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Comparative study between Ketamine and Propofol versus Ketamine and Dexmedetomidine for Monitored Anaesthesia Care for Dilatation and Curettage surgeries in Daycare procedures

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ABSTRACT

Introduction. Anaesthesia is frequently administered through Monitored Anaesthesia Care (MAC) utilising various combinations of anaesthetic drugs for moderately painful operations like Dilatation and Curettage (D&C), which is preferably done as a daycare procedure. The hunt for improved drug combinations is always ongoing, and the pharmacological properties of the individual drugs are considered. In this regard, anaesthesiologists all over the world are quite fond of the combination of Ketamine and Propofol, which is also known as Ketofol. Recently, especially in situations involving MRI sedation, the combination of ketamine and dexmedetomidine (Dexket) has gained popularity. This study compares the combinations for MAC during D&C surgeries in a daycare setting.

Aim. The primary objective was to estimate the recovery times using either combination. Secondarily, we would also compare the duration of analgesia, the haemodynamics, and the side-effect profiles of the two combinations.

Material and methods. This study enrolled 60 patients posted for elective D&C. According to standard institutional protocols, they were administered Ketofol(KP group) or Dexket(KD group), depending on the anaesthesia provider's choice. The Ketofol group received Ketamine 1mg/kg and Propofol 1mg/kg with boluses of Ketamine 0.25mg/kg to maintain the depth of anaesthesia using Ramsay sedation score(RSS) >3. KD group received Dexmedetomidine intravenously 1mic/kg over 10 minutes followed by ketamine 1mg/kg boluses of Ketamine 0.25mg/kg to maintain the adequate anaesthetic depth of RSS>3.

Results. The Recovery time in post-operative period was significantly prolonged in the KD group (mean 22.77 minutes) compared to the KP group (mean 17.8 minutes). The total duration of analgesia was also longer in the KD group (250 minutes vs 220 minutes in the KP group). It was seen that the hemodynamic variables (HR, SBP, DBP) were consistently higher in the KD group compared to the KP group. There was a significant difference in SBP, DBP, and MAP in the intraoperative period between the KP and KD groups till 4hr in the postoperative period.

Conclusions. We conclude that a combination of Dexmedetomidine and Ketamine has longer recovery times and analgesia duration than a combination of Propofol and Ketamine. Side effects like postoperative nausea and vomiting are not significant. However, since the recovery times are comparatively longer in a daycare setting, dexmedetomidine and Ketamine may not be the preferred agents compared to the combination of Ketamine and Propofol in the context of a daycare setting.

Introduction

Short-duration and moderately painful surgeries can be performed under Monitored anaesthesia care[MAC] [1]. An ideal sedative medication should be consistently effective in having rapid onset, easy titration, high clearance, and low side effects, specifically a lack of cardiovascular and respiratory depression. Due to the lack of an ideal agent, sedation techniques for MAC frequently combine agents to provide analgesia, amnesia, and hypnosis with complete and rapid recovery that was appropriate for a particular surgical procedure with the least amount of side effects, such as postoperative nausea and vomiting (PONV), prolonged sedation, and cardiorespiratory depression.

Propofol has emerged as safe and efficacious for short-duration surgeries, daycare procedures, MRI sedation, dental, and other non-operating room anaesthesia (NORA) [2]. Its main drawback is its lack of analgesia; hence, it needs to be used in combination with an analgesic. Ketamine, an NMDA(n-methyl d-aspartate) receptor antagonist in sub-dissociative doses, acts as a good analgesic.

Ketamine and Propofol combination has been widely used worldwide and is fondly termed 'Ketofol.' After the advent of Dexmedetomidine in the past few years, studies have been done to see if Ketamine and Dexmedetomidine (Dexket) can be a favourable combination in this regard. Dexket combination has gained traction in the paediatric population and for MRI sedation [3]. We wanted to compare this newer combination of Dexket against the gold standard Ketofol in managing cases with mild to moderate pain like dilatation and curettage. The study aimed to assess the recovery times and duration of analgesia of the two drug combination groups. The secondary objectives were to compare hemodynamic stability, side effects (PONV), and the need for additional boluses to maintain anesthetic depth.

Materials and methods

This experimental, double-blinded, randomized study was conducted from November 2019 to May 2021 in a tertiary care hospital in southern India. The sample size was calculated from previous studies as a reference [2,3]. During the sample size calculation, we have taken β(type 2 error) as 20pc, which gives 80 percent power to the study(power=1-β). We got a sample size of 30 in each group. After receiving approval from the institutional ethics committee (IEC/NRIIMS/A/2/2017), out of all the patients posted for dilatation and curettage electively in the gynaecological operation theatre, 60 patients were enrolled into the study retrospectively from the anaesthesia charts after observing the medications received. As per the ethics committee's decision, informed consent was taken from all patients. According to our departmental protocol, Ketofol and Dexket are administered in our institute in a predetermined dosage: Ketofol: 1% Propofol 1 mg/kg and Ketamine 1mg/kg at induction. Dexket: Dexmedetomidine 1mic/kg was administered intravenously over 10 minutes, followed by ketamine 1mg/kg. Any further requirement of an anaesthetic drug was to be managed using boluses of Ketamine 0.25mg/kg to maintain adequate depth in either of the groups. Patients were

divided into two groups based on their medications: Ketamine and Propofol (Group KP) or Dexmedetomidine and Ketamine (Group KD). Each group was allotted 30 patients. The anesthesia consultants who administered anesthesia made decisions about the anaesthetic regimen based on their preferences without being aware of the patient's enrollment status in the study. The researchers conducting the study enrolled the patients using computer-generated random allocation. Researchers took the data from anaesthesia charts of the respective enrolled patients once the computer-generated sequence was received

We included patients in the American Society of Anesthesiologists (ASA) grade II group, those aged between 18 and 65 years, undergoing elective surgery, and having no routine analgesic use in the last 24 hours. Whereas patients who were receiving extra opioid analgesics, with a known heart, kidney, liver, haematological, psychiatric disease, anaemia, analgesic hypersensitivity, morbidly obese, patients who were very anxious, patients who developed any complications during or after surgery, and could not cooperate in the postoperative period, were excluded from the study.

After shifting the patient to the operation theatre, both groups received similar fluids and monitoring. IV (intravenous) cannula of 18G and ringers lactate were started for all patients. All patients were monitored by Electrocardiogram (ECG), heart rate (HR), non-invasive blood pressure (NIBP), peripheral oxygen saturation (SPO2), and respiratory rate (RR). Airway supplementation in the form of oxygen by mask was instituted.

Patients were ventilated with a bag mask when required. Recovery time was calculated from the time of loading dose till the patient achieved Ramsay sedation score < 2. Duration of analgesia was calculated from the time of loading dose till the patient complained of pain with VAS >3. Rescue analgesia in PACU was done with Inj. Tramadol 100mg iv if VAS score >3, and this marks the end point of the study.

Several intra-operative additional doses of in. ketamine (0.25mg/kg) IV as a supplemental dose if Ramsay Sedation Score <3 was noted, and the number of such supplemental doses was documented. Post-operative nausea and vomiting, Ramsay sedation score, and visual analogue score (VAS) for pain were recorded hourly for 6 hours in the post-anaesthesia care unit (PACU).

Data collected was entered in the Microsoft Excel [4] spreadsheet and later transferred into Jamovi software [5] for analysis. Parametric data was represented by means and standard deviations, and numbers and percentages expressed non-parametric data. Statistical tests like t-test for continuous data and chi square for categorical data were used. P Value ≤0.05 was considered statistically significant.

Results

Baseline characteristics like Age, Weight, Height, and BMI were compared, and the groups were evenly matched with no significant variations (**Tables 1, 2**). The pre-operative baseline values of HR, SBP, DBP, MAP, SPO2, Respiratory rate, and Ramsay sedation scores were comparable in both groups (**Table 2**). In the intraoperative period, among all the monitored parameters, we observed that the hemodynamic variables (SBP, DBP, MAP, HR) were consistently higher in the KD group compared to the KP group (**Figures 1–8**). There was a significant difference in SBP, DBP, and MAP in the intraoperative period between

Table 1. Baseline characteristics.

	Group	N	Mean	Std. Deviation	P Value
Age	KP	30	44.83	9.05	0.216 (NS)
	KD	30	41.43	11.80	
Weight	KP	30	59.37	5.67	0.812 (NS)
	KD	30	59.73	6.18	
Height	KP	30	158.77	4.38	0.82 (NS)
	KD	30	158.53	3.48	
BMI	KP	30	23.59	2.00	0.791 (NS)
	KD	30	23.72	1.88	

NS – non-significant

the KP and KD groups until 3hr in the postoperative period. The Recovery time in the postoperative period was also statistically significant, with the KD group (mean 22.77 mins) having a delayed recovery compared to the KP group (mean 17.8 mins).

The blood pressure (SBP, DBP, MAP) and Heart rate (**Figures 2, 4, 6**) were persistently higher up

Table 2. Pre-operative baseline vitals.

	Group	N	Mean	Std. Deviation	P Value
HR	KP	30	80.53	11.063	0.087 (NS)
	KD	30	75.6	10.912	
SBP	KP	30	119.53	12.311	0.487 (NS)
	KD	30	117.13	14.224	
DBP	KP	30	71.8	8.438	0.766 (NS)
	KD	30	71.13	8.85	
MAP	KP	30	86.13	8.161	0.094 (NS)
	KD	30	90.13	9.947	
SPO2	KP	30	99.6	0.498	0.087 (NS)
	KD	30	99.23	0.728	
RR	KP	30	12.27	1.66	0.094 (NS)
	KD	30	13.03	0.999	
RSS	KP	30	2	0	
	KD	30	2	0	

NS – non-significant; HR – Heart rate, SBP = Systolic blood pressure, DBP = Diastolic blood pressure, MAP = Mean arterial pressure, SPO2 = Pulse oxygen saturation; RR – Respiratory rate, RSS – Ramsay sedation score

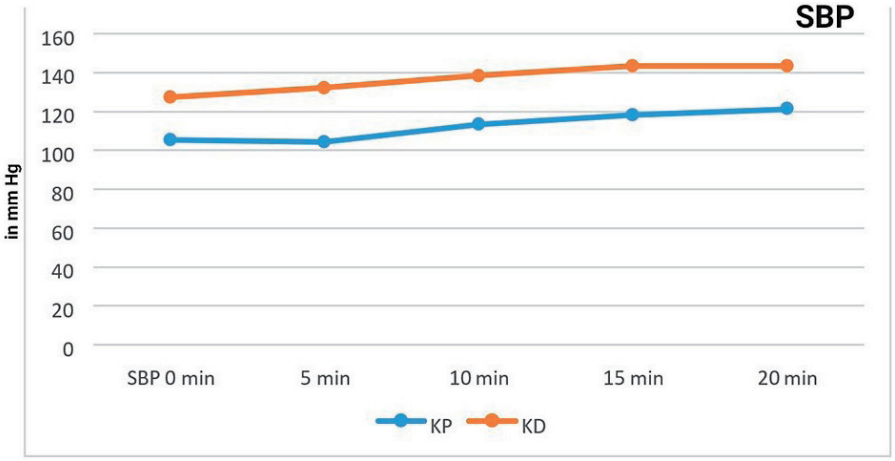

Figure 1. Mean Systolic Blood Pressure (SBP) in the Intraoperative period.

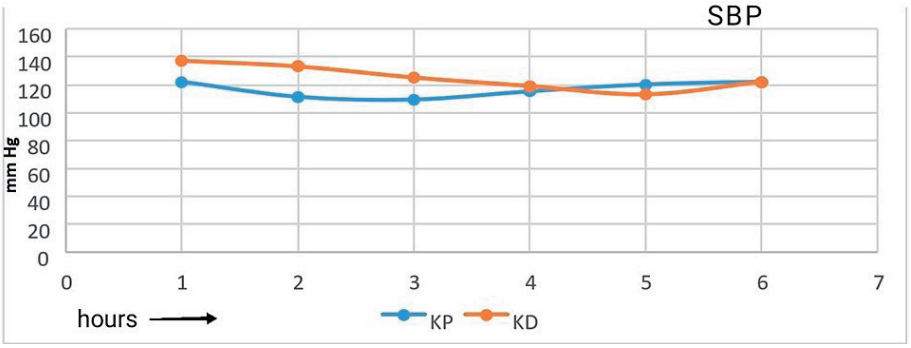

Figure 2. Mean Systolic Blood Pressure (SBP) in the Postoperative period.

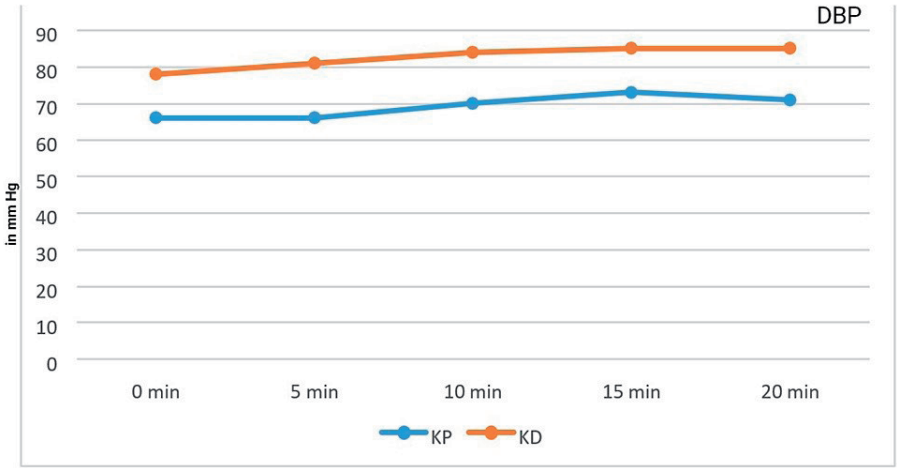

Figure 3. Mean Diastolic Blood Pressure (DBP) in the Intraoperative period.

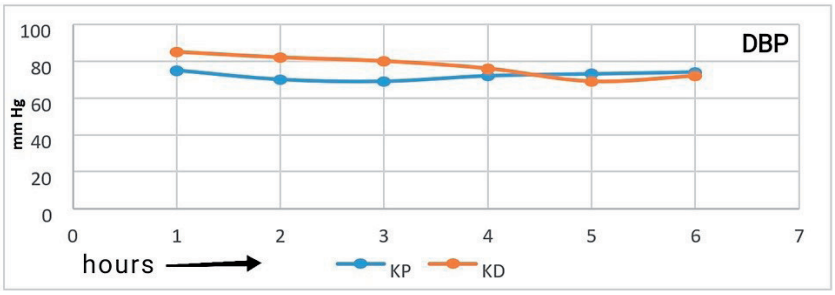

Figure 4. Mean Diastolic Blood Pressure (DBP) in the Postoperative period.

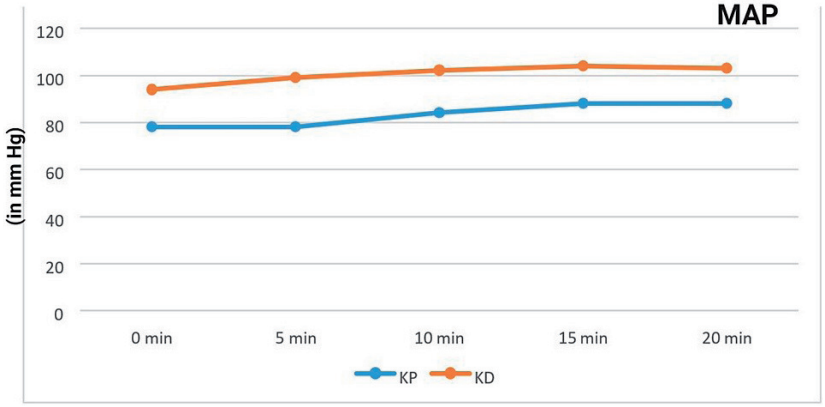

Figure 5. Mean Arterial Blood Pressure (MAP) in the Intraoperative period.

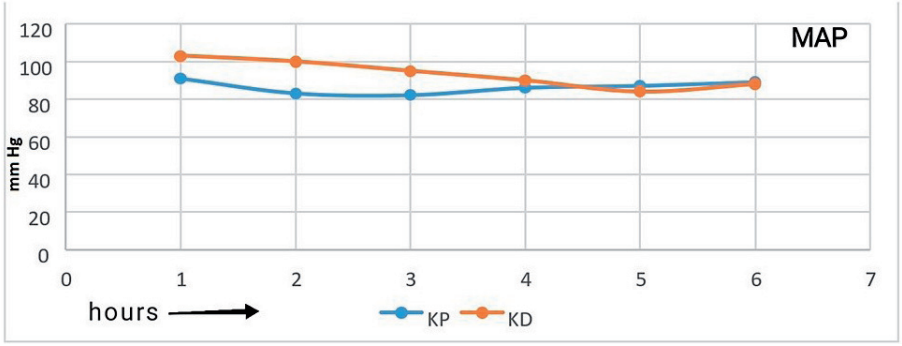

FIGURE 6: Mean Arterial Pressure (MAP) in the Postoperative period.

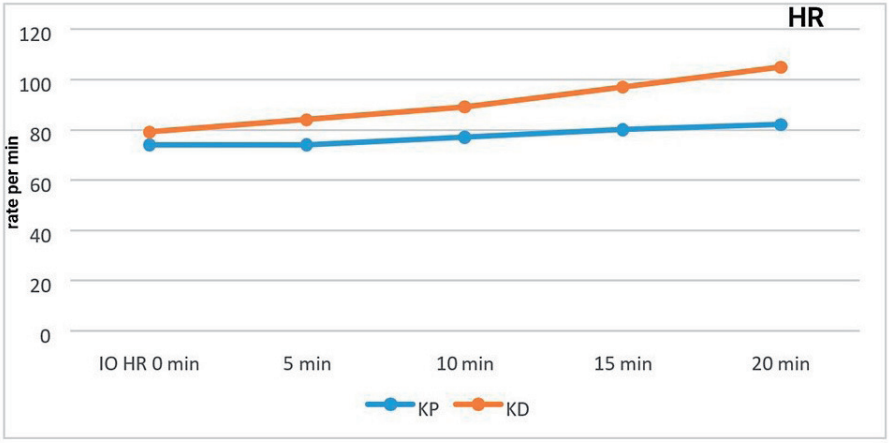

Figure 7. Mean Heart Rate (HR) in the Intraoperative period.

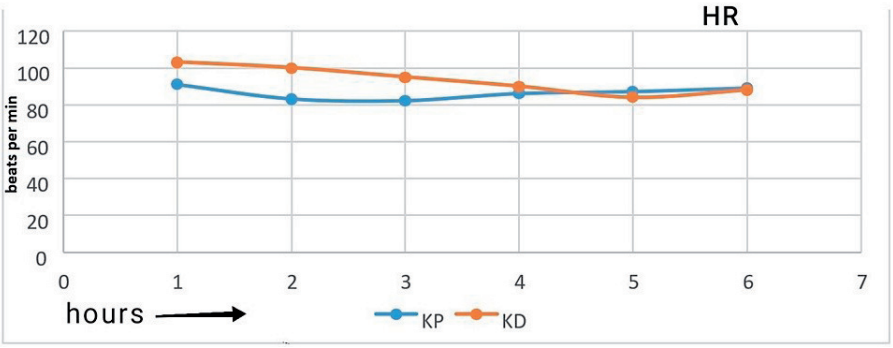

Figure 8. Mean Heart Rate (HR) in the Postoperative period.

Table 3. Time of recovery (in minutes).

Group	N	Mean	Std. Deviation	P Value
KP	30	17.8	2.759	*0.001 (Sig)
KD	30	22.77	2.991	

Sig – significant

Table 4. Repeat Ketamine boluses (number of doses).

Group	N	Mean	P-Value
KP	30	45.5	*0.001 (Sig)
KD	30	15.5	
Total	60		

Sig – significant

Table 5. Post-operative nausea and vomiting.

Ponv	Group		Total(%)	P-Value
	KP	KD		
YES	4	7	11 (18.33%)	0.317 (NS)
NO	26	23	49 (81.67%)	
TOTAL	30	30	60	

NS – nonsignificant

Table 6. Total duration of analgesia (in minutes) (rescue analgesia).

Group Rec	N	Mean	Std. Deviation	P-Value
KP	30	220	15	*0.01 (Sig)
KD	30	250	13	

Sig – significant

to 3 hours and gradually became comparable around 4 hours in the postoperative period. The difference between the recovery times in the KP group was 17.8 mins vs 22.7 mins in the KD group (**Table 3**). This difference was statistically significant. Repeat boluses of Ketamine were much lesser in the KD group (Mean 15.5 times) vs the KP group (Mean 45.5 times) (**Table 4**). PONV in both groups was comparable, with four incidences in the KP group compared to 7 times in the KD

group. It was statistically insignificant (**Table 5**). The duration of analgesia or time for rescue analgesia was longer in the KD group than in the KP group. (Mean= 250 mins vs 220 mins) (**Table 6**).

Discussion

Dexmedetomidine, when used individually, is not effective for painful procedures undergoing surgery [6], but along with other agents, it may prove extremely beneficial due to its sedative action, no respiratory depression, and good hemodynamic stability. Ketamine, an N-methyl-D-aspartate receptor antagonist, is one of those adjuvant drugs due to its sedative, analgesic, and sympathomimetic effects [7]. The combination of ketamine with dexmedetomidine can serve not only to eliminate the slow onset of sedation but also to prevent the bradycardia and hypotension that occur when dexmedetomidine is used as a sole agent [8]. However, a pilot study by Sethi P et al. Dexmedetomidine was found to be superior to propofol in D&C procedures [9].

The combination of Ketamine and Propofol is widely popular as they are complementary; Propofol has no analgesic action, is hypotensive, and causes respiratory depression, while Ketamine has very good analgesia, is sympathomimetic, and doesn't cause respiratory depression. In addition, Propofol has antiemetic properties. In this regard, a meta-analysis has shown that Ketofol has shown high efficacy for procedural sedation and analgesia when compared to Propofol alone [10].

In another meta-analysis comparing Ketofol and Dexket, the authors observed that both combinations can provide effective sedation and maintain stable hemodynamics. They suggested Dexket as the preferred combination as there were very few respiratory complications compared to Ketofol, but they also stated that Dexket had longer recovery times compared to Ketofol [11].

The primary outcome of this study was to compare the recovery times between the two groups, as this would affect the turnover times in daycare procedures. Our study found a statistically significant difference in the recovery times between the two groups, shorter in the Ketofol group than in the Dexket group by nearly 5 minutes per case. This accounted for about 50 minutes, on average, over 10 cases/day. This directly affects the number of cases that could be performed per day and the number of caregivers required in the PACU. The longer recovery time seen with dexmedetomidine compared to propofol can be explained by the difference in the pharmacokinetic profile between the two drugs. The elimination half-life of dexmedetomidine in healthy volunteers was about 2.1–3.1 hours [4], and for propofol, it was nearly 40 minutes, irrespective of a bolus dose or short-term infusion (< 8 hours) [12].

We went into this study with our null hypothesis that Dexket and Ketofol would both be equally effective anaesthetic agents, but our research revealed that hemodynamic variables were not effectively regulated in the KD group. Despite the fact that other studies have not encountered this problem, we believe that Propofol has a better hypotensive effect than Dexmedetomidine. However, the raised hemodynamic persisted at an elevated level for 4 hours after surgery, which is difficult to explain but might be related to two factors: a) a much lower number of repeat boluses administered in the KD group, 15.5 times vs 45.5 times in KP group [TABLE 5] b) relatively small sample size of the study population. Koruk et al. [13] in paediatric cardiac catheterization and Canpolat et al. [14] for paediatric burn dressing changes, both studies reported that ketamine dexmedetomidine combination led to lower recovery time than ketamine propofol combination in paediatric cardiac catheterization. This was in contrast to our findings, as the KD group was found to have longer recovery times. Tosun et al. [15] concluded that ketamine dexmedetomidine combination led to a longer recovery time in paediatric cardiac catheterization; this finding is in line with our observation.

The duration of analgesia in the KD group was 250 minutes vs 220 minutes in the KP group, which was statistically significant. Canpolat et al. [14] also report similar results of longer analgesia with the Dexmedetomidine combination group.

PONV incidence was 4 in the KP group and 7 in the KD group. By comparison, Goyal et al. [16] observed vomiting episodes in 4 patients with the Dexket combination for upper gastrointestinal endoscopy compared to the Ketofol group, which had no incidence of PONV. Our results were slightly higher in the KD group than in other studies since Propofol has antiemetic proper-

ties. Repeat bolus doses of Ketamine were higher in the KP group than in the KD group (45.5 times vs 15.5 times). This may be explained due to the anaesthesia provider's inexperience with the new drug combination, as Ketofol is still the preferred regimen for most MAC cases in our hospital.

Conclusions

Based on the findings of our study, it may be concluded that adding dexmedetomidine to ketamine is a reasonable alternative to the combination of ketamine and propofol for Monitored anaesthesia care. However, due to the longer recovery times of the combination, it may not be suitable for daycare procedures, especially procedures that are conducted later in the operating room schedule. The Dexmedetomidine and Ketamine combination was found to have a longer duration of analgesia, which may be useful for some surgeries and in non-day-care surgeries. The inferior hemodynamic stability of this combination needs further studies to corroborate our findings, preferably with better objective monitors like BIS to assess the depth of anaesthesia.

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Conflict of interest statement
The authors declare no conflict of interest.

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