PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Anaesthesia Modalities during Laser Photocoagulation for Retinopathy of Prematurity: A Retrospective, Longitudinal Study
AUTHORS	Jing-bo, Jiang; Strauss, Randy; luo, xianqiong; nie, chuan; wang, yanli; zhang, jiawen; Zhang, Zhiwei

VERSION 1 - REVIEW

REVIEWER	Deepak Chawla Associate Professor Department of Paediatrics Government Medical College Hospital Chandigarh India
REVIEW RETURNED	19-Aug-2016

GENERAL COMMENTS	This study presents an interesting retrospective data about effects of different methods of anaesthesia used during laser photocoagulation in neonates with retinopathy of prematurity. Health facilities in many developing countries lack expertise for neonatal general anaesthesia and laser therapy is conducted with local anaesthesia with or without oral sucrose. In such a scenario this non-randomised study provides important insights into cardiorespiratory side effects of different methods of anaesthesia. However there are many limitations in the study and manuscript. - First of all the manuscript needs to be seen by an English language expert. There are numerous examples of grammatical and style errors and it is not possible to point out these individually. An example “Only yet all the mild cardio-respirotary instability in general anaesthesia and fentanyl sedation attributed to difficulties to excubate within 24 hours after surgery" - Second major issue with the study is this being a retrospective study association between method of anaesthesia and outcomes is difficult to prove. For example time taken to complete laser therapy is lower with fentanyl or GA. However this may be because of increasing expertise of the eye surgeon. As mentioned in the manuscript same surgeon performed laser it is expected that with increasing experience time taken to complete the procedure will decrease. Author may consider including secular trend within groups over time to evaluate this phenomenon. - Similarly as GA and fentanyl were accompanied by intubation and assisted ventilation it is difficult to establish whether better cardiorespiratory scores are because of assisted ventilation or because of method of anaesthesia. What would have happened if neonates given local anaesthesia were also intubated and given assisted ventilation during the procedure. - As pain scores are not available in the three groups it is not

	possible to comment on difference in pains scores in the three groups - In results authors have presented too much text. Results may be summarised and presented in tabular format for ease of understanding. - Objective stated in abstract is not clear. - Introduction is not supported by references.

REVIEWER	Clyde Matava Hospital for Sick Children Canada
REVIEW RETURNED	23-Aug-2016

GENERAL COMMENTS	Thank you for the opportunity to review this paper. 1. Overall, a well planned study 2. It is unclear as to the primary hypothesis and outcomes for this retrospective study. Please delineate these clearly. 3. The are numerous grammatical and spelling errors - ?incubation versus intubation. Please correct these. 4. What were the pain scores - N-PASS after the procedure? How did these interact with the higher CRI in the local anesthesia group? 5. The results section is a little unclear can benefit from a rewrite. 7. A major limitation in this study is the lack of N-PASS scores in the local anesthesia group. Please provide data for this N-PASS for this group especially in view of the previews reported scores of 7.5 in this group for the same procedure. 8. Please provide evidence/results supporting your statement on page 11 line 56 ' Lengthy treatment times were more painful for infants.' 9. Can you explain why there were were 3 life threatening events in the local anesthesia group. 10. As your results suggest a lot of negative outcomes and consequences of the local anesthesia group, please highlight how these findings have/are impacting practice at your institution. 11. Please specify which components of CRI contributed to the scores. Apnoea? what was the oxygen FiO2 used in the cases? 12 What was the halothane MAC used in the cases?

VERSION 1 – AUTHOR RESPONSE

For reviewer 1

Thank you for your informative and specific suggestions. It is great honor to learn from you, especially as I'm just starting out my career.

1. The entire manuscript has been revised by a native English speaker with medical background in order to address the grammatical and spelling errors.

2. With regards to the retrospective study, it is indeed difficult, or impossible to prove the association between treatment (anaesthesia in our study) and outcomes. As mentioned in the manuscript, the RCT study will be valuable in the future. However, it takes a much longer time to get a prospective clinical trial approved. Nevertheless, this study could provide the preliminary data to support a clinical trial submission.

3. As for the time taken to complete laser therapy, our hospital started this surgery in 2004 by Dr. Xuelin Huang, an experienced ophthalmologist who has conducted more than 300 laser therapy procedures and more than 4000 ROP screenings before this study. Examining secular trends within groups over time to evaluate the increasing experience is a convincing suggestion. Therefore, we analyzed the operation time within each of the 3 groups by dividing the patients in 3 subgroups.

Results from a one-way ANOVA test didn't show any significance. These results have been added to the 1st paragraph under the "Result" section.
4. Regarding a potential confounding variable of respiratory support in contributing to the cardiorespiratory score, CRI is a combination result of laser therapy, stress response, basal illness and the overall states of infant, as well as anaethesia methods and life support. It is expected that intubation and assisted ventilation during topical anaethesia could bring the sick infants more stable cardiorespiratory index, as any emergency could be handled immediately. However, proper sedation is needed in the alert infants, there is secondary strike while without any sedation nor anaethesia. In the end, the effect of anaethesia couldn't be isolated when the life support is taken into account. In this setting, we can't draw the firm conclusion that "GA or Fentanyl result in better CRI".
5. A major limitation in our study is the lack of N-PASS in all the three groups, making it impossible to comment on differences. Unfortunately it's too late to evaluate the score now because all the procedures have been completed. Initially we are especially interested in Fentanyl group because it was a new approach when doing laser therapy in our unit since 2013. Our priority purpose was to compare the tolerance of Fentanyl anesthesia with standard NICU procedure, such as blood drawing and glucose monitoring, presuming to compare the N-PASS with previously reported one. On the other hand, the understaffed condition in NICU made it even difficult to record pain score in every single child. As a result, we didn't draw any conclusion from comparing pain score in three groups, we could only compare the tolerability of Fentanyl with other published N-PASS while doing less stressful procedure. Hopefully further attention is given to the pain score in different anaethesia methods. I have added this statement in the "strengths and limitations of this study" section.
6. The result section has been rewritten for easy understanding.
7. The objective in abstract has been rewritten as "Laser photocoagulation surgery is a routine treatment for threshold retinopathy of prematurity. However, little is known about which anaesthesia protocols provide efficient pain control while minimizing exposure risk to vulnerable infants. In this study, therefore, we assessed the efficacy and tolerability of multiple anaesthesia techniques used on premature infants during laser therapy.."
8. Several references have been added to support the introduction.

For reviewer 2:
Thank you for your informative and specific suggestions. It is great honor to learn from you, especially as I'm just starting out my career.
1. Thank you for your kind words.
2. The Objective section has been rewritten to elaborate the purpose of our study. As not many publication are available to evaluate efficacy and safety of different anaethesia methods during ROP treatment, in order to establish the optimal anesthesia strategy, we analyze the patients' condition before and after operation by cardiorespiratory index; for efficacy of laser treatment, we analyzed the fundus vascularization results; for efficacy of pain control under fentanyl anaethesia, we assessed the N-PASS, and compared the parameter with some other standard NICU procedure, such as blood drawing and glucose monitoring, The outcome is consistent with our hypothesis that while the disease has been treated properly, fentanyl provides sufficient sedation effect and maintain the infants in stable overall condition.
3. All the manuscript has been revised by a native English speaker with medical background in order to address the grammatical and spelling errors.
4. It is wise to take the N-PASS after the procedure, but unfortunately we didn't record it. Partly because the infants didn't show significant stress response during the procedure, we assume that after the laser photocoagulation has completed, there shouldn't be any increased pain. Neither did we record the pain scores in local anesthesia group, because it's usually busy for the assistants to handle the baby along with surgeon during local anesthesia, the mess situation made them unavailable to observe the N-PASS.
5. The result section has been rewritten for easy understanding.
6. A major limitation in our study is the lack of N-PASS in all the three groups, making it's impossible

to comment on differences, unfortunately it's too late to evaluate the score now because all the procedures have been completed. Initially we are especially interested in Fentanyl group because it was a new approach when doing laser therapy in our unit since 2013. Our preliminary purpose was to compare the tolerance of Fentanyl anesthesia with standard NICU procedure, such as blood drawing and glucose monitoring, presuming to compare the N-PASS with previously reported one. On the other hand, the understaffed condition in NICU made it even difficult to conduct pain score in every child. As a result, we didn't draw any conclusion from comparing pain score in three groups, we could only compare the tolerability of Fentanyl with other published N-PASS while doing less stressful procedure. Hopefully further attention will be aroused to comment on pain score in different anesthesia methods. I have added this statement in the "strengths and limitations of this study" section.

7. We estimate that the more time an infant exposed to laser photocoagulation, the more stressful it should be, but we can't provide any direct evidence to support this speculation. The only phenomenon we observed it that it took averagely 12-16 minutes to fulfill one procedure in anaesthesia group due to extra effort to comfort the restless baby and it was in this group that encounter more and severe cardiorespiratory stabilities. Therefore, to be more rigorous, this statement has been revised as "Prolonged treatment are speculated to be more painful for infants".

8. In our study, SpO2 dropped drastically in one infant when laser therapy started about 8 minutes. We did the resuscitation immediately, but irresistible pneumorrhagia was diagnosed according to X-Ray and clinical manifestation. Life support was weaned 1 week later. The baby was transferred from another hospital with sepsis and lung infection, the overall condition was very poor even before the laser procedure, almost qualified the criteria to get mechanical ventilation. In this case, laser therapy was like a trigger to the deterioration. We attribute pneumorrhagia be the lung infection and hopyxemia induced by the operation, probably due to oculocardiac reflex and pain stress. Another 2 infants need bag and mask oxygen and intubation due to hypoxemia and bradycardia, mechanical ventilation remained for more than 24 hours and laser procedure had to be terminated and rescheduled.

9. We have seen some side effects in ROP screening. It is obvious that in some cases, infants remain restless even after local anaesthesia had been administrated, with enough dose and prevention from leak before it is permeated.Together with the fact that negative outcomes were accumulated as the cases for laser therapy under local anaethesia increased in our institution, we were doing efforts to minimized the pain strike during operation, such as adding a topical anesthetic before dilatation to change the stress responses induced by mydriatic eyedrops; use a certain kind of scleral depressor (a blunt pediatric surgical localizer or a cotton- tipped wooden stick) instead of the muscle hook to perform scleral depression; keep the babies NPO in case the patient develops apnea and relaxation of the esophageal sphincter causing aspiration, diazepam to settle down the baby before or during the operation, conduct the procedure with oral sucrose. In some extremely weak baby, however, negative events show off without any extra head movement or crying, the first sign is bradycardia or decreased SpO2.

10. Both increased oxygen requirement and apnoeas contributed to the CRI, when apnoeas can't be diminished by stimulation, intubation and mechanical ventilation is necessary, and increased oxygen requirement inevitable, initially FiO2 was 40% in most cases, even the baby's performance is better, FiO2 were adjusted every 30 minutes until 21%.

11. Conc. of helothane is usually 2-3%, however, we didn't test the MAC on prematurity, in term baby undergo general surgery, the time for equilibration of helothane from lung to brain is approximately 10-15 minutes.

VERSION 2 – REVIEW

REVIEWER	Dr Deepak Chawla Department of Pediatrics Government Medical College Hospital Chandigarh India
REVIEW RETURNED	05-Nov-2016

GENERAL COMMENTS	Authors have addressed most of concerns raised in the previous review. The English language used has improved considerably. However, some minor changes may be needed to improve the readibility. * Please correct last line of introduction from "...also used to evaluate the tolerability performed under fentanyl sedation." to "...also used to evaluate the tolerance of fentanyl sedation." * Page 4 para 2: Change from "Group A involved infants..." to "Group A comprised of infants...." * Page 4 para 2: Change from "Fentanyl dosed.." to "Fentanyl was administered at a dose of ..." * Page 6 para 2: Change from "...prematurity cases....." to "..premature neonates...." * Page 7 para 1 belongs to method section.

VERSION 2 – AUTHOR RESPONSE

Thank you very much for the critical reading and professional revision of our manuscript. We have further modulated the manuscript according to your advises.

1. The last line of introduction has been corrected from "...also used to evaluate the tolerability performed under fentanyl sedation." to "...also used to evaluate the tolerance of fentanyl sedation."
2. Page 4 para 2 has been changed to "Group A comprised of infants...."
3. Page 4 para 2 has been changed to "Fentanyl was administered at a dose of ..."
4. Page 6 para 2 has been change from "...prematurity cases..." to "..premature neonates...."
5. Page 7 para 1 has been replaced to the method section.