## PEER REVIEW HISTORY

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## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | NOPAIN-ROP' trial Intravenous Fentanyl and Intravenous Ketamine for Pain Relief during Laser Photocoagulation for Retinopathy of Prematurity (ROP) In Preterm Infants – A Randomised Trial |
| **AUTHORS** | Madathil, Shamnad; Thomas, Deena; Chandra, Parijat; Agarwal, Ramesh; Sankar, M Jeeva; Thukral, Anu; Deorari, Ashok; |

## VERSION 1 – REVIEW

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| **REVIEWER** | Balasubramanian, Haribalakrishna<br>Surya Hospitals |
| **REVIEW RETURNED** | 13-Nov-2020 |

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| **GENERAL COMMENTS** | This is an interesting and well presented study and I appreciate the investigators for addressing an important area of research. The authors have assessed the efficacy of two regimens of intravenous fentanyl and ketamine in reducing the pain associated with laser photocoagulation in neonates. The primary composite outcome is the achievement of a PIPP-R score of <7 and a reduction in crying time.<br><br>The authors found that adequate analgesia was achieved in less than a quarter of the study infants. But they might have missed a modest analgesic response given their choice of primary outcome and hypothesis.<br><br>My comments/suggestions/queries:<br><br>1) The investigators have used an RCT design, however, the hypothesis (parallel groups not compared for superiority, non inferiority or equivalence) qualifies for a prospective observational study.<br><br>2) How did the authors assume that 90% infants would achieve adequate analgesia with these interventions? A run in phase prior to trial enrolment would have helped in framing the hypothesis and most importantly in choosing a primary outcome for such a study.<br><br>3) Laser photocoagulation is an intensely painful procedure due to the multiple factors (procedural time, lighting, retractors) as rightly mentioned by the authors. To the best of my knowledge, even a combination of interventions have not been successful in reducing the PIPP scores to less than 7. Primary Comparisons of PIPP |

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| | scores between the two groups (provided they do not vary as much through the procedure) or within groups for incremental doses could have possibly helped to measure a modest analgesic response from fentanyl. Only then can the authors recommend their fentanyl regimen inspite of their primary findings. The discussion needs to be modified accordingly.<br><br>4) PIPP –R is a validated tool to measure pain. But, it could be challenging to score the facial and eyelid/brow responses during such procedures particularly since laser is carried out in a dark room. From personal experience, it is extremely difficult to appreciate facial responses with spotlight illumination in a dark room. How did the investigators address this issue?<br><br>5) The authors frequently cite resource constraints as the only rationale for testing fentanyl/ketamine as opposed to general anaesthesia, for laser ablation. Skill required to effectively laser the eyes of mature infants that could be inconsolable, safety concerns, day care procedural ethics are important considerations. Infact, the findings from this study should be equally relevant to the resourceful settings. Please modify accordingly.<br><br>6) It is also important to think, if a 24 hour hospital stay is acceptable in exchange for a possible pain reduction. It would be more important to study these interventions among neonates that may need laser before discharge from the NICU.<br><br>7) The statement of principal finding suggests that a 24 hour observation was considered only for a minority of the infants that experienced adverse events. Is this correct?<br><br>8) The suggestion for use of midazolam should not come under principal findings. |

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| **REVIEWER** | Miller, Jamie<br>University of Oklahoma |
| **REVIEW RETURNED** | 03-Dec-2020 |

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| **GENERAL COMMENTS** | Overall comments to authors: There are many grammatical errors throughout the paper. I did not comment on many of these in my specific, as I felt they would be addressed later in the editing process. In addition, there are several abbreviations that are only used once in the paper and could be eliminated. Also, there are several abbreviations that are introduced multiple times [(e.g., gestational age (GA)]. Make sure to go back and define it only the first time it is used and use the abbreviation through the remainder of the paper. There needs to be a clearer description of the study site and the study procedures since this outpatient/day clinic practice may differ from what many are accustomed to with these procedures being performed in the NICU or OR.<br>Specific comments to authors:<br>Abstract: |

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| | - Results: in the main portion of the text, it states 4.5% with ketamine had adequate analgesia. Please change in abstract to match.<br>Introduction:<br>- A brief introduction of ROP is needed to orient readers who may have less familiarity with neonatal disease states. This may require cutting some of the information already in the introduction section to avoid too long of an introduction.<br>- Paragraph 1, sentence 2: remove abbreviation SAP, it is not used elsewhere in the paper other than in the “what is already known” section. Abbreviation can be removed from there also.<br>- Paragraph 1, sentence 3: remove abbreviation LMIC, it is not used elsewhere in the paper.<br>- Paragraph 1, last sentence: suggest to add a couple of examples of the long-term neurodevelopmental consequences of untreated pain in the neonate.<br>Methods:<br>Setting:<br>- Paragraph 2: consider also including if they received ophthalmic anesthetics as part of the typical regimen.<br>- Paragraph 2, sentence 4: consider describing where patients are discharged to (e.g., back to referring hospital, home, general floor at same facility). Also, it is stated here they are observed for a few hours and discharged, but in another section it states 24 hours of observation.<br>Study design and participants:<br>- Sentence 2: please revise sentence. Consider changing to “A control arm was not included in the study design since is would be considered unethical to not provide analgesia for this procedure”<br>- Sentence 5: I am confused by this exclusion criteria based on the setting for the study, which is a day treatment center. I was surprised to see “receiving any respiratory support” or “sick enough to require NICU care” as exclusions since this seemed to be a day treatment center and they were discharged shortly after the procedure. This may be a misunderstanding on my part since we do these procedures inpatient. Maybe a better explanation of the day treatment center – can they be sent over from a NICU for the procedure and sent back to the NICU after?<br>- 2nd paragraph, first sentence: abbreviation IEC is not used again, so could be deleted.<br>Intervention:<br>- Fentanyl group: abbreviation F-123 is included, but not really used throughout paper. Would suggest to remove abbreviation.<br>- Fentanyl group: Suggest to remove wording about the definition of inadequate response and include it in the paragraph above after discussing the nonpharmacologic measures and ophthalmic drops.<br>- Fentanyl group: suggest to change “hiked up” to “titrated”<br>- ketamine group: abbreviation K-0.5/2 is included, but not really used throughout paper. Would suggest to remove abbreviation.<br>Outcomes:<br>- Paragraph 2, sentence 2: abbreviation BS is not used throughout the text. Suggest to remove abbreviation.<br>- Consider putting the definitions for apnea, bradycardia in parenthesis after those words to decrease the number definitions |

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| | that are introduced one after another. I got bogged down when reading this section.<br>Procedure:<br>- Sentence 1: abbreviation pHDU is not used anywhere else in paper. Can delete abbreviation.<br>- Last sentence: were all patients monitored for 24 hours or only those that required supplemental oxygen?<br>Additional data collection:<br>- Additional data collection, sentence 1: would avoid use of etc. in the sentence. Instead could change to "…antenatal risk factors (e.g., pregnancy induced hypertension, gestational diabetes mellitus)."<br>- Last sentence: suggest to change "worst of two eyes" to "…were affected, the greatest severity of disease was documented"<br>Statistical analysis<br>- Sentence 1: CRF is not used throughout paper, can delete abbreviation<br>Results:<br><br>- Paragraph 1, sentence 1: don't need to capitalize fentanyl or ketamine. Please change throughout results section and subsequent sections.<br>- Recommend to include a heading of "Initial Regimen Phase" similar to the "revised regimen phase" prior to the paragraph where you are discussing Table 1. I had to read it twice to realize that you were only talking about the initial regimen group in this paragraph.<br>- Would be helpful to include the number of patients that required laser photocoagulation on only one eye versus on both eyes. This could affect procedure duration, so would be helpful to the reader.<br>- Paragraph 3, sentence 1: I am confused by this sentence because the denominator is 49 in the fentanyl group and 44 in the ketamine group. This differs from the n that is included in the table, 51 and 46, respectively.<br>- Posthoc analysis: change "PIPP" to "PIPP-R"<br><br>Discussion:<br>- First paragraph, last sentence: consider changing to "Despite the worrisome consequences of leaving pain untreated, the reasoning for lack of treatment has become widely accepted in lieu of limited resources."<br>Statement of principal findings,<br>- Sentence 3: stated that "a minority did experience significant side effects that mandated in-hospital observation for at least 24 hours". However, no where in the results section do you include information about the n (%) of patients that required additional monitoring. Please include that info in the results section. Also, it was stated in the study methods that they would be observed for 24 hours, but it wasn't clear if that was all patients or just those needing oxygen.<br>- Last sentence: recommend to change to "…like midazolam may be considered for optimal sedation during laser therapy" to emphasize the sedative effects of midazolam versus analgesic. Also, may want discuss that this agent is commonly used in some protocol (and cite those studies) and is recommended in the Italian Pediatric guidelines. |

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| | - Strengths and weaknesses of the study, sentence 5-6: please change to (underline words are those that are changed) "…incomplete birth and caregiver data. However, we believe, this should not have affected…"<br>- How does the fentanyl dose used in your study compare to fentanyl doses utilized in previous studies? How does your ketamine dose compare to the one study you cited that previously reported the use of ketamine? Need to expand discussion section to include these details and cited studies.<br>- Strengths and weaknesses in relation to other studies, paragraph 2, last sentence: please include 1-2 sentences explaining what Orge and colleagues and Sato and colleagues observed.<br>- Need to include a paragraph about limitations of this study.<br>Tables and Figures:<br>Table 1:<br>- What do the asterisks indicate in the table? Based on the key below the table it looks like it is referring to the data represented as n (%), mean (SD). But there are some variables that are n (%) that don't have an asterisk.<br>- In the key below the table 1 you have # median (IQR), but I don't see the # symbol used in the table<br>- For the antenatal steroids data, it would be helpful to know how many patients that this data was available for. It seems based on the % that is provided that you just used 51 and 46 patients as your denominator. But, if this data was not available for all patients, then it should be presented differently to make clearer to the reader.<br>- The n's for the groups will likely need to be changed. Looked like you only ended up including 49 and 44 patients in each group respectively. If so, please correct the % reported to include those as the demonimator<br>Table 2:<br>- Based on the percentages provided for infants achieving adequate analgesia, it looks like you calculated this number out of 49 and 44 patients for each group, whereas the n at the top of the table is 51 and 46, respectively. This differs from the % calculated for all PIPP-R scores which the denominator of 51 and 46 are used.<br>- I am confused by the data presented for "proportion of time spent crying <5%". To me, this should be presented as n (%) to indicate the number of kids in that group who spent <5% of the procedure time crying. As listed as 9.5, I am not sure what this represents. Is this the median % of the procedure time that infants spent crying? If that is the case, then the description in the characteristic column should be changed.<br>- I am unsure what is meant by the variable "change in cardiorespiratory stability scores". It this the n (%) of patients that had a change in score? If so, this is difficult for me to interpret as a reader because I don't know if their score improved or they were more unstable. Consider splitting out information to include those that improved from baseline, had no change, or had more instability.<br>Table 3: |

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| | - Same comment about “proportion of the time spent crying <5%” and “change in cardiorespiratory stability scores” as in table 2. Unsure of what this data means.<br>Table 4:<br>- Header of third column should be changed from “ketamine revised dose” to “ketamine initial dose”.<br>- In last row of table, change to “neonates with maximum PIPP-R…”<br>Table 4 -supplementary table:<br>- Suggest to format this table the same as you did for table 1 for consistency (e.g., mean (SD) versus mean + SD).<br>- See previous comment about asterisk on table I and what this means<br>Figure 1 study flow:<br>- The numbers in the analyzed boxes for the initial phase need to be changed to 49 and 44, respectively based on the 2 patients in each group excluded for cry duration.<br>- The exclusion criteria listed in this figure don’t match all of the exclusion criteria listed in the body of the paper.<br>- For the exclusion box, what is meant by letter e – Excluded (n=19). What were these patients excluded for? Please describe or change to “other” to indicate that you grouped together some of the less common exclusion reasons. |

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| **REVIEWER** | Stoddard, Gregory<br>University of Utah |
| **REVIEW RETURNED** | 27-Dec-2020 |

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| **GENERAL COMMENTS** | As a biostatistician reviewer, I found your statistical methods to be sound. I agree with you that there is no need to statistically compare the two study arms, but to simply show point estimates and 95% confidence intervals separately for the two study arms. Similarly, powering the study based on precision (width of the confidence intervals) was the appropriate approach. Performance of an intervention, which in your case is analgesia, is always weighed in the clinician's mind relative to something. By having two analgesia study arms, it made it easier for the clinician reader to interpret the performance of the analgesia interventions being reported. Had you simply used one analgesia study arm, the results would be far less informative. I have no suggested changes to your manuscript, which I found to be of excellent scholarship. However, please look at the following sentence in your strength and weaknesses of the study section, "However, we believe, this should have affected internal or external validity of the study." Did you mean to say, "have not affected?" |

## VERSION 1 – AUTHOR RESPONSE

We are thankful to the editor and the reviewers for the pertinent comments on our paper. Necessary modifications suggested have been incorporated and the article is being resubmitted. All the valuable comments and modifications suggested by the reviewers have also been incorporated.

## VERSION 2 – REVIEW

| REVIEWER | Balasubramanian, Haribalakrishna<br>Surya Hospitals |
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| REVIEW RETURNED | 10-May-2021 |

| GENERAL COMMENTS | The authors have satisfactorily addressed the queries raised. |
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| REVIEWER | Miller, Jamie<br>University of Oklahoma |
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| REVIEW RETURNED | 22-Apr-2021 |

| GENERAL COMMENTS | Overall comments to authors: Overall, the manuscript is much improved with the revisions made to the manuscript. There are still many grammatical errors throughout the paper; however, I did not comment on many of these in my specific comments, as I felt they would be addressed later in the editing process. I have provided specific comments below for revisions.<br>Specific comments to authors:<br>Abstract:<br>- Interventions: consider adding the dose that was administered for both the initial and the revised dosing<br>Introduction:<br>- Paragraph 1, 2nd sentence: suggest to include a reference citation to support this statement.<br>- Paragraph 2, last sentence: how was adequate analgesia defined in this study that you are referring to? Suggest to include the definition in parenthesis at the end of the sentence.<br>Methods:<br>Setting:<br>- Last sentence: suggest to change to “If an infant developed any complications or required prolonged observation, they were transferred to the NICU for further management.”<br>Intervention:<br>- Sentence 2: based on the sentence structure it appears that 0.5% paracaine drops are being considered a nonpharmacological measure. Consider changing sentence to “…groups received 0.5% ophthalmic paracaine drops for topical anaesthesia every 20 minutes during the procedure and nonpharmacological measures, namely swaddling and containment.”<br>- If they change suggested above is not made, at a minimum need to change “min” to “minutes” in the sentence.<br>- For increased crying, how is this defined? Increased from what? From baseline? Or, is increased crying based on percentage of procedure time that patient what crying (e.g., >40%, >25%, etc.)<br>- Fentanyl group, last sentence: suggest to change to “If the response was inadequate, the infusion rate was titrated…”<br>Results:<br>- 3rd paragraph, 2nd sentence: a statement that no difference in side effects post-procedure between groups, but were side effects monitored during the procedure as well? This would seem to be more important than adverse effects in the post-procedure period when the drug is discontinued. I see this information in the table, but I think a few sentences are needed in the text to draw the reader’s attention to this detail. Also, it is not clear in the methods |
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| | section that this type of data was collected during the procedure in addition to the 24 hour period after the procedure.<br>- Revised regimen phase, 2nd sentence: need to define APROP in text when first used<br><br>Discussion:<br>- Statement of principal findings, sentence 1: be consistent, % in results section is 4.5%, but you have 4.6% here in discussion.<br>- Statement of principal findings, sentence 2: be consistent with percentages reported. Here you have 25% and 7%, but in results you have 23.1% and 7.1%<br>- Strengths and weaknesses in relation to other studies, last paragraph, first sentence: add space between dose and units (i.e., change to “0.5 mg/kg to 4 mg/kg”)<br>- Limitations of study, first sentence: please revise this sentence, it does not make sense as currently written<br>- Adverse events of fentanyl and ketamine paragraph: this paragraph seems really out of place and really should be incorporated earlier in the text of the discussion.<br>- Adverse events paragraph, first sentence: Recommend to include a citation for this sentence to support this statement<br>- Adverse events, 2nd paragraph, sentence 3: is the rise in intraocular pressure with ketamine a concern in patients with ROP procedures?<br>Conclusion:<br>- First sentence: uncapitalize fentanyl and ketamine<br>Tables and Figures:<br>Table 1:<br>- For Stage of ROP in the ketamine column, those numbers add up to 47 instead of 46<br>Table 4:<br>- You have a PIPP-R <12 and crying time 5-14.9% as the alternate definition for adequate analgesia, however, wouldn’t it be better to define as “PIPP-R <12 AND crying time <14.9%” so that those with crying time <5% would also be included? |

## VERSION 2 – AUTHOR RESPONSE

- **Reviewer 1 Comments**

| Sl No | Suggested correction | Correction done | Page, line & Section number |
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| | The authors have satisfactorily addressed the queries raised. | We thank the review for the kind words and comments. | |

- **Reviewer 2 Comments**

| Sl No | Suggested correction | Correction done | Page, line & Section number |
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| | Overall, the manuscript is much improved with the revisions made to the manuscript. | We thank the review for the kind words and comments. | |
| | Abstract:<br><br>- Interventions: consider adding the dose that was administered for both the initial and the revised dosing | We have updated the intervention section with necessary modifications. | Page 2,<br>Line 14-20<br>Abstract section |
| | Introduction:<br><br>● - Paragraph 1, 2nd sentence: suggest to include a reference citation to support this statement. | Reference citation added to support the statement. | Page 5, Line 6,<br>Introduction section |

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| | | | Page 5, Line 21-24, Introduction section |
| | • - Paragraph 2, last sentence: how was adequate analgesia defined in this study that you are referring to? Suggest to include the definition in parenthesis at the end of the sentence. | Above study measured proportion of procedure time infant spent crying as primary outcome and PIPP-R scores as secondary outcome. We did a post-hoc analysis of the above study data with adequate analgesia defined as PIPP-R less than seven **and** proportion of the procedure time the infant spent crying less than 5%. We have updated the same in the paragraph. | |
| | Methods:<br><br>*Setting:*<br><br>- Last sentence: suggest to change to "If an infant developed any complications or required prolonged observation, they were transferred to the NICU for further management." | We have changed the last sentence to "If an infant developed any complications or required prolonged observation, they were transferred to the NICU for further management." | Page 6, Line 18-19, Methodology section. |

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| | *Intervention:*<br><br>- Sentence 2: based on the sentence structure it appears that 0.5% paracaine drops are being considered a nonpharmacological measure. Consider changing sentence to "...groups received 0.5% ophthalmic paracaine drops for topical anaesthesia every 20 minutes during the procedure and nonpharmacological measures, namely swaddling and containment."<br><br>- If they change suggested above is not made, at a minimum need to change "min" to "minutes" in the sentence.<br><br>- For increased crying, how is this defined? Increased from what? From baseline? Or, is increased crying based on percentage of procedure time that patient what crying (e.g., >40%, >25%, etc.)<br><br>- Fentanyl group, last sentence: suggest to change to "If the response was inadequate, the infusion rate was titrated..." | Sentence 2 now reads "In addition, infants in both the groups received 0.5% ophthalmic paracaine drops for topical anaesthesia every 20 minutes during the procedure and nonpharmacological measures, namely swaddling and containment."<br><br>Increased crying is defined as "increased crying from baseline". The same has been updated in the manuscript.<br><br>Last sentence now reads "If the response was inadequate, the infusion rate was titrated.." | Page 7,<br>Line 20-22,<br>Methodology section.<br><br>Page 7,<br>Line 23,<br>Methodology section.<br><br>Page 8,<br>Line 4,5,<br>Methodology section. |

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| | Results:<br><br>3rd paragraph, 2nd sentence: a statement that no difference in side effects post-procedure between groups, but were side effects monitored during the procedure as well? This would seem to be more important than adverse effects in the post-procedure period when the drug is discontinued. I see this information in the table, but I think a few sentences are needed in the text to draw the reader's attention to this detail. Also, it is not clear in the methods section that this type of data was collected during the procedure in addition to the 24 hour period after the procedure. | We thank the reviewer for the pertinent comment.<br><br>Yes, the side effects were monitored during the procedure as well. We have modified both the methodology and results section with necessary changes. | Page 9,<br>Line 4-7<br>Methodology section<br><br>Page 14,<br>Line 3-7<br>Results Section<br><br>Table II<br>Page 14 |
| | - Revised regimen phase, 2nd sentence: need to define APROP in text when first used<br><br>. | Definition of APROP update in the manuscript | Page 15,<br>Line 7<br>Results section |

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| | Discussion:<br><br>- Statement of principal findings, sentence 1: be consistent, % in results section is 4.5%, but you have 4.6% here in discussion. | We have corrected sentence 1. | Page 18, Line 19<br>Discussion section |
| | - Statement of principal findings, sentence 2: be consistent with percentages reported. Here you have 25% and 7%, but in results you have 23.1% and 7.1% | We have corrected sentence 2. | Page 18, Line 22<br>Discussion section |
| | - Strengths and weaknesses in relation to other studies, last paragraph, first sentence: add space between dose and units (i.e., change to “0.5 mg/kg to 4 mg/kg”) | Space added between dose and units | Page 20, Line 20<br>Discussion section |
| | - Limitations of study, first sentence: please revise this sentence, it does not make sense as currently written | We have revised the first sentence in the limitations of the study | Page 21, Line 2-4<br>Discussion section |

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| | - Adverse events of fentanyl and ketamine paragraph: this paragraph seems really out of place and really should be incorporated earlier in the text of the discussion. | Have updated the manuscript with necessary changes | Page 18,<br>Line 5-14<br>Discussion section |
| | - Adverse events paragraph, first sentence: Recommend to include a citation for this sentence to support this statement | Citation added to support the statement | Page 18, Line 7<br>Discussion section |
| | - Adverse events, 2nd paragraph, sentence 3: is the rise in intraocular pressure with ketamine a concern in patients with ROP procedures? | We thank the reviewer for the pertinent comment. Though theoretically a concern, we may need further studies in this regard for a definite answer as the studies on ketamine during laser photocoagulation is relatively sparse. | |
| | 8. Conclusion:<br><br>- First sentence: uncapitalize fentanyl and ketamine | We have modified the manuscript with the necessary changes. | Page 22,<br>Line 1<br>Conclusion section |

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| 8 | Tables and Figures:<br><br>*Table 1:*<br><br>● - For Stage of ROP in the ketamine column, those numbers add up to 47 instead of 46 | Table 1 has been modified accordingly | Page 13, Results section |
| | *Table 4*:<br><br>● - You have a PIPP-R <12 and crying time 5-14.9% as the alternate definition for adequate analgesia, however, wouldn't it be better to define as "PIPP-R <12 AND crying time <14.9%" so that those with crying time <5% would also be included? | Table 4 has been modified accordingly | Page 16, Results section |