Original Article

Comparison of the effects of opioid-free anesthesia (OFA) and opioid-based anesthesia (OBA) on postoperative analgesia and intraoperative hemodynamics in patients undergoing spine surgery: A prospective randomized double-blind controlled trial

ABSTRACT

Background: Opioids form the basis of perioperative pain management but are associated with multiple side effects. In opioid-free anesthesia (OFA), several non-opioid drugs or neuraxial/regional blocks are used as substitutes for opioids. Ketamine, a N-methyl-d-aspartate antagonist, provides intense analgesia. However, there is a shortage of literature on the effects of ketamine-based OFA on hemodynamics (HD) and postoperative analgesia in patients undergoing thoracolumbar spine surgery.

Materials and Methods: This prospective randomized controlled trial included 60 adult patients. The patients in Group OFA (n = 30) received OFA with ketamine and ketofol (1:5) infusion, and those in Group OBA (n = 30) received opioid-based anesthesia (OBA) with fentanyl and propofol infusion. The postoperative pain-free period, pain scores, rescue analgesia, intraoperative HDs, and postoperative complications were assessed.

Results: The mean pain-free period in Group OFA (9.86 ± 1.43 hr) was significantly higher than that in Group OBA (6.93 ± 1.93 hr) (P = 0.002). During the postoperative 48 hours, the total requirement of fentanyl was considerably lower in Group OFA ($P < 0.05$). There was a significantly higher incidence of hypertension in Group OFA (46%) and hypotension (43%) in Group OBA (43%), respectively. Postoperative nausea vomiting (PONV) was more common in Group OBA at the 2nd and 6th hr (P = 0.046 and P = 0.038)

Conclusion: OFA with ketamine and ketofol provided adequate postoperative analgesia with a lower incidence of PONV after spine surgery. However, hypertension in the ketamine group and hypotension in the propofol group required fine titration of the infusion rate of drugs during the intraoperative period.

Key words: Ketamine, ketofol, opioid-free anesthesia, pain-free period, propofol, spine surgery

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Introduction

Opioid-based anesthesia (OBA) is a standard anesthesia technique with opioids as the mainstay of intraoperative and postoperative pain management, especially in major surgical cases. Following spine surgeries, the intensity of pain is high in the postoperative period, resulting in delayed mobility and a prolonged hospital stay. Providing adequate pain relief is one of the major goals of anesthetic care and an important aspect of postoperative care for these patients to enhance recovery and improve surgical outcomes.

Perioperative use of opioids is known to be associated with various adverse effects such as delayed emergence, respiratory depression, postoperative nausea vomiting (PONV), urinary retention, and the potential for acute tolerance and opioid-induced hyperalgesia.[1,2] Recent concerns have been raised about impaired healing, immunosuppression, and worsening of oncologic outcomes with the use of systemic opioids.[3-5] The use of opioids for perioperative pain management is also responsible for opioid addiction. Given the serious side effects and development of dependency with the use of opioids in the perioperative phase of care, there have been efforts to reduce opioid exposure, which has generated interest in opioid-free anesthesia (OFA).

OFA is a multimodal non-opioid analgesic technique used to completely eliminate intraoperative systemic, neuraxial, or intracavitary use of opioids.[6] Different anti-nociceptive agents that target the central nervous system can be used, like non-steroidal anti-inflammatory drugs, N-methyl-d-aspartate (NMDA) antagonists (ketamine), alfa-2 agonists (dexmedetomidine), lidocaine, gabapentin, corticosteroids, along with the central neuraxial block, and loco-regional blocks, for providing multimodal pain management.[7-9] The utilization of OFA not only mitigates the detrimental impacts of opioids but also facilitates prompt ambulation and restoration of bowel function, thereby conferring a distinct benefit even in the context of bariatric surgery.[10] Ketamine, at sub-anesthetic dose, either as a bolus or in a continuous infusion, avoids the use of opioids, improves the intraoperative hemodynamic (HD) stability, and improves the management of postoperative pain.[11]

The present study aimed to compare the effect of OFA using ketamine and ketofol (ketamine and propofol) with OBA using fentanyl and propofol in providing postoperative analgesia and intraoperative HD stability in patients undergoing thoracic and lumbar spine surgery.

Material and Methods

A prospective randomized, double-blind controlled trial was conducted at the Department of Anesthesia and Intensive Care, PGIMER, Chandigarh, India, after obtaining Institutional Ethics Committee approval (INT/IEC/2019- 002178) and registration under the Clinical Trial Registry of India (CTRI/2020/04/024936). This study was conducted between May 2020 and December 2020.

Study participants

Patients aged 18–65 years with American Society of Anesthesiologists (ASA) I and II status posted for thoracic or lumbar spine surgeries involving 2-4 intervertebral spaces were enrolled in the study after obtaining written informed consent. Patients with coronary artery disease, renal or hepatic insufficiency, psychiatric disorders, pregnancy, allergy to test drugs, or severe pain scores (Numeric Rating Score $\geq$ 8) before surgery were not included in the study. A thorough pre-anesthetic evaluation was performed one day before surgery. Patients were educated about the Numeric Rating Scale (NRS) 0–10, where 0 was identified as no pain and 10 as the worst pain ever possible.[11,12]

Randomization and blinding of the study

The patients were randomized using a computer-generated random number table. The opaque sealed envelope technique was used for concealment, and consecutive envelopes were opened immediately before shifting the patient inside the operation theater. For the blinding of the study, the anesthesia resident (who collected the data), the operating surgeon, and the patients were blinded to the study drug administered to the patient. The study drug was prepared by an anesthesiologist who was not involved in the study, according to the protocol. Sixty patients were included in the study. The patients were randomized into two groups:

Group OFA: Patients received OFA with ketamine and ketofol.
Group OBA: Patients received OBA with fentanyl and propofol.

Study drug preparation

Two loaded syringes were prepared for each patient: one 10 ml syringe (written analgesic agent) and one 50 ml syringe (written anesthetic agent).

For Group OFA[13,14]**:** Around 10 ml syringe (labeled as an analgesic agent) contains ketamine (in a dose of 1 mg/kg) diluted with saline to a total volume of 10 ml. Around 50 ml syringe (labeled as an anesthetic agent) contains ketofol (ketamine and propofol in a ratio of 1:5), which contains 8 ml of ketamine (10 mg/ml) and 40 ml of

propofol (10 mg/ml) [1 ml of ketofol contains 1.67 mg of ketamine and 8.33 mg of propofol.]

For Group OBA: Around 10 ml syringe (analgesic agent) contains fentanyl (in a dose of 2 μg/kg) diluted with saline to a total volume of 10 ml. Around 50 ml syringe (labeled as an anesthetic agent) contains 48 ml of propofol (10 mg/ml). [1 ml of propofol contains 10 mg of propofol]

Anesthesia protocol

All monitors were attached as per the ASA guidelines, such as a 5-lead electrocardiogram, non-invasive blood pressure, pulse oximetry, capnography, temperature, and urine output. An intra-arterial line was secured before anesthesia induction for invasive blood pressure measurements and arterial blood gas analysis. Entropy and neuromuscular monitoring were also initiated. Patients were hydrated with 0.9% saline (5–6 ml/kg) to maintain a systolic pressure variation <13.

For Induction of Anesthesia: In both groups, the contents of a 10 ml syringe (analgesic agent) were given as a bolus over 10–20 s, followed by induction with an infusion of the contents of a 50 ml syringe (anesthetic agent) at a rate of 2.4 ml/kg/hr and was decreased to 0.3 ml/kg/hr at the loss of verbal response or State Entropy of <60. Following anesthesia induction, the trachea was intubated after ensuring adequate muscle relaxation with vecuronium 0.1 mg/kg.

For maintenance of anesthesia: the contents of a 50-ml syringe (anesthetic agent) were infused at a rate of 0.3–0.6 ml/kg/hr, and the drug infusion rate was titrated to maintain state entropy 40–60. Also, 10 ml syringe contents were reloaded with 1 μg/kg fentanyl in 0.9% saline (10 ml) in the OBA group and with 0.9% saline only (10 ml) in the OFA group. These 10 ml syringe contents were infused over 1 hr in both groups. Depending on the duration of surgery, 10 ml syringe contents were reloaded after 1 hr if required.

All patients were ventilated with oxygen and nitrous oxide (50:50), maintaining the total gas flow at 1–2 liters to maintain PaCO2 between 35 and 40 mmHg. Inj. glycopyrrolate 0.2 mg was administered before placing the patient in a prone position to reduce oral secretion.

Hemodynamic parameters, such as heart rate (HR) and mean arterial pressure (MAP), were recorded every 10 min during the intraoperative period. If SE >60 and HD parameters exceeded >20% of baseline levels, then the infusion rate of the maintenance agent was increased. If the state entropy was <60 and HD parameters exceeded >20% baseline levels, labetalol 5 mg (IV bolus) was administered. If MAP fell below 20% and SE <40, then the infusion of maintenance agents was decreased to achieve an SE of approximately 50. Simultaneously, volume status and blood loss were assessed and corrected accordingly. If the patient was found to be hypovolemic, a fluid bolus (5 ml/kg) was administered, and if euvolemic, phenylephrine (50 mcg aliquots) was administered. If the patient was still hypotensive, then a noradrenaline infusion was initiated. All rescue measures to maintain the HD parameters were recorded.

For emergence from anesthesia, the infusion rate of the maintenance anesthetic agent was decreased to 50% at the beginning of surgical closure and stopped after the patient was turned to the prone position. All the patients received ondansetron (0.1 mg/kg) and paracetamol (15 mg/kg). The standard anesthesia reversal technique was followed, where a combination of neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg was administered to antagonize residual neuromuscular blockade, guided by a train of four count response of 4 and a percentage >80%. Extubation was performed in a supine position, observing the clinical signs of complete reversal (optimal respiratory effort, ability to follow simple commands) and when a train of four counts >0.9 was observed.

Patients were shifted to the high-dependency unit or neurosurgical intensive care unit. In the postoperative period, all patients received intravenous paracetamol 15 mg/kg for 48 h. Pain scores were assessed at 2, 6, 12, 24, and 48 hr. NRS 1-3 was considered mild pain, NRS 4-6 was moderate pain, and NRS 7–10 was severe pain, respectively. Fentanyl 1 μg/kg was administered as a rescue analgesic when the NRS score was >4. The pain-free period was defined as the interval between stopping the anesthetic study drug and administering the rescue analgesic drug for the first time. The pain-free period, pain scores, and total rescue analgesic drug requirement within 48 hr were noted.

Additionally, patients were assessed for HD instability and postoperative complications, such as respiratory depression, hallucinations, disorientation, delirium, nystagmus, and PONV. Any rescue drugs, if required, were also recorded.

Statistical analysis

The statistical analysis was carried out using Statistical Package for Social Sciences (IBM SPSS Inc., Chicago, IL, version 22). Discrete categorical data are represented as a number or a percentage (%). Normally distributed continuous data was presented as the mean and standard deviation. The normality of quantitative data was checked using measures of Kolmogorov–Smirnov tests. For normally distributed data, the

means of the two groups were compared using the student independent *t*-test. Proportions were compared using either the Chi-square test or Fisher's exact test, depending on their applicability. A *P* value of <0.05 was considered statistically significant.

Sample size calculation

The sample size was calculated through the clinicalcalc.com web calculator from the data of a published study, based on a post-operative pain-free period (860 min) and an SD of 2, using an alpha error of 0.05, a beta error of 0.2, and a power of 80% sample size was calculated to be 56.[15] Considering the attrition of data, it was decided to include a total of 60 patients in the study, with 30 patients in each group.

Result

Sixty-six patients were assessed for eligibility to be included in the study, of whom six did not meet the inclusion criteria and were excluded. Sixty patients were enrolled in the study, and data from all patients were analyzed at the end of the study [Figure 1]. Patients in both groups were comparable in demographic characteristics, level of intervertebral disc involvement, spine pathology, and site of surgery [Table 1]. Only 6.66% of patients had a fusion, while 93.34% underwent discectomy.

The pain-free period was significantly higher in Group OFA (9.86 ± 1.43 hr) than in Group OBA (6.93 ± 1.93 hr) ($P < 0.001$) [Table 2]. During the first 2 hr postoperatively, no pain was observed in 63.3% of the patients in Group OFA and 36.7% of the patients in Group OBA ($P = 0.039$). The rest of the patients had mild pain. At the 6th postoperative hour, 10% of patients in Group OBA

Table 1: Demographic characteristics of the patients

	Group OBA (*n*=30)	Group OFA (*n*=30)	*P*
Age (Years)	41.73±12.79	40.93±12.07	0.804
Weight (Kg)	65.76±7.88	65.16±11.55	0.815
Gender (M/F)	23/7	21/9	0.559
ASA (I/II)	21/9	22/8	0.774
Site of involvement Thoracic/ Lumbar/Thoracolumbar	13/15/2	10/20/0	0.310
Intervertebral discs involved (2/3/4)	27/1/2	29/1/0	0.302
Duration of surgery (mins)	178±14	182±21	0.561
Duration of anesthesia (mins)	199±08	196±15	0.725
Total Intravenous Fluid (liters)	2.25±0.3	2.36±0.12	0.643
Total Blood Loss (ml)	640±40	652±30	0.427

*P<0.05 is statistically significant, *n* indicates the number of patients

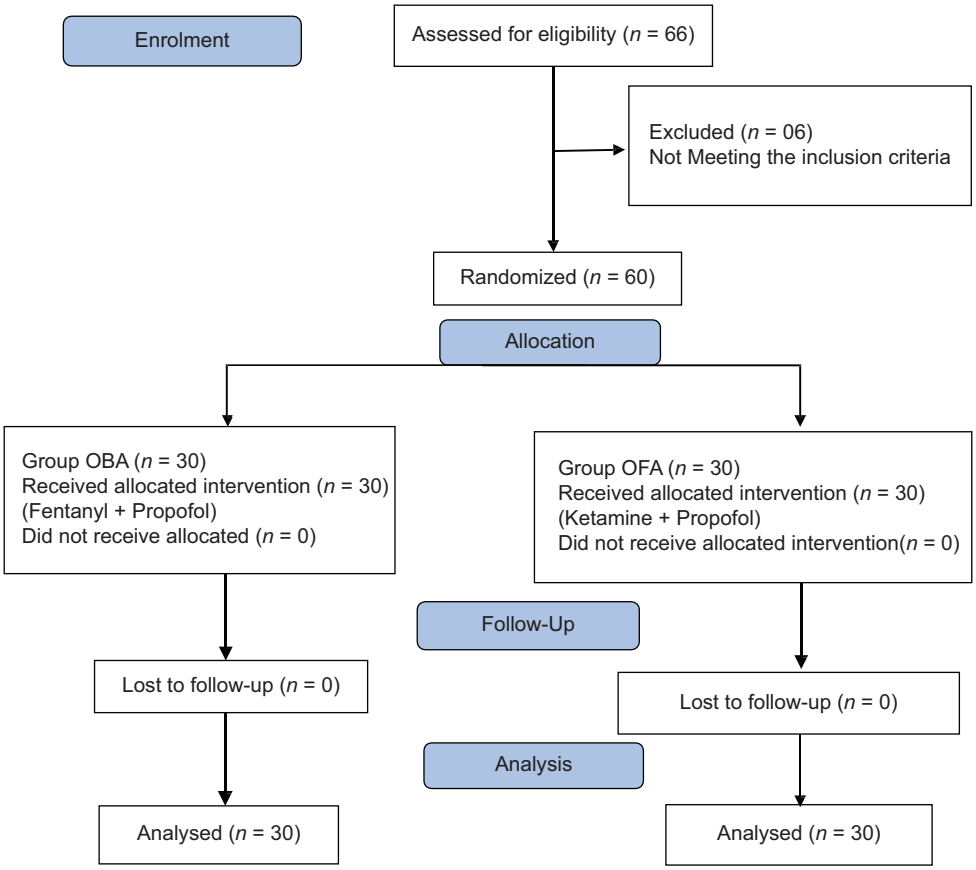

Figure 1: Consort diagram for patient recruitment

Table 2: Comparison of pain parameters

Pain Parameters	Group OBA $n=30$	Group OFA $n=30$	*P*
Pain-free period (hr)	6.93±1.93	9.86±1.43	0.001*
Total Rescue Analgesic required (micrograms/patient)	98±21.09	84.17±9.25	0.002*
Time interval in which rescue analgesic required (n)			
3–6 h	13 (43.3%)	0	0.001*
6–9 h	13 (43.3%)	13 (43.3%)	1
9–12 h	4 (13.3%)	17 (56.7%)	0.001*
Postoperative pain scores (NRS scale) No/Mild/Moderate/Severe			
2nd h	11/19/0/0 (36.7%/63.3%/0/0)	19/11/0/0 (63.3%/36.7%/0/0)	0.039*
6th h	3/4/9/14 (10%/13.3%/30%/46.7%)	6/14/8/2 (20%/46.7%/26.7%/6.6%)	0.003*
12th h	0/4/15/11 (0%/13.3%/50%/36.7%)	7/3/12/8 (23.3%/10%/40.1%/26.6%)	0.028*
24th h	0/20/9/1 (0%/66.7%/30%/3.3%)	7/16/7/0 (23.3%/53.4%/23.3%/0%)	0.557
48th h	0/30/0/0 (0%/100%/0%/0%)	4/26/0/0 (13.3%/86.7%/0/0)	0.313

*$P<0.05$ is statistically significant. Values are expressed as the number or percentage of patients. The Numeric Rating Score varies between 0 and 10, where 0 indicates no pain, 1–3 indicates mild pain, 4–6 indicates moderate pain, and 7–10 indicates severe pain

and 20.0% of patients in Group OFA had no pain, while severe pain was seen in 46.7% and 6.6% of patients in Group OBA and Group OFA, respectively ($P = 0.003$).

Most patients in Group OFA had mild pain (46.6%), whereas patients in Group OBA had severe pain (46.7%) at the 6th postoperative hour ($P = 0.003$). At the 12th postoperative hour, 23.3% of patients in Group OFA were pain-free, while severe pain was seen in 26.6% and 36.7% of patients in Group OFA and Group OBA, respectively ($P = 0.028$). At 24 hours postoperative period, 23.3% of patients in Group OFA had no pain, while mild, moderate, or severe pain was comparable in both groups ($P = 0.557$). At the 48th hr postoperative period, none of the patients in either group had moderate to severe pain, while a comparable number of patients in both groups had mild pain ($P = 0.313$) [Table 2].

The first rescue analgesic agent was required at 6–9 hours and 3–6 hours in Group OFA and Group OBA, respectively ($P = 0.001$). In Group OBA, 43.3% of the patients required rescue analgesics in 3–6 hr and 6–9 hr; an equal number of patients (43.3%) in both groups required rescue analgesics. At 9–12 hr, 56.7% and 13.3% of patients in Group OFA and Group OBA required rescue analgesics, respectively ($P = 0.001$). The total requirement for rescue analgesics was significantly higher in Group OBA group than in Group OFA group. The mean fentanyl (rescue analgesia) requirement in Group OFA was 84.17 ± 9.25 μg/patient in comparison to 98 ± 21.09 μg/patient in Group OBA ($P = 0.002$) [Table 2].

Hemodynamics parameters and complications

Intraoperatively, the mean HR values were comparable in both groups except at 120 min, when a significant increase in HR was observed in Group OFA ($P = 0.02$) [Figure 2a]. Similarly, intraoperative mean MAP values were comparable between the groups except for a higher MAP after intubation and at 90 min in Group OFA (P value = 0.03 and P value = 0.01, respectively) [Figure 2b]. Also, oxygen saturation, end-tidal carbon-dioxide, and entropy were comparable in both groups ($P > 0.05$).

There was a significantly higher incidence of hypertension (MAP >20% of baseline) in Group OFA (n = 18) compared to Group OBA (n = 10), and the requirement for a rescue drug (inj Esmolol) was also higher in Group OFA ($P = 0.001$). However, the incidence of hypotension (SBP <90 mm Hg) was significantly higher in Group OBA (n = 13) compared to Group OFA (n = 05), and consequently, the requirement of phenylephrine was higher in Group OBA ($P < 0.001$) [Table 3].

In the postoperative period, the mean HR in Group OFA was slightly higher than Group OBA; however, no significant difference was noted. The systolic and diastolic blood pressure and oxygen saturation were comparable in both groups.

PONV was observed in three patients in the 2nd hr and four patients in the 6th hr in Group OBA, and two of them required a rescue antiemetic agent. No patient in Group OFA had PONV. The difference in the incidence of PONV between the groups was significant at both the 2nd hr and the 6th hr ($P = 0.046$ and $P = 0.038$). None of the patients in either group had PONV after 6 postoperative hours. In the immediate postoperative period, nystagmus was noted in two patients in Group OFA, which resolved within 2 hr. None of the patients in either group complained of hallucinations, delirium, disorientation, or respiratory depression.

Discussion

In this prospective randomized double-blind control study in patients undergoing spine surgery, we found that OFA

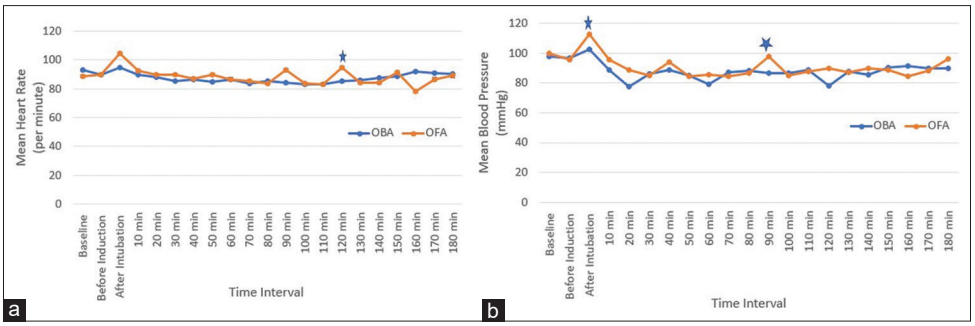

Figure 2: Line diagram showing intraoperative trends of (a) heart rate, (b) mean blood pressure in study groups. *$P < 0.05$

Table 3: Intra-operative rescue drugs to maintain hemodynamics

Parameters	Group OBA ($n=30$)	Group OFA ($n=30$)	P
Hypertension (>20% baseline MAP)	10 (33.3)	18 (60)	0.001*
Rescue drug for hypertension (Esmolol)	10 (33.3)	18 (60)	0.001*
Hypotension	13 (43.3)	5 (16.6)	0.001*
Rescue drug for hypotension (Phenylephrine)	13 (43.3)	2 (6.6)	0.001*

*$P<0.05$ is statistically significant. Values are expressed as the number or percentage of patients

was associated with a longer pain-free period ($P = 0.001$), lower pain scores ($P = 0.03$), and a reduced requirement for rescue analgesic drugs ($P = 0.002$) compared to OBA. Intraoperatively, the incidence of hypertension was higher in the OFA group ($P = 0.001$), whereas the incidence of hypotension was significantly higher in the OBA group ($P = 0.001$). Additionally, the incidence of PONV was significantly higher in the OBA group.

In the current study, the OFA technique using ketamine and ketofol was compared with the OBA technique using fentanyl and propofol. The OFA technique provided prolonged analgesia, and the need for rescue analgesia was seen after 9.86 + 1.43 hr following surgery, and only 6.6% of patients complained about severe pain. The analgesic property of intraoperative ketamine decreased pain scores and reduced the dose of rescue analgesics postoperatively.

The painful stimuli in the peripheral areas trigger the NMDA receptor, which activates the windup phenomenon, where repetitive stimuli lead to a prolonged increase in neuron excitability and an increase in subjective pain.[16] Further, the windup phenomenon generates central sensitization and pain memory.[16] Ketamine, a NMDA antagonist, provides analgesic action by interrupting the central sensitization in the nociceptive pathway.[11] Literature suggests that ketamine enhances the endogenous anti-nociceptive system, increases the activity of descending inhibitory serotoninergic pathway, and suppresses pain transmission by limiting astrocyte and microglial activation.[17] In addition, ketamine provides pre-emptive analgesia by non-adrenergic action.[18]

Garg *et al*.[15] found a higher mean postoperative pain-free period in patients who received ketamine (860 min) than those who received dexmedetomidine (580 min) following spine surgery ($P < 0.001$). They also noted a significant decrease in the rescue analgesic requirement in the ketamine group. Hadi *et al*.[19] observed that postoperative pain was significantly lower when ketamine was used during the intra and postoperative periods as an adjunct to remifentanil, thereby decreasing the need for opioids and minimizing their side effects. Urban *et al*.[20] found that the patients in the ketamine group had significantly less pain during the first postoperative day compared to the fentanyl group in narcotic-tolerant patients following spinal fusion.

In line with the previous studies, the present study showed that OFA using ketamine and ketofol intraoperatively has decreased pain scores postoperatively in comparison to OBA using fentanyl and propofol. Simultaneously, the requirement for rescue analgesics for breakthrough pain was lower in the patients receiving ketamine and ketofol. Thus, the OFA provides superior-grade analgesia compared to the OBA technique in spine surgery involving more than one vertebral segment.

The HD parameters were assessed during the intraoperative period. The intraoperative HR was comparable in both groups; however, the overall mean HR was higher in the OFA group compared to the OBA group. The MAP was also comparable in most of the intraoperative period except at two time points: once after intubation and at 90 min in an intraoperative period in which there was a significantly higher MAP in the OFA group compared to the OBA group ($P < 0.05$). However, higher episodes of hypotension were seen in the OBA group compared to OFA group ($P < 0.001$). Similar results were shown in the literature by other authors.[21-23] Attalla *et al*.[21] reported a

statistically significant difference between the ketamine and fentanyl groups in terms of HDs, sedation ranking, pain scores, first-call analgesia, and complications, in which the ketamine group was superior to the fentanyl group ($P < 0.05$). Ongewe A *et al*. evaluated HD responses before laryngoscopy and at 2.5, 5, 7.5, and 10 min between the ketamine and fentanyl groups.[22] They found a higher incidence of hypertensive episodes in the ketamine group, though the finding was not statistically significant. The fentanyl-propofol group had more episodes of hypotension compared to the ketamine-propofol group during short emergency surgical procedures.[23] These results can be explained by the sympathomimetic action of ketamine, hence the better maintenance of HDs with fewer episodes of hypotension in the ketamine and ketofol group compared to the fentanyl and propofol group.

In our study, we observed that a significant number of patients presented with PONV at 2nd hr and 6th hr in the postoperative period in the OBA group compared to the OFA group ($P < 0.05$). It may be due to the use of opioids in the OBA group despite the administration of antiemetics. Bell RF documented a significant reduction in the incidence of PONV with the use of perioperative ketamine in adult patients undergoing various surgical procedures.[24] Friedberg B. reported a PONV rate of 0.6% and a universally high level of patient satisfaction in a patient population undergoing office-based surgery with propofol-ketamine-based anesthesia.[25]

Ketamine exhibits a proclivity to induce neuropsychiatric manifestations. Nonetheless, the aforementioned symptoms, such as hallucinations, delirium, disorientation, and respiratory depression, were not observed. The co-administration of a hypnotic dose of propofol and ketamine has been found to effectively prevent the occurrence of hallucinations.[26] Around 26.66% of patients had nystagmus in the OFA group, which improved within 2 hours.

The strength of this study was that it was a well-structured, randomized, controlled trial conducted after obtaining clearance from the Institute Ethics Committee, registration in the clinical trial registry, and informed consent from the patients who participated in the study. However, this study had a few limitations, such as its single-center design. The depth of anesthesia was assessed using entropy and maintained within 40–60 throughout the intraoperative period; however, the entropy to measure the depth of anesthesia with ketamine was not validated. Also, we could not use patient control analgesia, which could have given better follow-up with rescue analgesic agents.

Conclusion

There was a longer duration of the pain-free period with lower pain scores and a lesser requirement for rescue analgesic drugs in the OFA compared to the OBA. However, hypertension in the ketofol group and hypotension in the propofol group require fine titration of the infusion of drugs in the intra-operative period. Ketamine in lower doses was devoid of significant side effects. Contrary to fentanyl, the incidence of PONV was significantly lower with ketamine.

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Conflicts of interest

There are no conflicts of interest.

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