PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Ketamine for the treatment of prehospital acute pain: a systematic review of benefit and harm
AUTHORS	Sandberg, Mårten; Hyldmo, Per Kristian; Kongstad, Poul; Dahl Friesgaard, Kristian; Raatiniemi, Lasse; Larsen, Robert; Magnusson, Vidar; Rognås, Leif; Kurola, J; Rehn, Marius; Vist, Gunn Elisabeth

VERSION 1 – REVIEW

REVIEWER	Evan Schwarz Washington University School of Medicine United States
REVIEW RETURNED	30-Mar-2020

GENERAL COMMENTS	Thanks for putting the work into this study. I think you ask an important question that should be addressed. My major issue is the inclusion of some of the studies. I'm not sure why you would include a study that compared ketamine by itself to nothing. I think we already know that ketamine has analgesic properties so the proper comparison would be to something else unless it is like ketamine and an opioid to just an opioid. Also probably limiting studies to those whose main purpose is to look at analgesic based ketamine is probably most important as those studies are going to likely be best designed to answer your question. abstract: page 3, results: Would be helpful to include some number here aside from just stating pain was significantly reduced. Pain scores can be statistically significantly different but not clinically meaningful. page3, conclusion: Would probably just limit this to it being an effective analgesic as I'm not sure you truly prove that it is safe, although I do agree that it is safe. Intro: In general, a lot of this can be cut down as it gets in to a lot of extraneous detail. Really should focus on why this is an important question. So why does this matter? Can't we just continue to use opioids pre-hospital? I think that should be the focus of the intro establishing why your study is important. Some of what is included could be used to introduce that thought or as part of building your case for why this is an important question. page 5, lines 31-34; I'm not sure this is correct. I'd say in many places there is a well established dosing for analgesic based ketamine, generally 0.1-0.3 mg/kg and maybe up to 0.5 mg/kg. page 5, line 39-40: While this may be true, I'd say losing consciousness from a very low dose is very unlikely. Can get

	neuropscyho side effects for sure but LOC is rare and this should probably be noted if including this line. page 5, line 51: Probably need to clarify about rapid injection. Kind of an odd sentence as sentence before discusses its safety. I'd reword to say someting such as that while generally preserves respiratory function if pushed quickly can cause respiratory depression. page 5, lines 55-56: Really much more of an issue for sedation than pain. And even then, we generally don't give antisialogogue prior to ketamine even for sedations anymore. Methods: I'd honestly exclude the ketamine vs no ketamine study that also uses pentazocine. I don't think it is truly an applicable study. Also the ones looking at the PSS and focusing on mortality don't really make sense for this review either and would consider excluding them as well since they really don't offer much about pain. Could include in the discussion when comparing adverse effects to what is seen in other literature you didn't include. page 7, outcomes: These need to be defined. What did you mean by pain reduction, duration of effect, etc? page 7, population: Define adults page 7, lines 37-38: What does this mean? How did you identify these groups? page 7, line 49: Define children page 7: Does this mean case reporters were included? page 9, line 3: Was this done with a priori with a premade data collection tool? Was it piloted? Was there overlap between articles to generate a kappa for data that was pulled by different authors to make sure it was done accurately? Results: Overall, a little hard to read and follow as after reading it was still confusing if ketamine was any good as an analgesic. This as more clear when looked at the figures. page 10, lines 16-17: Can likely be included in the preceding paragraph. page 11, lines 8-14: This paragraph is unnececcary and I'd honestly exclude study 34 as 1) comparing against nothing is ridiculous and 2) comparing to pentazocine is also a fairly useless comparator page 11, lines 19026: Would be helpful to include the actual reduction, either at least found in each study or your result when you combined the studies or both. page 11, lines 29-36: I don't think any of this answers your question. At least I'm assuming the change of 1.5 referred to the PSS which is not helpful to the main point of your study. If you wanted to, you could discuss this study in your discussion as further proof that ketamine is as safe as opioids. page 11, lines 40-43: Only 1 study included adverse events? The others ones didn't? Overall, I think it is likely clearer to say that adverse events were found (maybe how often) in the studies in this subsection and then refer to a table where all the adverse events can be placed in it. page 12, lines 3-17: Please include actual numbers of change in pain scores and what the combined meta analysis found here. page 12, lines 21-23; I'm not sure what the significance of pointing out nausea and vomiting here is. page 12, lines 36-39: Did they report the time that the boluses were given over? What I'm getting at is this a question of

	ketamine's efficacy (i.e. it didn't work well or last long) or that some transports were longer so it would make sense to have to give more pain medication. page 12, line 45; What is meant by shorter treatment time? What does this refer to? Time in ambulance? Time between dosing? What? page 13, lines 15-19: Regarding the different scoring systems, you explain them multiple times. Can probably just in the methods discuss the pain scores and how they work so don't need to keep repeating this. page 13 lines 36-45; I'd exclude this study as really isn't helpful to guide management. Discussion: Much of this discussion is repetitive to the results. I'd reconfigure it based on what you really want to talk about and highlight in your study and go into more depth about how your study compares to other studies and why the comparisons are relevant. Right now it just reads as very much a repetition of the results. page 16, lines 12-13: True, but were they as significant as the adverse events from opioids? page 16, lines 24-27: While I agree, I think it is important to note that there were not enough patients, nor did it appear that the studies were designed, to truly test the safety of ketamine. page 16, lines 50-51: What is the relevance of this sentence? It doesn't really connect to the rest of the paragraph and is somewhat irrelevant. page 16-17; I'd go into more depth about these different reviews and studies to discuss why they did or did not find the same results as you and what the significance of that all is. Conclusion: page 17, lines 32-33: I'd limit this to the efficacy as you really don't have the power to make conclusions about the safety, although I do agree that tit is safe.

REVIEWER	Sergey Motov Maimonides Medical Center, USA
REVIEW RETURNED	24-Apr-2020

GENERAL COMMENTS	Excellent SR! Thank you!

REVIEWER	Lucas Oliveira J. e Silva Mayo Clinic, United States.
REVIEW RETURNED	21-Jul-2020

GENERAL COMMENTS	I read with great interest the systematic review performed by Sandberg and coworkers. This is an extremely important topic as the use of ketamine for treatment of acute pain is progressively increasing and a systematic evaluation of currently available evidence is paramount. While the authors performed a comprehensive literature review, there are several issues that need to be addressed as described below. (1) In the Methods, Page 8, Line 34, authors report that study selection was based on full text and risk of bias assessment. However, it is not clear if authors excluded studies based on low versus high risk of bias. It seems that studies were not excluded based on risk of bias. I'd suggest clarifying this in the Methods.

	(2) In the Methods, page 7, line 40, it is described that systematic reviews were eligible for inclusion. I'd suggest clarifying that original reports included in previous systematic reviews were considered rather than the inclusion of systematic reviews. (3) When evaluating adverse events between ketamine and another comparison group (eg. opioids), I'd suggest that authors follow the PRISMA harms checklist (http://prisma-statement.org/documents/Prisma%20Harms%20BMJ.pdf). I'd suggest that authors be consistent in the nomenclature and reporting of adverse events throughout the manuscript. I'd suggest that authors define adverse events designations (serious vs. non-serious) and report consistently throughout the Results. For example, in the Methods it is described that "emergence phenomena" is part of "relevant adverse effects" and in the Results, there are studies reporting "agitation". As agitation may be part of emergence phenomena, the definition and reporting needs to be clarified in the Methods as well as in the Results. (4) As outcomes were reported in different manners and sometimes not reported at all, I'd suggest that the authors clarify in the Methods whether study investigators were contacted to provide information not described in the original manuscripts. (5) While for all comparisons the studies reported the outcome of change in pain score, it is not clear what timeframe was considered for each. I'd suggest clarifying the timeframe that change in pain score was evaluated. For instance, one study may have evaluated pain reduction in 15 minutes versus 30 minutes of medication administration, and the results may be significantly different based on timeframe. Timeframe was only mentioned in the comparison between ketamine and nitrous oxide vs. nitrous oxide alone. I'd suggest clarifying the timeframe in which change in pain score was measured throughout all comparisons. The same clarification for other outcomes is also important. For example, it is unclear when "change in Glasgow coma scale" was measured. This information is especially useful for future researchers who want to design future studies. (6) In the Results, risk of bias assessments for observational and randomized controlled trials are presented together. I'd suggest that the authors present it separately given the fact that these two designs have significantly different criteria for the assessment of risk of bias. Also, I'd suggest changing the word "some trials" in Page 10, line 45, to the exact number of studies deemed to have high risk of bias. (7) In the Results, while the authors created forest plots for almost all comparisons, I'd suggest avoiding the presentation of the data in forest plots when the effect estimate is based on only 1 study, especially because these data are repeated in Table 2 (GRADE assessment). For outcomes in which only 1 study reported the effect estimate for the comparison, I'd suggest reporting the actual relative and absolute difference in the Results rather than referring to Figures. (8) In the Results, for the comparison of ketamine versus ketamine and morphine, the authors described that the Swedish study reported a trend for shorter treatment time. One needs to define what "treatment time" is. Also, I'd avoid the word "trend" as this may be misleading. (9) In the Results, in Table 1, it is reported that serious adverse events were reported in both the study from Bronsky et al as well as the study from Tran et al. However, in Table 2, the effect estimate for serious adverse events is presented from only 1 study rather than the two. I'd suggest authors to update Table 2 as well

	as to clarify if there was an absence of events or an absence of reporting. (10) In the Results, GRADE section. The reasons for upgrading or downgrading the certainty in the evidence is not clear for all comparisons in Table 2. For example, for the comparison between continuous vs. bolus ketamine, the estimate for change in pain score is from 1 randomized controlled trial and there is one footnote saying that the sample size of the study was of concern. As in the GRADE approach RCT starts as high certainty, authors need to describe the exact reason for downgrading two levels (e.g. risk of bias and imprecision because of small sample size). I'd suggest to be consistent in the footnotes using the GRADE original terminology. For instance, when certainty was downgraded two levels, provide the exact reason (e.g. "imprecision" as only 50 patients were included, "risk of bias" as there was lack of blinding and lack of allocation concealment). (11) In the Discussion, page 16, the authors initially acknowledged that analgesic doses of ketamine resulted in more non-serious adverse events than opioids alone. However, later in the same page, line 38, they reported that it is unclear whether adverse events are more likely to occur with opioids than with ketamine. I'd suggest to be consistent in the interpretation. For example, while nausea and vomiting seems to be more frequent in patients receiving opioids as compared to ketamine, patients receiving ketamine seems to be more likely to have agitation. I'd suggest to be consistent and clear when it comes to describing the differences of adverse events occurring between comparison groups. (12) In the Discussion, page 16, line 41, I'd suggest avoiding the word "recommendation" as systematic reviews should inform rather than provide recommendations. (13) In the Discussion and in the Conclusion, the authors make an argument about ketamine being administered by trained physicians, however there is no description of who administered ketamine in the included studies. For example, Bronsky et al is a study performed in the USA where physicians often do not work in the pre-hospital setting and non-physician paramedics most likely were responsible for administering ketamine. As the provider training most likely was not evaluated in the included studies, I'd suggest not making the claim that ketamine seems to be safe and effective when administered by providers with "relevant training". There seems to be no such data to support this conclusion from the included studies. However, I think this is an important Discussion point as trained providers most likely know how to deal with severe adverse events. Future studies should maybe evaluate whether provider training increases the safety of ketamine use in the prehospital setting. (14) I'd suggest adding a separate Limitations section. Thank you for the opportunity to review this manuscript.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Thanks for putting the work into this study. I think you ask an important question that should be addressed.

-Many thanks for this kind comment

My major issue is the inclusion of some of the studies. I'm not sure why you would include a study that compared ketamine by itself to nothing. I think we already know that ketamine has analgesic properties so the proper comparison would be to something else unless it is like ketamine and an opioid to just an opioid. Also probably limiting studies to those whose main purpose is to look at analgesic based ketamine is probably most important as those studies are going to likely be best designed to answer your question.

-The study that compares ketamine to nothing also compares ketamine to pentazocine (and pentazocine to nothing), hence, we would include this study for comparison one anyway. Therefore, we suspect this comment is about comparison five rather than about the study per se. We think that even comparison with no treatment is important, because we are interested in both effect and safety. Therefore, we wish to include information about adverse events and side effects from as many patients as possible.

Furthermore, this is what we said in the protocol that we would do.

Abstract: page 3, results: Would be helpful to include some number here aside from just stating pain was significantly reduced. Pain scores can be statistically significantly different but not clinically meaningful.

-Please see response to similar comment above.

Abstract: page3, conclusion: Would probably just limit this to it being an effective analgesic as I'm not sure you truly prove that it is safe, although I do agree that it is safe.

-We agree. The conclusion is revised to not state that ketamine is safe.

Intro: In general, a lot of this can be cut down as it gets in to a lot of extraneous detail. Really should focus on why this is an important question. So why does this matter? Can't we just continue to use opioids pre-hospital? I think that should be the focus of the intro establishing why your study is important. Some of what is included could be used to introduce that thought or as part of building your case for why this is an important question.

-Thank you for making this fair point. We have revised the Introduction aiming for building a clearer case for why we should investigate the effect and safety profile of ketamine. We have included the following statement – “Opioids are most frequently used, but their cerebral, haemodynamic, and respiratory side effects remain a challenge in unstable and undifferentiated prehospital

patients[1]. Ketamine is an alternative to opioids." – informing the reader why it is important to have an alternative to opioids.

Intro: page 5, lines 31-34; I'm not sure this is correct. I'd say in many places there is a well established dosing for analgesic based ketamine, generally 0.1-0.3 mg/kg and maybe up to 0.5 mg/kg.

-We have removed the section pertaining to detailed description of doses.

Intro: page 5, line 39-40: While this may be true, I'd say losing consciousness from a very low dose is very unlikely. Can get neuropscyho side effects for sure but LOC is rare and this should probably be noted if including this line.

-We have removed the section pertaining to detailed description of doses, making the paragraph on LOC superfluous and it was therefore omitted.

Intro: page 5, line 51: Probably need to clarify about rapid injection. Kind of an odd sentence as sentence before discusses its safety. I'd reword to say something such as that while generally preserves respiratory function if pushed quickly can cause respiratory depression.

-We have edited the sentence as requested.

Intro: page 5, lines 55-56: Really much more of an issue for sedation than pain. And even then, we generally don't give antisialogogue prior to ketamine even for sedations anymore.

-We have removed the sentence pertaining to secretions and administration of antisialogogue.

Methods: I'd honestly exclude the ketamine vs no ketamine study that also uses pentazocine. I don't think it is truly an applicable study. Also the ones looking at the PSS and focusing on mortality don't really make sense for this review either and would consider excluding them as well since they really don't offer much about pain. Could include in the discussion when comparing adverse effects to what is seen in other literature you didn't include.

-Please see comment above. We consider that these studies fulfil our inclusion criteria and therefore that they should be included in the review.

Methods: page 7, outcomes: These need to be defined. What did you mean by pain reduction, duration of effect, etc?

Outcomes were not specifically defined in the literature search. Outcomes were included as defined by the study authors. This is now specified in the Methods section.

Methods: page 7, population: Define adults

We defined adults as 18 years of age and above, according to Norwegian hospital definitions. This information has been added to the Methods section.

Methods: page 7, lines 37-38: What does this mean? How did you identify these groups?

We have revised the sentence to better depict that we sought to identify adverse effects that are not previously reported.

Methods: page 7, line 49: Define children

We defined children as 17 years of age and younger, according to Norwegian hospital definitions. This information has been added to the Methods section.

Methods: page 7: Does this mean case reporters were included?

-Case series are included but single case reports are not.

Methods: page 9, line 3: Was this done with a priori with a premade data collection tool? Was it piloted? Was there overlap between articles to generate a kappa for data that was pulled by different authors to make sure it was done accurately?

-The information that were to be collected were predefined in the protocol. We designed a form in Covidence to comply with this list. Then two persons independently filled in and completed the form for each of the included studies. After independent data extraction, the two forms were compared and discrepancies solved by discussion. We did not make kappa calculations.

Results: Overall, a little hard to read and follow as after reading it was still confusing if ketamine was any good as an analgesic. This as more clear when looked at the figures.

-We agree that figures are an effective way of displaying results. We also acknowledge that presenting results from five different comparisons in one article is difficult. However, we think it is important, especially regarding safety, that they be presented together.

Results: page 10, lines 16-17: Can likely be included in the preceding paragraph.

-We have included this sentence in the preceding paragraph.

Results: page 11, lines 8-14: This paragraph is unnececcary and I'd honestly exclude study 34 as 1) comparing against nothing is ridiculous and 2) comparing to pentazocine is also a fairly useless comparator

-Please see response to this suggestion above.

Results: page 11, lines 19026: Would be helpful to include the actual reduction, either at least found in each study or your result when you combined the studies or both.

-We have added: “Figure 3 shows that both studies reported a greater reduction in pain scores with ketamine than with the opioids fentanyl (MD -3.0 (95% CI -3.86 to -2.14)) and morphine (MD -0.4 (95% CI -0.08 to 0.0)).”

Results: page 11, lines 29-36: I don't think any of this answers your question. At least I'm assuming the change of 1.5 referred to the PSS which is not helpful to the main point of your study. If you wanted to, you could discuss this study in your discussion as further proof that ketamine is as safe as opioids.

-We interpret this as a request to exclude the Losvik study. We find that hard to do without violating the study protocol. Please see comments above.

Results: page 11, lines 40-43: Only 1 study included adverse events? The others ones didn't? Overall, I think it is likely clearer to say that adverse events were found (maybe how often) in the studies in this subsection and then refer to a table where all the adverse events can be placed in it.

-Please see comment above. A subsection about adverse events and side effects across the comparisons is now included.

Results: page 12, lines 3-17: Please include actual numbers of change in pain scores and what the combined meta analysis found here.

-Thank you. We have revised this section accordingly.

Results: page 12, lines 21-23; I'm not sure what the significance of pointing out nausea and vomiting here is.

-We have described nausea and vomiting throughout the text and included it here for the sake of consistency.

Results: page 12, lines 36-39: Did they report the time that the boluses were given over? What I'm getting at is this a question of ketamine's efficacy (i.e. it didn't work well or last long) or that some transports were longer so it would make sense to have to give more pain medication.

-The time for administering each bolus was not reported. This information has been added to the Results section.

Results: page 12, line 45; What is meant by shorter treatment time? What does this refer to? Time in ambulance? Time between dosing? What?

-In this study ketamine was administered nasally. «Nasal as opposed to intravenous analgesia may reduce the time spent on the scene of the accident and most likely reduces the need to expose the

patient to the environment in especially challenging cases of prehospital analgesia. « The route of administration is now specified in the manuscript.

Results: page 13, lines 15-19: Regarding the different scoring systems, you explain them multiple times. Can probably just in the methods discuss the pain scores and how they work so don't need to keep repeating this.

-We have revised the sentence and omitted the duplicate explanation of pain scores.

Results: page 13 lines 36-45; I'd exclude this study as really isn't helpful to guide management.

Discussion: Much of this discussion is repetitive to the results. I'd reconfigure it based on what you really want to talk about and highlight in your study and go into more depth about how your study compares to other studies and why the comparisons are relevant. Right now it just reads as very much a repetition of the results.

-Please see comment above regarding excluding studies. The Discussion section has been edited several places to accommodate reviewers requests.

Discussion: page 16, lines 12-13: True, but were they as significant as the adverse events from opioids?

-The section on “Adverse events and side effects” has been revised.

Discussion: page 16, lines 24-27: While I agree, I think it is important to note that there were not enough patients, nor did it appear that the studies were designed, to truly test the safety of ketamine.

- We have added a sentence to the “Strengths and limitations of this systematic review” section that “none of the studies were designed or powered to truly test the safety of ketamine”. Further, a call for studies investigating the safety of ketamine has been included in the end of the Discussion section.

Discussion: page 16, lines 50-51: What is the relevance of this sentence? It doesn't really connect to the rest of the paragraph and is somewhat irrelevant.

-The sentence has been removed

Discussion: page 16-17; I'd go into more depth about these different reviews and studies to discuss why they did or did not find the same results as you and what the significance of that all is.

--We have added a sentence acknowledging that the work from Yousefifard et al echoes our findings. The section also questions transportability of data from the ED-setting to the prehospital arena.

Conclusion: page 17, lines 32-33: I'd limit this to the efficacy as you really don't have the power to

make conclusions about the safety, although I do agree that tit is safe.

-We have edited the conclusion to focus on the efficacy of ketamine and its role in prehospital care.

Reviewer: 2

Excellent SR! Thank you!

-Many thanks for the positive comment

Reviewer: 3

I read with great interest the systematic review performed by Sandberg and coworkers. This is an extremely important topic as the use of ketamine for treatment of acute pain is progressively increasing and a systematic evaluation of currently available evidence is paramount. While the authors performed a comprehensive literature review, there are several issues that need to be addressed as described below.

-Many thanks for the positive comment.

In the Methods, Page 8, Line 34, authors report that study selection was based on full text and risk of bias assessment. However, it is not clear if authors excluded studies based on low versus high risk of bias. It seems that studies were not excluded based on risk of bias. I'd suggest clarifying this in the Methods.

- Thank you pointing out this possible misleading combination. Studies were not excluded based on risk of bias assessments. We have moved the paragraph on use of Covidence for several tasks.

In the Methods, page 7, line 40, it is described that systematic reviews were eligible for inclusion. I'd suggest clarifying that original reports included in previous systematic reviews were considered rather than the inclusion of systematic reviews.

-We have revised this section to accommodate Reviewer`s concerns

When evaluating adverse events between ketamine and another comparison group (eg. opioids), I'd suggest that authors follow the PRISMA harms checklist (http://prisma-statement.org/documents/Prisma%20Harms%20BMJ.pdf). I'd suggest that authors be consistent in the nomenclature and reporting of adverse events throughout the manuscript. I'd suggest that authors define adverse events designations (serious vs. non-serious) and report consistently throughout the Results. For example, in the Methods it is described that "emergence phenomena" is part of "relevant adverse effects" and in the Results, there are studies reporting "agitation". As agitation may be part of emergene phenomena, the definition and reporting needs to be clarified in the Methods as well as in the Results.

-We have revised the terminology according to the checklist and amended accordingly.

As outcomes were reported in different manners and sometimes not reported at all, I'd suggest that the authors clarify in the Methods whether study investigators were contacted to provide information

not described in the original manuscripts.

-A sentence depicting that “We did not contact any study investigators to provide information not described in the original manuscripts” has been added to the Methods section.

While for all comparisons the studies reported the outcome of change in pain score, it is not clear what timeframe was considered for each. I’d suggest clarifying the timeframe that change in pain score was evaluated. For instance, one study may have evaluated pain reduction in 15 minutes versus 30 minutes of medication administration, and the results may be significantly different based on timeframe. Timeframe was only mentioned in the comparison between ketamine and nitrous oxide vs. nitrous oxide alone. I’d suggest clarifying the timeframe in which change in pain score was measured throughout all comparisons. The same clarification for other outcomes is also important. For example, it is unclear when “change in Glasgow coma scale” was measured. This information is especially useful for future researchers who want to design future studies.

-The reported time frame was similar in all studies; i.e. from drug administration to admission to hospital. This is now emphasised in the Results section.

In the Results, risk of bias assessments for observational and randomized controlled trials are presented together. I’d suggest that the authors present it separately given the fact that these two designs have significantly different criteria for the assessment of risk of bias. Also, I’d suggest changing the word “some trials” in Page 10, line 45, to the exact number of studies deemed to have high risk of bias.

-We have updated the RoB Figure to accommodate Reviewer´s concerns. We have also changed this to: “Our assessments regarding each bias domain is provided in figure 2. Three of the five RCTs had a high risk of bias, with the main reasons being lack of random sequence generation, lack of allocation concealment and lack of blinding of patients, personnel and outcome assessors.”

In the Results, while the authors created forest plots for almost all comparisons, I’d suggest avoiding the presentation of the data in forest plots when the effect estimate is based on only 1 study, especially because these data are repeated in Table 2 (GRADE assessment). For outcomes in which only 1 study reported the effect estimate for the comparison, I’d suggest reporting the actual relative and absolute difference in the Results rather than referring to Figures.

-Because several of the included studies reported results for each group only without comparing the groups, we had to calculate the comparison. This we considered a reason in itself to show the forest plots. Additionally, one of the other peer reviewers said that the figures were helpful to interpret the messages. We leave it to the editor to decide if we keep these figures with forest plot including one study or delete them.

In the Results, for the comparison of ketamine versus ketamine and morphine, the authors described that the Swedish study reported a trend for shorter treatment time. One needs to define what “treatment time” is. Also, I’d avoid the word “trend” as this may be misleading.

-See response above regarding this paragraph

In the Results, in Table 1, it is reported that serious adverse events were reported in both the study from Bronsky et al as well as the study from Tran et al. However, in Table 2, the effect estimate for serious adverse events is presented from only 1 study rather than the two. I'd suggest authors to update Table 2 as well as to clarify if there was an absence of events or an absence of reporting.

-Bronsky et al reported four serious adverse events, called so in table 2, footnote b changed to: Downgraded one level for imprecision, only 4 events and all four of them in the same group. There were no events in the other group and therefore RR cannot be estimated. Tran et al stated that they measured serious adverse events, they reported nausea and vomiting, and agitation. All three of these outcomes are present in Table 2.

In the Results, GRADE section. The reasons for upgrading or downgrading the certainty in the evidence is not clear for all comparisons in Table 2. For example, for the comparison between continuous vs. bolus ketamine, the estimate for change in pain score is from 1 randomized controlled trial and there is one footnote saying that the sample size of the study was of concern. As in the GRADE approach RCT starts as high certainty, authors need to describe the exact reason for downgrading two levels (e.g. risk of bias and imprecision because of small sample size). I'd suggest to be consistent in the footnotes using the GRADE original terminology. For instance, when certainty was downgraded two levels, provide the exact reason (e.g. "imprecision" as only 50 patients were included, "risk of bias" as there was lack of blinding and lack of allocation concealment).

-Thank you for this point, footnotes are now improved:
Ketamine compared to opioids for prehospital pain management
a. Downgraded one level for high risk of bias,
b: Downgraded one level for imprecision, only 4 events and all four of them in the same group. There were no events in the other group and therefore RR cannot be estimated.

Ketamine and morphine compared to only morphine for prehospital pain management
a. Downgraded one level for imprecision, this cohort only has 27 patients included b, Downgraded one level for risk of bias due to unclear randomization and open label design

Continuous administration of ketamine compared to ketamine given as a bolus for prehospital pain management
a. Downgraded one level for imprecision, one study included with 63 patients, b. Downgraded one level for imprecision, only 3 events

Ketamine and nitrous oxide compared to only nitrous oxide for prehospital pain management
a. Downgraded one level for imprecision, only one study with a total of 120 patients. There are also large effects, but with unclear blinding we do not upgrade

In the Discussion, page 16, the authors initially acknowledged that analgesic doses of ketamine resulted in more non-serious adverse events than opioids alone. However, later in the same page, line 38, they reported that it is unclear whether adverse events are more likely to occur with opioids than with ketamine. I'd suggest to be consistent in the interpretation. For example, while nausea and vomiting seems to be more frequent in patients receiving opioids as compared to ketamine, patients receiving ketamine seems to be more likely to have agitation. I'd suggest to be consistent and clear when it comes to describing the differences of adverse events occurring between comparison groups.

-We have revised the section in the Discussion on “Adverse events” aiming to be more consistent in our reporting.

In the Discussion, page 16, line 41, I’d suggest avoiding the word “recommendation” as systematic reviews should inform rather than provide recommendations.

-The sentence has been rephrased, emphasising that reviews should inform rather than provide recommendations.

In the Discussion and in the Conclusion, the authors make an argument about ketamine being administered by trained physicians, however there is no description of who administered ketamine in the included studies. For example, Bronsky et al is a study performed in the USA where physicians often do not work in the pre-hospital setting and non-physician paramedics most likely were responsible for administering ketamine. As the provider training most likely was not evaluated in the included studies, I’d suggest not making the claim that ketamine seems to be safe and effective when administered by providers with “relevant training”. There seems to be no such data to support this conclusion from the included studies. However, I think this is an important Discussion point as trained providers most likely know how to deal with severe adverse events. Future studies should maybe evaluate whether provider training increases the safety of ketamine use in the prehospital setting.

-We have removed our speculations on “trained physicians” from the Discussion and the Conclusion sections.

I'd suggest adding a separate Limitations section.

-The manuscript now has one “Strengths and limitations” and one “Adverse events and side effects” sections.