

Format for ANSWERING REVIEWERS

August 25, 2014

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 12799-edited.docx).

Title: Vasopressors in obstetric anesthesia: a current perspective

Please note, title has been modified from "Vasopressors in obstetrics: a current perspective" to "Vasopressors in obstetric anesthesia: a current perspective" as suggested by one of the reviewers

Authors: Deb Sanjay Nag, Devi Prasad Samaddar, Abhishek Chatterjee, Himanshu Kumar, Ankur Dembla

Name of Journal: World Journal of Clinical Cases

ESPS Manuscript NO: 12799

The manuscript has been improved according to the suggestions of reviewers:

Reviewer No 2453015

Comment: This is a comprehensive and neat review article regarding the application of vasopressors in obstetric surgeries. A table comparing the pros and cons of each drug, as well as a flow chart showing the choice of drug under each condition, are highly recommended. The authors also need to point out the benefit of their review article compared to other similar ones.

Authors: A table comparing the pros and cons of each drug (Table 1), as well as a flow chart showing the choice of drug under each condition (Figure 1) has been added. Although not stated explicitly in the article, this review article, as compared to the only available reviews on this topic since 2008 (References 18, 21 & 47) is the only article discussing the recent evidence which shows that the genetic composition could be responsible for protection from neonatal acidosis in some parturients. Besides, this is the only review article which suggest a clinical protocol to guide the use of vasopressors in obstetric anesthesia.

Reviewer No 527225

The generic names of the drugs should not be capitilizeed. The inclusion of a figure demonstrating the mechanisms of spinal induced hypotension and perhaps a table evaluating the pros and cons of the vasopressor treatments on maternal and infants would be helpfull.

Authors: Capitalization of the drugs have been corrected. A table comparing the pros and cons of each drug (Table 1), as well as a flow chart showing the choice of drug under each condition (Figure 1) has been added.

Reviewer No 742121

This is a well-written review article suitable for publication after major revision, according to the following comments: 1) Title: The title should be changed to "Vasopressors in Obstetrical Anesthesia: a current perspective", since vasopressors are administered by Anesthetists rather than Obstetricians. 2) Running Title:

The running title should be changed to “Vasopressors in Obstetrical Anesthesia”, since it should not be identical to the main title (“a current perspective” should be removed from the running title). 3) Abstract, line 1: “counteract the hypotension” should be changed to “counteract hypotension”. 4) Abstract, line 2: “obstetrics” should be changed to “Obstetrics”. 5) Abstract, lines 6-8; Core tip, line 1; Conclusion, lines 1-2: The authors clearly express their preference for Phenylephrine over other vasopressors. However, as the authors discuss under the subheading “The Choice of Vasopressor: The recent evidence” (in pages 7-10) and at the end of the “Conclusion” section, the whole issue remains rather controversial. Actually, in many countries, Epinephrine remains the agent of choice. Hence, the authors should rephrase these sentences accordingly, in order to preserve objective presentation of their work. 6) Abstract line 6, Core tip line 3 and Conclusion lines 3, 4 and 13: “Cesareans” should be changed to “Cesarean sections”. 7) Abstract line 7: The authors should provide more details about what sort of “indirect evidence” they mean. 8) Core tip, line 1: “obstetrics” should be changed to “Obstetrics”. 9) Core tip, line 4: “to definitively suggest the benefit of...” should be rephrased (to e.g. “in order to clarify whether there is a benefit of...”). 10) Introduction, line 9: What do the authors mean by “dwelling”? 11) The authors mention spinal anesthesia throughout the text (in line 2 of the Introduction, the last line of page 2, lines 11, 16 and 18 of page 3, lines 4 and 24 of page 4, line 5 and 16 of page 5, line 3 and last line of page 6, line 11 of page 7, line 1 of page 8, lines 17, 24 and 26 of page 9), but there is not a word about epidural anesthesia! 12) Page 3, lines 22 and 23: “obstetrics” should be changed by “Obstetrical Anesthesia”. 13) Page 4, line 1: “It is an $\alpha 1$ receptor agonist which cause...” should be changed to “Methoxamine is an $\alpha 1$ receptor agonist which causes...”. 14) Page 4, lines 2 and 16: “pressures” should be better changed to “pressure”. 15) Page 6, lines 3-5: This paragraph should be re-phrased and written in more proper English. 16) Page 6, lines 11-12: A paragraph should include at least two sentences (not one sentence in just one paragraph). 17) Page 6, line 15: “Recent studies...” should be changed to “A recent study...”. 18) Page 6, line 21: “...evade the obstetric anesthesiologist...” should be rephrased. What do the authors actually mean? 19) Page 8, line 21: “The National...” should be changed to “The UK National...”. 20) Page 8, line 23: “obstetrics” should be changed to “Obstetrical Anesthesia”. 21) Page 9, lines 8-10: A paragraph should include at least two sentences (not one sentence in just one paragraph). 22) Page 10, last three lines: The authors should specify how “larger trials, especially in non-elective” Cesarean sections should be conducted. Non-elective cesarean sections are performed based on certain indications; how should cesarean sections and cesarean section indications should be classified in such trials? 23) A “conflict of interest statement” should be included. 24) The authors should provide an overview of information given for each vasopressor in a Table.

Authors:

1. Title has been corrected.
2. Running title has been corrected.
3. counteract the hypotension” has been changed to “counteract hypotension”.
4. Abstract, line 2: “obstetrics” has been changed to “Obstetrics”.
5. The opinion of the authors that phenylephrine is the preferred vasopressor is not being changed as it is in line with American Society of Anesthesiologists Task Force on Obstetric Anesthesia stating "phenylephrine may be preferable", as also for the Belgian and Canadian Guidelines as stated in page 9, lines 5-16. As stated there, evidence for this is Grade 1-A.
6. As suggested, "Cesareans" haven been changed to "Cesarean sections".
7. The abstract clearly states that "absence of definitive evidence showing absolute clinical benefit", the choice is based on benefit shown through "indirect evidence on fetal acid-base status". This issue has been discussed in detail page 9, line 22 (reference 48).
8. "obstetrics" changed to "Obstetrics" as suggested.
- 9) Core tip, line 4: “to definitively suggest the benefit of...” has rephrased to “in order to clarify whether there is a benefit of...” as suggested.
10. "dwelling on" replaced with "discussing" as suggested.
11. Words "Neuraxial anesthesia" has been used in Core Tip Line 10, 11, in the heading "Hypotension after neuraxial anesthesia", in line 1,10 & 18 under that heading, page 5 line 3, page 7 (3rd last line) and several other places. "Neuraxial anesthesia" includes both spinal and epidural. However, most commonly spinal anesthesia is given for Cesarean sections. In epidural, due to the slower onset, the hypotension, and thus the need for vasopressor is infrequent. That is why, sometimes, in cardiovascular unstable patients where

hypotension is not desirable, epidural anesthesia is used.

12. Page 3, lines 22 and 23: "obstetrics" has been changed by "Obstetrical Anesthesia" as suggested.

13. Page 4, line 1: "It is an $\alpha 1$ receptor agonist which cause..." has been changed to "Methoxamine is an $\alpha 1$ receptor agonist which causes..." as suggested.

14. Page 4, lines 2 and 16: "pressures" has been changed to "pressure" as suggested.

15. Page 6, lines 3-5: This paragraph has re-phrased and written in more proper English as suggested by Reviewer No 742261. "with respect to limiting maternal symptoms" has been added to bring more clarity.

16. Page 6, lines 11-12 has been merged with previous paragraph. Now no paragraph contains just one sentence. Changes made as per suggestion.

17. Page 6, line 15: "Recent studies..." has been changed to "A recent study..."

18. Page 6, line 21: "...evade the obstetric anesthesiologist..." has been rephrased to better explain what the authors intend to state.

19. Page 8, line 21: "The National..." has been changed to "The UK National..." as suggested.

20. Page 8, line 23: "obstetrics" has been changed to "Obstetrical Anesthesia" as suggested.

21. Page 9, lines 8-10 has been merged with previous paragraph. Now no paragraph contains just one sentence.

22. The authors suggest that further studies should be done in emergency Cesarean sections. Studies need to be designed in such a manner that the insult to the fetus is similar when decision to do a Cesarean section is taken. Suggesting the design of such trials is beyond the scope of this review article.

23. Conflict of interest is mentioned just below the authorship credits.

24. Overview of information for each vasopressor is now added in Table 1.

Reviewer No 742261

Svein Rasmussen This is a valuable contribution. I have only some minor remarks. The authors use the slang term "cesarean" instead of cesarean delivery or section. Page 2: "This review article briefly explores the present understanding of the mechanism causing hypotension before dwelling on the current use of the various vasopressors in obstetrics today." This sentence should be made more understandable. Page 2: "The sympathectomy resulting from the neuraxial blockade ...": Rather "chemical sympathectomy". Page 3: "Although this understanding of hypotension still remains "current"⁶, prophylactic therapeutic interventions based upon our present understanding do not definitively prevent hypotension after neuraxial anaesthesia in Cesarean sections⁶." The sentence should be made easier to understand. Page 3: "The "endothelium-dependent alteration of vascular smooth muscle function"⁶ and increased presence of "vasodilator prostaglandins and nitric oxide"⁶ during pregnancy have a vasodilatory effect which is counteracted by the intrinsic sympathetic vascular tone⁶": The quotation marks are unnecessary. Page 6: "Recent studies by Siddik-Sayyid et al.³¹ failed ..": "A recent study" seems to be more correct. Page 9: "... APGAR": "Apgar" is more correct.

Authors:

"Cesareans" have been replaced with "Cesarean Sections" as also suggested by Reviewer No 742121. "chemical sympathectomy" words are not being used as it is not commonly used terminology in anesthesia.

"Although this understanding of hypotension still remains "current"⁶, prophylactic therapeutic interventions based upon our present understanding do not definitively prevent hypotension after neuraxial anaesthesia in Cesarean sections⁶." has been replaced by "Although our present interpretation of the mechanism causing hypotension are still based on these principles⁶, prophylactic therapeutic interventions based upon this understanding do not definitively prevent hypotension after neuraxial anaesthesia in Cesarean sections⁶." The sentence has been made easier to understand as suggested.

Page 3: "The "endothelium-dependent alteration of vascular smooth muscle function"⁶ and increased presence of "vasodilator prostaglandins and nitric oxide"⁶ during pregnancy have a vasodilatory effect which is counteracted by the intrinsic sympathetic vascular tone⁶": The quotation marks have been used as these words are a direct quote from the referred article.

"Recent studies by Siddik-Sayyid et al.³¹ failed ..": has been changed to "A recent study" as suggested.

Page 9: "... APGAR" has been changed to "Apgar" as suggested. All "APGAR" in the article has been changed to "Apgar".

Reviewer No 506135

This manuscript is a well-written review article on the vasopressors for spinal anesthesia-induced hypotension in Cesarean section. The paper is well-organized and covers relevant recent publications.

Authors:

All the minor changes made in the document have been incorporated.

References and typesetting were corrected

PubMed Citation Numbers and DOI (wherever available, not available for many articles published 2002-03) have been added.

The references not available on PubMed, References 11,12,17,20,22,52, & 56 are available with the corresponding authors. Please share the e-mail address where these references can be sent.

Thank you again for publishing our manuscript in the **World Journal of Clinical Cases**.

Sincerely yours,

A handwritten signature in blue ink, reading "Deb Sanjay Nag", with a horizontal line drawn through it.

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