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Effects of Intravenous Ketamine after Spinal Anaesthesia for Non-Elective Caesarean Delivery: A Randomised Controlled Trial

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Title page

Analgesic Effects of Intravenous Ketamine after Spinal Anaesthesia for Non-Elective Caesarean Delivery: A Randomised Controlled Trial

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Abstract

Objectives: This study aimed to determine if low dose intravenous ketamine is effective in reducing opioid use and pain after non-elective caesarean delivery.

Design: Prospective, randomised, double-blind.

Setting: Tertiary hospital, BPKIHS, Dharan, Nepal

Participants: 80 patients undergoing non-elective caesarean section with spinal anaesthesia.

Interventions: Patients were allocated in 1:1 ratio to receive either intravenous ketamine 0.25 mg/kg or normal saline before the skin incision.

Primary and secondary outcome measures: The primary outcome was the total amount of morphine equivalents needed up to postoperative 24 hours. Postoperative pain scores and the time to the first perception of pain were observed. Maternal adverse effects (nausea, vomiting, hypotension, ketamine related) and neonatal outcome (Apgar score at 1 and 5 min, respiratory depression, NICU referral) were also noted.

Results: The median (range) cumulative morphine consumption during the first 24 hours of surgery was 0 (0-4.67) mg in ketamine group and 1 (0-6) mg in saline group (p=0.003). The median (range) time to first perception of pain was 6 (1-12) hours and 2 (0.5-6) hours in ketamine and saline group respectively (p<0.001). Postoperatively, the numeric rating scale sores for pain was significantly higher in the saline group compared to ketamine group only at 2 hours in the post anesthesia care unit and 6 hours in the ward (p<0.05). Maternal adverse effects and neonatal outcomes were comparable between the two groups.

Conclusions: Pre-incisional intravenous low dose ketamine was associated with the lower opioids requirement after non-elective caesarean delivery. Significant decrease in pain scores

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was observed only in the early hours after surgery in parturients receiving ketamine than those receiving normal saline.

Trial registration: clinicaltrial.gov- No. NCT03450499

Strengths and limitations of this study:

- In this randomised, double-blind study, analgesic effect of pre-incisional ketamine in non-elective caesarean delivery was explored.
- 80 patients received either IV ketamine 0.25 mg/kg or normal saline before surgical incision.
- Ketamine reduced total opioid requirement up to 24 hours after surgery compared to placebo group.
- Administration of low-dose ketamine has opioid-sparing effect.
- One limitation is that the end point of the study was limited to postoperative 24 hours only.

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A competing interests statement: None

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Introduction

Effective analgesia following caesarean delivery (CD) is important as it enhances maternal recovery, reduces the risk of deep vein thrombosis, and facilitates the mother's ability to care for her baby.[1] In recent years, both pharmacological and non-pharmacological modalities for post-caesarean analgesia have been extensively studied; yet, none of them are able to provide optimum post-operative analgesia.[2] Importantly, multimodal analgesia provides superior analgesia with fewer adverse effects related to opioids, and therefore, use of non-opioid analgesic in alleviating postoperative pain is generally preferred.[2] In this regard, opioid-sparing drugs, such as ketamine may be valuable in providing better analgesia without major adverse effects.[3]

Both central and peripheral mechanisms have been postulated for ketamine, as it not only abolishes peripheral afferent noxious stimuli but also prevents central sensitization.[4, 5] A recent meta-analysis demonstrated that perioperative administration of non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist ketamine reduces postoperative pain intensity and analgesic consumption.[6]

Non-opioid analgesia plays a vital role in providing good quality analgesia during CD. The effect of ketamine on postoperative pain following spinal anaesthesia in an elective CD has been investigated.[7, 8] However, its analgesic role in a non-elective CD has not been explored to date. In this study, we examined the effect of low-dose intravenous (IV) ketamine on opioid requirement as morphine equivalent and pain intensity (as measured by numeric rating scale scores) following spinal anaesthesia for non-elective CD.

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Methods

This prospective, randomised, placebo-controlled, double-blind study was conducted at B.P. Koirala Institute of Health Sciences (BPKIHS), Dharan, Nepal, between April 2, 2018, and March 7, 2019. This study was approved by the BPKIHS Institutional Review Committee (IRC #1089/017) and written informed consent was obtained from all subjects participating in the trial. The trial was registered prior to patient enrollment at clinicaltrials.gov (NCT03450499, Principal investigator: Prahlad Adhikari, Date of registration: March 1, 2018). The study was conducted according to the ethical principles reported in the Declaration of Helsinki and adheres to the CONSORT (Consolidated Standards of Reporting Trials) statement.

Parturients at term undergoing non-elective, category 2 and 3 (according to NICE guideline classification of urgency of emergency caesarean),[9] lower segment CD under spinal anaesthesia with American Society of Anesthesiologists physical status (ASA PS) II were eligible for this trial. Women with body mass index $\geq$ 40 kg/m^2, height <150 cm, current use of pain medication including opioids, history of substance abuse or hallucinations, cardiovascular disease, diabetes, multiple gestations, known fetal abnormality, chronic pain were excluded. Other exclusion criteria were contraindications to the spinal anaesthesia, severely compromised fetus requiring general anaesthesia and those patients who received labour analgesia.

Independent anaesthesia supporting staff randomly assigned the patients in a 1:1 ratio to receive either ketamine or normal saline using a computer-generated simple random sequence. 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

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it. The study subject and the investigators assessing the outcome were blinded to the group assignment. Group KET received IV ketamine (Ketamax®, Troikaa Pharmaceuticals Ltd, Gujarat, India) 0.25 mg/kg and group NS received 0.9 % normal saline.

A total of 80 (40 in each group) patients were enrolled. Each eligible patient was informed about the nature of the study in the labour room or emergency ward once the decision was made regarding CD. Subsequently, written informed consent was obtained, and pre-anaesthetic checkup was done. During this visit, patients were also educated on the use of a 10-cm numeric rating scale (NRS), with 0 representing no pain and 10 representing the worst imaginable pain. All patients received IV metoclopramide 10 mg and ranitidine 50 mg for aspiration prophylaxis. Patients were transferred to the operating room and standard monitoring was applied. An infusion of Lactated Ringer's (RL) solution was initiated at a minimal rate via18-gauge IV cannula placed on the forearm.

With the patient in an appropriate position, a 25 gauge Quincke needle was inserted at L3-4 or L4-5 interspace; and intrathecal (IT) 2.2 ml of 0.5% bupivacaine with 10 µg fentanyl was administered. An anaesthesiologist who was unaware of the study group injected the spinal drug. RL was administered at a rapid rate beginning at the time of the intrathecal injection. After noting the time of injection, the patient was placed in a supine position with 15 degrees left tilt. The study drug, according to the allocated group was injected intravenously just before the surgical incision. Oxygen was administered via the face mask at the rate of 5 L/min.

The onset of a sensory block was assessed using alcohol-soaked cotton swabs. At every minute, the sensory block level was checked. When the sensory block reached the T6 level, surgery was started. Intraoperative pain was managed with fentanyl 20 µg titrated to a maximum of 100 µg

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by the attending anaesthesiologist. Intraoperative fall of systolic arterial pressure >20% of the baseline or < 100 mmHg and heart rate (HR) < 50 beats/min were considered significant. Hypotension was managed with increasing fluid administration (RL) rate and IV phenylephrine 50 µg (if HR>50 beats/min) or ephedrine 6 mg (if HR< 50 beats/min). Bradycardia (HR<50 beats/min) was managed with Atropine 0.4 mg IV. Time from the spinal injection to the delivery was noted. After the delivery of baby, 3 IU of oxytocin was administered IV over ≥ 30 sec followed by an infusion of 10 IU/hr (oxytocin 40 IU in 500 ml of Hartmann's solution). Newborn Apgar score was noted at 1 and 5 min after birth. Both groups received 1 g IV paracetamol every 6 hours and 30 mg IV ketorolac every 8 hours starting at the end of surgery.

Postoperative pain was evaluated using NRS at rest and on an attempt to move or bend forward from the bed. During the stay at postanaesthesia care unit (PACU; On arrival, 1 and 2 hours thereafter), if NRS score was >3, the patient received IV fentanyl 15 µg, and it was repeated every 5 minutes until NRS was ≤ 3. In the post-operative ward (6, 12, and 24 hours) IV morphine 2 mg was administered for NRS score >3, and it was repeated until NRS ≤ 3.

The primary outcome was the total consumption of opioids as morphine equivalents up to 24 hours after surgery. Secondary outcomes were postoperative pain scores at rest and on movement; time to the first perception of pain (in hours); maternal adverse effects (incidence of nausea, vomiting, shivering, diplopia, nystagmus, hallucination); neonatal Apgar scores; neonates requiring resuscitation and intensive care admission. Maternal adverse effects were noted intraoperatively and up to 24 hours after surgery. Nausea and vomiting were rated on a scale of 0 to 3 (0, No nausea, no vomiting, 1 Light nausea, no vomiting episodes, 2 Moderate nausea, one or two vomiting episodes, 3 severe nausea, three or more vomiting episodes).[10] IV Ondansetron 4 mg was given when the score was ≥ 2. Shivering was graded using a scale

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described by Tsai and Chu. [11] Pethidine 20 mg was administered IV if shivering involved the whole body. The equivalent dose of fentanyl consumed (intraoperative and PACU) for pain and pethidine needed for shivering was converted to morphine from online dose equivalent calculator (www.globalrph.com/medcalcs/opioid-pain-management-converter-advanced).

Statistical analysis:

The data collected in the case report form were entered in the Microsoft Excel 2016 software. All analysis was conducted using STATA software version 15 (Stata Corporation, College Station, TX, USA). Normality of the data were checked using histogram, Kurtosis Skewness test and Sapiro Wilk test. Parametric data were presented as mean ± standard deviation and non-parametric data as median (range). For the normally distributed data, Student *t*-test and for the non-normally distributed data, Mann-Whitney *U* test were applied. Time to the first perception of pain was analyzed using the Kaplan-Meier curve and compared using the log-rank test. The categorical data were compared using the chi-square test or Fisher exact test as appropriate. A p-value of less than 0.05 was considered statistically significant.

Sample size

The sample size was calculated based on a previous study,[12] which showed a mean ± SD consumption of pethidine in the ketamine group as 54.17 ± 12.86 mg and 74.44 ± 33.82 mg in the placebo group. To detect this difference, assuming $\alpha = 0.05$ and $\beta = 0.1$ (90% power) and using the 2-tailed Student t-test, 34 subjects were required in each group (STATA version 15, Stata Corporation, College Station, TX, USA). Finally, forty patients were assigned to each group to allow for possible dropouts.

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Results

Among 92 women eligible for the study, 80 were enrolled, as eight subjects did not meet the inclusion criteria and four refused to give consent. (Fig.1) The demographic and clinical characteristics of both groups are demonstrated in Table 1.

The median (range) 24 hours morphine equivalent required in KET group was 0 (0-4.67) mg compared to 1 (0-6) mg in NS group (p=0.003). Mean 24 hours morphine consumption was 0.53 ± 1.22 mg in the KET group and 1.58 ± 1.87 mg in the NS group (mean difference – 1.05 mg, p=0.004). In PACU, median (range) dose of fentanyl consumed was 0 (0-0) µg in parturients receiving ketamine versus 0 (0-20) µg in those receiving normal saline (p=0.01). In the surgical unit, median morphine consumed was 0 (0-4) mg in the KET group and 0 (0-4) mg in the NS group (p=0.02). Significant differences between the two groups in terms of postoperative pain scores at rest were observed only at 2 hours and 6 hours (Table 2). Likewise, the pain scores during movement between the two groups were significant at 2 hours and 6 hours after surgery (Table 2). The pain-free period in 50 percent of subjects in the KET group was 6 hours whereas in the NS group this period was reduced to 2 hours ($p < 0.001$, Fig. 2).

There were no significant differences in maternal adverse effects between the two groups (Table 3). The median pethidine required for shivering was 0 (0-20) mg in the KET group and 20 (0-20) mg in the NS group (p=0.36). In the KET group, one patient complained of diplopia and one patient manifested nystagmus. There were no cases of hallucination in either group. Neonatal APGAR scores at 1 and 5 min, number of neonates requiring resuscitation or intensive care admission were comparable between the two groups (Table 3). No neonatal deaths were observed.

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Discussion:

Our study showed that pre-incisional IV low dose ketamine reduced perioperative opioid requirement in patients undergoing non-elective CD under spinal anaesthesia as compared to the placebo. Lower pain scores were observed in the ketamine group as compared to the placebo at 2 and 6 hours postoperatively. In addition, the time to the first perception of pain was earlier in the normal saline group than the ketamine group.

Opioids will continue to play an important role in perioperative pain management during CD; but because of several unwanted effects associated with its use, non-opioid analgesics are generally added.[13,14] Moreover, in resource-limited settings, longer acting neuraxial opioids are less frequently used for post-CS analgesia because of its poor availability and lack of dedicated monitoring postoperatively.[13] In this regard, opioid sparing agents such as ketamine may prove to be beneficial. Though ketamine is widely used as an anesthetic induction agent, in recent times, its role has widened. Among several new indications, perioperative administration of low-dose systemic ketamine has demonstrated analgesic properties. [6]

A sub-group study from a meta-analysis in 2015 that evaluated five trials performed under spinal anesthesia for elective CD found a significant reduction in cumulative morphine consumption with ketamine compared with the placebo group.[15] However, high heterogeneity was observed among the studies, and this was probably due to variation in ketamine regimen. Two studies had used a pre-incisional single dose of 0.15 mg/kg ketamine and the other one had used a fixed dose of 30 mg, while the remaining two studies had continued the infusion of ketamine either until the end of surgery or up to 24 h postoperatively. We administered a single dose of 0.25 mg/kg ketamine immediately after spinal injection because bolus dose up to 1 mg/kg IV is considered a

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sub-anaesthetic dose.[16] A recent meta-analysis also supported this fact where more than 50% of the studies included in the analysis had used doses of ketamine boluses ≤ 1mg/kg.[6]

Although we observed a statistically significant difference for the mean cumulative morphine requirement in the first 24 hours, it may be regarded as clinically insignificant because the mean difference was 1 mg. One reason for this small difference in overall opioid consumption and no significant change in pain intensity in late hours is likely due to the use of multimodal analgesia. In both the groups we used IV paracetamol and ketorolac round the clock while an opioid was used as rescue analgesia. Unlike other studies where a single bolus dose of pre-incisional ketamine was administered, analgesics in postoperative period were given only for breakthrough pain.[8,12] As a result, in those studies a larger difference in total morphine equivalent consumption was observed that ranged from 2.11 mg to 6.8 mg. In another study, contradict to our findings, low dose ketamine did not offer any postoperative benefits despite using multimodal analgesia. [7] In the above study, IT morphine was administered, and therefore, the prolonged analgesic effect of IT morphine could have overshadowed the analgesic effect of ketamine.

Several studies have explored the association between perioperative ketamine administration and postoperative nausea and vomiting (PONV). In patients with high risk for PONV undergoing lumbar spine surgery, ketamine increased the incidence of nausea.[17] The emetogenic effect of ketamine is likely due to its inhibitory action on serotonin uptake at the synaptic terminal; however, the precise mechanism remains elusive.[18, 19] Although we did not observe a significant change in the incidence of PONV, the role of ketamine for PONV during CD is still uncertain. While one study found a reduced incidence of intraoperative nausea and vomiting, another showed an increased frequency of vomiting.[20, 21] As a result, there are assumptions made for and against the role of ketamine on PONV: emetogenic versus opioid-sparing effects; whether a

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reduction in the frequency of hypotension indirectly minimizes the PONV episodes. Because PONV following spinal anaesthesia is multifactorial, it is difficult to establish a causal relationship between ketamine and PONV. Nevertheless, large clinical trials are warranted before any conclusion can be drawn. Prophylactic use of low doses of ketamine is effective in preventing shivering post-spinal anaesthesia for CD.[22] Although we found fewer parturients from ketamine group required pethidine for shivering in comparison to normal saline group, the difference was not significant statistically. The reason for this observation could be because our study not powered enough to detect this difference.

Ketamine crosses the placenta rapidly and has a mean fetal-maternal (F: M) ratio of 1.26 following an intravenous induction dose of anaesthesia.[23] As a result, concern has been expressed as to whether or not ketamine administered in clinical doses at the time of delivery produces neurotoxic effects in newborns. Animal studies have shown the dose and exposure dependent effect of ketamine on developing brain. A 5-h ketamine infusion in pregnant rhesus female monkey produced neuronal apoptosis in the fetal brain; [24] On the other hand, no serious complication was observed in lamb fetus after pregnant ewes were anaesthetized with 20 mg/kg of IV ketamine for caesarean delivery.[25] Based on clinical studies, a meta-analysis on the role of intravenous ketamine in parturients undergoing CD demonstrated no differences in the Apgar scores of neonates between ketamine-treated and placebo group.[15] Likewise, ketamine administered at 1 mg/kg IV in parturient did not worsen the newborn acid-base status in comparison to either thiopentone anesthesia or placebo group.[26, 27] We too observed no significant difference in neonatal outcomes between the two groups. As there is a paucity of data related to the neurodevelopmental effects in neonates after exposure of ketamine during CD, it is wise not to exceed ketamine doses above 1.5 mg/kg IV, and infusions are probably best avoided.

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In conclusion, our findings indicate that administration of pre-incisional low dose ketamine during non-elective caesarean delivery under spinal anaesthesia reduces perioperative overall opioid requirement and lowers the pain scores in the early hours after surgery.

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Table 1. Comparison of patient demographic, block characteristics and surgical profiles.

Variables	KET group n=40	NS group n=40	*p*-value
Age (in years)	24.90 ± 4.80	25.87 ± 5.53	0.40
Height (in cm)	155.45 ± 3.75	156.82 ± 4.25	0.12
Body mass index (in kg/m^2)	25.47±2.18	26.27±3.16	0.19
Gestational age (in weeks)	38.77±1.36	38.8±1.69	0.94
Indication for Cesarean section			0.65
Non reassuring non-stress test	11 (28)	16 (40)	
Previous CS presenting in labour	8 (20)	6 (15)	
Meconium stained liquor	6 (15)	6 (15)	
Failed induction	6 (15)	7 (17)	
Others (CPD, Malpresentation)	9 (22)	5 (13)	
Onset block to T6 dermatome (in min)	2 (1-7)	2 (1-5)	0.23
Highest sensory block (dermatome)	T4 (T2-T4)	T4 (T2-T4)	0.74
Spinal injection to delivery interval (in min)	20 (13-35)	19 (14-40)	0.65
Intraoperative fentanyl needed (μg)	0 (0-0)	0 (0-40)	0.15

Values are expressed as mean ± SD, number (%), or median (range). CPD = Cephalopelvic disproportion

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Table 2. Comparison of pain scores between two groups.

Time points	KET group n=40	NS group n=40	*p*-value
At Rest			
On arrival to PACU	0 (0-1)	0 (0-4)	0.15
1 h	0 (0-2)	0 (0-5)	0.06
2 h	0 (0-2)	2 (0-5)	<0.001
In Surgical Unit			
6 h	2 (1-4)	2 (0-5)	0.02
12 h	2 (0-4)	2 (0-5)	0.07
24 h	2 (1-4)	2 (0-5)	0.23
During Movement			
On arrival to PACU	0 (0-2)	0 (0-5)	0.08
1 h	0 (0-3)	1 (0-6)	0.05
2 h	2 (0-3)	2 (0-5)	< 0.001
In Surgical Unit			
6 h	2 (0-4)	3 (2-6)	0.001
12 h	3 (2-4)	3 (2-6)	0.22
24 h	3 (2-6)	3 (2-6)	0.81

Values are expressed in median (range)

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Table 3. Maternal adverse effects and neonatal outcomes

	KET group n=40	NS group n=40	*p*-value
Hypotension	13 (32)	16 (40)	0.48
Nausea or vomiting	4 (10)	5 (12)	0.72
Shivering requiring pethidine	5 (12)	8 (20)	0.36
APGAR score 1 min	8 (6-8)	8 (6-8)	0.54
APGAR score 5 min	9 (7-9)	9 (8-9)	0.67
Resuscitation needed in neonate (n)	1 (2%)	1 (2%)	1.0
Neonatal intensive care unit admission (n)	1 (2%)	2 (5%)	1.0

Values are in median (range) and number (percentage)

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Figure legends

Fig. 1 Consort flow diagram of the study.

Fig. 2 Kaplan meier graph showing time to first perception of pain between two groups.

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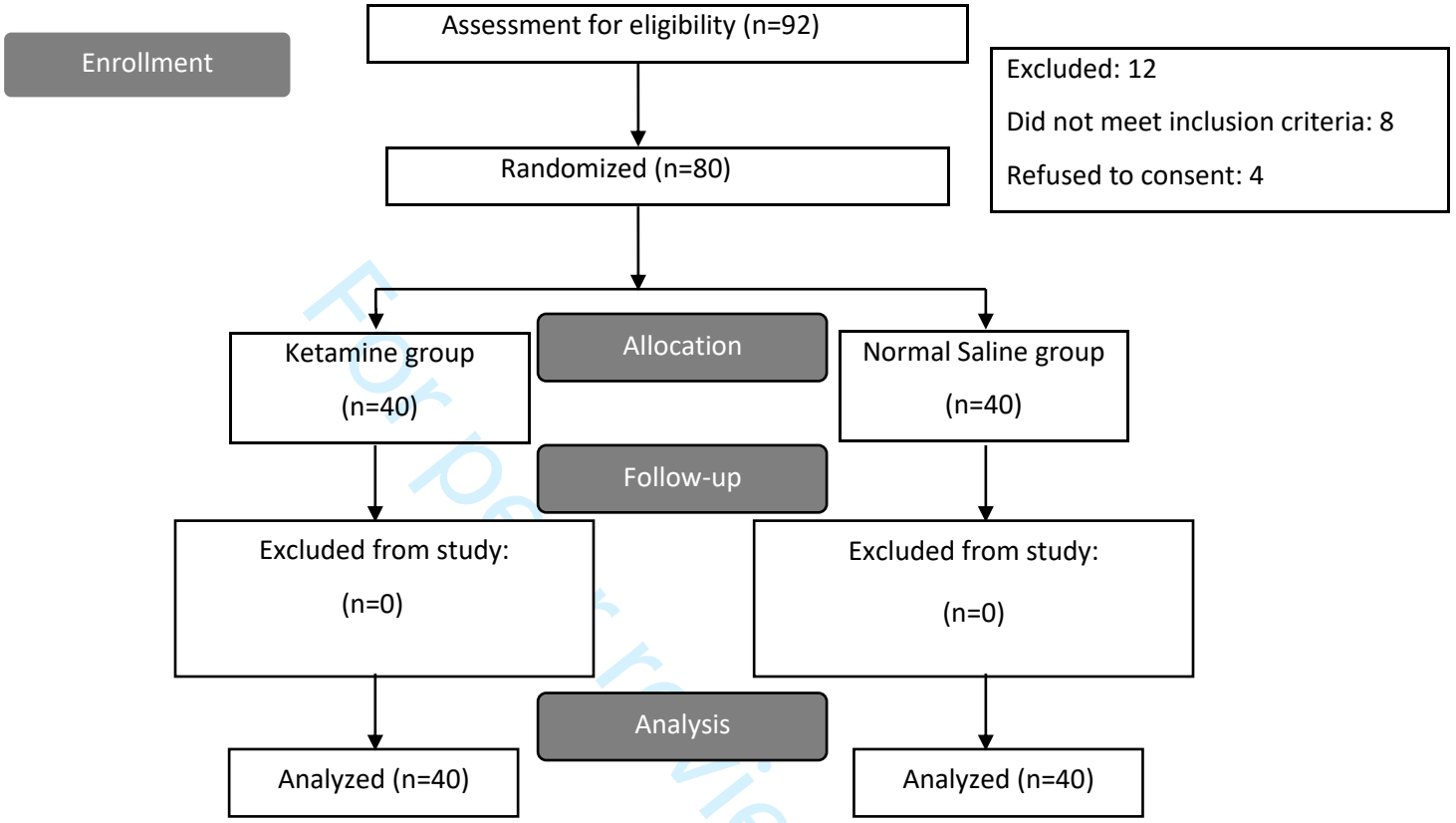
Authors' Contributions

Prahlad Adhikari: This author helped in study design, patient recruitment, data collection and writing up of the first draft of the paper

Asish Subedi: This author helped in study design, pateint recruitment, analysis and interpretation of data, manuscript revision and final draft

Birendra Prasad Sah: This author helped in study design, data collection and manuscript revision.

Krishna Pokharel: This author helped in study design, patient recruitment and final draft



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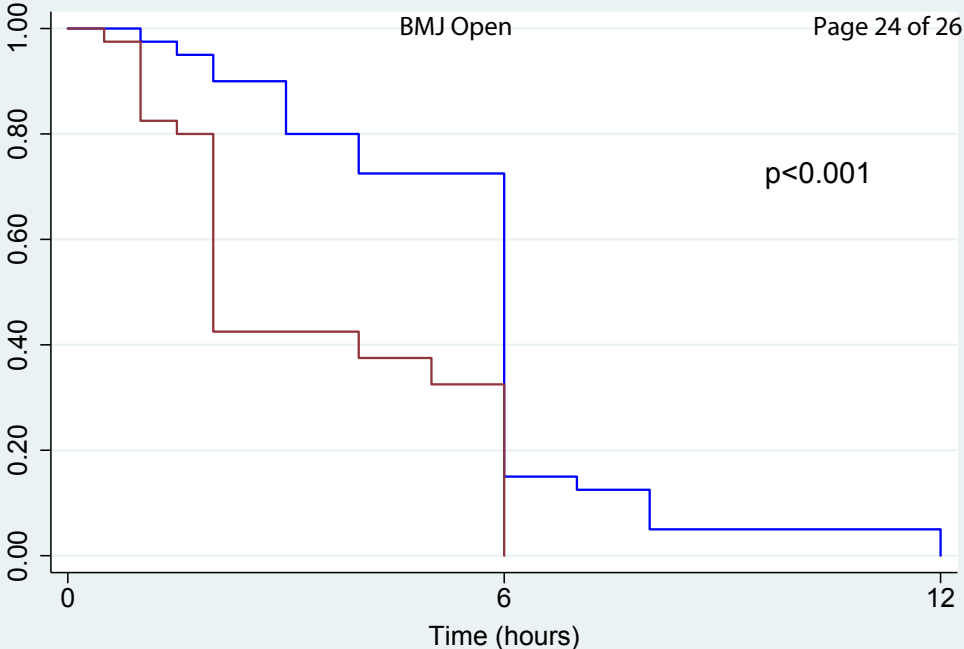

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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2,3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7,8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	8
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	5
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	5
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	5
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	5
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	6

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		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	6
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	8
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	N/A
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	5,7
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Figure 1
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Page 9. Figure 2
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Table 3
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	N/A
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Table 3
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	11,12
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	10-12
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	10-13
Other information			
Registration	23	Registration number and name of trial registry	No. NCT03450499. clinicaltrial.gov
Protocol	24	Where the full trial protocol can be accessed, if available	Enclosed as supplementary file

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Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	Non-funded

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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Effects of Intravenous Ketamine after Spinal Anaesthesia for Non-Elective Caesarean Delivery: A Randomised Controlled Trial

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Title page

Analgesic Effects of Intravenous Ketamine after Spinal Anaesthesia for Non-Elective Caesarean Delivery: A Randomised Controlled Trial

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Keywords: Caesarean Delivery; Ketamine; Opioid; Postoperative pain.

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Abstract

Objectives: This study aimed to determine if low dose intravenous ketamine is effective in reducing opioid use and pain after non-elective caesarean delivery.

Design: Prospective, randomised, double-blind.

Setting: Tertiary hospital, BPKIHS, Dharan, Nepal

Participants: 80 patients undergoing non-elective caesarean section with spinal anaesthesia.

Interventions: Patients were allocated in 1:1 ratio to receive either intravenous ketamine 0.25 mg/kg or normal saline before the skin incision.

Primary and secondary outcome measures: The primary outcome was the total amount of morphine equivalents needed up to postoperative 24 hours. Secondary outcome measures were postoperative pain scores, time to the first perception of pain, maternal adverse effects (nausea, vomiting, hypotension, shivering, diplopia, nystagmus, hallucination) and neonatal Apgar score at 1 and 5 min, neonatal respiratory depression and neonatal intensive-care referral.

Results: The median (range) cumulative morphine consumption during the first 24 hours of surgery was 0 (0-4.67) mg in ketamine group and 1 (0-6) mg in saline group (p=0.003). The median (range) time to the first perception of pain was 6 (1-12) hours and 2 (0.5-6) hours in ketamine and saline group respectively (p<0.001). Postoperatively, the numeric rating scale scores for pain was significantly higher in the saline group compared to ketamine group only at 2 hours in the post anaesthesia care unit and 6 hours in the ward (p<0.05). Maternal adverse effects and neonatal outcomes were comparable between the two groups.

Conclusions: Pre-incisional intravenous low dose ketamine was associated with the lower opioids requirement after non-elective caesarean delivery. A significant decrease in pain scores

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was observed only in the early hours after surgery in parturients receiving ketamine than those receiving normal saline.

Trial registration: clinicaltrial.gov- No. NCT03450499

Strengths and limitations of this study:

- In this randomised, double-blind study, analgesic effect of pre-incisional ketamine in non-elective caesarean delivery was explored.
- 80 patients received either IV ketamine 0.25 mg/kg or normal saline before surgical incision.
- Ketamine reduced total opioid requirement up to 24 hours after surgery compared to placebo group.
- Administration of low-dose ketamine has opioid-sparing effect.
- One limitation is that the end point of the study was limited to postoperative 24 hours only.

A funding statement: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors

A competing interests statement: None

Patient consent for publication: Not required.

Ethics approval: The study was approved by the Institutional Review Committee of BPKIHS (IRC #1089/017). All participants gave informed consent before taking part in the study.

Data availability statement: Data are available upon request from the first author:

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Introduction

Effective analgesia following caesarean delivery (CD) is important as it enhances maternal recovery, reduces the risk of deep vein thrombosis, and facilitates the mother's ability to care for her baby.[1] In recent years, both pharmacological and non-pharmacological modalities for post-caesarean analgesia have been extensively studied; yet, none of them are able to provide optimum post-operative analgesia.[2] Importantly, multimodal analgesia provides superior analgesia with fewer adverse effects related to opioids, and therefore, use of non-opioid analgesic in alleviating postoperative pain is generally preferred.[2] In this regard, opioid-sparing drugs, such as ketamine may be valuable in providing better analgesia without major adverse effects.[3]

Both central and peripheral mechanisms have been postulated for ketamine, as it not only abolishes peripheral afferent noxious stimuli but also prevents central sensitization.[4, 5] A recent meta-analysis demonstrated that perioperative administration of non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist ketamine reduces postoperative pain intensity and analgesic consumption.[6]

Non-opioid analgesia plays a vital role in providing good quality analgesia during CD. The effect of ketamine on postoperative pain following spinal anaesthesia in an elective CD has been investigated.[7, 8] However, its analgesic role in a non-elective CD have not been explored to date. In this study, we examined the effect of low-dose intravenous (IV) ketamine on opioid requirement as morphine equivalent and pain intensity (as measured by numeric rating scale scores) following spinal anaesthesia for non-elective CD.

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Methods

This prospective, randomised, placebo-controlled, double-blind study was conducted at Bisheshwar Prasad Koirala Institute of Health Sciences (BPKIHS), Dharan, Nepal, between April 2, 2018, and March 7, 2019. This study was approved by the BPKIHS Institutional Review Committee (IRC #1089/017) and written informed consent was obtained from all subjects participating in the trial. The trial was registered prior to patient enrollment at clinicaltrials.gov (NCT03450499, Principal investigator: Prahlad Adhikari, Date of registration: March 1, 2018). The study was conducted according to the ethical principles reported in the Declaration of Helsinki and adheres to the CONSORT (Consolidated Standards of Reporting Trials) statement.

Parturients at term undergoing non-elective, category 2 and 3 (according to NICE guideline classification of urgency of emergency caesarean),[9] lower segment CD under spinal anaesthesia with American Society of Anaesthesiologists physical status (ASA PS) II were eligible for this trial. Women with body mass index $\geq$ 40 kg/m^2, height <150 cm, current use of pain medication including opioids, history of substance abuse or hallucinations, cardiovascular disease, diabetes, multiple gestations, known fetal abnormality, chronic pain were excluded. Other exclusion criteria were contraindications to the spinal anaesthesia, severely compromised fetus requiring general anaesthesia and those patients who received labour analgesia.

Independent anaesthesia supporting staff randomly assigned the patients in a 1:1 ratio to receive either ketamine or normal saline using a computer-generated simple random sequence. 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

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it. The study subject and the investigators assessing the outcome were blinded to the group assignment. Group KET received IV ketamine (Ketamax®, Troikaa Pharmaceuticals Ltd, Gujarat, India) 0.25 mg/kg and group NS received 0.9 % normal saline.

A total of 80 (40 in each group) patients was enrolled. Each eligible patient was informed about the nature of the study in the labour room or emergency ward once the decision was made regarding CD. Subsequently, written informed consent was obtained, and a pre-anaesthetic checkup was done. During this visit, patients were also educated on the use of a 10-cm numeric rating scale (NRS), with 0 representing no pain and 10 representing the worst imaginable pain. All patients received IV metoclopramide 10 mg and ranitidine 50 mg for aspiration prophylaxis. Patients were transferred to the operating room and standard monitoring was applied. An infusion of Lactated Ringer's (RL) solution was initiated at a minimal rate via18-gauge IV cannula placed on the forearm.

With the patient in an appropriate position, a 25 gauge Quincke needle was inserted at L3-4 or L4-5 interspace; and intrathecal (IT) 2.2 ml of 0.5% heavy bupivacaine with 10 µg fentanyl was administered. An anaesthesiologist who was unaware of the study group injected the spinal drug. RL was administered at a rapid rate beginning at the time of the intrathecal injection. After noting the time of injection, the patient was placed in a supine position with 15 degrees left tilt. The study drug, according to the allocated group was injected intravenously just before the surgical incision. Oxygen was administered via the face mask at the rate of 5 L/min.

The onset of a sensory block was assessed using alcohol-soaked cotton swabs. Initially, every minute, the sensory block level was checked. When the sensory block reached the T6 level, surgery was started. Intraoperative pain was managed with fentanyl 20 µg titrated to a maximum

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of 100 µg by the attending anaesthesiologist. Intraoperative fall of systolic arterial pressure >20% of the baseline or < 100 mmHg and heart rate (HR) < 50 beats/min were considered significant. Hypotension was managed with increasing fluid administration (RL) rate and IV phenylephrine 50 µg (if HR>50 beats/min) or ephedrine 6 mg (if HR< 50 beats/min). Bradycardia (HR<50 beats/min) was managed with Atropine 0.4 mg IV. Time from the spinal injection to the delivery was noted. After the delivery of baby, 3 IU of oxytocin was administered IV over ≥ 30 secs followed by an infusion of 10 IU/hr (oxytocin 40 IU in 500 ml of Hartmann's solution). Newborn Apgar score was noted at 1 and 5 min after birth. Both groups received 1 g IV paracetamol every 6 hours and 30 mg IV ketorolac every 8 hours starting at the end of surgery.

Postoperative pain was evaluated using NRS at rest and on an attempt to move or bend forward from the bed. During the stay at the postanaesthesia care unit (PACU; On arrival, 1 and 2 hours thereafter), if NRS score was >3, the patient received IV fentanyl 15 µg, and it was repeated every 5 minutes until NRS was ≤ 3. In the post-operative ward (6, 12, and 24 hours) IV morphine 2 mg was administered for NRS score >3, and it was repeated until NRS ≤ 3.

The primary outcome was the total consumption of opioids as morphine equivalents up to 24 hours after surgery. Secondary outcomes were postoperative pain scores at rest and on movement; time to the first perception of pain (in hours); maternal adverse effects (incidence of nausea, vomiting, shivering, diplopia, nystagmus, hallucination); neonatal Apgar scores; neonates requiring resuscitation and intensive-care admission. Maternal adverse effects were noted intraoperatively and up to 24 hours after surgery. Presence of hallucination was based on a criterion of verbally reporting of sensory experiences with or without intuition and not triggered by a relevant stimulus.[10] Nausea and vomiting were rated on a scale of 0 to 3 (0, No nausea, no

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vomiting, 1 Light nausea, no vomiting episodes, 2 Moderate nausea, one or two vomiting episodes, 3 severe nausea, three or more vomiting episodes).[11] IV Ondansetron 4 mg was given when the score was ≥ 2. Shivering was graded using a scale described by Tsai and Chu. [12] Pethidine 20 mg was administered IV if shivering involved the whole body. The equivalent dose of fentanyl consumed (intraoperative and PACU) for pain and pethidine needed for shivering was converted to morphine from an online dose equivalent calculator (www.globalrph.com/medcalcs/opioid-pain-management-converter-advanced).

Statistical analysis:

The data collected in the case report form were entered in the Microsoft Excel 2016 software. All analysis was conducted using STATA software version 15 (Stata Corporation, College Station, TX, USA). Normality of the data was checked using histogram, Kurtosis Skewness test and Sapiro Wilk test. Parametric data were presented as mean ± standard deviation and non-parametric data as median (range). For the normally distributed data, Student *t*-test and for the non-normally distributed data, Mann-Whitney *U* test were applied. The categorical data were compared using the chi-square test or Fisher exact test as appropriate. Post-hoc analysis using the Bonforrini correction was applied for comparisons of postoperative pain scores between the two groups. For this, an adjustment of the alpha value was made as 0.05 divided by six-time points of assessment, i.e. 0.05/6= 0.008.

Sample size

The sample size was calculated based on a previous study,[13] which showed a mean ± SD consumption of pethidine in the ketamine group as 54.17 ± 12.86 mg and 74.44 ± 33.82 mg in the placebo group. To detect this difference, assuming $\alpha = 0.05$ and $\beta = 0.1$ (90% power) and

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using the 2-tailed Student t-test, 34 subjects were required in each group (STATA version 15, Stata Corporation, College Station, TX, USA). Finally, forty patients were assigned to each group to allow for possible dropouts.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

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Results

Among 92 women eligible for the study, 80 were enrolled, as eight subjects did not meet the inclusion criteria and four refused to give consent. (Fig.1) The demographic and clinical characteristics of both groups are demonstrated in Table 1.

The median (range) 24 hours morphine equivalent required in KET group was 0 (0-4.67) mg compared to 1 (0-6) mg in NS group (p=0.003). Mean 24 hours morphine consumption were 0.53 ± 1.22 mg in the KET group and 1.58 ± 1.87 mg in the NS group (mean difference –1.05 mg, p=0.004). In PACU, the median (range) dose of fentanyl consumed was 0 (0-0) µg in parturients receiving ketamine versus 0 (0-20) µg in those receiving normal saline (p=0.01). In the surgical unit, median morphine consumed was 0 (0-4) mg in the KET group and 0 (0-4) mg in the NS group (p=0.02). Significant differences between the two groups in terms of postoperative pain scores at rest were observed only at 2 hours and 6 hours (Table 2). Likewise, the pain scores during movement between the two groups were significant at 2 hours and 6 hours after surgery (Table 2). However, after adjustment for multiplicity (p = 0.008), the difference in the pain scores after surgery between the two groups was only significant at 2 hours at rest and 2 hours and 6 hours during movement (Table 2). The median (range) time to the first perception of pain in the KET group was 6 (1-12) hours whereas in the NS group this period was reduced to 2 (0.5-6) hours (p < 0.001).

There were no significant differences in maternal adverse effects between the two groups (Table 3). In the KET group, one patient complained of diplopia and one patient manifested nystagmus. There were no cases of hallucination in either group. Neonatal outcomes were comparable between the two groups (Table 3). No neonatal deaths were observed.

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Discussion:

Our study showed that pre-incisional IV low dose ketamine reduced perioperative opioid requirement in patients undergoing non-elective CD under spinal anaesthesia as compared to the placebo. Lower pain scores were observed in the ketamine group as compared to the placebo at 2 and 6 hours postoperatively. In addition, the time to the first perception of pain was earlier in the normal saline group than the ketamine group.

There is little evidence to suggest that there is any difference in postoperative pain intensity between the elective and non-elective CD.[14] However, previous studies have shown that woman who had an emergency CD was more likely to encounter negative birth experience, high anxiety level and post-traumatic disorder than a woman who underwent elective CD.[14-16] Because there is a significant link between psychological distress and pain after surgery, focus on good quality perioperative analgesia during the non-elective CD is also needed. Therefore, we tested the analgesic role of ketamine in a non-elective CD because all previous studies were conducted in elective CD.

Opioids will continue to play an important role in perioperative pain management during CD; but because of several unwanted effects associated with its use, non-opioid analgesics are generally added.[17,18] Moreover, in resource-limited settings, longer-acting neuraxial opioids are less frequently used for post-CS analgesia because of their poor availability and lack of dedicated monitoring postoperatively.[17] In this regard, opioid-sparing agents such as ketamine may prove to be beneficial. Though ketamine is widely used as an anaesthetic induction agent, in recent times, its role has widened. Among several new indications, perioperative administration of low-dose systemic ketamine has demonstrated analgesic properties. [6]

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A sub-group study from a meta-analysis in 2015 that evaluated five trials performed under spinal anaesthesia for the elective CD found a significant reduction in cumulative morphine consumption with ketamine compared with the placebo group.[19] However, high heterogeneity was observed among the studies, and this was probably due to variation in ketamine regimen. Two studies had used a pre-incisional single dose of 0.15 mg/kg ketamine and the other one had used a fixed dose of 30 mg, while the remaining two studies had continued the infusion of ketamine either until the end of surgery or up to 24 h postoperatively. We administered a single dose of 0.25 mg/kg ketamine immediately after spinal injection because bolus dose up to 1 mg/kg IV is considered a sub-anaesthetic dose.[20] A recent meta-analysis also supported this fact where more than 50% of the studies included in the analysis had used doses of ketamine boluses ≤ 1mg/kg.[6]

We used IV ketamine before surgical incision, despite administration of spinal anaesthesia because pre-emptive administration of ketamine can block the development of central sensitization in the postoperative period. Moreover, the analgesic effect is maximized when pre-incision ketamine is given in conjunction with other analgesics such as opioids and local anaesthetics pre-emptively.[21] At a low bolus dose, ketamine produces analgesia by directly inhibiting NMDA receptors.[20] Intravenous single dose of ketamine has an elimination half-life of 2–3 hours,[22] however, some traces of ketamine is still present 24 hours after injection.[23] In addition, an active metabolite of ketamine (norketamine) which also produces analgesia has slow elimination compared to its parent compound.[22,23] These are the likely reasons why a single dose of ketamine produces analgesia that may last beyond its elimination half-life.

Although we observed a statistically significant difference for the mean cumulative morphine requirement in the first 24 hours, it may be regarded as clinically insignificant because the mean

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difference was 1 mg. One reason for this small difference in overall opioid consumption and no significant change in pain intensity in late hours is likely due to the use of multimodal analgesia. In both the groups, we used IV paracetamol and ketorolac round the clock while an opioid was used as rescue analgesia. Unlike other studies where a single bolus dose of pre-incisional ketamine was administered, analgesics in the postoperative period were given only for breakthrough pain.[8,13] As a result, in those studies, a larger difference in total morphine equivalent consumption was observed that ranged from 2.11 mg to 6.8 mg. In another study, contradict to our findings, low dose ketamine did not offer any postoperative benefits despite using multimodal analgesia. [7] In the above study, IT morphine was administered, and therefore, the prolonged analgesic effect of IT morphine could have overshadowed the analgesic effect of ketamine.

Several studies have explored the association between perioperative ketamine administration and postoperative nausea and vomiting (PONV). In patients with high risk for PONV undergoing lumbar spine surgery, ketamine increased the incidence of nausea.[24] The emetogenic effect of ketamine is likely due to its inhibitory action on serotonin uptake at the synaptic terminal; however, the precise mechanism remains elusive.[25, 26] Although we did not observe a significant change in the incidence of PONV, the role of ketamine for PONV during CD is still uncertain. While one study found a reduced incidence of intraoperative nausea and vomiting, another showed an increased frequency of vomiting.[27, 28] As a result, there are assumptions made for and against the role of ketamine on PONV: emetogenic versus opioid-sparing effects; whether a reduction in the frequency of hypotension indirectly minimizes the PONV episodes. Because PONV following spinal anaesthesia is multifactorial, it is difficult to establish a causal relationship between ketamine and PONV. Nevertheless, large clinical trials are warranted

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before any conclusion can be drawn. Prophylactic use of low doses of ketamine is effective in preventing shivering post-spinal anaesthesia for CD.[29] Although we found fewer parturients from ketamine group required pethidine for shivering in comparison to normal saline group, the difference was not significant statistically. The reason for this observation could be that our study not powered enough to detect this difference.

Ketamine crosses the placenta rapidly and has a mean fetal-maternal (F:M) ratio of 1.26 following an intravenous induction dose of anaesthesia.[30] As a result, concern has been expressed as to whether or not ketamine administered in clinical doses at the time of delivery produces neurotoxic effects in newborns. Animal studies have shown the dose and exposure dependent effect of ketamine on the developing brain. A 5-h ketamine infusion in pregnant rhesus female monkey produced neuronal apoptosis in the fetal brain; [31] On the other hand, no serious complication was observed in lamb fetus after pregnant ewes were anaesthetized with 20 mg/kg of IV ketamine for CD.[32] Based on clinical studies, a meta-analysis on the role of intravenous ketamine in parturients undergoing CD demonstrated no differences in the Apgar scores of neonates between ketamine-treated and placebo group.[19] Likewise, ketamine administered at 1 mg/kg IV in parturient did not worsen the newborn acid-base status in comparison to either thiopentone anaesthesia or placebo group.[33,34] We too observed no significant difference in neonatal outcomes between the two groups. As there is a paucity of data related to the neurodevelopmental effects in neonates after exposure to ketamine during CD, it is wise not to exceed ketamine doses above 1.5 mg/kg IV, and infusions are probably best avoided.

There are several limitations. First, the endpoint of the study was limited to postoperative 24 hours only. Second, we did not assess patient satisfaction and quality of recovery postoperatively.

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In conclusion, our findings indicate that administration of pre-incisional low dose ketamine during non-elective caesarean delivery under spinal anaesthesia reduces perioperative overall opioid requirement and lowers the pain scores in the early hours after surgery.

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Table 1. Comparison of patient demographic, block characteristics and surgical profiles.

Variables	KET group n=40	NS group n=40	*p*-value
Age (in years)	24.90 ± 4.80	25.87 ± 5.53	0.40
Height (in cm)	155.45 ± 3.75	156.82 ± 4.25	0.12
Body mass index (in kg/m^2)	25.47±2.18	26.27±3.16	0.19
Gestational age (in weeks)	38.77±1.36	38.8±1.69	0.94
Indication for Cesarean section			0.65
Non reassuring non-stress test	11 (28)	16 (40)	
Previous CS presenting in labour	8 (20)	6 (15)	
Meconium stained liquor	6 (15)	6 (15)	
Failed induction	6 (15)	7 (17)	
Others (CPD, Malpresentation)	9 (22)	5 (13)	
Onset block to T6 dermatome (in min)	2 (1-7)	2 (1-5)	0.23
Highest sensory block (dermatome)	T4 (T2-T4)	T4 (T2-T4)	0.74
Spinal injection to delivery interval (in min)	20 (13-35)	19 (14-40)	0.65
Intraoperative fentanyl needed (μg)	0 (0-0)	0 (0-40)	0.15

Values are expressed as mean ± SD, number (%), or median (range). CPD = Cephalopelvic disproportion

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Table 2. Comparison of pain scores between two groups.

Time points	KET group n=40	NS group n=40	*p*-value
At Rest			
On arrival to PACU	0 (0-1)	0 (0-4)	0.15
1 h	0 (0-2)	0 (0-5)	0.06
2 h	0 (0-2)	2 (0-5)	<0.001
In Surgical Unit			
6 h	2 (1-4)	2 (0-5)	0.02
12 h	2 (0-4)	2 (0-5)	0.07
24 h	2 (1-4)	2 (0-5)	0.23
During Movement			
On arrival to PACU	0 (0-2)	0 (0-5)	0.08
1 h	0 (0-3)	1 (0-6)	0.05
2 h	2 (0-3)	2 (0-5)	< 0.001
In Surgical Unit			
6 h	2 (0-4)	3 (2-6)	0.001
12 h	3 (2-4)	3 (2-6)	0.22
24 h	3 (2-6)	3 (2-6)	0.81

Values are expressed in median (range)

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Table 3. Maternal adverse effects and neonatal outcomes

	KET group n=40	NS group n=40	*p*-value
Hypotension	13 (32)	16 (40)	0.48
Nausea or vomiting	4 (10)	5 (12)	0.72
Shivering requiring pethidine	5 (12)	8 (20)	0.36
APGAR score 1 min	8 (6-8)	8 (6-8)	0.54
APGAR score 5 min	9 (7-9)	9 (8-9)	0.67
Resuscitation needed in neonate (n)	1 (2%)	1 (2%)	1.0
Neonatal intensive care unit admission (n)	1 (2%)	2 (5%)	1.0

Values are in median (range) and number (percentage)

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Figure legends

Fig. 1 Consort flow diagram of the study.

Authors' Contributions

Prahlad Adhikari: This author helped in study design, patient recruitment, data collection and writing up of the first draft of the paper

Asish Subedi: This author helped in study design, pateint recruitment, analysis and interpretation of data, manuscript revision and final draft

Birendra Prasad Sah: This author helped in study design, data collection and manuscript revision.

Krishna Pokharel: This author helped in study design, patient recruitment and final draft

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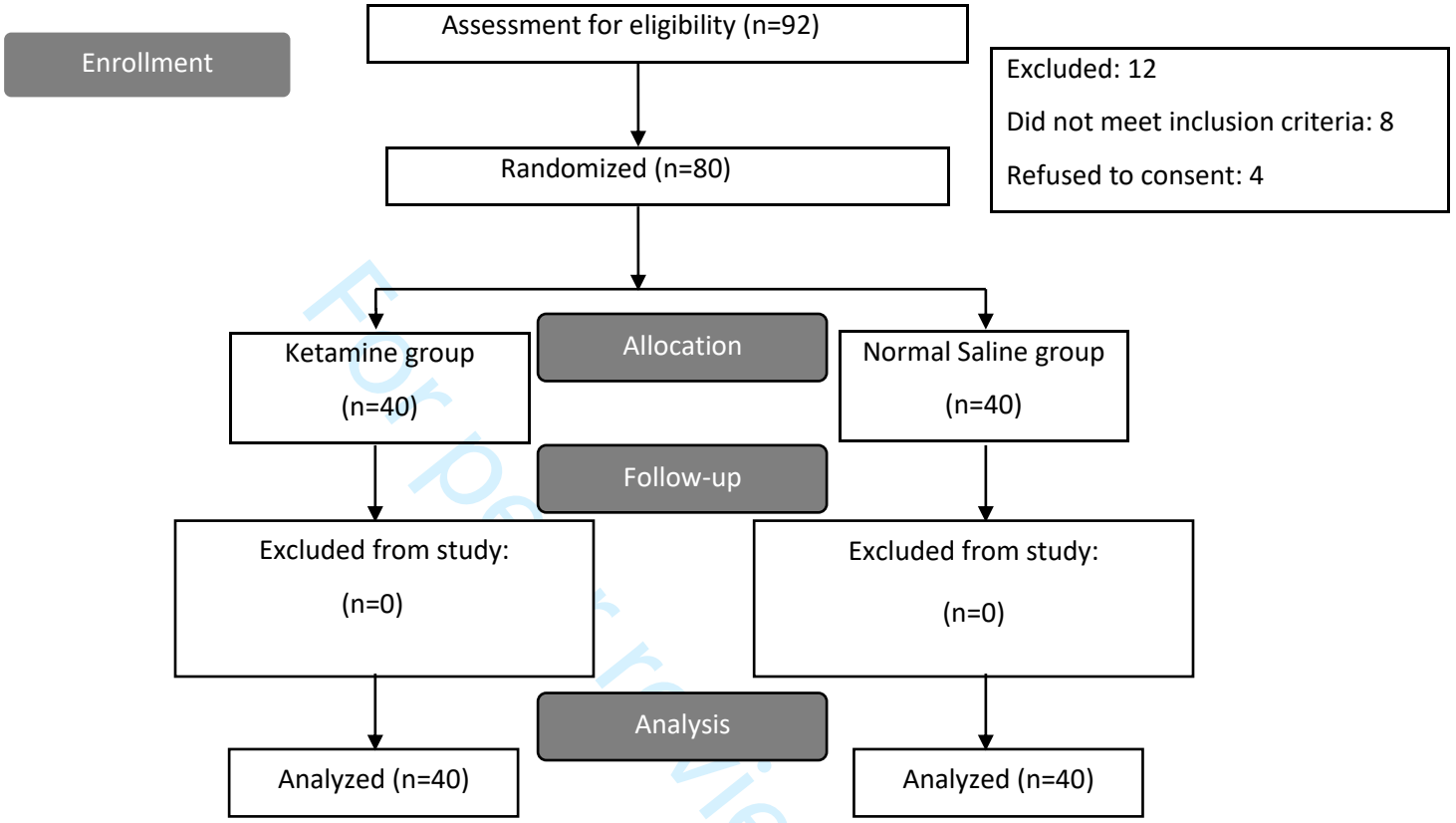

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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2,3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7,8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	8
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	5
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	5
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	5
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	5
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	6

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		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	6
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	8
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	N/A
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	5,7
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Figure 1
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Page 9. Figure 2
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Table 3
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	N/A
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Table 3
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	11,12
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	10-12
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	10-13
Other information			
Registration	23	Registration number and name of trial registry	No. NCT03450499. clinicaltrial.gov
Protocol	24	Where the full trial protocol can be accessed, if available	Enclosed as supplementary file

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Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	Non-funded

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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Effects of Intravenous Ketamine after Spinal Anaesthesia for Non-Elective Caesarean Delivery: A Randomised Controlled Trial

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Title page

Analgesic Effects of Intravenous Ketamine after Spinal Anaesthesia for Non-Elective Caesarean Delivery: A Randomised Controlled Trial

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Abstract

Objectives: This study aimed to determine if low dose intravenous ketamine is effective in reducing opioid use and pain after non-elective caesarean delivery.

Design: Prospective, randomised, double-blind.

Setting: Tertiary hospital, BPKIHS, Dharan, Nepal

Participants: 80 patients undergoing non-elective caesarean section with spinal anaesthesia.

Interventions: Patients were allocated in 1:1 ratio to receive either intravenous ketamine 0.25 mg/kg or normal saline before the skin incision.

Primary and secondary outcome measures: The primary outcome was the total amount of morphine equivalents needed up to postoperative 24 hours. Secondary outcome measures were postoperative pain scores, time to the first perception of pain, maternal adverse effects (nausea, vomiting, hypotension, shivering, diplopia, nystagmus, hallucination) and neonatal Apgar score at 1 and 5 min, neonatal respiratory depression and neonatal intensive-care referral.

Results: The median (range) cumulative morphine consumption during the first 24 hours of surgery was 0 (0-4.67) mg in ketamine group and 1 (0-6) mg in saline group (p=0.003). The median (range) time to the first perception of pain was 6 (1-12) hours and 2 (0.5-6) hours in ketamine and saline group respectively (p<0.001). A significant reduction in postoperative pain scores was observed only at 2 hours and 6 hours in the ketamine group compared with placebo group (p<0.05). Maternal adverse effects and neonatal outcomes were comparable between the two groups.

Conclusions: Intravenous administration of low dose ketamine before surgical incision significantly reduced the opioid requirement in the first 24 hours in patients undergoing non-elective caesarean delivery.

Trial registration: clinicaltrial.gov- No. NCT03450499

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Strengths and limitations of this study:

- The nature of the study design (RCT) allows a causal inference i.e. whether pre-incisional administration ketamine during caesarean delivery has opioid sparing effect.
- Due to the small sample size the findings cannot be generalized.
- The end point of the study was also limited to postoperative 24 hours only.

A funding statement: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors

A competing interests statement: None

Patient consent for publication: Not required.

Ethics approval: The study was approved by the Institutional Review Committee of BPKIHS (IRC #1089/017). All participants gave informed consent before taking part in the study.

Data availability statement: Data are available upon request from the second author:

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Introduction

Effective analgesia following caesarean delivery (CD) is important as it enhances maternal recovery, reduces the risk of deep vein thrombosis, and facilitates the mother's ability to care for her baby.[1] In recent years, both pharmacological and non-pharmacological modalities for post-caesarean analgesia have been extensively studied; yet, none of them are able to provide optimum post-operative analgesia.[2] Importantly, multimodal analgesia provides superior analgesia with fewer adverse effects related to opioids, and therefore, use of non-opioid analgesic in alleviating postoperative pain is generally preferred.[2] In this regard, opioid-sparing drugs, such as ketamine may be valuable in providing better analgesia without major adverse effects.[3]

Both central and peripheral mechanisms have been postulated for ketamine, as it not only abolishes peripheral afferent noxious stimuli but also prevents central sensitization.[4, 5] A recent meta-analysis demonstrated that perioperative administration of non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist ketamine reduces postoperative pain intensity and analgesic consumption.[6]

Non-opioid analgesia plays a vital role in providing good quality analgesia during CD. The effect of ketamine on postoperative pain following spinal anaesthesia in an elective CD has been investigated.[7, 8] However, its analgesic role in a non-elective CD have not been explored to date. In this study, we examined the effect of low-dose intravenous (IV) ketamine on opioid requirement as morphine equivalent and pain intensity (as measured by numeric rating scale scores) following spinal anaesthesia for non-elective CD.

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Methods

This prospective, randomised, placebo-controlled, double-blind study was conducted at Bisheshwar Prasad Koirala Institute of Health Sciences (BPKIHS), Dharan, Nepal, between April 2, 2018, and March 7, 2019. This study was approved by the BPKIHS Institutional Review Committee (IRC #1089/017) and written informed consent was obtained from all subjects participating in the trial. The trial was registered prior to patient enrollment at clinicaltrials.gov (NCT03450499, Principal investigator: Prahlad Adhikari, Date of registration: March 1, 2018). The study was conducted according to the ethical principles reported in the Declaration of Helsinki and adheres to the CONSORT (Consolidated Standards of Reporting Trials) statement.

Parturients at term undergoing non-elective, category 2 and 3 (according to NICE guideline classification of urgency of emergency caesarean),[9] lower segment CD under spinal anaesthesia with American Society of Anaesthesiologists physical status (ASA PS) II were eligible for this trial. Women with body mass index $\geq$ 40 kg/m^2, height <150 cm, current use of pain medication including opioids, history of substance abuse or hallucinations, cardiovascular disease, diabetes, multiple gestations, known fetal abnormality, chronic pain were excluded. Other exclusion criteria were contraindications to the spinal anaesthesia, severely compromised fetus requiring general anaesthesia and those patients who received labour analgesia.

Independent anaesthesia supporting staff randomly assigned the patients in a 1:1 ratio to receive either ketamine or normal saline using a computer-generated simple random sequence. 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. The study

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subject and the investigators assessing the outcome were blinded to the group assignment. Group KET received IV ketamine (Ketamax®, Troikaa Pharmaceuticals Ltd, Gujarat, India) 0.25 mg/kg and group NS received 0.9 % normal saline.

A total of 80 (40 in each group) patients was enrolled. Each eligible patient was informed about the nature of the study in the labour room or emergency ward once the decision was made regarding CD. Subsequently, written informed consent was obtained, and a pre-anaesthetic checkup was done. During this visit, patients were also educated on the use of a 10-cm numeric rating scale (NRS), with 0 representing no pain and 10 representing the worst imaginable pain. All patients received IV metoclopramide 10 mg and ranitidine 50 mg for aspiration prophylaxis. Patients were transferred to the operating room and standard monitoring was applied. An infusion of Lactated Ringer's (RL) solution was initiated at a minimal rate via18-gauge IV cannula placed on the forearm.

With the patient in an appropriate position, a 25 gauge Quincke needle was inserted at L3-4 or L4-5 interspace; and intrathecal (IT) 2.2 ml of 0.5% heavy bupivacaine with 10 µg fentanyl was administered. An anaesthesiologist who was unaware of the study group injected the spinal drug. RL was administered at a rapid rate beginning at the time of the intrathecal injection. After noting the time of injection, the patient was placed in a supine position with 15 degrees left tilt. The study drug, according to the allocated group was injected intravenously just before the surgical incision. Oxygen was administered via the face mask at the rate of 5 L/min.

The onset of a sensory block was assessed using alcohol-soaked cotton swabs. Initially, every minute, the sensory block level was checked. When the sensory block reached the T6 level, surgery was started. Intraoperative pain was managed with fentanyl 20 µg titrated to a maximum of 100

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μg by the attending anaesthesiologist. Intraoperative fall of systolic arterial pressure >20% of the baseline or < 100 mmHg and heart rate (HR) < 50 beats/min were considered significant. Hypotension was managed with increasing fluid administration (RL) rate and IV phenylephrine 50 μg (if HR>50 beats/min) or ephedrine 6 mg (if HR< 50 beats/min). Bradycardia (HR<50 beats/min) was managed with atropine 0.4 mg IV. Time from the spinal injection to the delivery was noted. After the delivery of baby, 3 IU of oxytocin was administered IV over ≥ 30 secs followed by an infusion of 10 IU/hr (oxytocin 40 IU in 500 ml of Hartmann's solution). Newborn Apgar score was noted at 1 and 5 min after birth. Both groups received 1 g IV paracetamol every 6 hours and 30 mg IV ketorolac every 8 hours starting at the end of surgery.

Postoperative pain was evaluated using NRS at rest and on an attempt to move or bend forward from the bed. During the stay at the postanaesthesia care unit (PACU; On arrival, 1 and 2 hours thereafter), if NRS score was >3, the patient received IV fentanyl 15 μg, and it was repeated every 5 minutes until NRS was ≤ 3. In the post-operative ward (6, 12, and 24 hours) IV morphine 2 mg was administered for NRS score >3, and it was repeated until NRS ≤ 3.

The primary outcome was the total consumption of opioids as morphine equivalents up to 24 hours after surgery. Secondary outcomes were postoperative pain scores at rest and on movement; time to the first perception of pain (in hours); maternal adverse effects (incidence of nausea, vomiting, shivering, diplopia, nystagmus, hallucination); neonatal Apgar scores; neonates requiring resuscitation and intensive-care admission. Maternal adverse effects were noted intraoperatively and up to 24 hours after surgery. Presence of hallucination was based on a criterion of verbally reporting of sensory experiences with or without intuition and not triggered by a relevant stimulus.[10] Nausea and vomiting were rated on a scale of 0 to 3 (0, No nausea, no vomiting, 1 Light nausea, no vomiting episodes, 2 Moderate nausea, one or two vomiting episodes, 3 severe

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nausea, three or more vomiting episodes).[11] IV Ondansetron 4 mg was given when the score was ≥ 2. Shivering was graded using a scale described by Tsai and Chu. [12] Pethidine 20 mg was administered IV if shivering involved the whole body. The equivalent dose of fentanyl consumed (intraoperative and PACU) for pain and pethidine needed for shivering was converted to morphine from an online dose equivalent calculator (www.globalrph.com/medcalcs/opioid-pain-management-converter-advanced).

Statistical analysis:

The data collected in the case report form were entered in the Microsoft Excel 2016 software. All analysis was conducted using STATA software version 15 (Stata Corporation, College Station, TX, USA). Normality of the data was checked using histogram, Kurtosis Skewness test and Sapiro Wilk test. Parametric data were presented as mean ± standard deviation and non-parametric data as median (range). For the normally distributed data, Student *t*-test and for the non-normally distributed data, Mann-Whitney *U* test were applied. The categorical data were compared using the chi-square test or Fisher exact test as appropriate. Post-hoc analysis using the Bonforrini correction was applied for comparisons of postoperative pain scores between the two groups. For this, an adjustment of the alpha value was made as 0.05 divided by six-time points of assessment, i.e. 0.05/6= 0.008.

Sample size

The sample size was calculated based on a previous study,[13] which showed a mean ± SD consumption of pethidine in the ketamine group as 54.17 ± 12.86 mg and 74.44 ± 33.82 mg in the placebo group. To detect this difference, assuming $\alpha = 0.05$ and $\beta = 0.1$ (90% power) and using the 2-tailed Student t-test, 34 subjects were required in each group (STATA version 15, Stata

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Corporation, College Station, TX, USA). Finally, forty patients were assigned to each group to allow for possible dropouts.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

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Results

Among 92 women eligible for the study, 80 were enrolled, as eight subjects did not meet the inclusion criteria and four refused to give consent. (Fig.1) The demographic and clinical characteristics of both groups are demonstrated in Table 1.

The median (range) 24 hours morphine equivalent required in KET group was 0 (0-4.67) mg compared to 1 (0-6) mg in NS group (p=0.003) (Fig. 2). Mean 24 hours morphine consumption were 0.53 ± 1.22 mg in the KET group and 1.58 ± 1.87 mg in the NS group (mean difference – 1.05 mg, p=0.004). In PACU, the median (range) dose of fentanyl consumed was 0 (0-0) µg in parturients receiving ketamine versus 0 (0-20) µg in those receiving normal saline (p=0.01). In the surgical unit, median morphine consumed was 0 (0-4) mg in the KET group and 0 (0-4) mg in the NS group (p=0.02). Significant differences between the two groups in terms of postoperative pain scores at rest were observed only at 2 hours and 6 hours (Fig. 3). Likewise, the pain scores during movement between the two groups were significant at 2 hours and 6 hours after surgery (Fig. 4). However, after adjustment for multiplicity (p = 0.008), the difference in the pain scores after surgery between the two groups was only significant at 2 hours at rest and 2 hours and 6 hours during movement (Fig. 3 & Fig. 4). The median (range) time to the first perception of pain in the KET group was 6 (1-12) hours whereas in the NS group this period was reduced to 2 (0.5-6) hours ($p < 0.001$).

There were no significant differences in maternal adverse effects between the two groups (Table 2). In the KET group, one patient complained of diplopia and one patient manifested nystagmus. There were no cases of hallucination in either group. Neonatal outcomes were comparable between the two groups (Table 2). No neonatal deaths were observed.

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Discussion:

Our study showed that pre-incisional IV low dose ketamine reduced perioperative opioid requirement in patients undergoing non-elective CD under spinal anaesthesia as compared to the placebo. Lower pain scores were observed in the ketamine group as compared to the placebo at 2 and 6 hours postoperatively. In addition, the time to the first perception of pain was earlier in the normal saline group than the ketamine group.

There is little evidence to suggest that there is any difference in postoperative pain intensity between the elective and non-elective CD.[14] However, previous studies have shown that woman who had an emergency CD was more likely to encounter negative birth experience, high anxiety level and post-traumatic disorder than a woman who underwent elective CD.[14-16] Because there is a significant link between psychological distress and pain after surgery, focus on good quality perioperative analgesia during the non-elective CD is also needed. Therefore, we tested the analgesic role of ketamine in a non-elective CD because all previous studies were conducted in elective CD.

Opioids will continue to play an important role in perioperative pain management during CD; but because of several unwanted effects associated with its use, non-opioid analgesics are generally added.[17,18] Moreover, in resource-limited settings, longer-acting neuraxial opioids are less frequently used for post-CS analgesia because of their poor availability and lack of dedicated monitoring postoperatively.[17] In this regard, opioid-sparing agents such as ketamine may prove to be beneficial. Though ketamine is widely used as an anaesthetic induction agent, in recent times, its role has widened. Among several new indications, perioperative administration of low-dose systemic ketamine has demonstrated analgesic properties. [6]

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A sub-group study from a meta-analysis in 2015 that evaluated five trials performed under spinal anaesthesia for the elective CD found a significant reduction in cumulative morphine consumption with ketamine compared with the placebo group.[19] However, high heterogeneity was observed among the studies, and this was probably due to variation in ketamine regimen. Two studies had used a pre-incisional single dose of 0.15 mg/kg ketamine and the other one had used a fixed dose of 30 mg, while the remaining two studies had continued the infusion of ketamine either until the end of surgery or up to 24 h postoperatively. We administered a single dose of 0.25 mg/kg ketamine immediately after spinal injection because bolus dose up to 1 mg/kg IV is considered a sub-anaesthetic dose.[20] A recent meta-analysis also supported this fact where more than 50% of the studies included in the analysis had used doses of ketamine boluses ≤ 1mg/kg.[6]

We used IV ketamine before surgical incision, despite administration of spinal anaesthesia because pre-emptive administration of ketamine can block the development of central sensitization in the postoperative period. Moreover, the analgesic effect is maximized when pre-incision ketamine is given in conjunction with other analgesics such as opioids and local anaesthetics pre-emptively.[21] At a low bolus dose, ketamine produces analgesia by directly inhibiting NMDA receptors.[20] Intravenous single dose of ketamine has an elimination half-life of 2–3 hours,[22] however, some traces of ketamine is still present 24 hours after injection.[23] In addition, an active metabolite of ketamine (norketamine) which also produces analgesia has slow elimination compared to its parent compound.[22,23] These are the likely reasons why a single dose of ketamine produces analgesia that may last beyond its elimination half-life.

Although we observed a statistically significant difference for the mean cumulative morphine requirement in the first 24 hours, it may be regarded as clinically insignificant because the mean difference was 1 mg. One reason for this small difference in overall opioid consumption and no

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significant change in pain intensity in late hours is likely due to the use of multimodal analgesia. In both the groups, we used IV paracetamol and ketorolac round the clock while an opioid was used as rescue analgesia. Unlike other studies where a single bolus dose of pre-incisional ketamine was administered, analgesics in the postoperative period were given only for breakthrough pain.[8,13] As a result, in those studies, a larger difference in total morphine equivalent consumption was observed that ranged from 2.11 mg to 6.8 mg. In another study, contradict to our findings, low dose ketamine did not offer any postoperative benefits despite using multimodal analgesia. [7] In the above study, IT morphine was administered, and therefore, the prolonged analgesic effect of IT morphine could have overshadowed the analgesic effect of ketamine.

Several studies have explored the association between perioperative ketamine administration and postoperative nausea and vomiting (PONV). In patients with high risk for PONV undergoing lumbar spine surgery, ketamine increased the incidence of nausea.[24] The emetogenic effect of ketamine is likely due to its inhibitory action on serotonin uptake at the synaptic terminal; however, the precise mechanism remains elusive.[25, 26] Although we did not observe a significant change in the incidence of PONV, the role of ketamine for PONV during CD is still uncertain. While one study found a reduced incidence of intraoperative nausea and vomiting, another showed an increased frequency of vomiting.[27, 28] As a result, there are assumptions made for and against the role of ketamine on PONV: emetogenic versus opioid-sparing effects; whether a reduction in the frequency of hypotension indirectly minimizes the PONV episodes. Because PONV following spinal anaesthesia is multifactorial, it is difficult to establish a causal relationship between ketamine and PONV. Nevertheless, large clinical trials are warranted before any conclusion can be drawn. Prophylactic use of low doses of ketamine is effective in preventing shivering post-spinal anaesthesia for CD.[29] Although we found fewer parturients from ketamine group required

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pethidine for shivering in comparison to normal saline group, the difference was not significant statistically. The reason for this observation could be that our study not powered enough to detect this difference.

Ketamine crosses the placenta rapidly and has a mean fetal-maternal (F:M) ratio of 1.26 following an intravenous induction dose of anaesthesia.[30] As a result, concern has been expressed as to whether or not ketamine administered in clinical doses at the time of delivery produces neurotoxic effects in newborns. Animal studies have shown the dose and exposure dependent effect of ketamine on the developing brain. A 5-h ketamine infusion in pregnant rhesus female monkey produced neuronal apoptosis in the fetal brain; [31] On the other hand, no serious complication was observed in lamb fetus after pregnant ewes were anaesthetized with 20 mg/kg of IV ketamine for CD.[32] Based on clinical studies, a meta-analysis on the role of intravenous ketamine in parturients undergoing CD demonstrated no differences in the Apgar scores of neonates between ketamine-treated and placebo group.[19] Likewise, ketamine administered at 1 mg/kg IV in parturient did not worsen the newborn acid-base status in comparison to either thiopentone anaesthesia or placebo group.[33,34] We too observed no significant difference in neonatal outcomes between the two groups. As there is a paucity of data related to the neurodevelopmental effects in neonates after exposure to ketamine during CD, it is wise not to exceed ketamine doses above 1.5 mg/kg IV, and infusions are probably best avoided.

There are several limitations. First, the endpoint of the study was limited to postoperative 24 hours only. Second, we did not assess patient satisfaction and quality of recovery postoperatively.

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In conclusion, our findings indicate that administration of pre-incisional low dose ketamine during non-elective caesarean delivery under spinal anaesthesia reduces perioperative overall opioid requirement and lowers the pain scores in the early hours after surgery.

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Table 1. Comparison of patient demographic, block characteristics and surgical profiles.

Variables	KET group n=40	NS group n=40	*p*-value
Age (in years)	24.90 ± 4.80	25.87 ± 5.53	0.40
Height (in cm)	155.45 ± 3.75	156.82 ± 4.25	0.12
Body mass index (in kg/m^2)	25.47±2.18	26.27±3.16	0.19
Gestational age (in weeks)	38.77±1.36	38.8±1.69	0.94
Indication for Cesarean section			0.65
Non reassuring non-stress test	11 (28)	16 (40)	
Previous CS presenting in labour	8 (20)	6 (15)	
Meconium stained liquor	6 (15)	6 (15)	
Failed induction	6 (15)	7 (17)	
Others (CPD, Malpresentation)	9 (22)	5 (13)	
Onset block to T6 dermatome (in min)	2 (1-7)	2 (1-5)	0.23
Highest sensory block (dermatome)	T4 (T2-T4)	T4 (T2-T4)	0.74
Spinal injection to delivery interval (in min)	20 (13-35)	19 (14-40)	0.65
Intraoperative fentanyl needed (μg)	0 (0-0)	0 (0-40)	0.15

Values are expressed as mean ± SD, number (%), or median (range). CPD = Cephalopelvic disproportion

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Table 2. Maternal adverse effects and neonatal outcomes

	KET group n=40	NS group n=40	*p*-value
Hypotension	13 (32)	16 (40)	0.48
Nausea or vomiting	4 (10)	5 (12)	0.72
Shivering requiring pethidine	5 (12)	8 (20)	0.36
APGAR score 1 min	8 (6-8)	8 (6-8)	0.54
APGAR score 5 min	9 (7-9)	9 (8-9)	0.67
Resuscitation needed in neonate (n)	1 (2%)	1 (2%)	1.0
Neonatal intensive care unit admission (n)	1 (2%)	2 (5%)	1.0

Values are in median (range) and number (percentage)

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Figure legends

Fig. 1 Consort flow diagram of the study.

Fig. 2 Total morphine equivalent for 24 h postoperatively in patients receiving ketamine and saline.

Fig. 3 Postoperative numerical rating pain (NRS) scores at various time points at rest. After adjustment for multiplicity significant difference between the groups was detected at 2 hours (♦$p < 0.05$).

Fig. 4 Postoperative numerical rating pain (NRS) scores at various time points during movement. After adjustment for multiplicity significant difference between the groups was detected at 2 hours and 6 hours (♦$p < 0.05$).

Authors' Contributions

Prahlad Adhikari: This author helped in study design, patient recruitment, data collection and writing up of the first draft of the paper

Asish Subedi: This author helped in study design, pateint recruitment, analysis and interpretation of data, manuscript revision and final draft

Birendra Prasad Sah: This author helped in study design, data collection and manuscript revision.

Krishna Pokharel: This author helped in study design, patient recruitment and final draft

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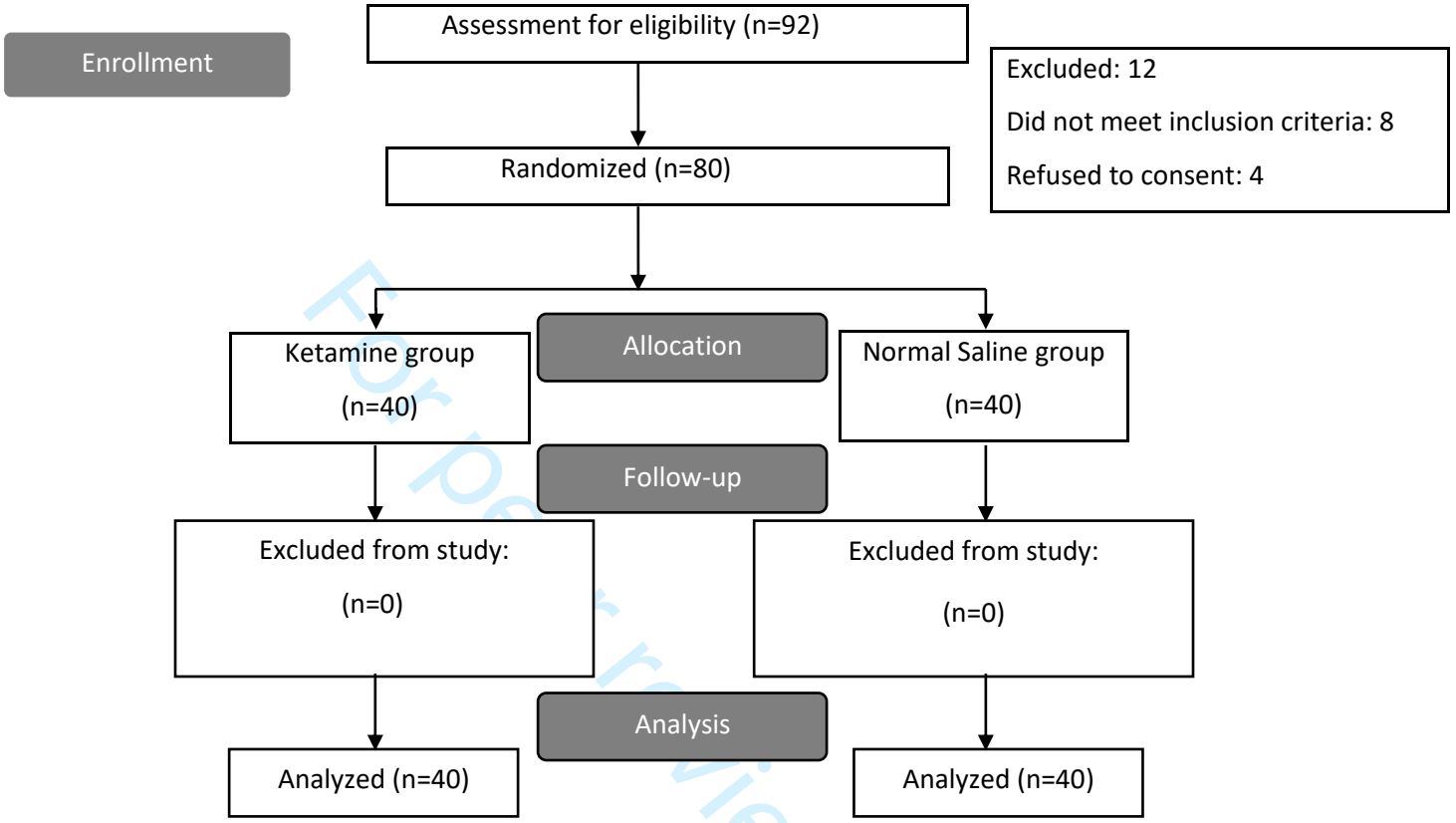

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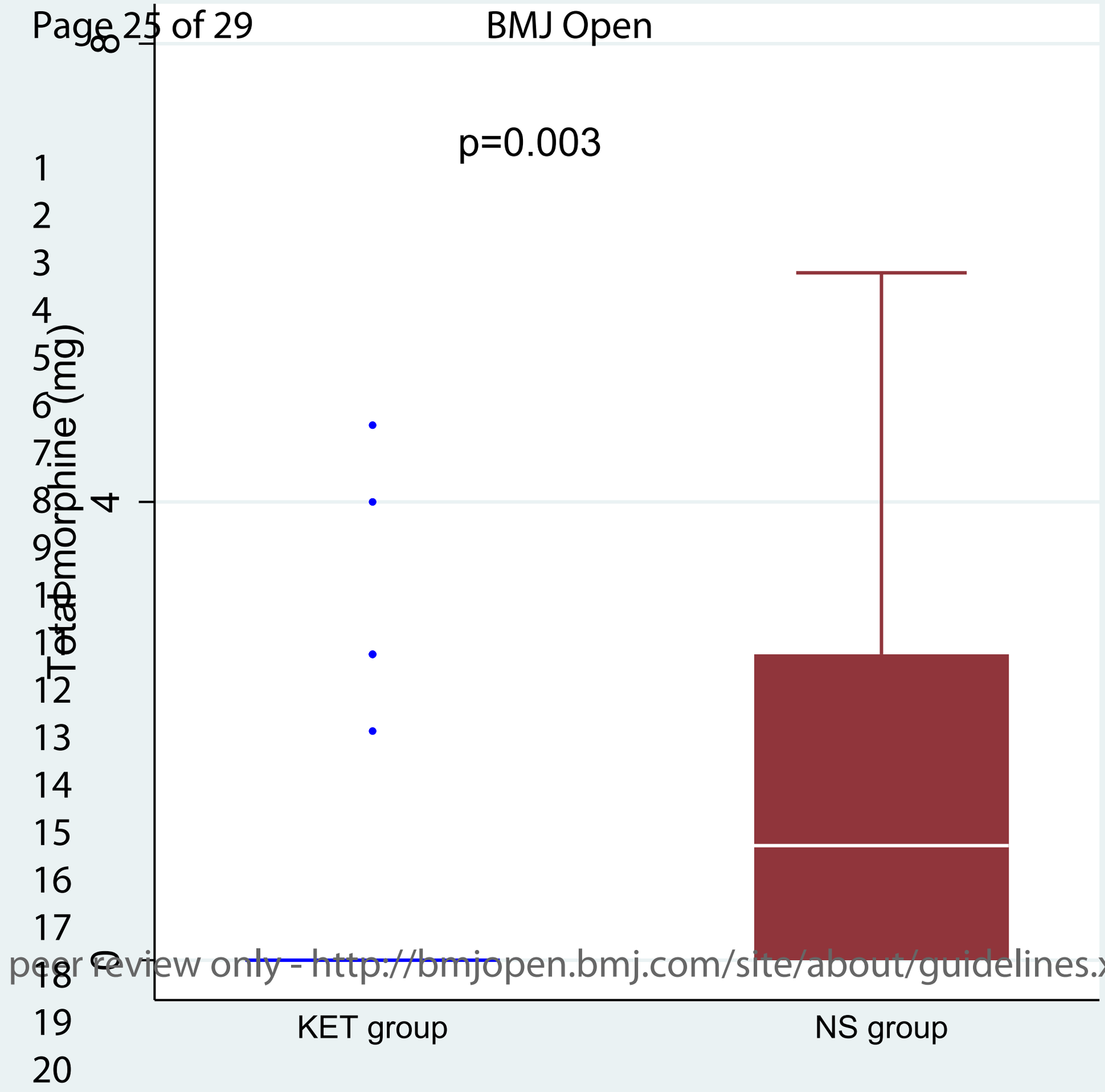

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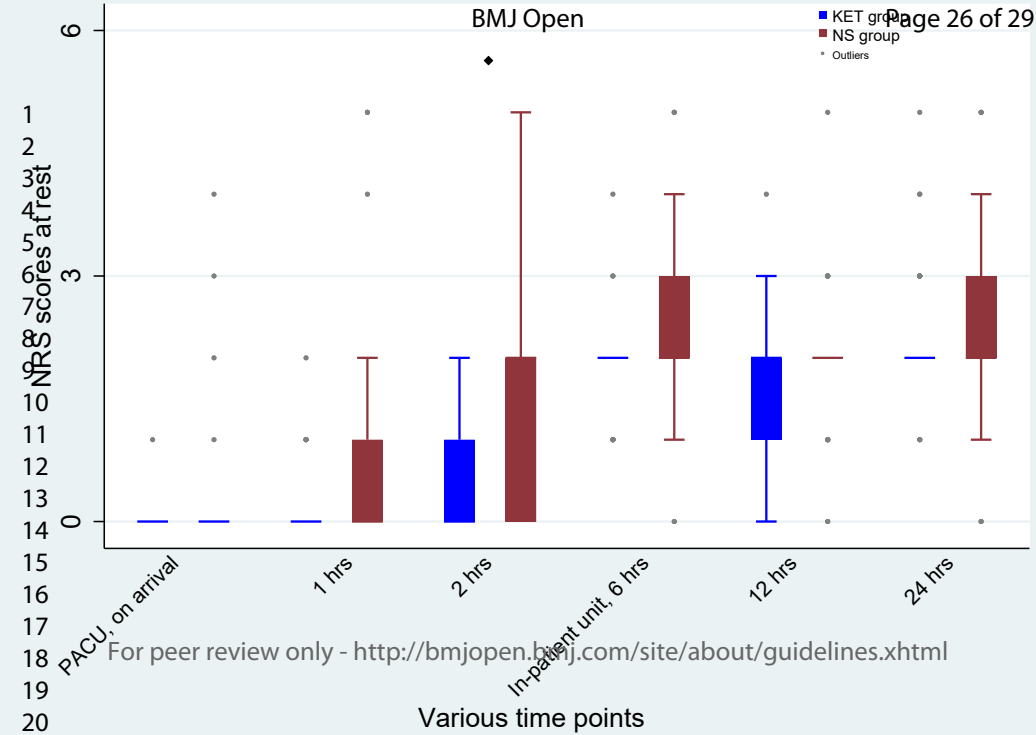

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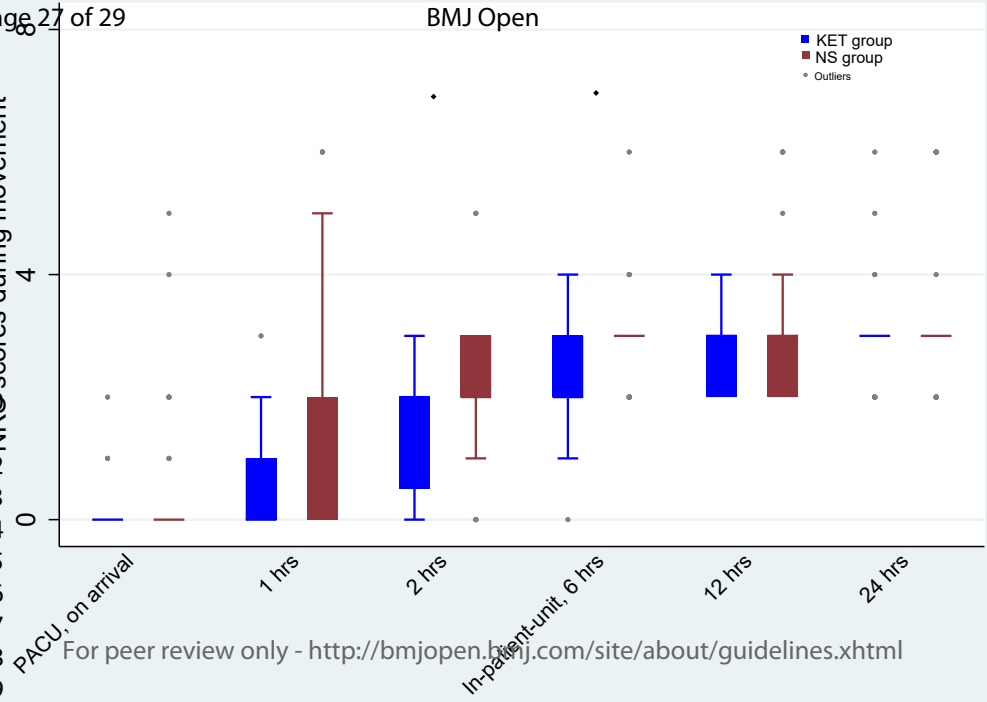

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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2,3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7,8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	8
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	5
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	5
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	5
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	5
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	6

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		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	6
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	8
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	N/A
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	5,7
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Figure 1
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Page 9. Figure 2
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Table 3
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	N/A
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Table 3
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	11,12
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	10-12
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	10-13
Other information			
Registration	23	Registration number and name of trial registry	No. NCT03450499. clinicaltrial.gov
Protocol	24	Where the full trial protocol can be accessed, if available	Enclosed as supplementary file

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Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	Non-funded

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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