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Title	Topical nitroglycerin ointment as salvage therapy for peripheral tissue ischemia in newborn infants: a systematic review
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Reviewer 1	Michael Rieder
Institution	Department of Clinical Pharmacology, Children's Hospital of Western Ontario, London, Ont.
General comments (author response in bold)	1. This is an interesting analysis of the potential efficacy of topical nitroglycerin versus glycerin trinitrate for the therapy of peripheral ischaemia in newborns, primarily preterm newborns. The authors have demonstrated superior efficacy and safety for nitroglycerin, which sadly appears to now be unavailable in Canada due to drug shortages. **The search strategy is well laid out and the methodology is clear and robust. The findings are based on data and the arising conclusions and recommendations, notably for regulators, are sound.** 2. As a point of interest were there differences in outcome as to the aetiology of the ischaemia (apart from the noted Purple Glove Syndrome case)? It does appear that one could separate PAL as an aetiology from other causes. **Thank you for this comment. We examined the included studies to determine if there was a difference in outcomes based on the cause of the ischemia. This analysis is presented in the Supplementary table of this submission. For the aetiologies of ischemia that had more than one case, the cause of dopamine extravasation (n=3) had a 100% total recovery, the cause of PICC (n=4) had a 100% total recovery, spontaneous cause (n=2) had a 100% total recovery, umbilical line cause (n=7) had a 71% total recovery, PAL cause (n=16) had a 56% total recovery, and PIV cause (n=2) had a 50% total recovery. However, due to the study methodologies (primarily case reports), the small number of studies, and the primary objective of the current review, which is investigation of safety-efficacy of three available products for topical administration of nitroglycerin, we chose not to include this information in the actual manuscript.** **PLEASE NOTE THAT THE SUPPLEMENTARY TABLE DETAILING THIS INFORMATION IS ONLY FOR RESPONDING TO THIS REVIEWER'S COMMENT. WE DO NOT WISH TO PUBLISH THE SUPPLEMENTARY TABLE THAT PRESENTS THIS INFORMATION.** 3. As a minor point in the second sentence in the Introduction "non-negotiable" seems like an odd way to describe the situation where there are no alternative approaches. **As per this comment, we have made the following change to the Introduction section of the manuscript.** **Page 4, line 2:** **Extremely low birth weight (ELBW) infants in the Neonatal Intensive Care Unit (NICU), require venous with or without arterial cannulation to maintain their therapeutic needs. Although these interventions are "non-negotiable," peripheral tissue ischemia is a well-described complication of vascular**

	catheterization. **Changed to** **Preterm and term newborn infants admitted to Neonatal Intensive Care Units (NICU), require venous access, with or without arterial cannulation, to meet their therapeutic needs, including hemodynamic and nutritional balance.[1]** **Although an imperative need, peripheral tissue ischemia is a well-described complication of vascular catheterization.[2,3,4,5,6]**
Reviewer 2	Peter Fowlie
Institution	Paediatrics, Ninewells Hospital and Medical School, Dundee, UK
General comments (author response in bold)	1. The authors address a very reasonable issue that is relatively common in neonatal practice. Conducting a systematic review is an appropriate approach. The authors present a lot of useful data/evidence and their work is to be commended. My main comments and suggestions are focused on how the work is described ie the methodology - and the presentation of the findings. The clinical question/hypothesis being addressed by the review should be clearly stated at the outset. I think the details are almost there but it should be explicit perhaps using PICO type framework. It is much easier to describe "comparison" intervention if you know or think there will be some studies with such eg clnical trials rather than case studies but that should not stop the investigators from outlining the clinical question a priori with a comparator intervention. Similarly it might be helpful to state the outcome[s] of interest here again a priori eg loss of digit/limb, vascular flow patterns [?], pain [?] "recovery" . Again I suspect the relative lack of detail presented here is because the authors may have been aware beforehand of the limited data they might find but that should not stop them presenting the clinical question in detail. **Thank you for this comment. We have now made the following changes to improve the methodology and the presentation of our findings.** **Specifically, we have** **(a) created a PICO box;** **(b) clarified our clinical question using the PICO framework;** **(c) specified the comparator of interest; and** **(d) specified our outcomes as per the available evidence** **Page 21:** **In our utilization of the PICO framework we have attempted to clearly state the clinical question that our review addresses.** **Page 21, line 7:** **Using the PICO framework also allowed us to clearly explicate our comparator of interest, which was standard of care or any other therapeutic intervention without the application of topical nitroglycerin products (ointment, nitroglycerin spray, or glyceryl trinitrate patch).** **Page 21, line 10:** **Finally, we have specified a priori our outcomes of interest along a continuum from no effect of the intervention on the area of tissue ischemia to partial effect, which includes partial loss of finger or toe or reported neurovascular change in the affected limb, to complete resolution of the peripheral tissue ischemia injury.** 2. The search seems robust. The study selection depends on what I guess again should be an a priori agreement regarding what type of study/evidence was to be included. Often in SRs it will be stated up front that only RCTs will be included and

	again here I wonder if the way the data are presented reflects the fact that the authors knew they were unlikely to find any clinical "trials". That being the case, it might be suggested that a priori, the authors should explicitly state that they were going to include, all types of clinical evidence in their review including RCTs, nonrandomized trial, cohort studies, case reports. Again, I think this is essentially what they have done but for the reader who does not understand the methodology around SRs, the way this is currently presented may be a bit confusing. **As per this recommendation, we have made the following change to the Methods section of the manuscript.** **Page 5, line 21:** **All randomized controlled trials (RCTs), prospective and retrospective cohort studies, and case reports describing the use of TNG ointment or GTN patch in the treatment of tissue ischemia in hospitalized newborn infants of any gestational age and postnatal age were eligible for inclusion, irrespective of the dose, administration frequency and duration of treatment. Standard practice was the comparator in studies with a control group. If there was no comparator group, the reported efficacy and safety of TNG ointment or GTN patch during the observation period were extracted.** **Changed to** **All randomized controlled trials (RCTs), cohort studies, case reports, and study abstracts describing TNG ointment, TNG spray, or GTN patch in the treatment of tissue ischemia in hospitalized newborn infants of any gestational age and postnatal age were eligible for inclusion, irrespective of the dose, administration frequency and duration of treatment. We did not apply any language or study design limitations. Animal studies and duplicate studies were excluded. Standard practice or any other therapeutic intervention was the comparator in studies with a control group. If there was no comparator group, the reported efficacy and safety of TNG ointment or GTN patch were extracted.** 3. Included studies – the description of the included studies is appropriate as laid out in the table. I wonder if the reader might find it easier to picture the "typical" baby being described here if in the text there was some summary data for example median and range gestation, time/duration of administration etc. **Thank you for this suggestion. We have made the following change to the Results section of the manuscript.** **Page 7, line 11:** **The majority of infants were extremely or very preterm (n = 24, 66%) and within the first two weeks of life at the time of injury (n = 25, 69%). Placement of an umbilical artery catheter or peripheral arterial line was the most common cause of identified tissue ischemia (n = 20, 54%), followed by intravenous drug administration (n = 5, 14%).** **Changed to** **The majority of newborn infants were extremely or very preterm (n = 25, 67.6%) and within the first two weeks of life at the time of injury (n = 26, 70.3%). The mean gestational age was 29.1 weeks (23 weeks - term). Placement of an umbilical artery catheter or peripheral arterial line (PAL) was the most common cause of identified tissue ischemia (n = 22, 56.1%), followed by intravenous drug administration (n = 5, 12.8%). Mean treatment duration was 10.4 days (one dose - 36 days).**

	4. Interpretation – quite a lot of the data are repeated here? Perhaps focus more on the interpretation rather than listing the data? **Thank you for this comment. We have made the following change to the Interpretation section of the manuscript.** **Pages 10 to 12** **We have edited the Interpretation section to avoid repeating data presented in the result section and have now focused on interpretation of the data through making links and references to relevant literature and suggesting future steps to move the evidence forward on this topic.** 5. I think the interpretation is a bit too positive? The authors quite reasonably highlight the potential for bias given the level of evidence presented and there are no data presented to describe outcome without this intervention. Are there any data to be found that could be presented describing the outcome when nitroglycerin is not used?? Perhaps not, but it might be worth stating such? **As per this comment, we have added the following statement to the Interpretation section of the manuscript.** **Page 12, line 13:** **As the evidence on this topic exclusively uses case report and case series methodology, we were unable to compare outcomes among infants who were exposed and unexposed to TNG products.** 6. I wonder if more caution is needed when describing the "risks" of the treatment. Although the adverse events reported seem to have been reversible the authors seem to highlight potentially 7 adverse events/serious adverse events in around 36 infants? 20% seems a fair risk? [See specific comment re MetHb adverse outcomes below] **Thank you for this comment. For those treated with TNG ointment, adverse events occurred in four out of 23 infants, at a rate of about 17%. These included decreased blood pressure in three infants and the occurrence of swelling bulla in a fourth infant. For the three infants who experienced hemodynamic changes, two were already being treated with inotropes to maintain blood pressure prior to treatment with TNG ointment and the hypotension event of the third infant resolved spontaneously within 30 minutes of the occurrence. The occurrence of swelling bulla resolved by discharge on day 16 of the clinical course. None of the four above occurrences was identified by authors as drug related or serious. This information is reflected as follows in the manuscript.** **Page 10, line 16:** **Based on the available limited evidence, TNG ointment seems to be well tolerated in preterm and term neonates, with no serious adverse events identified as drug-related. Reports of mild decrease in blood pressure were in neonates already receiving inotropes for blood pressure support before TNG ointment application,36,31 or resolved spontaneously without intervention. The results of our review point towards efficacy with no serious drug-related adverse events of TNG ointment for the treatment of neonatal peripheral tissue ischemia. However, the limited data warrant further investigation through experimental trials to confirm the optimal efficacy-safety profile of this drug.**

	Minor comments 7. In the abstract the methods section describes the literature search and little/nothing else? I would suggest that in the abstract, it should be clear that a "systematic review" was undertaken. **As per this comment, we have made the following change to the Methods section of the Abstract.** **Page 3, line 7:** **EMBASE, CINAHL, MEDLINE, PubMed, and Web of Science were searched from inception to April 2020 for articles that reported use of TNG ointment or GTN patch for treatment of peripheral tissue ischemia in newborns.** **Changed to** **We conducted a systematic review of EMBASE, CINAHL, MEDLINE, PubMed, and Web of Science for studies on TNG for the treatment of neonatal tissue ischemia. We did not apply language or design limitations. Animal experiments and duplicate records were excluded. The Tool for Evaluating the Methodological Quality of Case Reports and Case Series was used to assess the risk of bias of individual studies.** 8. I note in PRISMA flow diagram, one study was excluded on basis of the intervention being nitroglycerin "spray". If the authors explicitly stated they were only interested in evidence on ointment or patches a priori, then this is I guess appropriate but if the intention was to review as much of the evidence as possible accepting it would likely be challenging to focus too rigidly in this review, then why miss it out given presumably similar theoretical pharmacological effect? **Thank you for this suggestion. We have now included all available nitroglycerin products available for topical administration (nitroglycerin ointment, nitroglycerin spray, or glyceryl trinitrate patch) in this systematic review and this change has been reflected appropriately throughout the manuscript.** 9. In table of descriptions, the 2 cases of MetHb described appear under Mintoff 2018. The "dose" listed here is "9cm^ patches containing 18.7mg GTN". It struck me that this would be a much higher dose of GTN that listed against any of the other studies if indeed the whole patch was used. It might be worth describing this issue a little more given the serious nature of the apparent side effect? **As per this recommendation, we have added the following statement to the Interpretation section of the manuscript.** **Page 11, line 3:** **Added** **Although the GTN dose administered in the two cases with methemoglobinemia was higher than the doses administered in any of the other studies, the available limited evidence with GTN patches creates worry around their use in this vulnerable population. Furthermore, dosing flexibility, which is of paramount importance in newborns, may be less with a patch than with ointment, which may increase the risk of adverse event (overdosing) or therapeutic failure (underdosing).** General comment

	10. I was interested in the inclusion in the paper of reference to the fact that GTN is no longer available in Canada and this is seen by the authors as having a negative impact on neonatal care provide. I wonder about two things here. How much of this discussion around GTN being available in Canada is relevant to the presentation/reporting of the SR? I would say it is not relevant at all and this issue should be raised and debated in a separate forum – letter, editorial etc making reference to the evidence now available from the SR but I guess this is an editorial decision. **Thank you for this comment. In our manuscript we have now referenced (Reference 17) the discontinuation of TNG ointment by the Canadian manufacturer and also provided reference to clinical guidelines (Reference 10-15), supporting the off-label use of TNG ointment in the treatment of neonatal peripheral tissue ischemia. This change is reflected in the following sections of our manuscript:** **Page 4, line 20:** **In July 2018, the Canadian manufacturer discontinued the production of TNG ointment.[17]** **Page 4, line 17:** **Topical nitroglycerin (TNG) products with Canadian labeled indications for prevention angina pectoris in adults, have been used, off-label, as salvage therapy for tissue ischemia in neonates since the 1980s.[10–15]** **As per the inclusion of discussion around TNG ointment shortage in the current systematic review, we do agree that a systematic review should provide an objective overview of the available evidence and that merging this advocacy discussion in our systematic review might raise a question around investigator bias. The decision on raising the important issue of TNG drug shortage in the current manuscript, was reached after much reflection among authors and the following discussion:** **a. A timely advocation for the renewed production of TNG ointment in Canada appears necessary. We therefore mixed both a rigorous systematic review with an opinion in order to expedite potential action regarding this important drug shortage.** **b. We made every effort to keep an objective report throughout the manuscript by rigorously following the best available guidelines to conduct and report a systematic review and to provide clear acknowledgment of our study's limitation.** **Considering the above and also that the use of systematic reviews as a tool for patient advocacy have been previously reported in the literature (O'Leary et al., 2017) we planned the current manuscript to present both a systematic review of the literatures on the safety and efficacy of topical nitroglycerin products and to provide an opinion on potential implications of this drug shortage on neonatal population.** **Nevertheless, the authors are willing to follow the ultimate editorial decision in this regard and submit the advocacy opinion as a separate letter if the final editorial recommendation remains as such.** 11. And my second slight worry, is that in presenting the "Canadian position" and a call for the drug to be made available, there is a risk that the authors may be seen as having a degree of bias [unintended or not] even before they undertook the

	review and that this is impacting on how the paper is written and presented. I think the authors have probably undertaken a robust piece of work here and the review is potentially an important addition to the literature. I think it could/should be presented in a more “clinical” style - again perhaps one for the editorial board to call. **Thank you for this comment. In response to this, we have made the following changes throughout the manuscript, in an attempt at reducing any bias that we unintentionally conveyed in the presentation of our systematic review. We have modified the Interpretation section (pages 10 to 12) to further focuses on the analysis and explanation of the clinical results of our systematic review. We highlighted that the existing data on this topic is limited and warrants future more rigorous methods to clearly establish the efficacy and safety of TNG ointment in the neonatal population. We also added the following information.** **a. Page 10, line 16:** **Based on the available limited evidence, TNG ointment seems to be well tolerated in preterm and term neonates, with no serious adverse events identified as drug-related.** **b. Page 10, line 21:** **However, the limited data warrant further investigation through experimental trials to confirm the optimal efficacy-safety profile of this drug.** **c. We have also removed the Call to Action heading from the Interpretation section. Instead of the Call to Action, we have taken a more neutral stance, requesting that Health Canada re-examine the availability of TNG ointment in Canada, based on an assessment of the available evidence.** **Furthermore, the authors are willing to follow the ultimate editorial decision in regard to presence of advocacy opinion in the systematic review and submit the advocacy opinion as a separate letter if the final editorial recommendation remains as such.**