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Effect of midazolam, dexmedetomidine or ketaminepremedication on the recovery profile after balanced anaesthesia: arandomized clinical trial

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Abstract:
Background*:Pre-medication is commonly used to reduce preoperative anxiety and to facilitate smooth transition into induction of anaesthesia. The following study was carried out to assess the effect of three different drugs: midazolam, dexmedetomidine and ketamine on the recovery profile after balanced anaesthesia.*
Materials and Methods*: The study was a randomized, double-blinded clinical trial conducted on 99 patients of either sex in age group of 18 to 60 years with ASA I and II who underwent major surgeries of moderate duration (< 3 hours). There were 3 groups, Group M: received Midazolam 0.04 mg/kg iv 10 mins before induction of anaesthesia after dilution in 10 ml NS. Group D: received Dexmedetomidine 0.5 µg/kg diluted in 10 ml NS over 10 mins. Group K: received Ketamine 0.25 mg/kg diluted in 10 ml NS. Intra-operative haemodynamic parameters were monitored. Emergence time, recovery time and time to first rescue analgesia were assessed.*
Results*: Amongst the three groups, Group D showed the fastest emergence time while Group K showed the slowest emergence time (15.09 ± 0.84 minutes vs 17.55 ± 1.00 minutes; p <0.01). Comparing the mean recovery times, Group D showed the fastest recovery time (31.79 ± 2.32 minutes). Amongst the three groups, Group D required the fastest rescue analgesia while Group K required the slowest rescue analgesic (24.39 ± 2.12 minutes vs 34.73 ± 2.05 minutes).*
Conclusion:*It was concluded that the recovery profile was much better in the dexmedetomidine group.*
Key Words*:Recovery profile, balanced anaesthesia, midazolam, dexmedetomidine, ketamine*

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I. Introduction

Pre-medication is commonly used to reduce preoperative anxiety and to facilitate smooth transition into induction of anaesthesia. Drugs having different mechanisms of actions might affect the recovery profile differently.

Midazolam, a benzodiazepine and GABA (gamma-amino-butyric-acid) agonist is well known for its anxiolytic and sedative properties[1]. However, some recent study showed that midazolam maintains implicit memory for potentially peri-operative stressful events[2].

Dexmedetomidine is an alpha 2 adrenergic receptor agonist, and by acting at locus coeruleus, it produces a physiological sleep like state (locus coeruleus removes its inhibitory effect on ventrolateral preoptic nucleus of the hypothalamus) with a characteristic arousable sedation[3].

Ketamine, a phencyclidine derivative, is a non-competitive NMDA (N-methyl D-aspartate) receptor antagonist. It does not activate the sleep centre nor does it suppress the wake centers. It produces sleep by suppressing frontal-parietal connectivity[4,5]. It has sedative and analgesic effect at 0.2 to 0.8 mg/kg. Under stable anaesthesia, a small dose of ketamine does not increase the Bispectral Index (BIS)[6]

The bispectral index (BIS) is a continuous processed electroencephalography parameter that has been developed to measure the hypnotic effects of anesthetic and sedative agents on the brain[7]. A patient is considered to be appropriately anaesthetized (i.e., unconscious) when the BIS value is between 40 and 60[8,9].

Some investigators[10] maintain that dexmedetomidine, by acting at the subcortical sleep-wake neurons, primarily affect the level of consciousness. And, ketamine, by their effects mediated through thalamocortical

and cortico-cortical networks, primarily affect the content of consciousness. Some drugs like propofol and sevoflurane act at both levels.

Meanwhile, one recent study[11] has suggested that postoperative pain and agitation can be reduced (up to 31%) by avoiding abrupt awakening from deep level of anaesthesia.

Hence, we have decided to assess the effect of three different drugs: midazolam, dexmedetomidine and ketamine on the recovery profile after balanced anaesthesia.

II. Material And Methods

The study was a randomized, double-blinded clinical trial conducted in the Department of Anaesthesiology, Regional Institute of Medical Sciences, Imphal, between November 2019 and October 2021, over a period of two years. After obtaining approval from Research Ethics Board (REB), RIMS, informed written consent of patients was taken before recruitment for the study. The inclusion criteria were patients of either sex in age group of 18 to 60 years with ASA[12] category I and II who underwent major surgeries of moderate duration (less than 3 hours). Patients with hepatic, renal, neurological disorders and neuropathies, those with compromised cardiovascular and respiratory problems and anticipated difficult airway were excluded.

Sample size was calculated based on a previous study by Ohtani N et al[13] for alpha value of 10% and power of 80% taking mean scores of SOMCT[14] (Short Orientation Memory Concentration Test) at 20 minutes after tracheal extubation to be 22.1 and 18.7 with standard deviation of 2.6 and 7.4 respectively. After calculation, it came out to be 33 in each group. For three groups, we had 99 patients.

Based on a computer-generated randomization, the 99 patients were divided into three groups; **Group M**: received Midazolam 0.04 mg/kg intravenously (IV) 10 minutes before induction of anaesthesia after dilution in 10 ml normal saline. **Group D:** received Dexmedetomidine 0.5 µg/kg diluted in 10 ml normal saline over 10 minutes. **Group K**: received Ketamine 0.25 mg/kg diluted in 10 ml normal saline.

Pre-operative assessment was done the day before the surgery. During this visit, a good rapport was established with the patient. All the patients received Tab. Alprazolam 0.25 mg the night before the surgery. In the morning, Tab Pantoprazole 40 mg and Tab Metoclopramide 10 mg was given with a small sip of water before induction of anaesthesia (up to 150 ml of water is allowed 2 hours before surgery). In the pre-operative room, intravenous access was established to start the maintenance intravenous fluid. Inj. Glycopyrrolate 0.004 mg/kg IM was given. On arrival at the operation theatre, baseline monitoring of pulse rate (PR), non-invasive blood pressure, oxygen saturation (spO_2) and electrocardiogram (ECG) was started. Care was taken to maintain normothermia in the operation theatre. BIS (bispectral index) monitoring was started before induction of anaesthesia. Fentanyl 2µg/kg IV was given before induction of anaesthesia as analgesic. After pre-oxygenation for 3 minutes, anaesthesia was induced with propofol (1.5 – 2 mg/kg) IV followed by rocuronium 0.6 mg/kg to facilitate endotracheal intubation. Just after endotracheal intubation, anaesthesia was maintained with 50% nitrous oxide in oxygen with a fresh-gas flow of 2L/min and sevoflurane 0.6 to 1.5% titrated to maintain a BIS value of 40 to 60. Ventilation was adjusted to keep end-tidal carbon dioxide ($ETCO_2$) between 30-35 mmHg.

Intra-operative haemodynamic parameters were monitored every 5 minutes for the first 30 minutes then every 15 minutes for the rest of the period unless interventions become necessary for bradycardia (Inj. Atropine in 0.3 mg IV increments for HR < 50/min) and/or hypotension (Inj. Mephentermine 3 mg IV increments for systolic blood pressure, SBP <90 mmHg). Sevoflurane was cut 10 minutes before the anticipated end of skin closure. Nitrous oxide was cut 2 minutes before the anticipated reversal of residual neuromuscular blockade. Inj. Neostigmine 0.05 mg/kg and Inj. Glycopyrrolate 0.008 mg/kg IV was used for reversal of residual neuromuscular blockade.

Emergence time was taken as the time from cutting the inhalational agents to opening eye on command. Endotracheal extubation was done after reversal of neuromuscular blockade when the spontaneous tidal breathing was adequate and the patient had the tendency to cough on the tube. Recovery time (assessed in the post anaesthetic care unit or PACU) was taken as the time from cutting the inhalational agents to reaching a Modified Aldrete Score of > 9. Time to first rescue analgesia was noted in the post-anaesthetic care unit. Rescue analgesia was given with Inj. Diclofenac 75mg intramuscularly when the Visual Analogue Scale[15] (VAS) >4. Other complications like post-operative nausea and vomiting (PONV) will be recorded.

All the data were tabulated in the Excel format and was analyzed using SPSS software Version 21 for Windows. One-way ANOVA test was utilized for parametric numerical data and Chi-square test for nonparametric data. A p-value of less than 0.05 will be considered statistically significant.

III. Results

The study protocol was completed in all the enrolled 99 patients. The demographic parameters such as given below were comparable in all the three groups and were found to be statistically insignificant.

Table 1: Demographic profile

Mean ± SD	*Group M (MIDA-ZOLAM)*	*Group D (DEXMEDE-TOMIDINE)*	*Group K (KETAMINE)*	*F value or Chi-square value*	*P value*
Age (in years)	**36.76 ± 7.076**	**34.97 ± 9.590**	**38.21 ± 8.771**	**F =1.193**	**0.308**
Weight (in kgs)	**57.39 ± 4.220**	**58.39 ± 5.256**	**58.24 ± 5.494**	**F =0.380**	**0.685**
Gender (F:M)	**26 : 7**	**25 : 8**	**23 : 10**	**X^2 = 0.749**	**0.688**
ASA Status (I:II)	**31 : 2**	**28 : 5**	**28 : 5**	**X^2 = 1.707**	**0.426**

There was minimal fluctuation in the heart rate (bpm) from the baseline value in comparing all the three groups. However, when we do multiple comparisons amongst the three group, we found that at post intubation and at 5 minutes time, comparison between Group D and Group K was statistically significant with a P value of 0.049 and 0.020 respectively. From 10 to 40 minutes, comparison between Group M vs. Group D and between Group D vs. Group K were all found to be statistically significant.

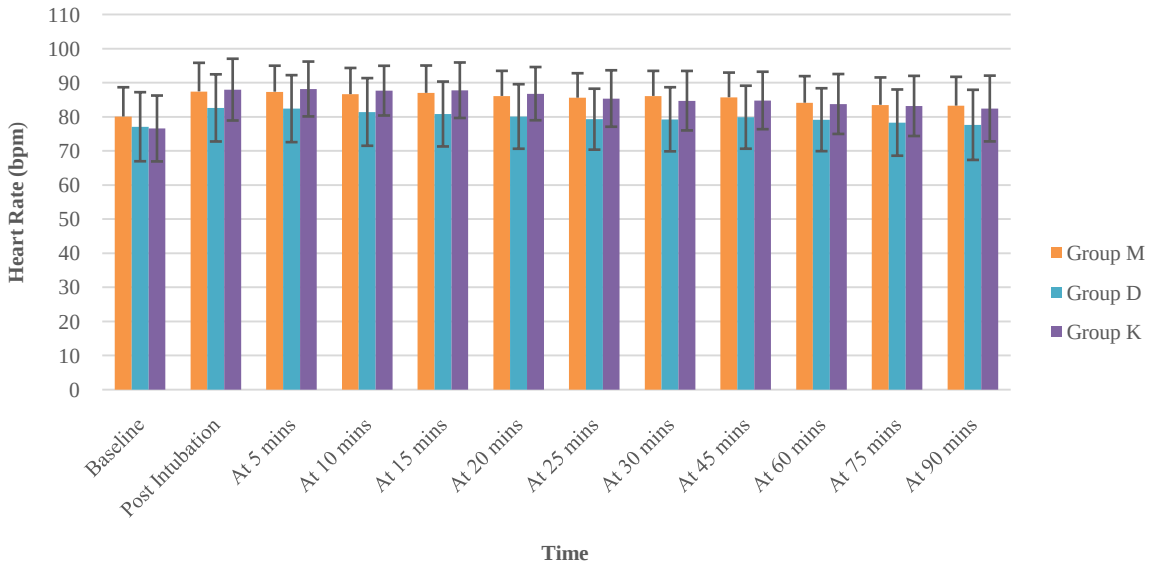

Figure 1: Graph showing the comparison of the mean intra-operative Heart Rate (HR) in the three groups with corresponding standard deviations

A comparison of the intra-operative Mean arterial pressures (MAP) between the three groups showed that the baseline MAP among the three groups was not statistically significant with a P value of 0.394. When we do multiple comparisons amongst the three groups, we found that at post-intubation period up to 45 minutes period, the comparison between Group D vs Group K and between Group K vs Group M were all statisticallysignificant (P value <0.05).

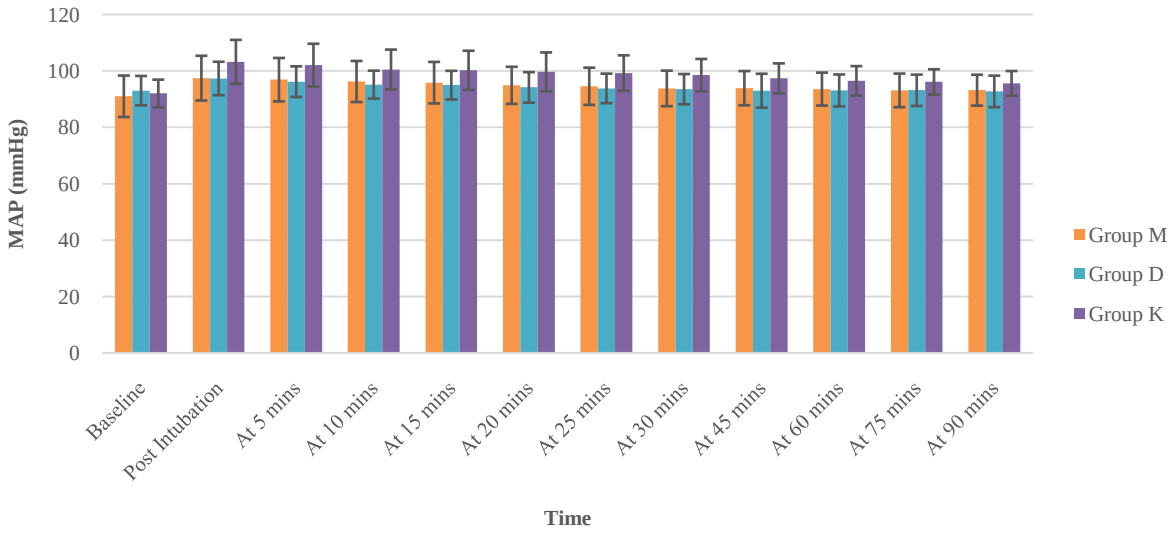

Figure 2: Graph showing the comparison of the mean intra-operative Mean Arterial Pressures (MAP) in the three groups with corresponding standard deviations.

A comparison of the intra-operative BIS values showed that the baseline BIS among the three groups was not statistically significant with a P value of 0.985. When we do multiple comparisons amongst the three groups, we found that there were significant differences between Group M vs Group D and between Group D vs Group K from post intubation period up to 90 minutes (P value <0.05).

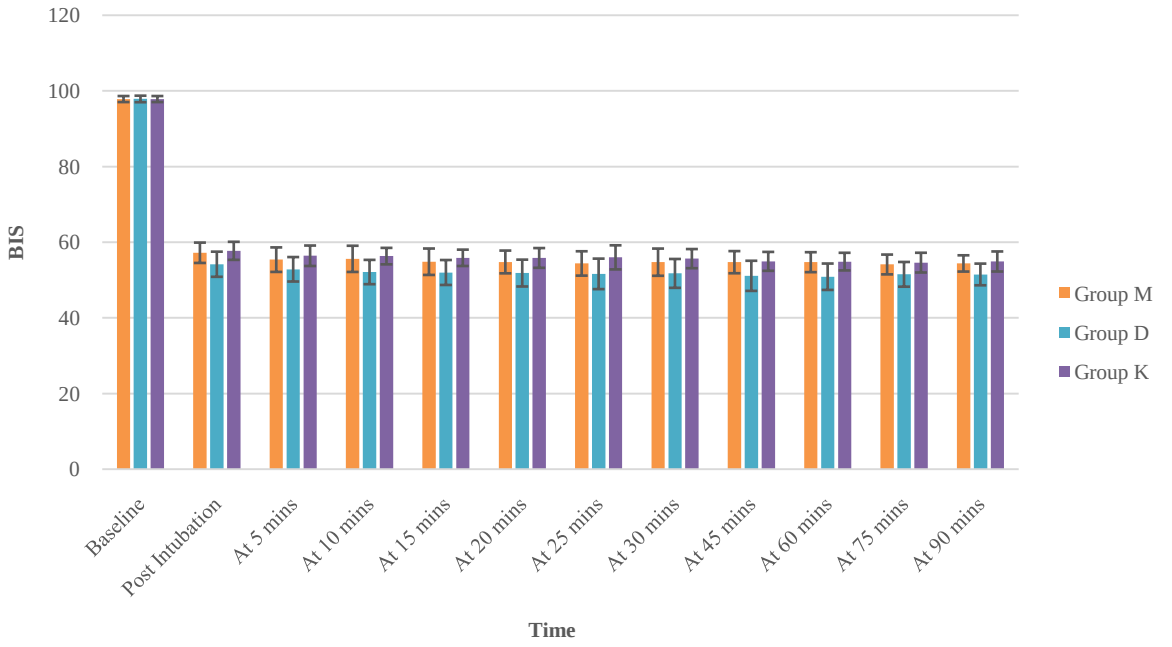

Figure 3: Graph showing the mean intra-operative BIS values among the three groups with corresponding standard deviations.

Table 2: Comparison of main study variables in the three groups of patients studied

Variables	Group M	Group D	Group K	F value	P value
Emergence Time (in minutes)	**16.27±0.87**	**15.09±0.84**	**17.55±1.00**	**60.082**	**< 0.01**
Recovery Time (in minutes)	**33.85±1.58**	**31.79±2.32**	**36.79±2.13**	**50.101**	**< 0.01**
Time to first rescue analgesic (in minutes)	**28.91±1.54**	**24.39±2.12**	**34.73±2.05**	**239.380**	**< 0.01**

Amongst the three groups, Group D showed the fastest emergence time (15.09 ± 0.84 minutes) followed by Group M (16.27 ± 0.87 minutes) while Group K showed the slowest emergence time (17.55 ± 1.00) with P value <0.01. Comparing the mean recovery times, Group D showed the fastest recovery time (31.79 ± 2.32 minutes) followed by Group M (33.85 ± 1.58 minutes). Group K had the slowest recovery time (36.79 ± 2.13 minutes). Amongst the three groups, Group D required the fastest rescue analgesia (24.39 ± 2.12 minutes) followed by Group M (28.91 ± 1.54) while Group K required the slowest rescue analgesic (34.73 ± 2.05). Group K had the maximum number of post-operative nausea and vomiting comparatively to the other groups with a p value of 0.002 using the Chi Square Test. Group K showed the highest incidence of patients with history of dreaming (3 out of 33) though this was not found to be statistically significant using Chi Square Test (P value of 0.161). No patient in any of the three groups had any evidence of awareness.

IV. Discussion

Emergence from general anaesthesia may be associated with cough, agitation, hypertension and tachycardia. These events are often aggravated by pain, shivering and postoperative nausea and vomiting (PONV) in the post-anaesthetic care unit (PACU). Quicker recovery is often associated with better airway care, protection against aspiration, better oxygenation of the patient, lesser hospital-stay and faster mobility in out-patient settings. In a previous study, Royse et al[16] concluded that pain and nausea in the post operative period contributed to incomplete patient satisfaction. Patient satisfaction is an important tool for prompting improvements in clinical care. When we discuss from the economic point of view, quick anaesthesia recovery often favours fast-tracking, increases the case-turnover and thus improve the use of resources[17].

The Bispectral Index (BIS) is used for monitoring the depth of anaesthesia using a proprietary algorithm derived from complex electroencephalogram (EEG) parameters. Clinical utility studies have shown also that BIS monitoring allows for better titration of anaesthesia, resulting in lower hypnotic drug use and improved recovery.[18]In a study conducted by Hankala et el[19], it was concluded that BIS monitoring decreased the consumption of both propofol and sevoflurane and hastened the immediate recovery after propofol anaesthesia. Recently, BIS monitoring has proved to be useful to control anaesthesia depth, reduce drug consumption, and decrease adverse effects.[20]

Comparing all three groups in our study, there was no significant statistical difference (P > 0.05) in age, weight, gender, ASA status, baseline haemodynamic parameters and baseline BIS value.

In our study, Group D showed the fastest emergence time (15.09 ± 0.84 minutes) followed by Group M (16.27 ± 0.87 minutes) while Group K (17.55 ± 1.00 minutes) showed the slowest emergence time. Group D showed statistically significant faster emergence time in comparison to both Group M and Group K. When we compare the recovery time amongst the three groups in our study, we obtained similar results i.e., Group D showed the fastest recovery time (31.79 ± 2.32 minutes) while Group K had the slowest recovery time (36.79 ± 2.13 minutes). The difference in the recovery times between Group D and Group M (P value of < 0.01) was statistically significant. And comparison between Group K to Group M and Group D was also found to be statistically significant (P values of < 0.01 in both groups).

Dexmedetomidine has an elimination half-life of 2-2.5 hours[21] while the elimination half-lives of midazolam and ketamine are 1.7-3.5 hours[22] and 2.5-2.8 hours[23] respectively. A study conducted by Aouad et al[24] concluded that dexmedetomidine with a dose of 0.5µg/kg controls emergence phenomena from general anaesthesia. In a previous study conducted by Kang et al[25], the study suggested that intraoperative dexmedetomidine infusion was associated with lower incidence of emergence agitation in adults after lung surgery. The sedative effects of dexmedetomidine acts through endogenous sleep-promoting pathways, thus generating natural sleep patterns.[26] A possible explanation for the delayed recovery time in Group K is that both ketamine and nitrous oxide have been found to induce loss of consciousness via NMDA receptor antagonism with possible synergistic action.[27]

In our study, Group D (24.39 ± 2.12 minutes) required the earliest rescue analgesic, followed by Group M (28.91 ± 1.54 minutes) and Group K (34.73 ± 2.05 minutes) was the last to require a rescue analgesic. In a study conducted by Petrenko et al[28] on the role of NMDA receptors in pain, it was found that NMDA receptors antagonists produce anti-nociception by multi-model analgesia by reducing central as well as peripheral

sensitivity to pain. This could be a possible explanation to the lower requirement of analgesic in the ketamine group.

Group K demonstrated the highest intra-operative heart rate (HR) and mean arterial pressure (MAP) which was statistically significant ($P < 0.05$) at immediate post-intubation period up to 90 minutes for heart rate (HR) and up to 75 minutes for mean arterial pressure (MAP). Group D showed the minimum variability in intra-operative heart rate values while when we compare the mean arterial pressures, Group M and Group D showed similar values. In a study conducted by Doenicke et al[29], HR and BP showed a significant rise after injection of racemate and isomer ketamine, without any significant differences between groups. This was also seen for norepinephrine and cortisol plasma levels. Epinephrine levels, however, differed between groups, showing a significant rise after racemate mixture compared to isomer of ketamine. In a study conducted by Talke P et al[30], it was found that after an infusion of dexmedetomidine, plasma norepinephrine concentrations decreased on average by 72% (range 40%-97%), and plasma epinephrine decreased by 72% (range 47%-92%), consistent with our finding that dexmedetomidine attenuates intraoperative increases in heart rate and blood pressure but does not entirely abolish sympathetic tone, so as to produce significant hypotension and bradycardia.

In our study, baseline BIS values in all the three groups were not statistically significant. Intra-operative BIS value was lower ($P <0.001$) immediately after induction of general anaesthesia. However, all the three groups received the same induction and maintenance anaesthetic drugs, and BIS values were in the clinically acceptable range (40-60).

Group K had the maximum number (30.3%) of patients with post operative nausea and vomiting (PONV) while 12.1% of Group M patients had PONV. On the contrary, Group D patients had no episode of PONV (P value = 0.002). This was found to be statistically significant. In a study conducted by Modir et al[31], he concluded that amongst three tested groups (dexamethasone, dexmedetomidine, and ketamine) dexmedetomidine provides the best efficacies in the reduction of nausea and vomiting although more liable in lowering blood pressure and heart rate.

V. Conclusion

In conclusion, the results of our study suggest that the recovery profile in terms of emergence time and recovery time was much better in the dexmedetomidine group. Dexmedetomidine showed the fastest emergence and recovery time while maintaining haemodynamic stability intra-operatively while ketamine group showed the most prolonged emergence and recovery time. However, ketamine group had much better postoperative analgesia while dexmedetomidine group required the fastest rescue analgesic.

In regards to intra-operative haemodynamic parameters, ketamine group had the highest intra-operative haemodynamic instability, which may make it unsuitable for patients with co-morbidities like hypertension and other cardiovascular and neurological diseases. The ketamine group had the least analgesic requirement which highlights both the analgesic efficacy of ketamine. The BIS guided intra-operative monitoring served as an adequate measure in maintaining the depth of balanced anesthesia along with further stabilization of the intra-operative hemodynamic parameters in relation to the surgical stimuli and plane of anaesthesia.

Dexmedetomidine also had no incidence of nausea and vomiting therefore better in postoperative period while ketamine had the highest incidence of postoperative nausea and vomiting. No adverse effects like severe bradycardia, hypotension and respiratory depression were observed intra-operatively while in the postoperative period, no adverse effects like severe nausea and vomiting, awareness and recall of intra-operative events were noted.

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