PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effects of Intravenous Ketamine after Spinal Anaesthesia for Non-Elective Caesarean Delivery: A Randomised Controlled Trial
AUTHORS	Adhikari, Prahlad; Subedi, Asish; Sah, Birendra; Pokharel, Krishna

VERSION 1 – REVIEW

REVIEWER	Cheng, Davy London Health Sciences Centre University Hospital, Anesthesia & Perioperative Medicine
REVIEW RETURNED	08-Oct-2020

GENERAL COMMENTS	General and Specific Comments: The authors performed a well designed double-blinded RCT attempted to determine the effectiveness of low dose iv ketamine in reducing opioid use and pain after non-elective C/S. They concluded this intervention was associated with lower opioids requirement and significantly lower pain score post C/S. However, such investigations have been well published in literature with conflicting results, and there are a few fundamental limitations in this design and methodology: 1) The low dose ketamine of 0.25 mg/kg injected post spinal anesthesia with its pharmacokinetic and pharmacodynamic likely will determine the need to supplemental analgesia during C-section than expected its long term analgesia effect over 24 hours. Repeating similar study as published in the literature on similar surrogate outcomes did not contribute any new information. 2) What is the clinical problem being resolved in this study when the control spinal anesthesia group at the authors' institutions resulted in a median pain score of 0-3/10 from 1-24 h post C/S? The low dose ketamine resulted in no clinical relevant differences, despite a p value <0.001! 3) What assessment tool was used in diagnosing hallucination? 4) Any patient satisfactory assessment post C/S in comparing the intervention?

REVIEWER	Kim , Hyun-Chang Gangnam Severance Hospital, Anesthesiology and Pain Medicine
REVIEW RETURNED	28-Oct-2020

GENERAL COMMENTS	General comment Authors found that pre-incisional ketamine decreases opioid requirements and pain scores. It is interesting finding but I wonder that ketamine is allowed for the pregnant patients. Ketamine may be toxic to the neuron. This is ethical issue regarding safety. At least, authors have to discuss this in the limitation parts.

	Specific comments Methods 1. Height <150cm : Why did you exclude patients with short stature? 2. Were patients with ASA I excluded? Why? Results 1. Authors may add the figure regarding pain scores. 2. Authors should add the information regarding hemodynamic variables perioperatively. Discussion 1. Limitations : Author should discuss the limitations of this investigation.

REVIEWER	Lonnée, Herman St Olavs Hospital Universitetssykehuset i Trondheim
REVIEW RETURNED	24-Dec-2020

GENERAL COMMENTS	ad 2. Secondary outcome measures not clearly defined in abstract as such (however done in "methods-section"). ad 5. the "participant informed consent form" doesnot clearly state in layman english what the study was all about. ad 6. Methods section: primary outcome clearly defined, however in methods section first explained how sec outcome measured and then primary outcome, should be reversed. In methods section; inculion/exclusion criteria unclear. Primi/multigravida, previous Caesarean (more postop pain) delivery in- or excluded (however this suddenly appears in Table 1)? Is the use of the NRS scale for illeterate patients validated? Plain or heavy bupivacaine used? Why fentanyl used in PACU and not morphine? ad 10: Results; Figure 1 quite messy but probably problems with uploading. Table 3 is explained again in the text, it should be either the one or the other. Figure 2 is informative but abundant since the result is mentioned in writing in one sentence in the result section. ad 11. The discussion is too long. PONV has too much attention, as does the ketamine neonate section. ad 15. mixture of " american" and UK english. In general the article needs "proofreading" because of grammar/spelling mistakes. BP Koirala written out fully into Bisheshwar Prasad first time. In general the article is too long.

REVIEWER	Wong, SSC University of Hong Kong
REVIEW RETURNED	16-Feb-2021

GENERAL COMMENTS	Comments This is a statistical review invitation. Most of the statistics and methodology is appropriate. There are a couple of comments 1) For the pain score results, multiple comparison adjustment method should be applied in the analysis (eg Bonferroni). This has not been mentioned in the manuscript and it is not clear if it has already been done. 2) The result of KM curve (log-rank test) is redundant as this is the result of Table 2. CONSORT check

	1) Outcomes (Item 6a) Completely defined pre-specified primary outcome measure including how and when it was assessed Is it clear (1) what the primary outcome is (usually the one used in the sample size calculation), (2) how it was measured (if relevant; e.g. which score used), (3) at what time point, and (4) what the analysis metric was (e.g. change from baseline, final value)? Reply: Primary outcome, the measurement method and number of time are stated but the analysis method is problematic. The author should perform appropriate analysis method and multiple comparison adjustment should be done. 2) Sample size (Item 7a) How sample size was determined Is there a clear description of how the sample size was determined, including (1) the estimated outcomes in each group; (2) the α (type I) error level; (3) the statistical power (or the β (type II) error level); and (4) for continuous outcomes, the standard deviation of the measurements? Reply: The calculation of sample size is clearly stated 3) Sequence generation (Item 8a) Method used to generate random allocation sequence Does the description make it clear if the “assigned intervention is determined by a chance process and cannot be predicted”? Reply: The author described “a computer-generated simple random sequence”. This method is appropriate 4) Allocation concealment (Item 9) Mechanism used to implement random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned Is it clear how the care provider enrolling participants was made ignorant of the next assignment in the sequence (different from blinding)? Possible methods can rely on centralised or “third-party” assignment (i.e., use of a central telephone randomisation system, automated assignment system, sealed containers). Reply: The author mentioned “The patient allocation was concealed in sealed opaque envelopes marked with the study identification number. The anaesthesia assistant who was not involved in the study opened the concealed envelope and prepared the study drug in a syringe according to the group allocation and labelled it.” Allocation concealment was appropriate. 5) Blinding (Item 11a) If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes)

	Is it clear if (1) healthcare providers, (2) patients, and (3) outcome assessors are blinded to the intervention? General terms such as “double-blind” without further specifications should be avoided. Reply: The author mentioned “The study subject and the investigators assessing the outcome were blinded to the group assignment.”. Healthcare providers and patients were blinded. It is clear. 6) Outcomes and estimation (Item 17a/b) For the primary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence intervals) Is the estimated effect size and its precision (such as standard deviation or 95% confidence intervals) for each treatment arm reported? When the primary outcome is binary, both the relative effect (risk ratio, relative risk) or odds ratio) and the absolute effect (risk difference) should be reported with confidence intervals. Reply: The author should take into account impact of multiple tests in different time points to avoid the inflation of type I error. KM curve (log-rank test) is not appropriate to perform in the analysis part. 7) Harms (Items 19) All important harms or unintended effects in each group Is the number of affected persons in each group, the severity grade (if relevant) and the absolute risk (e.g. frequency of incidence) reported? Are the number of serious, life threatening events and deaths reported? If no adverse event occurred this should be clearly stated. Reply: Several adverse effects such as hypotension and nausea / vomiting are reported 8) Registration (Item 23) Registration number and name of trial registry Is the registry and the registration number reported? If the trial was not registered, it should be explained why. Reply: Yes, has been done 9) Protocol (Item 24) Where trial protocol can be accessed Is it stated where the trial protocol can be assessed (e.g. published, supplementary file, repository, directly from author, confidential and therefore not available)? Reply: Yes 10) Funding (Item 25) Sources of funding and other support (such as supply of drugs) and role of funders

	Are (1) the funding sources, and (2) the role of the funder(s) described? Reply: The author mentioned the study is non-funded.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Davy Cheng, London Health Sciences Centre University Hospital
Comments to the Author:
General and Specific Comments:
The authors performed a well designed double-blinded RCT attempted to determine the effectiveness of low dose iv ketamine in reducing opioid use and pain after non-elective C/S. They concluded this intervention was associated with lower opioids requirement and significantly lower pain score post C/S. However, such investigations have been well published in literature with conflicting results, and there are a few fundamental limitations in this design and methodology:
1) The low dose ketamine of 0.25 mg/kg injected post spinal anesthesia with its pharmacokinetic and pharmacodynamic likely will determine the need to supplemental analgesia during C-section than expected its long term analgesia effect over 24 hours. Repeating similar study as published in the literature on similar surrogate outcomes did not contribute any new information.
Reply: We have now addressed the reason why ketamine was co-administered along with spinal anaesthesia pre-emptively. Also, we have provided the reasons why ketamine works beyond its elimination half-life. Please refer to discussion section, page 37, lines 30-51.
2) What is the clinical problem being resolved in this study when the control spinal anesthesia group at the authors' institutions resulted in a median pain score of 0-3/10 from 1-24 h post C/S? The low dose ketamine resulted in no clinical relevant differences, despite a p value <0.001!
Reply: We agree with reviewer that although statisticically significant difference was observed between two groups in terms of early postoperative pain scores it did not result in clinical significance. Similary, in terms of 24 hr opioid consumption, although, statistically significant difference was observed there was no clinical significance. We have addressed this issue. Please refer to discussion section, page 37, lines 53-57 and page 38, lines 3-28
However, we feel that ketamine is an important adjunt to perioperative analgesic regimen especially in developing countries where opioids are not available regularly.
3) What assessment tool was used in diagnosing hallucination?
Reply: We did not use any specific tool to assess hallucination. However, it was based on a definition as verbally reporting of sensory experiences with or without intuition, and not triggered by a relevant stimulus. We have now added this. Please refer to method section, page 32, lines 51-56
4) Any patient satisfactory assessment post C/S in comparing the intervention?
Reply: Patient satisfaction was not assessed postoperatively. We have now added it as our limitation. Please refer to dicussion section, page 39, lines 50-56

Reviewer: 2
Dr. Hyun-Chang Kim , Gangnam Severance Hospital
Comments to the Author:
General comment
Authors found that pre-incisional ketamine decreases opioid requirements and pain scores. It is interesting finding but I wonder that ketamine is allowed for the pregnant patients. Ketamine may be toxic to the neuron. This is ethical issue regarding safety. At least, authors have to discuss this in the limitation parts.

Reply: We have discussed in detail the effects of ketamine on neonates developing brain. Please refer to discussion section, page 39, lines 17-49

Specific comments
Methods
1. Height <150cm
: Why did you exclude patients with short stature?
Reply: In general, for short stature parturients (height <150 cm), the lower dose of bupivacaine for spinal anaesthesia is given because fixed doses of bupivacaine can cause haemodynamic instability. In our study, in order to standardize and to avoid bias we had used a fixed dose of bupivacaine. Therefore, we excluded patients with short stature.
2. Were patients with ASA I excluded? Why?
Reply: Due to physiological changes uncomplicated pregnancy is categorized as ASA II.
Results
1. Authors may add the figure regarding pain scores.
Reply: Initially we did plan to display pain scores as figures. However, the median socres were low and the figures were barely understandable. Therefore, we decided to present the pain scores in table format.

2. Authors should add the information regarding hemodynamic variables perioperatively.
Reply: Although we observed the hemodynamics we did not document it. However, any episode of hypotension or bradycardia was recorded. The episodes of hypotension is shown in table 3.
Discussion
1. Limitations
: Author should discuss the limitations of this investigation.

Reply: We have now added the limitations. Please refer to discussion section, page 39, lines 50-56.

Reviewer: 3
Dr. Herman Lonnée, St Olavs Hospital Universitetssykehuset i Trondheim
Comments to the Author:
ad 2. Secondary outcome measures not clearly defined in abstract as such (however done in "methods-section").
Reply: We have now clearly specified the term secondary outcome measures. Please refer to abstract section, page 27, lines 23-25

ad 5. the "participant informed consent form" doesnot clearly state in layman english what the study was all about.

Reply: We accept that the participant informed consent form was not simplified in layman english. However, to all our patients the participant informed consent form was was provided in simplified and understandable Nepali language since Nepali was the mother language for all patients.
ad 6. Methods section: primary outcome clearly defined, however in methods section first explained how sec outcome measured and then primary outcome, should be reversed.
Reply: In method section we first mentioned the primary outcome (the total consumption of opioids as morphine equivalents up to 24 hours after surgery) and then secondary outcomes. Please refer to method section, page 32, lines 40-50.
In methods section; inculion/exclusion criteria unclear. Primi/multigravida, previous Caesarean (more postop pain) delivery in- or excluded (however this suddenly appears in Table 1)?
Reply: Both primi and multigravida patients were included in the study. Also, patients with previous caesarean section were included in the study. Had we selected only primi and not multigravida or first time CS against previous CS then we would have specified in the inclusion/exclusion criteria.

However, we did record the proportion of previous CS. There was no difference in the distribution of previous CS between two groups as shown in table 1. Therefore, there is less chance of bias. Moreover, there is inconsistent reporting of postop pain differences between primary and repeated CS.

Is the use of the NRS scale for illiterate patients validated?

Reply: None of our patients were illiterate. During the pre-anaesthetic visit, patients were made familiar with the use of NRS. All our paients were able to comprehend the NRS scale.

Plain or heavy bupivacaine used? Why fentanyl used in PACU and not morphine?

Reply: We used heavy bupivacaine. We have now specified it. Please refer to method section, page 31, lines 35-36.

In our place due to irregular supply of the opioids fentanyl is supplied for use in PACU and morphine for the use in surgical unit. Nevertheless, we had converted all opioids to morphine equivalent.

ad 10: Results; Figure 1 quite messy but probably problems with uploading.

Reply: It may be due to technical issue. When we downloaded the submission in pdf version, the figure 1 was clear and readable.

Table 3 is explained again in the text, it should be either the one or the other.

Reply: We have now made changes in the text. Please refer to Result section, page 35. Lines 46-56.

Figure 2 is informative but abundant since the result is mentioned in writing in one sentence in the result section.

Reply: We have now removed the figure 2.

ad 11. The discussion is too long. PONV has too much attention, as does the ketamine neonate section.

Reply: Effect of ketamine on PONV and neonates are controversial topic, therefore, we have focussed on these issues as well. We have not exceeded the word limit.

ad 15. mixture of " american" and UK english. In general the article needs "proofreading" because of grammar/spelling mistakes. BP Koirala written out fully into Bisheshwar Prasad first time.

Reply: We have corrected and improvized our manuscript. We have now written BP in full. Please refer to method section, page 30, lines 9-10.

In general the article is too long.

Reply: We apologize for this. However, we have not exceeded the word limit.

Reviewer: 4

Dr. SSC Wong, University of Hong Kong

Comments to the Author:

Comments

This is a statistical review invitation. Most of the statistics and methodology is appropriate. There are a couple of comments

Reply: Thank you for the positive feedback.

1) For the pain score results, multiple comparison adjustment method should be applied in the analysis (eg Bonferroni). This has not been mentioned in the manuscript and it is not clear if it has already been done.

Reply: We have now analysed pain scores using Bonferroni correction. Please refer to method section,page 33, lines 37-45 and result section, page 35, lines 35-40.

2) The result of KM curve (log-rank test) is redundant as this is the result of Table 2.

Reply: We have now removed figure 2.

CONSORT check

1) Outcomes (Item 6a)
Completely defined pre-specified primary outcome measure including how and when it was assessed

Is it clear (1) what the primary outcome is (usually the one used in the sample size calculation), (2) how it was measured (if relevant; e.g. which score used), (3) at what time point, and (4) what the analysis metric was (e.g. change from baseline, final value)?

Reply: Primary outcome, the measurement method and number of time are stated but the analysis method is problematic. The author should perform appropriate analysis method and multiple comparison adjustment should be done.

2) Sample size (Item 7a)
How sample size was determined

Is there a clear description of how the sample size was determined, including (1) the estimated outcomes in each group; (2) the α (type I) error level; (3) the statistical power (or the β (type II) error level); and (4) for continuous outcomes, the standard deviation of the measurements?

Reply: The calculation of sample size is clearly stated

3) Sequence generation (Item 8a)
Method used to generate random allocation sequence

Does the description make it clear if the “assigned intervention is determined by a chance process and cannot be predicted”?

Reply: The author described “a computer-generated simple random sequence”. This method is appropriate

4) Allocation concealment (Item 9)
Mechanism used to implement random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned

Is it clear how the care provider enrolling participants was made ignorant of the next assignment in the sequence (different from blinding)? Possible methods can rely on centralised or “third-party” assignment (i.e., use of a central telephone randomisation system, automated assignment system, sealed containers).

Reply: The author mentioned “The patient allocation was concealed in sealed opaque envelopes marked with the study identification number. The anaesthesia assistant who was not involved in the study opened the concealed envelope and prepared the study drug in a syringe according to the group allocation and labelled it.”

Allocation concealment was appropriate.
5) Blinding (Item 11a)
If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes)

Is it clear if (1) healthcare providers, (2) patients, and (3) outcome assessors are blinded to the intervention? General terms such as “double-blind” without further specifications should be avoided.

Reply: The author mentioned “The study subject and the investigators assessing the outcome were blinded to the group assignment.”. Healthcare providers and patients were blinded. It is clear.

6) Outcomes and estimation (Item 17a/b)
For the primary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence intervals)

Is the estimated effect size and its precision (such as standard deviation or 95% confidence intervals) for each treatment arm reported? When the primary outcome is binary, both the relative effect (risk ratio, relative risk) or odds ratio) and the absolute effect (risk difference) should be reported with confidence intervals.

Reply: The author should take into account impact of multiple tests in different time points to avoid the inflation of type I error. KM curve (log-rank test) is not appropriate to perform in the analysis part.

7) Harms (Items 19)
All important harms or unintended effects in each group

Is the number of affected persons in each group, the severity grade (if relevant) and the absolute risk (e.g. frequency of incidence) reported? Are the number of serious, life threatening events and deaths reported? If no adverse event occurred this should be clearly stated.

Reply: Several adverse effects such as hypotension and nausea / vomiting are reported

8) Registration (Item 23)
Registration number and name of trial registry

Is the registry and the registration number reported? If the trial was not registered, it should be explained why.

Reply: Yes, has been done

9) Protocol (Item 24)
Where trial protocol can be accessed

Is it stated where the trial protocol can be assessed (e.g. published, supplementary file, repository, directly from author, confidential and therefore not available)?

Reply: Yes

10) Funding (Item 25)
Sources of funding and other support (such as supply of drugs) and role of funders

Are (1) the funding sources, and (2) the role of the funder(s) described?

Reply: The author mentioned the study is non-funded.

Reviewer: 1
Competing interests of Reviewer: None declared

Reviewer: 2
Competing interests of Reviewer: None.

Reviewer: 3
Competing interests of Reviewer: None declared

Reviewer: 4
Competing interests of Reviewer: none declared

VERSION 2 – REVIEW

REVIEWER	Kim , Hyun-Chang Gangnam Severance Hospital, Anesthesiology and Pain Medicine
REVIEW RETURNED	20-Apr-2021

GENERAL COMMENTS	General comment Authors found that pre-incisional ketamine reduced the opioid requirements and pain scores at the immediate postoperative period in patients undergoing non-elective cesarean section without serious complications. My only concern is that ketamine is approved for parturients and safe for the neonates. Is it ethical? Otherwise, this finding is very interesting. Specific comments. Methods 1. When and how did authors infuse ketamine? 2. Postoperative pain management : Authors should present more information about pain management. Do patients use PCA? PCA-regimen? What is the rescue analgesic protocol? Results 1. I recommend to add the figures regarding pain scores and opioid requirements.

REVIEWER	Lonnée, Herman St Olavs Hospital Universitetssykehuset i Trondheim
REVIEW RETURNED	19-Apr-2021

GENERAL COMMENTS	Thank you for the revised article and the replies to most of the issues mentioned. I however still have problems reading some parts of the article regarding the english. For example the abstract; 41-45 and 50 (page 2)-6 (page 3). Page 3; the strengths and limitation section, here results are mentioned except for the last point, so not addressing "strengths and limitations"

REVIEWER	Wong, SSC University of Hong Kong
REVIEW RETURNED	26-Apr-2021

GENERAL COMMENTS	This is a statistical review only as requested The changes are acceptable and I have no additional comments

VERSION 2 – AUTHOR RESPONSE

Reviewer: 3

Dr. Herman Lonnée, St Olavs Hospital Universitetssykehuset i Trondheim

Comments to the Author:

Thank you for the revised article and the replies to most of the issues mentioned.

I however still have problems reading some parts of the article regarding the english. For example the abstract; 41-45 and 50 (page 2)-6 (page 3).

Reply: We have reframed the sentences as suggested. Please refer to the abstract section, page 25, lines 40-46 & 50-55.

Page 3; the strengths and limitation section, here results are mentioned except for the last point, so not addressing "strengths and limitations"

Reply: We have now revised the ‘Strengths and limitations’ section as suggested. Please refer to the page 26, lines 8-15

Reviewer: 2

Dr. Hyun-Chang Kim , Gangnam Severance Hospital

Comments to the Author:

General comment

Authors found that pre-incisional ketamine reduced the opioid requirements and pain scores at the immediate postoperative period in patients undergoing non-elective cesarean section without serious complications.

My only concern is that ketamine is approved for parturients and safe for the neonates. Is it ethical? Otherwise, this finding is very interesting.

Reply: We are thankful to the reviewer for raising this issue. Before administration of ketamine to the parturients it is important to focus on the following points:

1. Is ketamine approved for parturients?

Ketamine is used in hemodynamically unstable parturients (eg. Antepartum haemorrhage) undergoing emergency caesarean section as an induction agent in doses up to 1 mg/kg intravenous. And, it is widely used in low resource settings.

Due to a lack of data from controlled studies in humans, the Federal Drug Administration has not assigned a pregnancy risk category to ketamine.

2. What are the dose and the duration of ketamine administration that may cause neurotoxic effects?

Most of the animal studies that revealed neurotoxic effects of ketamine were related to high doses and prolonged infusion. Animal studies cannot be translated to human due to differences in the brain complexity. The current data in humans suggest that a single brief anaesthetic in young children does not affect subsequent neurodevelopment.

US Food and Drug Administration Website: http://www.fda.gov/Drugs/DrugSafety/ ucm532356.htm; accessed December 23, 2016

A recent clinical study found that there was no evidence of lower neurodevelopmental scores in neonates with increasing doses of maternal ketamine (doses up to 3.8 mg/kg IV)

Gilder, M.E., Tun, N.W., Carter, A. et al. Outcomes for 298 breastfed neonates whose mothers received ketamine and diazepam for postpartum tubal ligation in a resource-limited setting. BMC Pregnancy Childbirth 21, 121 (2021). https://doi.org/10.1186/s12884-021-03610-1

Importantly, in our study, we had used a single low dose of ketamine and the doses in this range are less likely to have harmful effects on the neonates.

We have extensively elaborated on this issue in our discussion section. Please refer to discussion section, page 37, lines 16-37.

Specific comments.

Methods

1. When and how did authors infuse ketamine?

Reply: We had used ketamine single dose of 0.25mg/kg IV. The study drug, according to the allocated group was injected intravenously just before the surgical incision. We have mentioned it in the method section. Please refer to method section, page 29, lines 6-9 & lines 44-48.

2. Postoperative pain management

Authors should present more information about pain management. Do patients use PCA? PCA-regimen? What is the rescue analgesic protocol?

Reply: Both groups received 1 g IV paracetamol every 6 hours and 30 mg IV ketorolac every 8 hours starting at the end of surgery.

For rescue analgesia in the PACU, the patient received IV fentanyl 15 µg while in the surgical unit patient received IV morphine 2 mg

We had mentioned it earlier. Please refer to method section page 30, lines 20-38.

PCA device is expensive and it is not available in our centre.

Results

1. I recommend to add the figures regarding pain scores and opioid requirements.

Reply: As suggested we have now added the figures. Please refer to page 48,49. 50

Reviewer: 4

Dr. SSC Wong, University of Hong Kong

Comments to the Author:

This is a statistical review only as requested

The changes are acceptable and I have no additional comments