

Peer Review File

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Reviewer A

This is an interesting study looking at short term effects of anesthesia exposure on very young children. I am particularly intrigued by their observation that although potentially not observed in all children, there is a vulnerable population (up to 20%) that may suffer cognitive decline post-anesthesia thus posing a need for preoperative detection of vulnerable children, which is in my mind crucially important.

I like the model used in this study since it is prospective in nature, and it compares pre-and post-anesthesia outcomes using each child as his/her own control thus enabling a smaller sample size to yield meaningful information.

I find their exclusion criteria to be appropriate.

Comment 1: I question why only cognitive aspects of perioperative assessment was done in these children. The Authors state that this is because it is least likely to be impaired which seems to be a good reason, but I am sad that the rest of the testing was not done since we do not have almost any information regarding the acute effects on other aspects of neurodevelopment that are known to show long-term impairment.

Reply 1: We thank you for your comment and completely agree with it. We have included additional reasons for this in the manuscript. During the acute post-operative period, acute post-operative pain and surgical wounds may affect the evaluation of the motor domain. In addition, negative behavioral changes have been reported to be multifactorial, not limited to anesthetic neurotoxicity but also including post-operative stress, hospitalization, and other psychosocial factors. We have also addressed this point in the limitation as well.

Changes in the text: Page 9-10, Line 145-149 and Page 17, line 296-298.

Comment 2: How were the reference chosen to summarize the animal findings when the report is clinical in nature? More appropriate citations should be used especially using earlier reports.

Reply 2: Thank you for your comment. We have added appropriate citations (number 3–7) as per your suggestion.

Changes in the text: Page 6, Line 79

Comment 3: What type of developmental intervention was applied to children with baseline cognitive composite scores 2 SD below the mean during the study period?

Reply 3: We have added additional details to the manuscript to address this. Specifically, the developmental interventions included speech therapy and early intervention for fine motor-adaptive skill.

Changes in the text: Page 13, Line 217-218

Comment 4: The Authors state that, ‘among the 39 participants in the anesthesia group who received both baseline and post- anesthesia assessments, the post-anesthesia cognitive composite score was statistically higher than that at baseline’ and yet they report mean (SD) of baseline and post-anesthesia cognitive composite scores were 101.28 (10.87) and 97.05 (9.85), $P = 0.039$. This would suggest that the scores post-anesthesia are lower and not higher. I would recommend revising the statement to correctly reflect their findings.

Reply 4: We apologize for this mistake. Upon review our data, the correct values were presented in Table 3. As you mentioned, the correct baseline score was 97.05 (9.85) and the correct post-anesthesia score was 101.28 (10.87). The statement has been revised to correctly reflect our findings.

Changes in the text: Page 13, Line 201-203, Abstract Page 3, Line 42-45

Comment 5: They go on to say, ‘However, the clinical significance could not be concluded’. I am not sure what that means. This should be clarified.

Reply 5: We apologize for the unclear sentence. The statement has been revised to: “Among the 39 participants in the anesthesia group who received both baseline and post-anesthesia assessments, the post-anesthesia cognitive composite score was statistically higher than that at baseline, but without clinical significance (Table 3)”.

Changes in the text: Page 13, Line 201

Comment 6: The Authors state in the Discussion that in the anesthesia group, the post-anesthesia cognitive scores did not decrease compared with the baseline assessment’ which is an incorrect statement considering the findings that they present in the results.

Reply 6: We apologize once again for this oversight. The respective portion of the results has been changed accordingly, as noted above.

Changes in the text: Page 13, Line 201-203, Abstract Page 3, Line 42-45

Comment 7: The confusion continues when the Authors state as follows, ‘However, to compare each participant with one's baseline, 17.9% of the anesthesia group had post- anesthesia assessment lower than baseline with clinical significance.’ This statement is followed with another one contradicting it. ‘Our results were consistent with studies regarding short-term outcomes (1-week post-operative to pre-discharge) after cardiac surgery by Limperopoulos et al. (19) and Campbell et al. (14) that pre-operative and post-operative assessments of cognitive and motor function remained unchanged’. How is their study similar to the two cited ones that do not show a difference?

Reply 7: We apologize for this. We have thoroughly revised paragraph 2 of the discussion to further improve clarity of concepts.

Changes in the text: Page 14-15, Line 238-251

Comment 8: It is too bad that parent questionnaire was not part of the assessment since these are very valuable in this line of research.

Reply 8: Thank you for the valuable comment. To address your point, we have added the following sentence to discussion: “Parental questionnaires should be included to identify potential psychosocial factors.”

Changes in the text: Page 17, Line 304-305

Comment 9: The Discussion should focus more on key finding in the study, i.e., children at risk could be really badly affected by an early exposure to anesthesia which requires careful pre-operative assessment. Although they mentioned it, it is somehow buried at the very end of the Discussion.

Reply 9: Thank you for your comment. We have revised paragraphs 2 and 3 of the discussion to emphasize the decline cognitive function after anesthesia in some participants and the need to identify at-risk patients pre-operatively, in accordance with your valuable suggestion.

Changes in the text 9: Page 14-16, Line 238-267

Reviewer B

1. Please provide an explanation of “*” in the author list.

*Response: * Correspondence*

2. We’ve added the city and country names of the Affiliations, please confirm.

Response: confirm.

3. Keywords for an article are limited to 3-5 words. It is suggested to delete 3-4 words to meet the requirement. (Please provide the keywords in the format as: “Keywords: XXX; XXX; XXX;...”)

Response: Keywords have been changed to General anesthesia; developmental disabilities; child development.

4. Tables

a. We failed to find below information in **Table 2**. Please check.

7 (9.88), $P < 0.001$. The mean difference (95% CI) was -14.37 (-8.28 to -20.47). Four (8.5%)

8 participants in the anesthesia group were categorized as having cognitive delay (cognitive

9 composite score < 1 SD below the mean). One participant in the anesthesia group (2.1%) had a

10 baseline cognitive composite score of ≤ 2 SD below the mean. ↵

Response: Four (8.5%) participants with cognitive delay are described in Table 2 below. The last sentence (One participant with score ≤ 2 SD) is the additional information that is not required to be presented in the Table 2.

Table 2 Comparison of baseline cognitive composite scale scores in the control and anesthesia groups; data presented as mean (SD) or number (%)

Score	Control group (N=20)	Anesthesia group (N=47)	Mean difference (95% CI)	P
Scaled score	12.30 (2.34)	9.36 (2.10)	-2.94 (-1.70 to -4.17)	< 0.001
Composite score	111.50 (11.71)	97.13 (9.88)	-14.37 (-8.28 to -20.47)	< 0.001
Percentile Rank	72.30 (20.90)	43.68 (21.69)	-28.62 (-17.19 to -40.05)	< 0.001
<i>Category by the composite score</i>				
I Above average cognitive development (116-160)	7 (35.0)	2 (4.3)		
II Normal cognitive development (85-115)	13 (65.0)	41 (87.2)	N/A	0.002
III Cognitive delay (40-84)	0	4 (8.5)		

N/A – not applicable; P < 0.05, significant

b. Please recheck the following data in Table 4. (13/39≈33.3%)

Normal Labor ☐ 13 (34.2) ☐ 13 (41.9) ☐
 Birth problem ☐ 10 (26.3) ☐ 8 (25.8) ☐

Response: We have 1 missing data in the not-declined group. A remark has been added.

c. Data mentioned in the following sentence are inconsistent with **Table 4**. Please check and revise. *The incidence of intraoperative adverse events among the 46 anesthetized individuals was one (2.2%) hypoxia, one (2.2%) hypotension, two (4.3%) bradycardia, and fourteen (30.4%) hypocarbia.*

Intraoperative adverse event ☐	13 (33.3) ☐	10 (31.3) ☐	3 (42.9) ☐	0.666 ☐ ☐
Hypoxia ☐	1 (2.6) ☐	0 ☐	1 (14.3) ☐	0.179 ☐ ☐
Hypocarbia ☐	12 (30.8) ☐	10 (31.3) ☐	3 (42.9) ☐	0.666 ☐ ☐
Hypotension ☐	1 (2.6) ☐	1 (3.1) ☐	0 ☐	1.000 ☐ ☐
Bradycardia ☐	1 (2.6) ☐	0 ☐	1 (14.3) ☐	0.179 ☐ ☐

Response: We confirm the accuracy of the data in the text. In the text, the overall intraoperative adverse events were reported based on 46 anesthetics. In the table, the comparison of the intraoperative adverse events between declined and not-declined group were reported based on 39 anesthetics that included in the final analysis. We have added “the overall” in the text for clarification.

We apologize for the inaccuracy in the table. We have rechecked and corrected.

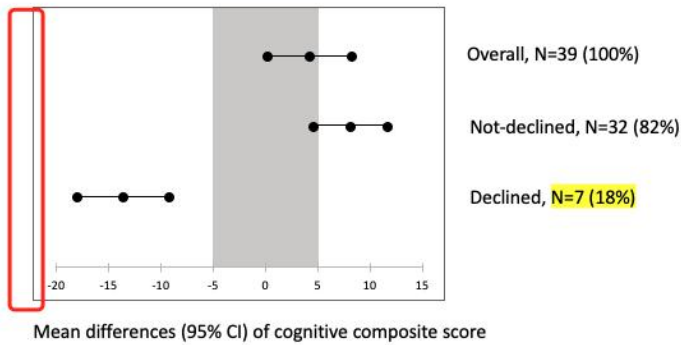
d. Data mentioned below is inconsistent with **Figure 2**. Please check and revise.

Seven (17.9%) participants had post-anesthesia scores lower than the baseline by more than 5 points and were considered in the declined group.

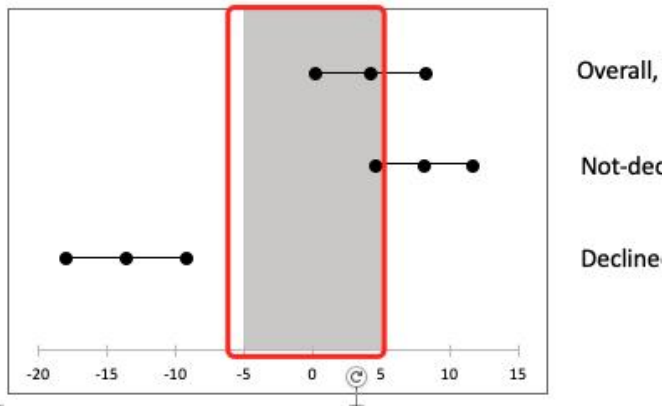
Declined, N=7 (18%)

Response: We apologize for the rounded number. The label 18% in the figure has been changed to 17.9%.

5. Please check if the Y-axis should be added to Figure 2.



Please also define the grey area in figure legends.



Response: Thank you for your suggestion. Figure 2 has been revised and explanation has been added.

6. Please also check all your data in this article (together with all figures and tables) for accuracy.
Response: Thank you for your suggestion. The inaccuracy was corrected in the revised file.

7. Please provide the complete affiliations (which hospital) of Chalita Jiraphorncharas, Wanpen Ritthita, Julaporn Pooliam and Miss Arporn Pimtong in the Acknowledgments.

Response: Affiliations have been added.

8. There's no need to provide the registration information for your study, we've removed them, please confirm.

69 composite score in 17.9% of the participants. ↵

70 **Clinical Trial Registration: thaiclinicaltrials.org (TCTR20211209006).** ↵

129 study was approved by the [Siriraj](#) Institutional Review Board (No. Si456/2017) and was
 130 registered at thaiclinicaltrials.org (TCTR20211209006). Written informed consent was obtained

Response: Although it is not mandatory to provide trial registration number in the non-randomized controlled trial, I agree to remove the number from the abstract but I disagree to remove the registration

number from the manuscript. The trial number should be kept in order to report which manuscript is published after the trial registration.

9. Please be specific about the name of the ethics board, should it be “Institutional Review Board of Siriraj Hospital”? Please supplement.

129 study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This

130 study was approved by the Siriraj Institutional Review Board (No. Si456/2017). Written

Response: We confirm the name of the ethics board, according to certificate of approval below.

2 WANGLANG Rd. BANGKOKNOI BANGKOK 10700		Tel. +66 2419 2667-72 Fax. +66 2411 0162
Siriraj Institutional Review Board Certificate of Approval (Renewal)		
		COA no. <u>Si 456/2017</u>
Protocol Title(English) : Effect of anesthesia on neurocognitive function in children 0-3 years old.		