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Indian Journal of Clinical Anaesthesia

Journal homepage: www.ijca.in

Original Research Article

Comparison of postoperative recovery after opioid-free total intravenous anaesthesia with propofol-ketamine vs. propofol-dexmedetomidine: A ramdomised controlled trial

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Abstract

Background and Aims: Opioid-free anaesthesia (OFA) is an emerging approach in modern anaesthesiology aimed at reducing opioid consumption and its associated side effects. The combination of total intravenous anaesthesia (TIVA) with agents such as propofol, ketamine, and dexmedetomidine has shown promise in enhancing recovery while minimizing opioid use. This study aimed to compare the postoperative recovery time between two opioid-free total intravenous anaesthesia regimens, propofol-ketamine and propofol-dexmedetomidine, in patients undergoing routine surgical procedures.

Methods: Sixty patients aged between 18-50 yrs, ASA I & II undergoing elective surgery of duration 1-4 hrs were randomly divided in two equal groups: group I propofol-ketamine and group II propofol-dexmedetomidine. Group I received ketamine 1mg/kg over 10 mins followed by 0.5mg/kg/hr. Group II received dexmedetomidine 1µg/kg over 10 mins followed by 0.5µg/kg/hr. Anaesthesia was induced by propofol 200µg/kg/min titrated to maintain BIS 40-60 and endotracheal intubation facilitated by rocuronium 0.6mg/kg. Hemodynamic parameters and BIS were recorded. Recovery time (modified Aldrete score), total propofol consumption, peri-operative complications, PONV, explicit recall, hallucinations and 24 hrs analgesic requirement were noted. Appropriate statistical tests were applied and $p<0.05$ was considered significant.

Results: Recovery time was longer in group I [21 (CI: 19-22) min] compared to group II [17 (CI: 16-18) min; $p< 0.001$]. There was no statistical difference in the incidence of tachycardia, hypotension, and hypertension between the two groups. Total propofol consumption and BIS were higher in group 1 ($p<0.001$). PONV was more in group I (26.7% vs 16.7%). Total 24 hrs analgesic requirement was more in group II but was statistically insignificant.

Conclusion: Although mean BIS, total propofol consumption and time required to achieve modified Aldrete score ≥9 was higher with ketamine as compared to dexmedetomidine, the difference is not significant clinically and either agent can be used depending on the patient condition and anaesthesiologist's discretion.

Keywords: Total intravenous anaesthesia, Opioid free anaesthesia, Ketamine, Dexmedetomidine, Modified Aldrete score, Postoperative recovery.

Received: 09-09-2025; **Accepted:** 03-10-2025; **Available Online**: 31-10-2025

1. Introduction

Total Intravenous Anaesthesia (TIVA) is a technique of general anaesthesia which uses a combination of agents given exclusively by the intravenous route without the use of inhalation agents. Opioids are commonly used in modern methods of anaesthesia. The use of opioids is based on their ability to provide analgesia during the peri operative period.[1] Opioids used as the part of a balanced anaesthesia are known to have a lot of side effects such as sedation, respiratory depression, post-operative nausea and vomiting, urinary retention, constipation and opioid induced hyperalgesia.[2] These side effects can delay post-operative recovery and early mobilization of patients. Opioid free anaesthesia provides an alternative for this. Principle of opioid free anaesthesia is to gain analgesic effects from different drugs while minimizing side effects of opioids[3] with added advantages of decreased post-operative nausea and vomiting and analgesic requirement post operatively. Although opioid free anaesthesia has been studied for short, day care

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https://doi.org/10.18231/j.ijca.13274.1761294930

procedures, literature for surgical management along with TIVA are few and sparse.

Ketamine, an NMDA antagonist and dexmedetomidine, an α 2 adrenoreceptor agonist have been used in lieu of opioids to provide analgesia intraoperatively. This study was planned to compare the postoperative recovery profile of patients receiving opioid free TIVA with either ketamine or dexmedetomidine. We hypothesized that the use of dexmedetomidine in TIVA would significantly reduce recovery time compared to ketamine. The primary objective was to compare time to post-operative recovery (Modified Aldrete score ≥ 9) after opioid free total intravenous anaesthesia using propofol with ketamine or dexmedetomidine. The secondary objectives included any haemodynamic complications (bradycardia, tachycardia, hypotension, and hypertension), Bi-spectral index, total propofol requirement (µg/kg/min), total 24 hours post-operative analgesic requirement, occurrence of post-operative nausea and vomiting, irrelevant talk and hallucinations and explicit recall between the two groups.

2. Materials and Methods

This study was conducted after approval by the Institutional Ethics Committee (LHMC/IEC/2020/PG Thesis/11;29-10-2020), from February 2021 to May 2022. The trial was registered prior to patient enrolment at www.ctri.nic.in (CTRI/2021/02/030967).This study was conducted in accordance with the Ethical Principles for Medical Research Involving Human Subjects, outlined in the Helsinki Declaration of 1975 (revised 2013).

Patients in age group 18-50yrs, ASA I & II undergoing elective surgical procedure of duration 1-4 hrs were recruited for the study. A careful pre-anaesthetic check-up was performed. A written informed consent was obtained for anaesthesia, surgery and participation in the study. An investigator with no further involvement in the study generated a list of random numbers between 1-60 by using computer randomization into two equal groups of 30 each. The unique randomization code was allocated to randomize patients equally with no restrictions or bias to either of the two study groups: Group (I) and Group (II). The result of the allocation was concealed in sequentially numbered sealed opaque envelopes mentioning the code and the group number. On the day of surgery, the coordinator handed over an envelope to the senior anaesthesiologist supervising the operation theatre (OT).

Patient was wheeled in and routine monitors were attached including the Bispectral index (BIS) and neuromuscular monitoring (NMT). Intravenous access was obtained. Appropriate regional block was administered according to the surgery. Patients were premedicated with injection glycopyrrolate 0.2mg iv and injection midazolam 0.02mg/kg iv.

Drug as mentioned in the randomised envelopes was prepared by a resident not involved in the study. The drug syringes were labelled as drug as I or drug II depending on the group. Ketamine or dexmedetomidine was prepared in 50 ml syringe with a dilution of 2mg/ ml and 2µg/ ml respectively by a resident not involved in any further participation in the anaesthesia procedure and study. The coding was revealed only after all the cases had been completed and data analysed. Patients in Group I received ketamine@ 1mg/kg over 10 minutes. Patients in group II received dexmedetomidine @ 1µg/kg over ten minutes. This was followed by intravenous lignocaine 1.5mg/kg and induction of anaesthesia with propofol to achieve BIS between 40-50. Intubation with endotracheal tube was facilitated by injection rocuronium @ 0.6 mg/kg. Capnography was applied and mechanical ventilation with by O_2+Air to achieve FiO_2 of 0.4 was adjusted to maintain $EtCO_2$ at 30–35 mmHg. Anaesthesia was maintained by infusion of propofol @ 200µg/ kg/min and adjusted in aliquots of 25 µg/kg/min to maintain a BIS of 40-60. Analgesia was maintained by either ketamine (Group I) @0.5mg/kg/hr or dexmedetomidine (group II) @ 0.5µg/kg/hr. Muscle relaxation was titrated to a train of four count of 1 or less.

BIS was recorded every 10 minutes. Haemodynamic parameters were observed intraoperatively at 5 m in intervals. Any perturbation such as hypotension (BP <20% baseline), bradycardia (HR <50/min), hypertension (BP >20% baseline) and tachycardia (HR >20% baseline) was recorded. Each episode was given one count. Hypotension was managed by infusing 5-10 ml/Kg of crystalloid, and if it persisted, norepinephrine was started. Tachycardia and hypertension were initially managed by increasing the infusion rate of propofol, and if not controlled, by administering 0.5 µg/Kg fentanyl. Bradycardia was managed by administering 0.2 mg glycopyrrolate and further by 0.6mg atropine. At the end of the surgery, infusions were switched off when train of four count was 4 (To). Residual muscle relaxant was reversed using glycopyrrolate and neostigmine. Time was noted from switching off the infusion to extubation of the trachea (Te). Modified Aldrete score was observed every minute post extubation. Time to post operative recovery, which was the primary objective, was defined as time to achieve Modified Aldrete score ≥9 (Tr) from switching off the infusions (To). Presence of irrelevant talk, hallucination was noted. Patients were asked if they remember any events during the procedure after recovery. Total propofol consumed was noted at the end of procedure. Mean bi spectral index was calculated. Post-operative analgesia was provided with the help of inj. diclofenac 1mg/ Kg (max 75 mg) on demand at 8 hourly intervals. If pain was not relieved by diclofenac, iv tramadol 1mg/Kg was administered. A note was made of the episodes of nausea and vomiting in 24 hours. Patients were administered ondansetron 0.08 mg/ kg (max 8mg) iv on demand for nausea and/ or vomiting at 8 hrly interval. Total 24 hrs analgesic requirement was noted.

Sample size was calculated on the basis of study by Abdalla et al., who reported recovery times of 5.7±1.7 (min) with propofol+ dexmedetomidine and 22.2±8.2 (min) with propofol+ ketamine for ERCP.[4] Since no studies are available comparing these two drugs in combination with propofol for surgical procedures, assuming an alpha error of 5% and a beta error of 95%, the calculated sample size required was 5 in each group. However, due to potential variations in response, the complexity of surgical procedures beyond ERCP, and the desire to enhance the precision and reliability of the results, a larger sample size of 30 patients per group was recruited. Data was tabulated and analysed. The quantitative variables were expressed as Mean±SD and evaluated using Student's unpaired t test/ Mann Whitney U test. The qualitative variables were expressed as Mean±SD and evaluated using Chi square test/ Mann Whitney U test. Statistical Package for Social Sciences (SPSS) was used for analysis and a p value <0.05 was considered statistically significant.

3. Results

A total of 72 patients were screened. Seven patients did not meet the inclusion criteria and five refused consent for inclusion in the study. A total of 60 patients were recruited and randomised to the two groups equally. The patient's characteristics were comparable between the two groups as shown in **Table 1** and **Table 2**. The mean duration of surgery in group I was 117.6 min (CI: 105-129.40 min) and in group II was 140.9 min (CI: 127.03-154.20 min) which was statistically significant (p 0.018).

The median To-Te in group I was 14 min (CI: 13 – 16 min) and in group II was 13 min (CI: 12-14 min). Time to extubation of trachea was shorter in group II, statistically significant (p= 0.041). Median Te-Tr in group I was 7 min (CI: 5-8 min) and in group II was 4 min. Time from extubation of trachea to achieving modified Aldrete score≥9 was shorter in group II as compared to group I and was statistically significant (p <0.001). Time from stopping of infusion to achieving modified Aldrete score≥9 was shorter in group II (17 min; CI: 16-18 min) as compared to group I (21 min; CI: 19-22 min) and was statistically significant (p <0.001; **Table 3**, **Figure 1**).

Hemodynamic parameters such as tachycardia, bradycardia, hypotension and hypertension were comparable between the two groups (p > 0.05; **Table 4**).

Mean propofol consumption (in mg) in group I was 1524.7 mg (CI: 1340.33-1694.32 mg) and in group II was 1447.7 mg (CI: 1287.67-1593.30 mg). There was no statistical difference in mean propofol consumption between the groups (p= 0.531). Total propofol consumed (µg/kg/min) in group I was much higher than in group II. Median propofol consumption (µg/kg/min) in group I was 215.20 (CI: 194.13-239.72) and in group II was 176.24 (CI: 151.50-184.53) which was statistically significant (p <0.001). BIS value was higher in group I as compared to group II. The median BIS in group I was 53 (CI: 52.5-54) and in group II was 49 (CI: 48-51) which was statistically significant (p <0.001; **Table 5**, **Figure 2**). PONV was more in group I (26.7%) as compared to group II (16.7%) and was statistically insignificant (p 0.347; **Table 6**).

Analgesic requirement was more in group II as compared to group I and was statistically insignificant (p >0.05). There was no incidence of hallucination and explicit recall among both the groups.

Table 1: Patients characteristics

	Group I n=30	**Group II n=30**	**p-value (Chi square test)**
Male	17 (56.7%)	10 (33.3%)	0.069
Female	13 (43.3%)	20 (66.7%)	
Age in years (Mean ± SD) [95%CI]	38.5 ± 9.7 [35.1- 41.8]	39.1 ± 9.3 [35.73 - 42.40]	0.787
Weight in kg [Median (IQR)] [95%CI]	63.0 (55.25 - 68) [60.0 - 66.5]	60.0 (55-65) [59.20 - 73.67]	0.390

Table 2: Type of surgery

Surgery	**Group I n=30**	**Group II n=30**	**Chi square test p-value**
Debridement maxilla	0 (0.0%)	1 (3.3%)	0.453
Laparoscopic cholecystectomy	6 (20.0%)	6 (20.0%)	
Laparoscopic mesh hernioplasty	13 (43.3%)	16 (53.3%)	
Laparoscopic sleeve gastrectomy	3 (10%)	5 (16.7%)	
Laparotomy	3 (10%)	0 (0.0%)	
Breast Surgery	4 (13.3%)	1 (3.3%)	
Open cholecystectomy	1 (3.3%)	1 (3.3%)	
Total	30 (100.0%)	30 (100.0%)	

Table 3: Recovery time

	Group I n=30	Group II n=30	Mann Whitney U test p-value
To-Te [Median (IQR)] [95%CI] min	14.0 (11-16) [13 - 16]	13.0 (10-14) [12-14]	0.041
Te-Tr [Median (IQR)] [95%CI] min	7.0 (5-8) [5 – 8]	4.0 (4-6) [4-6]	0.001
To-Tr [Median (IQR)] [95%CI] min	21.0 (18-24) [19 -22]	17.0 (15-19) [16-18]	<0.001

To: Time zero when infusions were stopped; Te: Time when trachea was extubated; Tr: Time when Aldrete score was ≥9.

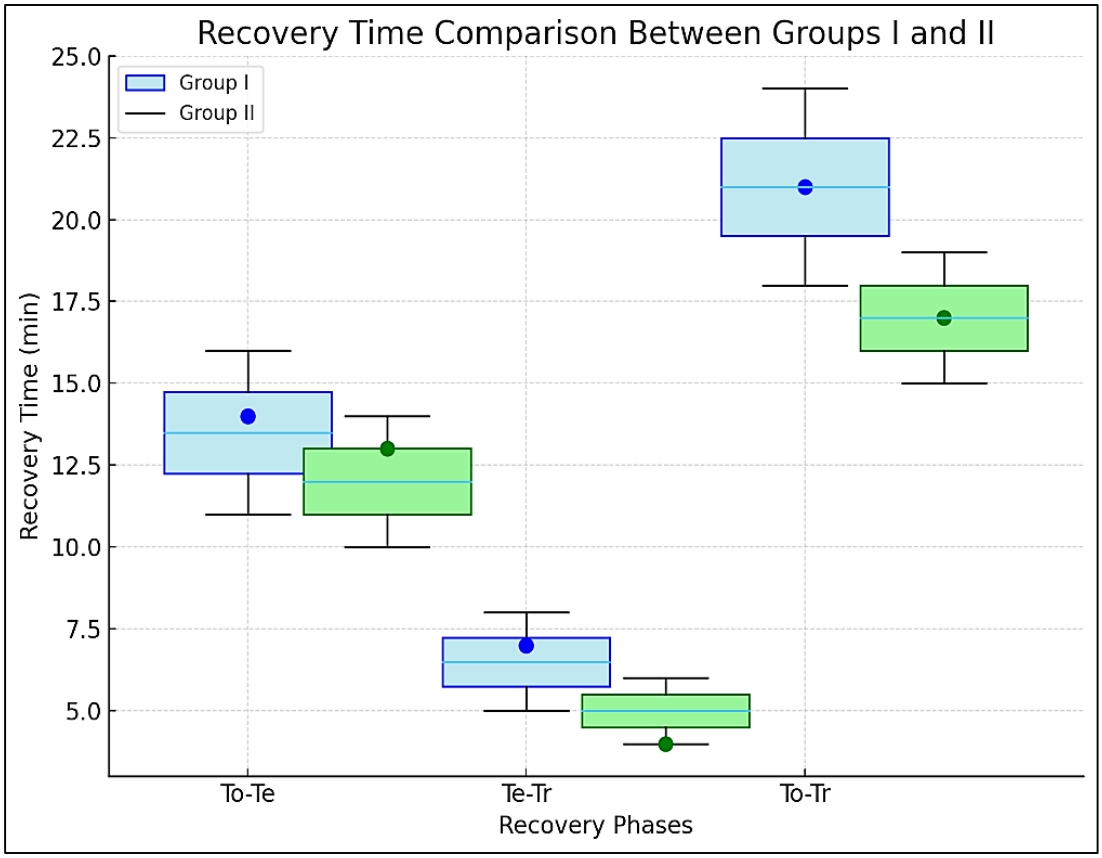

Figure 1: The boxplots show the median, interquartile range (IQR), and any outliers, highlighting the differences between the two groups. The median values for each phase are marked as dots for both groups.

Table 4: Hemodynamic variables

	Group I n=30	Group II n=30	Chi square test p-value
Tachycardia	4 (13.3%)	2 (6.7%)	0.389
Bradycardia	0	0	
Stable Heart Rate	26 (86.7%)	28 (93.3%)	
Normotension	25 (83.3%)	26 (86.7%)	0.896
Hypotension	2 (6.7%)	2 (6.7%)	
Hypertension	3 (10.0%)	2 (6.7%)	

Table 5: Intraoperative variables

	Group I n=30	Group II n=30	Unpaired t test p-value
Duration of surgery in minutes (Mean ± SD) [95%CI]	117.6±34.5 [105-129.40]	140.9±39.2 [127.03-154.20]	**0.018**
Total Propofol in mg (Mean ± SD) [95%CI]	1524.7±491.8 [1340.33-1694.32]	1447.7±453.3 [1287.67-1593.30]	0.531
Propofol µg/kg/min [Median (IQR)] [95%CI]	215.20 (163.14-250.29) [194.13-239.72]	176.24 (141.85-187.50) [151.50-184.53]	**<0.001**
Study drug used (ml) (Mean ± SD) [95%CI]	90.58±35.79 [77.77-103.39]	104.60±54.72 [85.00-124.18]	0.077
BIS [Median (IQR)] [95%CI]	53.0 (52-54) [52.5-54]	49.0 (48-51)	**<0.001**
No. of diclofenac doses [Median (IQR)] [95%CI]	2 (1, 2)	2 (2, 2)	0.122
No. of patients requiring tramadol	2 (6.7%)	4 (13.3%)	0.884

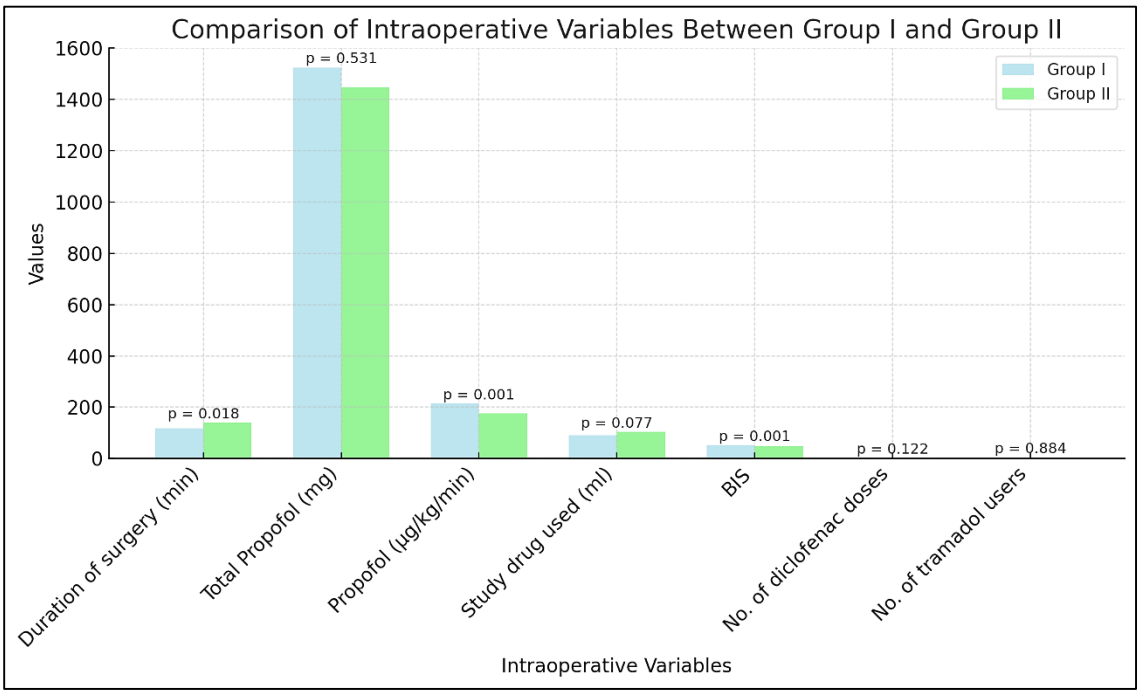

Figure 2: Each bar represents the mean value of a specific variable for both groups, with p-values displayed above the bars to indicate the statistical significance of the differences

Table 6: Postoperative nausea and vomiting

PONV	Group I n=30	Group II n=30	Chi square test p-value
Yes	8 (26.7%)	5 (16.7%)	0.347
No	22 (73.3%)	25 (83.3%)	
Total	30 (100.0%)	30 (100.0%)	

4. Discussion

Opioids have long been used to supplement general anaesthesia. The common practice of administering opioids during anaesthesia has been challenged by clinical studies suggesting that opioid-free anaesthesia (OFA) may be effective in providing adequate pain control, while reducing postoperative opioid consumption and hopefully reducing opioid-related side effects.[5] Although the definition of OFA varies in the literature and between centres, lidocaine,

ketamine, and α-2 agonists such as clonidine or dexmedetomidine have been proposed to replace opioids either alone or in combination.[5]

Although dexmedetomidine is known to cause bradycardia due to central alpha 2 agonism and ketamine tachycardia due to sympathetic stimulation, hemodynamic parameters were comparable between the two groups in our study. Relatively stable hemodynamics could be due to the fact that although the dose of these two drugs was fixed, the dose of propofol was varied according to BIS to maintain the depth of anaesthesia and more propofol was required with ketamine as compared to dexmedetomidine which could have balanced the effect on sympathetic discharge by the other two drugs.

However, Bakan et al. reported an increase in heart rate in patients receiving dexmedetomidine (0.3µg/kg loading dose followed by 0.3µg/kg/min) for laparoscopic cholecystectomy as part of TIVA regimen.[6] This could be due to inadequate analgesia as both the loading as well as maintenance dose is much less than that prescribed for analgesia. Whereas, bradycardia was reported by Hasanein et al. in 1% patients in ketamine propofol group compared to 9% in fentanyl propofol group in obese patients undergoing ERCP.[7] The airway was not secured and the bradycardia could have been associated with the desaturation episodes. Beloeil et al. have reported an incidence of bradycardia in 19.1% (30/157) in patients receiving dexmedetomidine (0.4-1.4 µg/kg/hr) out of which 5 developed severe bradycardia. This could be attributed to a high dose of dexmedetomidine (up to 1.4µg/kg/hr).[8] After these episodes, the dose of dexmedetomidine was limited to 1µg/kg/hr, and there were no further instances of bradycardia. We did not find any instance of bradycardia in any of the patients in our study. This may be due the fact that all patients were premedicated with iv glycopyrrolate 0.2mg prior to induction of anaesthesia.

An increase in mean blood pressure has been reported by Abdalla et al. with ketamine as compared to dexmedetomidine when administered with propofol for ERCP which was mainly due to elevated diastolic pressures attributed to increased systemic vascular resistance.[4] On the other hand, Bakan et al. observed an increased incidence of hypertension (27.5%) with a combination of propofol, dexmedetomidine (0.6 µg/kg loading followed by 0.3 µg/kg/min) and lignocaine for laparoscopic cholecystectomy of which 9 patients required treatment with nitro-glycerine. This could be due to lower loading and maintenance dose of dexmedetomidine.[6]

Hasanein et al. have reported hypotension in 3% of the patients who received ketamine (50µg/kg/min) with propofol for ERCP. This could be due to hypoxia as the airway was not secured. The hypotensive episodes in our study were managed by infusion fluids and were transient.[7]

The mean duration of surgery in group I was 117.6±34.5 min (CI: 105-129.40 min) and in group II was 140.9±39.2 min (CI: 127.03-154.20 min; p= 0.018) but was within the study protocol. Our study showed that mean total propofol consumption between the two groups was statistically insignificant (p= 0.531), despite a significant longer infusion in group II. However, when the propofol consumption was adjusted for duration of infusion, median rate of propofol consumption (µg/kg/min) in group II was 176.24 (CI: 151.50-184.53), which was statistically lower (p <0.001) than group I [215.20 (CI: 194.13-239.72) µg/kg/min]. Dexmedetomidine and propofol have a synergistic effect in suppression of EEG, whereas, ketamine increases the EEG activity and consequently BIS. Since the titration of propofol was based on BIS in our study, more propofol was required in the ketamine group despite a shorter duration of infusion to maintain BIS within the range of 40-60.

Increased propofol consumption with ketamine has been reported by other authors (Aydogan et al., Abbas et al).[9,10] However, when compared with the addition of fentanyl or ketamine to propofol, Hasanein et al reported a significantly lower consumption of propofol with ketamine.[7] Abdalla et al. concluded that propofol consumption was lower with dexmedetomidine as compared to ketamine in patients undergoing ERCP, although there was no statistical difference (p = 0.288).[4] Bakan et al. reported increased propofol consumption in dexmedetomidine lidocaine group vs the remifentanil group (p=0.003).[6]

Sengupta et al. observed that a bolus dose of ketamine at 0.5 mg/kg under stable propofol anaesthesia led to an increase in BIS (bispectral index) values, indicating deeper anesthesia, while a lower bolus dose of 0.2 mg/kg did not produce any significant change in BIS values.[11] Wang et al. studied effects of different loading doses of dexmedetomidine on BIS under propofol target-controlled infusion.[12] They found that dexmedetomidine in a loading dose of 1 µg/kg/min followed by 0.5 µg/kg/hr produced a significant decrease in BIS. In our study, BIS in group I was higher as compared to group II, which was statistically significant (p <0.001) but maintained within normal range. Although ketamine produces a consistently elevated BIS due to its excitatory effect, in our study significantly higher dose of propofol was administered to maintain BIS within the normal range as mandated by study protocol.

Koruk et al. concluded that the recovery time (modified Steward score) was significantly longer in the ketamine group than in the dexmedetomidine group [10.5 (93.4) vs 5.7 (0.8)] minutes; p= 0.01) in paediatric patients undergoing transcatheter atrial septal defect closure.[13] These results were echoed by Tewari et al. (ketamine propofol 35±12 min and dexmedetomidine propofol: 22±10 min) in young adult patients undergoing cardiac catheterisation.[14] Abdalla et al. reported shorter recovery time (modified Aldrete score) with propofol dexmedetomidine (5.7±1.7 min) as compared to

propofol ketamine (22.2±8.2 min) for ERCP, which is both statistically and clinically significant.[4] Although the time required for recovery with ketamine was almost similar to ours, the duration was longer with dexmedetomidine, probably because of the difference in duration and the longer context sensitive half life of dexmedetomidine as compared to ketamine.

The median time from stopping of infusion to extubation of trachea (To-Te) in group I was 14 (CI: 13 - 16) min and in group II was 13 (CI: 12- 14) min which although was statistically significant (p =0.041) but not clinically significant in our study. Bakan et al. reported extubation time of 10 (IQR 7-16) min with dexmedetomidine which is less than ours. This could be because they have used almost half the dose of dexmedetomidine as compared to ours.[6]

Time from extubation of trachea to achieving modified Aldrete score ≥9 (Te-Tr) was shorter in group II 4 (CI: 4-6) min as compared to group I 7 (CI: 5-8) min and was statistically significant (p=0.001) but not clinically significant. This difference may be explained on the subjective criteria used by the anaesthesiologist to extubate the trachea.

The time from stopping the infusion to achieving a modified Aldrete score of ≥9 (ToTr) was significantly shorter in Group II (17 minutes, CI: 16–18) compared to Group I (21 minutes, CI: 19–22), with a p-value of <0.001 in our study. This difference in recovery time may be attributed to the increased propofol consumption required in the ketamine group to maintain a BIS value <60, despite the shorter duration of surgery. Additionally, it is important to note that we could not identify any defined or studied range for the context-sensitive half-life of ketamine infusion, which may further contribute to the observed differences in recovery

Agitation and irritability ranges from 2-33% in patients receiving propofol ketamine combination for short procedures,[4,7,15] while none with dexmedetomidine-propofol. None of our patients experienced irrelevant talk and hallucinations in the postoperative period. This may be due to use of subanaesthetic dose of ketamine and premedication of all patients with midazolam prior to the induction of anaesthesia and use of propofol both of which are known to mitigate the delirious effects of ketamine.

Similarly, the incidence of postoperative nausea and vomiting (PONV) after administration of ketamine with propofol ranges from 2% to 46.67% in the literature for upper GI endoscopy,[4,7,9] whereas no episodes of PONV were reported with the use of Dexmedetomidine.[4] We observed a higher incidence of PONV in group I 26.7% as compared to group II 16.7% which was not statistically significant (p= 0.347). Although TIVA is attributed to a lower incidence of PONV, the nature of surgery and absence of additional prophylactic antiemetic may be the reason for this also we have considered nausea and vomiting as a single entity and not classified the severity. Ketamine is a known to increase incidence of PONV especially in females due to inhibition of serotonin uptake at synaptic terminals and causing an increase in intragastric pressures. Dexmedetomidine, on the other hand due to suppression of the central sympathetic system and decreased opioid requirement is known to decrease the incidence of PONV. However, the incidence in our study was comparable. This could be due to other factors and non-matching of patients with relative risk of developing PONV.

Singh et al. concluded that both intraoperative or postoperative infusions of dexmedetomidine lead to significant opioid sparing in early and postoperative period.[16] Although 24 hrs analgesic requirement was more in group II as compared to group I but was not statistically significant. This may due to the fact that (56.7%) of patients in group I received regional anaesthesia as compared to group II (36.7%). However, further dedicated studies are needed to determine the quality of analgesia provided by dexmedetomidine and ketamine.

None of the patients had experienced explicit recall in either of the group. This could be because the BIS was maintained between 40-60 throughout the study.

Dexmedetomidine is considerably more expensive than ketamine. However, both drugs were found to be safe and exhibited similar recovery profiles in our study. While we did not perform a cost-benefit analysis or assess their effects in patients with substantial cardiovascular morbidity, the choice of one drug over the other would likely depend on factors such as cost, patient characteristics, and the familiarity of the anaesthesiologist with the respective agents.

We could not find any studies comparing propofol-ketamine and propofol-dexmedetomidine for routine surgical procedures. Most existing literature has focused on these combinations in the context of opioid-free TIVA for conscious sedation in day-case surgeries or short surgical procedures. However, our study does have several limitations. We did not use a target-controlled infusion pump, so a weight-based regimen for propofol was employed, potentially introducing variability in anaesthetic depth and recovery. That said, the use of BIS and maintaining it within the range of 40-60 helped mitigate this limitation. Despite randomization, the surgery duration was longer in Group II than in Group I, but this did not affect recovery times. In fact, Group II showed faster recovery despite the longer infusion times.

It is also well-documented that ketamine can influence BIS. In our study, we had to administer more propofol with ketamine (approximately 39 µg/kg/min) to maintain BIS <60, which could have contributed to a delayed recovery in the ketamine group, rather than differences between ketamine and dexmedetomidine themselves. Additionally, post-operative analgesia was not consistently assessed, as not all

patients received regional blocks, and variations in nociception could have influenced episodes of hypertension and tachycardia. While we observed the incidence of PONV, we did not measure its severity, which may differ.

Also, we only included ASA I and II patients, excluding those with significant cardiovascular morbidity. The effects of dexmedetomidine and ketamine on cardiovascular stability and other side effects in ASA III patients, particularly those with advanced cardiovascular disease, remain areas for future research and further evaluation.

5. Conclusion

Ketamine and dexmedetomidine are both safe and effective for maintaining anaesthesia in routine surgical procedures, however, ketamine prolongs time required to achieve modified Aldrete score ≥ 9 by 4 min as compared to dexmedetomidine. The choice of agent can be guided by factors such as cost, patient condition, and the anaesthesiologist's preference. Although the 4-minute difference in recovery is unlikely to be clinically relevant for routine elective surgeries, its potential impact on day-care surgeries and turnover times requires further investigation.

6. Data Sharing

De-identified data may be requested with reasonable justification from the authors (email to the corresponding author) and shall be shared after approval as per the author's Institution policy.

7. Source of Funding

None.

8. Conflict of Interest

None.

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Cite this article: Kumar N, Alam S, Pandey M. Comparison of postoperative recovery after opioid-free total intravenous anesthesia with propofol-ketamine vs. propofol-dexmedetomidine: A randomized controlled trial. *Indian J Clin Anaesth*. 2025;12(4):668–675.