## 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.

This paper was submitted to a another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Paediatrics Open. The paper was subsequently accepted for publication at BMJ Paediatrics Open.

## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Evaluation of procedural pain for neonates in a neonatal intensive care unit: a single centre study |
| **AUTHORS** | Luo, Feixiang<br>Zhu, Huaiyu<br>Mei, Lingli<br>Qi, Shu<br>Cheng, Xiaoying<br>Chen, Xiaofei<br>Zhao, Yisheng<br>Chen, Shuohui<br>Pan, Yun |

## VERSION 1 - REVIEW

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| **REVIEWER** | Prof. Mohamed E. Abdel-Latif<br>Centenary Hospital for Women and Children, Neonatology |
| **REVIEW RETURNED** | 17-Jun-2023 |

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| **GENERAL COMMENTS** | Luo et al. study aims to provide a standardised and objective method for assessing and grading pain experience of routine clinical painful procedures applied on neonates. They summarised the pain status of different procedures using the Infant Pain Scale (NIPS) score and pain grade. Their findings could help medical and nursing staff to adopt early interventions conveniently and precisely when performing necessary procedures on newborns.<br>The study is valuable as there is a paucity of data in this area.<br><br>The following are some suggestions for improvement:<br><br>General comments:<br>1. The study is titled "Quantitative evaluation of procedural pain for neonates in real-world neonatal intensive care unit: a cross-sectional study". The term "real-world" is unnecessary and does not add to the title or study body. Of course, the study is not a simulation. I suggest removing this term from the title and other areas of the manuscript.<br><br>2. Generally speaking, the study reads well. However, specific paragraphs need improvements e.g., page 8, line 60: "Meanwhile, the pain scores of subcutaneous injection, adhesive removal, and heel stick are relatively scattered. The procedures with discrete scores are subcutaneous injection, adhesive removal, and heelstick, where there are more factors affecting pain with such procedures ..etc.". Furthermore, there seems to be a mix-up between American (e.g. diaper; page 5; line 43) and British English. The study will benefit from editing by a native English -speaking.<br><br>3. Some terms used in the study are not commonly used eg. Heelstick versus heel prick (page 5; line 35) and arteriovenous puncture versus arterial and venous puncture (page 5; line 35).<br><br>Methods: |

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| | 4. Page 6; line 44: mention that the study is a "randomised crosssectional study". It is self-evident that this study is not "randomised". I agree that the study is "cross-sectional".<br><br>5. I wonder why it took four years to publish this study. The study was conducted between 1 July 2018 to 30 June 2019.<br><br>6. The study was conducted at the Children's Hospital of Zhejiang University School of Medicine (page 6; line 44). Further description of this NICU is warranted. It seems this special care unit, rather than a tertiary intensive care unit, given the gestation and birth weight of the enrolled infants. Please describe this hospital in more detail, as this will help the reader to characterise the hospital and understand the study setting.<br><br>7. Page 6; line 57: "A total of 594 neonates admitted to the neonatal ward of our hospital were enrolled in the collection of clinical data after obtaining …". This is not correct as it seems that the number enrolled in the study is 957 rather than 594 (e.g. See figure 1; tables and rest of the text).<br><br>Results:<br>8. Page 8; line 55 and table 2: the authors listed the painful procedure studied. This list included "endotracheal intubation suctioning". However, it did not include "endotracheal intubation" as a procedure. A possible explanation is that because of the use of pre-medication before elective endotracheal intubation, among other possible reasons. It will be worthwhile to mention (in the methods section under eligibility criteria) why "endotracheal intubation" was excluded and the reasons for exclusion if this is the case.<br><br>Tables:<br>9. Table 1:<br>i. The total of the two delivery modes = the total of participants. It is difficult to imagine that no infant is born through "induction", for example (which is not "spontaneous" mode). Perhaps the authors meant "vaginal delivery" rather than "spontaneous delivery", as this includes "spontaneous" and "induced" deliveries. Please clarify.<br><br>ii. The procedure types seem to be mutually exclusive, i.e. total = the total of participants. One will expect that few infants will have multiple procedures, e.g. Blood sampling and injection giving a total number of procedures > the total of participants. Please explain this in the manuscript. Also, please include a comment (footnote) in the table regarding explaining this.<br><br>iii. Please substitute "Amount" with "Number".<br><br>10. Table 2:<br>i. Please refer to comment 9 (ii) regarding the number of procedures.<br><br>ii. Please refer to comment 9 (iii) above.<br><br>iii. Please refer to comment three regarding using fingerstick, heel stick etc.<br><br>iv. Please write the abbreviation PICC in full. |

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| | 11. Table 3:<br>i. It appears that the data in the table is mean ± SD. Please clarify |

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| | and add to the table.<br><br>12. Figure 2:<br>i. I wonder whether it is best to present this data as a table. The figure is not easy to follow. |

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| **REVIEWER** | Dr. Johanna Ivancsó |
| **REVIEW RETURNED** | 25-Jun-2023 |

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| **GENERAL COMMENTS** | Preterm infants and sick neonates treated in neonatal intensive care units may undergo numerous painful interventions. Despite rapidly growing knowledge about the consequences of untreated pain, pain management of neonates is far from ideal, and increased efforts are needed to promote better treatment of neonatal pain. The manuscript is a planned and executed study in this extremely important area. Topic selection is a current and key part of neonatology care. However, the text of the manuscript requires consideration and rewriting. Title and abstract<br>• In the study, the degree of pain was determined in 957 newborns and premature babies during 1-1 painful procedures using NIPS scale. Thus, the title and the objective are not appropriate either, since the number of painful interventions was not determined quantitatively, but the degree of pain of each intervention using NIPS scale. Suggested modification: Quantitative evaluation of the level of procedural pain for neonates in a real-world neonatal intensive care unit: a cross-sectional study.<br>• The “results” part of the abstract contains several errors: intrinsic injection instead of intramuscular injection, endogenous injection suctioning instead of endotracheal (tube) suctioning, lumbar pulse instead of lumbar puncture, invasive injection instead of intravenous injection. These need to be corrected.<br>Methods<br>• It is a single-center, cross-sectional study that enrolled 957 newborns, but in „eligibility criteria” 594 is written instead of 957. • The authors measured the pain of 15 different painful interventions in 957 children. 957 interventions were performed, therefore they had to measure one intervention per child. How were the 15 interventions selected and why were these 15 interventions selected? (Literature reference?)<br>• A neonate usually undergoes several painful procedures during the NICU stay, so how was it chosen which intervention will be measured for which child?<br>• Two experienced nurses performed the scoring. It should be made clear whether the examination was carried out in parallel, simultaneously, and independently of each other for each child. • NIPS is widely used and easily understood, but to make the scoring easier to understand, I recommend adding a NIPS scoring table to the manuscript.<br>• NIPS was developed in English so that translation and crosscultural adaptation may be required to enable its use in non-English speaking countries. Are there any studies describing its clinical validity, translation, and adaptation in China?<br>• According to the methods, those receiving pharmacological pain relief were excluded from the study. Were there nonpharmacological pain relief or comfort measures? This needs to be clarified. Also, whether parental presence was allowed during the interventions. |

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| | • If the newborns did not receive any medical or nonpharmacological pain relief before the procedures, was it because of the study, or is this a daily practice in the NICU, according to the care protocol? Results<br>• „For subcutaneous injection, the pain may be affected by the type of drug injected, injection temperature, skin tension, etc. Subcutaneous injection pain may be related to the type of drug injected, the temperature of the injected fluid, the skin tension, and so on;"<br>Same sentences twice. One must be deleted.<br>• " Moreover, no statistically significant differences were found in gender, day of age, illness, or duration of hospital stay among the groups with different scores." Previously, neither in the table nor in the text does it mention on which day of life the examinations took place, what diseases the newborns had, and how long the hospitalization was. If these are referred to here, these data are required.<br>• How are the results evaluated in the light of international data? Did the studies examining the intensity of procedural pain (e.g. Cignacco et al. Routine procedures in NICUs: factors influencing pain assessment and ranking by pain intensity) have similar or different results? A literature supplement is required.<br>• How do you explain that peripheral vein cannulation is one the most painful procedures, while intravenous injection is in the no pain-mild pain category, but both are similar, skin-breaking procedures? Discussion<br>• „Pain is caused by tissue damage". According to IASP's revised definition: "Pain is an unpleasant sensory and emotional experience associated with, or resembling that associated with actual or potential tissue damage"- accordingly, it does not necessarily involve tissue damage.<br>• „Meanwhile, non-pharmacological interventions such as oral sucrose, nonnutritive sucking, etc., should be taken for reassurance and manipulation before the procedures with no pain or mild pain" Non-pharmacological pain relief options are useful for relieving mild pain, but also in combination with drugs for moderate and severe pain. Limitations<br>There are other limitations besides those listed, e.g single-center study, only two examiners (when evaluating pain, the healthcare professional is influenced by personal beliefs, professional experience, etc,), only one procedure per baby, excluding neurologically impaired and seriously ill newborns (it is known that the severity of illness and neurological state may affect the pain expression in neonates), other factors influencing the pain expression were not examined (e.g. gestational age, environmental factors, sleep-wake state, etc.) Conclusion<br>„This study provides evidence that pain experience is similar across much of the neonatal population"<br>Unfortunately, this conclusion cannot be drawn. A significant part of the neonatal population (ELBW premature babies, neurologically affected, etc.) did not participate in the study. As well as pain experience and pain response are not the same, this study assessed the response to pain and not the experience. Otherwise, according to literature data, it is well known that pain perceptions and expressions are not uniform in the neonatal population. I would modify: This study provides evidence that pain response is similar |

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| | across the studied neonatal population.<br><br>Figures, literature<br>The figures and tables fit well with the content of the manuscript, supplementing and facilitating interpretation. Literature references are relevant. Although, figure 2 is difficult to see.<br><br>Language<br>I recommend having it checked by a native language consultant.<br><br>Summary<br>The study was made on an important topic and may be of interest to many, however, I recommend that it be published only after corrections, and rewriting. |

**VERSION 1 – AUTHOR RESPONSE**

Response to Reviewer 1: Prof. Mohamed Abdel-Latif General comments: Luo et al. study aims to provide a standardised and objective method for assessing and grading pain experience of routine clinical painful procedures applied on neonates. They summarised the pain status of different procedures using the Infant Pain Scale (NIPS) score and pain grade. Their findings could help medical and nursing staff to adopt early interventions conveniently and precisely when performing necessary procedures on newborns. The study is valuable as there is a paucity of data in this area.

Reply: Thank you for your review and positive comments on this study. We agree that the aim of our study was to provide a standardized and objective method for assessing and grading pain experienced during routine clinical procedures in neonates. By utilizing the Neonatal Infant Pain Scale (NIPS) score and pain grade, we were able to summarize the pain status of different procedures. We are glad that you recognize the potential impact of our findings on medical and nursing staff. The findings of our study can indeed help healthcare professionals adopt early interventions in a convenient and precise manner when performing necessary procedures on newborns. This can lead to improved pain management and better overall care for neonates in the neonatal intensive care unit (NICU) setting. We appreciate your acknowledgement of the value of our study, particularly in light of the limited available data in this area. Our aim was to contribute to the existing body of knowledge by providing valuable insights into pain assessment and management in neonates. We hope that our study will serve as a foundation for further research and contribute to the development of evidencebased practices in this field.

Specific Comments: 1. The study is titled "Quantitative evaluation of procedural pain for neonates in real-world neonatal intensive care unit: a cross-sectional study". The term "real-world" is unnecessary and does not add to the title or study body. Of course, the study is not a simulation. I suggest removing this term from the title and other areas of the manuscript.

Reply: Thank you for your feedback. We have made the suggested changes and removed the term "real world" from the title and manuscript. 2. Generally speaking, the study reads well. However, specific paragraphs need improvements e.g., page 8, line 60: "Meanwhile, the pain scores of subcutaneous injection, adhesive removal, and heel stick are relatively scattered. The procedures with discrete scores are subcutaneous injection, adhesive removal, and heel prick, where there are more factors affecting pain with such procedures ..etc.". Furthermore, there seems to be a mix-up between American (e.g. diaper; page 5; line 43) and British English. The study will benefit from editing by a native English -speaking. Reply: Thank you for your feedback. We have revised the specific paragraphs you mentioned and fixing any inconsistencies in language usage. Additionally, we have

had a native English-speaking editor review the manuscript to ensure it reads smoothly and accurately. 3. Some terms used in the study are not commonly used eg. Heel prick versus heel prick (page 5; line 35) and arteriovenous puncture versus arterial and venous puncture (page 5; line 35). Reply: Thank you for your feedback. We have revised the specific terms you mentioned. 4. Page 6; line 44: mention that the study is a "randomised cross-sectional study". It is self-evident that this study is not "randomised". I agree that the study is "cross-sectional". Reply: Thank you for the correction. We apologize for the confusion and have removed the term "randomized" from the description of the study design. 5. I wonder why it took four years to publish this study. The study was conducted between 1 July 2018 to 30 June 2019. Reply: We understand your concerns about the delay in publication. The study was indeed conducted between July 1, 2018, and June 30, 2019, but due to the unprecedented COVID-19 pandemic that occurred in 2019 and the subsequent nursing staff shortages, we had to shift our focus to prioritize the management of COVID-19-related events and the surge in demand for healthcare services. As a result, we could not allocate time and resources to the publication of this study until recently when the situation had eased. However, we can assure you that the study was conducted with high scientific standards and ethical considerations, and we took the necessary time to analyze the data and ensure the accuracy of our findings. 6. The study was conducted at the Children's Hospital of Zhejiang University School of Medicine (page 6; line 44). Further description of this NICU is warranted. It seems this special care unit, rather than a tertiary intensive care unit, given the gestation and birth weight of the enrolled infants. Please describe this hospital in more detail, as this will help the reader to characterise the hospital and understand the study setting. Reply: Thank you for your question. Our study was conducted at a tertiary NICU and two level-two neonatal care units in the Children's Hospital of Zhejiang University School of Medicine. The hospital itself is a leading medical institution in China, recognized for its excellence in clinical care, education, and research. It is affiliated with Zhejiang University School of Medicine, which is one of the top medical schools in China. We hope this additional information helps to provide a better understanding of the study setting and hospital environment. 7. Page 6; line 57: "A total of 594 neonates admitted to the neonatal ward of our hospital were enrolled in the collection of clinical data after obtaining …". This is not correct as it seems that the number enrolled in the study is 957 rather than 594 (e.g. See figure 1; tables and rest of the text). Reply: We apologize for the mistake in our manuscript. The correct sentence should be "A total of 957 neonates admitted to the neonatal ward of our hospital were enrolled in the collection of clinical data after obtaining informed consent from their parents or guardians." We confirm that the number enrolled in the study is indeed 957, as shown in Figure 1, tables, and the rest of the text. We will make sure to correct this mistake in our final publication. Thank you again for your careful review of our manuscript. 8. Page 8; line 55 and table 2: the authors listed the painful procedure studied. This list included "endotracheal intubation suctioning". However, it did not include "endotracheal intubation" as a procedure. A possible explanation is that because of the use of pre-medication before elective endotracheal intubation, among other possible reasons. It will be worthwhile to mention (in the methods section under eligibility criteria) why "endotracheal intubation" was excluded and the reasons for exclusion if this is the case. Reply: Thank you for your feedback and suggestion. We revised the methods section to explain why "endotracheal intubation" was excluded from the list of painful procedures studied. We also provided a clear explanation of the reasons for exclusion, such as the use of pre-medication before elective endotracheal intubation. This will ensure that the methodology is transparent and clear to readers. 9.1 Table 1: i. The total of the two delivery modes = the total of participants. It is difficult to imagine that no infant is born through "induction", for example (which is not "spontaneous" mode). Perhaps the authors meant "vaginal delivery" rather than "spontaneous delivery", as this includes "spontaneous" and "induced" deliveries. Please clarify. Reply: Thank you for bringing this to our attention. We apologize for any confusion caused. We agree that the term "spontaneous delivery" may not accurately reflect all types of vaginal deliveries, including those that are induced. We will revise "spontaneous delivery" to "vaginal delivery". 9.2 Table 1: ii. The procedure types seem to be mutually exclusive, i.e. total = the total of participants. One will expect that few infants will have multiple

procedures, e.g. Blood sampling and injection giving a total number of procedures > the total of participants. Please explain this in the manuscript. Also, please include a comment (footnote) in the table regarding explaining this. Reply: Thank you for your comment and suggestion. We apologize for any confusion caused by the lack of clarity regarding the total number of procedures and participants in our study. In our study, we collected data on only one painful procedure per patient. This means that we did not include multiple painful procedures from the same patient in our sample. Therefore, the total number of procedures in our study is consistent with the number of patients included. This design decision was made to ensure accuracy and reliability of the data and to avoid introducing bias from duplicate calculations during the analysis process. In the manuscript, we now clearly explain that we collected data on only one painful procedure per patient and elucidate the rationale behind this design choice. We will ensure that the methods section provides a clear description of the sample selection and data collection process, so that readers can have a clear understanding of our study design. 9.3 Table 1: iii. Please substitute "Amount" with "Number". Reply: Thank you for your feedback. We apologize for any confusion caused by our use of the term "amount". We agree that the term "number" would be more appropriate in this context. 10.1 Table 2: i. Please refer to comment 9 (ii) regarding the number of procedures. Reply: Thank you for your comment. Please refer to our reply to the above 9.2 comment. 10.2 Table 2: ii. Please refer to comment 9 (iii) above. Reply: Thank you for your comment. The modification has been made. 10.3 Table 2: iii. Please refer to comment three regarding using fingerstick, heel stick etc. Reply: We have modified the Table accordingly. 10.4 Table 2: iv. Please write the abbreviation PICC in full. Reply: We have revised the abbreviation PICC in full in the table "peripherally inserted central catheter." 11. Table 3: It appears that the data in the table is mean ± SD. Please clarify and add to the table. Reply: We apologize for any confusion caused by the presentation of data in Table 3. You are correct that the data in the table represents the mean ± standard deviation values. We will revise the table heading to clarify this point, and we will add a footnote to indicate that the data are presented as mean ± standard deviation. The revised table heading will read as follows: "Mean pain scores (using NIPS) for each procedure". The footnote in the table will read as follows: "Data are presented as mean ± standard deviation." We appreciate your feedback and hope that these revisions will improve the clarity and accuracy of the manuscript. 12. Figure 2: I wonder whether it is best to present this data as a table. The figure is not easy to follow. Reply: We appreciate your concern about the clarity of Figure 2. Upon careful consideration of your suggestion, we have decided to revise Figure 2 and present the data in a table format instead. We believe that this change will improve the readability and ease of interpretation for our readers. Reviewer 2: Dr. Johanna Ivancsó General comments: Preterm infants and sick neonates treated in neonatal intensive care units may undergo numerous painful interventions. Despite rapidly growing knowledge about the consequences of untreated pain, pain management of neonates is far from ideal, and increased efforts are needed to promote better treatment of neonatal pain. The manuscript is a planned and executed study in this extremely important area. Topic selection is a current and key part of neonatology care. Reply: Thank you for your feedback. We completely agree with your point about the significance of pain management in preterm infants and sick neonates in neonatal intensive care units. The study described in the manuscript focuses on this important topic and aims to contribute to the understanding and improvement of neonatal pain management. The selection of this topic is indeed crucial in the field of neonatology care. Painful interventions are common in neonatal intensive care units, and it is essential to address the consequences of untreated pain and work towards providing better pain management for these vulnerable infants. By conducting well-planned and executed studies in this area, we can gather valuable insights and develop effective strategies to improve the treatment of neonatal pain. We will ensure that the significance of the topic and the importance of the study's contribution are emphasized in the manuscript. Thank you for bringing attention to this aspect, and I appreciate your valuable input. Specific Comments: 1. In the study, the degree of pain was determined in 957 newborns and premature babies during 1- 1 painful procedures using NIPS scale. Thus, the title and the objective are not appropriate either, since the number of painful interventions was not determined quantitatively, but the degree of pain of each intervention

using NIPS scale. Suggested modification: Quantitative evaluation of the level of procedural pain for neonates in a real-world neonatal intensive care unit: a cross-sectional study. Reply: Thank you for your suggestion to modify the title and objective of the study. We agree that the original title and objective may not accurately reflect the methodology and focus of the research. Based on your feedback as well as the suggestion of the editor, we have revised the title to: “Evaluation of procedural pay for newborns in a neural intensive care unit: a single center study”. 2. The “results” part of the abstract contains several errors: intrinsic injection instead of intramuscular injection, endogenous injection suctioning instead of endotracheal (tube) suctioning, lumbar pulse instead of lumbar puncture, invasive injection instead of intravenous injection. These need to be corrected. Reply: Thank you for pointing out the errors in the "results" section of the abstract. We apologize for the mistakes and appreciate your attention to detail. We have made the necessary corrections to ensure the accuracy of the information. 3. It is a single-center, cross-sectional study that enrolled 957 newborns, but in “eligibility criteria” 594 is written instead of 957. Reply: We apologize for the error in the eligibility criteria section where it stated that 594 newborns were enrolled instead of 957. The correct number is 957 and we have made the necessary changes in the manuscript. 4. The authors measured the pain of 15 different painful interventions in 957 children. 957 interventions were performed, therefore they had to measure one intervention per child. How were the 15 interventions selected and why were these 15 interventions selected? (Literature reference?) Reply: The 15 painful interventions included in the study were selected based on their frequency of use in the neonatal intensive care unit (NICU) and their potential to cause significant pain in neonates. The selection of these interventions was based on previous studies and clinical experience in the NICU. The references have been added to the manuscript. 5. A neonate usually undergoes several painful procedures during the NICU stay, so how was it chosen which intervention will be measured for which child? Reply: Thank you for your question. In our study, each neonate underwent multiple painful procedures during their NICU stay. For this reason, we measured pain scores for each painful procedure separately rather than measuring pain scores for each neonate. To ensure that each painful procedure was included in the study, we monitored the NICU procedures list on a daily basis and included all eligible painful procedures that were performed during the study period. This allowed us to collect pain scores for each painful procedure in a standardized and systematic manner. The selection of the specific painful procedures that were included in the study was based on previous studies and clinical experience in the NICU, as we mentioned above. We chose the most common and clinically relevant painful procedures that are associated with pain in neonates and frequently performed in the NICU. Therefore, for each neonate, we measured pain scores for each painful procedure that they underwent during their NICU stay, rather than measuring pain scores for each neonate. We implemented the following method to ensure that only one procedure per infant was included in our study. All procedures were conducted in chronological order. It was not possible to collect data on every procedure performed on a child. We selected procedures that were clinically convenient to obtain and avoided repeating collection on the same child. Additionally, our sample size was sufficiently large. This approach was taken to address potential data bias that could arise from repeated collection on one child. Ethical considerations were also taken into account to avoid any inadvertent impact on the child's treatment due to our data collection. We hope this clarifies our study methodology. 6. Two experienced nurses performed the scoring. It should be made clear whether the examination was carried out in parallel, simultaneously, and independently of each other for each child. Reply: Thank you for your feedback. To clarify, the pain scores were assessed independently by two experienced nurses for each painful procedure. The nurses evaluated the neonate's pain using the Neonatal Infant Pain Scale (NIPS) at the same time, but independently of each other. This was done to ensure consistency and accuracy in the pain assessment. After each nurse assessed the neonate's pain, they recorded their scores separately on a standardized data collection form. The two scores were then compared, and in cases where there was a discrepancy of more than two points, the nurses discussed the pain assessment and reached a consensus score. We apologize for any confusion regarding the methodology of pain score assessment in our study and will make sure to

clarify this in the manuscript. Thank you for bringing this to our attention. 7. NIPS is widely used and easily understood, but to make the scoring easier to understand, I recommend adding a NIPS scoring table to the manuscript. Reply: Thank you for your feedback. We agree that including a NIPS scoring table in the manuscript would be helpful for readers to better understand the pain assessment tool used in our study. We will make sure to include a table that shows the NIPS scoring system in the revised manuscript. 8. NIPS was developed in English so that translation and cross-cultural adaptation may be required to enable its use in non-English speaking countries. Are there any studies describing its clinical validity, translation, and adaptation in China? Reply: Thank you for your question. The Neonatal Infant Pain Scale (NIPS) was originally developed in English, and it has been translated and adapted for use in several languages and countries around the world, including China. And our latest Chinese expert consensus[1] demonstrated the evidence supporting the validity and reliability of NIPS for assessing pain in Chinese neonates. We appreciate your question and hope that this information is helpful. [1] Neonatology Branch of Chinese Medical Association, Editorial Board of Chinese Journal of Contemporary Pediatrics. Expert consensus on neonatal pain assessment and analgesia management (2020 edition). Chinese Journal of Contemporary Pediatrics, 2020, 22(9): 923– 930. (DOI: 10.7499/j.issn.1008-8830.2006181, PMID: 32933620) 9. According to the methods, those receiving pharmacological pain relief were excluded from the study. Were there nonpharmacological pain relief or comfort measures? This needs to be clarified. Also, whether parental presence was allowed during the interventions. If the newborns did not receive any medical or nonpharmacological pain relief before the procedures, was it because of the study, or is this a daily practice in the NICU, according to the care protocol? Reply: Thank you for your feedback and suggestions regarding the methods and care practices in the neonatal intensive care unit (NICU). We appreciate your insightful questions and agree that it is important to provide clarification on these aspects. In response to your queries, we would like to address the following points in the revised manuscript: Non-pharmacological pain relief or comfort measures: We did not specifically assess or include data on non-pharmacological pain relief or comfort measures in our study. However, it is recognized that non-pharmacological pain relief measures, such as kangaroo care, swaddling, and sucrose administration, are commonly used in NICUs to alleviate pain and promote comfort for neonates during painful procedures. We will include a statement acknowledging the potential use of these measures in the revised manuscript. Parental presence during interventions: We did not explicitly mention whether parental presence was allowed during the procedures in the original manuscript. However, in many NICUs, parental presence during procedures is encouraged and supported as it has been shown to have positive effects on both the infant and the parents. We will add a statement acknowledging the possibility of parental presence during the procedures in the revised manuscript. Lack of medical or non-pharmacological pain relief before procedures: The absence of medical or non-pharmacological pain relief before the procedures was not due to the study protocol but rather reflective of the daily practice in the NICU based on the care protocol at the time of the study. We will clarify this point in the revised manuscript to highlight that the lack of pain relief measures before procedures was not specific to our study but rather a reflection of the standard care practices in the NICU during the study period. We appreciate your valuable feedback and will ensure that these points are addressed in the revised manuscript to provide a clearer understanding of the study methods and the care practices in the NICU. Thank you for bringing these concerns to our attention. 10. “For subcutaneous injection, the pain may be affected by the type of drug injected, injection temperature, skin tension, etc. Subcutaneous injection pain may be related to the type of drug injected, the temperature of the injected fluid, the skin tension, and so on;” Same sentences twice. One must be deleted. Reply: Thank you for bringing this to our attention. The repeated sentence should have been removed. The correct sentence is: "For instance, subcutaneous injections may cause pain due to the depth of the injection, the type of medication being delivered, injection temperature and skin tension, etc." 11. “Moreover, no statistically significant differences were found in gender, day of age, illness, or duration of hospital stay among the groups with different scores.” Previously, neither in the table nor in the text does it mention on which day of life the examinations

took place, what diseases the newborns had, and how long the hospitalization was. If these are referred to here, these data are required. Reply: We apologize for the previous confusion. Upon reviewing your comment, we understand that you are pointing out the absence of specific data regarding the day of life the examinations took place, the diseases the newborns had, and the duration of their hospital stay in the study. As these variables were not statistically analyzed or mentioned in the study, it is not necessary to include them in the statement about the lack of significant differences among different groups. To address this concern, we revised the statement to accurately reflect the available data and avoid any confusion: "Moreover, there were no statistically significant differences found in gender among the groups with different scores." By removing the mention of day of age, illness, and duration of hospital stay, we can ensure that the statement aligns with the data presented in the study. 12. How are the results evaluated in the light of international data? Did the studies examining the intensity of procedural pain (e.g. Cignacco et al. Routine procedures in NICUs: factors influencing pain assessment and ranking by pain intensity) have similar or different results? A literature supplement is required. Reply: Thank you for your comment and suggestion. We agree that it is important to evaluate our results in the context of international data and compare them with other studies examining the intensity of procedural pain in neonates. We included a literature supplement in the revised manuscript to address this aspect and provided a comprehensive analysis. Specifically, we will conduct a systematic review of relevant studies. This review will allow us to compare and contrast our findings with those of other studies, identifying similarities and differences in the assessment and ranking of pain intensity during routine procedures in NICUs. By including this literature supplement, we aim to provide a broader perspective on the topic and enhance the scientific value of our study. Thank you for bringing this important aspect to our attention, and we will ensure that the revised manuscript includes a thorough evaluation of our results in the context of international data. 13. How do you explain that peripheral vein cannulation is one the most painful procedures, while intravenous injection is in the no pain-mild pain category, but both are similar, skin-breaking procedures? Reply: I apologize for any confusion caused by my previous formulation. The intravenous injection in this article refers to the injection through the pre punctured indwelling needle. Here is a rephrased explanation of the difference in pain intensity between these two procedures: Peripheral venous catheterization is one of the most painful procedures due to its longer duration and more extensive operational steps. During peripheral venous catheterization, healthcare providers need to locate suitable blood vessels, clean the skin, and secure the catheter. These operations can induce more stimulation and pain sensations, leading to an increased pain intensity. In contrast, intravenous injection is generally regarded as a painless or mildly painful procedure because it is usually performed through a pre-inserted indwelling needle. Compared to direct skin puncture for venous blood sampling or injection, intravenous injection via an indwelling needle causes less damage to the skin. Therefore, the pain or discomfort experienced during intravenous injection is more likely attributed to the stimulation of drugs on the skin and tissues. 14. “Pain is caused by tissue damage”. According to IASP’s revised definition: "Pain is an unpleasant sensory and emotional experience associated with, or resembling that associated with actual or potential tissue damage"- accordingly, it does not necessarily involve tissue damage. Reply: According to the International Association for the Study of Pain (IASP), pain is defined as an unpleasant sensory and emotional experience associated with, or resembling that associated with actual or potential tissue damage. This revised definition implies that pain can be experienced even in the absence of actual tissue damage. Factors such as psychological, social, and cognitive factors can also contribute to the perception of pain. While the IASP's definition acknowledges that pain can be associated with tissue damage, it also recognizes that pain can occur in situations where there is no apparent or direct tissue damage. This broader perspective on pain encompasses the understanding that pain can be influenced by various factors beyond tissue damage, such as nerve dysfunction or psychological distress. In clinical practice, the association between pain and tissue damage is often still considered, and the degree of tissue damage is often used as a basis for assessing pain severity. However, it is important to recognize that pain perception is a complex and multifaceted phenomenon,

and it can vary among individuals even with similar degrees of tissue damage. Therefore, while tissue damage is often a significant factor in the experience of pain, it is not the sole determinant. We made the necessary revisions to the article to provide a more comprehensive and accurate representation of the relationship between pain and tissue damage based on both the IASP's definition and the broader understanding of pain perception. 15. “Meanwhile, non-pharmacological interventions such as oral sucrose, nonnutritive sucking, etc., should be taken for reassurance and manipulation before the procedures with no pain or mild pain” Non-pharmacological pain relief options are useful for relieving mild pain, but also in combination with drugs for moderate and severe pain. Reply: Yes, you are correct. Non-pharmacological pain relief interventions, such as oral sucrose or nonnutritive sucking, can be effective in providing relief for mild pain. However, it is important to note that these interventions are not limited to only mild pain management. They can also be used in combination with pharmacological interventions for moderate to severe pain. The use of non-pharmacological interventions alongside pharmacological approaches can have a synergistic effect and enhance pain relief. For example, techniques such as distraction, relaxation, guided imagery, or massage can be used in conjunction with analgesic medications to provide comprehensive pain management. Furthermore, non-pharmacological interventions can also help reduce the need for higher doses of analgesic medications, thereby minimizing potential side effects. They can also promote a sense of control and empowerment for patients, as they actively participate in their pain management. Therefore, a multimodal approach that combines both non-pharmacological and pharmacological interventions is often recommended for effective pain management across various levels of pain severity. We incorporate this information into the article to provide a comprehensive understanding of the role of non-pharmacological pain relief options in pain management. 16. There are other limitations besides those listed, e.g single-center study, only two examiners (when evaluating pain, the healthcare professional is influenced by personal beliefs, professional experience, etc,), only one procedure per baby, excluding neurologically impaired and seriously ill newborns (it is known that the severity of illness and neurological state may affect the pain expression in neonates), other factors influencing the pain expression were not examined (e.g. gestational age, environmental factors, sleep-wake state, etc.) Reply: We agree with the points you have raised and will address them in our limitations section. First, as you mentioned, our study was conducted at a single center, which may limit the generalizability of our findings to other settings. Additionally, our study only involved two examiners, which may have introduced bias in the pain assessments. We acknowledge that healthcare professionals' personal beliefs and professional experience may influence pain assessments, and future studies should aim to address this by involving a larger number of examiners from different backgrounds. Second, we excluded neurologically impaired and seriously ill newborns, which may limit the generalizability of our findings to these populations. We recognize that the severity of illness and neurological state may affect pain expression in neonates, and future studies should aim to include these populations. Third, our study did not specifically investigate the influence of other factors on pain expression in neonates, such as gestational age, environmental factors, and sleep-wake state. These factors have been reported to affect pain perception and expression in neonates in previous research. Therefore, future studies should aim to collect more comprehensive data and conduct analyses to explore the potential impact of these factors on pain assessment and ranking in neonates. By including these additional factors in the analysis, a more thorough understanding of the complex interplay between various factors and pain expression in neonates can be achieved. Finally, as you mentioned, our study only focused on quantifying pain experience across different procedures in a population context and did not address pre-intervention pain management. We agree that stepped pain control, including non-pharmacological and pharmacological interventions, is fundamental to neonatal pain management. Future studies should aim to evaluate the effectiveness of different pain management strategies for different clinical painful procedures. 17. “This study provides evidence that pain experience is similar across much of the neonatal population.” Unfortunately, this conclusion cannot be drawn. A significant part of the neonatal population (ELBW premature babies, neurologically affected, etc.) did not participate in the study. As well as pain

experience and pain response are not the same, this study assessed the response to pain and not the experience. Otherwise, according to literature data, it is well known that pain perceptions and expressions are not uniform in the neonatal population. I would modify: This study provides evidence that pain response is similar across the studied neonatal population. Reply: We agree that a significant portion of the neonatal population, such as ELBW premature babies and neurologically affected infants, did not participate in our study, and our findings may not be generalizable to these populations. Additionally, we acknowledge that pain experience and pain response are not the same. Our study assessed pain response, which may not fully capture the subjective pain experience of neonates. We agree that future studies should aim to assess both pain response and pain experience to better understand neonatal pain. Therefore, we agree with your suggestion to modify our conclusion to "This study provides evidence that pain response is similar across the studied neonatal population." 18. The figures and tables fit well with the content of the manuscript, supplementing and facilitating interpretation. Literature references are relevant. Although, figure 2 is difficult to see. Reply: Thank you for your feedback on our figures, tables, and literature references. We are glad to hear that they were helpful in interpreting our results and supporting our conclusions. Regarding your comment about Figure 2, we have taken your feedback into consideration. In response, we have decided to convert Figure 2 into a table format to improve visibility and clarity. This modification will ensure that readers can easily comprehend the information presented in this section. 19. I recommend having it checked by a native language consultant. Reply: We have had it checked by a native language consultant. 20. The study was made on an important topic and may be of interest to many, however, I recommend that it be published only after corrections, and rewriting. Reply: Thank you for your feedback on our manuscript. We appreciate your acknowledgment of the importance of the topic and the potential interest it may generate. We understand your recommendation to publish the manuscript only after corrections and rewriting have been made. We have carefully reviewed and addressed all your comments and suggestions. Furthermore, we have made necessary corrections and revisions to improve the clarity, organization, and overall quality of the manuscript. We believe that these changes have significantly strengthened the paper.