

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form ([see an example](#)) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

This paper was submitted to the ADC but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open where it was re-reviewed and accepted.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Does Neonatal Pain Management in Intensive Care Units differ between night and day? An observational study
AUTHORS	Guedj, Romain; Danan, Claude; Daoud, Patrick; Zupan, Véronique; Renolleau, Sylvain; Zana-Taieb, Elodie; Aizenfisz, Sophie; Lapillonne, Alexandre; de Saint Blanquat, Laure; Granier, Michele; Durand, Philippe; Castela, Florence; Coursol, Anne; Hubert, Philippe; Cimerman, Patricia; Anand, Sunny; Khoshnood, Babak; Carbajal, Ricardo

VERSION 1 - REVIEW

REVIEWER	Simons, Sinno VU medical center, Neonatology
REVIEW RETURNED	01-Aug-2013

GENERAL COMMENTS	<p>The current paper describes the results of a sub analysis of the EIPPAIN study concerning the use of analgesics for painful neonatal procedures during day and night. The EIPPAIN study was a large well performed multicenter trial that investigated the number of painful procedures and the use of analgesics in France. This unique database of prospectively collected data is now used to further explore differences in pain management during different parts of the day. The paper is well written. This is the first study that looked at this topic in such an extensive way. The study is again well performed and analyses are clear and extensive. It is unclear why it took more than 7 years before the analyses were performed. Although I do think that the pain management in the included ICUs did not change very much during the last years I do think that the authors need to discuss this.</p> <p>Abstract: please provide absolute changes instead of relative reductions. Introduction: well written and clear. Heading is missing. Methods: the first sentence at page 8 is repeated. Please delete one. Why were 5 procedures selected? Why not 10? Please explain. Results: Figure 2 might be deleted because it is not that informative (or maybe published online?) Discussion: Again only relative reductions are given that might suggest a larger difference between day and night than the actual difference. Please give absolute changes.</p>
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	<p>Add limitation of data from > 7 years ago. P 14 analgesia in stead of analgesia</p> <p>Furthermore I would like the authors to extend the discussion on how to improve the use of analgesics during the night.</p> <p>Table 1: duration of participation vs Overall; what is the difference. This is not clear. Table 2: what is difference between 2 shifts per day and day-night nurse rotation Table 6: consider publishing online only.</p> <p>Figure 3: This is the most important figure according to me. Here it is clearly visualized that the most analgesic therapy is administered in the morning. So maybe there is a difference between the morning and the rest of the day instead of the suggested difference between the morning and night. Best practice in the morning and a decrease thereafter? What would be the reasons for that?</p>
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REVIEWER	Boyle, Elaine University of Leicester, Department of Health Sciences
REVIEW RETURNED	04-Sep-2013

GENERAL COMMENTS	<p>This study is part of the previously published EIPPAIN Study, conducted some years ago in France. This paper addresses the issue of round-the-clock pain management in neonatal care. To my knowledge, there are no previous published data on this subject. With increasing emphasis and scrutiny of quality of care issues, differences in care associated with time of day or week will likely become increasingly important to monitor. Pain management might be expected to be constant regardless of time of day, yet this study shows that this is not the case.</p> <p>The abstract is appropriate. The introduction appropriately summarises the background to both the study and the subject area.</p> <p>Methods The methods appear to be appropriate. My one concern is the potential for introducing recall bias by returning to collect some further data by report from the head nurse some 4-5 years after the original study was conducted. However, the authors are careful to state that the person providing the information for each centre had been present at the time of the original data collection.</p> <p>Statistical methods are described in detail. I do not have sufficient statistical expertise to comment on the appropriateness or otherwise of these. However, I would comment that some of the tables reporting the analyses are quite complex (particularly tables 5 and 6) and therefore the results may not be easily interpreted by the journal readership.</p> <p>Results The results do appear to show a convincing difference in management depending on the time of day and this is very interesting. I am particularly interested in the apparent influence of parental presence, but am uncertain as to whether this relates to actual parental presence during procedures or simply to the</p>
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	<p>presence of a policy in the unit of allowing parents 24 hour access. This could be made clearer. It is also interesting to see the relationship between increased pain management and shorter working hours of nurses. If verified in other quality of care studies, this could potentially have far-reaching implications for staff working patterns.</p> <p>In summary, this is an interesting, if rather complexly-written paper. I would like to see it simplified a little and would suggest that perhaps not all of the figures and tables are necessary. The message is an important one and has relevance for all neonatal practitioners. The authors appropriately address the limitations of the study.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Comments to the Author

The current paper describes the results of a sub analysis of the EPIPAIN study concerning the use of analgesics for painful neonatal procedures during day and night.

The EPIPAIN study was a large well performed multicenter trial that investigated the number of painful procedures and the use of analgesics in France.

This unique database of prospectively collected data is now used to further explore differences in pain management during different parts of the day.

The paper is well written. This is the first study that looked at this topic in such an extensive way.

The study is again well performed and analyses are clear and extensive.

It is unclear why it took more than 7 years before the analyses were performed. Although I do think that the pain management in the included ICUs did not change very much during the last years I do think that the authors need to discuss this.

Abstract: please provide absolute changes instead of relative reductions.

Response: We think that relative reduction is a better reflect of practice differences than absolute changes. However, absolute changes are shown in table 4, table 5 and in figure 3, so the reader can have a clear idea of their magnitude

Introduction: well written and clear. Heading is missing.

Methods: the first sentence at page 8 is repeated. Please delete one.

Response: We deleted the repeated sentence.

Why were 5 procedures selected? Why not 10? Please explain.

Response: We selected these 5 procedures because these procedures were the more frequent and accounted for 90% of all painful procedures. Then, they were both readily performed at any time in the intensive care unit and represented the majority of painful procedures. We assumed they represented fairly procedural practices

Results: Figure 2 might be deleted because it is not that informative (or maybe published online?)

Discussion: Again only relative reductions are given that might suggest a larger difference between day and night than the actual difference. Please give absolute changes.

Response: Please see previous response (abstract)

Add limitation of data from > 7 years ago.

P 14 analgesia in stead of analgesia

Furthermore I would like the authors to extend the discussion on how to improve the use of analgesics during the night.

Response: We have mentioned in the discussion section that organisational factors were associated

with change of practices between day and night and we suggested that their improvement might contribute to homogenization of quality of care around the clock. However, variation of care quality during the day is a complex phenomenon and thus we should be cautious, at this stage, of drawing definite conclusion

Table 1: duration of participation vs Overall; what is the difference. This is not clear.

Table 2: what is difference between 2 shifts per day and day-night nurse rotation

Table 6: consider publishing online only.

Response: Table 1: there is a one line shift in the column 2, 3 and 4. We have corrected this

Table 2 : As explained in the methods section, day-night nurse shift rotation means that nurses work some days during daytime and some other days during nighttime.

Figure 3: This is the most important figure according to me. Here it is clearly visualized that the most analgesic therapy is administered in the morning. So maybe there is a difference between the morning and the rest of the day instead of the suggested difference between the morning and night. Best practice in the morning and a decrease thereafter? What would be the reasons for that?

Response: As presented in the result section, we agree there is a difference between the morning and the rest of the day.

Reviewer: 2

Comments to the Author

This study is part of the previously published EPIPAIN Study, conducted some years ago in France. This paper addresses the issue of round-the-clock pain management in neonatal care. To my knowledge, there are no previous published data on this subject. With increasing emphasis and scrutiny of quality of care issues, differences in care associated with time of day or week will likely become increasingly important to monitor. Pain management might be expected to be constant regardless of time of day, yet this study shows that this is not the case.

The abstract is appropriate. The introduction appropriately summarises the background to both the study and the subject area.

Methods

The methods appear to be appropriate. My one concern is the potential for introducing recall bias by returning to collect some further data by report from the head nurse some 4-5 years after the original study was conducted. However, the authors are careful to state that the person providing the information for each centre had been present at the time of the original data collection.

Statistical methods are described in detail. I do not have sufficient statistical expertise to comment on the appropriateness or otherwise of these. However, I would comment that some of the tables reporting the analyses are quite complex (particularly tables 5 and 6) and therefore the results may not be easily interpreted by the journal readership.

Results

The results do appear to show a convincing difference in management depending on the time of day and this is very interesting. I am particularly interested in the apparent influence of parental presence, but am uncertain as to whether this relates to actual parental presence during procedures or simply to the presence of a policy in the unit of allowing parents 24 hour access. This could be made clearer.

Response : The model included both the influence of parental presence during procedures and parental policy in center, then adjusted to each other.

It is also interesting to see the relationship between increased pain management and shorter working hours of nurses. If verified in other quality of care studies, this could potentially have farreaching implications for staff working patterns.

In summary, this is an interesting, if rather complexly-written paper. I would like to see it simplified a little and would suggest that perhaps not all of the figures and tables are necessary. The message is an important one and has relevance for all neonatal practitioners. The authors appropriately address

the limitations of the study.

VERSION 2 – REVIEW

REVIEWER	Rollin Brant Child and Family Research Institute University of British Columbia Canada
REVIEW RETURNED	26-Oct-2013

GENERAL COMMENTS	<p>I think this is a very interesting paper. The underlying study design is strong and has the potential expanding our understanding of the issue of under-medication in paediatric critical care. The reporting of basic descriptive results needs to be expanded and the statistical analysis needs to be further refined, as noted in the points below. Additionally, the authors should endeavour to align their discussion with the particular findings of the analysis.</p> <p>page 10, line 23. It is not clear whether calculation of these P-values was derived from simple chi-square tests or on the multilevel model described in line 43. Simple chi-square tests are not appropriate. These p-values should be derived from the hierarchical effects model, which may or may not include centre x time of day interactions, depending on the assessment suggested in my remarks 10:43.</p> <p>page 10, line 43. Since patterns of practise may vary between centres, the model needs an interaction term (a random effect) between center and time of day. If this term is found to improve the model in terms of AIC (Akaike's information criterion) or BIC (it's Bayesian analogue) then it would be helpful to derive centre specific odds ratios and confidence intervals for display in a forest plot. This is especially relevant to making generalizations over the entire population of centres in France.</p> <p>page 11, line 38. In accordance with my suggestion about interaction between centre and time of day, it would be informative to further stratify this table by time of day.</p> <p>page 11, line 50. Figure 3 is partly redundant, as it includes the overall percentages for the 5 procedures, which were reported in the Abstract (though not in the Results). It is not clear why only two of the 5 procedures are described. I would suggest re-iterating the overall percentages in the text and providing procedure specific findings for all 5 procedures in the figure.</p> <p>page 12, line 21. To be transparent about which factors and/or interactions were included in the model, a table of corresponding odds ratios, with confidence limits, should be provided.</p> <p>page 12, line 26. Note that the this pattern is not merely attenuated, but in fact is reversed when parents are present.</p> <p>page 12, line 46. This observation is not supported by the data. There is a sharp decrease from morning to afternoon followed by a gentle (and possibly non-significant) decline.</p> <p>page 14, line 30. This statement is not justified unless an examination of centre-specific daytime/night-time odds ratio over centres indicates such homogeneity.</p> <p>page 15, line 12. Parental presence actually reverses the effect.</p>
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VERSION 2 – AUTHOR RESPONSE

Reviewer : page 10, line 23. It is not clear whether calculation of these P-values was derived from simple chi-square tests or on the multilevel model described in line 43. Simple chi-square tests are not appropriate. These p-values should be derived from the hierarchical effects model, which may or may not included centre x time of day interactions, depending on the assessment suggested in my remarks 10:43.

Response : To follow this suggestion, we have added the p-values derived from the multilevel model so that readers can see the p-values observed in the univariate analysis. We have indicated this in the table 3 and in the materials and methods section.

Reviewer : page 10, line 43. Since patterns of practise may vary between centres, the model needs an interaction term (a random effect) between center and time of day. If this term is found to improve the model in terms of AIC (Akaike's information criterion) or BIC (it's Bayesian analogue) then it would be helpful to derive centre specific odds ratios and confidence intervals for display in a forest plot.

This is especially relevant to making generalizations over the entire population of centres in France. page 11, line 38. In accordance with my suggestion about interaction between centre and time of day, it would be informative to further stratify this table by time of day.

Response : As suggested, we have included an interaction term (a random effect) between center and time of day:

- As indicated in figure 3, a random effect analysis, without adjusting for individual variables showed an OR of 1.36 [1.17-1.59]. There was significant center variability associated with the time of day effect. (The between-center Tau-Squared was 0.06). As suggested, we have added a forest plot (figure 3)

- Given the results of above analyses, we have decided to include a random effect between center and time of day in the multilevel model. As described in the materials and methods section (on page 10), this hierarchical model had three levels: level 1 was procedures, level 2 was children and level three was centers. We included a random effect for time of day at both children and center levels. The variance of the random effect for center was 0.04 [0.01-0.13] and for children was 0.30 [0.21-0.44]. As requested, we stratified Table 4 by time of day. Because of the number of tables, we suggest to include this table in the appendix.

Reviewer : page 11, line 50. Figure 3 is partly redundant, as it includes the overall percentages for the 5 procedures, which were reported in the Abstract (though not in the Results). It is not clear why only two of the 5 procedures are described. I would suggest re-iterating the overall percentages in the text and providing procedure specific findings for all 5 procedures in the figure.

Response : We have modified this figure as requested. The overall percentages are reported in the Abstract and in the results section of the text (on page 11).

Reviewer : page 12, line 21. To be transparent about which factors and/or interactions were included in the model, a table of corresponding odds ratios, with confidence limits, should be provided.

Response : We have added in the appendix section a table of corresponding odds ratios of factors and interactions used in the model (appendix 3).

Reviewer : page 12, line 26. Note that the this pattern is not merely attenuated, but in fact is reversed when parents are present.

Response : We added a sentence in the results section to note this point. (on page 12)

Reviewer : page 12, line 46. This observation is not supported by the data. There is a sharp decrease from morning to afternoon followed by a gentle (and possibly non-significant) decline.

Response : We have modified the sentence as requested in the discussion section on page 13

Reviewer : page 14, line 30. This statement is not justified unless an examination of centre-specific daytime/night-time odds ratio over centres indicates such homogeneity.

Response : We have modified this sentence and noted that time of day effect varied across centers on page 13. (The extrapolation of these results...)

Reviewer : page 15, line 12. Parental presence actually reverses the effect.

Response : This has been mentioned in the result section on page 12.

Because of the number of table and figures, Figure 2 is suggested as Appendix 1 and table 3 is suggested as Appendix 2. (so previous figure 3 is now figure 2 in revised submission and previous table 4, 5 and 6 becomes respectively table 3, 4 and 5.)