PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Efficacy and Safety of Vasopressin and Terlipressin in Preterm Neonates:A Protocol for a Systematic Review
AUTHORS	Alsaadi, Abdulrahman Salim Sushko, Katelyn Bui, Vivian Van Den Anker, John Razak, Abdul Samiee-Zafarghandy, Samira

VERSION 1 – REVIEW

REVIEWER	Reviewer name: Dr. Michael Reed Institution and Country: Case Western Reserve University, Pediatrics, 11100 Euclid Ave, Cleveland, United States Competing interests: None
REVIEW RETURNED	26-Mar-2021

GENERAL COMMENTS	1. “What is Known….”: Considering terlipressin is a focus of this paper should any comment about this agent be noted here? (See page 7, lines 6-11). 2. Page 5, lines 19-26: Is this difference solely do to complete differential receptor distribution or does vasopression concentration at the receptor site also play a factor? 3. Page 5, line 31: Maybe best reworded as – “…vasoplegic shock” was “described for the…”. 4. Page 5, line 45: Please add a sentence here summarizing the positive/negative effects/outcomes described in the paper of Meyer. 5. Page 5, lines 51-54: For completeness and for the reader, please provide the average/expected duration of effect and t ½ values for both AVP and terlipressin for a comparative understanding. 6. Page 6, line 52: neonates not neonate. 7. Page 7, line 47: “We also” planned “to search..”. 8. Page 9, line33: Would this be better worded as – “’’will be” resolved “through discussion…”? 9. Page 9, section 1.6: Please provide 1 to 2 sentences describing exactly how you plan to have “public involvement”, as I do not understand this within the construct of a systematic review of published literature. 10. Page 10, line 3: Should this read – “outcomes” will be……? 11. Page 10, lines 3-31: Are you confident you will be able to glean this (deep) level of granularity from published papers to achieve the specific parameters you outline here? For example, who will be performing the GMFCS, BSID? What about specific lab data at specific time points outlined? Will you be contacting the published paper authors to obtain the specific information obtained at the specific time points you outline here? What do you plan to do if this information is not available? I am confused.

	12. Page 10, lines 55-60: How do you plan to “address the gap”, lines 58-60, if “The difficulty in performing….” Exists, lines 55 to 58? Consider rewording.

REVIEWER	Reviewer name: Dr. Sinno Simons Institution and Country: Erasmus MC Sophia, Pediatrics, Netherlands Competing interests: None
REVIEW RETURNED	26-Mar-2021

GENERAL COMMENTS	With great interest I have reviewed your manuscript that describes your planned systematic review on the safety and efficacy of vasopressin and terlipressin in preterm newborns. The introduction clearly describes the rationale and potential for both drugs in preterm infants. Although interesting I am not sure if there is sufficient data to draw valuable conclusions afterwards. In comparable review (Reem Masarwa et al, Crit Care. 2017 Role of vasopressin and terlipressin in refractory shock compared to conventional therapy in the neonatal and pediatric population: a systematic review, meta-analysis, and trial sequential analyses) that also included term infants in the PICU concluded a couple of years ago that further large studies are necessary to demonstrate and establish benefits of AVP/TP in children. I agree that preterm newborns are a separate population and that new studies might have been out in the last 4 years. This may be a good argue for your planned efforts. From a pharmacological point of view it might be very interesting to also have a systemic search on the knowledge/data of dosing these drugs in preterms. Is there evidence on a target in older infants / term newborns? Will this be equal in preterms? Is there pk-studies / pop Pk models (maybe you could use a grading comparable to Silke Gastine et al: Review Expert Rev Clin Pharmacol. 2019 Dec;12(12):1091-1098. GAPPS (Grading and Assessment of Pharmacokinetic-Pharmacodynamic Studies) a critical appraisal system for antimicrobial PKPD studies - development and application in pediatric antibiotic studies) . Knowledge on the half-live / pk might also be somewhat helpful to decide which drug might be most suitable… The discussion of your manuscript is a bit conflicting because you already state that the availbale data on efficacy and safety are limited… and therefore you will perform a systematic review. Won’t you do the review to see what the extend of data are? And maybe to find the knowledge gaps that need to be filled?

VERSION 1 – AUTHOR RESPONSE

Professor Imti Choonara, MCChB, MD, FRCPCH, DTM&H

Editor-in-Chief

BMJ Pediatrics Open

imti.choonara@nottingham.ac.uk

Dear. Dr. Choonara,

I am writing this letter in regard to our revised manuscript titled, "Efficacy and Safety of Vasopressin and Terlipressin in Preterm Neonates: A Protocol for a Systematic Review" (manuscript ID bmjpo-2021-001067) for consideration as a *BMJ Pediatrics Open* research article. We are grateful for the valuable feedback that we have received from the Editor-in-Chief and the two reviewers. Based on this feedback, we have made a number of changes to our manuscript, which has helped us to improve the methodological quality and presentation of our review protocol. Below we have carefully responded to all of the comments.

Thank you in advance for your consideration of our revised manuscript.

Sincerely,

Abdulrahman Al-saadi, MD
Division of Neonatology,
Department of Pediatrics,
McMaster University

Response to Editor-in-Chief Comment

Worth clarifying that you will utilise RCTs and prospective cohort studies for evaluation of efficacy and all studies including retrospective cohort studies, case series and case reports for evaluation of safety/toxicity.

We thank the Editor-in-Chief for this comment.

Given the scarcity of data on this topic, we chose to include all interventional and observational original research studies, including randomized controlled trials (RCTs), quasi RCTs, prospective and retrospective cohort studies, descriptive studies, case series and case reports to assess our primary (efficacy) and secondary (safety) outcomes. We agree with the Editor-in-Chief that efficacy outcome would be best established through prospective

interventional studies. However, considering the limited available data, we aim to include all available evidence while providing a robust qualitative assessment of studies using standardized risk of bias assessment tools appropriate for each study design.

Response to Reviewer 1 Comments:

Dr. Michael Reed, Case Western Reserve University

1. "What is Known….": Considering terlipressin is a focus of this paper should any comment about this agent be noted here? (See page 7, lines 6-11).

Thank you for this comment. We have made the following change to the manuscript

Page 2, line 2:

1. Arginine vasopressin, an endogenous peptide, is a potent systemic vasoconstrictor and pulmonary vasodilator.
2. The efficacy of arginine vasopressin to treat septic shock and hemodynamic instability in adult and pediatric patients is well established.

Changed to:

1. Arginine vasopressin and terlipressin are potent systemic vasoconstrictors and pulmonary vasodilators.
2. The efficacy of arginine vasopressin and terlipressin to treat septic shock and hemodynamic instability in adult and pediatric patients is well established.

2. Page 5, lines 19-26: Is this difference solely do to complete differential receptor distribution or does vasopression concentration at the receptor site also play a factor?

Thank you for this comment. We agree with the reviewer that the sensitivity to vasopressin might differ amongst target organs and that activation of V1Rs (located in vascular smooth muscles) need higher concentration than V2Rs (located in the kidney) that readily respond to lower circulating concentration of vasopressin. The contradictory actions of vasopressin, however, appear to be mainly related to the distribution pattern and function of receptors (vasoconstriction via V1R in vascular smooth muscle and vasodilation via V2R expressed in endothelium by NO formation) (Vasopressin: physiology, assessment
and osmosensation L. Bankir et al. doi: 10.1111/joim.12645).
Therefore, we have mentioned in our manuscript:

Page 4, Line 3:
At supra-physiologic concentrations, AVP exerts moderate vasoconstrictor effects via vasopressin receptor 1 (V1R) (2). The contradictory actions of vasopressin, however, appear to be mainly related to the distribution pattern and function of receptors (vasoconstriction via V1R in vascular smooth muscle and vasodilation via V2R expressed in endothelium by NO formation) (3-6).

3. Page 5, line 31: Maybe best reworded as – "…vasoplegic shock" was "described for the…".

Thank you for this comment. We have applied the suggested edit.

4. Page 5, line 45: Please add a sentence here summarizing the positive/negative effects/outcomes described in the paper of Meyer.

Thank you for this comment. We have made the following addition to the manuscript

Page 4, line 14
Following the administration of AVP, investigators observed a substantial increase in arterial blood pressure and urine output among three infants with septic shock and a mortality rate

of one out of three. However, among the infants with non-septic shock, blood pressure and urine output only improved briefly, and the mortality rate was three out of three (10).

5. Page 5, lines 51-54: For completeness and for the reader, please provide the average/expected duration of effect and t ½ values for both AVP and terlipressin for a comparative understanding.

Thank you for this comment. We have made the following change to the manuscript

Page 4, line 22

Similar to AVP, terlipressin, a synthetic long-acting analogue of vasopressin, has potent vasoconstrictor properties. Terlipressin selectively binds to V1R and has a longer half-life
and duration of action than AVP.
Changed to:
Similar to AVP, terlipressin, a synthetic long-acting analogue of vasopressin, has potent vasoconstrictor properties. Terlipressin, however, selectively binds to V1R and has a longer half-life and duration of action. Available evidence on pharmacokinetics of these two drugs in premature neonates are limited. Current data has shown vasopressin has an elimination half-life of ≤10 minutes with onset of the pressor effect within 15 minutes that fades within 20 minutes after stopping the infusion. For terlipressin, the estimated half-life is up to 3 hours with time to peak plasma concentration of approximately 2 hours and duration of action of 4-6 hours (Tga.gov.au. 2021. [online] Available at: <https://www.tga.gov.au/sites/default/files/auspar-terlipressin-acetate-121126.pdf> [Accessed 16 April 2021]; Tga.gov.au. 2021. [online] Available at: <https://www.tga.gov.au/sites/default/files/auspar-terlipressin-acetate-121126.pdf> [Accessed 16 April 2021]).

6. Page 6, line 52: neonates not neonate.

Thank you for noticing this error. We have applied the suggested edit.

7. Page 7, line 47: "We also" planned "to search.."

Thank you for noticing this error. We have applied the suggested edit.

8. Page 9, line33: Would this be better worded as – "''will be" resolved "through discussion…"?

Thank you for this comment. We have applied the suggested edit.

9. Page 9, section 1.6: Please provide 1 to 2 sentences describing exactly how you plan to have "public involvement", as I do not understand this within the construct of a systematic review of published literature.

Thank you for this comment. We have made the following change to the manuscript

Page 8, line 19

Patients are not directly involved in the design or conduct of this study. We will plan for public involvement mostly concerned with the dissemination of the results of the review and knowledge translation upon the completion of our review, to contribute to wider dissemination of the review to patients and public. We will plan to provide clear explanation of the concept and develop a glossary of research terms specific to our review. We will also provide detailed explanation of the purpose of patient and public involvement and the expectations of their roles (INVOLVE: Public involvement in systematic reviews, October 2012).

10. Page 10, line 3: Should this read – "outcomes" will be……?

Thank you for this comment. We have applied the suggested edit.

11. Page 10, lines 3-31: Are you confident you will be able to glean this (deep) level of granularity from published papers to achieve the specific parameters you outline here? For example, who will be performing the GMFCS, BSID? What about specific lab data at specific time points outlined? Will you be contacting the published paper authors to obtain the specific information obtained at the specific time points you outline here? What do you plan to do if this information is not available? I am confused.

Thank you for this comment. In the current systematic review, we will be investigating our primary and secondary outcomes as identified and published in the included studies. We agree that the current definitions of our secondary outcomes can make it challenging to find the exact match in the included primary studies. We therefore made the following change to our secondary outcome definitions:

Page 9, line 8:

Our secondary outcomes are i) major neurosensory disability defined as moderate to severe motor or cognitive impairment or severe visual or hearing impairment as identified in the primary study; and ii) the occurrence of adverse events defined as reports of peripheral tissue ischemia, gastrointestinal events (occurrence of perforation, necrotizing enterocolitis, or gastrointestinal bleed), hepatic events, renal events or hyponatremia as identified in the primary studies.

12. Page 10, lines 55-60: How do you plan to "address the gap", lines 58-60, if "The difficulty in performing…." Exists, lines 55 to 58? Consider rewording.

Thank you for this comment. We have made the following change to the manuscript

Page 9, line 19

The difficulty in performing clinical trials in preterm neonates limits their evidence-based pharmacological treatment. We aim to address this gap concerning the use of vasopressin and terlipressin among this vulnerable population.

Changed to:

The difficulty in performing clinical trials in preterm neonates limits their evidence-based pharmacological treatment. We aim to complete a high-quality synthesis of the entirety of available data concerning the use of vasopressin and terlipressin among this vulnerable population in order to further the evidence on this important topic.

Response to Reviewer 2 Comments:

Dr. Sinno Simons, Erasmus MC Sophia

1. With great interest I have reviewed your manuscript that describes your planned systematic review on the safety and efficacy of vasopressin and terlipressin in preterm newborns.
The introduction clearly describes the rationale and potential for both drugs in preterm infants. Although interesting I am not sure if there is sufficient data to draw valuable conclusions afterwards. In comparable review (Reem Masarwa et al, Crit Care. 2017 Role of vasopressin and terlipressin in refractory shock compared to conventional therapy in the neonatal and pediatric population: a systematic review, meta-analysis, and trial sequential analyses) that also included term infants in the PICU concluded a couple of years ago that further large studies are necessary to demonstrate and establish benefits of AVP/TP in children. I agree that preterm newborns are a separate population and that new studies might have been out in the last 4 years. This may be a good argue for your planned efforts.

Thank you for this comment. We have made the following change to the manuscript

Page 5 line 22

A recent systematic review and meta-analysis that examined the role of vasopressin and terlipressin in refractory shock in children, reported a lack of benefit on mortality or length of hospital stay, despite improvements in hemodynamic indices (23).

Changed to:

A recent systematic review and meta-analysis that examined the role of vasopressin and terlipressin in refractory shock in pediatric patients, reported improvements in hemodynamic indices but lack of benefit on mortality or length of hospital stay with a trend toward a higher risk for tissue ischemia (23). In critically ill preterm neonate with complex and poorly understood hormonal dysfunction, the risk of such undesired short and long-term adverse effects is of serious concern (20,22). In view of the increasing use of AVP and terlipressin in neonates of NICUs and high risk of serious adverse events, the need for enhancement of data on efficacy and safety of these drugs in this vulnerable population becomes clear.

2. From a pharmacological point of view it might be very interesting to also have a systemic search on the knowledge/data of dosing these drugs in preterms. Is there evidence on a target in older infants / term newborns? Will this be equal in preterms? Is there pk-studies / pop Pk models (maybe you could use a grading comparable to Silke Gastine et al: Review Expert Rev Clin Pharmacol. 2019 Dec;12(12):1091-1098. GAPPS (Grading and Assessment of Pharmacokinetic-Pharmacodynamic Studies) a critical appraisal system for antimicrobial PKPD studies - development and application in pediatric antibiotic studies) . Knowledge on the half-live / pk might also be somewhat helpful to decide which drug might be most suitable…

Thank you for this comment. We agree that a comprehensive review and presentation of the available data on pharmacokinetics and optimal dosing of vasopressin and terlipressin in premature neonates is of utmost importance. Unfortunately, the available data on the PK of AVP and its analogues in preterm neonates is so scarce that does not allow a systematic review. We therefore, in the current review, chose to provide data on safety and efficacy of this drug while presenting the dosing regimen that was applied in each primary study. We believe the current systematic review could emphasize the importance of future studies on PK-PD of these drugs in preterm neonates.

3. The discussion of your manuscript is a bit conflicting because you already state that the available data on efficacy and safety are limited… and therefore you will perform a systematic review. Won't you do the review to see what the extend of data are? And maybe to find the knowledge gaps that need to be filled?

Thank you for this comment. We have made the following change to the manuscript.

Page 9, line 19

Nevertheless, the available data on the efficacy and safety of AVP and terlipressin in preterm neonates remains limited. Therefore, we aim to conduct a systematic review on this topic using explicit and reproducible methods to produce rigorous and high-quality evidence synthesis and identify evidence gaps that could be the subject of future research.

Changed to:

Nevertheless, the available data on the efficacy and safety of AVP and terlipressin in preterm neonates remains in need of comprehensive review, using explicit and reproducible methods, to produce rigorous and high-quality evidence synthesis and identify evidence gaps that could be the subject of future research.

VERSION 2 – REVIEW

REVIEWER	Reviewer name: Dr. Michael Reed Institution and Country: Case Western Reserve University, Pediatrics, 11100 Euclid Ave, Cleveland, United States Competing interests: None
REVIEW RETURNED	11-May-2021

GENERAL COMMENTS	The authors have addressed all of my comments.