

Conscious Sedation for Management of Dental Anxiety in Children: A Systematic Review

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Introduction

Dental procedures have mostly been considered as an anxiety-provoking experience especially in children. The role of previous dental experiences has been one of the major factors to explain dental anxiety and have been linked to increased perception of pain and negative cognitions.¹ Studies have confirmed that children with high dental anxiety have reported significantly more traumatic past experiences than individuals with lower dental anxiety.²

Behavioural management and prevention, coupled with local anaesthesia when required, form the foundation of the delivery of anxiety free treatment to children.³ The pediatric dentist uses a variety of pharmacological and non-pharmacological behaviour management techniques to reduce the anxiety of children and to improve their cooperation. Pharmacological behaviour management

technique include conscious sedation and general anaesthesia and non-pharmacological behaviour technique include symbolic modelling, desensitization, tell-show-do, visual imagery. Drugs that are used include inhalational agents such as nitrous oxide, orally or parenterally administered midazolam, other benzodiazepines, tramadol, zolpidem, sevoflurane, ketamine.⁶

Nitrous oxide inhalation sedation is one of the preferred pharmacological behaviour management technique for the management of anxious paediatric dental patients, with anxiolytic and sedative effects combined with varying degree of analgesia and muscle relaxation.⁴ Midazolam is a benzodiazepine sedative capable of inducing sleep while acting as an effective anxiolytic, muscle relaxant, and amnesic agent. Oral midazolam at

doses between 0.5 mg/kg to 0.75 mg/kg act as sedative agent to manage apprehensive pediatric dental patients.¹⁰

Sevoflurane is a volatile anaesthetic agent with a sweet, non-pungent odour that can also be used for conscious sedation. Studies showed that 40-70% nitrous oxide and 0.6- 0.8% Sevoflurane produced comparable amnesia and sedation.⁵

Ketamine is a drug with a bioavailability of only 16% when administered orally. In low dosages, it produces variable anxiolytic results and in higher dosages is associated with psychomimetic and sympathomimetic side effects. The combination of midazolam and ketamine when administered orally maintains the anxiolysis provided by midazolam and adds the sedative and analgesic properties of ketamine, while reducing the undesirable side-effects.⁷

Zolpidem, a non-benzodiazepine drug, has been used singly and with tramadol in producing conscious sedation due to its rapid absorption on oral administration, strong sedative-hypnotic action, anxiolytic/amnesiac properties, and short elimination half life.⁸

Although dental anxiety is a well-known condition that can be managed both with pharmacological and non-pharmacological intervention, available research on this topic offers a heterogeneous and undefined picture. Anxiety improvement during dental treatment is often included only as secondary outcome in trial protocols, with different outcome measures. Hence, the aim of this systematic review is to formulate evidence on efficacy of various conscious sedative agents on the anxiety level of children during dental procedure.

Research question

What is the efficacy of different conscious sedative agents in the management of dental anxiety level during

dental treatment?

Materials and Method

Information Sources and Search Strategy: This review was carried out following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines. The protocol for this review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) with registration ID CRD42021275956.

Eligibility Criteria

Inclusion Criteria

1. Randomised control trial conducted during 1991-2021.
2. Randomised control trials on conscious sedation agents on children undergoing dental treatment.
3. Children of age group 3 to 10 years.

Exclusion Criteria

1. Case reports, Case series, none randomised control trials.
2. Review of Literature and animal studies.
3. Articles in other language than English.

Only studies with the following requirements were included in the study:

Type of participants: Children with anxiety requiring sedation before any dental treatment.

Type of intervention: Inhalational nitrous oxide combined with intravenous/intranasal (iv/in) midazolam, ketamine, tramadol and zolpidem conscious sedation before dental treatment

Comparison: Inhalational nitrous oxide or midazolam used along with sevoflurane, tramadol, ketamine and zolpidem for conscious sedation before dental treatment

Outcome: Primary outcome: The efficacy of different conscious sedative agent in the management of dental anxiety level during dental treatment.

Secondary outcome: the behaviour changes exhibited by anxious children treated under various conscious sedative agents.

Search Strategy

A thorough literature search was conducted and primary database used was PubMed, Cochrane library, Google scholar and Directory of Open Access Journal. The key words used were Conscious sedation, nitrous oxide, midazolam, anxiety, haupt scale. Year of study selected was from 1991 to 2021, and only studies published in the English language were included in the present review.

Data collection

Three investigators were involved in extracting key data from the included articles. For each article, study features (i.e. study design, year of publication, country, number and age of enrolled patients), type of sedation, and anxiety measures were extracted. First two investigators collected and screen the records and third investigator checked the extracted data. The decision whether to involve a paper or not was reached through discussion. During selection of articles, the reviewers were blinded to the journals and the authors of the journals. Kappa coefficient used to test reliability amongst reviewers regarding data extraction was found to be highly reliable. ($k > 0.91$).

Risk of bias assessment

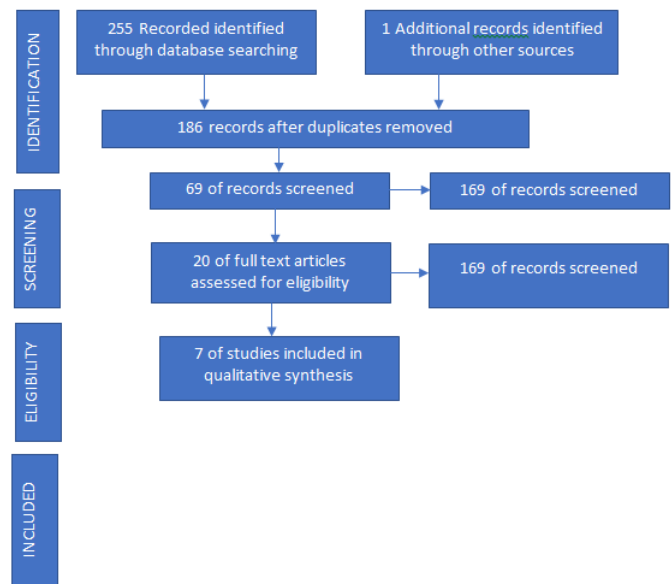
Two investigators independently appraised the risk of bias of the included studies by using the criteria reported in the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2). Five specific domains related to risk of bias of RCTs were assessed with signalling questions as yes, probably yes, no, probably no. The risk of bias was categorized as high, low, or some concern. Any

inconsistencies were resolved by consensus with the third investigator.

Results

Study Selection: The search identified 256 articles from digital database and manual search. After excluding 236 articles full text assessment were carried out for 20 articles. Of these 13 were excluded due to different design or different outcome measures and this review included a total of 7 randomised control trials.

Prisma Flow Chart



Study characteristics

The analysis included seven RCTs based on the inclusion and exclusion criteria. Characteristics of included studies are reported in Table 1. The drugs that are used for conscious sedation included nitrous oxide, midazolam, sevoflurane, ketamine, zolpidem and tramadol. Studies investigated patient reporting anxiety and behaviour of child during sedation.

Table 1

| Sn. | Author | Year | Country | Type of study | Comparison group | Control | Methodology | Summary of study |
|-----|---|------|---------|---------------|---|---------------------------------|---|---|
| 1 | P. A. Averley N. M. Girdler, S. Bond, N. Steen and J. Steele | 2004 | UK | RCT | nitrous oxide + midazolam + sevoflurane | inhaled medical air + midazolam | 697 were recruited and randomly assigned to three groups: group 1 – a combination of inhaled medical air and titrated intravenous midazolam group 2 – a combination of inhaled 40% nitrous oxide in oxygen and titrated intravenous midazolam group 3 – a combination of an inhaled mixture of sevoflurane 0.3% and nitrous oxide 40% in oxygen with titrated intravenous midazolam. | The lowest saturation of 94% was recorded in one child in Group 1. Heart rates and blood pressure remained \pm 20% of normal base values throughout treatment and recovery for every patient. |
| 2. | I. E. Musani N. V. Chandan | 2015 | INDIA | RCT | midazolam | nitrous oxide | 30 children was sedated with a combination of either oral midazolam and nitrous oxide–oxygen sedation or intranasal midazolam and nitrous oxide–oxygen sedation at subsequent dental treatment visits. During the treatment procedure, recorded scales for drug acceptability, onset of sedation, acceptance of nasal mask, sedation, behavioural, safety, overall behaviour and alertness. | The results did not show any statistically significant differences. All the parameters were highly satisfactory. |
| 3. | Ilasrinivasan, Jyothsna V Setty, Shyamachalam, Priya Mendiretta | 2018 | INDIA | RCT | midazolam + ketamine | nitrous oxide | 30 children were divided into 2 groups, oral midazolam-ketamine group- 0.25mg/ kg midazolam with 3mg/kg ketamine in combination and Nitrous oxide-oxygen | The results found no statistically significant differences between the groups in all the parameters except for the duration of sedation and the time taken to achieve |

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| | | | | | | | group -nitrous oxide oxygen inhalation. The parameters evaluated were the drug/ mask acceptance, need for the use of a physical restraint. Houpt's sedation. | maximum sedation which were higher in oral MK group than the Nitrous oxide oxygen inhalation group. |
| 4. | Bandana Koirala, R.K. Pandey ,A.K. Saksen, Rakesh Kumar and Shivalal Sharma. | 2006 | NEPAL | RCT | Midazolam | Ketamine + Zolpidem + Tramadol | Patients were randomly assigned into: Midazolam (I), Ketamine (II), Zolpidem (III), Midazolam plus Ketamine (IV), Midazolam plus Tramadol (V) and Zolpidem plus Tramadol (VI) groups of 20 each. Onset of action, level of sedation, ease of treatment completion, recovery time, and post-operative amnesia were assessed for all and compared. | Midazolam plus ketamine was found the most effective combination providing a fast and adequate analgo-sedation in anxious and uncooperative child patients. |
| 5. | K. E. Wilson, N. M. Girdler and R. R. Welbury | 2006 | UK | RCT | midazolam | nitrous oxide | children aged 5–10 years were randomly allocated to be given nitrous oxide 30% in oxygen or oral midazolam 0.3 mg.kg) at the first visit, the other technique being used at the second visit. Vital signs, sedation levels and behavioural scores were recorded, and postoperative recall and satisfaction were reported by the patients | Physiological parameters remained within acceptable clinical limits for both types of sedation. |
| | J. M. ThompsonN. Neave M. C. Moss A. B. Scholey K. Wesnes and N. M. Girdler | 1997 | UK | RCT | midazolam | nitrous oxide | On each of three separate visits, patients performed a computerised test battery to determine baseline cognitive | Relative to baseline performance, midazolam administration produced significantly slower reaction times |

| | | | | | | | | |
|--|---|------|-------------|-----|----------------------|----------------|--|---|
| | | | | | | | performance. Then, following administration of either midazolam, nitrous oxide, or no drug, patients re-performed the test battery. Finally, patients completed visual analogue scales assessing their subjective mood state. | compared with nitrous oxide and no-drug conditions. |
| | Joji Sado-Filho, Karolline Alves Viana, Patrícia Corrêa-Faria, Luciane Rezende CostaID, Paulo Sucasas Costa | 2019 | SWITZERLAND | RCT | ketamine + midazolam | oral midazolam | Children under seven years of age, were randomized into three groups: (KMIN) intranasal ketamine and midazolam; (KMO) oral ketamine and midazolam; or (MO) oral midazolam. The dental sedation appointments were videotaped, and the videos were analyzed using the Ohio State University Behavioral Rating Scale (OSUBRS) to determine the success of the sedation in each group. | Children's baseline and the dental sedation session characteristics were balanced among groups. |

Risk of bias in included studies

The study used the two-part tool to address the five specific domains (namely, Randomization process, Deviations from intended interventions, Missing outcome data, Measurement of the outcome, Selection of the reported result). Two review authors undertook the risk of bias assessment independently and in duplicate as part of the data extraction process. After taking into account additional information provided by the authors of the trials, studies were grouped into the following categories (**Figure 2 and Figure 3**). There was a good reliability between the two reviewers with a high kappa coefficient ($k > 0.89$). We completed a 'Risk of bias'

table & summary for each included study. After analysis of risk of bias it was observed that the domains had shown that the included studies were at low risk of bias. After analysis of risk of bias it was observed that the randomization process was unclear in some studies while the other domains had shown that the included studies were at low risk of bias.

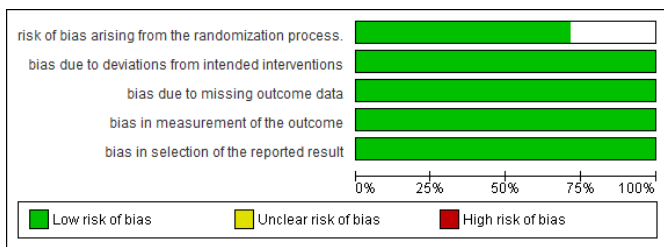


Figure 2: Risk of bias graph: Review authors' judgments about each risk of bias item presented as percentages across all included studies.

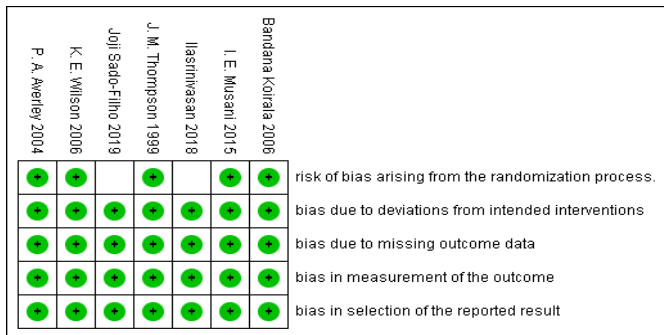


Figure 3: Risk of bias summary: Review authors' judgments about each risk of bias item for each included study.

Discussion

This review highlights the efficacy of different sedative agents in the management of dental anxiety level during dental treatment. Conscious sedation lowers patient anxiety, reduced pain, increases patient satisfaction and inhibit gag reflex. This review assess the efficacy of conscious sedative agents in reducing the child anxiety and effect of various conscious sedation drugs in improving the behaviour of child during a dental treatment.

In a study by Averly et al, successful treatment in nitrous oxide midazolam group were not significantly greater than those in midazolam alone group with an odds ratio of 6.33, p-value did not reach statistical significance (p = 0.075) whereas nitrous oxide sevoflurane and midazolam were significantly greater than those in nitrous oxide midazolam group, with an odds ratio of

3.94. There was no difference (p = 0.48) between the groups for the level of co-operation recorded and also differences in recovery times were not statistically significant (p = 0.26).⁵ There was no statistical significance in child perception of pain (p = 0.95) and anxiety in recovery (p = 0.98) or parent's satisfaction (p = 0.5). The combination of inhalation sedation and intravenous midazolam rather than intravenous midazolam alone, resulting in a higher rate of successfully completed treatment, reduces the dose of midazolam required and produces good amnesia.⁵ Sivaramakrishnan et al stated that nitrous oxide inhalational sedation has been reported as an effective sedation to reduce dental treatment-induced fear and anxiety.¹ N₂O-O₂ inhalation sedation under different concentrations reduces the anxiety of the patient and produces adequate sedation with vital signs within normal limits.¹⁰

According to the study by Musani et al, there was a significant difference (p> 0.001) between the time of onset of sedation, with intranasal administration of midazolam being significantly quicker than oral administration of midazolam. This indicates the better efficacy of this route.⁶ The difference between the overall behaviour in the two groups were not statistically significant (p = 0.348). The intranasal route of midazolam administration has a quick onset of action and a quick recovery of the patient from sedation compared to the oral route. Both intranasal and oral administrations of midazolam were equally effective in reducing the anxiety during dental treatment.⁶ The oral route of drug administration was better accepted than the intranasal route.¹¹

Ilasreenivasan et al, evaluated the efficacy of nitrous oxide compared with midazolam and ketamine, a

statistically significant difference was found between the two groups in terms of the time taken to reach the maximum sedation and duration of sedation. ($p < 0.001$)

The time taken to reach maximum sedation was longer with the MK group (33 ± 9.4 min) than N group (27 ± 3.3 min). The duration of sedation as measured from the onset of drug administration till complete recovery and was found to be higher with the MK group (199 ± 24 min). No statistically significant differences was found between the two groups in terms of behaviour of child during treatment.⁷ An overall success rate of 90% for anxiolysis and behaviour was seen in MK group. Midazolam and ketamine combination was found to be most effective in relieving dental anxiety in children.⁷

A study conducted by Bandana et al, showed sedative score was found to be best for midazolam and ketamine group and children of zolpidem group showed poor sedation, highly significant results were found when compared the scores ($p < 0.001$). No significant change in any of the vitals except in patients who received zolpidem either alone or in combination. In these two groups, mild increase in heart rate and blood pressure were observed during the early period of treatment.⁸

According to this study children of midazolam ketamine group responded excellently in terms of better sedative effect and ease during treatment was found to be the best for conscious sedation in pediatric patients with minimal systemic adverse effects⁸ Corcuera et al concluded after comparing midazolam with other sedative drugs such as diazepam, ketamine, clonidine, and dexmedetomidine in double- and triple-blind randomized studies that midazolam provided the best results in terms of onset time of action, depth of sedation, and anxiolysis.¹²

According to a study by Wilson et al, when maximum sedation score was assessed between poral midazolam

and nitrous oxide, the difference was found to be significant, with midazolam producing a greater level of sedation ($p < 0.001$) and the behaviour of children during sedation was not statistical significance ($p = 0.253$). Hence, this study shows that oral midazolam is as effective as nitrous oxide in producing a satisfactory level of sedation.⁹ According to Thompson et al, midazolam administration produces severe cognitive impairments, not only in the ability to both detect and process information in all of the cognitive tasks. Midazolam administration again produced a significant slowing of reaction time relative to the other conditions ($p = 0.001$).¹⁰ Joji Shado et al, conducted a study comparing oral midazolam and ketamine group with intranasal midazolam and ketamine group, Vital signs remained within normal limits and did not significantly change during the dental sedation procedure ($P > 0.05$). The combination of ketamine and midazolam delivered through the intranasal route improves the behaviour of children undergoing dental treatment and is effective in relieving anxiety in paediatric patients.¹¹

According to this systematic review, overall and peak scores for anxiety were significantly reduced in the nitrous oxide group when compared to midazolam, ketamine, sevoflurane. There was no significant change in any of the vitals except in patients who received zolpidem either alone or in combination, mild increase in heart rate and blood pressure were observed during the early period of treatment.

The combination of midazolam and nitrous oxide proved to be an effective combination, resulting in good to excellent behaviour in uncooperative children. The findings of this review should be interpreted within its limitations, the heterogeneity in comparisons, assessment and outcome measures prevented from

pooling the findings of the included studies. Considerable information on safety and anxiolytic effectiveness of different molecules is available in literature, priority should be given to drugs that showed better anxiolytic effect and lower risk of adverse effects, easiness of use and higher patient satisfaction especially in pediatric patients.

Conclusion

In accordance with this systematic review

- Nitrous oxide inhalational sedation is been reported as an effective sedation to reduce dental treatment induced fear and anxiety.
- Midazolam is as effective as nitrous oxide in relieving dental anxiety in pediatric patients.
- Midazolam when compared with other sedative drugs like sevoflurane, zolpidum, ketamine and tramadol showed midazolam provided the best results in terms of onset time of action, depth of sedation, and anxiolysis.
- Intravenous route of administration of conscious sedation agents was found to have better efficacy than oral route.

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