PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Incidence of Adverse Events in Pediatric Procedural Sedation in the Emergency Department: A systematic review and meta-analysis
AUTHORS	Bellolio, M. Fernanda; Puls, Henrique; Anderson, Jana; Gilani, Waqas; Murad, M. Hassan; Barrionuevo, Patricia; Erwin, Patricia; Wang, Zhen; Hess, Erik

VERSION 1 - REVIEW

REVIEWER	Stacy Reynolds Carolinas Medical Center and Levine Children's Hospital 1000 Blythe Blvd. Medical Education Building, Suite 306-B Charlotte, NC 28203 United States
REVIEW RETURNED	25-Feb-2016

GENERAL COMMENTS	Project Summary: The authors compiled a systematic review and meta-analysis of the reported incidence of adverse events during procedural sedation for children undergoing moderate to deep sedation in the emergency department. The paper provides useful and relevant data and is well organized and transparent. The authors performed a thoughtful review with careful attention to the PRISMA checklist. The decision to use a random effects model is supported. The transparent acknowledgement of the high clinical and statistical heterogeneity with a clear rationale for pooling the data is provided. Opportunities to strengthen the review: A few minor revisions would strengthen the review. Methods: The authors state that individual authors were contacted to obtain missing data. Missing data were classified as "unclear" if they were not subsequently available. It is unclear from the methods how this impacted the analysis. Were adverse events for key outcomes missing in parts of the data set? It would be helpful to consistently report the denominator of total patients rather than exclusively an adverse event incidence per 1,000 patients. This is done for some outcomes but not for others in the current paper. Discussion of limitations: The search strategy is comprehensive for published literature. It is not clear that the authors explored the grey literature and sources in languages other than English. This should be acknowledged in the limitations of the paper. Publication bias should also be acknowledged in the limitations based on the search strategy.

	Supplemental reporting: Was the trial registered on PROSPERO previously? If so, this should be stated in the methods as it would strengthen the review.

REVIEWER	Mr Daniel Cohen Pennine Acute NHS Trust, UK
REVIEW RETURNED	27-Feb-2016

GENERAL COMMENTS	The study is well designed and presented. Your anticipation of results stated in the introduction clearly identifies the potential use of the study. In addition to the limitations you have specified, another limitation worth highlighting is that the studies analysed included patients under 18 years of age, which would have included children who were physiologically adults.

REVIEWER	Juan Carlos Rivillas Research Award Recipient Maternal and Child Health Program, International Development Research Centre IDRC, Canada
REVIEW RETURNED	01-Mar-2016

GENERAL COMMENTS	This paper systematic review under (PRISMA) statement and meta-analysis to evaluate the incidence of adverse events in the Emergency department (ED) during procedural sedation in the pediatric population (Adverse events like vomiting, agitation, hypoxia and apnea). It is based on a designed and conducted comprehensive search of eight electronic databases over the last 10 years: Ovid MEDLINE, Ovid EMBASE, EBSCO CINAHL, Ovid CENTRAL, Ovid Cochrane Database of Systematic Reviews. The main strength of the paper is the appropriate use of the method to carry out a proper systematic review and processing of 258 selected studies through a meta-analysis rigorously well developed. However, the importance and interest of topic is fairy developed. But overall, the Adequacy of the research method and accuracy of data analysis is very good. It is important to highlight the grammatical construction; writing style and clarity of idea, these are characterized by having a very appropriate way, even for me that I don't know broadly the field. Statistics used in the meta-analysis and the software procedures are appropriate and described fully. Finally, the use of references and resources available to develop a systematic reviews and meta-analysis is very good, how it is described, this analytical model can be easily verifiable and reproducible. One of the intentions of such studies.

REVIEWER	Orestis Efthimiou University of Ioannina
REVIEW RETURNED	09-Mar-2016

GENERAL COMMENTS	1. I have some concerns about the statistical method that the authors used for their meta-analyses. They say that they "used "OpenMetaAnalyst" software for meta-analyses using a random effects model as described by DerSimonian-Laird". Note that what

	the authors are describing is not a usual meta-analysis of relative treatment effects. They meta-analyze incidence rates (absolute effects), and also note that the event rates are very low. Applying the usual inverse variance method for meta-analysis in such an instance may be problematic. I refer the authors to the following article where a more robust method is described: Meta-analysis of prevalence, Jan J Barendregt, Suhail A Doi, Yong Yi Lee, Rosana E Norman, Theo Vos, J Epidemiol Community Health 2013;67:11 974-978 Published Online First: 20 August 2013 doi:10.1136/jech-2013-203104. http://jech.bmj.com/content/67/11/974.short 2. Page 16, it writes: “Sources of clinical heterogeneity included variable sample size…”. I do not understand this statement. Why should sample size affect the event rate? Note that you are synthesizing rates, not the absolute number of events (which is of course proportional to the sample size). Why should a larger study have a larger/smaller event rate? 3. The original studies are included in the meta-analysis per arm, i.e. the authors consider every arm of each study as if it was a separate study to be included in the meta-analysis. E.g. in figure 2 Koo 2013 has six entries. Obviously, given that these arms correspond to the same population, settings etc., they give very similar results and they are correlated. E.g. Oktay 2005 provides 2 estimates in this graph, and they are both to the far right. Disregarding such correlations by including each arm in the meta-analysis as if they were independent observations drives the estimate for heterogeneity down and artificially decreases CI of the pooled estimate (for a random effects meta-analysis). I think that studies like Koo (entering multiple times in a subgroup) could be better collapsed into a single entry. 4. In the discussion section it writes “The RCTs reported higher incidences of adverse events; this is likely due to more rigorous data collection procedures than in observational studies.” Could it also be due to differences in population characteristics? RCTs usually have strict inclusion criteria (e.g. more severe patients?). If this is not the case in this review please disregard this comment. 5. In the forest plots: 95% CIs should be truncated to zero. Event rate is a number between 0 and 1, so there is no point in having negative values in the CIs. 6. In the forest plots: there are some studies that seem to be extreme outliers. For example, in figure 2 the pooled rate is 1.8% but there is a study Ghane 2012 that reports 67%. Likewise Oktray 2005 etc. Such differences are huge, may be due to reasons other than chance alone, and should be further explored or at the very least they should be discussed. For example, for the agitation outcome the authors note in the discussion: “Agitation occurred in 1.8% of children undergoing PSA in the ED. This was seen most frequently with midazolam on nearly 20% of sedations”. This statement is actually driven by the Ghane 2012 study alone; all other midazolam studies had few events. Thus, a comment about Ghane 2012 specifically would be more appropriate I think. 7. The observed heterogeneity in hypoxia and vomiting outcomes is very large, and I am wondering if pooling the incidence rates is clinically meaningfull. E.g. for hypoxia, subgroup Etomidate is remarkably different than all other groups, it might be more

	appropriate to include it in a seperate meta-analysis?

VERSION 1 – AUTHOR RESPONSE

Reviewer #1
Stacy Reynolds

Please leave your comments for the authors below
Project Summary: The authors compiled a systematic review and meta-analysis of the reported incidence of adverse events during procedural sedation for children undergoing moderate to deep sedation in the emergency department. The paper provides useful and relevant data and is well organized and transparent. The authors performed a thoughtful review with careful attention to the PRISMA checklist. The decision to use a random effects model is supported. The transparent acknowledgement of the high clinical and statistical heterogeneity with a clear rationale for pooling the data is provided.

Opportunities to strengthen the review:
A few minor revisions would strengthen the review.

Methods: The authors state that individual authors were contacted to obtain missing data. Missing data were classified as "unclear" if they were not subsequently available. It is unclear from the methods how this impacted the analysis. Were adverse events for key outcomes missing in parts of the data set?
It would be helpful to consistently report the denominator of total patients rather than exclusively an adverse event incidence per 1,000 patients. This is done for some outcomes but not for others in the current paper.
-Thank you for your comments. When data was not provided we excluded the patients from the denominator, example: Among 13,883 sedations 6,215 had data available on apnea, 1,315 on bradycardia, etc.
In the tables we reported the absolute number of events per patients. We used rates per 1,000 to be able to compare the events between medications and standardize the measurements.

Discussion of limitations: The search strategy is comprehensive for published literature. It is not clear that the authors explored the grey literature and sources in languages other than English. This should be acknowledged in the limitations of the paper. Publication bias should also be acknowledged in the limitations based on the search strategy.
-Thank you for your comments. We only looked at peer-reviewed sources as cited. Non-medical literature (grey literature) was not searched. We did not apply language restriction in the search. This was added to the methods and limitations.

Supplemental reporting: Was the trial registered on PROSPERO previously? If so, this should be stated in the methods as it would strengthen the review.
-We wrote a protocol prior to the initiation of the trial, however we did not register it in PROSPERO.

Reviewer: 2
Mr Daniel Cohen

Please leave your comments for the authors below
The study is well designed and presented. Your anticipation of results stated in the introduction clearly identifies the potential use of the study.

In addition to the limitations you have specified, another limitation worth highlighting is that the studies analysed included patients under 18 years of age, which would have included children who were physiologically adults.
-Thank you for your comments. We added the age restriction into the limitation section.

Reviewer: 3
Juan Carlos Rivillas

Please leave your comments for the authors below
This paper systematic review under (PRISMA) statement and meta-analysis to evaluate the incidence of adverse events in the Emergency department (ED) during procedural sedation in the pediatric population (Adverse events like vomiting, agitation, hypoxia and apnea). It is based on a designed and conducted comprehensive search of eight electronic databases over the last 10 years: Ovid MEDLINE, Ovid EMBASE, EBSCO CINAHL, Ovid CENTRAL, Ovid Cochrane Database of Systematic Reviews. The main strength of the paper is the appropriate use of the method to carry out a proper systematic review and processing of 258 selected studies through a meta-analysis rigorously well developed.

However, the importance and interest of topic is fairy developed. But overall, the Adequacy of the research method and accuracy of data analysis is very good. It is important to highlight the grammatical construction; writing style and clarity of idea, these are characterized by having a very appropriate way, even for me that I don't know broadly the field. Statistics used in the meta-analysis and the software procedures are appropriate and described fully. Finally, the use of references and resources available to develop a systematic reviews and meta-analysis is very good, how it is described, this analytical model can be easily verifiable and reproducible. One of the intentions of such studies.
-Thank you for your comments.

Reviewer: 4
Orestis Efthimiou

Please leave your comments for the authors below
1. I have some concerns about the statistical method that the authors used for their meta-analyses. They say that they "used "OpenMetaAnalyst" software for meta-analyses using a random effects model as described by DerSimonian-Laird". Note that what the authors are describing is not a usual meta-analysis of relative treatment effects. They meta-analyze incidence rates (absolute effects), and also note that the event rates are very low. Applying the usual inverse variance method for meta-analysis in such an instance may be problematic. I refer the authors to the following article where a more robust method is described: Meta-analysis of prevalence, Jan J Barendregt, Suhail A Doi, Yong Yi Lee, Rosana E Norman, Theo Vos, J Epidemiol Community Health 2013;67:11 974-978 Published Online First: 20 August 2013 doi:10.1136/jech-2013-203104.
http://jech.bmj.com/content/67/11/974.short
-We appreciate the reviewer comment regarding the software and methodology utilized. Prior to the conduction of the study we discussed the appropriate approach with our team methodologist Dr. M. Hassan Murad, and agree with the current used software and methodology used.

In OpenMeta software we used binary-random effects. We did not use binary-fixed effects or inverse variance. We agree with the reviewer that these methods are less conservative and more problematic.

We agree with the reviewer that when the events are infrequent (like in laryngospasm) it is better to

report the raw numbers rather than pulling in the meta-analysis. Uncommon events were reported as absolute events.

Transformation of proportions are to normalize the point estimate (the proportion after transformation). The methods to pool the point estimate and standard errors are the same.
As per reviewer suggestion, we run again the analyses using absolute proportion, maximum likelihood and empirical Bayes instead of DerSimonian-Laird.
See below the table with the results for the outcome of agitation and intubation with the different methods.

Absolute proportion (per 1,000) DerSimonian-Laird (used in the manuscript) Maximum likelihood Empirical Bayes
Agitation 175/7,226= 24.2 17.9 (12.2-23.7) I2=74.7 13.9 (9.7-18.1) I2=51.7 43.3 (18.3-68.2) I2=99.1
Intubation 4/9136=0.4 0.4 (0-0.8) I2=0 0.4 (0-0.8) I2=0 0.4 (0-0.8) I2=0

We read the recommended article and performed an analysis using arcsine transformation for uncommon events. Please note that the use of arcsine transformation is considered controversial (Warton DI, Hui FK. The arcsine is asinine: the analysis of proportions in ecology. Ecology. 2011 Jan;92(1):3-10. PubMed PMID: 21560670.) http://www.ncbi.nlm.nih.gov/pubmed/21560670

Using Freeman-Tukey Double Arcsine Transformation we obtained the following results:
Absolute proportion (per 1,000) DerSimonian-Laird (used in the manuscript) Freeman-Tukey Double Arcsine Transformation
Agitation 175/7,226= 24.2 17.9 (12.2-23.7) I2=74.7 25.9 (15.2-38.7) I2=84.0
Intubation 4/9136=0.4 0.4 (0-0.8) I2=0 0 (0-0) I2=0

2. Page 16, it writes: “Sources of clinical heterogeneity included variable sample size…”. I do not understand this statement. Why should sample size affect the event rate? Note that you are synthesizing rates, not the absolute number of events (which is of course proportional to the sample size). Why should a larger study have a larger/smaller event rate?
-Sorry for the misunderstanding. We meant that there were studies with large sample sizes and studies with small sample sizes. Agree with the reviewer that the size of the study should not affect the rates per se.

3. The original studies are included in the meta-analysis per arm, i.e. the authors consider every arm of each study as if it was a separate study to be included in the meta-analysis. E.g. in figure 2 Koo 2013 has six entries. Obviously, given that these arms correspond to the same population, settings etc., they give very similar results and they are correlated. E.g. Oktay 2005 provides 2 estimates in this graph, and they are both to the far right. Disregarding such correlations by including each arm in the meta-analysis as if they were independent observations drives the estimate for heterogeneity down and artificially decreases CI of the pooled estimate (for a random effects meta-analysis). I think that studies like Koo (entering multiple times in a subgroup) could be better collapsed into a single entry.
-Thank you for your comments. That is correct, we entered each study arm as a separate study to be able to analyze by different treatment arm. The cohorts did not overlap, so the patients were not counted twice in the analyses. Because the each study arm received different medications and had different events, we included them as separate cohorts.

Following reviewer suggestions we performed an analysis with the groups collapsed per study. This analysis does not allow us to compare different medications, so the data was not changed in the main

manuscript, but it is here for review.

For the outcome of agitation (175 events in 7,226 sedations) when the studies were collapsed and medication used was not into account the pooled estimate was 23.0 (15.3 to 30.8) per 1,000 sedations, I-square 85% compared to 17.9 (12.2 to 23.7) per 1,000, I-square 75%.
For the outcome of intubation (4 events in 9,136 sedations) when the studies were collapsed and medication used was not into account the pooled estimate was 0.3 (0 to 0.7) I squared 0% compared to 0.4 (0 to 0.8) per 1,000, I-square 0%.

A sentence was added in the limitation section regarding within study correlation based on separating the arms per medication.

4. In the discussion section it writes “The RCTs reported higher incidences of adverse events; this is likely due to more rigorous data collection procedures than in observational studies.” Could it also be due to differences in population characteristics? RCTs usually have strict inclusion criteria (e.g. more severe patients?). If this is not the case in this review please disregard this comment.
- Yes, the reviewer is right. Different population characteristics could also account for this difference. Thank you for the comment. This was added to the manuscript.

5. In the forest plots: 95% CIs should be truncated to zero. Event rate is a number between 0 and 1, so there is no point in having negative values in the CIs.
-Thank you for your comment. Yes, we agree. We did not want to manipulate the axis of the plots for transparency. The software we used does not truncate at 0, however we agree with your comment.

6. In the forest plots: there are some studies that seem to be extreme outliers. For example, in figure 2 the pooled rate is 1.8% but there is a study Ghane 2012 that reports 67%. Likewise Oktray 2005 etc. Such differences are huge, may be due to reasons other than chance alone, and should be further explored or at the very least they should be discussed. For example, for the agitation outcome the authors note in the discussion: “Agitation occurred in 1.8% of children undergoing PSA in the ED. This was seen most frequently with midazolam on nearly 20% of sedations”. This statement is actually driven by the Ghane 2012 study alone; all other midazolam studies had few events. Thus, a comment about Ghane 2012 specifically would be more appropriate I think.
-Thank you for your comments. We agree with the suggestion. A paragraph was added regarding these outliers.
The study by Ghane et al. reported sedation with intramuscular injection of midazolam in an emergency department in Iran. The authors report euphoria in 66.6% of the children and in their discussion acknowledge the high incidence of agitation and repot that could be secondary to the race of the patients.
The study by Oktay et al was performed in an ED in Turkey. They report 34 cases of recovery agitation including agitation, hallucinations, dysphoria, pleasant and unpleasant dreams. The incidence was similar in the group with ketamine alone versus ketamine plus midazolam.

7. The observed heterogeneity in hypoxia and vomiting outcomes is very large, and I am wondering if pooling the incidence rates is clinically meaningful. E.g. for hypoxia, subgroup Etomidate is remarkably different than all other groups, it might be more appropriate to include it in a separate meta-analysis?
-There are several possible sources of variability or heterogeneity among studies that are included in meta-analyses. Variability in the participants, the types or timing of outcome measurements, and intervention characteristics may be termed clinical heterogeneity; variability in the trial design and quality is typically termed methodological heterogeneity; variability in summary treatment effects between trials is termed statistical heterogeneity. Methodological and clinical sources of heterogeneity

contribute to the magnitude and presence of statistical heterogeneity. Significant statistical heterogeneity arising from methodological heterogeneity suggests that the studies are not all estimating the same effects due to different degrees of bias.

Clinical heterogeneity arises from differences in participant characteristics (e.g., sex, age, baseline disease severity, ethnicity, comorbidities), types or timing of outcome measurements, and intervention characteristics (e.g., dose and frequency of dose). This heterogeneity can cause significant statistical heterogeneity, inaccurate summary effects and associated conclusions, misleading decision makers and others.

Systematic reviews commonly show substantial heterogeneity in estimated effects (statistical heterogeneity), possibly due to methodological, clinical or unknown features in the included trials. To handle sources of heterogeneity we preplanned subgroup analyses by medication utilized during the procedural sedation and by study type (randomized controlled trial versus observational). We included all children and this could have introduced bias as some teenage children have physiology more similar to adults than toddlers.

We acknowledge greater heterogeneity in some outcomes, however we decided was appropriate to pool, as the clinical heterogeneity was similar to what we will see in clinical practice. Some physicians will prefer to use etomidate for short sedations, others will prefer ketamine. It will depend on the medications available in each emergency department and the comfort level of the provider with the medication for sedation.

Gagnier JJ, Moher D, Boon H, Beyene J, Bombardier C. Investigating clinical heterogeneity in systematic reviews: a methodologic review of guidance in the literature. BMC Med Res Methodol. 2012 Jul 30;12:111. PubMed PMID: 22846171; PubMed Central PMCID: PMC3564789.

Glasziou PP, Sanders SL. Investigating causes of heterogeneity in systematic reviews. Stat Med. 2002 Jun 15;21(11):1503-11. PubMed PMID: 12111916.

Cochrane Handbook for Systematic Reviews of Interventions. Version 5.0.1. Edited by Higgins JPT, Green S.: The Cochrane Collaboration; 2008. Available from www.cochrane-handbook.org.

VERSION 2 – REVIEW

REVIEWER	Stacy Reynolds, MD Carolinas Medical Center, Department of Emergency Medicine Charlotte, NC United States
REVIEW RETURNED	26-Apr-2016

GENERAL COMMENTS	Introduction: Despite the advances in monitoring and medication selection, there is no one single “safe” and “risk-free” medication to perform PSA with--- I would reword this to Despite the advance in monitoring and medication selection, there is no single "safe" and "risk-free" medication for PSA. Discussion: We found no events of agitation with etomidate, however the metaanalysis included only 2 small studies.--- I would use meta-analysis instead.

REVIEWER	Juan Carlos Rivillas International Development Research Centre
REVIEW RETURNED	14-Apr-2016

GENERAL COMMENTS	The study provide information in terms of each step and methods to address the research question posed. Types of studies, types of patients; types of interventions, outcomes measures, data extraction, etc and all details are completely described and allow to replicate this systematic review properly and anytime for other researchers interested in the model or in the field. However it is important specify if the children are under 18 years old or older to provide a completed abstract. Comments review 1. Is the research question or study objective clearly defined? Yes. The paper addresses a large systematic review and meta-analysis to determine the incidence of adverse events during PSA in children in the ED, including the frequency of events associated with individual drugs and different drug combinations 2. Is the abstract accurate, balanced and complete? Yes, it is. However it is important specify if the children are under 18 years old or older to provide a completed abstract. 3. Is the study design appropriate to answer the research question? Yes, the study provide information in terms of each step and methods to address the research question. 4. Are the methods described sufficiently to allow the study to be repeated? Yes, it is. Types of studies, types of patients; types of interventions, outcomes measures, data extraction, etc are completely described and allow to replicate this systematic review properly. 5. Are research ethics (e.g. participant consent, ethics approval) addressed appropriately? Yes. Any ethic requirement has been attended successfully. 6. Are the outcomes clearly defined? Yes, they provide a brief and concrete description for any outcome and before the discussion vert well. 7. If statistics are used are they appropriate and described fully? Yes. 8. Are the references up-to-date and appropriate? Yes, references are updated and under international standards. 10. Are they presented clearly? Yes. 11. Are the discussion and conclusions justified by the results? Yes, as discussion as well methods are connected and very well justified without lost any detail. 12. Are the study limitations discussed adequately? Yes.

	They are properly described in this study. 14. To the best of your knowledge is the paper free from concerns over publication ethics (e.g. plagiarism, redundant publication, undeclared conflicts of interest)? No any. 15. Is the standard of written English acceptable for publication? No needed to be edited by an English speaker.

REVIEWER	Orestis Efthimiou University of Ioannina, Greece
REVIEW RETURNED	08-Apr-2016

GENERAL COMMENTS	Just a few minor comments. One of my previous comments was that: " In the forest plots: 95% CIs should be truncated to zero. Event rate is a number between 0 and 1, so there is no point in having negative values in the CIs." The authors replied: "Thank you for your comment. Yes, we agree. We did not want to manipulate the axis of the plots for transparency. The software we used does not truncate at 0, however we agree with your comment" I am not sure I understand the author's reasoning. Some of the graphs are actually truncated to zero, (figures 3, 4, 5, 8), while figures 2, 6, 7 and 10 are not truncated, and include negative values. I don't understand why truncating all figures to positive values would lead to less transparent results. Page 7 ,last line: please correct the typo (first letter of "included" is in bold) Page 12, first line: please correct the typo Page 13, line 49: you write "…and repot that could be secondary to the race of the patients". Correct "repot" to "report". Also I am not sure I understand this sentence, are you sure you meant "race" and not "age"? Would the race of the patients have such a dramatic effect? Also, instead of "secondary" maybe you meant to write "due to" or something similar. So you maybe meant "… and report that this might be due to the age of the patients"? Apologies if I have misunderstood something.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 4
Orestis Efthimiou

Just a few minor comments.

One of my previous comments was that:
" In the forest plots: 95% CIs should be truncated to zero. Event rate is a number between 0 and 1, so

there is no point in having negative values in the CIs."
The authors replied: "Thank you for your comment. Yes, we agree. We did not want to manipulate the axis of the plots for transparency. The software we used does not truncate at 0, however we agree with your comment"
I am not sure I understand the author's reasoning. Some of the graphs are actually truncated to zero, (figures 3, 4, 5, 8), while figures 2, 6, 7 and 10 are not truncated, and include negative values. I don't understand why truncating all figures to positive values would lead to less transparent results.
Thank you for your comment. The figures are created by automatically by the software (OpenMeta Analyst, an open source R-based software), and I tried to re do the figures but still there were negative values. The plots created with subgroup (medication categories) were not truncated to zero (Figures 2,6,7 and 10).
Personally I think keeping the original figures created by the software is better to keep the integrity of the data. If the editor and reviewer prefers we can manually edit the figures and delete the negative values.

Page 7 ,last line: please correct the typo (first letter of "included" is in bold)
Thank you, this was corrected.

Page 12, first line: please correct the typo
Thank you, this was corrected.

Page 13, line 49: you write "…and repot that could be secondary to the race of the patients". Correct "repot" to "report". Also I am not sure I understand this sentence, are you sure you meant "race" and not "age"? Would the race of the patients have such a dramatic effect?
Thank you, "report" was edited.
The original study from a cohort in Iran reports that the high rate of agitation could be secondary to race. The authors do not elaborate more on why the racial background could affect this, and cite other papers. See Original article: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4004986/

Also, instead of "secondary" maybe you meant to write "due to" or something similar. So you maybe meant "… and report that this might be due to the age of the patients"? Apologies if I have misunderstood something.
Agree, this was changed to "due" thank you.

Reviewer: 3
Juan Carlos Rivillas

The study provide information in terms of each step and methods to address the research question posed. Types of studies, types of patients; types of interventions, outcomes measures, data extraction, etc and all details are completely described and allow to replicate this systematic review properly and anytime for other researchers interested in the model or in the field. However it is important specify if the children are under 18 years old or older to provide a completed abstract.
This was edited in the abstract, thank you.

Reviewer: 1
Stacy Reynolds, MD

Introduction: Despite the advances in monitoring and medication selection, there is no one single “safe” and “risk-free” medication to perform PSA with---
I would reword this to Despite the advance in monitoring and medication selection, there is no single "safe" and "risk-free" medication for PSA.
Thank you, this was edited.

Discussion: We found no events of agitation with etomidate, however the metaanalysis included only 2 small studies.---
I would use meta-analysis instead.
Agree, thank you, this was edited.