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ORIGINAL INVESTIGATION

Inkk Trial – Intraoperative ketamine for perioperative pain management following total knee endoprosthetic replacement in oncology: a double-blinded randomized trial

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Abstract
Background: There has been a growing interest in the use of ketamine following orthopedic surgeries. We hypothesized that low dose intravenous ketamine during surgery would help in mobilization following total knee replacement (TKR) in oncology patients as assessed by the timed to up and go (TUG) test at 72 hours post-surgery. Our secondary objectives were to compare the opioid requirement at the end of 72 hours, pain scores, satisfaction with pain management, adverse effects, range of joint movement achieved in the post-operative period and the functional recovery at the end of 1 month.
Methods: After the ethics commitee approval, registration of the trial with the Clinical Trial Registry - India (CTRI), and informed consent, this double-blinded trial was conducted. Using computer generated randomization chart, an independent team randomized the patients into ketamine group which received at induction, a ketamine bolus dose of 0.5 mg.kg^{-1} before the incision followed by 10 μg.kg^{-1}min^{-1} infusion which was maintained intraoperatively till skin closure and the saline group received an equivalent volume of saline. Postoperatively, patient controlled morphine pumps were attached and the pain score with morphine usage were recorded for 72 hours. The TUG tests and range of motion were assessed by the physiotherapists until 72 hours.

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Results: Fifty-two patients were enrolled in the trial. Demographics were comparable. No significant intraoperative hemodynamic changes and post-operative adverse events were noted between the groups. A decrease in the TUG test, along with decreased opioid usage with a better range of movements was noted in the ketamine group, but this was not statistically significant. Day of discharge, patient satisfaction score, and functional recovery assessed by Oxford Knee Score (OKS) were comparable between the groups.

Conclusion: In conclusion, low dose intraoperative ketamine infusion does not provide clinical benefit in perioperative pain management and postoperative rehabilitation following total knee endoprosthetic replacement in oncology.

Introduction and rationale

A pain-free postoperative period is imperative following total knee replacement (TKR) surgeries as it aids in early rehabilitation and faster recovery.[1] Currently available analgesic interventions during TKR include epidural analgesia, peripheral nerve block and opioids.[2] Epidural analgesia has failed to gain popularity because of incidences of hypotension, urinary retention, pruritis, motor weakness and increased transfusions and fluid requirements.[3,4] The use of opioids through intravenous patient-controlled analgesia (IV PCA) is associated with side effects including nausea, vomiting, constipation, sedation, and urinary retention[5]. Intra-articular local anesthetic infiltration has not gained popularity in our hospital. Additionally, peripheral nerve blocks are not favored as there is the risk of femoral quadriceps weakness leading to increased risk of fall. There are documentations of few cases of neuritis and femoral neuropathy following peripheral blocks. All of which can affect postoperative rehabilitation.[6] Hence, arose a need to have a suitable multi-modal analgesic regimen for these patients.

Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, has been used in few orthopedic surgeries, including knee and spine surgeries, with results suggesting a decrease in opioid requirement perioperatively. The literature is inconclusive about the optimum dose and duration for the continuation of ketamine infusion in the peri-operative period.[7,8] Also, there is a lack of data on whether ketamine is equally effective in endoprosthetic knee replacement surgeries, which involve a longer procedure with more soft tissue and neurovascular dissection. Here, normal soft tissues are excised to achieve negative surgical margins resulting in large structural defects which are reconstructed by tumor endoprosthesis.[9] As tissue handling and trauma is maximum during any surgery, we aimed to study the benefit of intraoperative use of ketamine in rehabilitation following endoprosthetic TKR, and we hypothesized that a low dose of intravenous ketamine during surgery would help in mobilization following endoprosthetic TKR in oncology patients as assessed by the timed to Up and Go (TUG) test.[7,10,11]

Our primary objective was to compare functional recovery using the TUG test at the end of 72 hours. Our secondary objectives were to compare the opioid requirement at the end of 72 hours, pain scores, satisfaction with pain management, the incidence of adverse effects and range of joint movement achieved in the postoperative period. We also compared the functional recovery at the end of one month.

Methods

This prospective double-blinded randomized control trial was conducted in our hospital from September 2017 till October 2018. After the Institutional Ethics Committee approval [IEC approval number: IEC/0817/1855/002], the trial was registered with the clinical trial registry of India [CTRI/2015/08/006130] and written informed consent was obtained from each patient/guardian. Patients with American Society of Anesthesiologists (ASA) physical status I and II, aged above 13 years undergoing total knee replacement for oncological indications were included. Patients undergoing reconstructive surgery with major plastic flaps or on preoperative opioid/drug abuse, on chronic pain medications, with preoperative pathological fracture, muscle weakness of affected limb leading to limitation to mobility, pregnant patients, patients with contraindications to ketamine such as raised intracranial pressure, glaucoma medications, raised intraocular pressure, history of vertigo, auditory/visual hallucinations, or on antipsychotic medications were excluded. Postoperative exclusion criteria included intraoperative common peroneal nerve damage and postoperative ventilation or hemodynamic instability preventing mobilization for more than 24 hours.

Previous observations by the physiotherapy team revealed that patients after endoprosthetic TKR in oncology patients with standard analgesic protocol at our center, take an average of 142 seconds at 72 hours to complete the TUG test. The standard analgesic protocol at our center includes the use of intraoperative opioid along with postoperative morphine PCA pumps (1 mg bolus and 10-minute lockout interval), and either intravenous (IV) paracetamol or diclofenac. Group sample sizes of 20 each was required with 80% power with mean difference of 35.5 (25% reduction in TUG Day 3) and with a significance level (alpha) of 0.05. Permitting a 30% drop out (for postoperative exclusion), 52 was taken as sample size.

Patients were preoperatively educated in the use of patient controlled analgesia (PCA) pumps and familiarized with the use of the Numeric Rating Scale (NRS; 0 to 10 scale where 0 = no pain and 10 = worst pain imaginable) for rating their postoperative pain at rest and movement. On the morning of the surgery, patients were randomized into
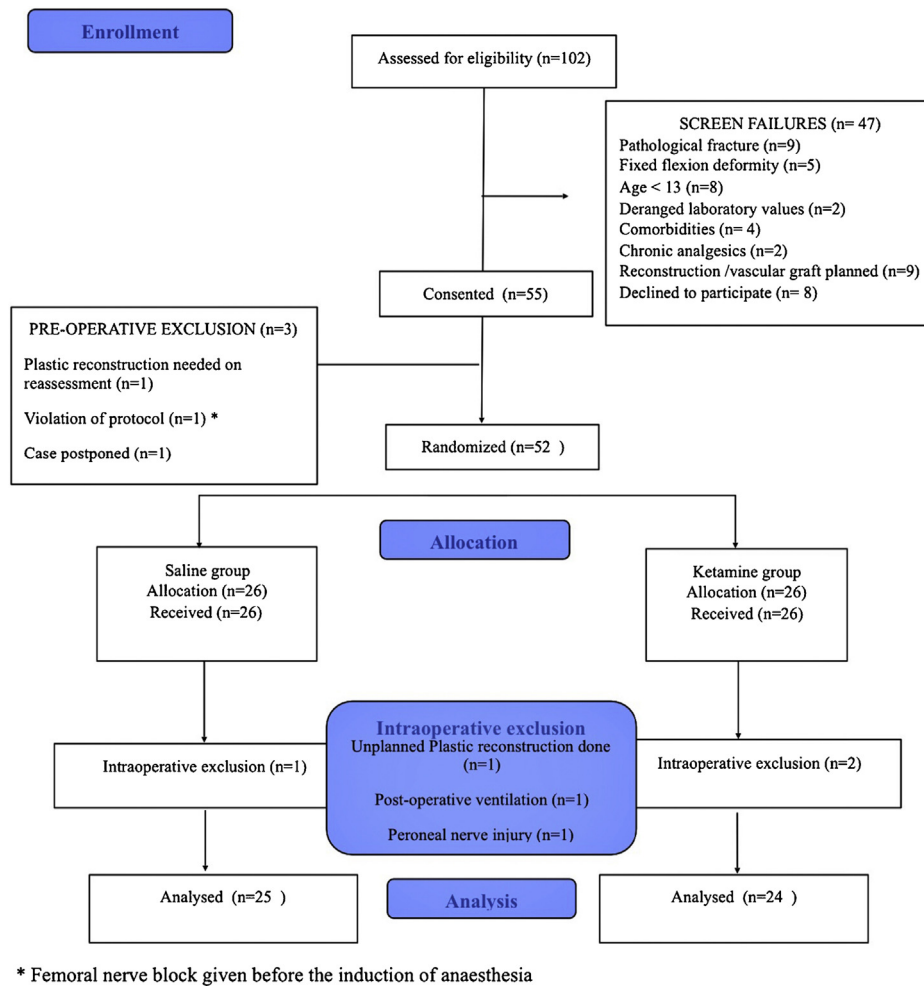
Figure 1 CONSORT Flow Diagram.

ketamine group or saline group. A team of residents, who were not part of the research team, randomized patients in accordance with computer generated randomization chart. This group prepared the study drug, labeled, and handed over the syringes to the concerned anesthesiologist. This ensured that the theatre team, patients, and the study team were blinded to the nature of the study drug. The ketamine group received at induction, a bolus dose of 0.5 mg.kg^{-1} followed by 10 μg.kg^{-1}.min^{-1} infusion, while the saline group received equivalent volume of saline.

Induction of general anesthesia and intraoperative management was standardized. Upon arrival in the operating room, baseline parameters – i.e., heart rate (HR), blood pressure (BP), oxygen saturation were noted. In addition, electrocardiogram was continuously monitored. Patients were induced with either propofol 2–3 mg.kg^{-1} or thiopentone sodium 5–7 mg.kg^{-1} intravenously; the need for neuromuscular blockade and airway management were decided as per the theatre anesthesiologists. Intraoperative analgesia included fentanyl 2 μg.kg^{-1} IV at induction, followed by morphine, 0.1 mg.kg^{-1} (lean body weight) IV after 30–45 minutes. If needed, fentanyl 1–2 μg.kg^{-1} could be repeated as and when required. The study drug bolus was administered after the airway was secured and was followed

by infusion as per instruction given by the unblinded team. The study drug was continued till the completion of skin closure. The procedures were performed by the same surgical team. Perioperatively, steroids, tranexamic acid, and peri-articular anesthetic injections were not used. A single negative suction drain was inserted in all patients.

At the end of surgery, injection paracetamol 500 mg–1g (> 50 kg: 1 g, 45–50 kg: 750 mg, less than 45 kg: 15 mg.kg^{-1} maximum of 500 mg) was given intravenously. In the postanesthesia care unit (PACU), the PCA pump with morphine was initiated with a standard setting of 1 mg bolus and lockout interval of 10 minutes. All patients were followed up by acute pain service (APS) and resting pain assessed using NRS scale. The worst pain during exercise was recorded by the physiotherapist at the end of each exercise session. Adverse effects were recorded as follows at 24, 48, and 72 hours. Vomiting was recorded at 24, 48, 72 hours as per vomiting score (0: no nausea, no vomiting; 1: nausea alone; 2: one episode of emesis; and 3: two or more episodes of emesis).[12] Sedation was assessed using the 6-point Ramsay sedation scale (in which 1 = awake, anxious, agitated, restless; and 6 = asleep, no response to light glabellar tap or loud auditory stimulus).[13]

Table 1 General demographics.

Parameters		Saline group	Ketamine group
Age (years)[a]		19.42 ± 6.09	24.62 ± 11.47
Sex	Male (n%)[b]	14 (53.8%)	15 (57.7%)
	Female (n%)[b]	12 (46.2%)	11 (42.3%)
Weight (kilograms)[a]		51.52 ± 11.67	54.98 ± 12.11
ASA	ASA I (n%)[b]	24 (92.3%)	25 (96.2%)
	ASA II (n%)[b]	2 (7.7%)	1 (3.8%)

ASA, American Society of Anesthesiologists physical status.
[a] Values as mean ± standard deviation.
[b] Number (percentages within the group); $p < 0.05$ is considered significant.

Table 2 Intraoperative details.

Parameters		Saline group	Ketamine group	p-value
Preoperative chemotherapy (n%)[a]		21 (80.8%)	16 (61.6%)	0.2
Heart rate	After bolus	78 [64.50−88]	75.50 [64.50−95]	0.8
(beats/min)[b]	At end of infusion	80.50 [72−97.50]	90 [80−97.25]	0.07
Systolic blood	After bolus	100 [94.50−110.25]	100 [92.75−117.25]	0.3
pressure (mmHg)[b]	At end of infusion	110 [101.50−117.25]	111 [101.50−125]	0.3
Diastolic blood	After bolus	60 [50−65.75]	57.50 [50−70.25]	0.4
pressure (mmHg)[b]	At end of infusion	65 [55−71.75]	67.50 [57.50−77]	0.4
Duration of surgery (minutes)[c]		100.74 ± 6.99	106.4 ± 12.11	0.1
Blood loss (milliliters)[c]		726.92 ± 360.62	890.38 ± 470.32	0.2
Length of resection (centimeters)[c]		16.38 ± 4.18	16.33 ± 4.40	0.7

$p < 0.05$ is considered significant.
[a] Number (percentages within the group).
[b] Values as Median [Inter-quartile range].
[c] Values as mean ± standard deviation.

Unpleasant feelings like hallucinations (auditory/visual), dizziness, nightmares were recorded on a score from 1−5, 5 = worst imaginable.[14] At 30-day follow-up in the outpatient department, details of ongoing pain killers and functional recovery were recorded on Oxford Knee Score (OKS), which is a validated 12-item knee questionnaire that scores patients from 12 (best possible) to 60 (worst possible).[15] The scale is available in English language and was administered by the investigator and patients' replies recorded.

The TUG measured the time it takes a patient to rise from an armed chair (at least up to knee length for the given patient), walk 3 meters, turn, and return to sitting in the same chair.[10] Patients were instructed to walk as quickly as they feel safe and comfortable. The use of the arms of the chair was permitted to stand up and sit down. A stopwatch was used to measure the time to complete the TUG within the nearest one-tenth of a second. Walking aids, if needed, were allowed for patients in the immediate postoperative period (24−48 hours) only.

All the raw data were entered and analyzed using SPSS Statistics version 25 software. Demographic data were expressed as mean ± standard deviation (age, weight, height, duration of surgery, anesthesia, or proportion (sex and ASA physical status). The continuous data were analyzed using Student's independent t-test when normally distributed (fentanyl use, morphine use, degrees of move-ment), and with Mann−Whitney U test if otherwise (Heart rate [HR], blood pressure [BP], minimum alveolar concentration [MAC] and pain scores). All the analyses were two-tailed and the confidence level was 95%; $p < 0.05$ was considered statistically significant.

Results

A total of 102 patients were screened and 52 patients were randomized; 49 were included for the final TUG analysis, refer to consort diagram (Fig. 1). The general demographics such as age, gender, weight, ASA physical status, duration of surgery and anesthesia were comparable between the two groups (Tables 1 and 2). We found that the functional recovery assessed using TUG test at end of 72 hours was better in the ketamine group with 103.25 ± 30.04 seconds as compared to the saline group with 125.91 ± 49.32 seconds. But this finding was not statistically significant ($p = 0.1$). The results of the TUG tests on each postoperative day along with degrees of flexion achieved are shown in Table 3. The comparison of perioperative opioid requirement is enumerated in Table 4. Interventions were required intraoperatively for six patients for tachycardia and hypertension (2 in the saline group and 4 in the ketamine group). No statistical difference was seen in this regard. There was no discontinuation of the study drug due to any hemodynamic instability intraoperatively. The postoperative pain scores at rest and

Table 3 Postoperative assessment of rehabilitation.

Outcomes	Saline	Ketamine	p
TUG at 24 h (s)[a]	170.58 ± 52.89	135.55 ± 55.12	0.2
TUG at 48 h (s)[a]	139.92 ± 47.69	140.64 ± 64.34	0.8
TUG at 72 h (s)[a]	125.91 ± 49.32	103.25 ± 30.04	0.1
Maximum flexion at 24 h (º)[a]	47.08 ± 19.12	51.25 ± 17.98	0.6
Maximum flexion at 48 h (º)[a]	68.00 ± 20.57	72.92 ± 24.53	0.3
Maximum flexion at 72 h (º)[a]	74.64 ± 18.96	81.15 ± 16.35	0.3

TUG, timed to Up and Go test.
$p < 0.05$ is considered significant.
[a] Values as mean ± standard deviation.

Table 4 Perioperative opioid usage.

Parameters	Saline	Ketamine	p
Intraoperative fentanyl usage (μg)[a]	213.25 ± 76.75	205.00 ± 86.12	0.7
Postoperative morphine usage at 2 h (mg)[a]	4.38 ± 3.07	4.11 ± 3.19	0.6
Post-operative morphine usage at 24 hours (mg)[a]	32.13 ± 19.99	28.52 ± 20.84	0.6
Postoperative morphine usage at 48 h (mg)[a]	48.64 ± 27.19	48.01 ± 30.32	0.6
Postoperative morphine usage at 72 h (mg)[a]	67.59 ± 40.58	61.34 ± 32.93	0.5

μg, micrograms; mg, milligrams.
$p < 0.05$ is considered significant.
[a] Values as mean ± standard deviation.

Table 5 Assessment.

Parameters		Saline	Ketamine	p-value
Preoperative	Overall	25 [24–26]	26 [22–27]	0.8
OKS[a]	Received preoperative chemotherapy	25 [24–26]	27 [25–28]	0.07
	No preoperative chemotherapy	26 [23–27]	22 [21–24]	0.1
Postoperative	Overall	34 [32–36]	33 [30–36]	0.7
OKS[a]	Received preoperative chemotherapy	34 [33–37]	35 [33–36]	0.8
	No preoperative chemotherapy	34 [31–35]	30 [29–32]	0.1
Day of discharge (days)[b]		6.35 ± 1.79	5.78 ± 1.41	1.0
Patient satisfaction score[c]		4 [3–4]	4 [4–4]	0.5

OKS, Oxford Knee Score.
[a] Values as Median [Inter-quartile range].
[b] Values as mean ± standard deviation; $p < 0.05$ is considered significant.
[c] On a Likert scale of 1–5 where 1 = very unsatisfied, and 5 = very satisfied.

during exercise were comparable between the two groups. Figure 2 shows the trend of postoperative pain scores during exercise. The median pain score at 24 hours during exercise was 7 [5-8] in the saline group and 5 [4-7.5] in the ketamine group (p = 0.2). No significant postoperative adverse events such as nausea, vomiting, sedation, and dysphoric symptoms were noted between the groups. Day of discharge, patient satisfaction score and functional recovery assessed by OKS at one month follow up were comparable between the groups (Table 5).

Discussion

From this study we found that intraoperative intravenous ketamine infusion at 10 μg.kg^{-1}.min^{-1} following a bolus of 0.5 mg.kg^{-1} did not improve post-operative rehabilita-

tion following endoprosthetic TKR in oncology. Though the ketamine group had a better performance with respect to the TUG test at the end of 72 hours, the difference was not statistically significant.

The difference in knee replacement done for tumors as compared to the conventional ones are that the part of the bone involved (femur or tibia) by the tumor is removed, keeping a safe margin with a cover of overlying muscles,[16] while in conventional TKR, only the articular surface is removed and replaced.[17] In tumour reconstruction, emphasis is placed on safe resection and reconstruction is secondary with the ligaments (collateral and cruciate) sacrificed in order to achieve complete resection. Postoperative rehabilitation is a challenge in tumor reconstruction. In distal femur reconstruction patients can be started on full weight bearing and gradual knee flexion. In proximal tibia
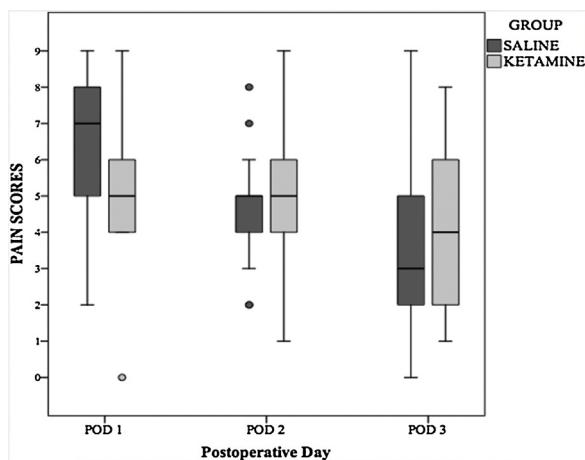
Figure 2 Boxplot of pain score after exercise.

reconstruction, the patients although started on full weight bearing, are advised to delay knee bending up to 6 weeks in order to protect the ligament reconstruction.[18] Nevertheless, despite the site of tumor, we presumed that the better functional scores at 48−72 hours could be translated in better prolonged rehabilitation which is most needed following these surgeries due to extensive tissue dissection. Hence, a review of functional recovery was done again at the end of one month for all trial patients. We found no difference between the two groups with respect to functional recovery as assessed by OKS.

Previous studies[19−21] suggest that perioperative use of ketamine may benefit in postoperative rehabilitation. Adam et al.[19] had demonstrated better knee flexion in the study group which was statistically significant when ketamine was used along with continuous femoral nerve block. In the above trial, the ketamine infusion was continued 48 hours postoperatively at 1.5 $\mu g.kg^{-1}.min^{-1}$ after an intraoperative infusion run at 3 $\mu g.kg^{-1}.min^{-1}$ with no serious adverse effects. Two continuous infusions along with a PCA pump for post-operative pain management can be seen as cumbersome and not practical in all scenarios. The role of ketamine in preventing or reducing central sensitization due to tissue damage has been well established.[22,23] Since the tissue damage is maximum during the intra-operative period of any surgery, we rationalized that ketamine infusion during this period should work. In our trial, the ketamine group consistently had better degree of flexion on all assessments postoperatively till 72 hours, although this was not statistically significant.

Similarly significant opioid sparing and analgesic effects have been observed with ketamine infusion in orthopedic surgeries and many of these studies[19,24−27] continued the ketamine infusion postoperatively for varied periods of time with a maximum recorded duration of 48 hours and at different dosages. There remains a chance of dosing errors with continuous infusions,[28] and hence as a policy ketamine infusions are not used inpatient wards at our hospital. Cengiz et al.[26] had recorded a reduction of morphine consumption up to 45% with an intraoperative ketamine infusion at 6 $\mu g.kg^{-1}.min^{-1}$ in total knee replacement surgeries. In our trial, the intraoperative fentanyl (205.00 $\pm$ 86.12 μg vs. 213.25 $\pm$ 76.75 μg) and the first 24 hours postoperative mor-

phine requirement (28.52 $\pm$ 20.84 mg vs. 32.13 $\pm$ 19.99 mg) recorded in the ketamine group were lower though not significant. Similarly the pain scores in ketamine group was lower than of saline group and of a different severity (moderate versus severe in case of saline, however this was not statistically significant). Similar to the other trials,[19,25,26] there were no adverse effects of ketamine such as hallucinations and delusions observed postoperatively. Thus, the question on the role of continuing ketamine infusion into the postoperative period to obtain opioid sparing with better analgesic effects and to improve rehabilitation still remains. The intraoperative hemodynamic parameters were higher, though not significant, in the ketamine group; whether this is attributable to the increase in blood loss of around 150 ml in the ketamine group, is speculative (Table 1).

Postoperative rehabilitation after TKR surgeries have been assessed using 2-minute walk tests, passive and active knee motion, performance measures such as TUG, IALS (Iowa level of assistance scale) and patient reported outcome measures (PROM).[11] We chose TUG test for our assessment. It is one of the most commonly used performance assessment tools. TUG test is quicker, less resource intensive and does not rely on clinician's perception and studies show that PROMs are less reliable than performance measures in the immediate post-surgery period.[29] The literature shows that TUG test has predictive values on both short[30] and long term[11] functional recovery following arthroplasties. Studies suggest that preoperative and acute TUG test is a better predictor of long-term functional outcome on the 6-minute walk test when not adjusted for age, sex, and preoperative functional outcomes. Bade et al.[11] also propose that postoperative day 2 range of motion is not a better predictor of long-term functional outcome following total knee arthroplasties for osteoarthritis as against pre-operative ROM. Nevertheless, does this finding apply to TKR with endoprosthesis performed for oncosurgeries is something that needs to be evaluated with a larger sample.

We used the OKS for the PROM assessment.[31] We found that the cohort of patients who underwent pre-operative chemotherapy had better pain relief and they performed well on the pre-operative OKS (26 [24−27] in patients who received preoperative chemotherapy vs 22 [21−26]) though there was no statistical significance on this ($p = 0.3$). Postoperatively, as expected, at one month follow up, the cohort which received preoperative chemotherapy had a median OKS of 35 [33−36] as compared to the non-receivers 32 [30−34] ($p = 0.007$). Items, such as ability to kneel and feeling of sudden ''give way'' were not applicable to all the patients. Literature shows that preoperative chemotherapy can lead to decrease in inflammation of tissues surrounding the tumors leading to actual reduction of the size of the lesion while responders to chemotherapy were found to have decrease or complete remission of pain and a decreased vascularity of the tumor. This could translate into better surgical margins and hence outcomes.[32]

There were limitations to the trial, ketamine infusion was restricted to the intraoperative period when tissue handling and trauma is maximum. The impact of this intervention was assessed by clinical parameters inclusive of rehabilitation and pain scores. We could have also looked at inflammatory markers to have a complete understanding of the role ketamine played in the body's response to surgical trauma.

In summary, we infer that intraoperative intravenous ketamine infusion at 10 μg.kg^{-1}.min^{-1} following a bolus of 0.5 mg.kg^{-1} does not improve postoperative rehabilitation following total knee endoprosthetic replacement surgeries in oncological settings.

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Conflicts of interest

The authors declare no conflicts of interest.

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