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Comparison of different dosage combinations of intranasal dexmedetomidine and ketamine used for procedural sedation in pediatric patients undergoing minor surgeries in day care setup

Suchismita Pal[1], Anirban Kundu[2], Sandip Roy Basunia[3], Anjana Ghosh Dastidar Bose[4], Sourav Chowdhury[5]

[1]Associate Professor, Department of Anesthesiology, Prafulla Chandra Sen Government Medical College and Hospital, Arambagh, [2]Assistant Professor, Department of Anesthesiology, North Bengal Medical College and Hospital, Siliguri, [3]Professor, Department of Anesthesiology, Calcutta National Medical College and Hospital, [4]Professor, Department of Anesthesiology, Medical College Kolkata, [5]Junior Consultant, Department of Transfusion Medicine, Apollo Multispeciality Hospital, Kolkata, West Bengal, India

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ABSTRACT

Background: Procedural sedation of pediatric patients is necessary to minimize physical pain and psychological trauma and return the patients safely to their parents. Although ketamine and dexmedetomidine have been studied separately for minor surgical procedures, an ideal combination of doses of these two drugs through the intranasal route remains unclear. **Aims and Objectives:** The aim of the study was to compare the different dosage combinations of intranasal dexmedetomidine and intranasal ketamine that can be utilized for procedural sedation in pediatric patients undergoing surgeries in a day care setup to find a suitable dose combination for future use. The objectives of the study were to determine the degree of sedation at the time separation from the parents along with hemodynamic changes after drug instillation. **Materials and Methods:** A total of 60 pediatric patients scheduled for day care surgeries were randomized into two groups. Group DK1 received intranasal dexmedetomidine 1 mcg/kg combined with ketamine 5 mg/kg, whereas Group DK2 received intranasal dexmedetomidine 1 mcg/kg with ketamine 7 mg/kg. Sedation level and parental separation were assessed 30 min after drug administration using the parental separation anxiety scale (PSAS) and Ramsay sedation score. **Results:** The DK2 group had significantly better parental separation with a mean PSAS score of 1.6 compared to 2.6 in Group DK1 ($P<0.001$). Adequate sedation as assessed by Ramsay sedation score was achieved in 13 patients (43%) in DK1 and 22 patients (73%) in DK2. **Conclusion:** The study observed that dexmedetomidine with the higher dose of ketamine, in the pediatric age group, decreases the parental separation anxiety without serious clinical side effects.

Key words: Dexmedetomidine; Ketamine; Intranasal; Pediatric; Sedation

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INTRODUCTION

Procedural sedation of pediatric patients is carried out for different diagnostic as well as minor surgical procedures. The uncooperative behavior of pediatric patients during such procedures arises from anxiety due to separation from parents in the unfamiliar environment, along with the fear of painful interventions. Not only it impacts the sympathetic nervous system of the patients, causing a rise in heart rate (HR) and blood pressure, but post-procedure psychological

Address for Correspondence:
Dr. Suchismita Pal, Associate Professor, Department of Anesthesiology, Prafulla Chandra Sen Government Medical College and Hospital, Arambagh, West Bengal, India. **Mobile:** +91-9474599093. **E-mail:** piu.suchismita.pal@gmail.com

trauma can also result in prolonged pain, bedwetting, etc.[1] This problem is a serious concern for the attending anesthesiologist, who takes help of counseling as well as pre-medication with drugs such as midazolam, ketamine, clonidine and most recently dexmedetomidine to minimize physical pain and psychological trauma and return the patient safely to a state where uneventful discharge is possible.

Ketamine, an N-methyl-D-aspartate receptor antagonist, is a potent anesthetic drug with a distinct analgesic property along with a relatively rapid onset of action and immediate recovery. However, the cardio-stimulatory effect of ketamine and delirium during recovery has been its disadvantage.[2] The drug is highly lipid soluble and rapidly absorbed after intravenous (IV), intramuscular, and intranasal administration, but oral administration is incomplete and delayed with significant first-pass metabolism.

The alpha-2 agonist drug dexmedetomidine has dose-dependent sedation and mild analgesic properties, and its characteristic effect on perioperative hemodynamic parameters can make it a useful adjunct to ketamine by the central sympatholysis due to alpha-2 adrenoceptor agonism. Dexmedetomidine-induced xerostomia is attenuated by the ketamine, causing increased secretion.[3]

The route of administration is also very important in the case of pediatric patients, as they are needle-phobic. Hence, there has been renewed interest in the non-invasive routes such as oral, nasal, or inhalational.[4] The oral route is a feasible option, but can result in low bioavailability. The intranasal route of drug administration can be a better option because it has many advantages, such as easy administration and increased bioavailability, as it bypasses first-pass metabolism and reaches the olfactory tissue, which is in direct contact with the central nervous system.[5] Intranasal drugs evade the necessity of bitter-tasting drugs, and an undiluted solution can be employed.[6] In contrast to midazolam, intranasal dexmedetomidine and ketamine also do not exhibit signs of nasal irritation, so they are most suitable for the pre-medication route.[7]

When administered through the intranasal route, studies conducted by Mostafa and Morsy demonstrated that pre-medication with intranasal dexmedetomidine at a dose of 1 μg/kg produced adequate sedation; however, it was associated with a significant decrease in HR, respiratory rate, and systolic blood pressure (SBP) after 30 min. These findings were further corroborated by Yuen et al. in their study.[8,9] Moreover, intranasal ketamine, when used for procedural sedation, has been used in various dosages ranging from 3 to 9 mg/kg and showed a significant difference in levels of sedation between low and high dosages. Pediatric patients who received 9 mg/kg experienced adequate sedation, which was comparable to the IV sedation dose used to provide deep anesthesia.[10-13]

Aims and objectives

Aims

The aim of this study was to compare the different dosage combinations of intranasal dexmedetomidine and intranasal ketamine that can be utilized for procedural sedation in pediatric patients undergoing surgeries in a day care setup to find a suitable dose combination for future use that will reduce the individual dosages of the drugs in combination, as well as minimize the side effects.

Objectives

1. The primary objective of the study was to determine the degree of sedation at the time of separation from the parents and if any supplemental IV sedation was required during the procedure
2. The secondary endpoint is hemodynamic changes after the instillation of drug combinations and any side effects of the study drugs.

MATERIALS AND METHODS

This prospective clinical study was undertaken with 60 pediatric patients in the institute after taking ethical clearance from the ethics committee, written informed consent from the patients' parents or legal guardians, and was conducted over a period of 1 year.

Inclusion criteria

- Pediatric patients of the American Society of Anesthesiologists categories I and II
- Age between 2 and 7 years
- Scheduled to undergo minor surgical procedures <30 min, who are divided into two equal groups under day care setup.

Exclusion criteria

- Known allergy or hypersensitivity to study drugs dexmedetomidine, ketamine
- Cardiac arrhythmia or congenital heart disease
- Mental retardation or developmental delay, or seizures
- Upper respiratory tract infection
- Anatomic airway abnormalities
- Parental refusal.

Patients were selected after careful evaluation through history and physical examination. Informed consents were taken from the parents, and fasting regulations were followed according to standard guidelines. The weight of the patient was measured to determine the dosage of the drugs to be instilled intranasally. Patients were randomized into two equal groups using a computer-generated table

of random numbers (https://www.randomizer.org/). Patients in group DK1 received dexmedetomidine in the dose of 1 mcg/kg and ketamine 5 mg/kg intranasally. Patients in group DK2 received dexmedetomidine in the dose of 1 mcg/kg with ketamine 7 mg/kg intranasally (the concentrations of dexmedetomidine and ketamine were 100 mcg/mL and 50 mg/mL, respectively). Study drugs were administered by nursing personnel not involved in data collection and assessment. In both groups, the combination was delivered by a 5 mL syringe and deposited gradually in each nostril equally at least 30 min before surgery. Then the alae of the nose were gently massaged to facilitate its absorption. The patients are to be encouraged to remain supine in the mother's lap to maximize their drug absorption.

Procedure

The patients were kept in the holding area, and blood pressure, HR, and oxygen saturation were measured before and after application of the pre-medication. After the application of the pre-medication drugs, the level of sedation was checked every 5 min, and parental separation was assessed at the time the patient was taken to the operating room after 30 min of administration of the drug. Continuous monitoring of the hemodynamic parameters was also done. The parental separation anxiety scale (PSAS) was used to assess the separation anxiety, which is a four-point scale: (1) Easy separation, (2) whimpers, but is easily reassured, not clinging, (3) cries and cannot be easily reassured, but not clinging to the parents, (4) crying and clinging to the parents. A PSAS score of 1 or 2 is taken as acceptable for minor surgical procedures, whereas a PSAS score of 3 or 4 is considered unacceptable.

The level of sedation was measured using the modified Ramsay sedation scale. (1) Patient is anxious and agitated or restless or both, (2) patient is cooperative, oriented, and tranquil, (3) patient responds to command only, (4) patient exhibits brisk response to light glabellar tap, (5) Patient exhibits sluggish response to light glabellar tap, (6) patient exhibits no response. Ramsay sedation scores 1 and 2 were considered unsatisfactory, and more than 2 was considered satisfactory sedation.

The hemodynamic parameters, namely HR, SBP, diastolic blood pressure, mean blood pressure, oxygen saturation, and end tidal carbon dioxide, were monitored continuously and documented every 5 min. All the patients received oxygen through a nasal cannula at a rate of 2–3 L/min during the entire procedure. In case the patient shows movement or failed sedation, they were provided rescue sedation through the IV route, propofol (IV 0.5 mg/kg bolus and 2 mg/kg/h by infusion). The amount of supplemental IV medication was noted. Any episode of bradycardia or hypotension was documented, and appropriate interventions were given accordingly. A heart rate <50/min or a 20% decrease from baseline was considered bradycardia, and atropine injection was given in a dosage of 0.02 mg/kg. Any decrease in blood pressure <20% baseline is taken as hypotension and treated with a bolus of fluid.

Statistical analysis

The data were presented as means±standard deviation for continuous variables and as counts and percentages for nominal data. The demographic data were analyzed by an independent t-test and the Chi-square test. Hemodynamic parameters were analyzed by paired t-tests. $P<0.05$ was taken to be significant.

RESULTS

Demographic characteristics and surgical procedures of the 60 patients are illustrated in Figure 1. The patient's demographic characteristics, type, and duration of the minor procedures undertaken showed no statistically significant difference between the groups of pediatric patients as shown in Table 1. The age distribution and weight of the patients in the two groups were also comparable.

The behavior of the pediatric patients was assessed periodically to assess the onset of sedation. Onset of sedation in the two groups was compared; it was found to be significant ($P<0.05$) and shorter in the DK2 group (25.7 vs. 20.86 min, respectively) as shown in Table 2.

PSAS score for measuring easy separation from the parents showed DK1 was 2.6, and in DK2 was 1.6, which was

Table 1: Demographic distribution and surgical procedure

Parameter	DK1	DK2
Surgery		
Dermoid	3	4
Eyelid repair	3	1
Foreign body removal	7	4
Incision drainage	9	10
K-wire	8	11
Age		
Mean (years)	4.1	4.16
Gender		
Male: Female ratio	1.3:1	1.3:1
Male	17	17
Female	13	13
Weight (kg)		
8–9.9	4	3
10–11.9	10	11
12–13.9	10	10
14–17	6	6

*Distribution among two groups

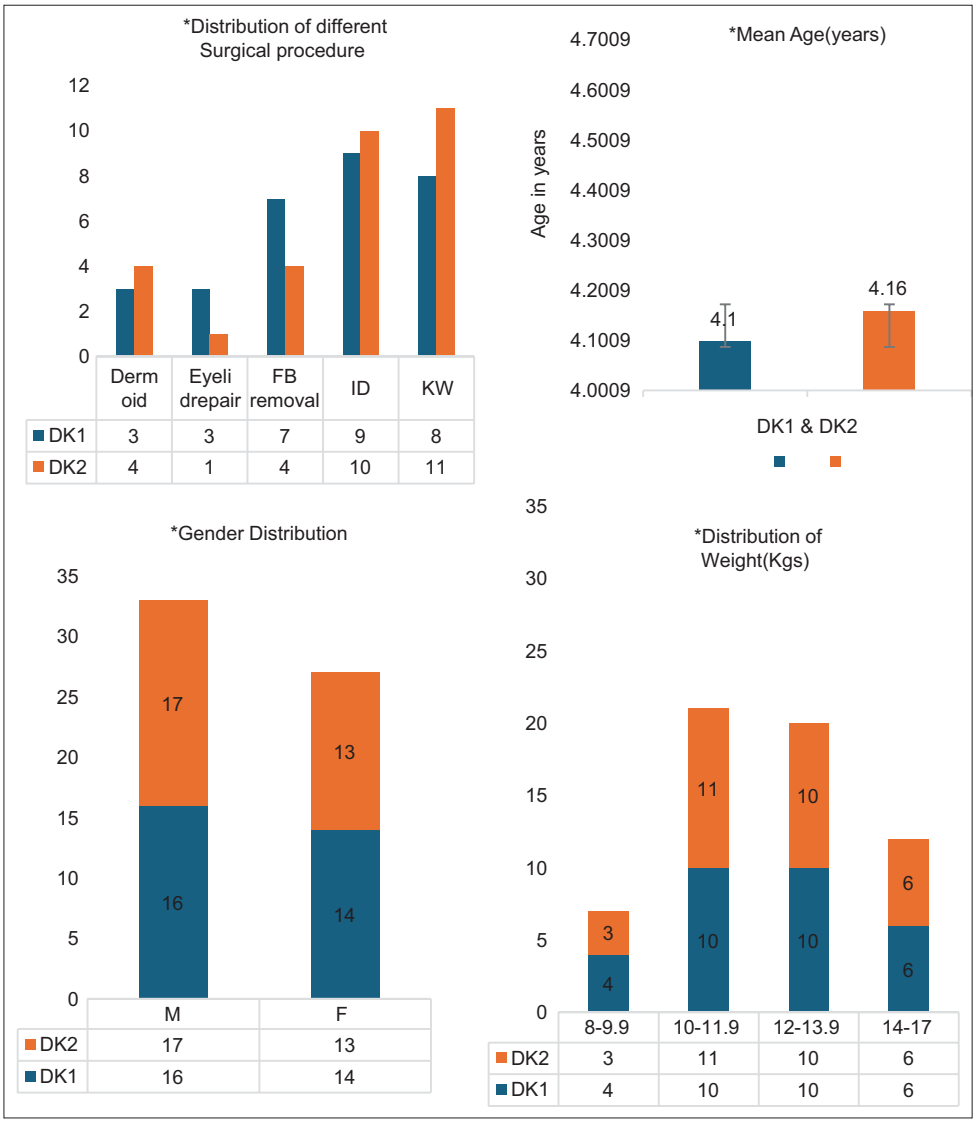

Figure 1: Comparison of demographic characteristics of DK1 versus DK2 group

Table 2: Student T-test analysis of demographic data and observed clinical data of both groups

Category	DK1*		DK2#		P-value
	Observation	Mean	Observation	Mean	
Weight (kg)	30	11.9 (±1.98)	30	11.9 (±2.01)	0.964
Age (years)	30	4.1 (±1.29)	30	4.2 (±1.28)	0.842
Sedation onset (min)	30	25.7 (±1.73)	30	20.9 (±1.69)	**<0.001$**
RSS score	30	2.6 (±0.78)	30	3.03 (±0.99)	0.08
PSA score	30	2.6 (±0.84)	30	1.6 (±0.96)	**<0.001$**

*DK1 group receiving dexmedetomidine 1 mcg/kg and ketamine 5 mg/kg (intranasal). #DK2 group receiving dexmedetomidine 1 mcg/kg and ketamine 7 mg/kg (intranasal). P<0.05 is significant. PSA: Parental separation anxiety, RSS: Respiratory severity score, $P value <0.05 is significant

significant between the groups (P<0.001) as shown in Table 2.

In the study, DK1 showed adequate sedation in 13 patients (43%), which increased to 22 patients (73%) in DK2 (Table 2). Moreover, number of rescue sedation needed in the DK1 group was 19 whereas only 8 patients in DK2 group needed rescue sedation, making it statistically significant (P<0.05) as shown in Table 3.

Overall, we did not observe any clinically significant changes in HR, blood pressure, or saturation between the two groups, as shown in Table 4.

DISCUSSION

All pediatric patients need pre-medication to decrease anxiety, allow smooth induction, and reduce post-operative psychological insult, so a better understanding of the efficacy of the combination of pre-medication drugs, dexmedetomidine, and ketamine administered intranasally for sedation and to combat separation anxiety among patients posted for day care surgeries is assessed by this study.

In the present study, the onset of sedation in the DK2 group occurred at 20 min, which was approximately 5 min earlier than in the comparison group, and this difference was found to be statistically significant. Yuen et al. reported an onset time of 45–60 minutes with intranasal dexmedetomidine alone at a dose of 1 μg/kg. In contrast, the addition of ketamine in our study appears to have contributed to a significantly faster onset of sedation, with a dose-dependent reduction observed at higher ketamine doses. This resulted in better parental separation, and the patient could be easily transferred to the operating room.

In a study by Gyanesh et al., intranasal dexmedetomidine (1 μg/kg) was compared with intranasal ketamine (5 mg/kg) in 150 patients for IV cannula placement during magnetic resonance imaging scanning, and both drugs were found to be equally efficacious.[14] The present study compared the same drugs, dexmedetomidine and ketamine, in different combinations to obtain the better option for sedation for pediatric patients with lesser side effects. The results demonstrated that the parental separation score improved in the DK2 group, which was statistically significant. The Ramsay sedation score was clinically better in the DK2 group as compared to the DK1 group, but not statistically significant. This is also corroborated by a study conducted by Bhat et al., which showed that a low dose of ketamine (2 mg/kg) when used with dexmedetomidine (1 mcg/kg) does not increase the success of pre-medication, though parental separation was acceptable, and they advocated for studies with higher doses.[7] Hence, this study showed that the sedative effect of intranasal dexmedetomidine could be effectively complemented by ketamine with higher dosages.

Parental separation was easier in the DK2 group, as the time of separation likely coincided with the peak effect of the drug combination. However, the success of sedation depended on the duration of action of the combined drug dosage throughout the procedure, which showed a comparable effect in the present study. Nevertheless, the requirement for rescue analgesia was lower in the DK2 group.

A study by Vivian et al. demonstrated that when dexmedetomidine was used in a dose of 1 mcg/kg, it produced reduced HR and SBP in the pre-operative period.[9] However, in the current study, when ketamine was added to dexmedetomidine, no episodes of bradycardia or hypotension were noticed in either of the groups. Moreover, when higher dosages of dexmedetomidine had been used in studies conducted by Yang et al., 7.3% patients showed unexpected changes in HR or blood pressure by more than 20% of normal age-adjusted values.[15]

A placebo group was not included in this study, as the effectiveness of these individual drugs, when compared with a placebo, was found to be superior in the previous studies.

Another limitation in this present study was the administration of a large volume of drug, where there is a chance of the drug being deposited in the pharynx, so the sedative

Table 3: Chi-square test results for categorical clinical data of both groups

Category	DK1*	DK2#	P-value
Satisfactory sedation	13	22	<0.05
Unsatisfactory sedation	17	8	
Rescue sedation	19	8	<0.05
No rescue sedation	11	22	

*DK1 group receiving dexmedetomidine 1 mcg/kg and ketamine 5 mg/kg (intranasal). #DK2 group receiving dexmedetomidine 1 mcg/kg and ketamine 7 mg/kg (intranasal). P<0.05 is significant

Table 4: Mean of vital parameters (heart rate, mean arterial pressure, oxygen saturation) of two groups of patients

Hemodynamic parameter	Baseline before instillation of the drug	5 min	15 min	30 min	At start of surgical procedure	5 min	15 min	30 min
Heart rate (beats/min)								
DK1	94.47	93.57	87.67	85.87	91.93	97.60	97.97	96.30
DK2	95.23	94.63	87.87	85.40	88.33	92.40	93.13	92.83
Mean arterial pressure (mm/Hg)								
DK1	65.50	60.43	59.10	57.73	58.17	60.53	62.10	63.40
DK2	58.17	60.53	62.10	63.40	58.87	61.00	61.70	63.48
Oxygen saturation (%)								
DK1	99.90	99.93	99.97	99.90	99.83	99.87	99.97	99.93
DK2	99.87	100.00	99.93	100.00	99.93	99.97	99.90	100.00

effect can result due to oral absorption. Hence, the use of specialized equipment may be used in future studies, but administration of intranasal medication is relatively painless, inexpensive, and easy to deliver with minimal training.

CONCLUSION

The study observed that the level of sedation achieved with intranasal dexmedetomidine combined with different doses of ketamine was comparable across groups. However, parental separation anxiety was significantly reduced with the higher dose of intranasal ketamine. Moreover, the requirement for rescue sedation decreased significantly while maintaining a stable hemodynamic state.

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SP- Concept, data collection, and manuscript writing; **AK**- Data collection; **SRB**- Manuscript writing and review; **AGDB**- Concept; **SC**- Statistics and manuscript writing.

Work attributed to:
Diamond Harbour Government Medical College and Hospital, Diamond Harbour, West Bengal, India.

Orcid ID:
Dr. Suchismita Pal - https://orcid.org/0000-0002-9893-9942
Dr. Anirban Kundu - https://orcid.org/0009-0007-7936-3793
Prof. Sandip Roy Basunia - https://orcid.org/0009-0006-3754-5954
Prof. Anjana Ghosh Dastidar Bose - https://orcid.org/0000-0001-5677-4863
Dr. Sourav Chowdhury - https://orcid.org/0000-0003-1916-7444

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