12th of December 2015,

Answering the reviewers

Re: ESPS Manuscript NO: 21828

Thank you for your constructive comments regarding the manuscript "**Should Dopamine be the first line inotrope in the treatment of neonatal hypotension? Review of the evidence.**"

Please find our responses to the reviewers critiques below. A revision of the manuscript with the suggested changes is attached. All amendments have been highlighted, and the references have been changed accordingly.

The abstract, running title, data sharing statement, and comments have been amended according to the editor's comments within the article. We have also changed the authors contributions.

I have also attached the decomposable figures.

Thank you for your further consideration of the revised manuscript for publication,

Yours sincerely,

Dr Sadaf Bhayat, Dr Harsha Gowda, Dr Michael Eisenhut.

Reviewed by 00503255:

Critique: How does dopamine induce transient pituitary dysfunction? This information may help readers to understand the paper.

Answer: Exogenous dopamine infusion suppresses PRL, TSH and T_4 secretion by acting on specific dopamine D_2 receptors [1]. It is believed that in preterm infants, unlike in adults, dopamine crosses the blood brain barrier and exerts its effects directly at the hypothalamic level as well as on the dopamine receptor trophic cells [2]. *(Inserted in paragraph dopamine versus dobutamine)*

1. **Wood, D**F, Johnston JM, Johnston DG. Dopamine, the dopamine D2 receptor and pituitary tumours. *Clin. Endocrinol. (Oxf).* 1992; **35,** 455–466 [PMID: 1837503 DOI: 10.1111/j.1365-2265.1991.tb00928.x]

2. **Seri, I**. Tulassay T, ·Kiszel J, Ruppert F, Sulyok E, Ertl T, Bódis J, Csömör S. Effect of low-dose dopamine infusion on prolactin and thyrotropin secretion in preterm infants with hyaline membrane disease. *Biol. Neonate.* 1985; **47,** 317–322 [PMID: 4027295 DOI 10.1159/000242134]

Reviewed by 00646241

Critique: Importantly, the authors do not only also ask for the immediate effect of the agents on blood pressure, but also for data concerning long-term neurodevelopmental outcome, which is very important, since this may be influenced by the different agents independently from blood pressure (direct effects on brain circulation, steroid effects on brain development etc.), however, the literature collected apparently was not focused to answer this question. Thus this should be noted in the text.

Answer: Additionally, the literature collected did not focus on direct long-term side effects of the drugs (such as direct effects on brain perfusion and development), independently from their effects on blood pressure. *(Inserted in the discussion)*

Critique: As the authors state themselves, several limitations are given with such a study. For example, whether the use of different agents in different situations (volume deficiency, sepsis, cardiac output failure or others) are not addressed.

Answer:

1/Thus it is important to consider different agents in specific situations such as volume deficiency, cardiac failure, sepsis, or adrenal insufficiency. *(Inserted in discussion)*

2/ Therefore, individual treatment for specific conditions was not addressed in this review. *(inserted in discussion)*

Reviewed by 00069139

Critique: Minor criticise - Ref. 1 has no publish year –

Answer: Amended

Critique: It might be more comprehensive if there are a couple of paragraph touching the pathophysiology of hypotension in the premature newborn. (see Ibrahim CPF. Indian Pediatr 2008;45:285. –

Answer: In very low birth weight infants, the aetiology of hypotension is unclear: left ventricular output, a large patent ductus arteriosus (PDA), and myocardial dysfunction may contribute to low blood pressure in this population. Volume depletion is not a common cause in preterm hypotension.

Furthermore, low mean arterial blood pressure in sick preterm infants could compromise cerebral autoregulation. Cerebral autoregulation is essential because it ensures appropriate cerebral blood flow, which is one of the major determinants of oxygen delivery to the brain. The minimal blood pressure required to maintain cerebral perfusion is unknown.[1]

1. **Ibrahim CP**. Hypotension in preterm infants. Indian Pediatr. 2008;**45**(4):285-294 [PMID 18451446]

Critique: Physiologic responses of inotropic drugs vary on dosage. It might be clearer to say something about drug dose that was regarded in the systematic review.

Answer: In the articles analysed, doses of dopamine used were not specified, but this drug was administered at treatment dose for hypotension. This is important as low doses of dopamine (0.5–2 micrograms/kg/min) act on dopaminergic receptors which usually increases renal perfusion. Medium doses (2-6 micrograms/kg/min) act on beta-receptors causing vasodilatation and a positive inotropic and chronotropic effect (increasing output and heart rate). At high doses (>6-10 micrograms/kg/min), dopamine acts on alpha-receptors leading mainly to peripheral vasoconstriction[1]. In preterm infants there are differences in receptor maturation depending on the gestation. Hence there is a vasoconstrictive effect in preterms even if dopamine is used at medium doses[2]. *(inserted in discussion)*

1. **Ibrahim CP**. Hypotension in preterm infants. *Indian Pediatr*. 2008;**45**(4):285-294 [PMID 18451446]

2. **Noori S**, Seri I. Neonatal blood pressure support: the use of inotropes, lusitropes, and other vasopressor agents. *Clin Perinatol*. 2012;**39**(1):221-238. [PMID 22341548 DOI:10.1016/j.clp.2011.12.010]

Critique: Is there any specific conditions that a certain inotrope is preferable, e.g. adrenal insufficiency from haemorrhage and steroid?

Answer:

1/Thus it is important to consider different agents in specific situations such as volume deficiency, cardiac failure, sepsis, adrenal insufficiency or other. *(Inserted in discussion)*

2/ Therefore, individual treatment for specific conditions are not addressed in this review. *(Inserted in discussion)*