

## Premedication with Nasal Sedation as an Aid for Behaviour Management in Dental Procedures for Children

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### Abstract

**Background:** In recent times major advancements in techniques, technologies and materials have resulted in benefits in the everyday clinical practice of dentistry, despite these gains, anxiety related to dental treatments in children is a problem suffered by many patients worldwide, and it remains a significant challenge in providing dental care.

**Patients and methods:** One hundred children, aged 5-8 years, presenting for simple extraction procedures were selected to participate in the study and randomly divided into two groups (50 patients each). Control group (the C group): were treated by conventional treatment (non-pharmacological behaviour management) while sedation group (the S group) were premeditated by intranasal sedation (3 mg/kg Ketamine and 0.5 mg/kg Midazolam). Perioperative sedative effects, pain, anxiety level changes were assessed, also Time of procedural were recorded.

**Results:** Children premeditated with intranasal sedation (S group) achieved significantly lower sedation levels ( $p=0.042$ ), pain score ( $p=0.032$ ), lower anxiety levels ( $p=0.036$ ), and easier child-parent separation ( $p=0.029$ ) than C group also, The S group showed decrease in the mean of the total time of procedural 20 minute  $\pm$  3.7 versus 25 min  $\pm$  2.8 in C group and this decrease was statistically significant in comparison with the C group ( $p<0.05$ ).

**Conclusion:** Intranasal sedation using ketamine and midazolam was associated with lower sedation levels, lower anxiety levels, and easier child-parent separation at the time of transferring patients to the operating room than children who were not sedated. Moreover the time needed to perform a simple extraction under intranasal sedation is significantly less than that of regular chair side procedure, which suggests possible balanced cost benefit.

**Keywords:** Dental; Anxiety; Children; Ketamine; Midazolam; Sedation

### Introduction

In recent times major advancements in techniques, technologies and materials have resulted in benefits in the everyday clinical practice of dentistry. Despite these gains, anxiety related to dental treatments in children is a problem suffered by many patients worldwide, and it remains a significant challenge in providing dental care [1]. The prevalence of dental anxiety is 5-20% in most of the populations which is seen more in children and this tends to decrease as age advances [2,3].

Dental anxiety is defined as a feeling of apprehension about dental treatment that is not necessarily connected to a specific external stimulus [4]. According to Chadwick and Hosey, anxiety is common in children and the symptoms of anxiety are dependent on the age of the child. Toddlers exhibit anxiety by crying, while older children manifest anxiety in other ways. Common anxieties among children include fearing the unknown and being worried about a lack of control both of which can occur with dental examination and treatment [5].

Many non-pharmacological behaviour management techniques have been introduced to manage anxious children such as Tell-show-do, behaviour shaping and positive reinforcement and modeling techniques [6].

Procedural sedation is frequently used for both diagnostic and therapeutic procedures, whether urgent or elective. It provides safe and effective relieve of pain and distress associated with dental procedures .It involves the use of one or more sedative and analgesic agents to relieve pain , anxiety and to control motor activity in patients undergoing diagnostic and therapeutic procedures [7].

The pre-anesthetic management of children can be a challenge for the anesthesiologist. Premedication should provide effective anxiolytics and conscious sedation to improve the conditions for parental separation [8].

Midazolam and Ketamine have been used as premedicants for children by different routes. The IM route is painful and therefore rarely used in pediatric patients. Rectal and oral application of midazolam [9,10] and ketamine [11] are widely used. With an onset time between 15 and 30 minutes, [11-13] they show a rather slow onset of sedation, and first pass hepatic metabolism which results in a low and unpredictable systemic availability [14,15]. Furthermore, both

routes can be used successfully only in children who generally accept premedication, otherwise either spitting out (oral route) or immediate defecation (rectal route) may result [8]. The intranasal route is preferable since it obviates the need for intravenous access, is easily accessible and allows a more rapid rate of absorption compared to the oral route [16,17].

Intranasal Midazolam for premedication in preschool children was first described and advocated by Wilton and colleagues [18] ketamine as a premedicant has been successfully administered via nasal route as well [19,20]. Combinations of Midazolam and Ketamine given orally [21,22] or rectally [12] have been shown to result in better premedication than either drug alone. Audenaert and colleagues investigated the cardiac effects of different pediatric premedication regimes and recommended the combination of intranasally administered Ketamine 5 mg/kg and Midazolam 0.2 mg/kg [23].

S-ketamine, one of the two ketamine isomers is now available. It has twice the anaesthetic potency of racemic ketamine [24]. Thus, a 50% reduction of the dosage is possible to achieve comparable results. Because of faster elimination of s-Ketamine, better control of anaesthesia will be provided [25]. Furthermore, it produces less psychomimetic side effects than r-Ketamine [26], the other enantiomer of racemic ketamine [27].

Ketamine differs from other sedatives and analgesics in that it does not display a dose-response continuum. Instead, there is a dissociative threshold where, when reached, administration of additional ketamine does not result in a deeper state of sedation. Also, Ketamine have some advantages of preservation of respiratory reflexes and an intrinsic positive inotropic effect. It is an excellent analgesic, sedative and amnesic agent [28,29].

Midazolam-Ketamine combination has been used for different pediatric procedures for its anxiolytic and analgesic effects, in order to obtain more analgesia, less hypotension, the use of lower doses of drugs and, consequently a lower risk of respiratory depression [30].

The effects of intranasal administered s-Ketamine and Midazolam for pediatric premedication remain unclear [8].

## Aim of study

This study was conducted to evaluate the perioperative sedative effects, anxiety level changes and the ease of child-parent separation (as a primary end-point) and to evaluate success of the first attempt for simple tooth extraction and the time needed to achieve the whole procedural (as a second end point).

## Patients and Methods

One hundred children, aged 5-8 years, presenting for simple extraction procedures were selected to participate in the study and randomly divided into two groups (50 patients each). Exclusion criteria included children who have ASA classification III or higher, a known allergy to benzodiazepines. An upper respiratory tract infection with nasal discharge, a known liver disease or respiratory distress and known allergy to Ketamine.

Risks, possible discomforts and benefits were explained to the parents and they were required to sign an informed consent form prior to the procedure. To ensure patient safety, the clinic was well equipped with age-appropriate emergency equipment which included a

ventilation bag and mask, Oxygen and a suction device. Resuscitation equipment and medications, including reversal agents were available.

The research team included two anesthetist, four pedodontists and two nurses. The anesthetist administered the medication, two pedodontists performed the procedure, and two nurses continuously monitored the patients and documented the vital signs. Two pedodontists recorded modified Yale preoperative anxiety scale short form (mYPAS-SF) [31] modified observer pain scale (MOPS) and modified from the observer assessment of alertness and sedation scale (MOAA/S).

**Control group (the C group):** This included 50 patients who were treated by conventional treatment (non-pharmacological behaviour management) while sedation group (the S group) included 50 patients who were treated by intranasal sedation (3 mg/kg Ketamine and 0.5 mg/kg Midazolam).

With respect to sample size calculation, it was calculated using PS (version 3.0.43, Department of Biostatistics, Vanderbilt University, located in Nashville, United States) with the following parameters: level of anxiety used as the primary goal where power of the study was 80%, SD was  $\pm 2$ , mean was 20, and  $\alpha$  error was 0.05.

## Study Design

The study was conducted in 3 stations.

### Station 1 (pre-extraction)

(The S group) received 3 mg/kg Ketamine and 0.5 mg/kg Midazolam intranasally in both nostrils by the anesthetist using a mucosal atomizing device (MAD) in the waiting area as follows: After drawing the full medication dose in luer-lock syringe, using a free hand to hold the head stable the tip of the MAD gently but firmly against the nostril aiming slightly up and outward (towards the top of the ear) then the syringe plunger is rapidly compressed to deliver the medication into each nostril. Sedation and anxiety levels were assessed before administration of the study drug (baseline values) and at the time of transferring to the dental clinic. Also, the ease of child-parent separation at the time of transferring to the dental clinic was assessed. Sedation level was assessed using a 6-point sedation scale, which was modified from the observer assessment of alertness and sedation scale (MOAA/S) (Table 1) [32].

Anxiety level was assessed using the modified Yale preoperative anxiety scale- short form (mYPAS-SF) [31]. The mYPAS is an instrument developed from the modified yale preoperative anxiety scale (mYPAS) and enables the evaluation of anxiety in children preoperatively and at induction of anaesthesia. It contains 22 specific behaviors within four domains (activity, emotional expressivity, state of arousal, and vocalization,) that are reflective of an anxious state and can be performed by an observer in less than 1 min. The range is 22.92-100 with an increased score being indicative of greater anxiety [31].

### Station 2 (extraction)

In the dental clinic, alphacaine topical anesthetic was applied, and a carpule 1.7 ml of Ubistesin-Forte was given to the child, and then extraction was done using extraction forceps. The level of pain was assessed using modified observer pain scale (MOPS) [33]. The score ranges from 2-10. The higher the score, it differs from objective pain score (OPS) of Broadman et al. by substituting posture assessment for

blood pressure, (MOPS=sum points of 5 parameters, minimum score=0 and maximum=10) the higher the score the greater the pain experience for the child Together with (MOAA/S) and (mYPAS) for sedation and anxiety

### Station 3 (post-extraction)

After extraction was completed, the level of sedation, pain and anxiety were reassessed again using the same scores, and the vital signs were also monitored until the patients met the criteria for safe discharge.

The child should be alert, with stable vital signs, and should be able to talk and sit unaided as appropriate for his age. The parents were provided with discharge instructions including information about the appropriate diet, medications, and activity level for the child.

Monitoring of vital signs including Oxygen saturation, heart rate, and blood pressure were continuously measured throughout the whole procedure also the duration of three stations was recorded and number of children failed to proceed for extraction and postponed for other session was counted for both groups.

Agitated	6
Responds readily to name spoken in normal tone (alert)	5
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly and/or repeatedly	3
Responds only after mild prodding or shaking	2
Does not respond to mild prodding or shaking	1
Does not respond to deep stimulus	0

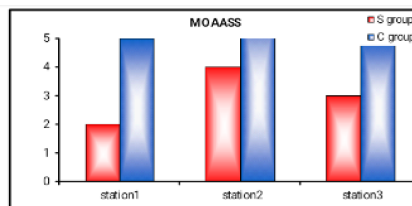
**Table 1:** Modified Observer’s Assessment of Alertness Sedation Scale (MOAASS).

### Results

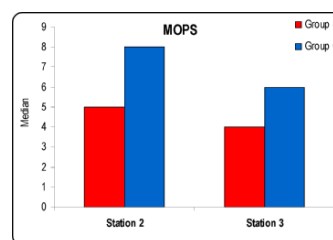
Statistical analysis was performed using computer software statistical package for the social science (SPSS, version 17.0; SPSS Inc., Chicago, Illinois, USA). Description of quantitative (numerical) variables was performed in the form of mean ± SD. Description of qualitative (categorical) data was performed in the form of number of cases and percent. Error bars represent 95% confidence interval. Analysis of unpaired numerical variable was performed using the unpaired Student t-test, whereas analysis of paired numerical variables was performed

The two groups were comparable with respect to the following variables; age, gender, weight (Table 2) also, baseline sedation and anxiety levels were comparable in both groups at time of transferal for dental clinic for extraction.

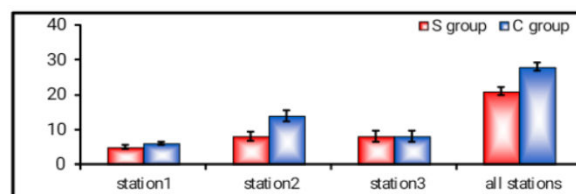
The S group achieved lower anxiety level (Table 3) and lower sedation levels (Figure 1) furthermore the S group had significantly lower level of pain during and after extraction compared to same value of control group (Figure 2). Finally the separation time (duration of station 1) and time of extraction (station 2) in S group was shorter while the time of recovery almost the same in both group (Figure 3).



**Figure 1:** Modified Observer’s Assessment of Alertness Sedation Scale (MOAASS).



**Figure 2:** Modified objective pain scale (MOPS).



**Figure 3:** Total time of the whole procedural.

### Demographic data

With respect to age, gender, and body weight of children, there were no statistically significant differences between both groups ( $p > 0.05$ ) (Table 2).

	S group	C group	Tests	
			X2/t	P-value
<b>Sex</b>				
Female	20 (20.0%)	17 (17.0%)	0.172	0.678
Male	30 (30.0%)	33 (33.0%)		
<b>Age</b>				
Range	7-Jun	8-May	1.166	0.246
Mean ± SD	7.05 ± 0.72	7.21 ± 0.65		
<b>Weight</b>				
Range	14-35	15-34	1.37	0.173

Mean ± SD	24.84 ± 2.3	24.15 ± 2.72		
C group: control group; S group: nasal sedation group; SD: standard deviation, %: percentage, showed no statistically significant differences between both groups (p >0.05)				

**Table 2:** Demographic data.

Variable	Groups	S (sedation)	C (control)	Student t test	P value
mYPAS-SF (base line)	Mean	56.69	55.53	1.348	0.180
	± SD	3.70	4.83		
mYPAS-SF station 1	Mean	42.44	65.44	58.808	<0.001*
	± SD	1.91	2.00		
mYPAS-SF station 2	Mean	64.6	67.93	3.219	0.005*
	± SD	5.68	4.25		
mYPAS-SF station 3	Mean	46.6	48.78	2.633	0.009*
	± SD	3.25	4.87		

mYPAS: Data presented as median; mYPAS-SF: was significantly less in group S (p<0.05); C group: control group; S group: nasal sedation group; mYPAS-SF: modified Yale preoperative anxiety scale short form; station 1: pre-extraction, station 2: during extraction; station 3: post extraction; \*: statically significant

**Table 3:** Anxiety level in the 2 groups at pre-intra and post extraction phase.

**Modified observer's assessment of alertness sedation scale (MOAASS):** Median MOAASS pre-extraction after sedation was 2 in group S, while it was 5 in group C while during extraction was 4 in group S and 5 in C group also, postoperatively was 4 versus 5 in group S and C respectively and this was a significant difference (p<0.05) show in figure 1.

**Modified observer pain scale (MOPS):** Median MOPS during extraction was 5 in group S and 8 in C group and, post-extraction was 4 versus 6 in group S and C respectively. This was significantly difference (p<0.05) shown in figure 2.

**Duration of the all procedural:** The S group showed decrease mean of the total time of procedural (time of separation time of operation time of discharge) 20 minute ± 3.7 versus 25 min ± 2.8 in C group and this decrease was statistically significant in comparison with the C group (p<0.05) (Figure 3).

## Discussion

Anxiety and fear are the main concern of a child being introduced to dental care and procedure. Children fear the unknown and this reflects on their behaviour in the dental office. Success depends on the ability to manage this behaviour to be able to introduce treatment and minimize psychological trauma to the child.

Non pharmacological behaviour management techniques have been introduced to manage anxious children during the first and second dental visits. Although most of children can be managed with different suitable behavioural techniques pharmacological support may be the answer for resistant uncooperative children. This may include the use

of anxiolytic medications, conscious or deep sedation or general anesthesia [34].

When managing uncooperative, very young, or extremely resistant or anxious fearful children the techniques taught in most of the pediatric dental training programs include protective stabilization, sedation, and general anesthesia [34]. The merging between both stabilization and sedation is more or less controversial yet it is reported to be the alternative approach in providing a young child with a safe and comfortable treatment experience [35,36].

As far as sedation is included in dental treatment for children different drugs were used including both Midazolam and Ketamine. Midazolam is a short-acting benzodiazepine strongly recommended for pediatric dental sedation with reported success rates [37-41]. Another three studies reported that the combination between midazolam and ketamine is both safe and effective [42-44] Nitrous oxide gas was not used in the study due to manufacturing issues in Egypt.

Basic concept of the study was that the simple extraction procedure is a short technique wise procedure, doesn't consume much time yet very scary for children. The choice of general anesthesia was evaluated to be extreme with respect to the little time needed and cost benefit of the procedure. Moderate sedation was the management of choice the midazolam-ketamine combination was introduced intra nasally being more rapid in absorption compared to oral route and eliminating the need for intra venous access [16,45]. Intranasal midazolam-ketamine combination was reported as the sedation drug that makes gastric aspirates easier to perform in children. Also successful sedation with intranasal ketamine was achieved during pediatric laceration repair [46].

The midazolam-ketamine combination dose used in our study was 3 mg/kg ketamine and 0.5 mg/kg midazolam. As the use of ketamine alone might result in agitated, confuse child even in a transient manner the use of the midazolam reduces the potential of those effects and causes amnesia [47], while the ketamine eliminates the burning sensation of midazolam with its anesthetic effect [45].

During the pre-extraction phase (station 1) child separation was evaluated to be an easy process went smoothly without any tension from the child's part. Our results meet the results discussed by Weber F et al. [8] that stated that sedation with ketamine improves conditions of parent-child separation.

Children vital signs were monitored during the whole procedure through oxygen saturation and heart rate for their safety; they were recorded every 5 minutes. Children in both groups maintained normal spo2 and HR values. In our study the sedation level changes were assessed using a 6 point sedation scale, which was modified from the MOAA/S and proved to be sensitive in the assessment of sedation level changes overtime in children [32]. Anxiety level changes were assessed by means of the mYAPS-SF in order to measure child's anxiety before, during and after the extraction and whether the whole experience was satisfying or traumatic. Results of our study as regards mYPAS-SF showed (group S) 42.44+1.9, 64.6+5.68, 46.6+3.25 versus (group C) 65.44+2.00, 67.93+4.25, 48.78+4.87 in the three station respectively. Median MOAASS pre-extraction after sedation was 2 in (group S), while it was 5 in (group C) while during extraction was 4 in (group S) and 5 in (C group) also, postoperatively was 4 versus 5 in group S and C respectively and this was a -significant difference (p<0.05) showed in figure 1 and table 3 which in turn suggests that the sedation is of



significant help in managing and reducing anxiety in children during dental procedure.

These results agree with Weber et al. [8] in the success of ketamine in reduction of anxiety in children. Also Moreira et al. [47] stated the success of the drug combination in behavioral management of the children during dental procedures describing them to be calm. They supplied exact dose of the combination yet orally.

We found that the sedated children experienced less pain during and after extraction when compared to control group (lower MOPS)

Median MOPS during extraction was 5 in groups S and 8 in C group and, post-extraction was 4 versus 6 in group S and C respectively. This was significantly difference ( $p < 0.05$ ) shown in figure 2 this may be related to ketamine persistent analgesic effects with preserving patient arousability.

Children were monitored till they fulfil age appropriate baseline criteria for a safe discharge, alertness, and stable vital signs. Most of our patients were discharged with vital signs HR 100-130 and oxygen saturation 97-100%. Our results agree with Weber et al. [8] and Audenaert et al. [23] stating that the intranasal administration of the drug combination results in no significant cardiovascular or respiratory side effects. In our study we used low ketamine dose to avoid the reported side effects including nausea, vomiting, and respiratory depression. Buonsenso et al. agrees with our results stating that the only side effect observed in the sedation group was the post-sedation agitation [46]. Other authors disagree stating that younger children required higher dosage in milligrams per kilogram of Ketamine for adequate sedation [48]. This may be explained by the faster metabolism and renal clearance leading to a shorter half-life of Ketamine in children compared to adults [28,49,50].

By the end of the process the time needed to perform a simple extraction under intranasal sedation using ketamine midazolam combination is significantly less (20.8 minutes and SD 3.68) than that of regular chair side procedure (26.8 minutes and SD 4.18), which suggests possible balanced cost benefit due to the successful elimination of child's anxiety before and during the procedure without affection of the time of recovery which later on protects the child from painful history as the combination of Midazolam-Ketamine causes amnesia on account of the Midazolam component.

## Conclusion

Intranasal sedation using ketamine and midazolam was associated with lower sedation (better moderate sedation levels), lower anxiety levels, and easier child-parent separation at the time of transferring patients to the operating room than children who were not sedated. Moreover the time needed to perform a simple extraction under intranasal sedation is significantly less than that of regular chair side procedure, which suggests possible balanced cost benefit.

## Ethics

The study was conducted in the pediatric dentistry department at Faculty of Oral and Dental Medicine, Future University, Egypt (FUE) from September 2014 to May 2015 after obtaining the approval from university ethics committee and written informed consent from the patients' parents or legal guardian.

## Clinical Implications

- Anxiety related to dental treatments in children is a problem suffered by many patients worldwide, and it remains a significant challenge in providing dental care. Midazolam-Ketamine combination has been used for different pediatric procedures for its anxiolytic and analgesic effects, in order to obtain more analgesia, less hypotension, the use of lower doses of drugs and, consequently a lower risk of respiratory depression. The effects of intranasal administered s-Ketamine and Midazolam for pediatric premedication remain unclear
- We studied intranasal sedation for pediatric dentistry versus conventional non pharmacological chair side techniques. The child's anxiety, pain, together with procedure time under intranasal sedation is significantly less than that of regular chair side. This suggests possible balanced cost benefit. The impact of intranasal sedation on the simple dental procedure done under general Anesthesia due to dental anxiety and failure of conventional chair side techniques should be further investigated.

## References

1. Nigam AG, Marwah N, Goenka P, Chaudhry A (2013) Correlation of general anxiety and dental anxiety in children aged 3 to 5 years: A clinical survey. *J Int Oral Health* 5:18-24.
2. Gatchel RJ, Ingersoll BD, Bowman L, Robertson MC, Walker C (1983) The prevalence of dental fear and avoidance: a recent survey study. *J Am Dent Assoc* 107: 609-610.
3. Locker D, Liddell AM (1991) Correlates of dental anxiety among older adults. *J Dent Res* 70: 198-203.
4. Folan MO1, Idehen EE, Ojo OO (2004) The modulating effect of culture on the expression of dental anxiety in children: a literature review. *Int J Paediatr Dent* 14: 241-245.
5. Chadwick BL, Hasey MT (2003) Child taming: How to manage children in dental practice. London: Quintessence Publishing 127.
6. Gupta A, Marya CMI, Bhatia HP, Dahiya V (2014) Behaviour management of an anxious child. *Stomatologija* 16: 3-6.
7. Krauss B, Krauss B, Green S (2014) Procedural sedation and analgesia in children. *N Engl J Med* 370: e23.
8. Weber F, Wulf H, el Saeidi G (2003) Premedication with nasal s-ketamine and midazolam provides good conditions for induction of anesthesia in preschool children. *Can J Anaesth* 50: 470-475.
9. Spear RM, Yaster M, Berkowitz ID, Maxwell LG, Bender KS, et al. (1991) Preinduction of anesthesia in children with rectally administered midazolam. *Anesthesiology* 74: 670-674.
10. Feld LH, Negus JB, White PF (1990) Oral midazolam preanesthetic medication in pediatric outpatients. *Anesthesiology* 73: 831-834.
11. Gutstein HB, Johnson KL, Heard MB, Gregory GA (1992) Oral ketamine preanesthetic medication in children. *Anesthesiology* 76: 28-33.
12. Warner DL, Cabaret J, Velling D (1995) Ketamine plus midazolam, a most effective paediatric oral premedicant. *Paediatr Anaesth* 5: 293-295.
13. Sekerci C, Danmez A, Ateay Y, Okten F (1996) Oral ketamine premedication in children (placebo controlled double-blind study). *Eur J Anaesthesiol* 13: 606-611.
14. Malinovsky JM1, Lejus C, Servin F, Lepage JY, Le Normand Y, et al. (1993) Plasma concentrations of midazolam after i.v., nasal or rectal administration in children. *Br J Anaesth* 70: 617-620.
15. Malinovsky JM, Servin F, Cozian A, Lepage JY, Pinaud M (1996) Ketamine and norketamine plasma concentrations after i.v., nasal and rectal administration in children. *Br J Anaesth* 77: 203-207.
16. Calligaris L, Davide Z, Alessandra M, De Bortoli R, Chiaretti A, et al. (2011) Concentrated midazolam for intranasal administration: a pilot study. *Pediatr Emerg Care* 27: 245-247.

17. Chiaretti A, Barone G, Rigante D, Ruggiero A, Pierri F, et al. (2011) Intranasal lidocaine and midazolam for procedural sedation in children. *Arch Dis Child* 96: 160-163.
18. Wilton NC, Leigh J, Rosen DR, Pandit UA (1988) Preanesthetic sedation of preschool children using intranasal midazolam. *Anesthesiology* 69: 972-975.
19. Weksler N, Ovadia L, Muati G, Stav A (1993) Nasal ketamine for paediatric premedication. *Can J Anaesth* 40: 119-121.
20. Diaz JH (1997) Intranasal ketamine preinduction of paediatric outpatients. *Paediatr Anaesth* 7: 273-278.
21. Funk W, Jakob W, Riedl T, Taeger K (2000) Oral preanaesthetic medication for children: double-blind randomized study of a combination of midazolam and ketamine vs midazolam or ketamine alone. *Br J Anaesth* 84: 335-340.
22. Lökken P, Bakstad OJ, Fonnélöp E, Skogedal N, Hellsten K, et al. (1994) Conscious sedation by rectal administration of midazolam or midazolam plus ketamine as alternatives to general anesthesia for dental treatment of uncooperative children. *Scand J Dent Res* 102: 274-280.
23. Audenaert SM, Wagner Y, Montgomery CL, Lock RL, Colclough G, et al. (1995) Cardiorespiratory effects of premedication for children. *Anesth Analg* 80: 506-510.
24. Hempelmann G, Kuhn DF (1997) [Clinical significance of S-(+)-ketamine]. *Anaesthesist* 46 Suppl 1: S3-7.
25. Adams HA, Werner C (1997) [From the racemate to the eutomer: (S)-ketamine. Renaissance of a substance?]. *Anaesthesist* 46: 1026-1042.
26. Doenicke A, Kugler J, Mayer M, Angster R, Hoffmann P (1992) [Ketamine racemate or S-(+)-ketamine and midazolam. The effect on vigilance, efficacy and subjective findings]. *Anaesthesist* 41: 610-618.
27. Kress HG (1997) [Mechanisms of action of ketamine]. *Anaesthesist* 46 Suppl 1: S8-19.
28. Green SM, Johnson NE (1990) Ketamine sedation for pediatric procedures: Part 2, Review and implications. *Ann Emerg Med* 19: 1033-1046.
29. Green SM, Krauss B (2000) The semantics of ketamine. *Ann Emerg Med* 36: 480-482.
30. Bahetwar SK, Pandey RK, Saksena AK, Chandra G (2011) A comparative evaluation of intranasal midazolam, ketamine and their combination for sedation of young uncooperative pediatric dental patients: a triple blind randomized crossover trial. *J Clin Pediatr Dent* 35:415-420.
31. Jenkins BN, Fortier MA, Kaplan SH, Mayes LC, Kain ZN (2014) Development of a short version of the modified Yale Preoperative Anxiety Scale. *Anesthesia and Analgesia*, September 119: 643-650.
32. Chernik DA, Gillings D, Laine H, Hender J, Silver JM (1990) Validity and reliability of the Observer's Assessment of Alertness/Sedation Scale: study with intravenous midazolam. *J Clin Psychopharmacol* 10: 244-251.
33. Wilson GA, Doyle E (1996) Validation of three paediatric pain scores for use by parents. *Anaesthesia* 51: 1005-1007.
34. Nathan JE (1989) Management of the difficult child: a survey of pediatric dentists' use of restraints, sedation and general anesthesia. *ASDC J Dent Child* 56: 293-301.
35. Adair SM, Rockman RA, Schafer TE, Waller JL (2004) Survey of behavior management teaching in pediatric dentistry advanced education programs. *Pediatr Dent* 26: 151-158.
36. Vargas KG, Nathan JE, Qian F, Kupietzky A (2007) Use of restraint and management style as parameters for defining sedation success: a survey of pediatric dentists. *Pediatr Dent* 29: 220-227.
37. Kupietzky A (2004) Strap him down or knock him out: Is conscious sedation with restraint an alternative to general anaesthesia? *Br Dent J* 196: 133-138.
38. Lima AR, da Costa LR, da Costa PS (2003) A randomized, controlled, crossover trial of oral midazolam and hydroxyzine for pediatric dental sedation. *Pesqui Odontol Bras* 17: 206-211.
39. Heard C, Smith J, Creighton P, Joshi P, Feldman D, et al. (2010) A comparison of four sedation techniques for pediatric dental surgery. *Paediatr Anaesth* 20: 924-930.
40. Shapira J, Kupietzky A, Kadari A, Fuks AB, Holan G (2004) Comparison of oral midazolam with and without hydroxyzine in the sedation of pediatric dental patients. *Pediatr Dent* 26: 492-496.
41. Day PF, Power AM, Hibbert SA, Paterson SA (2006) Effectiveness of oral midazolam for paediatric dental care: a retrospective study in two specialist centres. *Eur Arch Paediatr Dent* 7: 228-235.
42. Wan K, Jing Q, Zhao JZ (2006) Evaluation of oral midazolam as conscious sedation for pediatric patients in oral restoration. *Chin Med Sci J* 21: 163-166.
43. Roelofse JA, Joubert JJ, Roelofse PG (1996) A double-blind randomized comparison of midazolam alone and midazolam combined with ketamine for sedation of pediatric dental patients. *J Oral Maxillofac Surg* 54: 838-844.
44. Cagiran E, Eyigor C, Sipahi A, Koca H, Balcioglu T, et al. (2010) Comparison of oral Midazolam and Midazolam-Ketamine as sedative agents in paediatric dentistry. *Eur J Paediatr Dent* 11: 19-22.
45. Baygin O, Bodur H, Isik B (2010) Effectiveness of premedication agents administered prior to nitrous oxide/oxygen. *Eur J Anaesthesiol* 27: 341-346.
46. Chiaretti A, Barone G, Rigante D, Ruggiero A, Pierri F, et al. (2011) Intranasal lidocaine and midazolam for procedural sedation in children. *Arch Dis Child* 96: 160-163.
47. Buonsenso D, Barone G, Valentini P, Pierri F, Riccardi R (2014) Utility of intranasal Ketamine and Midazolam to perform gastric aspirates in children: a double blind placebo controlled randomized study. *BMC Pediatr* 14: 67.
48. Moreira TA, Costa PS, Costa LR, Jesus-Franca CM, Antunes DE (2013) Combined oral midazolam ketamine better than midazolam alone for sedation of young children: a randomized controlled trial. *Int J Paediatr Dent* 23: 207-215.
49. Riavis M, Laux-End R, Carvajal-Busslinger MI, Tschäppeler H, Bianchetti MG (1998) Sedation with intravenous benzodiazepine and ketamine for renal biopsies. *Pediatr Nephrol* 12: 147-148.
50. Grant IS, Nimmo WS, McNicol LR, Clements JA (1983) Ketamine disposition in children and adults. *Br J Anaesth* 55: 1107-1111.