ORIGINAL ARTICLE ASIAN JOURNAL OF MEDICAL SCIENCES

Comparison of intravenous ketamine hydrochloride plus dexmedetomidine hydrochloride and ketamine hydrochloride plus midazolam hydrochloride in procedural sedation for short surgical procedures: A prospective randomized double-blind study

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Submission: 22-04-2022 Revision: 29-11-2022 Publication: 01-01-2023

ABSTRACT

Background: The growing popularity of ambulatory anesthesia has led to the development of newer drug regimens and combinations. We decided to compare the effects of ketamine plus dexmedetomidine versus ketamine plus midazolam in procedural sedation. **Aims and Objectives:** The present study aimed to compare the effects of ketamine plus dexmedetomidine versus ketamine plus midazolam on the adequacy of anesthesia, level of sedation and analgesia, hemodynamic and respiratory parameters, recovery time, and post-operative side effects in short surgical procedures. **Materials and Methods:** Hundred adult patients were randomized into two groups: Group KD: A bolus dose of Dexmedetomidine 1 mcg/kg in 100 ml NS over 10 min and Group KM: A bolus dose of Midazolam 0.05 mg/kg in 100 ml NS over 10 min. Both groups received bolus dose of Ketamine 1 mg/kg at the start of the procedure. Level of sedation, adequacy of anesthetic technique, hemodynamic parameters, time for rescue analgesia, post-operative recovery time, and complications was measured. **Results:** In Group KD 7 (14%) patients and in Group KM 13 (26%) patients had inadequate anesthesia. A significant reduction in pulse rate ($P<0.001$) was observed in Group KD as compared to Group KM. MAP between the two study groups showed a statistically significant reduction in Group KD as compared to Group KM ($P<0.05$). Time for first rescue analgesia was delayed in Group KD (70.20 ± 14.35) compared to that of Group KM (49 ± 4.73) ($P=0.000$). Four (8%) patients in Group KD and 11 (22%) patients in Group KM had post-operative nausea and vomiting. **Conclusion:** Dexmedetomidine-ketamine combination is a good and safe alternative agent for procedural sedation in patients undergoing short surgical procedures.

Key words: Dexmedetomidine; Ketamine; Midazolam; Procedural sedation

Access this article online

Website: http://nepjol.info/index.php/AJMS

DOI: 10.3126/ajms.v14i1.44592

E-ISSN: 2091-0576

P-ISSN: 2467-9100

INTRODUCTION

Sedation is routinely used for minor surgeries of short duration and less complex procedures, where an injection of local anesthetic is insufficient but deeper general anesthesia is not necessary.[1] These include biopsies, diagnostic or therapeutic endoscopies, diagnostic investigations such as MRI, CT, and DSA. Medications used during sedation have additional benefits such as anxiolysis, amnesia, and analgesia. Sedatives generally possess more than one of these actions, although one among them may predominate. The ideal sedative would exhibit all of

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the above qualities, but most drugs do not have, hence medications with different qualities are commonly co-administered to compensate for any shortcomings.[2] Many drugs have been used for procedural sedation in the past such as barbiturates, benzodiazepines, phenergan, propofol, and ketamine.[3] However, the effects were found to be inadequate with more side effects.

Dexmedetomidine is a specific and selective alpha 2 adrenoreceptors agonist drug which acts by activation of the receptors in the spinal cord and the brain thus inhibiting the firing of the neurons and causing hypotension, sedation, bradycardia, and analgesia. Although it has been used as a sole agent providing effective sedation during non-invasive procedures,[4] it has not been uniformly successful in invasive procedures.[5] Hence, the combination of dexmedetomidine with other sedo-analgesic agents like ketamine is preferred for invasive procedures. Ketamine, a phencyclidine derivative having anesthetic, sedative, and analgesic properties acts by NMDA receptor antagonism. However, its cognitive dysfunction along with sympathetic stimulation restricts its use as the sole agent in short surgical procedures. Midazolam, a short-acting benzodiazepine having anxiolytic, sedative, hypnotic, and amnesic properties has been used in procedural sedation. We have used midazolam as another drug for the comparison which is widely used for monitored anesthesia care.[6] Midazolam when used alone for invasive procedures was associated with lower patient satisfaction, higher pain scores, and more use of rescue analgesic.[7,8]

The choice of dexmedetomidine with ketamine for sedation provides several advantages over conventional drugs. Dexmedetomidine provides anxiolysis and good sedation and ketamine give add up hemodynamic stability by counteracting the bradycardia produced by dexmedetomidine.[9] The combination of these two drugs reduces the incidence of postoperative cognitive dysfunction. The previous studies with the combination of dexmedetomidine-ketamine and midazolam-ketamine mainly focused on the sedation level provided by the combination.[10,11] Most studies also looked into the hemodynamic and respiratory variables and post-operative side effects.[12,13] Few studies focused on the sedation level and recovery time. No study so far included all these parameters in one study group; hence, we decided to conduct a randomized study to compare the effects of ketamine-dexmedetomidine and ketamine-midazolam combination on the adequacy of anesthesia, level of sedation and analgesia, hemodynamic and respiratory parameters, recovery time, and post-operative side effects in short surgical procedures in the adult population.

Aims and objectives

The present study aimed to compare the effects of ketamine plus dexmedetomidine versus ketamine plus midazolam on the adequacy of anesthesia, level of sedation and analgesia, hemodynamic and respiratory parameters, recovery time, and post-operative side effects in short surgical procedures.

MATERIALS AND METHODS

This prospective, randomized, and double-blind observational study was carried out from July 2020 to August 2021 at GRMC, Gwalior, Madhya Pradesh, after obtaining approval from the Institutional Ethics Committee and written informed consent, on 100 ASA Grade I/II patients between the age of 20–50 years of either sex and weighing between 40 and 60 kg scheduled for short surgical procedures. Any patient with refusal, emergency procedures, pregnancy, and lactating women, history of any significant systemic disease, chronic user of alpha 2 agonists, or sedatives were not included in the study. All the required routine and special investigations as per hospital protocol including complete blood count, random blood sugar, blood urea, serum creatinine, E.C.G. (above 30 years of age), and Chest X-ray (above 30 years of age) as per hospital protocol were carried out. The purpose and protocol of the study were explained to patients and informed written consent was obtained. All patients were kept fasting, 6 h for solid food and 2 h for clear liquids.

All selected 100 patients were divided into two groups (n=50 each) by envelope method as below-

Group KD

A bolus dose of dexmedetomidine 1 mcg/kg in 100 ml NS over 10 min followed by a bolus dose of ketamine 1 mg/kg at the start of the procedure.

Group KM

A bolus dose of midazolam 0.05 mg/kg in 100 ml NS over 10 min followed by a bolus dose of ketamine 1 mg/kg at the start of the procedure.

On the arrival of the patient in the operation theatre, a multipara monitor was attached to record hemodynamic parameters including basal pulse rate, systolic blood pressure, diastolic blood pressure, mean blood pressure, and oxygen saturation (SpO_2). All the patients were uniformly premedicated with Inj. Glycopyrrolate 0.02 mg iv, Inj.Ondansetron 8 mg iv and Inj. Ranitidine 50 mg iv. All the patients received 4 l/min oxygen through nasal prongs to maintain SpO_2 >95%.

An infusion of dexmedetomidine 1 mcg/kg in 100 ml NS over 10 min was given for group KD patients. Group KM

received an infusion of midazolam 0.05 mg/kg in 100 ml NS. Both the group received a bolus dose of ketamine 1 mg/kg at the start of the procedure. Rescue dose of Inj. Propofol 0.5 mg/kg was given for inadequate anesthesia. Following parameters were observed and recorded for data collection and statistics.

Assessment of adequate sedation

Sedation was assessed using the Ramsay sedation scale.[14]

Score 1- Fully awake and anxious.
Score 2- Calm adequate cooperation.
Score 3- Arousable to verbal commands.
Score 4 - Arousable to mild stimulation/vigorous reaction to pain.
Score 5 - Slow/incomplete reaction to painful stimulation.
Score 6 - No reaction to painful stimulation.
Score 4 and above were considered as adequate sedation.

Adequacy of anesthetic technique

Adequacy was defined depending on surgeon satisfaction (excellent, good, and poor) and depth of anesthesia (PRST SCORE).[15] PRST score more than 3 and poor surgeon satisfaction was considered as inadequate anesthesia.

Time for rescue anesthesia

For inadequate depth of anesthesia (PRST score >3) Inj. Propofol 0.5 mg/kg was used as a rescue anesthesia drug and the time was recorded.

Assessment of intraoperative and post-operative hemodynamic and respiratory parameters HR, SBP, DBP, MAP, RR, and SpO_2 were noted after intravenous infusion of study drugs, and then at 5, 10, 15, 20, 25, and 30 min. During the procedure, any fall in the MAP below 20% of baseline value was treated with a bolus dose of inj. Mephenteramine 0.1 mg/kg IV. PR <50 beats/min was treated with inj. Atropine sulfate 0.02 mg/kg IV. Any incidence of apnea (cessation of respiration for more than 20 s) and desaturation (SpO_2<90%) was treated with an airway device or mask ventilation. HR, SBP, DBP, MAP, RR, and SpO_2 were noted at 45, 60, 90, and 120 min postoperatively also.

Assessment of post-operative recovery time

All the patients were assessed for recovery time according to Modified Aldrete Score.[16] Patients were shifted to the post-operative ward once scoring >8–10.

Duration of post-operative analgesia

All patients were assessed for pain by a visual analog score (VAS) scale consisting of a 10 cm horizontal scale with gradations marked as 0 means no pain at all and 10 means worst pain imaginable.

VAS Score rating: (0=No pain, 1–3= Mild pain, 4–6=moderate pain, and 7–10=Severe pain). Score >3 was managed with rescue analgesia with inj. Tramadol 2 mg/kg i.v.in 100 ml normal saline and the time for rescue analgesia was recorded.

Side effects and complications

Any side effect or complication due to the drugs or anesthetic technique was noted including hypotension, hypertension, bradycardia, tachycardia, respiratory depression, shivering, post-operative nausea, and vomiting (PONV). These were treated with appropriate drugs or other supports.

Statistical analysis

Evaluation of study data in electronic form required performing additional statistical analyses. Data were composed in a suitable spreadsheet, that is, EXCEL and SPSS. After compilation of data, it was analyzed statistically by SPSS software version 20.0. Statistical tests used were Student t-test (paired and unpaired) and Chi-square test. Significance level will be 95% confidence level (P<0.05). Data were described as a frequency (Percentage) distribution as well as in Mean±SD. Data were presented through suitable statistical graphs.

RESULTS

In our study, patients in both groups are comparable (P>0.05) with respect to age, weight, and sex distribution. The mean duration of surgery was 32.70±2.51 min and 32.30±2.89 min in Group KD and Group KM, respectively, and are comparable (P>0.05). There was no significant difference in Ramsay sedation scores between the two study groups (P=0.538). In Group KD, 7 (14%) patients and in Group KM 13 (26%) patients had inadequate anesthesia, but statistically insignificant (P=0.133) (Table 1).

In Group KD, 7(14%) patients and in Group KM 12 (24%) patients required rescue anesthesia. The time of first rescue anesthesia was longer in Group KD (20.30±3.23 min) than Group KM (18.71±3.45 min), but statistically insignificant (Table 2).

In the Group KD, statistically highly significant (P<0.001) attenuation in pulse rate was seen till 30 min postoperatively

Table 1: Adequacy of anesthetic technique in two study groups

Adequacy of anesthetic technique	Group KD (n=50)	Group KM (n=50)	P-value
Adequate	43 (86%)	37 (74%)	0.133 (NS)*
Inadequate	7 (14%)	13 (26%)	

P>0.05-Not significant (NS)*

as compared to baseline, and after that pulse rate returned to baseline. Changes in pulse rate were similar in Group KM during the study time compared with the baseline level. When the two groups were compared, a statistically highly significant reduction in pulse rate (P<0.001) was observed in group KD as compared to group KM till the 90th min postoperatively (Graph 1).

In the Group KD, statistically highly significant (P<0.001) attenuation in MAP was seen throughout the study time as compared to baseline. Statistical analysis of MAP at different points of time between the two study groups showed a statistically significant reduction in group KD as compared to group KM during the intra-operative period (P<0.05) (Graph 2).

The changes in respiratory rate and SpO_2 at different time intervals in each group were within the normal range and were not significant (P>0.05).

Group KD patients had a shorter recovery time of 7.72±1.30 min as compared to Group KM (12.32±3.20 min) (P=0.000). Time for first rescue analgesia was delayed in group KD (70.20±14.35 min) compared to that of Group KM (49±4.73 min) and was statistically highly significant (P=0.000) (Table 3).

In Group KD 4 (8%) patients and in Group KM 11 (22%) patients had post-operative nausea and vomiting. In Group KM 3 (6%) patients experienced post-operative shivering. No episode of bradycardia, hypotension, and respiratory depression was observed in both the groups.

Table 2: Time for first Rescue anesthesia during procedure in two study groups

Parameters	Patients requiring rescue anesthesia		Time of rescue anesthesia (min)
	No.	%	Mean±SD
Group KD (n=50)	7	14	20.30±3.23
Group KM (n=50)	12	24	18.71±3.45
P-value	0.204		0.348 (NS)

P>0.05-Not significant (NS)*

Table 3: Post-operative recovery time and time of rescue analgesia

Groups	Group KD (n=50) (Mean±SD)	Group KM (n=50) (Mean±SD)	P-value
Time of complete recovery (min) (Score>8–10)	7.72±1.30	12.32±3.20	0.000 (HS)*
Time of rescue analgesia (min)	70.20±14.35	49±4.73	0.000 (HS)*

P<0.001-Highly significant (HS)*

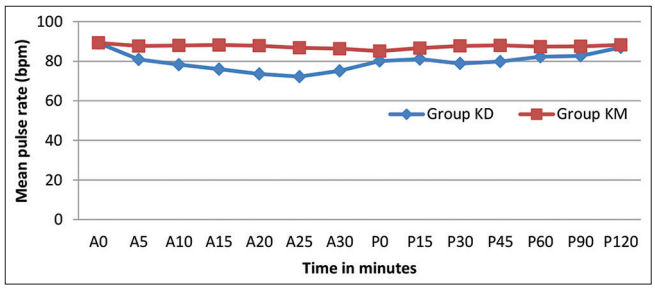
Hallucinations, which can result from ketamine use, were not reported in any patients in both the groups.

DISCUSSION

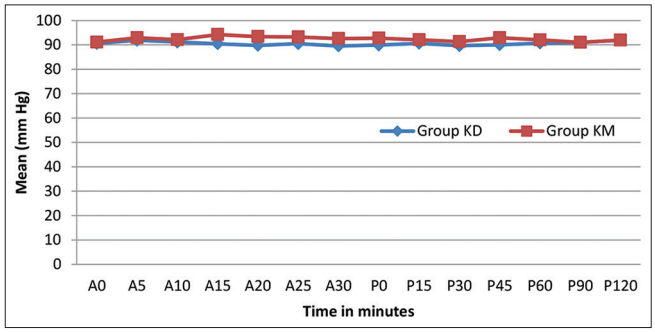
The anesthetic agents used in short surgical procedures must provide adequate analgesia, sedation, immobility, hemodynamic stability, minimal post-operative complications, early recovery, and rapid home discharge. The current study aimed to compare the effects of ketamine-dexmedetomidine and ketamine-midazolam combination on the adequacy of anesthesia, level of sedation and analgesia, hemodynamic, and respiratory parameters, recovery time, and post-operative side effects in short surgical procedures in the adult population.

In a study conducted by Tobiyas et al.,[2] a similar drug combination was used. In another study, Jalowiecki et al.,[5] used 1 mcg/kg dexmedetomidine over 15 min followed by an infusion of 0.2 mcg/kg/h, but the study was terminated because of adverse events such as pronounced hypotension and bradycardia.

In our study, patients in both groups are comparable (P>0.05) with respect to age, weight, and sex distribution. Group KM showed more female patients and Group KD showed an equal number of male and female patients. This variability of age and sex had no consequences on study parameters; hence, it had no clinical significance.



Graph 1 : Statistical analysis of changes in Mean Pulse rate (beats per min) at different time interval between two study groups



Graph 2 : Statistical analysis of changes in Mean Arterial Pressure (mmHg) at different time interval between two study groups

There was no significant difference in Ramsay sedation scores between the two study groups (P=0.538). In Group KD seven (14%) patients and Group KM 13 (26%) patients had inadequate anesthesia with less surgeon satisfaction and PRST score <3. The time of first rescue anesthesia was 18.71±3.45 and 20.30±3.23 min in Group KD and Group KM respectively and was statistically insignificant (P=0.348). Our results are in accordance with the study conducted by Kose et al.,[17] in which two patients in Group DM (6.7%) and three patients in Group KD (10%) needed rescue doses of midazolam. In our study, there is a reduction in the number of patients requiring additional propofol in the KD group than the KM group. Reduction in propofol requirement by dexmedetomidine is due to decreased neuronal activity and enhancement of vagal activity by activation of alpha-2 receptors. Dexmedetomidine provides sedation without respiratory depression hence producing a sleep like phenomenon in EEG by its action on locus coerulus.[18] Ketamine when used along with dexmedetomidine eliminates the slow onset of action when dexmedetomidine is used as a sole agent.

When the two groups were compared, a statistically highly significant reduction in pulse rate (P<0.001) was observed in group KD as compared to group KM. Since ketamine was used in similar doses in both the groups, the significant difference in pulse rate between both groups could be contributed to the central sympatholytic property of Dexmedetomidine. Statistical analysis of MAP at different points of time between the two study groups showed a statistically significant reduction in group KD as compared to group KM. The results of our study are in accordance with Gündüz et al.,[19] who compared the effects of ketamine-dexmedetomidine, ketamine-midazolam, and ketamine-saline on dressing changes of burn patients. Menshawi and Fahim[20] used same combination for sedation in patients undergoing cardiac catheterization and there was a statistically significant reduction in MAP throughout the study period in Group KD (P<0.05) with no intergroup significance.

Dexmedetomidine being a highly selective α2 agonist is sympatholytic and has hemodynamic stability properties leading a dose-dependent decrease in heart rate and blood pressure. Dexmedetomidine lowers central sympathetic outflow thus decreasing serum epinephrine and norepinephrine levels. It stimulates receptors in the medullary vasomotor center, reducing norepinephrine turn over and controlling central sympathetic outflow. Dexmedetomidine has a biphasic effect on blood pressure, causing a decrease in the mean arterial pressure at low plasma concentrations due to vasodilation from the activation of alpha-2A receptors.[21] At higher plasma concentrations activation of peripheral alpha-2B receptor results in vasoconstriction and a rise in blood pressure.[22]

The results of our study showed no statistically significant difference in respiratory rate and SpO_2 between the two study groups. None of the patients had apnea or oxygen desaturation (SpO_2<92%). Menshawi and Fahim also did not find a significant difference between the two groups as regard respiratory parameters. They attributed it to ketamine which kept respiration stable thus explaining the stability of SpO_2 and respiratory rate. Benzodiazepines can produce dose-dependent respiratory depression and this could be minimized by co-administration of ketamine.

Group KD patients had a shorter recovery time (7.72±1.30 min) as compared to Group KM (12.32±3.20 min). Dexmedetomidine has a shorter elimination half-life of 2 h whereas for midazolam it is 3–4 h which accounts for a faster recovery time in the dexmedetomidine group. Moreover, dexmedetomidine-induced sedation qualitatively resembles normal sleep and hence patients are easily arousable.[23] The findings of our study were consistent with the study by Nasreen et al.,[24] who reported a significant reduction in awakening time in patients receiving dexmedetomidine as compared to the placebo group.

Time for first rescue analgesia was delayed in group KD (70.20±14.35) compared to that of Group KM (49±4.73). 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. These results are in accordance with a previous study by Trivedi et al.,[25] who also showed lesser post-operative in patients who received dexmedetomidine.

The most commonly observed side effect in the study was nausea and vomiting. In Group KD 4 (8%) patients and in Group KM 11 (22%) patients had post-operative nausea and vomiting. The less incidence of PONV with dexmedetomidine group could be due to its direct anti-emetic properties. High catecholamine concentrations can induce PONV therefore a decrease in sympathetic tone could explain the antiemetic effect of dexmedetomidine. In Group KM 3 (6%) patients experienced post-operative shivering. This could be because of the impairment of thermoregulatory control by midazolam. Midazolam impairs the tonic thermoregulatory vasoconstriction,

allowing redistribution of body heat from core to peripheral body parts.

Limitations of the study

The present study has been done for short procedures such as cystoscopy, cyst removal, and biopsy. Hence, only short-term effects of anesthetic drugs have been studied. We had given only the loading dose of dexmedetomidine. A continuous infusion throughout the study would have given better results as seen in some other studies. The current study included only ASA I and II patients. The safety profile of the drugs and drug combinations in patients with other comorbidities and critically ill patients were not studied.

CONCLUSION

Dexmedetomidine-ketamine combination is a good and safe alternative agent for procedural sedation in patients undergoing short surgical procedures.

ACKNOWLEDGMENT

The authors are grateful to Gajra raja Medical college, Gwalior for all the support.

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Authors Contribution:
DK- Concept and design of the study, prepared first draft of manuscript; **SAS-** Interpreted the results; reviewed the literature and manuscript preparation; **AB-** Concept, coordination, statistical analysis and interpretation, preparation of manuscript and revision of the manuscript.

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Source of Support: Nil, **Conflicts of Interest:** None declared.