

Procedural sedation in children for fractionated radiation treatment: Intranasal dexmedetomidine versus oral midazolam and ketamine

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Submitted: 16-Apr-2022

Revised: 05-Oct-2022

Accepted: 07-Oct-2022

Published: 19-Oct-2022

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ABSTRACT

Background and Aims: Sedation in paediatric cancer for fractionated radiation treatment (RT) is unique as the child has to be still for accurate delivery of RT, monitoring of the child is from a remote location and sedation is repeated for multiple sessions of RT. The present study was undertaken to compare the efficacy of intranasal dexmedetomidine with oral midazolam and ketamine combination for repeated sedation during fractionated RT in paediatric oncology. **Methods:** Ninety children aged between 3-6 years, planned for 21 fractions of RT, were randomised to receive intranasal dexmedetomidine 2 µg/kg (group D) or oral midazolam 0.2 mg/kg and ketamine 5 mg/kg (group MK). The 21 sessions of fractionated radiotherapy were divided into three subgroups of seven consecutive exposures 1–7, 8–14 and 15–21 for comparison. The primary endpoint was to determine the incidence of successful sedation. The sedation score achieved, time to satisfactory sedation and discharge, rescue ketamine required, and side effects were secondary endpoints.

Results: The incidence of successful sedation in the three successive RT subgroups; sessions: 1–7, 8–14 and 15–21, was 82%, 75.6% and 66.7% in group D, as compared to 40%, 24.4% and 13.3% in group MK, respectively. ($P < 0.001$). A decrease in successful sedation was noted in the successive subgroups. Time to successful sedation and discharge was earlier in group D in comparison to MK ($P = 0.000$). More patients in group MK required rescue ketamine ($P = 0.000$). **Conclusion:** Intranasal dexmedetomidine produces more satisfactory sedation as compared to oral ketamine with midazolam for fractionated RT.

Key words: Dexmedetomidine, intranasal, ketamine, midazolam, radiation treatment, sedation

Access this article online
Website: www.ijaweb.org
DOI: 10.4103/ijja.ijja_340_22
Quick response code


INTRODUCTION

Oral and intranasal routes for procedural sedation in children undergoing diagnostic procedures like computed tomography (CT) scan, magnetic resonance imaging (MRI),^[1] ophthalmic examination,^[2] sedated auditory brainstem response^[3] and transoesophageal echocardiography^[4] are established and acceptable alternatives to injection. These routes are convenient for paediatric cancer patients undergoing radiation treatment (RT), as these children have poor performance status, are traumatised due to diagnostic and therapeutic procedures, and suffer from fear of injections. Sedation in these patients offers unique challenges as the child has to be still for accurate delivery of RT, monitoring of the

remotely located child is difficult, and sedation is repeated over days.

Oral midazolam and ketamine combination is a method of procedural sedation used in radiology and the radiation suite.^[5] It is used in our institute for children undergoing fractionated RT courses

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How to cite this article: Das R, Das R, Jena M, Janka J, Mishra S. Procedural sedation in children for fractionated radiation treatment: Intranasal dexmedetomidine versus oral midazolam and ketamine. *Indian J Anaesth* 2022;66:687-93.

for cancer. Although oral midazolam has good oral bioavailability and excellent anxiolysis, the distinct bad taste, associated with post-procedural delirium, restlessness, cognitive impairment and respiratory depression, limit its use. Oral ketamine produces a state of sedation, dissociative anaesthesia and analgesia, sometimes accompanied by emesis and emergence delirium. Combining midazolam with ketamine is supposed to increase the efficacy and minimise the adverse effects; however, this is not without side effects and failures. Other drawbacks relevant to the situation include unreliable absorption and vomiting, leading to unpredictable responses and neurotoxicity due to repeated use of these drugs for the course of fractionated RT.^[6]

Dexmedetomidine is a sedative and analgesic that produces a natural sleep-like state with smooth arousal.^[7] Intranasal dexmedetomidine has been safely and effectively used in procedural sedation in CT scans, MRI with predictable results.^[1] It is also considered a safe drug in ill patients and is preferred due to its neuroprotective effect.^[8] There has been no study on intranasal dexmedetomidine as a sole agent for repetitive sedation in children. Hence, we conducted this study to compare the sedation effects of dexmedetomidine with midazolam and ketamine combinations in oncology patients. We hypothesised that intranasal dexmedetomidine will produce better sedation than the oral midazolam–ketamine combination and will be a safe alternative to the latter in paediatric cancer patients during the fractionated RT course. The primary outcome was to note the incidence of patients who could lie still in the radiation suite and successfully undergo RT in successive serial radiation exposures. The secondary outcome was to determine the sedation score achieved, medication acceptance score, time to satisfactory sedation and discharge from the hospital, the requirement of rescue sedative and any untoward side effects.

METHODS

Children who were planned for RT underwent routine physical examinations and investigations once the radiation protocol was advised. Children of American Society of Anesthesiologists (ASA) physical classes I, II and III, aged between 3 and 6 years, planned for RT were included in the study. Each RT session takes about 5–10 min, and the number of sessions or fractionated treatments of each RT varies. In our study, we included those who received at least 21 sessions.

Children with upper respiratory tract infections, obstructive airway conditions, congenital heart disease, any other systemic disease other than cancer, allergy to study drugs and refusal to participate were excluded from the study.

The parent or the caretaker of the child was explained the procedure in the local language; after they understood the purpose, methodology, associated risks and benefits of the study, written consent was obtained and the study was carried out. A fasting protocol was followed before children were taken up for sedation in the radiotherapy holding area.

The study was a prospective randomised controlled trial conducted in a tertiary cancer hospital between October 2020 and February 2022. After obtaining institutional ethics committee permission (133-IEC-AHRCC dated 02.07.2020), the trial was registered in the Clinical Trial Registry of India (CTRI/2020/09/027579). Ninety eligible children were randomised into two equal groups, group D and group MK, using a computer-generated table of random numbers and allocated into the groups through sealed opaque envelopes.

Patients in group D received 2 µg/kg of dexmedetomidine (dextomid® 100 µg/ml, Neon Lab, India) intranasally and oral honey, and those in group MK received intranasal 1 ml of saline and 0.2 mg/kg midazolam (Mezolam® 5 mg/ml Neon Lab, India) with 5 mg/kg ketamine (Aneket® 50 mg/ml Neon Lab, India) mixed with honey orally. Intranasal dexmedetomidine was prepared as per the calculated dose of the individual child by adding normal saline to make the volume 1 ml in the tuberculin syringe. Study drug preparation was carried out by an anaesthesiologist not involved in administration, assessment, data collection or the subsequent study. In both groups, 0.5 ml of the drug was deposited into each nostril equally while the child was held on the parent's lap in the preprocedural holding area. The blood pressure (BP), heart rate (HR), respiratory rate (RR) and oxygen saturation (SpO₂) were monitored at 5-min intervals. The child's acceptance of medication was graded using a 4-point Likert scale; 1: excellent – child accepted the premedication easily; 2: good – child complained but then accepted the medication; 3: average – child complained, initially uncooperative, but eventually accepted medication; 4: poor – child refused medication. The depth of sedation was assessed using the Ramsay Sedation Scale (RSS).^[9] A minimum

RSS score of 3 was required to ensure motionless conditions or acceptable sedation.^[10] Assessment of sedation was done every 5 min by the observer using the RSS score and continuous monitoring by parents who reported when the child did not respond to command. The parents were allowed to hold their child on the RT couch and lay the child on the couch. The sedation level was reassessed. Children who lay still on the RT couch underwent RT; those who moved or were uncooperative, after 5–10 min were allowed to achieve a deeper sedation level. Children who could not be sedated after 20–30 min of drug administration received rescue sedation. This was administered as intravenous (IV) ketamine at 1 mg/kg, and a further top-up of 0.5 mg/kg IV was repeated if the patient moved. Physiological monitoring continued every 5 min till the patient attained an Aldrete score of 9 or more to be discharged. All patients were supplemented with oxygen via nasal prongs. The HR and BP were below 20% of the normal boundary of the age-specific normal range and were planned to be treated with atropine or ephedrine and fluids.^[11] Other side effects like oxygen desaturation, vomiting and emergence delirium were noted. Emergence delirium was assessed by the 4-point Watcha behaviour scale; 1 – calm, 2 – crying, but can be consoled, 3 – crying, cannot be consoled and 4 – agitated and thrashing around. Emergence delirium was defined on a scale of 3 and 4.^[12] For intragroup and intergroup comparison, the 21 sessions of fractionated RT were divided into three subgroups of seven consecutive radiation exposures, 1–7, 8–14 and 15–21.

We did an initial pilot study of 30 children, with 15 in each group who received either intranasal dexmedetomidine or oral midazolam–ketamine combination. The number of children who could complete initial RT was 12 (80%) in group D and 7 (46.6%) in the MK group. To keep a significant difference between the two groups with an alpha error of 5% and power of study of 90%, the estimated sample was calculated to be 42 in each group. Anticipating drop outs, we took 45 in each group. All data were entered and analysed using International Business Machines, Statistical Package for the Social Sciences (IBM, SPSS) version 21 (IBM Corp; Armonk, New York) for windows 2010. The Shapiro–Wilk normality test was used to assess the distribution of the continuous variable. Comparison of nonparametric data was done by the Mann–Whitney U test, and for normally distributed data, the Student's *t*-test was employed. The Friedman test was used for intragroup

repetitive analysis of categorical values, and the Kruskal–Wallis test was used for intergroup analysis. Categorical values were expressed as frequencies or percentages and compared by the Chi-square test.

RESULTS

The study included 90 patients, and everyone completed the study [Figure 1].

The demographic data included age, gender, ASA physical status and disease type and were comparable between the two groups [Table 1]. The incidence of successful sedation in the three successive RT subgroups; sessions: 1–7, 8–14, 15–21 was 82%, 75.6% and 66.7% in group D as compared to 40%, 24.4% and 13.3% in group MK, respectively, and the difference was significant ($P < 0.001$) [Tables 1 and 2]. Intragroup comparison of successful sedation did not show a significant decrease in the successive sessions of RT in group D ($P = 0.234$), while in group MK it was significant ($P = 0.015$).

Time to successful sedation and discharge was significantly less in group D as compared to group MK ($P = 0.000$) [Table 3].

The number of patients who required ketamine and the dose of ketamine was significantly more in group MK compared to group D ($P = 0.000$) [Table 4]. The rescue dose of ketamine and the number of patients requiring ketamine increased significantly in successive RT in group MK ($P = 0.015$) in comparison to group D, which did not show a significant increase ($P = 0.234$) [Table 5].

Side effects were seen in 12 (26.67%) patients as vomiting and emergence delirium in group MK, while 1 patient in group D had vomiting [Table 1].

DISCUSSION

In the present study, the efficacy of intranasal dexmedetomidine was compared with a combination of oral midazolam and ketamine to sedate children for repeated sessions of RT. It was observed that children who received intranasal dexmedetomidine achieved better sedation than those who received a combination of oral midazolam and ketamine. In the initial sessions, the success rate of sedation was 82% in the dexmedetomidine group. A review of published studies on intranasal dexmedetomidine in

Table 1: Demographic Data and Clinical Data

Parameter	Group D (n=45)	Group MK (n=45)	P
Age (months)*	50.09±11.48	49.11±11.48	0.674
Body weight (kg)*	16.59±3.31	16.66±3.18	0.889
Gender (Male: Female)	24:21	23:22	0.833
ASA I/II/III (frequency n)	20/22/3	20/21/4	0.673
Disease (frequency n)			
Primary CNS tumour/Retinoblastoma/Ewing's sarcoma/Rhabdomyosarcoma/Others	31/7/5/2/2	29/6/4/3/2	0.95
MAS (frequency n) excellent/good/fair/poor	41/4/0/0	35/6/4/0	0.087
RSS (frequency n)	0/8/28/6/3/0	6/4/17/13/3/2	0.003
1/2/3/4/5/6			
Side effects n (%)	1 (2.22%)	12 (26.67%)	0.001
Vomiting/EA/desaturation/bradycardia or tachycardia	1/0/0/0	8/4/0/0	

Data are presented as mean±standard deviation (marked *), n – number of patients, frequency as number (n), and percentage (%). Student's t test and Chi-square test applied. P<0.05 is significant. ASA – American Society of Anesthesiologists physical status, CNS – Central nervous system, MAS – Patient's acceptance of medication, RSS – Ramsay Sedation Scale score on first exposure, EA – Emergence agitation

Table 2: Incidence of successful sedation and sedation score in successive serial radiotherapy

RT exposures	Incidence of success*		Odds ratio (95% CI)	P	Sedation score†		P
	Group D (n=50)	Group MK (n=50)			Group D (n=50)	Group MK	
1-7	37 (82%)	18 (40%)	6.17 (2.4-15.8)	<0.001	03 (2-5)	3 (1-6)	0.261
8-14	34 (75.6%)	11 (24.4%)	9.54 (3.6-24.9)	<0.001	03 (2-5)	3 (1-5)	0.638
15-21	30 (66.7%)	6 (13.3%)	13 (4.5-37.5)	<0.001	03 (2-4)	2 (1-4)	0.012

Data marked *are presented as number, percentage, variables marked † are expressed as median with range, Chi-square test applied, P<0.05 is significant. RT – radiation treatment, n – number of patients, CI – confidence interval

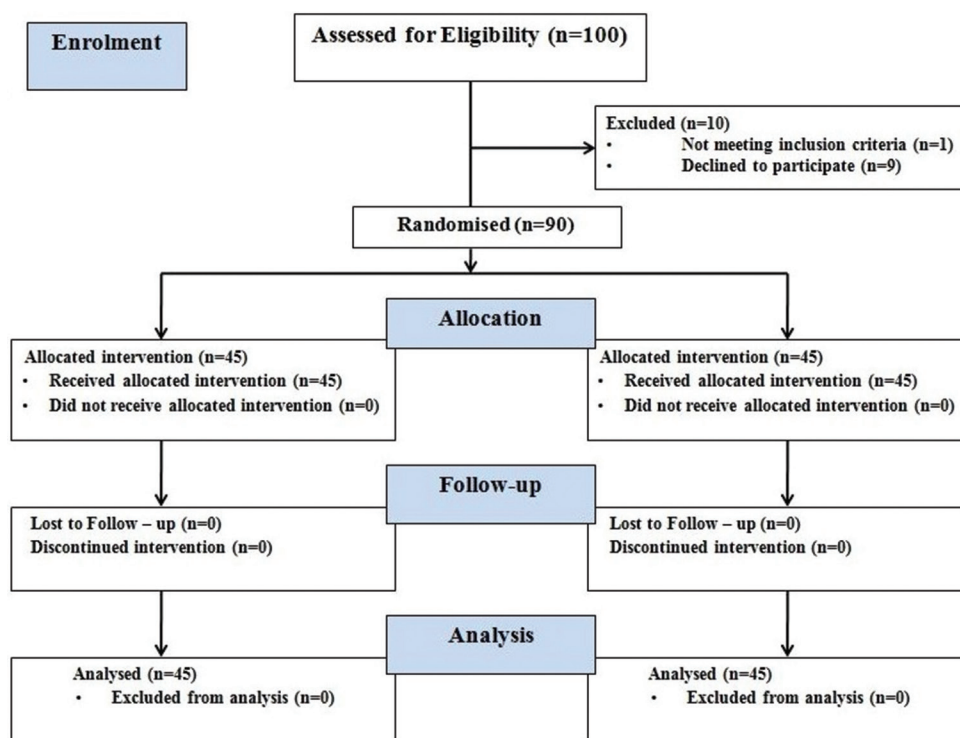


Figure 1: Consolidated Standards of Reporting Trials (CONSORT) flow diagram

children showed that 2 µg/kg of the drug produced reliable procedural sedation with a success rate of 95.2% (85.9–100%).^[13] In another study, 2.5 µg/kg intranasal dexmedetomidine used for sedation in CT scans resulted in desirable sedation in 67% of children. In the present study, the success rate with

intranasal dexmedetomidine is closer to that described in a review of studies on this topic.^[13] Our success rate of sedation in the oral midazolam–ketamine group was initially 40%, similar to the study where adequate sedation for CT scanning was achieved in 45.5% of children.^[5]

Table 3: Comparison of time to sedation and discharge

	Group D	Group MK	P
Time to achieve sedation	16 min 10s (14 min 50s-28 min 20s)	22 min 10s (20 min-38 min)	0.000
Time to discharge	78 min (65 min-95 min 10s)	98 min 20s (78 min 60s-118 min 10s)	0.000

Data are presented as median with range, Mann-Whitney U test applied, $P < 0.05$ is significant

Table 4: Sedation score in successive serial RT

RT exposures	Sedation score (median with range)		P
	Group D (n=50)	Group MK (n=50)	
1-7	3 (2-4)	3 (1-5)	0.261
8-14	3 (2-4)	3 (1-4)	0.638
15-21	3 (2-4)	2 (1-4)	0.012

Data are presented as median with range, Chi-square test applied, $P < 0.05$ is significant, RT – radiation treatment. No – number, n – number of patients

Table 5: Rescue dose of ketamine and number of patients requiring ketamine in successive serial RT

RT	Rescue dose of ketamine (mg/kg)*			Patients requiring ketamine*		
	Group D (n=45)	Group MK (n=45)	P	Group D (n=45)	Group MK (n=45)	P
1-7	0 (0-1.5)	1 (0-1.5)	0.000	8 (17.7%)	27 (60%)	0.000
8-14	0 (0-1.5)	1 (0-1.5)	0.000	11 (24.4%)	34 (75.5%)	0.000
15-21	0 (0-1.5)	1.5 (0-1.5)	0.000	15 (33.3%)	39 (86.6%)	0.000

Data marked as * are presented as median with range, †as number and percentage and compared using Chi-square test. $P < 0.05$ is significant, RT – radiation treatment, n – number of patients

The number of patients responding to the sedation effect of dexmedetomidine decreased in consecutive sessions of RT, but this was not statistically significant; in comparison, the decrease in the success rate of sedation in the midazolam–ketamine group was significant, showing that the children developed quicker tolerance to the drugs with more requiring supplemental IV ketamine. Tachyphylaxis has been reported with ketamine when used for repeated sessions of RT.^[14,15] Tolerance to midazolam has been seen when used for a prolonged time in cancer patients.^[16] However, there have been no reports of tolerance to the effects of dexmedetomidine. Most of these studies have been done with infusions.^[17,18] There are a few published case reports on IV dexmedetomidine sedation for fractionated RT courses in children.^[19-21] In these studies, few patients woke up and needed rescue sedation such as propofol or midazolam. Similarly, in the present study, sudden arousal of patients from sedation was seen. The duration of RT was 5–10 min, and patients received a single loading dose of the drug. Rescue ketamine was required for 17.7%, 24.4% and 33.3% of children in the first, second and third seven-day sessions of RT respectively.

Both the medications were well accepted by most children in our study cases. Nevertheless, in a study on intranasal dexmedetomidine and oral midazolam sedation, the acceptance of the medications by the children was evaluated, and it was seen that the acceptance of both the medications was good; there was no episode of vomiting or spitting out of the drugs.^[1]

In our study, the time to achieve successful sedation in the dexmedetomidine group was 16 min and 10 s, and the time to discharge was 78 min. A systematic review of 14 randomised controlled trials on intranasal dexmedetomidine for sedation in children found that the average time for onset of sedation was 15–30 min and the duration was 55 min.^[14] In yet another study, where intranasal dexmedetomidine was administered to children below 10 years, the onset time was less than 30 min and the discharge time was around 80 min.^[22] These studies show that the intranasal route of administration is efficacious and rapid, which makes it a suitable agent for procedural sedation. However, the concentration-time profiles showed that the plasma levels of dexmedetomidine fell quickly, so in procedures that were long, a repeated administration or a higher initial dose was necessary.^[23] In our study, as the duration of the procedure was within 10 min, a single bolus was appropriate.

The onset of action of oral midazolam–ketamine in our study was 22 min. In a study where oral midazolam–ketamine was administered at a similar dose, the onset time to adequate sedation was 32 min^[5] and 14 min when midazolam was used at a higher dose of 0.5 mg/kg for laceration repair.^[24] These differences in onset time can also be attributed to the metabolism of midazolam that is influenced by cytochrome P4503A (CYP3A) isoenzymes. The time to discharge in the midazolam–ketamine group in our study was 98 min 20 s, which was similar to a previous study where it was 105 min.^[5] In the dexmedetomidine group, the onset time and the time to discharge were significantly shorter than those in the midazolam–ketamine group, making it a more suitable drug for procedural sedation.

Many studies have been carried out using propofol, midazolam and/or ketamine for sedation in RT. Their repeated use has been associated with complications like sepsis, cardiovascular complications and airway complications.^[25] In one of the largest reviews done on the use of dexmedetomidine in paediatric

patients, it was shown that dexmedetomidine has a favourable adverse effect profile with minimal untoward haemodynamic and respiratory effects, is well-tolerated and efficacious in non-invasive procedures.^[26] Contrarily, some side effects due to infusions have been pointed out.^[27] In our study, we witnessed no untoward effects in the dexmedetomidine group except in one patient who had vomiting. They were haemodynamically stable and maintained oxygen saturation. Nevertheless, dexmedetomidine is now occupying a special place in the perioperative management of children.^[28]

There have been case reports where dexmedetomidine is used for sedation in less than 3 years old children receiving more than 20 sessions of RT. Nevertheless, we included children between 3 and 6 years of age in this study and plan to undertake a subsequent study in the lower age group.

CONCLUSION

Intranasal dexmedetomidine provides satisfactory sedation in paediatric patients receiving repeated RT. Compared to the oral midazolam–ketamine combination, the success rate of sedation in the repeated sessions is better. It is also safer, with a quicker onset of action and recovery. Although the increased need for rescue sedation in the repeated RT sessions was not significant, it cannot be overlooked. Considering its safety profile in paediatric patients, more studies may be undertaken with higher doses for more successful application in these patients.

Acknowledgements

The authors are very thankful to Ms Rachana Das, PhD student in Microeconomics, Ohio State University, USA Columbus for analysing and presenting the survey results

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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