Pediatric Dental Sedation Research: Where Do We Stand Today?

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Despite the voluminous literature addressing the safety and efficacy of various sedative agents in the pediatric dental setting, the quality literature to form evidence based pediatric dental sedation practice is not available. Our search through PUBMED showed that during 1985-2012, a total of 184 original research papers on pediatric dental sedation were reported, and midazolam clearly dominated with 88 trials on this agent. Despite these large numbers of papers, Cochrane Review was able to pool a weak evidence in favor of midazolam. Data pooling from five heterogeneous high risk of bias trials showed that oral midazolam is associated with more cooperative behavior when compared to a placebo. Further, a very weak evidence regarding efficacy of nitrous oxide was collected from two trials, which could not be pooled. These findings draw attention to the need to address the shortcomings in the current state of pediatric dental sedation research. The present article has been focused on the current status of pediatric dental sedation research, and the limitations in the current research methodology. This paper also suggests recommendations for future research in the field of pediatric dental sedation.

Key words: *Guidelines, Pediatric dental sedation, Research.*

INTRODUCTION

In pediatric dental practice, efficient behavior management, both pharmacological and non pharmacological, translates into efficient delivery of care. At times, owing to extreme anxiety and fear toward dentistry in the young pediatric population, a traditional non-pharmacological approach is deemed insufficient[1]. To cater to this proportion of the young and anxious population, pharmacological means of behavior management, such as sedation and general anesthesia, are needed[2]. It is well recognized that general anesthesia should largely be avoided due to its associated risks and greater cost when compared to sedation[2]; thus, it is an obvious preference to sedate a child to make delivery of treatment possible when other conservative means of behavior management fail.

However, it is unfortunate that there is a scarcity of evidence based literature to help clinicians select and administer a safe and efficient sedative agent. Such an existent paucity of quality literature in the field of pediatric dental sedation has been highlighted in a recent Cochrane Review[3]. Despite the adequate number of published research papers, it was impossible to conduct a meta-analysis owing to the paucity of low bias research papers. Also, heterogeneity amongst studies regarding drug regimen and dosages made pooling of data impossible for meta-analysis. Due to poor reporting, it was difficult to validate the findings of most of the studies. These disappointing findings focus on the need to conduct high quality research in order to build a sound evidence base for sedation of children undergoing dental treatment.

The purpose of this paper is to discuss the current state of pediatric dental sedation, i.e., the limitations in current research methodology and make recommendations for future research in the field of pediatric dental sedation.

Pediatric dental sedation: A journey up to date

The clinical and research arm of any medical field work in close tandem, pacing the development of each other. The same holds true for pediatric dental sedation. In the 1980s, agents such as hydroxyzine, promethazine, meperidine, morphine, diazepam and chloral hydrate were popular[4]. These were considered to be the best of pharmacopeia for pediatric sedation amongst practitioners in those days, only to be replaced by midazolam later. In the late 1980s, a plethora of research papers on midazolam were published. Its popularity rose amongst clinicians, possibly due to the variety of delivery routes[5,6] offered, and the availability of its antagonist flumazenil; which ensured greater safety. In addition, the introduction of pulse-oximetry to assess respiratory parameters revolutionized the field of sedation, as it ensured easier and more reliable monitoring and safety[7].

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In the 1990s, dissociative and sedative agents (ketamine, nitrous oxide) regained their popularity and were added to the existing pharmacopoeia for pediatric dental sedation[4]. Toward the end of this decade, ultra-short-acting agents used for total intravenous anesthesia (TIVA), such as propofol were incorporated[8]. Concomitant to this, technology for assessing sedation depth such as the Bispectral Index (BIS) monitoring[9,10], and more objective and precise methods of assessing ventilation such as capnography[10] were introduced. Currently, not much literature is available on utility of these essential tools in pediatric dental sedation.

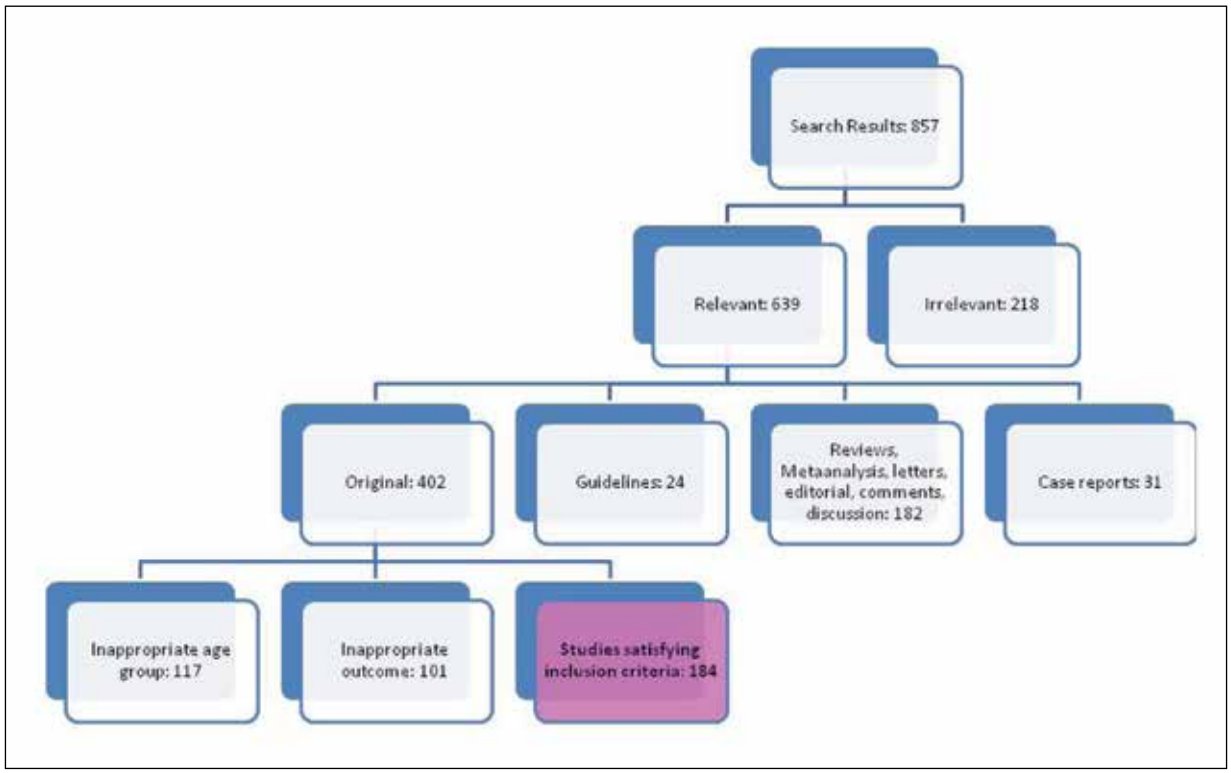
Trends in pediatric dental sedation research

For the purpose of getting an insight into the trends of the type of research papers published addressing pediatric dental sedation, a search through the search engine PUBMED for Mesh keywords 'sedation AND dentistry', with filters set for age (birth-18 years), species (humans) and publication dates (1/1/1985 to 31/12/2012) was conducted. A total of 857 results were obtained. The titles of these papers were scanned by NM and AG in duplication to assess the study type. Reviews, letters, comments, discussions, meta-analyses, guidelines and case reports were excluded. In case of doubt, full texts were referred to. A total of 402 original research papers were obtained. Abstracts of these papers were assessed by NM and AG in duplication for the content and type of study; and in case of doubt, the original articles were referred to. The studies were considered for inclusion in this review if an exclusive pediatric age group (0-18 years) had been included and the outcome measures were 'completion of procedure', 'adverse effects during intra-operative or post-operative period' or 'cardiopulmonary parameters'. This implies that either the efficacy or the safety of the sedative agent/regimen was studied. However, trials addressing the safety and efficacy of the sedative agents as a premedicant prior to general anesthesia were excluded. The study design was not a criteria for exclusion or inclusion of the papers. The quality of papers included in review was not assessed as recently a Cochrane analysis[3] has done that. We did not assess the strength of evidence generated from papers included in this review. We only assessed the papers quantitatively to have an insight towards sedative agents and regimen of interest. Retrospective, as well as prospective trials were included, as we aimed to have a quantitative overview of agents researched up to date.

Out of the 402 original research papers, 117 papers reported inclusion of subjects >18 years of age in addition to a pediatric age group, so these were excluded from further analysis. Further, outcome measures for 101 papers did not satisfy the inclusion criteria. Research papers addressing the efficacy and safety of sedative agents as a premedicant were also excluded. A total of 184 studies were found to be eligible for inclusion in this review (Figure 1).

A comparative bar diagram was drawn for 'the number of studies conducted in the past 5 years (2007-2012)' and 'the number of studies conducted from 1985-2006' (Figure 2). A total of 45 trials fulfilling the eligibility criteria were conducted during the years 2007-2012, versus 139 in the years 1985-2006 (Table 1). Midazolam dominated the pediatric dental sedation research in both the time periods studied, with a greater proportion in recent years compared to yester years (68.89% of total trials reported in 2007-2012, versus 41.10% in 1985-2006). Almost equal proportions of trials out of the total number of trials were conducted for nitrous oxide in both the time periods. A decrease in the number of published trials on chloral

Figure 1: Methodology: Inclusion of papers of interest



hydrate, hydroxyzine, promethazine and meperidine was seen in the time frame from 2007-2012. No reports on meperidine and promethazine were published in the years 2007-2012, though these drugs constituted 16.55% and 11.51% of the total trials published during 1985-2006. A two to three fold increase in published trials was seen for sevoflurane, propofol and fentanyl. Though few trials on intravenous sedation utilizing dexmedetomidine, an α_2 agonist, have been reported in the adult population undergoing minor oral surgical procedures in recent years[11]; none have been reported on its usage in the pediatric population, as revealed by our PubMed search. However, our search through Scopus found a randomized controlled trial of dexmedetomidine versus midazolam-propofol in a pediatric age group for miscellaneous dental procedures.[12]

Limitations in current research methodology

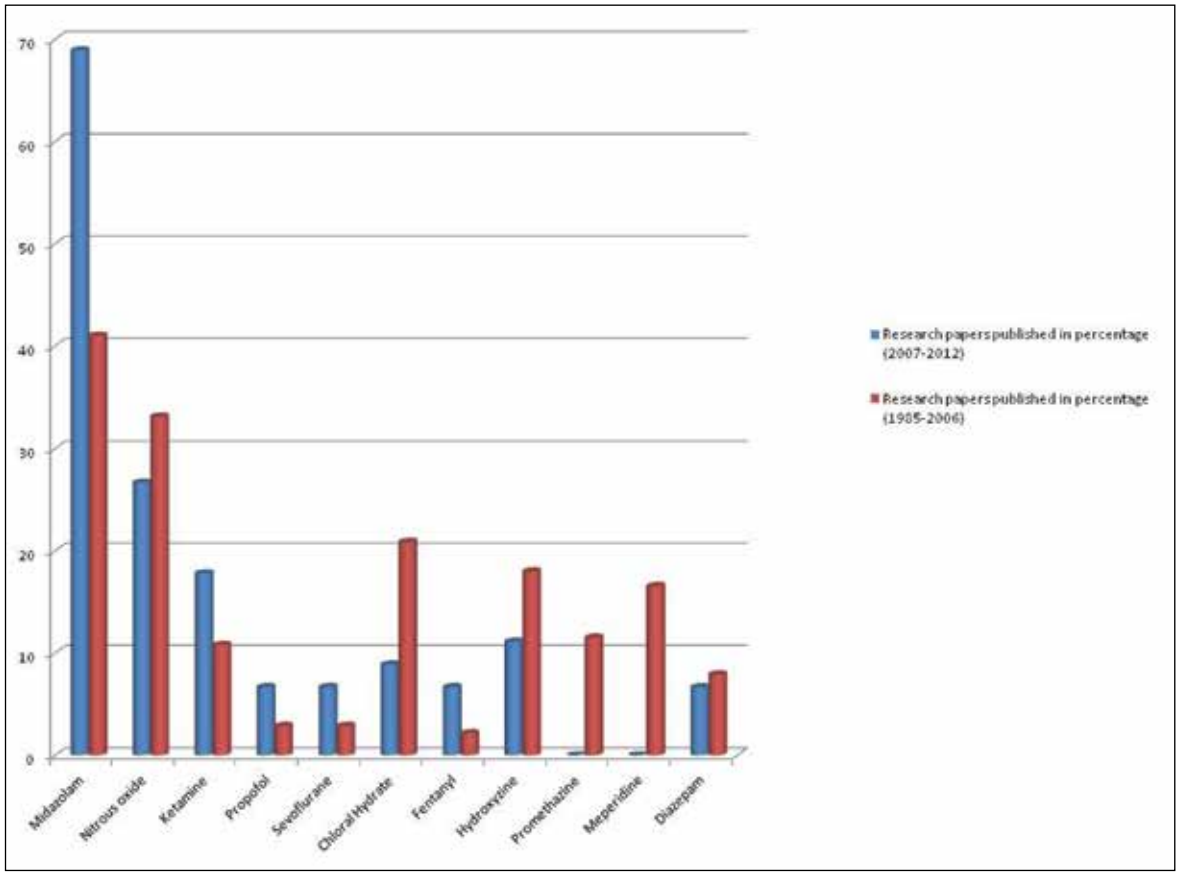
Recently concluded, The Cochrane Review[3] has listed various sources of bias in sedation trials like improper allocation, blinding, incomplete outcome data assessment and selective reporting of

Table 1: Trends in published literature on various sedative agents for pediatric dental sedation

Sedative agents	N (%) of papers published in 2007-2012* N = 45	N (%) of papers published in 1985- 2006* N = 139
Midazolam	31(68.89)	57 (41.10)
Nitrous oxide	12 (26.67)	46 (33.09)
Chloral hydrate	4 (8.89)	29 (20.86)
Ketamine	8 (17.78)	15 (10.79)
Propofol	3 (6.67)	4 (2.88)
Fentanyl	3 (6.67)	3 (2.16)
Hydroxyzine	5(11.11)	25 (17.99)
Promethazine	0 (0)	16(11.51)
Meperidine	0 (0)	23 (16.55)
Diazepam	3 (6.67)	11 (7.91)
Sevoflurane	3 (6.67)	4 (2.88)

*Total %age would be more than 100% as most of the trials were conducted on more than one agent.

Figure 2: Trends in published literature on various sedative agents for pediatric dental sedation



outcomes and baseline data. Apart from these sources of bias, the reported literature on sedation points toward poor clarity in the minds of sedation researchers regarding the choice of sedative agents, as well as their dosing, rescue measures in case of inadequate sedation, sedation assessment and reporting of adverse events.

Recommendations for future research

How to conduct a trial on sedation?

Define your objectives: Prior to initiating any trial, the researchers should decide whether they want to build new evidence or they want to strengthen the existing evidence. One may wish to test a newly introduced agent or an undiscovered aspect of a previously tested agent. For example, one can compare dexmedetomidine (a newly introduced agent) to midazolam (a widely tested agent); or one can conduct a trial on previously unreported aspects of midazolam (like newer modes of administration such as liposome encapsulated midazolam[13]).

Study design: Sedation trials have been conducted using both a cross-over design as well as a parallel design. It has been reported that sedation has long term effects on children, and it can affect their future behavior[14-16]. This implicates that experience during first time visits can be a determinant for baseline behavior and/or anxiety during the second visit. Any intervention that has long term effects should not be studied in a cross-over manner[17].

Recommendation: Sedation trials should be conducted exclusively with a parallel arm design.

Selection of suitable subjects: A wide variation in the age of included subjects and poor reporting of baseline behavior and anxiety, as well as eligibility criteria can make the results of the study unreliable. The age of a child is predictive of that child's behavior, such as children <2years of age are in the pre-cooperative stage[18], while the reasons for uncooperative behavior in children >12 years are usually extreme fear and anxiety toward dentistry; most commonly owed to previous direct/indirect unpleasant encounters with a dental/medical fraternity [18]. Hence, inclusion of subjects with a wide age range (for example 0-16 years) may lead to poor standardization with respect to baseline behavior and anxiety; and to ensure standardization in such a sample, a very large sample size would be required. This aspect has not been previously considered in the literature.

Another important consideration regarding sample selection is the physical health status of the subjects. The American Society of Anesthesia's physical status classification[19] should be employed to grade the general well being of subjects by a pre-anesthetic evaluation prior to inclusion in the study. It is recommended that only subjects belonging to physical health status ASA I and II should be included. Though it is not contraindicated to perform sedation in subjects belonging to physical health status ASA III, it has been reported that in these subjects there is a greater risk of adverse effects when compared to subjects belonging to physical health status I and II.[21] Thus, inclusion of all the three categories such as ASA I, II and III would lead to heterogeneous sampling. This would act as a confounding factor, especially when adverse effects/cardio-pulmonary parameters are one of the parameters being studied.

Recommendations: When including subjects in a trial, due consideration should be given to their age as well as the general physical status of the children. The British National Formulary (BNF) recommends dividing children into three broad age groups. These groups are: 1 to 6 years, 6 to 12 years and over 12 years of age.

Only subjects belonging to ASA status I and II should be included to ensure a uniform sample with adequate standardization.

Recruitment of subjects to different study groups; Sequence generation and allocation concealment: Non-random allocation of subjects to different study groups can lead to an introduction of selection bias[17]. Inappropriate methods of recruitment of participants to different study groups can distort the final outcome assessment.

Recommendations: A random sequence should be generated to assign a study intervention for subjects prior to their inclusion in a study[21]. This ensures baseline equivalence in different study groups. Various methods can be used for this. Measures such as block randomization and computer generated randomization ensure random sequence generation for group allocation and therefore, should be employed. No measures should be allowed to change the sequence after starting the trial. This process should be impervious to any influences by individuals making the allocations. Also, the sequence generated using true randomization should be administered by someone who is not responsible for recruitment of the subjects[17].

It is necessary to blind the observer to the allocated intervention to exclude bias[22-24]. Allocation concealment[17] can be done using various approaches such as:

- Centralized (e.g. Allocation by a central office, unaware of the subjects' characteristics) or pharmacy-controlled randomization
- Pre-numbered or coded identical containers, which are administered serially to participants
- An on-site computer system combined with allocations kept in a locked unreadable computer file that can be accessed only after the characteristics of an enrolled participant have been entered
- Sequentially numbered and sealed opaque envelopes

Blinding: Maintaining blinding during sedation trials is challenging, often due to obvious differences between sedatives, such as the physical appearance of propofol and the typical side effect of nystagmus observed in subjects sedated with ketamine. Also, different titration techniques for different sedatives such as midazolam versus nitrous oxide compound the difficulties associated with blinding.

Recommendation: It is important to blind the outcome assessor to various independent variables of the sedation trial.[25-27]. Preferably, observers should not be the ones who administer the drugs. Below are the following recommended measures to introduce blinding in a sedation trial:

1. In trials comparing propofol to other agents such as ketamine, opaque rubber tubing (in case of an infusion method of drug administration) or covered syringes (in case of a bolus method of drug administration) can be used to mask the milky appearance of propofol.
2. In trials comparing agents administered solely by an inhalation method (nitrous oxide or sevoflurane) to agents administered by various other routes, blinding can be done by administering a placebo. For example, if one wishes

to compare nitrous oxide to intravenous midazolam, the following strategy should be adopted. In the nitrous oxide group, subjects should be administered an intravenous saline placebo; and in the midazolam group, subjects should be administered medical air or supplemental oxygen as a placebo so that the observer cannot visually differentiate amongst the two groups.

3. Similarly, in the case of the same agent being administered by different routes, a placebo can be used to maintain blinding. For example, in a trial comparing oral, nasal and rectal midazolam, subjects should be administered the drug by a test route and the placebo by two other routes.
4. In trials evaluating ketamine, corneal taping must be used to mask nystagmus.

Furthermore, measures should be introduced in trials to test the success of blinding. One suggested measure might be letting the observer guess the sedative agent or protocol and calculating the correctness of his/her guess.

Test drug regimen: Approximately >65 sedative drug regimens (various drugs in various combinations and dosages) have been evaluated for pediatric dental sedation. Due to such a vast variety of drugs and their combinations, pooling of data from various studies becomes difficult owing to heterogeneity. Another problem is that most of the studies do not include a valid comparison group such as a placebo or an agent with known efficacy.

Additionally, many trials have supplemented sedation with papoose boards and other restraints. The effects of the latter on various commonly addressed outcomes such as efficacy of sedation have not been studied previously. Since the magnitude to which these can affect the outcomes in sedation trials has not yet been appreciable, this is another source of heterogeneity in sedation trials.

Recommendations: The choice for a particular sedative agent in a trial is liable to be governed by legal and communal aspects, as well as its availability. Matharu *et al* [3] suggested that either oral midazolam or possibly nitrous oxide sedation can be used in a comparison group. Agents of particular interest for different countries need to be identified and the research should be coordinated.

The effect of papoose boards and other restraints need to be studied. Few research questions that need to be addressed can be "whether the use of restraints would result in the requirement for lesser depth of sedation/lower drug requirements and thus, presumably decreasing the risk for adverse effects and hastening recovery and discharge."

Standardizing the dental treatment performed: No standardization or only partial standardization of types of dental interventions is another factor which can affect various other independent variables in a study. The invasiveness of a procedure can affect the level of sedation, as it appears to the observer. With an increase in the invasiveness of a procedure, a deeper plane of sedation is needed, which will result in increased dosing and might also result in greater chances of adverse events during/after the operative procedure.

Recommendations: Similar types of dental interventions in judiciously selected samples, with similar baseline anxieties and behaviors would ensure almost similar needs for the depth of sedation. This would allow for a uniform follow-up of study protocol.

The various different types of interventions can be endodontic treatment (pulpectomy, pulpotomy), simple restorative work (restoration without pulpal involvement, pit and fissure sealant treatment) or minor surgical procedures. Another important factor to bear in mind, apart from the invasiveness of the procedure is the expected duration of the procedure. A lengthy procedure will result in a greater requirement for sedative drugs, when compared to a short duration intervention. Along with the type of treatment, the units of treatment done should also be standardized for the above stated reasons; for example, how many teeth are to be treated in one go.

Define and classify outcome measure: The Cochrane Review recognized incomplete reporting of outcome measures, which precluded the possibility of data pooling for meta-analysis. The primary outcome measure in most of the studies was a successful procedure. The secondary outcome measures in most of the studies were adverse events, differences in preoperative and postoperative anxiety, procedural recall, etc.

Recommendations: Prior to the onset of the trial, what constitutes the primary and secondary outcome measures should be defined. The success of the procedure is usually measured as a dichotomous variable (either yes or no). However, the ease or difficulty encountered during operative intervention is usually not reported. Provisions should be made for recording this. Also, what constitutes the success of a procedure should be defined, such as 'completion of treatment', 'completion of treatment without any intraoperative adverse events' or 'completion of treatment without any interfering patient movement or complaints'.

Another frequently included measure is whether preference for the same protocol is required in the future. Though, operator satisfaction is important, it is necessary to make it more patient-centric. Along with operator satisfaction; patient/parents'/guardians' satisfaction should also be recorded. Usually, the latter is recorded immediately after the procedure. However, it should be measured after a followup period of 24 hours to 1 week instead. The idea is to record any deviation from normal sleep, behavior toward parents/siblings and disruption from their normal routine. Further, this should be recorded in a closed manner, by allowing the patient/parents/guardians to mark the results on a pro forma in a sealed envelope to be opened just prior to data analysis.

Sedation assessment: Most of the authors have done sedation depth assessment by employing validated scales. Commonly employed scales, for example, Ramsay sedation scale[28] and Houpt's sedation scale[29], assess sedation as a measure of how asleep the patient appears to the observer, or how the patient responds to stimulation. Thus, scoring sedation on the basis of the observer's assessment is a potential source of bias owing to components of associated subjectivity.

Another deficit is that few authors have reported a single overall score for depth of sedation throughout an entire procedure; while others have reported a sedation depth assessment at several discrete points such as during local anesthesia administration or separation from parents. It is to be emphasized that the responsiveness of a subject, and hence their sedation depth varies with the invasiveness of the procedure. A subject who might appear deeply sedated during separation from parents might appear in a lighter level of sedation during venepuncture or local anesthesia administration. For these reasons, it is erroneous to report sedation depth for the entire procedure as a single overall score.

Recommendations: Only previously validated sedation scoring tools should be used with the assessment of sedation during several discrete procedural steps. Sequential reporting of the sedation depth right from the baseline score until exit from the operatory to the recovery room should be done.

In addition to validated subjective scales such as Houpt's sedation rating scale/ Ramsay sedation scoring system; objective measures of sedation assessment such as Bispectral Index monitoring may also be used. This is a measure of cortical activity and is based on the principle that EEG waveforms change during activity, rest, sleep and during anesthesia[30]. The output from a BIS monitor is a single number from 0 to 100. At high values near 100, the patient is awake. According to the manufacturer, a BIS score of >90 indicates an awake patient; 71-90 shows mild to moderate sedation; 61-70 shows deep sedation; and 40-60 indicates that the patient is under general anesthesia. Good correlation between BIS and other commonly validated sedation scales has been reported[31].

Another important, but yet unexplored aspect is feasibility of target controlled infusion (TCI) devices for sedation in the pediatric population. Deficiency of research to incorporate pharmacodynamic/ pharmacokinetic parameters for a broader pediatric age group in these devices restricts their use[32]. Although sufficient evidence for us to make firm recommendations about the use of TCI versus MCI (manually controlled infusion) in clinical anaesthetic practice is lacking, it was reported that the use of the former resulted in lesser interventions than the latter[33]. This finding encourages research to develop pediatric models for TCI and test their practical applicability.

Defining rescue measures to maintain sedation: In the case of inadequate sedation at pre-decided dosing/protocol, it is recorded as a failure of sedation and subjects are excluded from the study at the time of final data analysis. This results in a loss of participants and disrupts the baseline equivalence established by random assignment.

Recommendations: In such cases, provision should be made to introduce standardized rescue measures to allow treatment completion and duly record these events. These standardized rescue measures can be provision for administration of drugs (sedatives/ analgesics) in addition to that of the standard drug protocol. For example, one may administer an additional bolus of sedative (same/ different to the test agent) at a pre-decided dose, in which case, sedation is not being maintained by the test drug at the test dose and duly recorded. These should be compared between different treatment groups. This will allow for an ' intention-to-treat' analysis to be carried out with inclusion of all the enrolled subjects in the final data analysis[17]. This prevents bias caused by the loss of participants, which may disrupt the baseline equivalence and reflect non-adherence to the protocol.

Standardizing reporting of adverse events: The rarity of adverse events in pediatric dental sedation[34-35] precludes the possibility of conducting trials which compare adverse events as primary outcome measures; as these will require a very large sample size. Hence, surrogate markers of adverse events have been used by most of the investigators, like apnea and desaturation as markers for respiratory depression. However, non-uniform methods of reporting these surrogate markers (for example desaturation has been reported by various authors as sPO_2 <90% or <92% or <94%) often complicate the judgment of these results. This might be because it has not yet been ascertained as to what level of desaturation constitutes clinical harm.

Another important attribute of the current available literature on pediatric dental sedation research is that most of the authors do not report the timing of when the adverse events occur, such as during the procedure or while in recovery.

Recommendations: Reporting of adverse events should be done in a standardized format with the consensus driven definition derived amongst all involved researchers prior to the onset of the trial. The usual method is to record the magnitude as well as the duration of adverse events; for example oxygen saturation ≤90% for ≥ 30 seconds. How much clinical harm can result from this magnitude and duration of adverse events is unknown. However, recording the intervention that resulted as a response to this adverse event might give an insight into the clinical severity of the adverse event. Some might argue that rescue interventions are rather dependent on the clinical orientation of the sedationist/anesthetist. Although this may be true, it is only partially so, since interventions are usually done in a sequential manner with the noninvasive and simplest being administered first in a series, whilst the invasive and complex are only administered later; in case the earlier one fails. For example, in the case of oxygen desaturation, the following steps are taken in a successive manner with the next one happening only in case of the inadequacy of the previous. These can be simple repositioning » suctioning » supplemental oxygen administration » application of positive pressure or ventilation with a bag mask » oral or nasal airway placement » tracheal intubation. Hence, recording of the intervention along with the adverse event allows for judgment to be made about the clinical importance of the adverse event.

Also, it is recommended that recording of adverse events should be done in a chronological order, right from the induction to the post discharge follow-up. For this purpose, the sedation appointment can be divided into distinct, well defined time intervals (Figure 3).

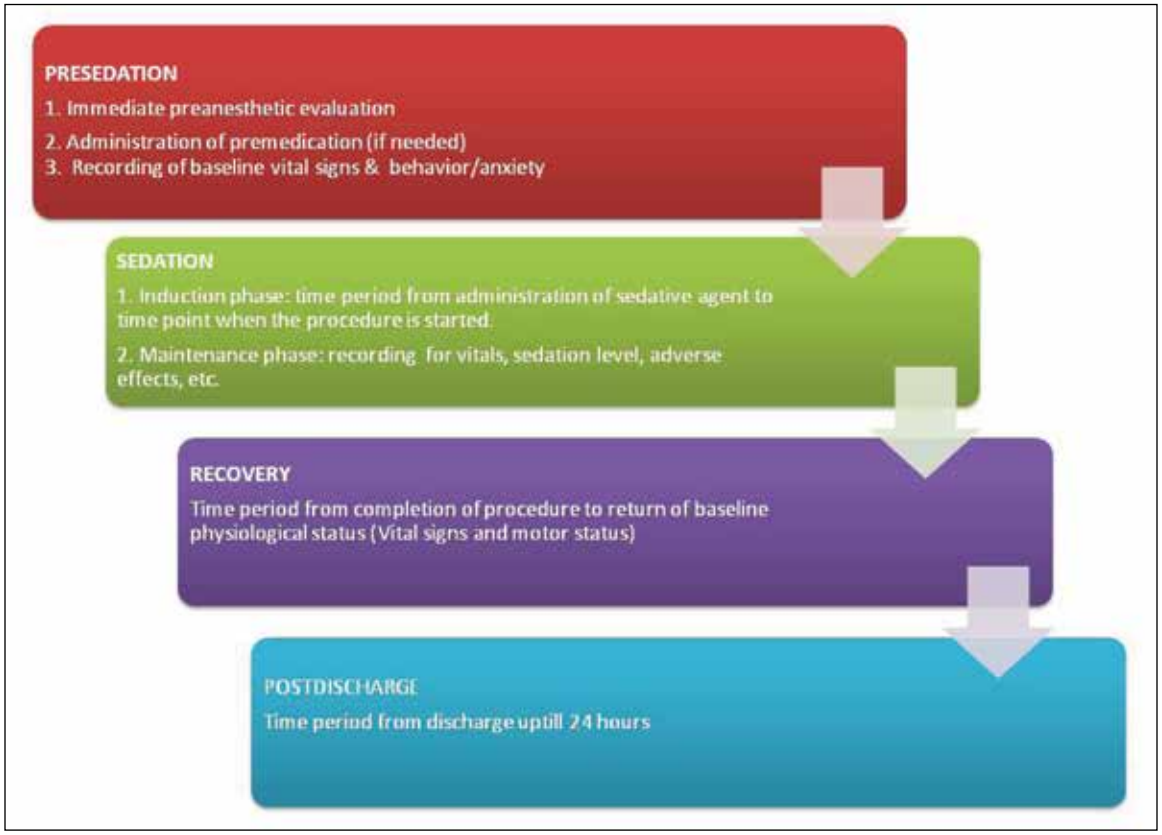
How to report a trial on sedation?

While reporting a trial on sedation, it is recommended that CONSORT (Consolidated Standards of Reporting Trials) guidelines[34] should be followed. A CONSORT statement provides guidance for reporting parallel groups of randomized and controlled trials. The main intent is to make the reports as free from ambiguity as possible, facilitating clarity, completeness and transparency of reporting, so that readers can make clear judgments about the validity of the results. It comprises a checklist of 25 items[36] and a flow diagram to help improve the quality of the reports of randomized controlled trials. Note, that the CONSORT 2010 Statement does not include recommendations for designing, conducting and analyzing trials. It solely addresses the reporting of what was done and what was found. A CONSORT statement indirectly addresses the deficits, if any, in trials.

CONCLUSION

The present article is an attempt to address the existing shortcomings in pediatric dental sedation research. With the help of recommendations stated in this article, it is expected that various sources of bias can be eliminated in pediatric dental sedation research. There is a definite need to conduct high quality research with a low risk of bias so that evidence based practice guidelines can be laid for pediatric dental sedation.

Figure 3: Sedation time intervals



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