Comparison of Intranasal Dexmedetomidine Versus Intranasal Ketamine as Premedication for Level of Sedation in Children Undergoing Radiation Therapy: A Prospective, Randomised, Double-Blind Study

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Abstract

Objective: Radiation therapy is indicated in many solid tumours in children. Absolute immobility is required to precisely position children for optimal delivery of radiation energy to the target tissues, improve success rate and reduce the damage to nearby normal tissues. Intranasal (IN) administration of drugs is well tolerated, effective and fast acting. The primary aim of the present study was to evaluate the effectiveness of IN ketamine and dexmedetomidine for providing sedation in children before shifting to the radiotherapy suite. The secondary objective was to assess the requirement of propofol dosage in these patients.

Methods: A total of 243 children aged between 1 and 5 years scheduled to undergo external beam radiotherapy were randomised to receive 5 mg kg−1 ketamine (group K, n=80), 2.5 μg kg^{-1} dexmedetomidine (group D, n=85) or 0.5 ml of saline (group S, n=78) in each nostril. After 45 min, sedation score was measured according to the modified Ramsay score (MRS) at the time of shifting for radiation. Time to awakening and time to discharge after the procedure were also noted.

Results: A significantly higher proportion of children in group D (84.7%) achieved an MRS score ≥3 as compared to group K (36.2%) and group S (3.84%). The total propofol dose (mg kg^{-1}) required was significantly less in group D (p<0.01). The patients in group D required more time to awakening, but this difference was not clinically significant.

Conclusion: The present study demonstrated that IN dexmedetomidine is superior to IN ketamine to provide procedural sedation for radiotherapy in children.

Keywords: Dexmedetomidine, intranasal, ketamine, propofol, radiotherapy, sedation

Introduction

Radiation therapy is indicated in many solid tumours in children who require optimal delivery of radiation energy to the target tissues. These patients need to be precisely positioned to ensure absolute immobility for improving the success rate and reducing the damage to nearby normal tissues (1). In addition, during such procedures, the child has to be observed at a distance from the slave monitor outside the radiation main unit; hence, a short acting and reliable drug for sedation is required.

The ideal medication for sedation should have minimum effects on haemodynamics and respiration, rapid onset, fast recovery and make anaesthetic induction with no side effects (2). Various sedation techniques (drugs and routes) for children have been reported in the literature. Each technique has its own advantages and limitations. An intravenous (IV)

access needs to be secured to administer the sedative agents, but it may be difficult in an anxious, crying and fighting child.

Intranasal (IN) premedication avoids the need for securing an IV access in combative children. It is well tolerated, effective and fast acting (3). IN drug delivery reduces first pass metabolism and has been used successfully for fentanyl, ketamine and midazolam premedication (4–6).

Ketamine, an N-methyl-D-aspartate receptor antagonist, causes dissociative anaesthesia and has been successfully used for its sedative and analgesic properties in paediatric patients in various non-operating room settings (7). However, emergence reactions, excessive salivation, nystagmus and vomiting have been frequently cited as reasons to limit its usage (8). Various studies have been mentioned in the literature regarding the usage of IN ketamine for sedation in children (9–11).

Dexmedetomidine is a highly selective α_2-adrenoceptor agonist with anxiolytic, sedative, analgesic and sympatholytic properties. It has been a useful adjunct for perioperative stress (12). There have been few studies quoted in the literature for IN dexmedetomidine in paediatric sedation (13–15).

There is no study in the literature that has previously compared IN dexmedetomidine and IN ketamine for sedation in the radiotherapy suite. We hypothesised that IN dexmedetomidine could be better than IN ketamine for providing sedation in children's undergoing radiotherapy.

Methods

The study was conducted in a tertiary cancer institute in AIIMS, New Delhi, India. The study was approved by the institute ethics committee (IECPG/13/00/2017) in accordance to the World Medical Association Declaration of Helsinki. The study was registered at the Clinical Trial Reg-

Main Points:

- Absolute immobility is required to precisely position children receiving radiotherapy. There has been no clear consensus on an ideal premedicant and the route of administration in these subset of population.

- There is no study in the literature that has previously compared Intranasal (IN) dexmedetomidine and IN ketamine for sedation in the radiotherapy suite.

- Children receiving IN dexmedetomidine (Group D) achieved better sedation score (MRS) than children receiving IN Ketamine (Group K) at the time of shifting to radiotherapy suite.

- The required propofol dosage for conduct of radiotherapy procedure was also significantly less in group D than in group K.

- Though the awakening and discharge times after the proceedure were longer in group D compared to group K, it was clinically not significant.

istry of India (registration no.: CTRI/2002/18/011781, date: 8 February 2018).

Children aged between 1 and 5 years scheduled to undergo external beam radiotherapy were included in the present study. Written informed consent was obtained from the parents/guardians after explaining the study protocol. Children with a history of severe cardiorespiratory, central nervous and hepatic system derangements were excluded from the study. All children underwent a routine pre-anaesthetic check-up before inclusion and maintained nil per oral as per the recent American Society of Anesthesiologists guidelines (16).

Study procedure

Randomisation, blinding and group allocation
Children were randomised in the pre-radiotherapy waiting area by a computer-generated randomisation schedule, and concealment was done by a sealed opaque envelope technique. The envelopes were opened by an independent anaesthesiologist who was not involved in the conduct of the study.

Children were randomised to receive IN ketamine 5 mg kg^{-1} (concentration of 50 mg mL^{-1}Aneket; Neon Laboratories Ltd., Mumbai, India) after diluting it to 1 mL or 1.5 mL with normal saline depending on the dosage, with half of the test drug volume in each nostril (group K, n=80), or IN dexmedetomidine 2.5 µg kg^{-1} (concentration of 100 µg mL^{-1} Dextomid; Neon Laboratories Ltd.) after diluting it to 1 mL with saline and distributing 0.5 mL in each nostril (group D, n=85) or IN saline (group S, n=78), receiving 0.5 mL of normal saline in each nostril.

One anaesthetist prepared the study drug and handed it over to the second anaesthetist who conducted the procedure and was blinded to the group allocation. Eutectic Mixture of Local Anaesthetics was applied 45 min before securing an IV line in the holding area. Premedication was administered 30 min after securing an IV access.

For IN administration, the child was positioned either in recumbent position in the caregiver's lap or in supine position on the bed. The response of the child to the administration of the sedative agent was assessed by Frankl's behavioural rating (17) (definitely negative: refuses treatment, cries forcefully, expresses overt negativism; negative: reluctant to accept treatment, uncooperative behaviour; positive: accepts treatment with caution and willing to comply; definitely positive: develops good rapport, takes interest, laughs). The child was made to lie down for 5 min after the drug administration for proper absorption of the drug. Any episode of vomiting/spitting out of the drug was recorded.

Following the administration of premedication, electrocardiogram (ECG) and pulse oximeter (SPO_2) were attached, and patients were shifted into the procedural room 45 min later. Sedation score was assessed according to the modified Ramsay score (MRS) scale as per the American Academy of Pediatrics (18) at the time of shifting to the radiotherapy suite (primary outcome) (1-awake, alert with no or minimal cognitive impairment; 2-awake but tranquil, purposeful response to verbal commands at conversational level; 3-appears asleep, purposeful response to verbal commands at conversational level; 4-appears asleep, purposeful response to verbal commands but at louder than usual conversational level or requiring light glabellar tap; 5-asleep, sluggish purposeful responses only to loud verbal commands or strong glabellar tap; 6-asleep, sluggish purposeful responses only to painful stimuli; 7-asleep, reflex withdrawal to painful stimuli only; 8-unresponsive to external stimuli including pain). The child is said to have attained sedation if he remains at least at grade ≥2 at the time of shifting to the radiotherapy suite.

The reaction of the child to parental separation was evaluated according to separation score [1-poor (crying, clinging), 2-fair (crying but not clinging), 3-good (whimpers, easily reassured), 4-awake excellent (easy separation)] (19).

In the procedural room, monitors including ECG and SPO_2 were connected. IV propofol was given at a bolus of 1 mg kg^{-1}, followed by 0.5 mg kg^{-1} additional dosages titrated to immobility in the radiotherapy suite. The dosage of propofol required to achieve the desired level of sedation was noted. Oxygen was administered throughout the procedure through a venturi mask, and expired carbon dioxide was analysed.

Post-procedural monitoring
After the procedure, the patients were nursed in the recovery room, and the times for awakening and discharge were noted. Time for awakening was calculated as the time required after the completion of the procedure till spontaneous opening of the eyes on verbal commands, and discharge time was noted when the child fulfils the discharge criteria (20).

Children were discharged to the ward when heart rate was within 20% of baseline, with airway patent, when they were easily arousable with protective reflexes and if the child could talk or sit up unaided (if age appropriate). Any untoward side effects, such as nystagmus, nausea, vomiting, behavioural changes and haemodynamic disturbances, were noted in the recovery room.

The satisfaction of the parents with the sedation procedure was assessed on a 5-point Likert scale (21) at the time of discharge from the recovery room (1-very dissatisfied, 2-dissatisfied, 3-unsure, 4-satisfied, 5-very satisfied).

Study outcomes
The primary outcome of the study was to evaluate the effectiveness of IN dexmedetomidine in comparison to IN ketamine as premedication for the level of sedation in children at the time of shifting to the radiotherapy suite. The secondary outcomes included propofol dosage requirement, recovery and discharge time between all three groups.

Statistical analysis
In our clinical practice, we have observed that there was an approximately 7% increase in mean sedation score when using dexmedetomidine in comparison to ketamine and 12% increase in sedation scores with dexmedetomidine in comparison to IN saline, hence considering a previous study (22), which has reported the mean sedation score for the dexmedetomidine group as 4.33±0.92. We have assumed approximately 7% less sedation score for the ketamine group than for the dexmedetomidine group (4.02±0.92) and the comparable placebo group with approximately 12% less sedation score than the dexmedetomidine group (3.81±0.92). Using the nQuery version 2.0 software for more than two groups, the required sample size for each group with 5% level of significance and 90% power was 73 (≈75) per group. Our calculated sample size was 225, considering for drop outs and exclusion, and a total of 270 samples were screened for the study. We have recorded each day of radiotherapy procedure for a single patient as a new case, so the sample size of 270 in our study is actually 270 sessions of radiotherapy procedures.

To describe the patient's morbidities condition, the behavioural and clinical data were summarised and analysed using IBM Statistical Package for Social Sciences version 24.0 (IBM SPSS Corp.; Armonk, NY, USA). Since our study involved three groups, for comparison of study parameters, MRS sedation scale, age, weight, time of onset of sedation, propofol dosage and awakening and discharge times were expressed as mean±standard deviation (SD). Number and percentage as appropriate for sex, Frankl's behavioural scale, separation score and satisfaction score have been used. Data were tested for normality using the Kolmogorov–Smirnov test and found to have normal distribution. An ANOVA (Analysis of variance), followed by Bonferroni method, was used to compare the parametric values among the groups for MRS scale, age, weight, propofol dosage, time of onset of sedation and awakening and discharge times. Kruskal–Wallis test, followed by Wilcoxon rank-sum test, was performed to compare the nonparametric values, such as Frankl's behavioural scale, separation score and satisfaction score, whereas Pearson's chi-square test was used to compare the categorical data, such as sex distribution. A p value <0.05 was considered as statistically significant.
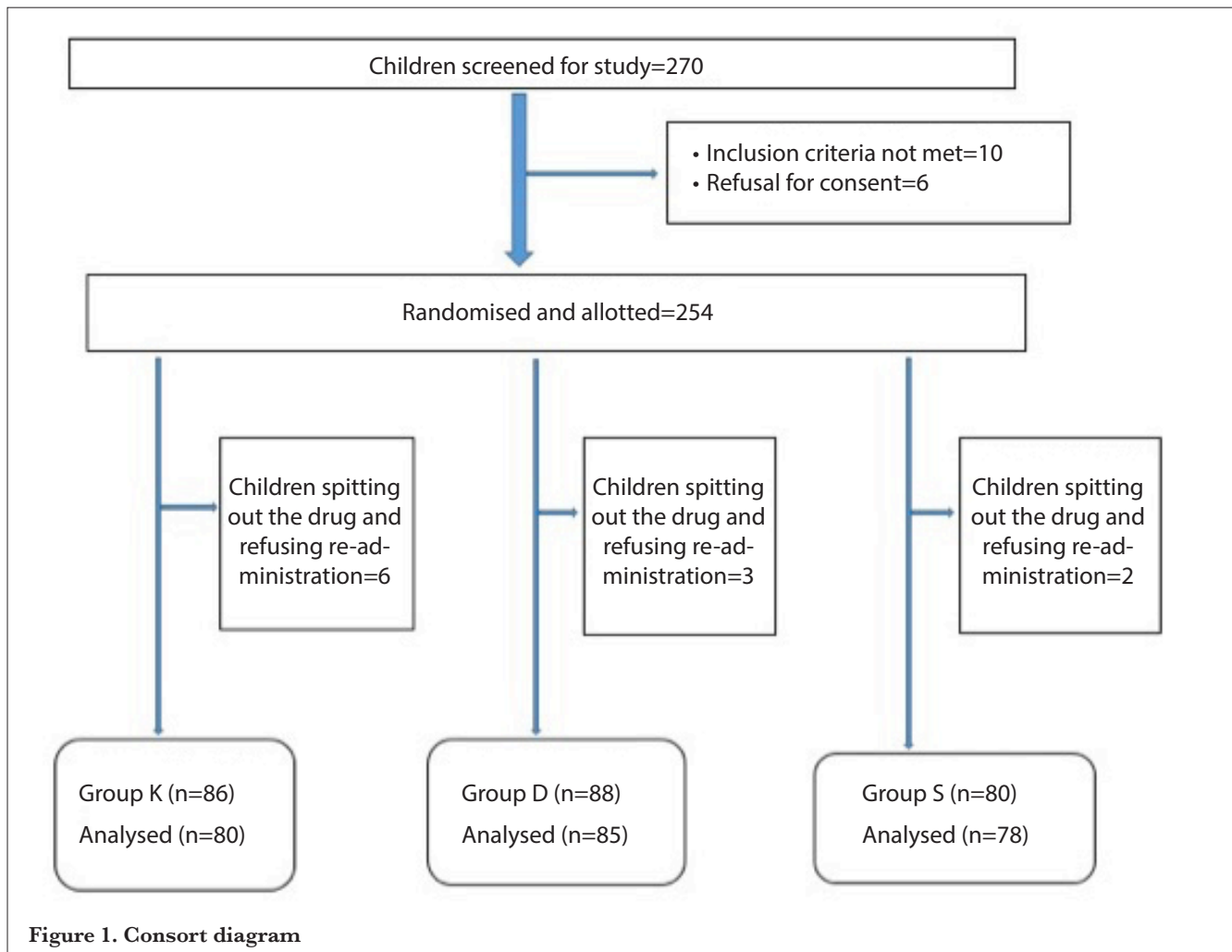
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Figure 1. Consort diagram

Table 1. Demographic parameters among the three groups

Parameter	Group K (n=80)	Group D (n=85)	Group S (n=78)	p
Sex (male/female)	32/48	44/41	33/45	0.271
Age (year) (mean±SD)	3.00±1.102	3.11±1.211	2.78±0.733	0.116
Weight (kg) (mean±SD)	11.16±2.979	11.46±2.918	11.01±2.621	0.594
Pre-sedation heart rate (mean±SD)	124.52±13.535	123.41±16.550	128.54±19.46	0.125
K: ketamine; D: dexmedetomidine; S: saline; SD: standard deviation				

Results

A total of 270 cases were screened, and 260 met the inclusion criteria. After obtaining the informed consent, a total of 254 cases (refusal of informed consent by parents/guardians in six cases) were randomised into three groups. A total of 243 patients successfully completed the studies and were included in the analysis (Figure 1).

The demographic profile was comparable in the three groups. Children in the three groups were comparable with regard to sex, age, weight and pre-sedation vitals (Table 1).

We have found that children in group D achieved better mean MRS score at the time of shifting to the radiotherapy suite than those in group K and group S (Table 2) (p<0.01). It was observed that seven children in group K and 63 patients in group S did not attain the desired MRS scale of ≥2, whereas all the patients in group D achieved the desired MRS scale after premedication.

Children in group D required significantly less dosage of propofol (mg kg⁻¹) for the conduct of the procedure than those in the other two groups (p<0.01). Dexmedetomidine prolonged both awakening and discharge times, though it was clinically non-significant (Table 2).

Table 2. MRS scale, propofol dosage, awakening discharge times, time of onset of sedation, Frankl's rating, separation scoring and satisfaction scale of parents among the three groups

Parameter	Group K (n=80)	Group D (n=85)	Group S (n=78)	p
MRS (mean±SD)	2.28±0.684	3.35±0.797	1.28±0.53	<0.001
Propofol dosage (mg kg^{-1}) (mean±SD)	2.303±1.049	2.083±0.834	3.382±0.961	<0.001
Awakening time (min) (mean±SD)	15.94±7.120	19.76±8.162	14.10±7.462	<0.001
Discharge time (min) (mean±SD)	20.75±6.986	25.12±7.714	19.10±7.418	<0.001
Time of onset of sedation (min) (mean±SD)	22.19±9.89 (n=73)	16.35±6.69 (n=85)	26.00±10.55 (n=15)	<0.001
Frankl's rating (1/2/3/4)	41/23/16/0	32/39/7/7	35/37/6/0	0.041
Separation scoring (1/2/3/4)	45/17/15/3	47/6/31/1	40/28/8/2	0.01
Satisfaction scale (1/2/3/4/5)	4/1/25/42/8	3/1/27/49/5	13/1/26/35/3	0.027

MRS: modified Ramsay score; K: ketamine; D: dexmedetomidine; S: saline; SD: standard deviation

Table 3. Sensitivity analysis

Parameter	Group K (n=86)	Group D (n=88)	Group S (n=80)	p
MRS (mean±SD)	2.17±0.723	3.28±0.870	1.29±0.532	<0.001
Propofol dosage (mg kg^{-1}) (mean±SD)	2.40±1.090	2.11±0.832	3.39±0.953	<0.001
Awakening time (min) (mean±SD)	16.05±6.908	19.83±8.110	14.31±7.494	<0.001
Discharge time (min) (mean±SD)	20.93±6.796	25.28±7.670	19.44±7.630	<0.001

MRS: modified Ramsay score; K: ketamine; D: dexmedetomidine; S: saline; SD: standard deviation

Table 4. Comparison of side effects among the three groups

Side effects	Group K (n=80)	Group D (n=85)	Group S (n=78)
Desaturation in the recovery room (SpO$_2$ <85%)	1	0	0
Vomiting (≥1 episodes after shifting to the ward)	5	0	1
Behavioural changes (increased agitation, excessive crying, screaming in the ward)	1	2	0

K: ketamine; D: dexmedetomidine; S: saline

Frankl's behavioural rating of a child's response to the administration of premedication showed that 71/85 patients in group D, 64/80 patients in group K and 72/78 patients in group S have shown either a definitely negative or a negative response to the administration of premedication, but all of the children had accepted the IN drug reasonably well. Separation scoring prior to placing on radiotherapy table was acceptable in 92.9% (79/85) of children in group D, 78.7% (63/80) of children in group K and 48.7% (38/78) of children in group S (p<0.01). In addition, parental satisfaction scale after the procedure was satisfactory in 63.5% (54/85) in group D, 62.5% (50/80) in group K and 48.7% (38/78) in group S (p=0.027) (Table 2).

We have also performed sensitivity analysis by including the previously excluded six patients in group K (n=86), 3 patients in group D (n=88) and two patients in group S (n=80) and re-analysed MRS score, propofol dosage and awakening and discharge times between the groups (Table 3).

None of the children had any adverse events after the administration of premedication in the pre-radiotherapy waiting room. Five children in group K and one child in group S had vomiting after being discharged to the ward which was relieved with IV injection ondansetron (0.08 mg kg^{-1}) bolus. One child in group K and two children in group D had increased agitation with screaming in the ward which spontaneously improved after consoling for some time. One patient in group K had desaturation till 85% after the procedure which improved after giving jaw thrust and oxygen administration for 5 min in the recovery room (Table 4).

Discussion

We observed from our study that IN dexmedetomidine provides better sedation score at the time of shifting to the radiotherapy suite, had better parental separation and required less dosage of propofol (mg kg^{-1}) for induction of anaesthesia than IN ketamine. Though the awakening and discharge

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times were slightly prolonged with dexmedetomidine, it was clinically not significant.

Our results are in accordance with previous studies (2, 23) that reported better sedation levels with using IN dexmedetomidine than IN ketamine. Gyanesh et al. (23) reported that the mean dosage of propofol in children receiving IN dexmedetomidine is less than that in children receiving IN ketamine. In addition, children receiving both IN dexmedetomidine and ketamine required significantly less amounts of propofol than children receiving IN saline.

In our study, the times to onset of sedation (mean±SD) were 16.35±6.69 min and 22.19±9.89 min in group D and group K, respectively. This was similar to that reported by Gupta et al. (13) who found duration of onset of sedation (14.3±3.4 min) with IN dexmedetomidine in a dosage of 1 µg kg⁻¹. Miller et al. (14) in 2016 reported the time of onset of IN dexmedetomidine to be 25–33 min in doses ranging from 1.0 to 3.0 µg kg⁻¹. Ibrahim et al. (2) reported the time to onset of action with IN ketamine as 14.65±4.9 min. This is less than our results probably due to a higher dosage of IN ketamine (7 mg kg⁻¹) used in their study.

We reported mean discharge times (mean±SD) with IN dexmedetomidine as 25.12±7.71 min in comparison to IN ketamine which was 20.75±6.99. Our results were in agreement with Mason et al. (24) and Ghai et al. (25) who reported mean recovery times of 32 min and 39 min with IN dexmedetomidine, respectively. We have observed that awakening and discharge times were slightly prolonged in our patients though the difference has been clinically insignificant. Dexmedetomidine has been used in the dose ranges of 1–3 µg kg⁻¹ (14, 15, 26). Therefore, based on the previous evidence, we have used a dosage of 2.5 µg kg⁻¹, which has been effectively used in previous studies (2, 15, 27, 28). Behrle et al. (15) in 2017 used a similar dose of 3 µg kg⁻¹ in children undergoing procedural sedation and have reported prolonged post-procedural sleep time in the dexmedetomidine cohort compared to the non-dexmedetomidine cohort. However, in view of increased discharge and awakening times, further studies may be required with lesser dosage and equivalent outcomes.

Dexmedetomidine has been used for various purposes, such as premedication, intensive care sedation, procedural sedation, use as an adjuvant in regional techniques, intra-articular use, obese patients, awake intubation, paediatric use and monitored anaesthesia care, with considerable safety (29). Sedation techniques in the radiotherapy suite need to be effective, reliable and safe with minimal failure rates. In providing anaesthesia in remote locations, the main concerns to the provider would be to administer the agent causing minimal haemodynamic compromise and respiratory depression, and none of these complications have been reported in our study. Hence, dexme-

detomidine can be safely administered in radiation therapy settings too, where the child could be monitored remotely in the console area. We found that IN dexmedetomidine can serve all these purposes and at the same time decrease the need for additional IV sedatives, with minimum side effects. On the other hand, ketamine may lead to excessive salivation, tachycardia, hallucination and increased intracranial pressure.

We have done an extensive review of the literature, but the equi-sedative dosages for IN dexmedetomidine and IN ketamine have not been described. Previous researchers have used IN dexmedetomidine in dosing ranges of 1.0–3.0 µg kg⁻¹ (14, 15, 26). IN ketamine has been used in dosing ranges of 3–9 mg kg⁻¹ (9, 30). Therefore, we have used dosages of 5 mg kg⁻¹ and 2.5 µg kg⁻¹ for IN ketamine and IN dexmedetomidine, respectively.

It is usually the practice to secure an IV access after the administration of premedication in children, but in our case as per radiation oncologist protocol, the child receives radiation therapy five times in a week, Monday to Friday. Thus, as per convention, IV cannula is secured on Monday and continued till Friday. As securing an IV cannula is not required every day, to maintain uniformity even on the first day, we have administered IN sedation after securing an IV cannula. We usually wait till the child stops crying after securing an IV cannula and then administer the IN drops.

There was a concern of the effectiveness of mucosal atomisation devices for better absorption of drugs into the systemic route in comparison to syringe administration for the IN route. Li et al. (31) studied the pharmacokinetics and pharmacodynamics of IN and IV dexmedetomidine and concluded that the bioavailability and degree of sedation is similar with atomisation or nasal drops technique of administration. An atomiser was not available in our institute so we have used 1 ml syringe to administer IN drug.

In our study, 10 out of 80 children receiving IN ketamine and seven out of 85 children receiving IN dexmedetomidine required no additional propofol dosing. Though the mean propofol dosage requirement was less in children receiving dexmedetomidine, it is still not good enough alone to accomplish radiotherapy procedures as a significant number of children still required dosages of IV propofol for the procedure. The administration of additional dosages of IV propofol may lead to hypotension, apnoea >60 s, circulatory collapse and other side effects; none of our patients experienced them. However, we advise that IV sedatives have to be used with extreme caution in remote areas.

Side effects observed in our study were clinically insignificant. A common concern with the usage of dexmedetomidine is the possibility of bradycardia after administration. Though

10 children who received IN dexmedetomidine had decrease in heart rate, it was not clinically significant that atropine administration was necessary.

There is a probability of accumulation of study drugs due to repeated administration over consecutive days in our patients. Previous data from healthy volunteers revealed that the elimination of half-lives ($t_{1/2}$) with IN dexmedetomidine was 114 (107–151) min (median (range)) (32), and IN ketamine over dosages of 3–9 mg kg^{-1} was ranging from 100 to 120 min (33). It is a known fact that after 5 $t_{1/2}$, 97% of the drug is eliminated from the body. Hence, after approximately 10 h of administration, a normal person would clear out the premedication drugs used in our study. Thus, the possibility of the accumulation of premedication drugs on consecutive days in our study is unlikely.

We have found a statistically significant difference in the Frankl's scale (p=0.04) during the acceptance of premedication drug, but this was not clinically significant.

Study limitations

Our study has a few limitations. First, we have recorded each day of the radiotherapy procedure for a single patient as a new case, so the sample size of 243 in our study is actually 243 sessions of radiotherapy procedures. We administered the study drugs using a syringe rather than an atomiser device. However, the efficacy of mucosal atomisation devices over syringe-based administration for IN drugs has not been elaborated and needs to be further researched. As we do not know about the equi-sedative dosages of IN ketamine and IN dexmedetomidine, we have used conventional dosages.

Conclusion

The present study demonstrated that IN dexmedetomidine is superior to IN ketamine in providing satisfactory sedation in children for radiation therapy. IN dexmedetomidine premedication may provide various advantages, such as reduction of additional IV sedative dosing and thus reducing their additional side effects. Dexmedetomidine appears to prolong the awakening and recovery times slightly, but this was not clinically significant.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of All India Institute of Medical Sciences (IECPG/13/00/2017).

Informed Consent: Written informed consent was obtained from the parents of the children who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Conception – P.S., S.M., S.B., R.G., S.J.B., N.G., V.K., M.A.K.; Design – P.S., S.M., S.J.B.; Supervision – P.S., S.M., S.B., R.G., S.J.B., N.G., V.K., M.A.K.; Materials – P.S., S.M., S.B., R.G., S.J.B., N.G., V.K., M.A.K.; Data collection and processing – P.S., S.M., R.G., S.J.B.; Analysis and interpretation – P.S., S.M., R.G., M.A.K.; Literature review – P.S., S.M., R.G., S.J.B., N.G.; Writing manuscript - P.S., S.M., R.G., S.J.B., N.G.; Critical review – P.S., S.M., S.B., R.G., S.J.B., N.G., V.K., M.A.K.

Conflict of Interest: The authors have no conflicts of interest to declare.

References

1. Buehrer S, Immoos S, Frei M, Timmermann B, Weiss M. Evaluation of propofol for repeated prolonged deep sedation in children undergoing proton radiation therapy. Br J Anaesth 2007; 99: 556-60. **[CrossRef]**

2. Ibrahim M. A prospective, randomized, double blinded comparison of intranasal dexmedetomodine vs intranasal ketamine in combination with intravenous midazolam for procedural sedation in school aged children undergoing MRI. Anesth Essays Res 2014; 8: 179-86. **[CrossRef]**

3. Arora P, Sharma S, Garg S. Permeability issues in nasal drug delivery. Drug Discov Today 2002; 7: 967-75. **[CrossRef]**

4. Kogan A, Katz J, Efrat R, Eidelman LA. Premedication with midazolam in young children: a comparison of four routes of administration. Pediatr Anesth 2002; 12: 685-9. **[CrossRef]**

5. Weber F, Wulf H, El Saeidi G. Premedication with nasal s-ketamine and midazolam provides good conditions for induction of anesthesia in preschool children. Can J Anesth 2003; 50: 470-5. **[CrossRef]**

6. Finkel JC, Cohen IT, Hannallah RS, Patel KM, Kim MS, Hummer KA, et al. The effect of intranasal fentanyl on the emergence characteristics after sevoflurane anesthesia in children undergoing surgery for bilateral myringotomy tube placement. Anesth Analg 2001; 92: 1164-8. **[CrossRef]**

7. Mason KP, Michna E, DiNardo JA, Zurakowski D, Karian VE, Connor L, et al. Evolution of a protocol for ketamine-induced sedation as an alternative to general anesthesia for interventional radiologic procedures in pediatric patients. Radiology 2002; 225: 457-65. **[CrossRef]**

8. Weksler N, Ovadia L, Muati G, Stav A. Nasal ketamine for paediatric premedication. Can J Anaesth 1993; 40: 119-21. **[CrossRef]**

9. Hall D, Robinson A. Intranasal ketamine for procedural sedation. Emerg Med J 2014; 31: 789-90. **[CrossRef]**

10. Poonai N, Canton K, Ali S, Hendrikx S, Shah A, Miller M, et al. Intranasal ketamine for procedural sedation and analgesia in children: A systematic review. PLoS One. 2017; 12: e0173253. **[CrossRef]**

11. Diaz JH. Intranasal ketamine preinduction of paediatric outpatients. Paediatr Anaesth 1997; 7: 273-8. **[CrossRef]**

12. Gertler R, Brown HC, Mitchell DH, Silvius EN. Dexmedetomidine: a novel sedative-analgesic agent. Proc Bayl Univ Med Cent 2001; 14: 13-21. **[CrossRef]**

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13. Gupta A, Dalvi NP, Tendolkar BA. Comparison between intranasal dexmedetomidine and intranasal midazolam as premedication for brain magnetic resonance imaging in pediatric patients: A prospective randomized double blind trial. J Anaesthesiol Clin Pharmacol 2017; 33: 236-40.

14. Miller JW, Divanovic AA, Hossain MM, Mahmoud MA, Loepke AW. Dosing and efficacy of intranasal dexmedetomidine sedation for pediatric transthoracic echocardiography: a retrospective study. Can J Anesth Can Anesth 2016; 63: 834-41. [CrossRef]

15. Behrle N, Birisci E, Anderson J, Schroeder S, Dalabih A. Intranasal Dexmedetomidine as a Sedative for Pediatric Procedural Sedation. J Pediatr Pharmacol Ther 2017; 22: 4-8. [CrossRef]

16. Practice Guidelines for Preoperative Fasting and the Use of Pharmacologic Agents to Reduce the Risk of Pulmonary Aspiration: Application to Healthy Patients Undergoing Elective ProceduresAn Updated Report by the American Society of Anesthesiologists Task Force on Preoperative Fasting and the Use of Pharmacologic Agents to Reduce the Risk of Pulmonary Aspiration*. Anesthesiology 2017; 126: 376-93. [CrossRef]

17. Riba H, Al-Zahrani S, Al-Buqmi N, Al-Jundi A. A Review of Behavior Evaluation Scales in Pediatric Dentistry and Suggested Modification to the Frankl Scale. EC Dental Science 2017; 16: 269-75.

18. Coté CJ, Wilson S. Guidelines for monitoring and management of pediatric patients before, during, and after sedation for diagnostic and therapeutic procedures: update 2016. Pediatr Dent 2016; 38: 13-39. [CrossRef]

19. Gharde P, Chauhan S, Kiran U. Evaluation of efficacy of intranasal midazolam, ketamine and their mixture as premedication and its relation with bispectral index in children with tetralogy of fallot undergoing intracardiac repair. Ann Card Anaesth 2006; 9: 25-30.

20. American Academy of Pediatrics, American Academy of Pediatric Dentistry, Coté CJ, Wilson S, Work Group on Sedation. Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures: an update. Pediatrics 2006; 118: 2587-602. [CrossRef]

21. Vagias WM. Likert-type Scale Response Anchors Citation. Clemson International Institute for Tourism. Res Dev Dep Parks Recreat Tour Manag Clemson Univ. 2006;

22. Bhat R, Santhosh MCB, Annigeri VM, Rao RP. Comparison of intranasal dexmedetomidine and dexmedetomidine-ketamine for premedication in pediatrics patients: A randomized double-blind study. Anesth Essays Res 2016; 10: 349-55. [CrossRef]

23. Gyanesh P, Haldar R, Srivastava D, Agrawal PM, Tiwari AK, Singh PK. Comparison between intranasal dexmedetomidine and intranasal ketamine as premedication for procedural sedation in children undergoing MRI: a double-blind, randomized, placebo-controlled trial. J Anesth 2014; 28: 12-8. [CrossRef]

24. Mason KP, Zurakowski D, Zgleszewski SE, Robson CD, Carrier M, Hickey PR, et al. High dose dexmedetomidine as the sole sedative for pediatric MRI. Pediatr Anesth 2008; 18: 403-11. [CrossRef]

25. Ghai B, Jain K, Saxena AK, Bhatia N, Sodhi KS. Comparison of oral midazolam with intranasal dexmedetomidine premedication for children undergoing CT imaging: a randomized, double-blind, and controlled study. Paediatr Anaesth 2017; 27: 37-44. [CrossRef]

26. Yuen VM, Hui TW, Irwin MG, Yao TJ, Chan L, Wong GL, et al. A randomised comparison of two intranasal dexmedetomidine doses for premedication in children. Anaesthesia 2012; 67: 1210-6. [CrossRef]

27. Miller J, Xue B, Hossain M, Zhang M-Z, Loepke A, Kurth D. Comparison of dexmedetomidine and chloral hydrate sedation for transthoracic echocardiography in infants and toddlers: a randomized clinical trial. Paediatr Anaesth 2016; 26: 266-72. [CrossRef]

28. Li BL, Ni J, Huang JX, Zhang N, Song XR, Yuen VM. Intranasal dexmedetomidine for sedation in children undergoing transthoracic echocardiography study--a prospective observational study. Paediatr Anaesth 2015; 25: 891-6. [CrossRef]

29. Naaz S, Ozair E. Dexmedetomidine in Current Anaesthesia Practice- A Review. J Clin Diagn Res 2014; 8: GE01-4. [CrossRef]

30. Tsze DS, Steele DW, Machan JT, Akhlaghi F, Linakis JG. Intranasal Ketamine for Procedural Sedation in Pediatric Laceration Repair: A Preliminary Report. Pediatr Emerg Care 2012; 28: 767-70. [CrossRef]

31. Li A, Yuen VM, Goulay-Dufaÿ S, Sheng Y, Standing JF, Kwok PCL, et al. Pharmacokinetic and pharmacodynamic study of intranasal and intravenous dexmedetomidine. Br J Anaesth 2018; 120: 960-8. [CrossRef]

32. Weerink MA, Struys MM, Hannivoort LN, Barends CR, Absalom AR, Colin P. Clinical pharmacokinetics and pharmacodynamics of dexmedetomidine. Clin Pharmacokinet 2017; 56: 893-913. [CrossRef]

33. Malinovsky JM, Servin F, Cozian A, Lepage JY, Pinaud M. Ketamine and norketamine plasma concentrations after i.v., nasal and rectal administration in children. Br J Anaesth 1996; 77: 203-7. [CrossRef]