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Changes in Diaphragmatic Activity Due to Caffeine Citrate Administration and Discontinuation in Preterm Infants

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1 Original submission

1 comment · 10 Jul 2024

Associate Editor

MAJOR REVISION 10 Jul 2024

Dear authors
Method
What are your inclusion and exclusion criteria?
In the methods section, you have to follow the STROBE instructions and give a title to each section.
In the methods section, you should not explain the role of Edipeak.
result: You shouldn't repeat the results from the table in the text.
Where is the effect of perinatal factors in the analysis?
What is the impact of Oligohydramnios on your study?
Does your analysis involve before-and-after comparisons or repeated measures?
In the discussion, you didn't talk about the impact of the data you gathered on your study.

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear Editors and Reviewer,

We sincerely appreciate the comprehensive and helpful review of our manuscript. We have carefully considered the points raised and revised our manuscript accordingly. Please, find next a detailed, point-by-point response to all your comments. We hope you find the revised version suitable for publication.

Reviewers' Comments:

Reviewer 1:
Thank you for your valuable research, but it needs some revisions.
In line 2 you wrote"The direct effect of caffeine citrate on the activation of diaphragmatic motion has not been common", but there are some studies about this.

A: We acknowledge that some studies have reported the effect of caffeine citrate on activation of the diaphragm, as described in the second paragraph of the main text (Page 2, Lines 8–15). However, the existing research is limited. Hence, we used the phrase “has not been commonly studied,” to convey the idea that there is a lack of abundant studies on this specific topic. To better convey this, we have replaced it with “has not been extensively researched.” (Abstract background & Main text Page 2, Line 9)

Please write the place of study in the method and abstract parts.

A: We have added the place of study in both sections (Abstract Methods Page 1, Lines 11–12 and Main text Page 3, Line 2).

Please discuss why Edipeak values tended to increase at 24 to 48 h after caffeine citrate discontinuation compared with those measured at 24 h of discontinuation, in the discussion part.

A: We have added a description on why Edi_{peak} values tended to increase in the later hours compared to the earlier hours after caffeine discontinuation (Page 7, Line 25-32).

An insignificant increase in caffeine which cannot be justified omitted from the abstract part.

A: The sentence starting with “Edi_{peak} showed an insignificant increase…” has been omitted from the abstract.

Associate Editor's Comments:

Associate Editor 1:
Dear authors
Method
what is you including and excluding criteria?
in method you have to follow strobe instructions and give title for each section
In method you should nt explain the role of The Edipeak

A: We have clarified the inclusion and exclusion criteria, based on the STROBE guidelines and included sub-headings (Page 3, Lines 1–4 and Lines 17–19; subheadings 3.1 and 3.2).

The explanation on the Edi values has been moved to the introduction section (Page 2, Lines 23–26).

result: you shouldnt repeat the results in the table in the text?
Where is the effect of perinatal factors in the analysis?
What is the impact of Oligohydramnios on your study
Your analysis seems to be before and after or repeated measure?

A: We have tried to minimize repetition of the content of the tables in the text.

Although oligohydramnios could have an impact on the pulmonary condition of preterm infants, which may ultimately affect the degree of caffeine citrate impact and respiratory drive, only two infants were affected by the status, for which the authors deferred analysis on it. As the sample size for the study is small, it was unlikely to yield a significant result based on an extremely imbalanced categorization of the included infants. However, we appreciate for pointing out this factor, as this portion may be of importance in future larger-scale research.

As mentioned in the methods section (Page 3, Lines 20–29), Edi values were retrieved from the NAVA software data at certain time intervals – for instance, 20 minutes before starting caffeine citrate administration to 20 minutes after the completion of the loading dose – which implies that the data included continuous Edi values collected from 20 minutes prior to drug administration continuing throughout 20 minutes after drug-administration completion.

In discussion you didnt talk about the impact of the data you gathered on your study

A: We have added more content regarding the impact of the data that we collected in the Discussion section (Page 9, Lines 36-38 and Page 10, Lines 6-14).

Associate Editor 2:
Overall, this study provides valuable preliminary data on an understudied aspect of a

commonly used medication in preterm infants. While the small sample size limits firm conclusions, the findings suggest interesting trends in diaphragmatic activity that warrant further investigation in larger studies. The use of NAVA technology is a particular strength that allows for more precise measurement than previous studies on this topic.

Potential areas for improvement:
1. Small sample size (13 infants) limits statistical power and generalizability.
2. Lack of control group makes it difficult to isolate caffeine effects from natural changes over time.
3. Early administration of caffeine may have introduced confounding from other interventions occurring in the immediate postnatal period.
4. Caffeine levels were not measured, so optimal dosing cannot be determined.
5. Discontinuation time point was defined as a range rather than a specific time.

A: Thank you for the comments. We acknowledge the limitations of this study that you have pointed out. We have described these limitations in the Discussion section (Page 9, Lines 6-31). These limitations will hopefully be addressed in future large-scale research.

Methodology:
Areas for improvement:
- Lack of a control group
- Small sample size
- No measurement of caffeine levels
- Early administration of caffeine may introduce confounding factors
- The authors could have considered including longer-term follow-up to assess sustained effects

A: Most of the points have been discussed in the limitations section. We have added the last point, which was not previously described in the manuscript (Page 9, Lines 31-34).

Results section:
- Limited statistical significance due to small sample size
- Lack of clear differentiation between statistically significant findings and observed trends
- Some results are presented without clear explanation of their clinical relevance
- Absence of power analysis to determine if the study was adequately powered to detect differences

A: We have tried to be consistent in using the words/phrases ‘significantly increased/decreased’ for statistically significant results, and ‘tended to increase/decrease’ or ‘trends’ for statistically insignificant results. While we deleted most of the numerical values to avoid repetition of the contents of the tables as per the reviewer’s comments, we have retained p-values in some portion of the results to clarify the statistical (in)significance.

The explanations for some results that have not been clearly defined were added in the Discussion section (Page 7, Line 35-38).

As mentioned, the first and foremost limitation of this study is the small sample size, which was determined by practical constraints rather than by a priori power analysis. Consequently, the study may not have been adequately powered to detect some statistically significant differences. Nonetheless, the trends observed in the Edi values after caffeine administration suggest clinically relevant changes that warrant further investigation in larger, adequately powered studies. We have added this content to the Discussion section to further clearly acknowledge the limitation and to make recommendations for future research (Page 10, Lines 6-20).

Discussion:
The authors could improve the discussion by:
- More clearly acknowledging the limitations of the study, particularly the small sample size
- Providing more context for how their findings compare to previous studies on caffeine in preterm infants
- Discussing the clinical implications of their findings more explicitly
- Offering more detailed suggestions for future research, including sample size calculations
- Exploring potential mechanisms for the observed effects of caffeine on diaphragmatic activity

A: We have revised our manuscript to more clearly acknowledge the limitations of the study, particularly regarding the small sample size (Page 9, Lines 8-9; Page 10, Lines 6-11). We also discuss the clinical implications of our findings more explicitly (Page 9, Line 36 through Page 10, Line 5). Additionally, we provide more detailed suggestions for future research, including sample size calculations (Page 10, Lines 11-20), and explore potential mechanisms for the observed effects of caffeine on diaphragmatic activity (Page 9, Line 38 through Page 10, Line 3).

References:
The references appear to be up-to-date and relevant. However, they could potentially strengthen the reference list by:
- Including more studies on NAVA technology in preterm infants
- Adding references on the long-term outcomes of caffeine use in preterm infants
- Including more systematic reviews or meta-analyses on caffeine use in neonatology, if available

A: Thank you for the suggestion. We have included additional references and related content in the main text (Page 2, Lines 27-29; Page 10, Lines 15-16; and reference numbers 6, 14, 15, 30, and 31).

2 Revision 1

1 comment · 7 Dec 2024

Associate Editor

ACCEPT 7 Dec 2024

Dear Authors,
We are pleased to accept your manuscript.