ORIGINAL RESEARCH

Comparative study between dexmedetomidine and ketamine with midazolam and ketamine in total intravenous anaesthesia in short surgical procedures

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ABSTRACT

Aim: Our aim was to compare the effectiveness of ketamine –dexmedetomidine combination and ketamine-midazolam combine on analgesia and sedation for patient undergoing minor procedure under TIVA. **Methods:** All the patients selected for the study were divided into two groups of 40 in each group. Group KD- ketamine and dexmedetomidine .Group KM- ketamine and midazolam. Patients in group ketamine-dexmedetomidine (KD) received intravenous (IV) dexmedetomidine (1 µg kg-1) diluted in 10 ml (1ml =10mcg) syringe over 10 minutes, before intervention, followed by 1 mg kg-1 of IV ketamine. Patients in group ketamine-midazolam (KM) received IV midazolam (0.05 mg kg- 1) in 10 ml syringe (1ml =0.25 mg) over 10 minutes, before intervention, followed by 1 mg kg-1 of IV ketamine. The hemodynamics, pain and sedation scores, and recovery time for all patients was recorded. **Results:** Intra operative evaluation showed a significant reduction in the mean HR in the KD group from 15 min onwards.SBP was evaluated in the study and there was a significant reduction the KD group as compared to the KM group. Postoperatively VAS scores were compared and there were significantly lower VAS scores in the KD group as compared to the KM group. Sedation scores were compared as well but there was no significant difference seen between the two groups. The time to first analgesic requirements were higher in the KD group as compared to the KM group. **Conclusion:** Dexmedetomidine and ketamine is a better alternative to midazolam and ketamine combine in total intravenous anaesthesia in short surgical processes

Key words: Dexmedetomidine, ketamine, midazolam, total intravenous anaesthesia

INTRODUCTION

Ketamine is widely used in TIVA, it is the only iv anaesthetic with hypnotic, analgesic and amnesic property.[1] It is a unique intravenous (IV) anaesthetic that produces a wide spectrum of pharmacological effects including sedation, catalepsy, somatic analgesia, bronchodilation, and sympathetic nervous system stimulation.[2] It has a wide range of clinical applications even today. Most of the modern anaesthesiologists receive minimal training with ketamine. Its mechanism of action is mainly by noncompetitive antagonism of the N-methyl D-aspartic acid (NMDA) receptor.[3] It also interacts with opioid receptors, monoamine, cholinergic, purinergic and adrenoreceptor systems as well as having local anaesthetic effects.[4] Midazolam is a benzodiazepine with a short elimination half-life anda relatively short duration of action. At physiological pH, midazolam is unionized and lipophilic. As a result the onset of action after i.v.administration is rapid because of rapid

uptake by the brain. Theoretically, the short elimination half-life of midazolam, and the negligible hypnotic effect of its metabolites, make the administration of midazolam by i.v.infusion potentially useful. So Ketamine is commonly used with Midazolam a benzodiazepine which is water soluble benzodiazepine commonly used with ketamine as it reduces the incidence of post operative delirium which is the most common and unpleasant side effect of ketamine. Dexmedetomidine is a highly selective a2 adrenoreceptor agonist that has been shown to have both sedative and analgesic effects.[5] A distinct advantage of dexmedetomidine is the maintenance of respiratory force and preserved airway patency. It converges on a natural sleep pathway, activating pathways that promote endogenous non-rapid eye movement to exert its sedative effect. Dexmedetomidine reduces the dose requirements of opioids and anesthetic agents and attenuates the hemodynamic responses to tracheal intubation and surgical stimuli.[6] Its hemodynamic effect are hypotension and bradycardia which counter acts the sympathetic stimulation of ketamine then by producing stable hemodynamics. [7]Hence the present study was planned to evaluate and compare the effectiveness of combination of ketamine and dexmedetomidine with ketamine midazolam in TIVA and compare side effect of both technique and specifically incidence of post op delirium.

PRIMARY OBJECTIVE

- To compare the effectiveness of ketamine – dexmedetomidine combination and ketamine-midazolam on analgesia and sedation for patient undergoing minor procedure under TIVA.
- To compare the hemodynamic changes by using both the techniques.

SECONDARY OBJECTIVE

- To evaluate and compare incidence of post op delirium by using both technique

METHODS

Study Design: Single center single blind prospective randomized study.

Place of Study: Various OTs in a tertiary care Hospital, Cuttack

Duration of Study: December 2020 to October 2022
Sample size: 80 patients divided into 2 groups of 40 patients each. Following ethical committee approval and informed written consent was taken from the study participants. Sample size was calculated based on the pilot study done before. Keeping power at 80%, alpha error at 5% minimum 37 patients needed for each group. So we allocated 80 patients for our study. Patients were allocated into 2 groups, who were scheduled to undergo short surgical procedure under TIVA.

INCLUSION CRITERIA

- Patients age group 18-60 years
- Patient with ASA grade I and II
- Elective surgeries with durations< 2hrs
- BMI<30

EXCLUSION CRITERIA

- Patient with known allergy to the study drug
- Patients with chronic respiratory disease, epilepsy
- Patients with difficult airway
- Pregnant patient
- BMI >30
- Patients converted to GA

STUDY PROCEDURE AND DATA COLLECTION

After detailed preanesthetic evaluation, all selected patients under study were randomly divided into two groups by closed envelope method. All the patients selected for the study were divided into two groups of 40 in each group. Group KD- ketamine and dexmedetomidine and Group KM- ketamine and midazolam. Patients included in the study were kept under fasting as per fasting guideline prior to surgery. Patients in group ketamine-dexmedetomidine(KD) (n = 40) received intravenous (IV) dexmedetomidine (1 µg kg-1)diluted in 10 ml (1ml =10mcg) syringe over 10 minutes, before intervention, followed by 1 mg kg-1 of IV ketamine. Patients in groupketamine-midazolam (KM) (n = 40) received IV midazolam (0.05 mg kg-1) in 10 ml syringe (1ml =0.25 mg) over 10 minutes, before intervention, followed by 1 mg kg-1 of IV ketamine. The number of patients requiring additional ketamine; and the pain and sedation scores, and recovery time for all patients was recorded. Hemodynamic parameters was recorded at baseline (before the study drug infusion), after loading dose of study drug, before and after ketamine administration, and at 5, 10, 15, 30, 45 and 60minutes after the procedure. Hypotension occurred (SBP < 90 mm Hg), the patients were primarily treated with fluid administration (0.9% saline 10mL kg-1h-1). The number of patients requiring additional ketamine; and the pain and sedation scores, and recovery time for all patients was recorded..A pain score of <5 was considered adequate . As when required to treat inadequate analgesia (e.g., increase in mean SBP, 25% above baseline; purposeful movements; swallowing; grimacing), the ketamine bolus (0.5-1 mg kg-1) was given as a rescue analgesic. The total dose of ketamine used for rescue analgesia was recorded. Pseudo analgesia time was recorded for all groups. Pseudo analgesia is defined primarily as VAS<5 and sedation scores > 2. During the study period, the number of patients requiring additional ketamine with 15min 30 min more than 30min and recovery time for all patients was recorded. Incidence and severity of side effects (e.g. post op delirum, nausea, vomiting, hemodynamic events), if any, are recorded. Outcome measures-1. To compare the effectiveness of ketamine

–dexmedetomidine combination and ketamine-midazolam on analgesia and sedation for patient undergoing minor procedure under TIVA.2. To evaluate and compare incidence of post op delirium by using both technique

STATISTICAL ANALYSIS

The data collected was entered in an excel spread sheet and was analysed using SPSS software version 20.All continuous variable were reported as mean ± standard deviation and all categorical variables were measured by proportions and reported as percentage. Continuous data were analysed by paired t test for intra group measurement and independent t test for inter group comparison. Categorical variables were compared using chi square test of association. A P value < 0.05 was considered statistically significant.

The present study is Single center single blind prospective randomized study to observe the comparative efficacy between dexmedetomidine and ketamine with midazolam and ketamine in total intra venous anaesthesia. A total of 80 participants were included in the study and 40 participants were in each group. The mean heart rate was compared between the groups and at baseline the mean heart rate was 80.96 ± 5.25 (beats/min) in group KD and in group KM it was 81.66 ± 6.25 (beats/min) and it was found to be not significant at baseline. During the surgery the heart rate was evaluate at various time points and at 15 min there was no significant difference between the two groups but after 15 mins there was a decreasing trend seen in heart rate in group KD as compared to group KM. Heart rate recorded at 30mins,45 mins and 60mins were significantly less in group KD compared to group KM.(table 1)

RESULTS

Table 1: Comparison of heart between the study groups

Heart Rate Mean ± SD	Group KD Dexmedetomidine + Ketamine (N=40)	Group KM Midazolam + Ketamine (N=40)	P value
Baseline	80.96 ± 5.25	81.66 ± 6.25	0.065
T 1 (15 min)	83.4 ± 4.5	81.2 ± 7.5	0.085
T 2 (30 min)	71.2 ± 7.5	76.22 ± 8.5	0.024
T 4 (45 min)	70.81 ± 9.1	78.2 ± 8.5	0.019
T 6 (60 min)	71.22 ± 3.5	79.11 ± 7.9	0.019

The systolic blood pressure was evaluated during the surgery and there it was 127.1± 9.82 mm of hg at baseline in group KD and it was 126.87±9.46 mm of hg in group KM. There was no significant difference between the SBP at baseline, but after 15 min the SBP mean values were significantly lower in group KD as compared to group KM and further it followed a stable but a decreasing trend as mentioned in the table below.(table 2)

Table 2: Comparison of Systolic Blood Pressure between the study groups

SBP (mmhg) Mean ± SD	Group KD Dexmedetomidine + Ketamine (N=40)	Group KM Midazolam + Ketamine (N=40)	P value
Baseline	127.1± 9.82	126.87± 9.46	0.548
T 1 (15 min)	120.1± 7.82	128.37± 8.46	0.018
T 2 (30 min)	115.1± 4.82	123.87± 5.46	0.024
T 4 (45 min)	115.1± 4.82	121.87± 3.16	0.007
T 6 (60 min)	114.1± 6.82	121.87± 5.12	0.019

The pain after the surgery was evaluated postoperatively at various time points as mentioned in the table below, at baseline in group KD the mean VAS score is 2.9 ± 2.46 and in group KM the mean VAS score is 2.8± 1.12. The VAS scores were evaluated at various time points post operatively and there was no significant difference between the two groups at baseline but after 1 hour there was higher VAS value in group KM and a similar trend was maintained till 12 hours as mentioned in the table below .(table 3)

Table 3: Comparison of VAS between the study group

VAS Mean ± SD	Group KD Dexmedetomidine + Ketamine (N=40)	Group KM Midazolam +Ketamine (N=40)	P value
Baseline	2.9 ± 2.46	2.8 ± 1.12	0.776
T 1 (1 Hour)	3.9 ± 2.46	3.8 ± 1.12	0.084
T 2 (2 Hour)	4.1 ± 2.46	5.2 ± 2.15	0.005
T 4 (4 Hour)	4.1 ± 2.46	5.2 ± 2.15	0.008
T 6 (6 Hour)	5.1 ± 2.46	6.2 ± 2.34	0.003
T 12 (12 Hour)	6.1 ± 2.46	7.2 ± 1.12	0.010

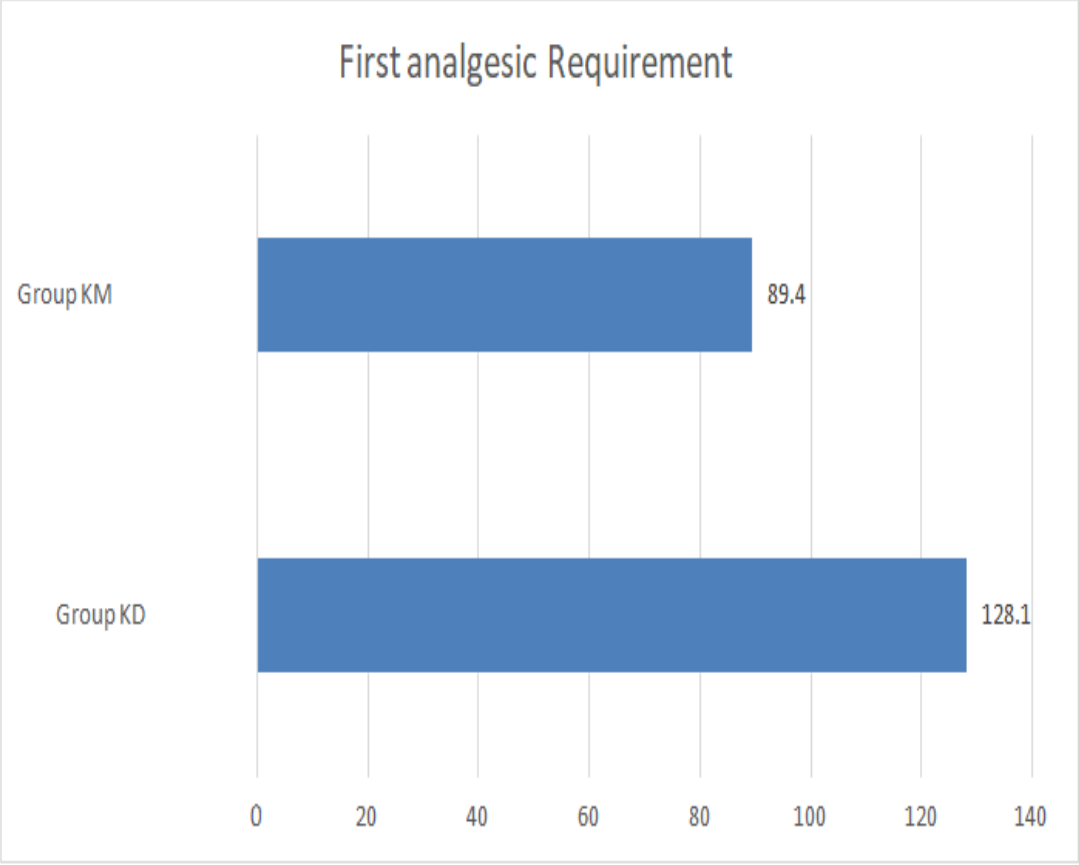
The sedation scored were compared between the groups and at baseline the sedation scores was 3.8 ± 1.16 in group KD and .6 ± 1.12 in group KM. On further evaluation at various time points there was no significant difference between the groups and this trend was maintained from 1 hour till the end of the study time period as mentioned in the table below.(table 4)

Table 4: Comparison of sedation scores between the study groups

Sedation Mean ± SD	Group KD Dexmedetomidine + Ketamine (N=40)	Group KM Midazolam + Ketamine (N=40)	P value
Baseline Mean +SD	3.8 ± 1.16	3.6 ± 1.12	0.876
T 1 (1 Hour)	3.1 ± 0.36	3.4 ± 1.22	0.054
T 2 (2 Hour)	3.0 ± 0.66	3.2 ± 0.92	0.065
T 4 (4 Hour)	2.9 ± 1.06	2.8 ± 1.33	0.078
T 6 (6 Hour)	2.4 ± 1.16	2.4 ± 1.55	0.123
T 12 (12 Hour)	2.4 ± 1.22	2.3 ± 1.23	0.231

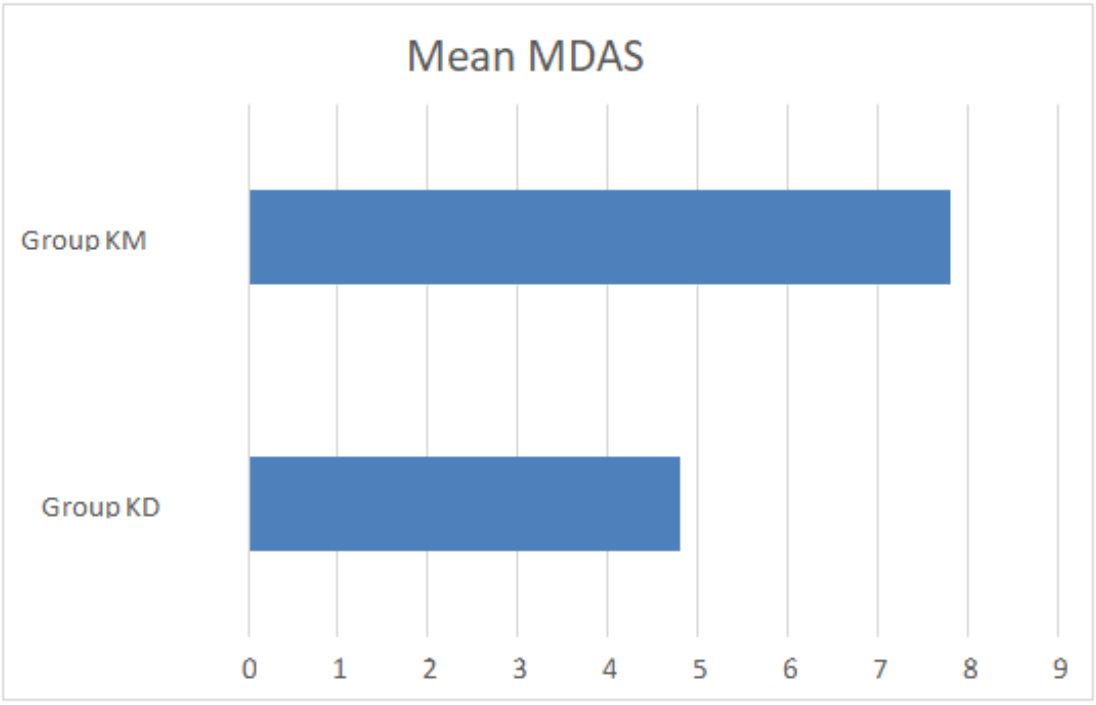
Post operatively the first analgesic requirement was evaluated in the study and it was seen the time to first analgesic requirement was significantly more in group KD as compared to group KM.Post operatively the first analgesic requirement was evaluated in the study and it was seen the time to first analgesic requirement was significantly more in group KD as compared to group KM.(figure 1)

Figure 1: Time to first analgesic Requirement



In the study population the group showed a higher reduction MDAS score, which is used to assess delirium in the study population as compared to the midazolam group as observed in the figure below.(fig 2)

Figure 2: Evaluation of delirium



DISCUSSION

Total intravenous anaesthesia (TIVA) is the use of intravenous agents for induction and maintenance of anaesthesia. TIVA is routinely used for minor surgeries of short duration and less complex procedures, with its advantage of easy reversibility after a shorter duration of surgery . It avoids the side effect and complication related to GA. Many drugs have been used for procedural sedation in the past such as barbiturates, benzodiazepines, Phenergan, propofol, and ketamine with different combination. Ketamine is widely used in TIVA, it is the only iv anaesthetic with hypnotic, analgesic and amnesic property along with a respiratory and cardiovascular stimulant effect.[8] In our study intra operative evaluation of heart was done and it was found that at the start of the study the heart was comparable between the group , bit after induction it was found that the mean heart rate was reduced a little at 15 minutes and reduced significantly as compared to the KM group from 30 minutes onwards. The maintained hemodynamic stability in the KD group and the bradycardia did not cause any adverse effects. The reduction in heat rate cannot be considered as an adverse effect because a similar bradycardia was also seen in the park et al. study at the initial loading dose.[9] Also, this is concordance with the Gurbet et al. study where in Dexmedetomidine did not cause any bradycardia in the study population. [10] The systolic blood pressure was evaluated and it was comparable at the start of the study and it was significantly lower in the KD group as compared to KM group from 15 min onwards. These results are in accordance with previous studies by Murat Gündüz et al. which showed a similar trend as well. Studies by Kothari et al. as well also showed a similar reduction in the systolic BP. [11-13] Preoperative administration of ketamine should prevent central sensitization have shown to improve postoperative pain relief. A small dose of ketamine, given before skin incision, was shown to decrease postoperative pain, reduce morphine consumption, and delay analgesia requirement after laparoscopic gynecologic surgery.[14]In our study the post operative pain relief was also evaluated in both the groups at various time points and it showed that, the post operative analgesic effect was comparable at 60 min but it started wearing off significantly from 2nd hour onwards and the mean VAS scores were lower in the KD group as compared to the KM group which was maintained till the 12th hour of evaluation in the study. This is in line with Kothari et al.[14] study which also showed a similar trend, this can be attributed to the fact that Dexmedetomidine by virtue of its alpha-2 adrenergic agonist action acts on the locus cerulus area, inhibiting nociceptive neurotransmission Alpha-2 adrenergic receptors also act on the presynaptic membrane, inhibiting the release of norepinephrine and thus inhibiting pain signals to the brain. Dexmedetomidine also promotes the release of acetylcholine from spinal inter-neurons which results in increased release of nitric oxide accounting for the analgesic effect. The study by Schimd et al. also is in line with our study. [15]The sedation scores were also evaluated post operatively and it was seen that the score although comparable at baseline, which after the surgery and it was also comparable between the groups at the first hour as well, but as the time passed from 2nd hour onwards there was reduction in the mean sedation, but over the period of evaluation there

was no significant difference in the sedation scores seen. Dexmedetomidine provides sedation without respiratory depression hence producing a sleep like phenomenon in EEG by its action on locus coeruleus. [16] A similar trend was also seen in the Anderson et al. study as well. [17] The first analgesic requirement was compared and it was found to be significantly higher in the KD group as compared to the KM group. Studies have discussed the requirement of analgesia and shown that a small dose of ketamine, given before skin incision, was shown to decrease postoperative pain, reduce morphine consumption, and delay analgesia requirement after laparoscopic gynaecologic surgery. The most commonly observed side effect in the study was nausea and vomiting. In Group KD 1 patient and in Group KM 3 patients had post-operative nausea and vomiting. Due to the reduction of norepinephrine release and the possible baroreflex activation, bradycardia and hypotension can be observed during dexmedetomidine use. In our study 3 patients had bradycardia in the KD group and 2 in the KM group. This study has evaluated the various hemodynamic parameters in the patients undergoing short surgeries under TIVA and evaluated the use of combination of Ketamine with dexmedetomidine for the first time in India. This study suggests the use of dexmedetomidine along with ketamine is an alternative option.

CONCLUSION

Intra operative evaluation showed a significant reduction in the mean HR in the KD group from 15 min onwards but bradycardia.SBP and DBP was evaluated in the study and there was a significant reduction the KD group as compared to the KM group. Postoperatively VAS scores were compared and there were significantly lower VAS scores in the KD group as compared to the KM group. Sedation scores were compared as well but there was no significant difference seen between the two groups. The first analgesic requirements were higher in the KD group as compared to the KM group

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