

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.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Use of intranasal and sublingual analgesia in children and adolescents in the paediatric emergency department
AUTHORS	Cozzi, Giorgio Chiappa, Sara La Fauci, Giovanna Calvi, Matteo Castagno, Emanuele Tappi, Eleonora Villa, Giovanna Tommasi, Paola Milani, Gregorio Paolo Cellai Rustici, Marta Casciana, Maria Luisa Tovaglieri, Nicola Masi, Stefano Vezzoli, Cesare Tilatti, Sofia Zeuditù GIANGRECO, Manuela Barbi, Egidio Benini, Franca

VERSION 1 - REVIEW

REVIEWER NAME	Dr. Luisa Cortellazzo Wiel
REVIEWER AFFILIATION	University of Trieste Piazzale Europa, 1 Trieste 34127 Italy
REVIEWER CONFLICT OF INTEREST	None
DATE REVIEW RETURNED	17-May-2024

GENERAL COMMENTS	<p>Dear author,</p> <p>Thank you for submitting the present manuscript to BMJ Paediatrics Open.</p> <p>I have suggested its acceptance following a minor revision.</p> <p>This study provides a reliable picture of the current limited use of the transmucosal routes in the PED setting in Italy, which, considering the available literature in support of their safety and efficacy, prompts the reader to reflect on the need for an implementation of their use.</p> <p>In the discussion you suggest the limited access by paediatricians to drugs administered through these routes, as a possible reason behind the limited use of the routes themselves for analgesia administration.</p> <p>I am wondering whether you have been able to identify any further</p>
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	<p>explanation and consequent issues to address.</p> <p>It is reported for example that only one out of three centres answering the survey used a Mucosal Atomizer Device. A wider availability of the device would probably increase the use of the intranasal route, following appropriate training.</p> <p>However, training itself and awareness of the data in support of the effectiveness of the transmucosal routes, does remain a cornerstone for the implementation of a change in clinical practice, and I believe your work provides an insight into the need to spread this awareness.</p> <p>While I would suggest a minor English revision, I think the following amendments would enhance clarity:</p> <p>Page 7, line 8: please add 'through any route' after 'Subjects who received pharmacological analgesia at the ED'</p> <p>Page 9: substitute 'to provide pharmacological analgesia' on line 19 with 'for analgesia administration' on line 15</p> <p>Thank you for your valuable contribution.</p> <p>Kind regards.</p>
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REVIEWER NAME	Dr. Ivy Ang
REVIEWER AFFILIATION	NUH Paediatrics 5 Lower Kent Ridge Road Singapore 119074 Singapore
REVIEWER CONFLICT OF INTEREST	No
DATE REVIEW RETURNED	28-Jun-2024

GENERAL COMMENTS	<p>It is interesting to see the varied use of transmucosal analgesia and oral/IV analgesia in Italian PEDs.</p> <p>It promotes awareness of the different routes and types of analgesia that can be given in a child experiencing pain.</p> <p>However, this article does not promote understanding of the limitations and the efficacy of the use of transmucosal analgesia.</p> <p>As a result, I am unsure if this article helps supplement knowledge as to what types of analgesia should be considered for different painful conditions in children.</p> <p>The relevant outcome measure for efficacy of analgesia would be</p> <ol style="list-style-type: none"> a) Reduction in pain / pain score b) Concomitant use of other analgesia due to failure to provide adequate analgesia with the initial agent, as a surrogate marker of efficacy / lack of efficacy <p>The painful conditions covered in this paper spanned from trauma/injury related, to abdominal pain.</p> <p>I wonder if it would be more relevant/value add to narrow down the different types of analgesia or different types of painful condition in order to look at the efficacy of analgesia given.</p> <p>Some of the medications eg: tramadol and paracetamol-codeine are only suitable for children >12 years and above. I wonder if it would be useful to</p>
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	<p>do subgroup analysis of analgesia for <12 year old and >12 year old.</p> <p>I would also be interested to know if paracetamol, ketorolac and tramadol given sublingual vs oral - what is the efficacy in relieving pain and how to ensure the administration was done in a way to ensure that the young patient took it sublingually instead of orally?</p> <p>Thank you for your consideration.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dear author,
 Thank you for submitting the present manuscript to BMJ Paediatrics Open.
 I have suggested its acceptance following a minor revision.

This study provides a reliable picture of the current limited use of the transmucosal routes in the PED setting in Italy, which, considering the available literature in support of their safety and efficacy, prompts the reader to reflect on the need for an implementation of their use.

In the discussion you suggest the limited access by paediatricians to drugs administered through these routes, as a possible reason behind the limited use of the routes themselves for analgesia administration.

I am wondering whether you have been able to identify any further explanation and consequent issues to address.

It is reported for example that only one out of three centres answering the survey used a Mucosal Atomizer Device. A wider availability of the device would probably increase the use of the intranasal route, following appropriate training.

However, training itself and awareness of the data in support of the effectiveness of the transmucosal routes, does remain a cornerstone for the implementation of a change in clinical practice, and I believe your work provides an insight into the need to spread this awareness.

Authors: Thank you for your comment and for the opportunity to improve our work. We added a comment in the text about other possible explanations behind the limited use of transmucosal routes of administration.

While I would suggest a minor English revision, I think the following amendments would enhance clarity:

Page 7, line 8: please add 'through any route' after 'Subjects who received pharmacological analgesia at the ED'

Page 9: substitute 'to provide pharmacological analgesia' on line 19 with 'for analgesia administration' on line 15

Authors: we modified the text accordingly. Thanks!

Reviewer: 2

It is interesting to see the varied use of transmucosal analgesia and oral/IV analgesia in Italian PEDs. It promotes awareness of the different routes and types of analgesia that can be given in a child experiencing pain.

However, this article does not promote understanding of the limitations and the efficacy of the use of transmucosal analgesia.

As a result, I am unsure if this article helps supplement knowledge as to what types of analgesia should be considered for different painful conditions in children.

Authors: Thank you for your comment. Our research primarily aimed to draw a picture focused on clinicians' everyday practice in Italian PEDs. Frequently, there is a gap between evidence, RCTs results and clinical practice. When we designed this research, we wanted to investigate if there were discrepancies in this topic. The study results highlighted that despite evidence suggesting that transmucosal routes of administration to provide analgesia are safe and effective their use is still limited. This study could lay the ground for future studies specifically aimed to investigate possible limitations to the use of transmucosal analgesia in clinical practice. Nevertheless, we implemented the discussion with possible causes that may have influenced our findings, such as: lack of awareness, evidence limitations, and use off label of drugs.

The relevant outcome measure for efficacy of analgesia would be

- a) Reduction in pain / pain score
- b) Concomitant use of other analgesia due to failure to provide adequate analgesia with the initial agent, as a surrogate marker of efficacy / lack of efficacy

Authors: We agree, but our research was not focused on measuring the efficacy of transmucosal analgesia. When we designed the study protocol, we decided not to collect data about pain scores precisely because the study design would have limited the strength of these data. We believe that analgesic efficacy can be really measured only through specifically designed RCTs. Providing data about analgesic efficacy in a study designed as the present study, would have exposed us to several biases, limiting the strength of our findings. Despite all this, in our population, most of the subjects who received transmucosal analgesia, didn't require other analgesics through other routes. We added a comment also about this point.

The painful conditions covered in this paper spanned from trauma/injury related, to abdominal pain. I wonder if it would be more relevant/value add to narrow down the different types of analgesia or different types of painful condition in order to look at the efficacy of analgesia given.

Authors: Through this paper, we found that the transmucosal route of administration was differently used considering the cause of pain. For example, intranasal administration was significantly more used in trauma patients compared to patients affected by abdominal pain. Nevertheless, we believe that our study design prevented us to any judgments about analgesic efficacy.

Some of the medications eg: tramadol and paracetamol-codeine are only suitable for children >12 years and above. I wonder if it would be useful to do subgroup analysis of analgesia for <12 year old and >12 year old.

Authors: drugs administered through the sublingual route such as ketorolac (in label in Italy only for patients older than 16 yrs of age) and tramadol are given off-label, not only for the way of administration, but also for patients' age. This could represent a further limitation in the use of these ways of administration.

We didn't perform a specific analysis in consideration of the age of patients considering that in general, drugs such as tramadol and paracetamol-codeine were used in only a very limited proportion of patients in our population. In particular, the administration of tramadol was equally distributed between school children and adolescents, 15 and 17 subjects respectively. On the contrary, paracetamol-codeine was given mostly to adolescents, namely 3 school children and 10 adolescents.

I would also be interested to know if paracetamol, ketorolac and tramadol given sublingual vs oral - what is the efficacy in relieving pain and how to ensure the administration was done in a way to ensure that the young patient took it sublingually instead of orally?

Authors: Ketorolac and tramadol intravenous formulations are employed when these drugs are administered sublingually, and no oral formulations are employed for this route. On the other hand, sublingual paracetamol is administered with a specifically developed powder. Nevertheless, all these formulations are at least in part swallowed, so we can't exclude some kind of "oral" efficacy. Moreover, to the best of our knowledge there are no RCTs comparing the same drug or different drugs administered through sublingual and oral route to investigate some different efficacy.

We hope that the modified manuscript could be taken into consideration for publication in your journal and we look forward to hearing from you at your earliest convenience.

VERSION 2 - REVIEW

REVIEWER NAME	Dr. Luisa Cortellazzo Wiel
REVIEWER AFFILIATION	University of Trieste Piazzale Europa, 1 Trieste 34127 Italy
REVIEWER CONFLICT OF INTEREST	None
DATE REVIEW RETURNED	23-Jul-2024

GENERAL COMMENTS	<p>Thank you for submitting the present revision of your manuscript. I have suggested its acceptance followed the below listed minor changes.</p> <p>Page 13: Line 14: Delete 'In this sense', change 'our' to 'The present'</p>
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	<p>Line 22: Change 'used for sublingual administration' to 'administered via the sublingual route'</p> <p>Line 24: Change 'not labelled' to 'off label'</p> <p>Line 26: Delete years after 16</p> <p>Line 34: Change 'effectiveness of the transmucosal routes and a consequent' to 'their effectiveness' and add 'which could explain the limited availability of MAD devices'</p> <p>Line 50: Change the second 'analgesic efficacy' in the sentence with 'the latter'</p> <p>Line 54: Change 'designed as the present one' to 'with the present design'</p>
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REVIEWER NAME	Dr. Ivy Ang
REVIEWER AFFILIATION	NUH Paediatrics 5 Lower Kent Ridge Road Singapore 119074 Singapore
REVIEWER CONFLICT OF INTEREST	No
DATE REVIEW RETURNED	25-Jul-2024
GENERAL COMMENTS	Nil issues

VERSION 2 – AUTHOR RESPONSE

Authors: We revised the English language of the manuscript following the suggestions of the Reviewer 1.

Also, Figure 1 as a pie chart is generally less informative. Consider if this can be moved to the text, or if the data can be enriched, to consider presenting in bar chart or other forms. Each number needs to be clear (absolute, percentage).

Authors: We agree. We deleted the Figure 1 and added the data regarding the age of the enrolled patients in the text. Please see the amended version of the manuscript.

Reviewer: 1

Comments to the Author

Thank you for submitting the present revision of your manuscript.

I have suggested its acceptance followed the below listed minor changes.

Page 13:

Line 14: Delete 'In this sense', change 'our' to 'The present'

Line 22: Change 'used for sublingual administration' to 'administered via the sublingual route'

Line 24: Change 'not labelled' to 'off label'

Line 26: Delete years after 16

Line 34: Change 'effectiveness of the transmucosal routes and a consequent' to 'their effectiveness' and add 'which could explain the limited availability of MAD devices'

Line 50: Change the second 'analgesic efficacy' in the sentence with 'the latter'

Line 54: Change 'designed as the present one' to 'with the present design'

Authors: Thank you for the possibility to improve the language of the manuscript. We modified the language following your suggestions.

Reviewer: 2

Comments to the Author

Nil issues

Authors: Thanks.

We hope that the modified manuscript could be taken into consideration for publication in your journal and we look forward to hearing from you at your earliest convenience.