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Evaluation of Safety of Using Sedative Anesthesia in Pediatric Dentistry: A Systematic Review

Suhael Ahmed[1*], Norah Khalid Alali[2], Ali Salem Alsalem[3], Naif Saleh Alosily[3], Omar Abdulkarim Altorbaq[4], Mashael Alsadoon[1], Ahmed Al Ghamdi[5]

[1]Faculty of College of Dentistry, Riyadh Elm University, Riyadh, Saudi Arabia
[2]Princess Nourah Bint Abdulrahman University, Riyadh, Saudi Arabia
[3]Ministry of Health, Saudi Arabia
[4]Mustaqbal University, Saudi Arabia
[5]Al-Baha University, Al-Baha, Saudi Arabia

ABSTRACT

Children are undergoing diagnostic and therapeutic procedures outside of the operating room on an increasing basis. To accomplish the co-operation and immobilization necessary for the successful completion of these procedures, a variety of methods, including conscious and profound sedation, and in some circumstances general anaesthesia, have been advocated. Safety and wellbeing of the child is the utmost priority while undergoing sedation. Awareness of the choice of the sedative and the dosage required and the potential side effects and hazards of using sedative anesthesia needs to be updated regularly. This systematic review aims to evaluate the safety and effectiveness of commonly used sedative anesthetics for children.

The PICO, population, intervention, comparator and outcomes strategy used was as follows: population, children requiring dental surgical procedures; intervention, oral sedation; comparator, placebo group or other oral drug administered; and outcomes, effectiveness: anxiety, sedation and satisfaction with the treatment and safety: adverse effect, heart rate, respiratory rate, blood pressure and oxygen saturation.

9 articles were selected out of a total of 1135 searched articles from various databases and all 9 were assessed for risk of bias.

Findings of our systematic review implies that to produce a deeper level of sedation, the combination of nitrous oxide, oxygen, and a hypnotic drug is effective, allowing pediatric patients to tolerate with low untoward incidents reported.

Key words: Anesthesia, Pediatric Dentistry

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Corresponding author: Suhael Ahmed

e-mail✉: drsuhael@riyadh.edu.sa

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INTRODUCTION

Children are undergoing diagnostic and therapeutic procedures outside of the operating room on an increasing basis. To accomplish the cooperation and immobilization necessary for the successful completion of these procedures, a variety of methods, including conscious and profound sedation, and in some circumstances general anaesthesia, has been used. Safety and wellbeing of the child is the utmost priority while undergoing sedation. Awareness of the choice of the sedative and the dosage required and the potential side effects and hazards of using sedative anesthesia needs to be updated regularly.

Various patient management strategies have been employed during complex dental procedures that include behavioral techniques, oral sedatives, inhaled nitrous oxide (N2O), and general anesthesia [1,2]. Although widely used, minimal or moderate sedation (for example using oral sedatives and N2O) is unpredictable especially in young children. General anesthesia is more successful, but is invasive and has higher risk. For a number of non and semi-invasive procedures in children, deep sedation provided by non-anesthesiologist specialists has shown

to be safe, efficient and cost effective [2].

According to the Scottish Dental Clinical Effectiveness Program Sedation Guidelines, inhalation sedation (IHS) with nitrous gas is the recommended initial step for patients who require conscious sedation. According to IACSD (2015) data, sedation is effective, safe, and well-tolerated for children as young as four years old. However Sedation brings with it cost, time, and safety concerns. The efficacy of IHS is backed by a foundation of fundamental behavioural management techniques and the safest, most effective amount of nitrous oxide, which enables patients to accept dental treatment.

In adolescents, however, success may be limited by significant oral anxiety and or complex dental treatment, and these patients may require alternative sedation or general anaesthesia [1]. For anxious adolescent patients, it is best to select the most effective treatment with caution, appropriate pharmacological technique for the individual patient to avoid progressing through a range of techniques that may possibly fail based on their clinical and dental need (SDCEP 2017).Many sedative agents including midazolam, temazepam, sevoflurane have been used over a period of time. However propofol remains the most used and most studied agent.

This systematic review aims to evaluate the safety and effectiveness of commonly used sedative anesthetics for children.

MATERIALS AND METHOD

The PICO, population, intervention, comparator and outcomes strategy used was as follows: population, children requiring dental surgical procedures; intervention, oral sedation; comparator, placebo group or other oral drug administered; and outcomes, effectiveness: anxiety, sedation and satisfaction with the treatment and safety: adverse effect, heart rate, respiratory rate, blood pressure and oxygen saturation.

Inclusion criteria

Participant Children requiring dental surgical procedures, such as dental extraction, surgery procedures, pulpotomy and pulpectomy procedures and other dental surgical interventions.

Exclusion criteria

Studies involving adults and studies involving children with respiratory diseases, were excluded.

Outcomes assessed

Primary outcomes

Effectiveness measured by improvement in anxiety by using the Dental Anxiety Scale (DAS), Oral Surgery Confidence Questionnaire (OSCQ) and/or other scales for anxiety symptoms.

Safety measured by the number of participants that reported side effects, number of adverse effects (or adverse drug reactions) and number of participants that dropped out due to side effects.

Secondary outcomes

Secondary outcomes of effectiveness were sedation and satisfaction with the treatment.

Secondary outcomes of safety were heart rate, respiratory rate, blood pressure and oxygen saturation.

Data extraction

The following Electronic databases were searched: Cochrane Central Register of Controlled Trials (CENTRAL), which includes Dentistry and Oral Health Group's Specialized Register, MEDLINE, Excerpta Medica Database (EMBASE) without restrictions on language or publication date, with the search encompassing articles published between inception and June 2022.

Data management

After performing the search strategies on each electronic database, the researchers imported the results from each search into an EndNote library. Duplicate entries were identified and removed.

Study eligibility determination

Relevant data from the eligible studies were independently extracted into Microsoft Excel, using a standardized data extraction form. Four reviewers, working in pairs and independently, selected potentially relevant titles and abstracts and applied the eligibility criteria. Full texts of the potentially eligible articles were obtained. Similarly, the reviewers checked the eligibility of each study. The same reviewers working in pairs and independently, used a standardized and pretested form for data extraction. Subsequently, the reviewers extracted the patient data, methods, interventions and outcomes. We contacted the authors for articles with incomplete methods and results data, if necessary. Disagreements were resolved by consensus and, when necessary, arbitrated by a third reviewer.

Risk of bias

A modified version of the Cochrane collaboration approach for assessing the risk of bias was used. The same reviewers, again in pairs and independently, evaluated the risk of bias for each clinical trial according to randomization; allocation concealment; blinding of patients, health professionals and outcome assessors, incomplete outcome data; selective outcome reporting; and major baseline imbalance characterizing the sample. The same reviewers attributed the standard answers 'definitely yes', 'probably yes', 'probably no' and 'definitely no' for each domain, with 'definitely yes' and 'probably yes' denoting a low risk of bias and 'definitely no' and 'probably no' attributing a high risk of bias. Disagreements were resolved by consensus and, when necessary, arbitrated by a third reviewer.

Data synthesis and analysis of the quality of evidence

A narrative synthesis of the findings was carried out. The extracted data were summarized in the Table 1 and Figure 1. Heterogeneity was explained by drug doses (higher vs lower) with greater effect than expected at

Table 1: Summarized data of the 9 included studies.

Author	Research Design	Research Purpose	Subject	Result	Conclusions
Yee, et al. [3]	Retrospective study (2020)	The database of all paediatric procedural sedations performed in the hospital ED from 01 January 2014 to 31 December 2016 was reviewed to identify cases where intramuscular ketamine sedation was administered for dentists' treatment of oro-dental trauma.	167 intramuscular ketamine sedations were administered by ED doctors for dental treatment of oro-dental trauma. Adverse events were risk stratified using the World SIVA adverse event reporting tool	All dental procedures were successfully completed. Nineteen adverse events were reported (11.4%, n=19) with the most common being emesis (9.0%) followed by transient desaturation (1.8%) and hyper salivation (0.6%).	The data supports the safety and effectiveness of intramuscular ketamine sedation administered by trained ED doctors to facilitate the management of paediatric oro-dental trauma emergencies.
Azevedo,et al. [4]	Randomized Controlled Trial(2013)	To determine the efficacy and safety of 3 different doses of midazolam for sedation in 2- to 4- year-old children with multiple dental needs and negative behavior.	Ten children participated in this crossover, controlled, double-blinded clinical trial, which evaluated their behavior, appointment length and patient response after administration of 3 different doses of midazolam or placebo. Oxygen saturation, heart rate, respiratory rate, and blood pressure were monitored in all sessions.	The use of midazolam allowed for longer appointments, and doses of at least 0.3 mg/kg produced a higher rate of positive behavior overall. No changes in oxygen saturation, heart rate, respiratory rate, and blood pressure were observed.	Midazolam was effective and safe for pediatric sedation in the dosages studied
Dixon, et al. [5]	Case Control (2020)	To evaluate the effect of PRF and Axiostat hemostatic activity after tooth extraction among cardiac patients on antiplatelet medication.	ASA Classifcation and Children's Fear Survey Schedule— Dental Subscale (CFSS-DS) completed pre-operatively. Behaviour ratings of the Frankl and Houpt scales were recorded followed by post-operative questionnaire and telephone consultation.	55 patients were recruited for the study, of which 49 (mean age 14.67 years) completed the sedation study and were treated safely with no post-operative complications	Propofol TCI sedation is an effective treatment modality for the management of dentally anxious adolescents as a safe alternative to general anaesthesia
Mittal, et al. [6]	Randomized double blinded Trial (2013)	to compare incidence of intraoperative and postoperative complications in propofol versus ketofol.	Subjects in group A (n=20) received 0.25 mg/kg IV ketamine (Ketalar® Parke Davis, India; 10mg/mL) and 1 mg/kg IV propofol (Diprivan® Astra Zeneca Pharmaceuticals; 10mg/mL) as bolus dose mixed with 2% of 1 ml lignocaine followed by 25-75 µg/kg/min of propofol infusion. Subjects in group B (n=20) received 1-1.5mg/ kg IV bolus of propofol mixed with 2% of 1 ml lignocaine followed by 25-75 µg/ kg/min of propofol infusion	The mean procedure time in propofol and ketofol group was 34.20 minutes and 38.40 minutes respectively	Propofol is superior to ketofol in terms of safety as it showed fewer adverse effects than the latter as observed in the present study. Ketamine is to be chosen with caution while operating in proximity to airway i.e. oral cavity
Shabbir, et al. [7]	Randomized double blinded Trial (2007)	The purpose was to evaluate two sedation protocols during dental sessions in anxious children.	Twenty children (36 to 84 months old) who exhibited "definitely negative" behavior according to the Frankl scale were assigned to receive oral chloral hydrate (40 mg/kg) (Group I) or Diazepamβ (5 mg) (Group II).	Overall behavior in the placebo session was better than in the CH session during local anesthesia, but there was no difference between the two drug regimens.	It was concluded that oral diazepam and chloral hydrate had no influence on the behavior management for dental treatment with the studied sample.
Pandey, et al. [8]	Randomized Trial (2010)	to comparatively evaluate the effectiveness of sub mucosal fentanyl when administered in conjunction with oral midazolam during pediatric procedural sedations.	Twenty three uncooperative ASA type I children who met the selection criteria were randomly assigned to receive either sub mucosal fentanyl (3µg/ kg) or placebo, along with oral midazolam (0.5mg/kg)	The overall success was 73.91% with oral midazolam and sub mucosal fentanyl regimen and 47.83% for oral midazolam and sub mucosal placebo regimen.	Sub mucosal fentanyl appears to improve the short working time associated with oral midazolam.
Damle, et al. [9]	Randomized trial (2008)	To evaluate the sedative effects of oral ketamine and oral midazolam prior to general anesthesia	Twenty uncooperative children in the age-group of 2-6 years were selected after thorough medical examination and investigations	The heart rate and respiratory rate were marginally higher with oral ketamine.	Study revealed a better response with oral midazolam; side effects were more prominent with oral ketamine.
Rai, et al. [10]	Randomized trial (2007)	The efficacy and safety of conscious sedation, using intravenous short acting group of drugs (midazolam, propofol and ketamine) in uncooperative children, requiring oral rehabilitation was thus evaluated in this study.	30 uncooperative children, aged 3-6 years, belonging to ASA I, II category formed the study group	Maximum cooperation during the procedure was obtained with ketamine and no adverse effects were encountered	Authors preferred ketamine from the results of our study and recommended future evaluation of ketamine in combination with other sedatives.

Alexopoulos, et al. [11]	Cohort study (2012)	To report on two separate child sedation cohorts; one undergoing propofol intravenous sedation (IVS) and the other, nitrous oxide inhalation sedation (IS) in respect to changes in dental anxiety and subject characteristics.	Observed patient behaviour during treatment, using the Frankl and a VAS scale, were recorded for each subject. Anxiety questionnaires were completed before and after treatment.	The observed behaviour was good for both cohorts.	Propofol target-controlled intravenous sedation (TCI) and nitrous oxide inhalation sedation were similarly efficacious at anxiety reduction in referred dentally anxious children

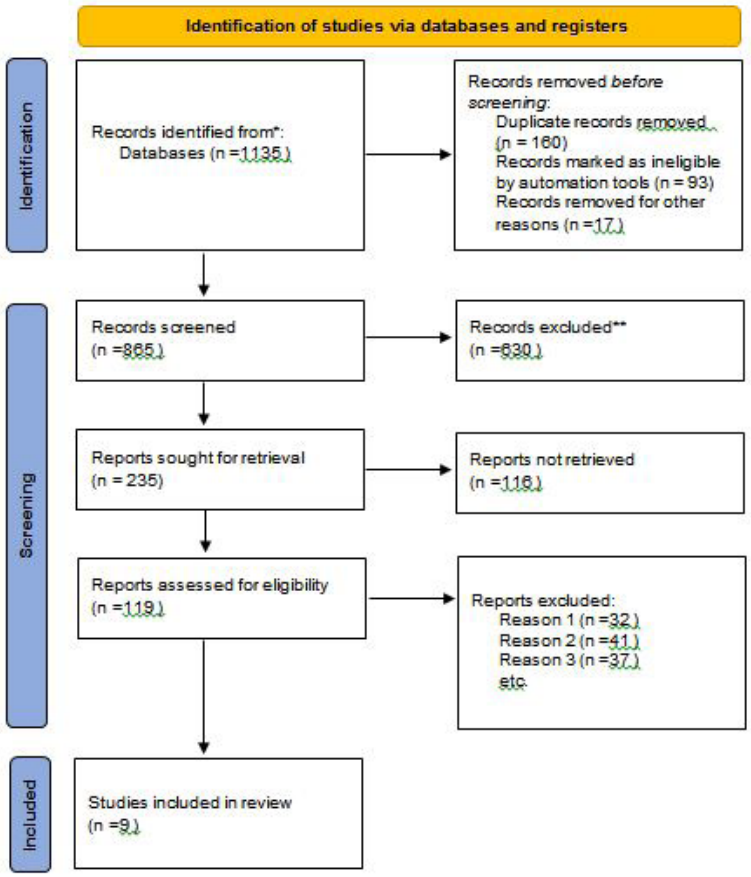

Figure 1: Prisma 2020 flow diagram.

higher doses and treatment time (longer *vs.* shorter). Due to the divergences between the drugs prescribed and the doses used and measured outcomes, a meta-analysis was not performed, and the Grading of Recommendations, Assessment, Development and Evaluation could not be produced.

Some research lacked sufficient information on the randomisation method, precluding assessment, and selection bias was present. Patients, according to some were randomly assigned to groups.

RESULTS

In this systematic review authors followed the PRISMA 2020 flow diagram as represented in flowchart in figure 1. In the identification stage, 1135 articles were found in the initial search. Duplicates found simultaneously between multiple databases were removed. In the screening stage, 630 articles were removed according to the titles and abstract summaries, a total of 119 articles remained after elimination. Further removal was done after reading the whole articles and relating them with the inclusion and exclusion criteria. Finally 9 articles were selected and all were assessed for risk of bias.

According to the SIGN checklist, cohort studies are acceptable and case-control studies are of good quality, while all selected publications are acceptable according to the JBI checklist. All nine studies from the selected databases meet the age requirement of 18 years old. Six of the nine studies were randomized clinical trials, one had case-control study research designs, one was a retrospective study and one had cohort study designs. RDC/TMD was utilized to assess and diagnose TMD in six of the investigations, RDC/TMD and Fonseca Index in one study, and FAI index in one study (Fonseca Anamnesis Index).

DISCUSSION

Although general anesthesia (GA) is generally considered

to be safe in a hospital setting, it is now accepted that GA should be avoided wherever possible due to an increased risk of complications, need for highly skilled personnel, equipment, and being expensive. Using deep sedation to carry out pediatric dental treatments is an alternative strategy. However, because of potential and real risks, it is often carried out in dental settings where other support resources are not immediately available.

In a study published in Lancet journal in the year 2001, In a variety of non-specialized settings, Olivier et al investigated the prevalence of adverse events in children sedated with 50% nitrous oxide and oxygen. A mean of 0.33% (SD 0.10%) of children experienced serious adverse effects. As a result, a mixture of 50% nitrous oxide and 50% oxygen appeared to be a safe option for pediatric procedural sedation [12].

However in recent years, the number of pediatric surgeries requiring sedation or analgesia has increased significantly, as have reports of adverse events. Although various guidelines have been published, there is limited consensus regarding which medications may be administered safely in a non-specialist setting. Sury, et al. [13] have demonstrated that for diagnostic imaging, oral sedation with chloral hydrate or benzodiazepines under the supervision of specialized nurses is effective and safe. However, the safety of regimens appropriate for painful procedures appears to be less proven [14-16].

The sedation of children for the delivery of dental care has been successfully executed using different drug regimens. These are currently the most common sedation techniques used by pediatric dentists: Nitrous oxide inhalation sedation using only oxygen, Midazolam (benzodiazepine) alone, or a mixture of both substances [17-19].

In-office sedation is also less expensive and safer than conscious sedation and general anaesthesia. Other alternatives include Dexmedetomidine hydrochloride, 2-adrenergic agonist, Chloral hydrate with inhibitory action on the cerebral hemisphere of the central nervous system, and General anaesthesia.

Nitrous oxide

As a sedative, nitrous oxide (N2O) gas, also known as laughing gas, is utilized. N2O2 appears as an odorless, colorless gas. The procedure is helpful because it produces a pleasant sensation, which calms the patient. The medicine is fast-acting, and its effects can be reversed quickly and easily when necessary. Because of this, it is considered a safe type of sedation [20-22].

Midazolam

Midazolam is a short-acting benzodiazepine derivative used to induce drowsiness and reduce anxiety before to surgery or other operations. When Midazolam is administered prior to surgery, the patient will not recall certain aspects of the process [23,24]. Midazolam has been an extensively studied drug and is reported to be associated with highest rate of adverse effects.

Propofol

Propofol is a powerful sedative characterized by rapid onset and short duration of action. Adverse effects include transient hypotension and dose-dependent respiratory depression [25]. Propofol has been shown to allow rapid recovery, making it an ideal agent for minor procedures outside operating suites. Bradycardia has been described as a possible adverse effect of propofol when administered alone or in combination with opioids [26]. The successful use of propofol in dentistry is widely reported [27].

Fentanyl

Fentanyl is often co-administered for pain control during procedural sedation [28]. However, this may have an additive respiratory depressant effect with propofol [29]. Similarly, a sub-dissociative dose of ketamine has been used for its analgesic effects as an adjunct to propofol, and has been shown to be effective in procedural sedations for painful procedure with less respiratory and hemodynamic depressant effects [30,31].

Administering an adjunct analgesic during propofol procedural sedation is not a routine practice. However, recently, recommendations were made to use propofol following achievement of analgesia with an opioid. Although sedated patients may not clearly recall procedural pain, painful stimuli can sensitize the nervous system of clinically unresponsive patients and may lead to increased post-operative pain and hyperalgesia [32]. The use of intravenous analgesics including opioids and ketamine has been encouraged to avoid this phenomenon [33,34]. Therefore, it is important to differentiate between sedation and analgesic effect and to treat expected intraoperative pain adequately during procedural sedation.

A variety of drugs have been used for moderate sedation for dental procedures. The efficacy and safety of IV midazolam, ketamine and propofol was assessed in 350 uncooperative children in multiple studies aged 3-6 years requiring oral rehabilitation [35,36]. Ketamine was most effective without adverse events followed by propofol and midazolam. The latter two drugs were not able to control body movement and crying throughout the procedure. Oral chloral hydrate and I/M Ketamine were compared by Campbell in 15 patients. Satisfactory completion of restorative dentistry longer than 40 minutes was obtained in the group with intramuscular ketamine [37]. In four studies, high-dose propofol, (alone or in combination with ketamine or fentanyl) was equally effective and safe for dental procedures.

Intercollegiate Advisory Committee for Sedation in Dentistry in its 2020 report has enlisted the following preferred sedation techniques (Table 2) [38].

CONCLUSION

Providing exceptional dental treatment to pediatric kids can be a challenge. The primary goal of paediatric dental sedation and treatment is to preserve the child's

Table 2: Intercollegiate advisory committee for sedation in dentistry in its 2020 report has enlisted the following preferred sedation techniques.

Nitrous oxide/oxygen sedation (inhalation sedation)	A titrated dose of nitrous oxide in oxygen is the first choice inhalation sedation technique.
Midazolam (intravenous sedation)	A titrated intravenous dose of midazolam is usually the first choice intravenous sedation technique.
Midazolam (oral sedation)	Midazolam is now considered the first choice agent for oral sedation. Oral techniques are not titratable and should only be used when titratable sedation techniques are inappropriate.
Temazepam (oral sedation)	Historically, temazepam was the first choice oral sedative for use in dentistry. Its use has been largely superseded by midazolam. Oral techniques are not titratable and should only be used when titratable sedation techniques are inappropriate.
Midazolam (intranasal sedation)	Intranasal sedation is one of a group of routes of administration referred to as trans mucosal sedation. These techniques have become more popular in recent years, especially in special care dentistry. As with oral sedation, these techniques are not titratable and should only be used when titratable sedation techniques are inappropriate.
Opioid and midazolam (intravenous sedation)	This is an intravenous technique where a single small dose of an opioid (usually fentanyl) is followed by a titrated dose of midazolam. It is used for patients for whom midazolam alone does not produce adequate anxiolysis.
Ketamine (oral/ intravenous sedation)	Ketamine is increasingly being used for paediatric dental conscious sedation. However, until more evidence on its use and safety is published, it is difficult to offer detailed guidance.
Midazolam (patient-controlled sedation)	The IACSD is unaware of anyone currently using patient-controlled midazolam for conscious sedation in dentistry in the UK but it is included here for completeness.
Propofol (patient-controlled sedation)	There have been a number of studies published in which patient-controlled propofol conscious sedation has been examined. The availability of safe and reliable, licensed delivery systems needs to be investigated.
Propofol (target-controlled infusion sedation)	Target controlled infusions of propofol are widely used for sedation in many medical and dental fields. These techniques require the presence of a dedicated seditionist. They are particularly useful for both very long and very short procedures as well as for patients who have developed a tolerance to benzodiazepines.
Midazolam and propofol (intravenous sedation)	This technique is particularly useful for longer dental procedures. The sedation is induced with a titrated dose of midazolam and then maintained with a continuous infusion of propofol. As with propofol administered alone, this technique requires a dedicated seditionist.
Sevoflurane (inhalation sedation)	Techniques involving the use of a titrated dose of sevoflurane in oxygen or in nitrous oxide and oxygen have been studied in paediatric dental patients. These techniques appear to be more effective than a titrated dose of nitrous oxide in oxygen but have yet to achieve widespread acceptance. A dedicated sedationist is required for these techniques owing to the lack of availability of a simple delivery system suitable for use in a dental environment.

confidence by delivering minimal stress. To explicitly establish a high safety standard and apply it in clinical practice, practitioners should attempt to limit patient risk by selecting medically fit patients for sedation. Behavior management and sedation are two of the most common methods used to treat anxious youngsters. Typically, when behavioral strategies are insufficient to control a child, pharmaceutical medications are employed. Findings of our systematic review implies that to produce a deeper level of sedation, combination of nitrous oxide, oxygen, and a hypnotic drug such as midazolam is effective, allowing pediatric patients to tolerate unpleasant treatments by lowering discomfort, anxiety, and or pain. Given the preference of parents and the rising prevalence of pediatric dental disease, it is projected that the demand for safe dental sedation would increase in the future.

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