Review Article

Trends for in-office usage of pharmacological sedation agents in India: A narrative review

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Abstract

Background and Aims: Conscious sedation plays a significant role in in-office pharmacological behavior management for short-term procedures in children and apprehensive adults. The advantage conscious sedation provides is by improving quality of care provided by decreasing pain and anxiety while maintaining a patent airway and adequate spontaneous ventilation.
Methodology: Present review was conducted to evaluate recent trends regarding use of in-office pharmacological sedation agents in India. A rigorous search was conducted through five electronic databases namely PubMed, Scopus, Web of Science, Cochrane Database, and CTRI (Clinical Trial Registry – India). The search period was defined to be last 5 years, that is, from 1st January 2014 to 31st July 2019. Terminologies "Conscious Sedation," "In-office Sedation," "Midazolam," "Nitrous Oxide," "India" were included in the search. The Boolean Operation "OR" and "AND" were applied to combine the terminologies.
Results: A total of 20 studies were identified following strict inclusion and exclusion criteria. The included studies were evaluated for study design, speciality involved, number of individuals and their age groups, drugs compared along with route and dosage, procedures undertaken, place of study and results. Dental fraternity (13) had more number of trials conducted as compared to medical fraternity (7) in the stimulated period, with South Indian region having maximum trials registered or published.
Conclusion: Midazolam was observed to the drug of choice for in-office sedation procedures in Indian Scenario. The limitation of study is that the published clinical studies are limited to a few states of India.

Keywords: Conscious sedation, India, Midazolam

Introduction

Conscious Sedation (Moderate Sedation/Analgesia) is a drug-induced depression of consciousness during which patients respond purposefully to verbal commands, either alone or accompanied by a little tactile stimulation.[1]

Since the introduction of nitrous oxide by Humpry Davy in 1789, sedative agents had become an imperative part of medical community.[2] Since then in a quest to find the best sedative many agents have been introduced. This included familiarization of chloral hydrate in 1870s,[3] midazolam in 1983, flumazenil in 1988, and propofol in 1990s[4] and in 1999 came dexmedetomidine as an approved agent for short-term sedative procedures (>24 h).[5]

Although the term conscious sedation was coined in 1985 to describe dental patients who were lightly sedated, but its use soon spread across areas of medical practice. It was in 1996 that the ASA Taskforce replaced it with a more precise term "sedation-analgesia," but the term "conscious sedation" continues to be widely used.[6]

In recent years, the healthcare world has seen a shift in preference for conscious sedation over general anesthesia. It

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can be contributed to the decreased risks of morbidity and mortality as compared to general anesthesia. Also, the delirium associated with general anesthesia is not an issue under conscious sedation.[7] However, the essential non feeding period has to be followed before undergoing general anesthesia or conscious sedation. Although, the time duration differs.[8]

Another advantage conscious sedation provides is by reducing anxiety, not just limited to children but extending to adults too. Aiding in its widespread popularity in the western world, wherein UK (2009) the rate of usage of sedation for pediatric patients was 90% irrespective of the dentist specialization.[3,9] Justifying the widespread usage of sedation in dentistry, National Commission on Recognition of Dental Specialties and Certifying Boards recognized Dental anesthesiology as 10th dental specialty on the basis of a resolution from the American Society of Dentist Anesthesiologists to recognize it as a separate dental specialty.[10] However, observing the scenario in India is tough because of the scarcity of data available with regards to specialist preference of sedative agents. Also, trials registered are less or incomplete till date. Further in this review, midazolam and nitrous oxide were taken as the gold standard drugs given to their popularity in the literature. Hence, this review has been carried out to observe the trend of change occurring in the field of in-office sedation in India.

Methodology

The present review was carried out using the framework provided by Arksey H (2005)[11] and Levac D (2010).[12] A rigorous search was carried out using five electronic databases: PubMed, Scopus, Web of Science, Cochrane Database, and CTRI (Clinical Trial Registry – India). The search period was defined to include literature for the last 5 years, that is, from 1st January 2014 to 31st July 2019. Terminologies "Conscious Sedation," "In-Office Sedation," "Midazolam," "Nitrous Oxide," "India" was included in the search. The Boolean operation "OR" and "AND" were applied to combine the terminologies.

The title and abstract of the searched articles were evaluated by the main author, to identify the studies that met with the inclusion criteria of the review. Observational studies (case-control, cross-sectional, cohort), experimental (both randomized or non-randomized clinical trials), which either used nitrous oxide or midazolam alone or in combination with other sedative agents, whose text was available in the English language, which were published between 2014 and July 2019 and were conducted in India were included in the review. Systemic reviews, case reports, guidelines, and incomplete registered trials were excluded. Studies were included irrespective of age groups, healthcare specialty, or their association with any specific medical or dental health procedures . After the initial screening, a manual search was executed in the reference list of included studies. Studies that were accessible through more than one database were considered only once.

Data from the included studies was extracted and assembled in a table form under various headings: study details (author (s), year of publication and state where the study was conducted), participants (number and age group), methodology (department where the study was conducted, study design, procedure performed and time duration), agents compared (agents along with route and its dosage) and results [Table 1]. If any clarification was required, it was sought out either directly by contacting the corresponding author (through email) or indirectly through the editor of the journal.

Results

Study selection

The search was conducted using various databases (PubMed, Scopus, Web of Science, Cochrane Database, and CTRI), which resulted in the identification of 4,607 articles. After the removal of duplicates, 4,000 records remained. The articles not related to the topic of this review were excluded via screening of title and abstract and the literature came down to 2,000. Adding the time constrain (2014–2019), the number of included literature reduced to 500. Further on reviews, meta-analysis, editorials, letter to editors, questionnaire studies, case reports, and incomplete registered trials whose results were unknown were excluded bringing down the included literature number to 18. Two studies were further included after manual searching of the reference list. Therefore, a total of 20 studies were found to be fulfilling the criteria and were included in this review [Figure 1].

Study characteristics

The characteristics of the included studies are mentioned in Table 1.[13-32] From the 20 studies included, 19 were randomized trial and 1 was a cross-sectional study. Based on blinding done in the Trial: double, triple and partial blinding was identified and was reported in 7, 1, and 1 trial, respectively, and no blinding was performed in 10 trials. All of the trials were prospective in conduct.

In the present review, an observation regarding the specialty conducting the trial was made. Out of total of 20 trials, 7 were conducted by medical fraternity with pediatric, otolaryngology, and pulmonary medicine department taking credit for 1 trial

Table 1: Characteristics of Studies Included

Author (Year) Nature of Trial	No of Individuals (Age Group)	Control drug (Route and dosage)	Agent compared (route and dosage)	Speciality (Type of procedure & Duration)	State where Trial was conducted	Results
Dhuvad J.M *et al.* (2014)[13] Randomized, parallel group study	90 (18-50 yrs)	Midazolam (Intravenous 1.5 mg/kg)	Propofol (Intravenous 20 µg/kg/min)	Oral and Maxillofacial Surgery (3rd Molar Extraction, 25 mins)	Maharashtra	Recovery rate was faster in propofol group (within 2 hrs) as compared to midazolam group. Side effects were least in propofol group. Patient satisfaction was higher in propofol group (96.66%) as compared to midazolam group (60%).
Mitra S *et al.* (2014)[14] Double blind randomized study	60 (1-10 yrs)	Midazolam (Intranasal 0.3 mg/kg)	Clonidine (Intravenous 4 µg/kg)	Anaesthesiology (minor elective surgical procedures such as hydrocele repair, herniorrhaphy, circumcision or eye surgery, 25 mins)	Chandigarh	Midazolam group had faster onset (P<0.05) compared to Clonidine whereas Clonidine has better drug acceptance (P<0.001).
Surender MN *et al.* (2014)[15] Randomized triple blind comparative study	84 (4-14 yrs)	Midazolam (0.2 mg/kg) (Intranasal)	Ketamine (Intranasal 5 mg/kg), Dexmedetomidine (2 diff dosages) (Intranasal D_1 1 µg/kg and D_2 1.5 µg/kg)	Pediatric and Preventive Dentistry (Early Childhood Caries treatment: extraction, restoration, pulp therapy, 30-45 mins)	Uttar Pradesh	The onset of sedation was significantly faster in midazolam and ketamine group as compared to both dexmedetomidine groups (P<0.001). Success rate was highest in D_2 (85.7%) followed by D_1 (81%), K1 (66.7%) and M1 (61.9%). However difference was not statistically significant (P>0.05)
Keerthy PH *et al.* (2015)[16] Double blind randomiZed study	40 (20-40 yrs)	Midazolam (Intravenous 75 µg/kg)	Propofol (Intravenous Induction 0.5 mg/kg and maintenance 50 µg/kg/min)	Oral and Maxillofacial Surgery (Disimpaction of Mand. 3rd Molar, 25 mins)	Karnataka	Pain during injection experienced in propofol group was statistically significant than in midazolam group (P=0.001). The onset of action was significantly earlier in propofol group than in midazolam group (P<0.001).
Takkar D *et al.* (2015)[17] Randomized, double-blinded, placebo-controlled parallel-group study	40 (7-10 yrs)	Nitrous Oxide+Oxygen (Inhalation 40%-60%)	Oxygen (Inhalation 100%)	Pediatric and Preventive Dentistry (Inferior alveolar block administration, 5 mins)	Karnataka	Significant difference was observed in the level of discomfort experienced by children between both the groups (P<0.01). Statistically significant difference in the behaviour of children during and after the procedure in both treatment groups (P<0.01).
Chopra R *et al.* (2015)[18] Cross sectional study	35 (2-6 yrs)	Midazolam (Intranasal 0.3 mg/kg)	Midazolam (Aerosol 0.3 mg/kg)	Pediatric and Preventive Dentistry (treatment requiring local anaesthesia: extraction, restoration, pulp therapy, 26.7±12.2 min)	Haryana	Significant improvement in movement and crying scores was observed after administration of drug (P<0.001). Overall behaviour at end of treatment was also significantly improved after sedation (P<0.001). Onset of sedation was 6.11 min faster in aerosol as compared to oral midazolam.

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Table 1: Contd...

Author (Year) Nature of Trial	No of Individuals (Age Group)	Control drug (Route and dosage)	Agent compared (route and dosage)	Speciality (Type of procedure & Duration)	State where Trial was conducted	Results
Musani IE *et al.* (2015)[19] Randomized, cross-over study	30 (4-10 yrs)	Midazolam (Oral 0.2 mg/kg) and Nitrous Oxide - Oxygen (Inhalation 40%-60%)	Midazolam (Intranasal 0.1 Mg/Kg) and Nitrous Oxide - Oxygen (Inhalation 40%-60%)	Pediatric And Preventive Dentistry (Extraction, Indirect Pulp Capping, Pulpotomy, Pulpectomy, 30-45 Mins)	Maharashtra	The onset of sedation was significantly faster in intranasal group :12.1 min as compared to oral group 20.1 min ($P<0.001$). The alertness was statistically higher in intranasal group as compared to oral group ($P<0.05$). Recovery was faster in intranasal group
Stephen MC *et al.* (2015)[20] Prospective, randomized, double blind, placebo controlled study	82 (1-6 yrs)	Midazolam (Intranasal 0.5 mg/Kg)	Chloral Hydrate (Oral 50 Mg/Kg)	Otolaryngology, speech and hearing (auditory brainstem response testing, 60-90 mins)	Tamil Nadu	Chloral Hydrate showed earlier onset of sedation (66%) as compared to Midazolam (33%). Recovery was faster in Chloral Hydrate group (78 Mins) as compared to Midazolam (108 Mins) ($P<0.05$)
Thota RS (2015)[21] Randomised trial	40 (18-75 yrs)	Fentanyl (Intravenous 1.5 µg/Kg) and Midazolam (Intravenous 0.03 mg/Kg)	Fentanyl (Intravenous 1.5 µg/kg) and Propofol (Intravenous 0.75 mg/kg)	Anaesthesiology (Tympanoplasty, 30-60 mins)	Maharashtra	Fentanyl and Propofol group showed faster recovery and less nausea and vomiting.
Done V *et al.* (2016)[22] Randomized, Factorial Design study	30 (3-9 yrs)	Midazolam (Oral 0.5 mg/kg) and Nitrous Oxide - Oxygen (Inhalation 70%-30%)	Oral Ketamine (Oral 5 mg/kg) and Nitrous Oxide - Oxygen (Inhalation 70%-30%)	Pediatric and Preventive Dentistry (Primary teeth Extraction, 15 mins)	Andhra Pradesh	No significant difference ($P>0.05$) on comparison of effectiveness of Oral Midazolam-N_2O with Oral Ketamine-N_2O when physiological parameters were taken into consideration. Psychomotor performance was found to be marginally better with Oral Midazolam-N_2O compared to Oral Ketamine-N_2O.
Shanmugaavel A.K. *et al.* (2016)[23] Randomized controlled trial	40 (3-5 yrs)	Midazolam (Intranasal 0.2 mg/kg)	Midazolam (Sublingual 0.2 mg/kg)	Pediatric and Preventive Dentistry (Extraction, Indirect Pulp Capping, Pulpotomy, Pulpectomy, 20-30 Mins)	Tamil Nadu	Sublingual route was preferred significantly as compared to intranasal route ($P=0.001$). Significantly reduced anxiety score was observed in both intranasal and sublingual groups ($P<0.001$) over time.
Malhotra P.U *et al.* (2016)[24] Prospective, randomized, double blind study	36 (3-9 yrs)	Midazolam (Oral 0.5 mg/kg) and Ketamine (Oral 5 mg/kg)	Dexmedetomidine (Intranasal 1 µg/kg)	Pediatric and Preventive Dentistry (Early Childhood Caries t/t (extraction, restoration, pulp therapy, 30-45 mins)	Himachal Pradesh	Hemodynamic changes were statistically insignificant in both groups. About 75% patients receiving Midazolam + Ketamine were successfully sedated as compared to 53.9% receiving Dexmedetomidine
Bishnoi V *et al.* (2016)[25] Randomized, parallel group study	52 (18-50 yrs)	Fentanyl And Midazolam (Intravenous Fentanyl - 0.5 Mg/Kg And Midazolam - 0.03 mg/kg for 10 mins followed by continuous infusion of 0.5 to 1.16 µg/kg/h and 0.03-0.07 mg/kg/h)	Dexmedetomidine (Intravenous 1 µg/kg over 10 mins followed by continuous infusion 0.03-0.7 µg/kg/h)	Anaesthesia and intensive care (burr hole surgery for chronic subdural hematoma, 60 mins)	Haryana	Dexmedetomidine group showed faster postoperative recovery ($P=0.00$). Surgeon satisfaction was better in dexmedetomidine group compared to midazolam and fentanyl group ($P=0.007$).

Contd...

Table 1: Contd...

Author (Year) Nature of Trial	No of Individuals (Age Group)	Control drug (Route and dosage)	Agent compared (route and dosage)	Speciality (Type of procedure & Duration)	State where Trial was conducted	Results
Ramaswamy SS (2016)[26] Prospective randomized trial	60 (50-70 yrs)	Fentanyl (Intravenous 12.5 µg/kg) and Midazolam (Intravenous 0.02 mg/kg)	Dexmedetomidine (intravenous 2 doses 0.5 µg/kg and 0.25 µg/kg for 10 mins, followed by titrated maintenance dose of 0.25-0.4 µg/kg/h)	Anaesthesiology (vitreoretinal surgery, 60 mins)	Karnataka	Dexmedetomidine (0.5 µg/kg) group had statistically significant bradycardia ($P<0.001$), hypotension ($P=0.008$). Midazolam-Fentanyl group had significantly higher incidence of nausea ($P=0.001$) and vomiting ($P=0.002$)
Subramaniam *P* et al. (2017)[27] Randomized, parallel group study	60 (5-10 yrs)	Nitrous Oxide-Oxygen (Inhalation 40%-60%)	Triclofos Sodium (Oral 70 mg/kg)	Pediatric and Preventive Dentistry (extraction, restorations and endodontic treatment, 30-45 mins)	Karnataka	Patient acceptance was statistically significant for Triclofos Sodium as compared to N_2O ($P=0.002$). Children sedated with Triclofos sodium were significantly more sleepy and disoriented as compared to N_2O ($P=0.005$).
Samir PV *et al.* (2017)[28] Randomized, parallel group study	60 (5-12 yrs)	Nitrous Oxide-Oxygen (Slow Induction 30%-70%)	Nitrous Oxide-Oxygen (Preadjusted mix+Rapid Induction Technique 30%-70%)	Pediatric and Preventive Dentistry (Pulp Therapy, 45 mins)	Telangana	Time taken to achieve minimal sedation was less in rapid induction group as compared to slow induction ($P<0.001$). No statistically significant difference was found in incidence of hypoxia in both groups ($P<0.512$)
Prabhudev AM *et al.* (2017)[29] Randomized, double - blind, placebo controlled study	144 (30-65 yrs)	Midazolam (Intravenous 0.035 mg/kg)	Fentanyl (Intravenous 50 µg/ml) and Midazolam (Intravenous 0.035 mg/kg)	Pulmonary Medicine (Bronchoscopy, 30-60 mins)	Karnataka	Patient satisfaction was highest in Fentanyl and Midazolam group followed by Midazolam and placebo group ($P<0.001$). Physician feasibility was also higher in Fentanyl and Midazolam group (P - 0.004)
Chayapathi V *et al.* (2018)[30] Partially blinded randomized, controlled study	152 (1-12 yrs)	Ketamine (Intravenous 2 mg/kg) and Midazolam (Intravenous 0.2 mg/kg)	Propofol (intravenous 2.5 mg/kg)	Pediatrics (intrathecal chemotherapy, 30 mins)	Delhi	Mean time to sedation and recovery was shorter in Propofol group ($P<0.001$) and mean depth of sedation was greater in Ketamine and Midazolam group ($P<0.001$).
Kunusoth R *et al.* (2019)[31] Randomized, parallel group study	60 (10-50 yrs)	Midazolam (Intravenous 0.1 mg/kg)	Midazolam (Intra nasal 0.1 mg/kg)	Oral and Maxillofacial Surgery (Minor Oral Surgery, 15-60 mins)	Telangana	Preoperative to postoperative anxiety scores have decreased significantly within both groups but there was no statistically significant difference in pre and post-operative anxiety scores between the groups.
Sivasubramini S.M. *et al.* (2019)[32] Randomized, double blinded study	60 (18-40 yrs)	Midazolam (Intravenous 0.05 mg/kg)	Dexmedetomidine (Intravenous 1 µg/kg for 10 mins additional dosage 0.5 µg/h)	Oral and Maxillofacial Surgery (bite force during minor oral surgery, 30 mins)	Tamil Nadu	Dexmedetomidine group had statistically significant sedation score as compared to midazolam ($P<0.05$). Bite force increased administration of either drugs (no significant result ($P>0.05$)

each and rest 4 being conducted by anesthesiology department. And dental specialty was credited for the conductance of 13 trials (9 were concerned with Pediatric and Preventive Dentistry and 4 with Oral and Maxillofacial Surgery Departments). However, observing the preference of conscious sedation for in-office procedures between dental and medical specialty, the difference was not statistically significant using Fisher's exact test ($P = 0.344$).

Observing the preference of agents used in the medical and dental setting as a conscious sedative agent for in-office procedures over the 5 years (2014–2019). Maximum studies

throughout the period have been conducted in 2016 for both medical and dental specialty. For medical in-office procedures midazolam alone remained a constant drug of choice from 2014 to 2017 and no trials reported for 2018 and 2019 [Graph 1].

Discussing the agents usage in procedures of different durations. For this parameter, the studies were divided into two groups—procedures requiring less than 30 min (<30 min) and more than 30 min (>30 min). The midazolam appeared to be the most used agent in procedures requiring <30 min (8) and >30 min (8), followed by dexmedetomidine and fentanyl both used in five times each for procedures requiring more than 30 min [Graph 2]. Based on the agent used in the trial midazolam was chosen as an agent in 15 trials (irrespective of the route) and nitrous oxide was used in 3 trials and 2 trials used combination of both. As comparative agents, Propofol was used in 4 trials, Ketamine in 4 trials, Dexmedetomidine in 5 trials, Clonidine in 1 trial, Triclofos Sodium in 1 trial, and Chloral Hydrate in 1 trial. Seven trials were those which used midazolam as an agent in combination with other drugs [Graph 1]. Midazolam had been administered 20 times in 17 studies, in varying concentrations (0.035 mg/kg, 0.03 mg/kg, 0.075 mg/kg, 0.05 mg/kg, 0.005 mg/kg, 0.1 mg/kg, 0.2 mg/kg, 0.3 mg/kg, and 0.5 mg/kg). The route of administration of midazolam was observed to be intravenous route (9 trials) followed by intranasal (6 trials), oral (4 trials), sublingual (1 trial), and buccal aerosol (1 trial), wherein 3 trials comparison between different routes was done. Propofol was used in concentration of 0.02 mg/kg, 0.5, 1, 0.75, and 2.5 mg/kg. Dexmedetomidine concentration used was 0.5–1.5 μg/kg. Ketamine concentration used was 2 mg/kg (1 study) and 5 mg/kg (3 studies). Clonidine concentration was 4 μg/kg intranasally, Triclofos Sodium in 70 mg/kg in oral form and Chloral Hydrate 50 mg/kg in oral form. The number of participants included in the selected trials ranged from 30 to 144. According to the age group involved, studies were characterized into 2 groups: Group 1- included studies where the age group was less than 16 years and Group 2 – where the age group was above 16 years of age. 12 studies were characterized under Group 1, with 7 studies under Group 2, and 1 study fell under both the groups.

Observing the distribution of trials throughout the Indian territory. South India dominated this distribution with 11 trials conducted within its region, with maximum trials been conducted in Karnataka (5) followed by the Northern region with 6 and 3 trials in Western India. While Central and Eastern India reportedly had no trials. All trials in the Western region were conducted in Maharashtra state (3) [Figure 2].

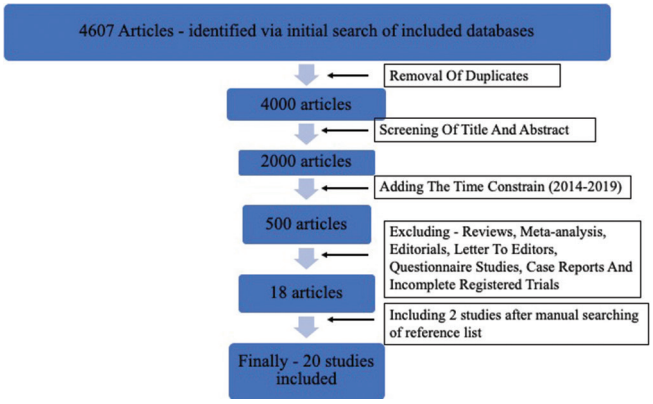
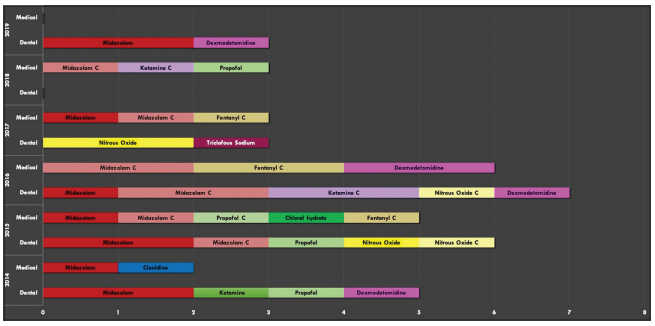
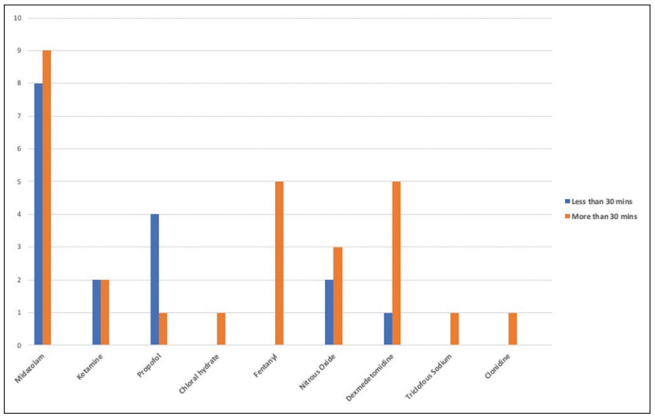


Figure 1: Flowchart demonstrating the selection of articles



Graph 1: Describing the distribution and choice of drugs for medical and dental procedures over period of 5 years

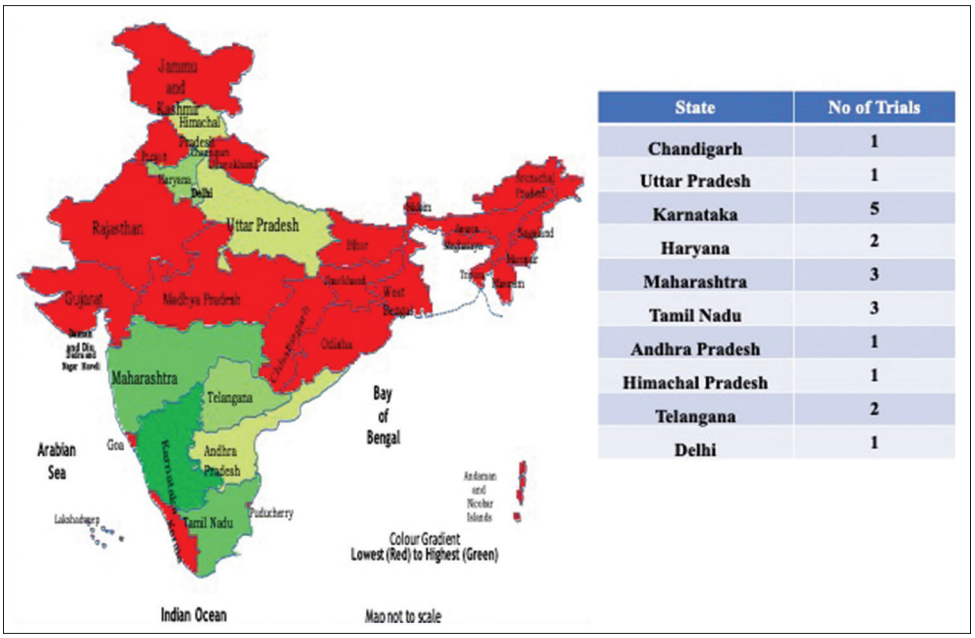


Graph 2: Distribution of Sedative Agents according to procedure duration

Discussion

Among the two pharmacological behavior management techniques, conscious sedation preference has increased over time compared to general anesthesia for procedures involving both dental and medical fraternity. The reason for this is the decline in the mortality risk and delirium, along with the improved recovery time and reduced reliance on anesthetic staff as it can be performed even without the presence of anesthesiologist.[33,34]

The primary goal for conscious sedation is to minimize or eliminate pain and anxiety during treatment.[35] While



State	No of Trials
Chandigarh	1
Uttar Pradesh	1
Karnataka	5
Haryana	2
Maharashtra	3
Tamil Nadu	3
Andhra Pradesh	1
Himachal Pradesh	1
Telangana	2
Delhi	1

Figure 2: Distribution of trials within India

maintaining a patent airway without assistance and cardiovascular function, adequate ventilation, and responses to the verbal communication.[36] This stage can be achieved via a range of drugs with different routes of administration (inhalation, oral, intravenous, intramuscular, rectal) and varying dosages.[13-32,37] Among these drugs are phenothiazines, butyrophenones, barbiturate and non-barbiturate hypnotics, benzodiazepines, and the Hypno-analgesic, ketamine.[38] Midazolam, being a popular benzodiazepine was included in this review. It has sedative, anxiolytic, anticonvulsant properties, and also causes anterograde amnesia. The major advantage it provides is of inducing a safe and effective moderate sedation stage without risk of any cardiopulmonary complications. As compared to other benzodiazepines, midazolam does not produce prolonged sedation.[39] Among the various routes for administration of midazolam, Musani IE *et al.* (2015)[19] observed that nasal route was more preferred as compared to oral route in terms of onset and recovery, whereas Kunusoth R *et al.* (2019)[31] reported that there was no statistically significant difference when comparing nasal route to intravenous route. However, other routes such as aerosol, sublingual routes were reported to have better acceptance and behavior management compared to the intranasal route.[18,23] Although all of these routes can induce an anxiolysis state but only intravenous route can induce deep sedation stage.[32] The reason for the lesser preference of the oral route can be contributed to its inability to titrate reliably. Also, if an additional dose is required, because of variability in absorption and onset of action the procedure is considered to be of high risk.[40,41]

Malhotra PU (2016),[24] Surender MN (2014)[15] preferred combination of ketamine and midazolam as compared to dexmedetomidine in terms of behavior management and duration for the onset of sedation respectively. Chayapathi V (2018)[30] reported propofol to be better than ketamine and midazolam combination in terms of sedation depth. The major advantage combination of midazolam and ketamine provides is that a lesser dosage is required for the sedative effect to occur.[42,43] The combination provides to overcome the issues presented by ketamine as sedative and midazolam as an anxiolytic agent. Lokken (1994),[42] Roelofse JA (1998),[43] and Moreira TA (2013)[44] in their studies have shown that a combination of midazolam and ketamine is better as compared to midazolam and ketamine individually.

In terms of cost-effectiveness, inhalation (nitrous oxide) costs around $25 to $100 (1,779–7,117 INR), light oral sedation is estimated to be around $150 to $500 (10,676–35,588 INR), depending upon the drug and i/v sedation is estimated around $250 to $900 (17,794–64,059 INR). However, the cost for GA procedure in the dental setting is higher around $7,303 (5,20,612 INR), as the procedure is to be conducted in the hospital setting.[45]

When comparing the drug of choice for procedures involving minors (less than 16 years) and adults (more than 16 years); Midazolam alone was observed to the preferred drug in procedures involving minors in the dental setting.[14,18,23] However, Stephen MC *et al.* (2015) preferred chloral hydrate for use in minors for auditory brainstem response testing procedure.[28] This finding

was in accordance to National Clinical Guideline Centre (UK), 2010 where midazolam was considered to the drug of choice for children undergoing dental procedures and in endoscopy procedure in children, it recommended intravenous midazolam (for upper endoscopy) and fentanyl in combination with intravenous midazolam for lower endoscopy procedures.[46] For children who have to undergo remove the, painful procedures (laceration or orthopaedic treatment) nitrous oxide (in oxygen) and/or midazolam (oral or intranasal) is recommended.[46]

The reason for the widespread popularity of midazolam can be contributed to the minimum side effects midazolam sedation is associated with. Although, oral midazolam preparation has a bitter taste but it can be easily disguised by giving/mixing it with apple juice or flavored juices.[47] In contrast to the National Clinical Guideline Centre (UK), Brown TB (2005) preferred Ketamine followed by Etomidate, fentanyl, and midazolam for usage in children.[48] The main reason for the preference of ketamine is its faster onset, analgesic and sedative effects, minimal respiratory depression, and adequate operating time.[49] However, the major side effect of ketamine offers is vomiting.[39] In the present review in the case of adults for dentistry and medical procedures various agents, either used alone or in combination were identified. For dental procedures, dexmedetomidine and propofol were considered better as compared to midazolam, Midazolam and ketamine combination.[16,32] Similarly, for medical procedures, dexmedetomodine,[25] propofol,[30] midazolam and fentanyl,[26,29] and fentanyl and propofol combination[21] were preferred sedative agents. Reason can be the advantage dexmedetomidine offers by producing milder analgesia without respiratory depression and sedation characterized by quick and easy arousal and lesser cognitive impairment.[24,50] The advantages propofol provides is of rapid onset and recovery, with clear headedness compared to other agents along with having an antiemetic and antipruritic properties, making it well suited ambulatory conscious sedative agent.[16,51] Also propofol can be administered as a target-controlled infusion (TCI) which can effectively be used to provide conscious sedation for dentistry.[52] In a study by Samir PV (2017) wherein he compared the effectiveness of slow and rapid infusion of nitrous oxide and reported faster achievement of sedation in rapid infusion group and no statistical difference in the incidence of hypoxia in between the groups (P value <0.512).[28] However, in a study by Stokes and Huston, they have demonstrated a lower incidence of apnea in patients who received slow induction as compared to rapid induction of sedative agent.[13,53]

The advantages conscious sedation provides over general anesthesia as a method for pharmacological behavior management makes it an easier and faster choice for use in short duration procedures, both in medical and dental setup. Based on the present results, midazolam can be crowned as the most preferred drug for conscious sedation involving children and adults. The use of sedation is surely becoming an indispensable part of a medical and dental fraternity in India. However, the number of trials present in the literature is limited and is not evenly distributed within Indian boundaries. The concentration of trials within some states does identify the need for other states to participate in these trials.

Limitation of Present Review

The present narrative review explores the literature related to both medical and dental fraternities exploring the trends in sedation practice. The major limitation is that the present review focuses on the published literature and may not highlight the true concerns of real practice (related to availability, cost-effectiveness). The present review was conducted as a narrative review. Hence, it focused on not a single research question but described an overview of the sedative usage in India. To answer various questions related to like complications (such as sedation, hypotension, and bradycardia) and preference of one drug over other, further surveys and systematic reviews are required

Conclusion

The choice of the sedative agent may vary according to social, economic, population group ethnicity, and even availability of conscious sedation facility. According to our review, midazolam appears to fulfil most of these criteria in a developing country like India. In summary, midazolam remains the drug of choice in both medical and dental worlds due to its various advantages. However other drug benefits can't be side-lined but to prove their dominance further trials are required.

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Conflicts of interest
There are no conflicts of interest.

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