adverse effects were transient, and a recent systematic review on vasopressor therapy for management of septic shock concluded that there was no evidence for any difference on short-term mortality between epinephrine (Epi) and norepinephrine (NE).

Is the case well presented / argued?

Yes

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, multicentre, randomised, double-blind study. Eligible patients were randomly assigned, in a 1:1 ratio, to receive either epinephrine alone or norepinephrine plus dobutamine (whenever needed) according to a computer-generated random list.

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?

French ICUs, doesn't give much detail on their casemix

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?

Inclusion, over 18 years and all 3 of:

1. Evidence of infection

2. At least two of the four criteria for SIRS (temperature above 38°C or below 36°C, HR> 90 bpm, respiratory rate > 20 cycles per min and arterial CO2 tension below 32 mmHg or need for mechanical ventilation, polymorphonuclear neutrophil count above 12)

3. At least two signs of tissue hypoperfusion or organ dysfunction (low PaO_2/FiO_2 ratio, low UO, Lactate >2, PLT below 100)

AND, all of these 3 criteria for less than 24 hours:

1. SBP <90 mm Hg or MAP < 70 mm Hg
2. Administration of fluid bolus of at least 1000 mL or PCWP 12 -18 mm Hg
3. Need for more than 15 µg per kg of bodyweight per min of dopamine or any dose of epinephrine or norepinephrine.

Exclusion criteria:

Pregnancy, evidence of obstructive cardiomyopathy, acute myocardial ischaemia, or pulmonary embolism; advanced stage cancer, malignant haemopathy, or AIDS with a decision to withhold or withdraw aggressive therapies; persistent (longer than a week) neutropenia; and inclusion in another clinical trial.

Power calculation:

"We expected an all-cause mortality rate at day 28 of 60% in the epinephrine group, on the basis of data from another trial we were doing in patients with septic shock when we planned this protocol. We calculated that we would need a sample size of 340 patients to be able to detect, in a two-sided test done with a 0·05 type I error, an absolute reduction of 20% in the mortality rate at day 28 with 95% probability."

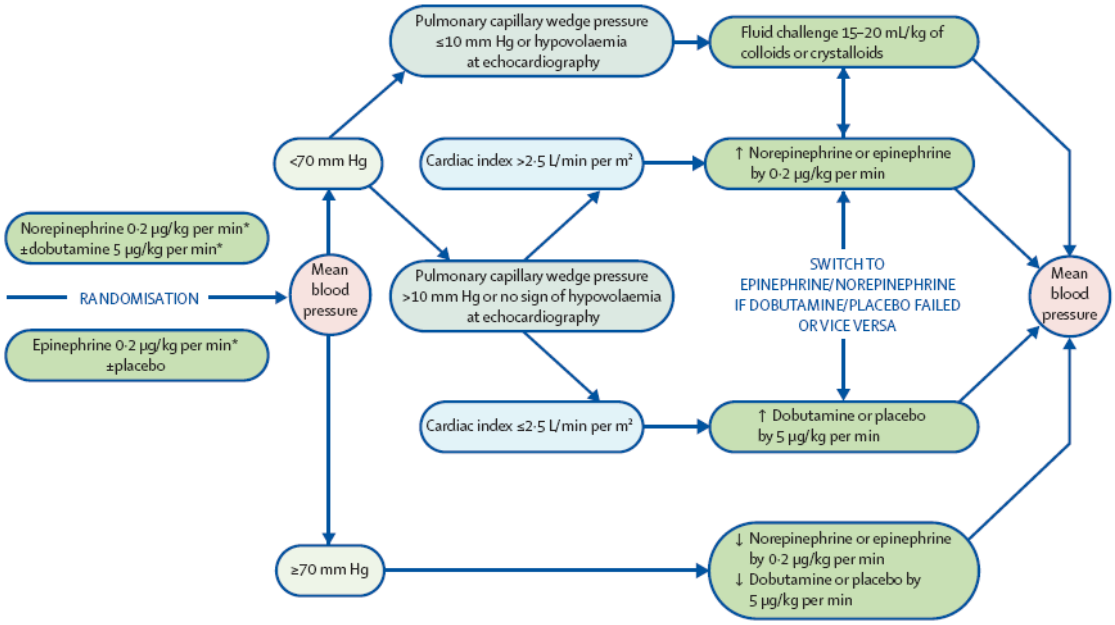
Criticised for an over-generous anticipation of outcome benefit when calculating sample-sizes.

Numbers:

1591 assessed for eligibility → 330 randomised

1261 excluded:
- 674 did not meet inclusion criteria
- 178 met exclusion criteria
- **409 other reasons**
- 283 consent refusal
- 98 physician refusal or missing

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?



Looks complicated but really it's:

- Is their MAP inadequate? If Y then: are they underfilled, if yes then give fluids, if no then check their cardiac output (by whatever means) and if it's ok increase the vasopressors, if it's not then increase the inotrope (or placebo in the control group).
- If the MAP is ok then bring down the primary vasoactive agent.

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?

1^{o} : Mortality at discharge from intensive care, at hospital discharge and by day 90.

2^{o} : time to haemodynamic success, time to vasopressor withdrawal, time course of SOFA score and rates of serious adverse events, costs, length of stay, pH/lactate, rate of invasive procedures…

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

Yes. No.

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

90 days. Notes/phone calls

Consider the validity of this study

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

"Randomisation was done centrally by an independent statistician to ensure appropriate concealment, was stratified by centre, and equilibrated by blocks of six. To ensure masking of treatment allocation, patients randomly assigned to the epinephrine group were given epinephrine plus a placebo in place of dobutamine. Study treatments were provided by the pharmacist at each site as identical syringes for norepinephrine and epinephrine."

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 similar, slightly older in epi group. Details given in Table 1.

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

Yes

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

Yes

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?

Consider the reported results

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

Y

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

No difference between groups. Yes

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

No clinically important difference between groups. Yes

Some delay to resolution of acidosis with epi and accompanying higher lactate levels

What was the measured adherence to treatment protocols?

Y

Where there any adverse events / effects reported?

	Overall (n=330)	Epinephrine (n=161)	Norepinephrine plus dobutamine (n=169)
During catecholamine infusion			
Supraventricular tachycardia >150 bpm	41 (12%)	19 (12%)	22 (13%)
Ventricular arrhythmias	20 (6%)	12 (7%)	8 (5%)
Acute coronary event	8 (2%)	5 (3%)	3 (2%)
Limb ischaemia	8 (2%)	2 (1%)	6 (4%)
Stroke	4 (1%)	2 (1%)	2 (1%)
Central nervous system bleeding	3 (0·9%)	3 (2%)	0 (0%)
After catecholamine infusion			
Arrhythmias	13 (4%)	6 (4%)	7 (4%)
Stroke	4 (1%)	2 (1%)	2 (1%)
Other neurological sequelae	2 (0·6%)	1 (0·6%)	1 (0·6%)
Others	6 (2%)	3 (2%)	3 (2%)

Data are n (%).

Table 6: Serious adverse events

Similar.

Consider the discussion

What were the strengths and weaknesses of this study?

Strengths: Largest study of this kind. Pragmatic (did not try and force any particular CO monitor). Of great clinical relevance.

Weakness: Numbers were large enough but still not very large. It must have been easy to work out that the placebo for dobutamine was a placebo. No mention of need for RRT. Possible real differences between groups. Did not look at difference in glycaemia (epi may induce more hyperglycaemia and perhaps this has adverse consequences). How many of the Norepi group actually received dobutamine?

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

Yes to the literature. No to the current standard of care – epi is rarely used as first line due to perceived increase in side effects and its use is usually reserved to resistant cases.

Describe the authors' conclusions. Are they reasonable?

"In practice, physicians could use either epinephrine alone, or norepinephrine alone or in combination with dobutamine in patients with low cardiac index."

Very reasonable.

What conclusions do you draw from this study?

- It's ok to use epi. It neither implies a worse prognosis nor a higher risk of arrhythmias, black fingers etc…
- It would have been interesting to know how much dobutamine they used in the Norepi+Dobutamine arm. We seem to seldom use dobutamine in the context of sepsis + low MAP + well filled but low CO, should we?
- It would have been interesting to look at the subgroup of patients who had an inotrope/placebo titrated against CO and if there was a difference between the groups. i.e. did using dobutamine make any difference compared to using placebo.
- Delayed improvement in acid base (even if by 3 days) makes no difference to clinical important outcomes.

How should this study affect our clinical practice?

Could use Epi as first line, particularly in cases where sepsis and a low CO are seen to co-exist from the beginning.

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

Is there really a correct MAP to aim for?

Should we be targeting an arbitrary CO with inotropes? If so, what and when?

Would we get the same results if the algorithm did not just look at static (and probably flawed) measures of preload or isn't preload responsiveness more important?

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?

Hollenberg SM, Ahrens TS, Annane D, et al. Practice parameters for hemodynamic support of sepsis in adult patients: 2004 update. Crit Care Med 2004; 32: 1928–48. – very good and comprehensive background reading

Any additional comments / information / points for discussion.

We seem to seldom use dobutamine in the context of sepsis + low MAP + well filled but low CO, should we?