COMPARATIVE EVALUATION OF INTRANASAL MIDAZOLAM AND DEXMEDETOMIDINE FOR PROCEDURAL SEDATION IN PEDIATRIC DENTAL PATIENTS

BABU BANARASI DAS UNIVERSITY, LUCKNOW

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DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation entitled **"COMPARATIVE EVALUATION OF INTRANASAL MIDAZOLAM AND DEXMEDETOMIDINE FOR PROCEDURAL SEDATION IN PEDIATRIC DENTAL PATIENTS"** is a bonafide and genuine research work carried out by me under the guidance of **Dr. Neerja Singh**, **Professor and Head,** Department of Pediatric and Preventive Dentistry, Babu Banarasi Das College of Dental Sciences, Babu Banarasi Das University, Lucknow, Uttar Pradesh.

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LIST OF ABBREVIATIONS

S.NO.	Abbreviation	Full form
1.	AAP	American Academy of Pediatrics
2.	AAPD	American Academy of Pediatric Dentistry
3.	IN	Intranasal
4.	M or MDZ	Midazolam
5.	D or DEX	Dexmedetomidine
6.	ASA	American Society of Anaesthesiologist
7.	CSF	Cerebro-Spinal fluid
8.	MAD	Mucosal Atomizer Device
9.	%	Percentage
10.	PSA	Procedural sedation and analgesia
11.	PR	Pulse rate
12.	SBP	Systolic blood pressure
13.	DBP	Diastolic blood pressure
14.	SP02	Oxygen Saturation

ABSTRACT

Background: Management of children's fear and anxiety during dental treatment is a primary concern of pediatric dental practitioners. There are a number of children who are difficult to be managed by basic behavior guidance techniques. Here, the role of pharmacological agents comes into the consideration.

Aim: To evaluate the safety and efficacy of intranasal midazolam and dexmedetomidine for procedural sedation in pediatric dental patients.

Materials and Methods: Subjects were randomly divided into two groups for different drugs .Group I for administration of midazolam (0.3mg/kg) and Group II for administration of dexmedetomidine (2.5μg/kg) intranasally.

Results:

This study was aimed to evaluate and compare the safety and efficacy of dexmedetomidine (2.5μg/kg) and midazolam (0.3 mg/kg) through intranasal route for procedural sedation in pediatric dental patients.

- Considering the efficacy parameters, midazolam had rapid onset time, early peak sedation time, faster recovery time and shorter discharge time as compared to dexmedetomidine.
- In both the experimental groups, the pulse rate, blood pressure and oxygen saturation remained within acceptable physiological limits and no post-operative complications was seen in either of the groups.
- The ease of treatment was better with midazolam while the drug acceptance was similar in both the groups.

Conclusions:

- The intranasal route for administration of sedative drugs is a safe and effective method to control the behavior of uncooperative children who require comprehensive dental treatment.
- Intranasal midazolam was found to be better than intranasal dexmedetomidine for procedural sedation.

INTRODUCTION

Interactions with dental health providers are stressful experiences for children. These interactions are necessary for the purpose of preventing and eliminating oro-facial diseases, infection and pain along with restoring the form and function of the dentition and correcting disfigurement or dysfunction in children. Providing dental treatments in uncooperative and struggling pediatric patients may pose a risk of injury both for clinicians as well as for patients. Protecting children from adverse consequences often requires restraint, including the limbs and head, whether mediated by a device or pharmacologic agent.

An efficient behavior management is a mandatory requirement for complex procedures providing safe and painless treatment and reducing potential psychological trauma. Non-pharmacological behavior guidance techniques are frequently used to relieve anxiety and perform quality oral health care treatment for infants, children, adolescents, and patients with special health care needs but in few cases they are not enough to reduce the anxiety effectively and make the treatment unpleasant. A traumatic dental experience may leave a negative impact on children leading to a lifelong dental phobia. Thus, a pharmacological means of behavior management comes into the consideration.

For the management of pain, anxiety and unwanted movements in children undergoing dental treatment, procedural sedation and analgesia (PSA) has developed during recent years and has reduced the need of general anaesthesia.[1]

The American College of Emergency Physician (ACEP) defines procedural sedation as “a technique of administering sedatives or dissociative agents with or without analgesia to bring a state that will let the patient to endure unpleasant procedures at the same time maintaining cardio-respiratory function”.[1]

The use of procedural sedation improves the patient's behavior, reduces apprehension and minimizes the negative psychological response towards the treatment by reducing anxiety and controlling behavior during dental treatment. Since decades pediatric dentists all over the world have searched for the ideal agents and route to provide procedural sedation.

There is a long list of drugs that are used for procedural sedation by various routes, through the years but none of them have been proved ideal. Dexmedetomidine was accepted by the Food and Drug Administration (FDA) in 1999 for short-term sedation procedures. It has emerged as an alternative to premedication in pediatric anesthesia. Dexmedetomidine is one of the advanced drug that has gained popularity among the list of drugs used for procedural sedation but has been sparingly used in our country (**Prakhar G. 2013**).[2] It is an alpha-2 agonist with both sedative and anxiolytic effects with minimum side effects which makes it a useful agent for providing procedural sedation.

Much interest has been focused on the use of midazolam for conscious sedation in pediatric dentistry. Midazolam HCl was first synthesized by Fryer and Walser in 1976. It is a short-acting, water soluble benzodiazepine drug that acts similarly to diazepam on GABA- (y-amino butyric acid) associated benzodiazepine receptors.[6] It has anxiolytic, sedative, hypnotic, anticonvulsant, muscle-relaxant, and anterograde amnesic effects. The drug has been used as a preanesthetic sedative in adults and in children.

Various types of routes are available for administration of sedatives; (oral, intranasal, sub mucosal, transmucosal, intramuscular, intravenous and rectal). Intranasal route includes many advantages like absence of first pass metabolism, shorter duration of action, painless technique and ease of administration. Intranasal administration is achieved by using a product known as a Mucosal Atomizer Device (MAD) or with the help of a nasal spray. Use of MAD or nasal spray for administration, reduces the need for obtaining intravenous access which is often painful and depressing for the child with an additional risk of needle stick injury[5]. Delivery of Intranasal medication is relatively painless, inexpensive, and easily rendered with a minimal training.

Hence, this study aims to evaluate and compare the safety and efficacy of midazolam and dexmedetomidine administered intra-nasally for procedural sedation in pediatric dental patients.

AIM

To evaluate and compare the safety and efficacy of intranasal midazolam and dexmedetomidine for procedural sedation in pediatric dental patients.

OBJECTIVES-

1. To evaluate the safety and efficacy of midazolam (0.3 mg/kg) administered through intranasal route.

2. To evaluate the safety and efficacy of dexmedetomidine (2.5 µg/kg) administered through intranasal route.

3. To compare the safety and efficacy of midazolam and dexmedetomidine administered intranasally.

REVIEW OF LITERATURE

In the nineteenth century, the development of general anesthetic drugs helped the dentist of the twenty first century to provide comfortable dental treatment to their patients. In the earlier days the dental patient was expected to cause considerable pain and distress.

Nitrous oxide was discovered by Joseph Priestley in the year 1772. The analgesic properties were discovered by Humphry Davy in 1798 and were used by Horace Wells for the first time in 1844.

Nitrous oxide was used for inhalational conscious sedation by dentist rather than general anesthesia was reported in early 1900s.By the 1930s, an intravenous barbiturate, hexobarbitone was in practice in UK dental clinics for sedation. Since then, there has been number of drugs that have been synthesized and tested, but none of them has proved to be ideal sedative agent.

In the recent years, dexmedetomidine and midazolam have emerged as an agent for procedural sedation. In the present study, midazolam an older sedative drug was compared with a newer sedative drug as well as a combination of both the drugs through the intranasal route with the help of a nasal spray for evaluation and comparison in terms of safety and efficacy.

Intranasal sedation is called as a non invasive way of drug administration, which is safe and is tolerated by children with direct absorption potential of the sedative agent into the bloodstream without entering into the liver and the stomach. It also saves the anxious child from receiving more injections.[8]Combination of two drugs provides

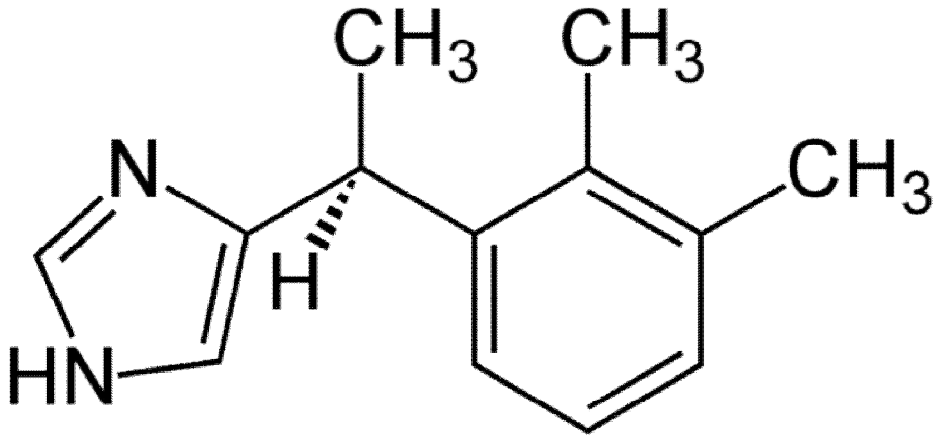
better patient control that allows the use of minimal dose of single agent, thus avoiding its undesirable effects.[9]

DEXMEDETOMIDINE:

The first α2-adrenoceptor agonist was synthesized in the 1960s to be used as a nasal decongestant. It has recently become evident that complete anesthesia is possible by using new, more potent α2 agonists, such as medetomidine and its stereoisomer, (Dex). The drug was reported to be safe and effective alternative for premedication in children. **(Saad A, Sheta A, Maha A, Sarheed AL, Ashraf A.2013)[9].**

CHEMICAL STRUCTURE

It's chemical formula is S)-4-[1-(2,3-Dimethylphenyl)ethyl]-3H-imidazole



MECHANISM OF ACTION

The hypnotic effect of dexmedetomidine is mediated by the hyperpolarization of noradrenergic neurons in the locus ceruleus of the brain stem (a small bilateral nucleus which contains many adrenergic receptors)**. Andreas S, Haarmann H, Klarner S, Hasenfuss G, Raupach T. (2014)[10]** conducted a study in which primary site in modulating wakefulness. When the α-2 adrenergic receptor is activated, it inhibits adenylyl cyclase. This enzyme further catalyzes the formation of cyclic AMP (cAMP), a crucial second messenger molecule that acts in many catabolic cell processes.

Dexmedetomidine favors anabolic pathway over catabolic pathways by reducing the amount of cAMP in the cells. Simultaneously, there is an efflux of potassium through calcium activated potassium channels and an inhibition of calcium entry into calcium channels in nerve terminal. **(Kamibayashi T, Maze M. 1999)[11]**.

The change in membrane ion conductance leads to a hyperpolarization of the membrane, which suppresses neuronal firing in the locus ceruleus as well as its activity in the ascending noradrenergic pathway **(Kamibiyashi T, Maze M. 2000)[12].**

The locus ceruleus is the site of origin for the descending medullo-spinal adrenergic pathway, which is known to be a key mechanism in controlling nociceptive neurotransmission. The similar mechanisms are seen with α-2 receptors and opioid receptors in the area of the brain, which has contributed to the thought that there must be extra spinal sites of action. When these sites are stimulated, they reduce the firing of nociceptor neurons stimulated by peripheral A and C fibers which inhibits the release of neurotransmitters. The analgesic effects are said to be in the dorsal horn of the spinal cord. When a hypnotic dose of dexmedetomidine was administered to either laboratory animal or epinephrine release from the locus ceruleus was inhibited. The absence of inhibitory control over the ventrolateral preoptic nucleus (VLPO) resulted in release of gama amino butyric acid (GABA) and galanin, which further inhibited the locus ceruleus and tuberomamillary nucleus (TMN). This inhibitory response also causes decrease in the release of histamine, which results in a hypnotic response.

This response is similar to that found in normal sleep, in that the reduction of nor does epinephrine release by the locus ceruleus trigger the release of GABA and galanin by the VLPO. These neurotransmitters further inhibit norepinephrine release by the locus ceruleus and suppress histamine secretion by the TMN. The reduced occupancy of the histamine receptors on the cells of the subcortical areas induces a state of hypnotism **(Nelson E, You T, Maze M, Franks P 2001)[13]**.

PHARMACOKINETICS-

Absorption - Bioavailability: Oral 16%, intranasal 65%, buccal 82%,

Intramuscular 100%, sublingual 84 %,

Metabolism - Almost complete glucoronidation, hydroxylation (via CYP2A6) and N-methylation in the liver.

Excretion - Elimination half-life: 2-2.5 hours

Dexmedetomidine follows linear or zero-order kinetics. Oral bioavailability is poor because of its extensive first pass metabolism. However, bioavailability of sublingually administered dexmedetomidine is (84%), intranasal (65%) and intramuscular (100%) offering a potential role in pediatric sedation and premedication **Anttila M, Penttilia J, Helminen A, Vuorilehto L, Scheinin.(2003)[14].**Dexmedetomidine is absorbed through the intranasal and buccal mucosa, a feature that could be of benefit while using in uncooperative children or geriatric patients.

Dexmedetomidine undergoes almost complete bio-transformation through direct glucuronidation and cytochrome P-450 (CYP 2A6) mediated aliphatic hydroxylation to inactive metabolites. Metabolites are excreted in the urine (about 95%) and in the feces (4%).

Gertler R, Brown HC, Mitchell DH, Silvius EN(2001)[15],Petroz GC, Sikich N, James M, Dyk H, Shafer SL, Schily M, Lerman J. (1997)[16] conducted a study in which they randomized 36 children, ranging in age from 2 to 12 years, to receive dexmedetomidine infused for 10 minutes at 2, 4 or 6 μg/kg/hr and they reported that no dose dependent kinetics, protein binding of 92.6%, weight adjusted total body clearance of 13mL/kg/min, a volume of distribution of the peripheral compartment of 1.0 liter/kg, and terminal elimination half-life of 1.8 hours. Contrary to above, **Díaz, Susan M, Rodarte FA, Alexander MD, Foley, Jennifer RN, Capparelli, Edmund V, Pharm D. (2007)[17]** studied with reduced dose i.e. ranging from 0.2-0.7μg/kg/hr for 8-24 hours to 10 children (0.3 to 7.9 years of age) and they reported a volume of distribution of 1.53 ±0.37 liter/kg, clearance of 0.57 ± 0.14 liters/kg/hr (approximately 9.5 mL/kg/min) and a terminal elimination half life of 2.65 ± 0.88 hours.

PHARMACODYNAMICS-

Cardiovascular system

The bolus dose of 1 μg/kg results in a limited increase in blood pressure and a reflex drop in heart rate. This response is more common often with young and healthy patients (**Bloor BC, Ward DS, Belleville JP, Maze M. 1992)**[18]. The rise in blood pressure can be attenuated by a slow infusion and by avoiding bolus administration of the drug **(Haselman MA. 2008)**[19]. The dose dependent bradycardiac effect of dexmedetomidine is primarily mediated by the decrease in sympathetic tone and partly by baroreceptor reflex and enhanced vagal activity **(Kamibiyashi T and Maze M. 2000)**[12] and **(Anttila M, Penttilä J, Helminen A, Vuorilehto L, Scheinin H. 2003)**[14].

Central nervous system

The amnestic effects of dexmedetomidine are far less than the benzodiazepines, which provide profound anterograde amnesia that may contribute to confused states on emergence. In contrast, anterograde amnesia is achieved with dexmedetomidine only at high plasma levels (≥ 1.9 ng.mL-1), without retrograde amnesia **(Ebert T, Hall E, Barney J, Uhrich T, Colinco MD. 2000)**[20]dexmedetomidine may also provide antinociception through non-spinal mechanisms– in addition to it intraarticular administration during knee surgery improves postoperative analgesia **(AL-Metwalli RR, Mowafi HA, Ismail SA, Siddiqui AK, Al-Ghamdi AM, Shafi MA, El-Saleh AR. 2008)**[21], this effect (analgesia) was achieved by activation of α-2a receptors, inhibition of the conduction of nerve signals through C and Aδ fibers, and the local release of encephalin **(Yoshitomi T, Kohjitani A, Maeda S, Higuchi H, Shimada M, Miyawaki T. 2008)**[22].

Respiratory System

Dexmedetomidine does not suppress respiratory function, even at high **doses (Hsu YW, Cortinez LI, Robertson KM, Keifer JC, Sum-Ping ST, Moretti EW, Young CC, Wright DR, Macleod DB, Somma J. 2004)**[23]. Despite profound sedative properties, it is associated with only limited respiratory effects, even when dosed to plasma levels up to 15 times of those normally achieved during therapy, leading to a wide safety margin **(Venn RM, Hell J, Grounds RM. 2000)**[24]**.**

Renal system

The effects of dexmedetomidine on renal function are complex. α-2 agonists exert a diuretic effect by inhibiting the antidiuretic action of vasopressin (AVP) at the collecting duct, most likely through α-2a receptors, resulting in decreased expression of aquaporin-2 receptors and decreased salt and water reabsorption **(Rouch AJ, Kudo LH, Hébert C. 1997)**[25].

USE OF DEXMEDETOMIDINE AS A SEDATIVE AGENT IN MEDICAL FIELD

Dexmedetomidine is a newer drug gaining popularity in neuroanesthesia and neurocritical care practice. This α2-adrenergic receptor agonist offers a unique cooperative sedation, anxiolysis and analgesia with no respiratory depression. Cerebral effects are generally consistent with a desirable neurophysiological profile, including neuroprotective characteristics. In addition, sympatholytic and antinociceptive properties allow for hemodynamic stability at critical moments of neurosurgical stimulation **(Bekker A and Sturaitis MK. 2005)**[26]. Some neurosurgical procedures have evolved toward minimally invasive, functional procedures including endoscopies, small-size craniotomies, stereotactic interventions and intraoperative imaging in which dexmedetomidine was used as sedative agent **(Tanskanen PE, Kyttä JV, Randell TT, Aantaa RE. 2006)**[27].

A study was conducted by **Alhashemi J A, Daghistani MF.** (**2006)**[32] in which they compared dexmedetomidine and midazolam in forty-four patients undergoing cataract surgery and found that dexmedetomidine did not come out to be suitable undergoing the surgery. While there was a slightly better subjective patient satisfaction, it was accompanied by relative cardiovascular depression and delayed recovery room discharge.

Bernardini DJ,Shairo FE. (2006)[35] reported dexmedetomidine as an excellent sedation agent when used in facial surgeries, during which oxygen increases the combustion.

It has also been used in various neurosurgical procedures which require intraoperative active patient participation, including assessment of responses following initial deep brain stimulation for treatment of Parkinson's disease, electrode implantation, surgical management of epilepsy, and surgery near Broca's and Wernicke's speech areas **(Rozet 2008)[28].**

Jamliya R.H. (2013)[33] evaluated the operative analgesia and adverse effects of dexmedetomidine given intrathecally with hyperbaric 0.5% bupivacaine or hyperbaric 0.5% bupivacaine alone for spinal anesthesia in sixty patients. Patients were randomly allotted to be given intrathecally either 15 mg hyperbaric bupivacaine plus 5 μg dexmetedomidine (group D, n = 30) or 15 mg hyperbaric bupivacaine (group S, n = 30) alone. The onset time to reach peak sensory and motor level, the regression time for sensory and motor block, hemodynamic changes and side effects were recorded. In patients undergone lower limb orthopedic surgeries under spinal analgesia, 15 mg hyperbaric bupivacaine supplemented with 5 μg dexmetedomidine produces prolonged motor and sensory block compared with hyperbaric 0.5% bupivacaine alone.

Dexmedetomidine is well suited for use in the intensive care environment, allowing sedated patients to be quickly aroused and oriented upon demand **(Rayner SG, Weinert CR, Peng H, Jepsen S, Broccard AF. 2012)[36]**. Dexmedetomidine was approved by the FDA for sedation in initially intubated patients for a period of 24hrs **(Anttila M, Penttilä J, Helminen A, Vuorilehto L, Scheinin H. 2003)[14]**. This time limitation was probably due to lack of data concerning adverse events for its use for more than 24hrs. Prospective studies were lacking regarding the use of dexmedetomidine in treating withdrawal symptoms from either opioids or benzodiazepines. **Joseph D and Tobias D. (2006)[37]** in 7 patients and **Baddigam K, Russo P, Russo J, Tobias JD.(2005)**[38] in 3 patients gave retrospective case reports and series support to its potential use, hemodynamic effects during withdrawal from illicit drugs and long-term sedation in the ICU. The infusion dose was in the range 0.25-0.7 μg/kg/h and the duration of treatment was ≤ 3 days.

Fiber-optic intubation require dry field to avoid the pulmonary aspiration. Dexmedetomidine provides an ideal solution in creating a dry field for the

anesthesiologist, as it is an anti sialogouge (**Anttila M, Penttilä J, Helminen A, Vuorilehto L, Scheinin H. 2003)[14]**, **(Makary L, Vornik V, Finn R, Lenkovsky F, McClelland AL, Thurmon J, Robertson B. 2010)[39].**

Hu R, Liu JX, Jiang H.(2013)[40] compared dexmedetomidine and remifentanil for conscious sedation during fiberoptic intubation; both dexmedetomidine and remifentanil were equally effective as sedatives in patients undergoing awake fiberoptic nasotracheal intubation. In another study done by **Gupta K, Jain M, Gupta PK, Rastogi B, Saxena KS. (2012)[41]** found that this procedure was found to be easier with dexmedetomidine along with infusion of propofol.

Gyanesh P, Haldar R, Srivastava D, Agrawal MP, Tiwari AK, Singh PK. (2013)[42]compared the intranasal dexmedetomidine and intranasal ketamine for procedural sedation undergoing MRI procedure and they concluded that both the drugs were equally effective intranasally .

USE OF DEXMEDETOMIDINEAS A SEDATIVE AGENT IN DENTAL FIELD

Makary L, Vornik V, Finn R, Lenkovsky F, McClelland AL, Thurmon J, Robertson B.(2010)[39] carried out a study to evaluate dexmedetomidine when used as a sole sedative agent in office-based oral and maxillofacial surgery procedures. Patients undergoing office-based oral and maxillofacial surgical procedures received dexmedetomidine as a sole sedative agent. The loading dose of dexmedetomidine (1 microg/kg infused over 10 minutes) was followed by a maintenance dose (0.2 to 0.8 microg/kg/hour) to achieve a Ramsay sedation score of 2 to 3.It was concluded that the prolonged recovery time makes this drug unsuitable for busy office-based practices.[96]

Kawaai H, Tomita S, Nakaike Y, Ganzberg S, Yamazaki S.(2013)[48] conducted a study to compare the amnesic action, recovery duration, and satisfaction of patients and doctors after the applying two different sedation regimens of Butorphanol, midazolam, dexmedetomidine (BMD) for 40 patients undergoing implant surgery.. It was concluded that both the regimens are appropriate for implant surgery.

Rummasak D and Apipan B. (2014)[49] used dexmedetomidine as hypotensive agent compared with nitro-glycerine in orthognathic surgery and they found that dexmedetomidine was better than nitroglycerine as hypotensive agent. Dexmedetomidine (DEX) is a potent highly selective α2 adrenergic agonist, possessing a differential specificity for the α2:α1 receptors of 1620:1. It has sedative, analgesic and anesthetic sparing effect, and sympatholytic properties.**(Bloor BC, Ward DS, Belleville JP, Maze M. 1992)**[18]. The central and peripheral sympatholytic action of DEX is mediated by α2 adrenergic receptors.**(Lakhlani PP, MacMillan LB and Guo TZ. 1997)**[50] and is manifested by dose-dependent decrease in arterial blood pressure, heart rate, cardiac output and nor epinephrine release. For complete dental rehabilitation.**(Saad A, Sheta A, Maha A, Sarheed AL, Ashraf A. 2013)**[9]compared the dexmedetomidine with midazolam administered intranasally for premedication in Seventy-two children of ASA physical status (I & II),of age group 3–6 years children and they found that intranasal dexmedetomidine (1 μg/kg) was superior sedative and safe alternative for premedication in children than midazolam (0.2 mg/kg). In another study, **(Sheta MA. Al-Sarheed, Ashraf A. Abdelhalim. 2014)**[51] found the similar result.

Yuen V, Hui TW, Irwin MG, Yao TJ, Chan L, Wong GL. (2012)[61] concluded that intranasal dexmedetomidine in a premedication dose of 2 μg/kg wasmore efficacious than 1 μg/kg in children. Similarly**, Kawaai H, Tomita S, Nakaike Y, Ganzberg S, Yamazaki S.(2010)**[62] found that higher dose of dexmedetomidine i.e. 0.4 μg/kg/hr was safer than 0.2 μg/kg/hr in intravenous sedation. **Peng L, Juan L, Mengchang Y, Jun G.(2012)**[64], compared the sedative effects of different doses of dexmedetomidine (DEX) i.e. 0.2, 0.8 and 1.4 μg/kg/hr, midazolam (MDZ) i.e.0.5, 1and 1.5 μg/kg/hr and combination of DEX and MDZ in sixty dental implant surgery and found that the combination of DEX and MDZ is superior to a single intravenous injection. Low-dose MDZ in combination with high-dose DEX achieved the highest quality of sedation.

Surendar MN, Pandey RK, Saksena AK, Kumar R, Chandra G.(2014)[55]conducted a study to evaluate and compare the safety and efficacy of three drug dexmedetomidine (D1-1 μg/kg and D2-1.5 μg/kg), midazolam (0.2 μg/kg) and ketamine (1-5 μg/kg) administered intra nasally and it was found that onset of sedation was significantly

fasterwith midazolam and ketamine group as compared to two different doses of dexmedetomidine group .There was no significant adverse effects with any group.

Surendar MN, Pandey RK, Saksena AK, Kumar R, Chandra G. (2014)[55] conducted a study to compare dexmedetomidine, midazolam and ketamine administered intra nasally for their sedative and analgesic properties. Eighty four ASA physical status grade I children of both genders aged 4-14 years, who could not be managed by basic behavior management techniques. It was concluded that the three drugs proved safe and effective in uncooperative pediatric dental patients for producing moderate level of sedation.

Zanaty OM, Metainy SA. (2015)[58] evaluated and compared dexmedetomidine, ketamine and the combination of these drugs as a premedication using nebulizers. Sixty children ASA physical status I and II, 3 to 6 year age group for pediatric outpatient dental surgeries and it was found that a combination of low-dose ketamine and dexmedetomidine produced more acceptable sedation and provided a smoother induction of general anesthesia than ketamine or dexmedetomidine alone, as well as it provided more rapid recovery with no adverse effects.

Corcuera-Flores JR, Silvestre-Rangil J, Cutando-Soriano A, López-Jiméne J. **(2016)**[92] conducted a review to discover the safest and most efficient sedative drugs so as to ensure successful sedation with the least adverse effects. 473 studies were then assessed for inclusion in this literature review. The result showed sedative drugs like ketamine, dexmedetomidine and propofol have also been proven safe and effective.[90]

Reshetnikov AP, Kasatkin AA, Urakov AL, Baimurzin DY. **(2017)**[93] reported a case of eliminating exaggerated gag reflex effectively with dexmedetomidine intravenously in a dental patient. It was concluded that dexmedetomidine use for sedation may be an alternative to other pharmacological agents in patients' suffering from dental anxiety along with exaggerated gag reflex.

Mohite V, Baliga S, Thosar N, Rathi N.(**2019)**[94] carried out a review to highlight the role of dexmedetomidine in pediatric dental sedation. It was concluded that it can be an alternative pediatric sedative.

INTRANASAL DEXMEDETOMIDINE IN COMPARISON WITH OTHER ROUTES-

Shirakami G, Tanimoto K, Matsuura S, Fukuda K. (2008)[95] reported a case of a 22-year-old male patient with autism and epilepsy. Oral premedication with dexmedetomidine and then followed by midazolam with ketamine intravenously was acceptable and effective to position intravenous cannula. It was found that Oral and intravenous dexmedetomidine was useful for anesthetic care in the patient with special health care needs.[95]

Cimen Z. S, Sivrikaya G. U, Kilinc L. T, Dobrucali H, Hanci.(2010)[59] found that intranasal route was better than oral route with rapid onset time and more effective sedation level, better parental separation conditions and mask tolerance at anesthesia induction and less hemodynamic effects. In successive study same author compared intranasal administration of dexmedetomidine with buccal administration and found the intranasal route to be more effective for premedication in 52 patients aged 2–6 years in ASA I□II children **(Cimen Z. S, Sivrikaya G. U, Kilinc L. T, Dobrucali H, Hanci. 2013)**[60]**.**

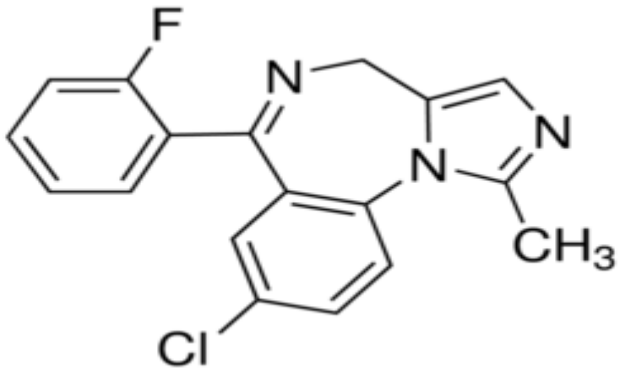
Patel V, Singh N, Saksena AK, Singh S, Sonkar S K, Jolly S M.(2018)[104] conducted a study to evaluate the safety and efficacy of intranasal and oral dexmedetomidine for procedural sedation in pediatric dental patients. Forty-four American Society of Anesthesiologists physical status uncooperative children, requiring dental treatment were randomly divided into four groups. They received different doses of dexmedetomidine intranasally and orally. It was concluded that dexmedetomidine is a safe and efficient drug for with intranasal route having many advantages over oral route.[104]

MIDAZOLAM:

Midazolam is a short-acting benzodiazepine with an elimination half-life of 1.5-2.5 hours. In the elderly, as well as young children and adolescents, the elimination half-life is longer. The therapeutic as well as adverse effects of midazolam are due to its effects on the $GABA_A$ receptors; midazolam does not activate $GABA_A$ receptors directly but, as with other benzodiazepines, it enhances the effect of the

neurotransmitter GABA on the $GABA_A$ receptors (↑ frequency of Cl− channel opening) resulting in neural inhibition. Almost all of the properties can be explained by the actions of benzodiazepines on $GABA_A$ receptors. These results in the following pharmacological properties being produced: sedation, induction of sleep, reduction in anxiety, anterograde amnesia, muscle relaxation and anticonvulsant effects.

CHEMICAL STRUCTURE-



MECHANISM OF ACTION-

It has been postulated that the actions of benzodiazepines are mediated through inhibitory neurotransmitter gamma-aminobutyric acid (GABA), which is one of the major inhibitory neurotransmitters in the brain. Benzodiazepines are said to increase the activity of GABA, thereby calming the patient, relaxing skeletal muscles, and in high doses, producing sleep. Benzodiazepines act as agonists at the benzodiazepine receptors, which have been seen to form a component of the benzodiazepine-GABA receptor-chloride ionophore complex. Most anxiolytics appear to act through at least one component of this complex to enhance the inhibitory action of GABA. Other actions of benzodiazepines, such as sedative, anticonvulsant, and muscle relaxant effects, may be mediated through a similar mechanism, although different receptors subtypes may be involved.[65]

The hypnotic effect of midazolam appears to be related to GABA accumulation and occupation of the benzodiazepine receptor. Midazolam has a relatively high affinity (twiceas that of diazepam) for the benzodiazepine receptor. It is believed that there are separate benzodiazepine and GABA receptors coupled to a common ionophore (chloride) channel, and that occupation of both receptors produces membrane

hyperpolarization and neuronal inhibition. Midazolam interferes with reuptake of GABA, thereby causing accumulation of GABA. [66]

PHARMACOKINETICS-

Absorption- Bioavailibility oral 40% intramuscular 90%.

Metabolised by cytochrome P450 (CYP) enzymes and by glucuronide conjugation.

Elimination half-life: 1.5-2.5 hours

After midazolam is absorbed from its administration site, it is carried to its action site by the blood plasma. In the plasma, midazolam is bound extensively to plasma proteins and the unbound drug is pharmacologically active only. The drug is metabolized to alpha-hydroxy-midazolam and immediately is conjugated by glucuronic acid to form a pharmacologically inactive end product that gets eliminated in the urine. Two other metabolites are excreted in insignificant amounts.[67] Peak serum concentrations of midazolam are reached at different times in children depending on the administration methods IM and rectal routes peak at 15 and 30 min after administration, respectively, while the oral route serum concentration peaks in less than i hr. The metabolic turnover of midazolam in children is more rapid than in adults due to children's more active fiver metabolism. The elimination half-life is approximately 45-60 min since a child as compared with 2-6 hr in an adult.[68, 69] Midazolam is eliminated significantly faster when compared with diazepam's elimination half-life of 24-57 hr. [70]

PHARMOCODYNAMICS-

Midazolam causes a moderate decrease in cerebrospinal fluid pressure (lumbar puncture measurements), similar to that produced by thiopental, when it is used for induction of anesthesia in patients without intracranial lesions. In intracranial surgical patients with normal intracranial pressure but decreased compliance (subarachnoid screw measurements), midazolam attenuates the increase in intracranial pressure because of intubation to a degree comparable to that of thiopental. [71]

Studies have shown that intraocular pressure is lowered moderately when midazolam is used for induction of anesthesia in patients without eye disease; studies have not been done in patients with glaucoma.[71] Midazolam, like other benzodiazepines, may have anti-cholinergic effects on patients with glaucoma (angle-closure, acute).

Respiratory depression is produced[67, 71] however, the respiratory depressant effect of midazolam is dose-related .[71, 72]

The cardiovascular effects of midazolam appear to be minimal. Cardiac hemodynamic studies have shown midazolam to cause slight to moderate decrease in mean arterial pressure, cardiac output, stroke volume, and systemic vascular resistance when used for induction of anesthesia.[73] In a study comparing the systemic vascular effects of midazolam and lorazepam in patients on cardiopulmonary bypass, midazolam was more effective than lorazepam in attenuating the increase in systemic vascular resistance accompanying cardiopulmonary bypass.[74]midazolam may cause slow heart rates (less than 65 per minute) to rise slightly, especially in patients taking propranolol for angina; it may cause faster heart rates (e.g., 85 per minute) to slow slightly .[70]

USE OF MIDAZOLAM AS A SEDATIVE AGENT IN MEDICAL FIELD

Mitra S, Kazal S, Anand LK. (2014)[76] carried out a study to evaluate anxiolysis produced by clonidine with midazolam administered intranasally as a premedication in children undergoing surgery. Sixty ASA physical status I-II surgical patients 1-10 yr of age were included in the study. They received either intranasal clonidine 4 mcg/kg with atropine or intranasal midazolam 0.3 mg/kg .It was concluded that though midazolam produced rapid sedation; both the agents produced satisfactory anxiolysis.

Plum AW, Harris TM.(2015)[77] performed a study to describe the unique topical use of intranasal midazolam for anxiolysis in two pediatric patients at the time of closed reduction of nasal fractures. A retrospective case study was considered. It was concluded that intranasal midazolam can provide effective anxiolysis for pediatric patients during closed reduction of nasal fractures.

Koekkoek JA, Postma TJ, Heimans JJ, Reijneveld JC, Taphoorn MJ.(2016)[78] carried out a study to assess the feasibility of non-oral Anti epileptic drug treatment in

an out-of-hospital setting according to an expert-based guideline. The patient's caregiver administered prophylactic treatment with buccal clonazepam and acute seizures were treated with intranasal midazolam. It was concluded that it is feasible to treat seizures with a combination of non-oral benzodiazepines in the end of life phase of glioma patients, as it seems to provide an important level of comfort among caregivers to be able to manage seizures at home.

Ku LC, Simmons C, Smith PB, Greenberg RG, Fisher K, Hornik CD, Cotten CM, Goldberg RN, Bidegain M(2018)[79] performed a study to evaluate the safety of intranasal midazolam and intranasal fentanyl in infants admitted to the Neonatal Intensive Care Unit. 7 infants received 25 intranasal doses. It was concluded that both the drugs intranasally in term and preterm infants appeared safe and well-tolerated.

USE OF MIDAZOLAM AS A SEDATIVE AGENTIN DENTAL FIELD

Clark RN, Rodrigo MR. (1986)[97] carried out a comparative study of intravenous diazepam and midazolam for oral surgery. The drugs produced comparable levels of sedation, stable vital signs, and good operating conditions in all patients. It was found that a significant majority of the patients preferred sedation to other techniques and midazolam to diazepam.

Krämer N, Krafft T, Kunzelmann KH, Hickel R.(1990)[99]conducted a study to evaluate Midazolam to be a valuable addition to the range of therapeutic options for non-cooperative children. In a clinical study the oral and rectal routes of administration were compared with each other. Rectal application allowed considerably better dose adjustment. While the quality of sedation and the therapeutic range were equal with both routes, rectal application had the advantage that treatment can be commenced sooner. The sedation was of shorter duration and left the patient with less unpleasant memories. It was found that rectal application was easier and required a smaller amount of Midazolam than oral administration.

Pruitt JW, Goldwasser MS, Sabol SR, Prstojevich SJ. (1995)[100]carried out a study to check the safety and efficacy of a new sedation technique for children with facial injuries in the emergency department. Thirty-seven children between the ages of 12 months and 7 years old who required sedation for minor surgical procedures were

administered an intramuscular injection of ketamine (3 mg/kg), midazolam (0.05 mg/kg), and glycopyrrolate (0.005 mg/kg).It was concluded that the use of intramuscular ketamine, midazolam, and glycoyrrolate is a safe, effective, and practical approach to managing selected pediatric injuries in the emergency department.

Singh N, Pandey RK, Saksena AK, Jaiswal JN. (2002)[101] conducted a study to evaluate the safety and efficacy of orally administered midazolam in children as a sedative agent and to compare it with two other older agents, triclofos and promethazine. The study was conducted on ninety child patients requiring some short dental procedure. All the patients were with a good physical status (ASA-I). The ages ranged between 3 and 9 years. It was found that Midazolam was found to be the best drug among the three to produce conscious sedation in children.

Pisalchaiyong T, Trairatvorakul C, Jirakijja J, Yuktarnonda W.(2006)[102]carried out a study to evaluate the efficacy of oral diazepam (0.3 mg/kg) and midazolam (0.5 mg/kg) in sedation for dental treatment in autistic children. It was found that midazolam was more efficient than diazepam in those patients with increased stimulation.

Damle SG, Gandhi M, Laheri V. (2008)[103] carried out a study assess the sedative effect of oral ketamine and oral midazolam prior to general anesthesia. Twenty uncooperative children in the of 2-6 years age-group were selected after thorough medical investigations. An anesthesiologist administered either 0.5 mg/kg midazolam or 5 mg/kg ketamine orally. It was concluded that oral midazolam showed better response whereas side effects were more prominent with ketamine orally.[103]

Wood M. (2010)[82] conducted a study to assess whether a combination of intranasal midazolam and inhalation sedation with nitrous oxide and oxygen is a safe alternative to dental general anesthesia. 100 children of age group between 3 and 13 years who were referred for DGA were treated with intranasal midazolam. It was concluded that this technique provides a safe and effective alternative to DGA and could decrease the number of patients referred for DGA.

Sheta SA, Al Sarheed MA, Abdelhalim AA. (**2014)**[84]performed a study to evaluate the use of dexmedetomidine and midazolam administered intranasally as a premedication in children undergoing dental rehabilitation. Seventy-two children of ASA physical status (I & II), aged 3-6 years, were randomly assigned to either of the groups who received intranasal midazolam (0.2 mg·kg(-1) and intranasal dexmedetomidine (1 μg·kg(-1)).It was concluded that 1mcg/kg dexmedetomidine is an effective and safe alternative intranasally; it resulted in superior sedation in comparison to 0.2 mg/kg midazolam.

Shanmugaavel AK, Asokan S, John JB, Priya PR, Raaja MT.**(2016)**[86]conducted a study to compare the difference in anxiety level and acceptance of drug after intranasal and sublingual midazolam sedation. Forty three- to seven-year-olds were randomly assigned to Group A (0.2 mg/kg intranasal midazolam) or Group B (0.2 mg/kg sublingual midazolam) sedation. It was concluded that both the groups were equally effective in reducing the child's anxiety but the sublingual route was better accepted than the intranasal route.

Manso MA, Guittet C, Vandenhende F, Granier LA.**(2019)**[93]conducted a review to check efficacy of oral midazolam for minimal and moderate sedation in pediatric patients. A total of 25 pediatric clinical studies, utilizing a variety of measures of sedation effectiveness, were selected. These studies included a total of 1472 patients (aged 4 months-18 years) treated with midazolam (0.25-1.5 mg/kg) and 138 patients treated with placebo. It was concluded that the probability of occurrence of adverse events and over-sedation increases with increasing doses.

INTRANASAL MIDAZOLAM IN COMPARISON WITH OTHER ROUTES-

Shavit I, Feraru L, Miron D, Weiser G. **(2012)**[75]conducted a study to examine the rate of urine culture contamination (UCC) in infants who underwent UC with and without sedation. One hundred and forty-one patients were treated with oral midazolam and twenty three received the drug intranasally. It was concluded that sedation with oral or intranasal midazolam reduced the risk of culture contamination during UC without causing serious adverse events.

Ransford NJ, Manley MC, Lewis DA, Thompson SA, Wray LJ, Boyle CA, Longman LP.(2010)[81] carried out a study to evaluate the combined intranasal/intravenous midazolam sedation technique. This study included patient with severe disabilities who were not able to co-operate with dental treatment. It was concluded that this study provided sufficient basis to justify its use by properly qualified dental practitioners in primary care.

Chopra R, Mittal M, Bansal K, Chaudhuri P.(2013)[83]performed a study to evaluate the acceptance of midazolam spray through buccal route as compared to intranasal route and compare the efficacy of the drug through both the routes. Thirty patients aged 2-8 years with Frankel's Behaviour Rating Scale I and II were selected who required similar treatment under local anesthesia on two teeth. Midazolam spray was administered randomly through buccal or intranasal routes for the two visits. It was found that Midazolam spray can be efficiently used through the buccal mucosa in children who give poor compliance with the intranasal administration.

Musani IE, Chandan NV.(2015)[85]carried out a study to evaluate oral midazolam with a dose of 0.2 mg/kg and nitrous oxide-oxygen sedation with a combination of dose 0.1 mg/kg intranasal midazolam and nitrous oxide-oxygen sedation for efficiancy, acceptance and safety in controlling the behaviour of 30 uncooperative children. It was found that the intranasal route of midazolam administration has a quick onset of action and a quick recovery of the patient from sedation as compared to the oral route of midazolam administration.

STUDIES COMPARING MIDAZOLAM AND DEXMEDETOMIDINE-

Ustün Y, Gündüz M, Erdoğan O, Benlidayi ME.(2006)[94]conducted a study to compare dexmedetomidine with midazolam during intravenous sedation in third molar surgery. Twenty healthy patients with impacted mandible third molars were included in this randomized study. Either dexmedetomidine (4 mg/kg (-1)/h (-1)) or midazolam (group M) (0.4 mg/kg (-1)/h (-1)) was administered intravenously. It was concluded that Dexmedetomidine may be a alternative to midazolam because it seems to be a reliable and safe method, with additional analgesic effect providing a satisfactory sedation level without any serious side effects.

In a Randomized double blind study dexmedetomidine and midazolam were compared for intravenous sedation during third molar surgery and concluded that dexmedetomidine is more acceptable to patients and no restlessness or disinhibition is seen in patients **(Cheung CW, Ying CLA, Chiu WK, Wong GTC, Ng KFJ, Irwin MG. 2007)**[43].During implant surgery dexmedetomidine and midazolam were equally effective (**Kuwaai Thawley VJ and Drobatz KJ 2014)**[44]. Contrary to above**,(Fan TW, Ti LK, Islam.2013**[45];**Sisi Li, Yang Y, Cong Y, Ying Y, Yujia W and Lian Q. 2015)**[46]found that dexmedetomidine provide better sedation, postoperative analgesia than midazolam during office-based artificial tooth implantation and a combination of dexmedetomidine and midazolam were found to be more effective than the sedatives alone **(Wakita R, Kohase H, Fukayama H. 2012)**[47].

To check safety and efficacy,**(Saad A, Sheta A, Maha A, Sarheed AL, Ashraf A 2013**[9]**; Sheta MA, AlSarheed, Ashraf A. Abdelhalim 2014**[51]**;Fan TW, Ti LK, Islam I. 2013)**[45] concluded that dexmedetomidine can be effective alternative to midazolam and **(Yuen VM,Hui TW Irwin MG,Yuen MK. 2008)**[52]and**(Linares S B, G MA, Ramírez Casillas IL, Romero G, Botello Buenrostro I, Monroy Torres. 2014)**[53]showed that dexmedetomidine was found to be more effective than midazolam and, contrary to these study(**Mostafa G. M and Khaled M. M. 2013)**[54]showed that the safety and efficacy of midazolam was better than dexmedetomidine.

Dexmedetomidine was compared with midazolam as a premedication **(Ghali AM, Mahfouz AK, Al-Bahrani. 2011)**[56]and **(Zhou C, Zhao J. 2014)**[57].In both the studies, dexmedetomidine was found to be a superior alternative to midazolam. However, dexmedetomidine was related with lower level of sedation and anxiety, but easier parent-child separation than the group who received midazolam orally.

Mahdavi A, Fallahinejad Ghajari M, Ansari G, Shafiei L.(2018)[87]conducted a study to compare the premedication effect of dexmedetomidine versus midazolam intranasally on the behavior of uncooperative children in the dental clinic. 20 uncooperative children 2-6 years of age group who needed at least two similar dental treatment visits were included in the study. The subjects were randomly given 1 μg/kg of dexmedetomidine and 0.5 mg/kg of midazolam intranasally. It was concluded that

both the groups were satisfactory and effective premedication regimens for uncooperative children.

MATERIALS AND METHODS

The present study was conducted in Department of Pediatric and Preventive Dentistry, BBDCODS, Lucknow. The study was done with an aim to evaluate and compare the efficacy and safety of midazolam and dexmedetomidine administered intranasally for procedural sedation in pediatric dental patients. After obtaining clearance from institutional ethical committee of BBDCODS, Lucknow**,** 76 patients, who fulfilled the inclusion and exclusion criteria, were enrolled for the study. A written informed consent from the parents/guardian and assent form from the child were obtained before the treatment**.**

SAMPLE SIZE CALCULATION

Healthy subjects aged between 3-9 years were included in the study.

The sample size per group was calculated by using the following formula-

$$n = \frac{t \times t \times p\,(1-p)}{e^{\wedge 2}}$$

$$= \frac{1.96 \times 1.96 \times 0.05\,(1-0.05)}{0.05^{\wedge 2}}$$

$$= 72.99$$

$$\approx 74$$

where, n= sample size ,t= confidence level of t statistic at 95%, standard value= 1.96 ,p= difference in sedation= 5% ,e= margin of error= 0.05%

Thus, a minimum 74 subjects should be recruited for two groups and 37 for one group.The data collected from the study was subjected for statistical analysis

INCLUSION CRITERIA:

- Fearful and anxious children of age group 3 – 9 years and of both genders who were uncooperative towards dental treatment and difficult to be managed by non-pharmacological means of behavior management.

- Children satisfying American Society of Anesthesiologists (ASA) classification – I physical status.

EXCLUSION CRITERIA:

- Patients for whom parental consent could not be obtained.
- Patients who are known allergic to the drugs to be used.
- Patients taking any other drug that causes sedation.
- Patients with nasal infections and nasal pathologies.

MATERIALS USED:

- Midazolam spray 5ml bottle with a dispenser of 0.5mg per puff (Midacip,Cipla Pharmaceuticals)
- Dexmedetomidine Hydrochloride injection 0.5 ml ampule with a concentration of 50 mcg/ml. (Dextomid, Neon Pharmaceuticals)
- Multipara monitor (Planet 50 n Lifecare)
- Nasal MAD (Mucosal atomizer device, LMA MAD nasal limited)
- Emergency drugs
- Procedure specific armamentarium

STUDY DESIGN:

76 children in age group of 3-9 years belonging to both genders for which basic behavior modification techniques were not successful in providing dental treatment were enrolled in the present study. The patient was then managed by pharmacological method of behavior management.

Patients were randomly divided into two groups, each group consisting of 38 participants. Group I - administration of intranasal midazolam (0.3 mg/kg) and Group II - administration of intranasal dexmedetomidine (2.5mcg/kg).

METHODOLOGY:

Seventy six systemic healthy children (ASA type I) between the age group of 3-9 years for whom basic behavior modification technique were not successful in providing dental treatment were considered for the study. The parent/guardian were requested to fill a written informed consent form (Annexure no 5) and children 8 years of age and above were asked to fill the assent form. Risks and benefits of the sedation were explained to the parent/guardian at the initial appointment.

A thorough dental and medical history was taken. A detailed evaluation of the airway (tonsillar hypertrophy, abnormal anatomy, ability to visualize only the hard palate or tip of uvula) to assess the risk of airway obstruction was carried out. A review of systems with a focus on abnormalities of cardiac, pulmonary, renal or hepatic functions that may alter the child's expected responses to sedating medication was carried out. Pre-sedation dietary instructions were given to the patient according to the American Society of anesthesiologist (Annexure no 6). A comprehensive preanaesthetic assessment was performed by an experienced anesthesiologist at Babu Banarasi Das College of Dental Sciences, Lucknow. The blood investigations and the chest X-ray was advised to the patient before the day of sedation. The sedation was only carried out when all the parameters were within the normal ranges.

On the day of dental treatment, they were re- evaluated by the anesthesiologist. The vital signs (pulse rate & blood pressure) and the peripheral oxygen saturation levels were examined and recorded with the help of multiparamonitor.

Before the administration of drug, the body weight was measured and the drug was calibrated according to the body weight. Half the volume of required amount of drug was administered into each nostril with the patient in semi recumbent position using a nasal spray or an atomizer device for intranasal administration.

During each sedation session the children were evaluated for the behavior response for acceptance of drug during the administration of drug while after the administration of drugs, they were evaluated to check onset of sedation, peak of sedation, ease of completion of treatment, recovery from sedation, side effects of drug. All the dental procedures were carried out by a single operator in the presence of an anesthesiologist.

The vital signs (Pulse rate, Blood pressure and Oxygen saturation (Annexure no 7) were noted down before the administration of the drug and at every 5 min interval after the administration of the drug till span of 60 minutes.

The Ohio State Behavioral Rating Scale (OSBRS) as described by Lochary and co-workers, 1992 was selected for the patient's drug acceptance (Annexure no 8) and noted down for every patient.

The time for the onset of sedation was noted down. The onset of sedation was noted when the level of sedation of the patient was relatable to score 2 according to the sedation rating scale (AAPD 2006 modified by **Padmanabhan et al. 2009**). Similarly the peak of sedation was noted when the level of sedation of the patient was relatable to score 3 according to the sedation rating scale.

The levels of sedation were measured using a scale given by **Padmanabhan et al. 2009** (Annexure no 9) scale depending upon the patients' response. The sedation levels were noted down for both the groups. The ease with which treatment (Annexure no 10) could be completed was scored. After the completion of the treatment, patient was transferred to the recovery room.

Post sedation side effects were also noted. The time required for complete recovery was recorded. Patient was noted as fully recovered after achieving certain criteria using the Aldrete Recovery Scoring 2015 (Annexure no 11). Vital signs were re-

evaluated and once AAPD sedation guidelines for discharge were fulfilled the patient was discharged (Annexure No 12). The discharge time was calculated from the end of the procedure till the patient left the hospital. Post discharge instructions were given to both the parents and the patient.

STATISTICAL ANALYSIS:

Continuous data were summarized as Mean ± SD (standard deviation) while discrete (categorical) in number (n) and percentage (%.) Continuous groups were compared by independent Student's t test. Continuous groups were also compared by repeated measures two factor (groups and periods) analysis of variance (ANOVA) and the significance of mean difference within (intra) and between (inter) the groups was done by Tukey's HSD (honestly significant difference post hoc test after ascertaining normality by Shapiro-Wilk's test and homogeneity of variance by Levene's test. Categorical groups were compared by chi-square (χ^2) test. A two-tailed (α=2) probability (p) value less than 0.05 ($p<0.05$) was considered statistically significant. Analyses were performed on SPSS software (Windows version 17.0).

RESULTS

The present study evaluated and compared intranasal midazolam and dexmedetomidine for procedural sedation in pediatric patients. Total 76 patients in age group of 3-9 years were recruited and randomized equally into two groups on the basis of drug administered with midazolam 0.3 mg/kg (Group 1, n=38) and dexmedetomidine 2.5 μg/kg (Group 2, n=38).

The outcome measures of the study were hemodynamic parameters (heart rate, SBP, DBP and oxygen saturation), acceptance of drug, level of sedation, ease of treatment, recovery time (minutes), onset time (minutes), peak sedation time (minutes), discharge time (minutes) and post operative complications. The hemodynamic parameters were assessed at 5 minutes regular interval up to 1 hr.

DEMOGRAPHIC CHARACTERISTICS

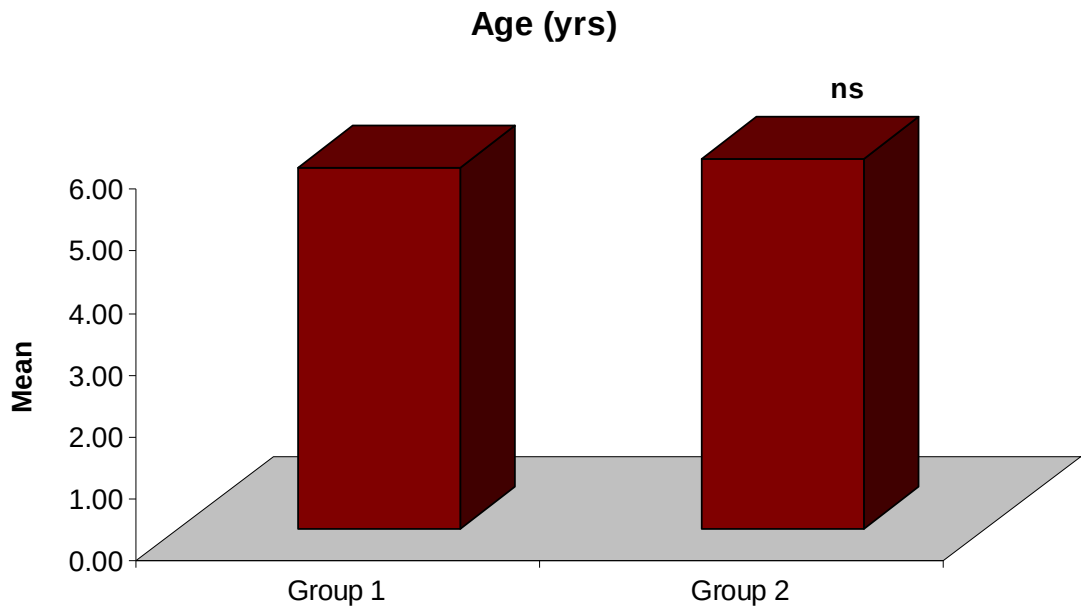
The demographic characteristics of both the groups (Group 1 and Group 2) are summarized in Table 1 and Graph 1 and 2.

In both the groups age ranged from 3 to 9 yrs, respectively with mean (± SD) 5.84 ± 1.48 yrs and 6.00 ± 1.96 yrs, respectively. Further, in Group 1, there were 18 (47.4%) females and 20 (52.6%) males whereas in Group 2, there were 17 (44.7%) females and 21 (55.3%) males. Comparing the mean age, subjects both the groups were age matched.

Table 1: Demographic characteristics of both the groups

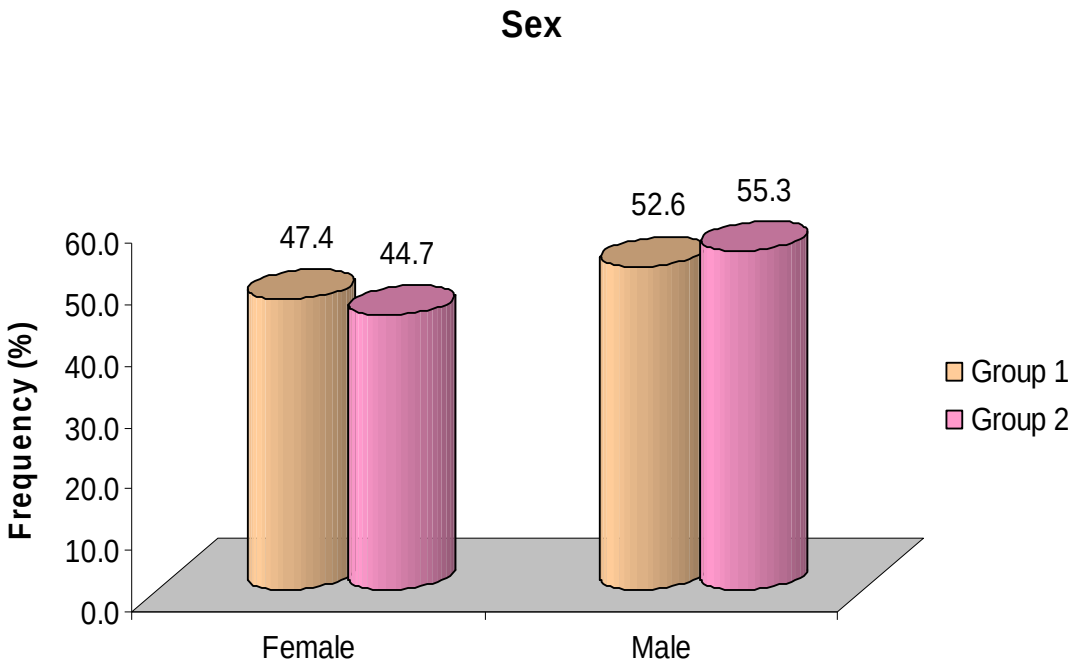
Demographic characteristics	**Group 1 (n=38) (%)**	**Group 2 (n=38) (%)**	**t/χ^2 value**	**p value**
Age (yrs):				
Mean ± SD	5.84 ± 1.48	6.00 ± 1.96	0.40	0.693
Range (minutes to max)	3 to 8	3 to 9		
Median	6	6		
Gender:				
Female	18 (47.4)	17 (44.7)	0.05	0.818
Male	20 (52.6)	21 (55.3)		

The age both the groups were summarized and compared by Student's t test whereas Gender were summarized compared by χ2 test.



[ns]p>0.05- as compared to Group 1

Graph 1. Mean age of subjects in both the groups.



Graph 2. Gender distribution between the groups.

HEMODYNAMIC PARAMETERS

I. Pulse rate

The pulse rate (PR) of both the groups over a period is summarized is Table 2 and Graph 3. In both groups, the mean PR increased after the administration of drug and remained higher till the end of 60 minute session as compared to baseline. Further, at most of the intra operative periods, it was comparatively higher in Group 2 as compared to Group 1.

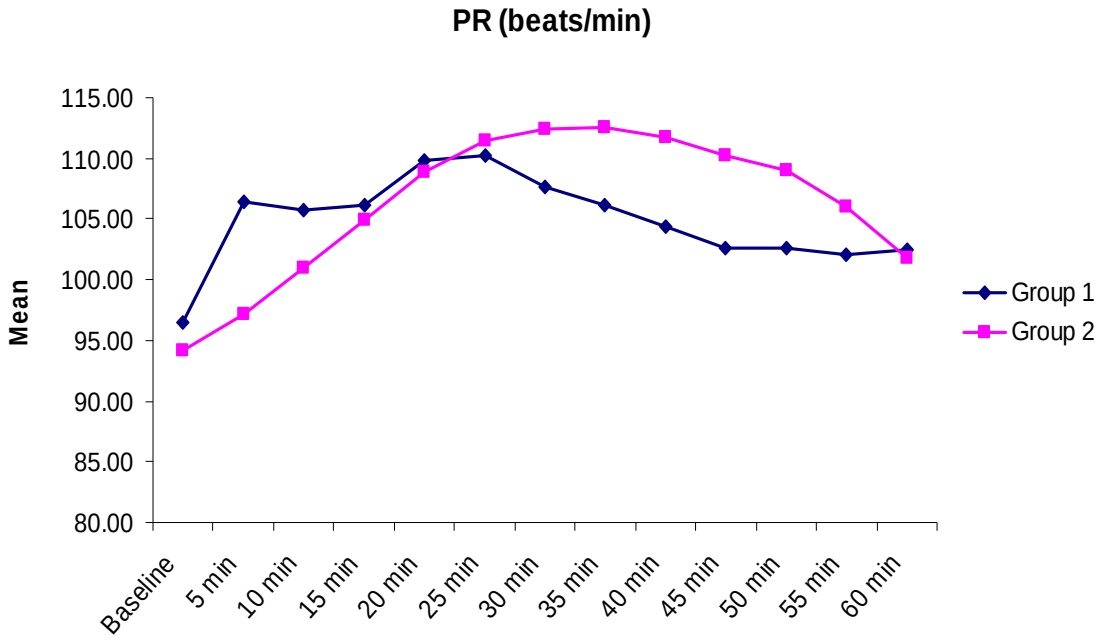
On intra group comparison, the difference in mean PR between baseline and intra operative periods, Tukey test showed significantly higher PR as compared to baseline and at 5 minutes in Group 2.

Similarly, on inter group comparison the difference in mean PR between groups for each period was taken out. Tukey test showed significantly lower PR in Group 2 as compared to Group 1 at 5 minutes In contrast, from 35 minutes to 50 minutes, it was found significantly higher in Group 2 as compared to Group 1. .

Table 2: Pulse Rate distribution (beats/minutes) of both the groups over a period of 60 minutes

Time period	Group 1 (n=38)	Group 2 (n=38)	p value
Baseline	96.47 ± 8.05	94.16 ± 6.28	1.000
5 minutes	106.42 ± 8.57***	97.21 ± 6.86ns	<0.001
10 minutes	105.76 ± 7.50***	100.95 ± 6.87***	0.323
15 minutes	106.18 ± 8.37***	104.87 ± 7.22***	1.000
20 minutes	109.76 ± 8.71***	108.92 ± 5.87***	1.000
25 minutes	110.29 ± 8.62***	111.47 ± 4.59***	1.000
30 minutes	107.63 ± 9.43***	112.37 ± 4.88***	0.358
35 minutes	106.13 ± 9.44***	112.50 ± 4.76***	0.018
40 minutes	104.37 ± 7.68***	111.68 ± 4.83***	0.001
45 minutes	102.55 ± 7.66***	110.18 ± 4.43***	0.001
50 minutes	102.63 ± 6.74***	109.03 ± 4.72***	0.016
55 minutes	102.11 ± 7.99***	106.08 ± 4.77***	0.732
60 minutes	102.45 ± 7.66***	101.84 ± 4.08***	1.000

Pulse Rate of both the groups were compared and summarized. The intra and inter group comparisons were done by repeated measures ANOVA followed by Tukey test. **ns**p>0.05 or ***p<0.001- as compared to baseline (intra group comparison). P value mentioned in last column is comparison between groups



Graph 3. Pulse Rate distribution between the groups over a period of 60 minutes

II. Systolic Blood Pressure

The systolic blood pressure (SBP) of both the groups over a period is summarized in Table 3 and Graph 4. In both the groups, the mean SBP increased after drug administration and remained higher till the end of 60 minute session as compared to baseline. Further, at most of the intra operative period, it was comparatively higher in Group 2 as compared to Group 1.

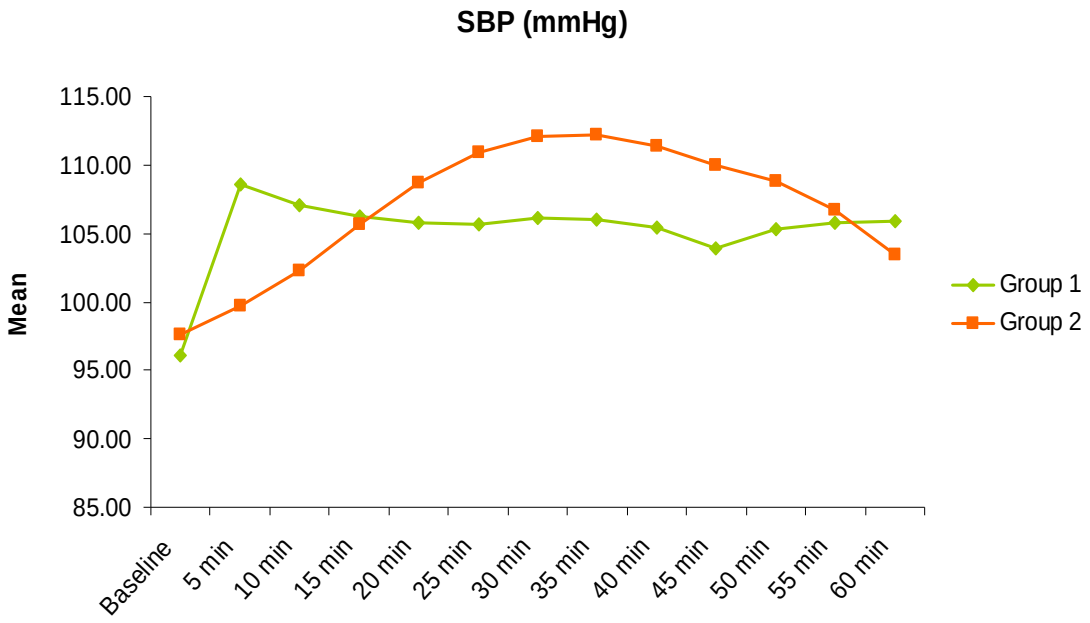
On intra group comparison, the difference in mean SBP between baseline and intra operative periods, Tukey test showed significantly higher SBP as compared to baseline in both groups and 5 minutes in Group 2.

On inter group comparison, the difference in mean SBP, Tukey test showed significantly lower SBP in Group 2 as compared to Group 1 at both 5 minutes and 10 minutes. In contrast, from 25 minutes to 45 minutes, it was found significantly higher in Group 2 as compared to Group 1.

Table 3: Systolic Blood Pressure distribution (mm Hg) of both the groups over a period of 60 minutes

Time period	Group 1 (n=38)	Group 2 (n=38)	p value
Baseline	96.05 ± 6.02	97.58 ± 3.87	1.000
5 minutes	108.58 ± 6.53***	99.71 ± 4.47ns	<0.001
10 minutes	107.05 ± 6.10***	102.26 ± 4.24***	0.009
15 minutes	106.21 ± 6.01***	105.68 ± 4.66***	1.000
20 minutes	105.82 ± 6.11***	108.66 ± 4.46***	0.750
25 minutes	105.66 ± 6.34***	110.95 ± 2.78***	0.001
30 minutes	106.11 ± 5.61***	112.08 ± 3.09***	<0.001
35 minutes	106.00 ± 5.93***	112.24 ± 2.42***	<0.001
40 minutes	105.39 ± 5.58***	111.34 ± 2.16***	<0.001
45 minutes	103.87 ± 6.27***	110.00 ± 2.90***	<0.001
50 minutes	105.34 ± 6.58***	108.79 ± 3.93***	0.343
55 minutes	105.76 ± 5.68***	106.74 ± 4.47***	1.000
60 minutes	105.87 ± 5.73***	103.50 ± 4.73***	0.951

Systolic Blood Pressure of both the groups were compared and summarized. The intra and inter group comparisons were done by repeated measures ANOVA followed by Tukey test. **ns**p>0.05 or ***p<0.001- as compared to baseline (intra group comparison). P value mentioned in last column is comparison between groups (inter group comparison).



Graph 4. Distribution of Systolic Blood Pressure between the groups over a period of 60 minutes.

III. Diastolic Blood Pressure

The diastolic blood pressure (DBP) of both the groups over the period of 60 minute is summarized in Table 4 and Graph 5. In Group 1, the mean DBP decreased after the drug administration and remained lower till the end of 60 minute session as compared to baseline. In contrast, in Group 2, it increased after the drug administration and remained higher up to 55 minutes. For all the time periods, (except at 60 minute), the DBP remained higher in group 2 as compared to group 1.

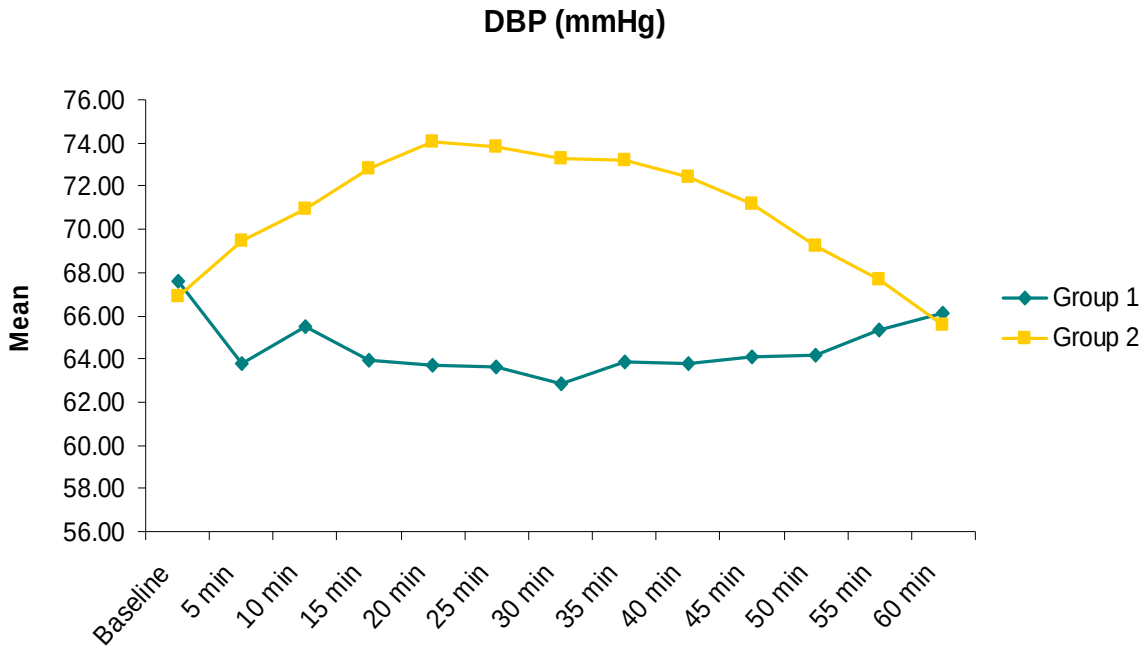
For Intra group comparison, the difference in mean DBP between baseline and intra operative periods, Tukey test showed significantly lower DBP at 5 minutes and from 15 minutes to 50 minutes as compared to baseline in Group 1 but did not differ at other periods (Table 4). In contrast, in Group 2, it was found significantly higher from 5 minutes to 45 minutes but did not differ at other periods.

Similarly, on Inter group comparison, the difference in mean DBP between the groups, Tukey test showed significantly higher DBP in Group 2 was compared to Group 1 from 5 minutes to 50 minutes.

Table 4: Diastolic Blood Pressure distribution (mm Hg) both the groups over a period of 60 minutes

Time period	Group 1 (n=38)	Group 2 (n=38)	p value
Baseline	67.61 ± 5.97	66.87 ± 2.77	1.000
5 minutes	63.82 ± 7.41***	69.47 ± 2.40*	0.001
10 minutes	65.53 ± 7.38ns	70.97 ± 2.21***	0.001
15 minutes	63.97 ± 7.00***	72.82 ± 2.20***	<0.001
20 minutes	63.68 ± 6.29***	74.05 ± 2.00***	<0.001
25 minutes	63.61 ± 6.92***	73.84 ± 2.28***	<0.001
30 minutes	62.82 ± 7.21***	73.29 ± 2.68***	<0.001
35 minutes	63.84 ± 7.39***	73.18 ± 3.40***	<0.001
40 minutes	63.82 ± 6.51***	72.45 ± 3.65***	<0.001
45 minutes	64.11 ± 5.98***	71.16 ± 3.21***	<0.001
50 minutes	64.18 ± 5.50***	69.21 ± 3.37ns	0.005
55 minutes	65.34 ± 6.34ns	67.68 ± 3.10ns	0.964
60 minutes	66.13 ± 6.82ns	65.61 ± 2.88ns	1.000

Diastolic Blood Pressure of both the groups were compared and summarized. The intra and inter group comparisons were done by repeated measures ANOVA followed by Tukey test. **ns**p>0.05 or *p<0.05 or ***p<0.001- as compared to baseline (intra group comparison). P value mentioned in past column is comparison between groups (inter group comparison).



Graph 5. Diastolic Blood Pressure distribution between the groups over a period of 60 minutes.

IV. Oxygen Saturation

The oxygen saturation (SPO2) of both the groups over a period of 6o minutes is summarized in Table 5 and Graph. 6. After administration of the drug, the mean SPO2 remained almost similar to that of baseline in Group 1. In contrast, in Group 2, it increased at 15 minutes to 45 minutes as compared to baseline. Further, at 15 minutes to 50 minutes, it was slightly higher in Group 2 as compared to Group 1.

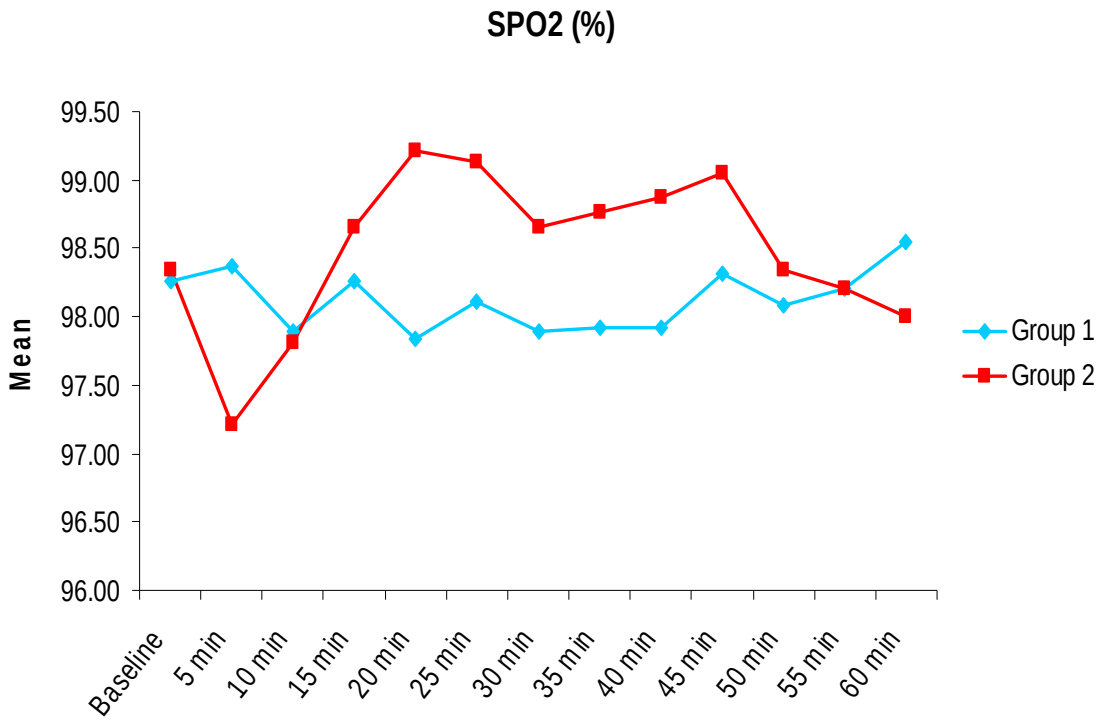
On Intra group comparison, the difference in mean SPO2 between baseline and intra operative periods for each group was taken out. Tukey test showed similar SPO2 at all periods as compared to baseline in both groups i.e. did not differ significantly.

Similarly, on Inter group comparison for each period, the difference in mean SPO2 between groups was taken out. Tukey test showed similar SPO2 between the groups at all periods except 20 minutes. At 20 minutes, it was found significantly higher in Group 2 as compared to Group 1.

Table 5: Oxygen Saturation distribution of both the groups over a period of 60 minutes

Time period	Group 1 (n=38)	Group 2 (n=38)	p value
Baseline	98.26 ± 1.72	98.34 ± 1.40	1.000
5 minutes	98.37 ± 1.57^{ns}	97.21 ± 1.04^{ns}	0.138
10 minutes	97.89 ± 1.67^{ns}	97.82 ± 1.43^{ns}	1.000
15 minutes	98.26 ± 1.80^{ns}	98.66 ± 1.40^{ns}	1.000
20 minutes	97.84 ± 1.70^{ns}	99.21 ± 1.26^{ns}	0.018
25 minutes	98.11 ± 1.50^{ns}	99.13 ± 1.34^{ns}	0.347
30 minutes	97.89 ± 1.61^{ns}	98.66 ± 1.34^{ns}	0.893
35 minutes	97.92 ± 1.68^{ns}	98.76 ± 1.26^{ns}	0.762
40 minutes	97.92 ± 1.78^{ns}	98.87 ± 1.34^{ns}	0.524
45 minutes	98.32 ± 1.58^{ns}	99.05 ± 1.09^{ns}	0.924
50 minutes	98.08 ± 1.40^{ns}	98.34 ± 1.55^{ns}	1.000
55 minutes	98.21 ± 1.77^{ns}	98.21 ± 1.60^{ns}	1.000
60 minutes	98.55 ± 1.62^{ns}	98.00 ± 1.39^{ns}	0.998

Oxygen Saturation of both the groups were compared and summarized. The intra and inter group comparisons were done by repeated measures ANOVA followed by Tukey test. **ns**p>0.05 - as compared to baseline (intra group comparison). P value mentioned in last column is comparison between groups (inter group comparison).



Graph 6. Oxygen Saturation distribution between the groups over a period of 60 minutes.

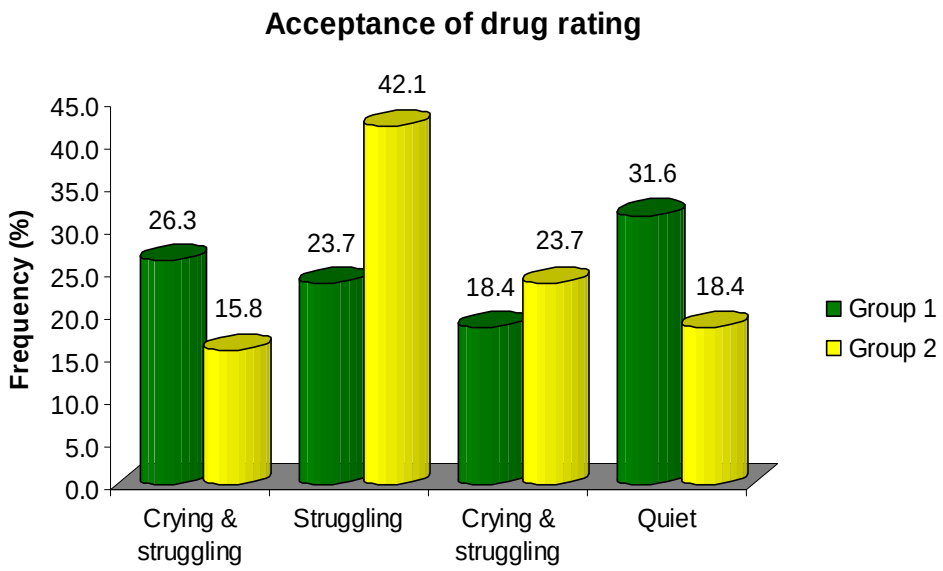
Acceptance of drug

The acceptance of drug of both the groups is summarized in Table 6 and Graph 7. On comparing, acceptance of drug did not differ significantly between the two groups. . The acceptance of drug rating in majority of patients in group 1 were Quiet (31.6%) where as in group 2 were struggling (42.1%).

Table 6: Comparison of acceptance of drug rating between the groups

Acceptance of drug rating:	**Group 1 (n=38) (%)**	**Group 2 (n=38) (%)**	**χ^2 value**	**p value**
Crying & struggling	10 (26.3)	6 (15.8)	4.53	0.210
Struggling	9 (23.7)	16 (42.1)		
Crying	7 (18.4)	9 (23.7)		
Quiet	12 (31.6)	7 (18.4)		

Acceptance of drug rating of both the groups were summarized and compared by $\chi 2$ test. **NA:** not applicable.



Graph 7. Comparison of acceptance of drug rating between the groups.

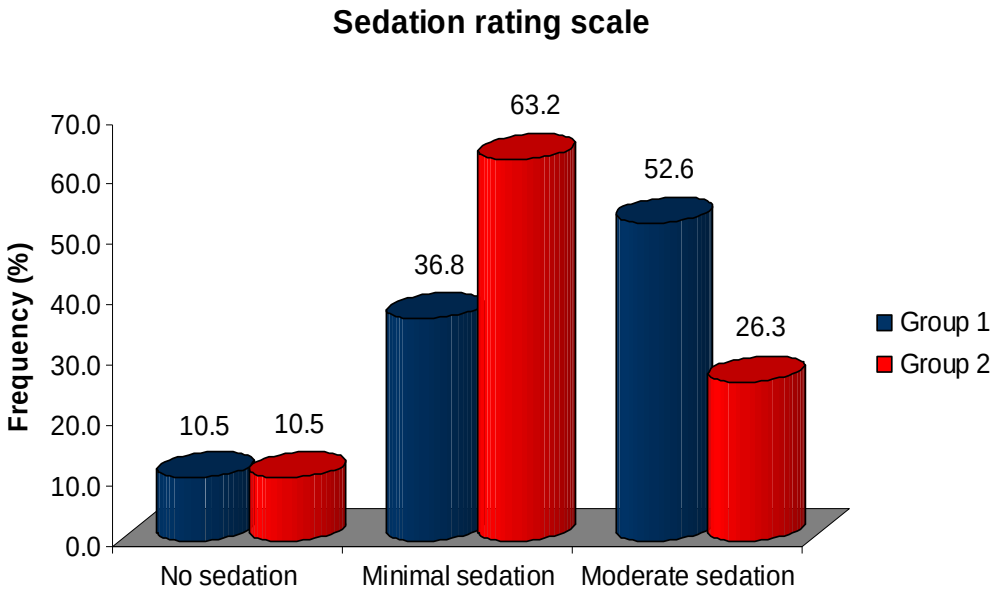
Level of Sedation

The Level of Sedation of both the groups is summarized in Table 7 and Graph. 8. On comparing, level of sedation between both the groups ,the rating in majority of patients in group 1 were moderate (52.6%) where as in group 2 the ratings were minimal (63.2%).

Table 7: Comparison of level of Sedation between the groups

Sedation rating scale	Group 1 (n=38) (%)	Group 2 (n=38) (%)	χ^2 value	p value
No sedation	4 (10.5)	4 (10.5)	5.97	0.051
Minimal sedation	14 (36.8)	24 (63.2)		
Moderate sedation	20 (52.6)	10 (26.3)		

Sedation rating scale of both the groups were summarized and compared by $\chi 2$ test.. **NA:** not applicable.



Graph 8. Comparison of level of sedation between the groups.

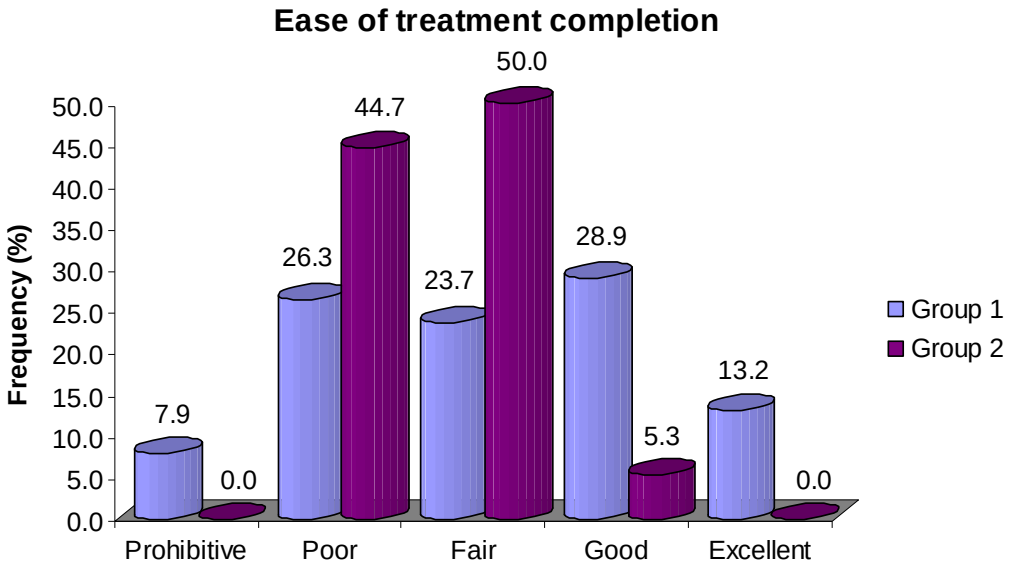
Ease of treatment completion

The Ease of treatment completion between the groups is summarized in Table 8 and Graph. 9. on comparing, ease of treatment completion was found significantly better (36.8%) in Group 1 (42.1%) as compared to Group 2 (5.3%). The ease of treatment rating were good (28.9%) in majority of patients in Group 1 whereas in Group 2, it were Fair (50%).

Table 8: Comparison of ease of treatment completion between the groups

Ease of treatment completion:	Group 1 (n=38) (%)	Group 2 (n=38) (%)	χ^2 value	p value
Prohibitive	3 (7.9)	0 (0.0)		
Poor	10 (26.3)	17 (44.7)	19.62	0.001
Fair	9 (23.7)	19 (50.0)		
Good	11 (28.9)	2 (5.3)		
Excellent	5 (13.2)	0 (0.0)		

Ease of treatment completion of both the groups were summarized and compared by $\chi 2$ test. **NA:** not applicable.



Graph 9. Comparison of ease of treatment completion between groups.

Post operative complication

There were no post operative complications in both the groups. (Table 9)

Table 9: Comparison of Post operative complications between the groups

Post operative complications	**Group 1 (n=38) (%)**	**Group 2 (n=38) (%)**	**χ^2 value**	**p value**
No	38 (100.0)	38 (100.0)	NA	-

OUTCOME MEASURES

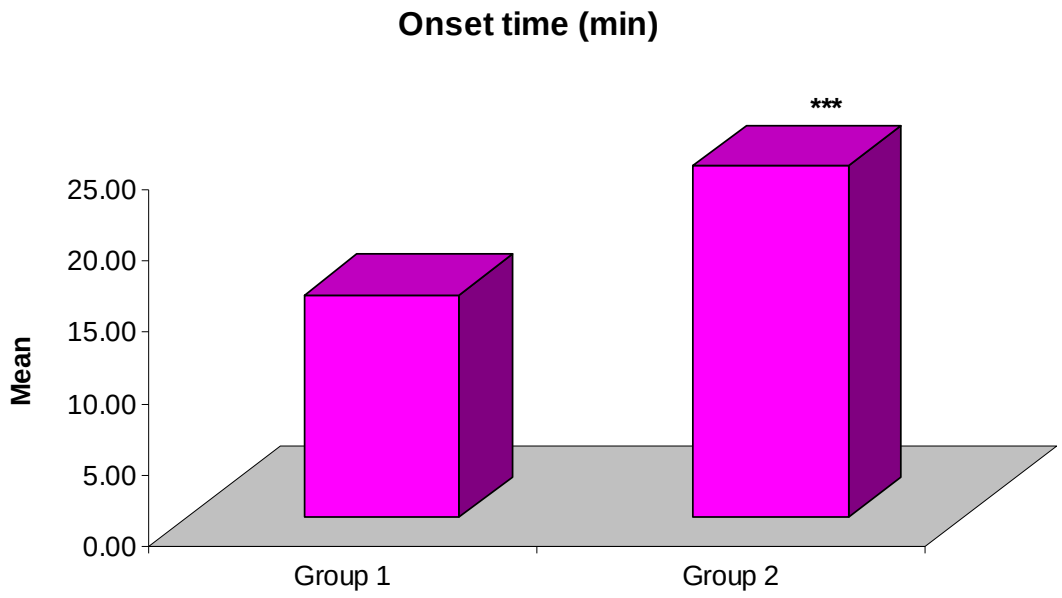
1. Onset time

Onset time of both the groups is summarized in Table 10 and Graph. 10. On comparing the mean, Student's t test showed significantly longer onset time (36.9%) in Group 2 as compared to Group 1.

Table 10: Comparison of onset time of sedative agent in both the groups

Parameter	**Group 1 (n=38)**	**Group 2 (n=38)**	**t value**	**p value**
Onset time (minutes)	15.53 ± 3.82	24.61 ± 4.25	9.79	<0.001

Onset time of both the groups were summarized and compared by Student's t test.



***p<0.001- as compared to Group 1

Graph 10. Comparison of onset time between the groups.

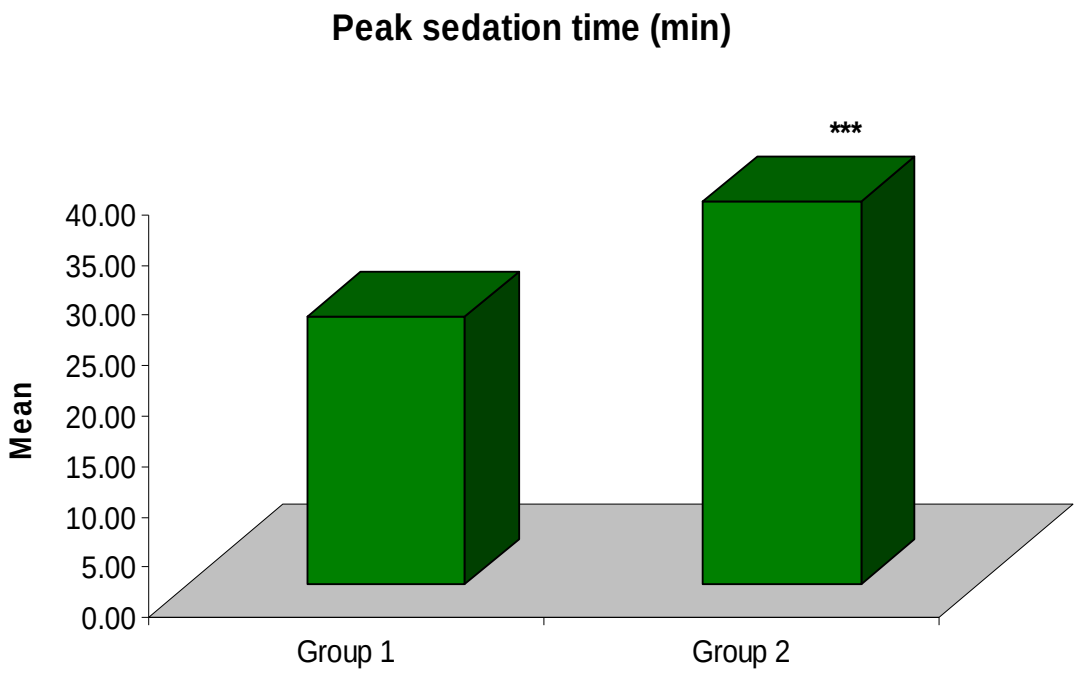
2. Peak sedation time

Peak sedation time of both the groups is summarized in Table 11 and Graph 11. On comparing the mean of peak sedation time, Student's t test showed significantly higher peak sedation time (30.2%) in Group 2 as compared to Group 1.

Table 11: Comparison of peak sedation time between the groups

Parameter	**Group 1 (n=38)**	**Group 2 (n=38)**	**t value**	**p value**
Peak sedation time (minutes)	26.45 ± 3.47	37.89 ± 5.41	10.98	<0.001

Peak sedation time of both the groups were summarized and compared by Student's t test.



***p<0.001- as compared to Group 1

Graph 11. Comparison of peak sedation time between the groups.

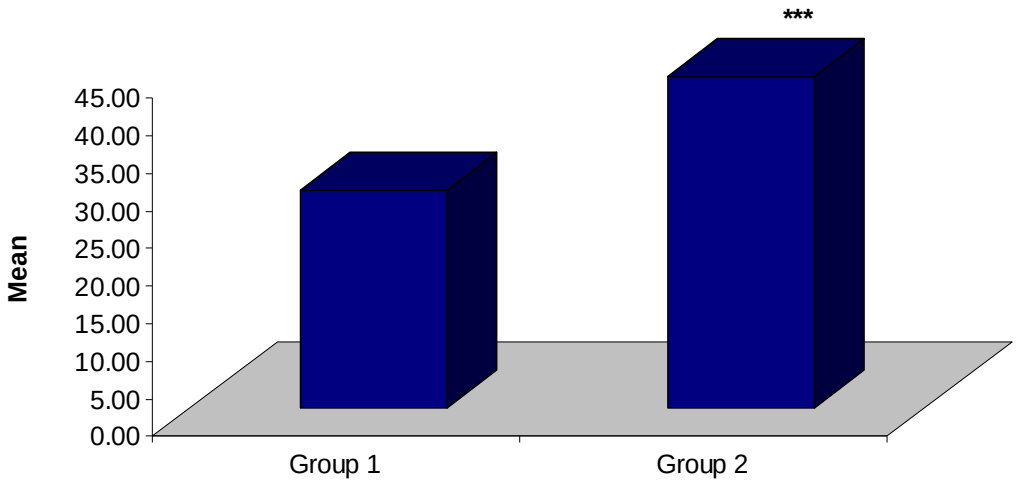
3. Recovery time

Recovery time of both the groups is summarized in Table 12 and Graph 12. On comparing the mean, Student's t test showed significantly higher recovery time (34.2%) in Group 2 as compared to Group 1.

Table 12: Comparison of patients' recovery time of both the groups

Parameter	**Group 1 (n=38)**	**Group 2 (n=38)**	**t value**	**p value**
Recovery time (minutes)	29.05 ± 5.47	44.13 ± 6.78	10.67	<0.001

Recovery time in groups was summarized and compared by Student's t test



***p<0.001- as compared to Group 1

Graph 12. Comparison of recovery time between the groups

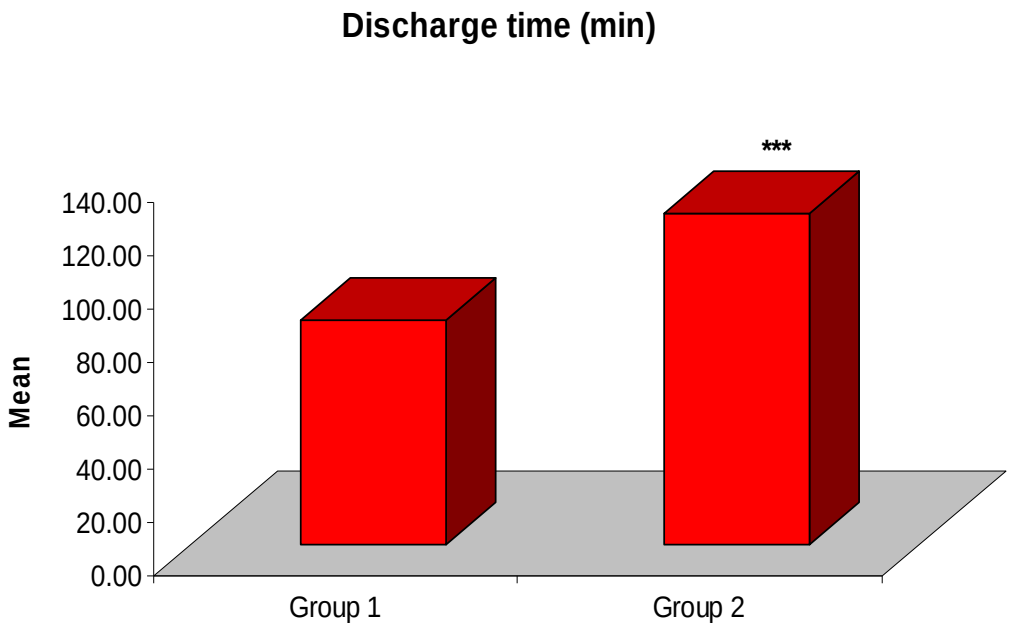
4. Discharge time

Discharge time of both the groups is summarized in Table 13 and Graph 13. On comparing the mean, Student's t test showed significantly higher discharge time (32.3%) in Group 2 as compared to Group 1.

Table 13 .Comparison of patients' discharge time of both the groups

Parameter	**Group 1 (n=38)**	**Group 2 (n=38)**	**t value**	**p value**
Discharge time (minutes)	84.08 ± 7.06	124.21 ± 8.10	23.03	<0.001

Discharge time of both the groups were summarized and compared by Student's t test.



***p<0.001- as compared to Group 1

Graph 13. Comparison of discharge time between the groups.

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DISCUSSION

Pediatric patients often suffer from poor oral health. Various reasons for avoidance of dental treatment in Pediatric patients may be anxiety or fear due to anticipation of pain. Hence, it is utmost duty of a pediatric dentist to perform the dental procedures with such care that the procedure is painless, existing anxiety is relieved and the child does not remember any unpleasant experience on subsequent visits.

One of the solutions to the treatment of unmanageable pediatric patients is the use of general anesthesia. . But, due to its high cost, questionable parental acceptability and associated complications, it is thought to be the less acceptable choice as a behavior management tool for providing dental treatment. Procedural sedation has been considered as one of the most reliable alternatives, to overcome high levels of interfering dental anxiety with acceptable levels of health and safety of the patient when used by skilled pedodontists. **Jorgensen N.B. 1992**[107] stated that moderate sedation (conscious sedation, procedural sedation) is an alternative for general anesthesia while providing dental treatment for uncooperative patients. **Hazha Ibrahim. 2012**[76] also stated that conscious sedation offers a cost effective adjunct for children with limited treatment needs and temperament as compared to general anesthesia. The goal of sedation in pediatric anesthesia is to relieve pre and post-operative anxiety, good child parent separation and ease of completion of procedures**.** Anxiety during pre operative period in children can produce aggressive reactions, increased distress, increased postoperative pain, behavioral changes, and agitation as claimed by **Litke J, Pikulska A, Wegner T. 2012**[108]**.**

Since decades, pediatric dentists have searched for ideal routes of drug administration for sedation. The most common route of sedation is oral route and it is most easily accepted among the various routes of sedation in children[104]. However, the main disadvantage of oral sedation is delayed onset in addition to a long recovery period

and high first pass metabolism as reported by **Fallahinejad Ghajari M, Ansari G, Soleymani AA, Shayeghi S, Fotuhi Ardakani F. 2014[109]. Ji Young Yoon and Eun Jung. 2016[117]** found that intravenous sedation has many advantages compared to other routes such as faster onset, easy titration and speedy recovery but has some major adverse effects that includes deep sedation, hypoxia , cardiovascular depression and venous irritation. **Kramer N, Krafft T, Kunzelmann KH, Hickel R. 1990[99]** stated that Rectal application is often painful and medications administered by this route, may be easily expelled from the rectum in younger children and can be embarrassing when used in older children. Intramuscular premedication has also been used but injection hurts, it often causes bruises and frightens the child. **Primosch RE, Bender F.2001[110]** concluded that transmucosal routes, including intranasal, sublingual and buccal administration, have been shown to be effective because of the rich mucosal blood supply. Moreover, compliance with nasal sedation is easier to achieve than with oral sedation in younger children as stated by **Primosch RE Bender F. 2001[110]**. In support, it had also been reported by **Löwhagen, G.Granerus, H. Wetterqvist. 2002[111]** that the intranasal route has faster onset as compared to the oral route. **Wood M. 2010[82]** concluded that intranasal administration is a safe and effective route for procedural sedation. Hence, in the field of sedation for pediatric dental patients, intranasal route has gained momentum through past few years because of bypass of the first pass metabolism. In an earlier study conducted in our department by **Patel V, Singh N, Saksena AK, Singh S, Sonkar S K, Jolly S M. 2018[104]** it was concluded that intranasal route had distinct advantages when compared to oral route. The study also showed that the intranasal route of conscious sedation is safe and effective for uncooperative children. Therefore, intranasal route was considered for the administration of drugs in the present study.

Various **pharmacological agents** like midazolam, butorphanol, propofol, ketamine, triclofos, promethazine, dexmedetomidine etc have been used by the dentists to provide sedation for dental procedures in pediatric patients[48, 59,101,102,103]. Midazolam has given promising results since its inception in the field of moderate sedation as it is short acting, has good anxiolytic properties and provides a greater margin of safety which explains its use in the pediatric patients[55].It is a short-acting benzodiazepine with an elimination half-life of 1.5-2.5 hours. The therapeutic as well as adverse effects of midazolam are due to its effects on the $GABA_A$ receptors. These effects

result in the following pharmacological properties being produced like sedation, reduction in anxiety, anterograde amnesia, muscle relaxation and anticonvulsant effects[65,76,79,85,93,102]. Recently, dexmedetomidine has been extensively explored in pediatric population as a premedication[35, 39,42,55,95,114] .The first α2-adrenoceptor agonist, dexmedetomidine was synthesized in the 1960s to be used as a nasal decongestant. The sedative and analgesic properties rendered are useful for anesthetic premedication. Despite profound sedative properties, dexmedetomidine is associated with only limited respiratory effects even when dosed to plasma level upto 15 times of the normal limit, thus providing a wide safety margin when used in children. The drug was reported to be safe and effective alternative for premedication in children **.Saad A, Sheta A,Maha A, Sarheed AL, Ashraf A. 2013[9].**

In the present study, the intranasal dose that was selected for dexmedetomidine and midazolam was 2.5mcg/kg and 0.3 mg/kg[61, 102,104]. Midazolam as well as dexmedetomidine produced minimal to moderate levels of sedation in children at the given dose (Table 7) with no significant difference between both the groups. Similar findings were reported by **Surendar MN, Pandey RK, Saksena AK, Kumar R, Chandra G. 2014[55]** who used two doses of dexmedetomidine (1 and 1.5 mcg/kg) which proved to be safe and effective in rendering dental treatments to uncooperative children. In the study conducted in our department by **Patel V, Singh N, Saksena AK, Singh S, Sonkar S K, Jolly S M. 2018[104]**, two routes with two different doses of dexmedetomidine were compared i.e Intranasal route (2mcg/kg and 2.5 mcg/kg) and Oral route (4mcg/kg and 5mcg/kg). It was concluded that the intranasal route with the above doses were safe and effective for procedural sedation. In cases of Midazolam, **Mahdavi A, Fallahinejad Ghajari M, Ansari G, Shafiei L.2018[87]** checked the intranasal dose for procedural sedation. The study concluded that the 0.5mg/kg dose of midazolam produced effective sedation for uncooperative children. **Mitra S, Kazal S, Anand LK.2014[76]** used 0.3 mg/kg dose intranasally as a premedication for a child undergoing surgery. This dose produced satisfactory anxiolysis. **Sayal, O, Sivrikaya, G U Erol, M.K, Dobrucali, H Hanci.2010[115]** compared the intranasal dexmedetomidine and midazolam for premedication in children. They concluded that, 0.5µg/kg dexmedetomidine can be alternative to intranasal 0.5mg/kg midazolam when used for premedication in pre-school children.

The sedative drug is considered to be efficacious, if it attains the adequate level of sedation that is needed to carry out a procedure with ease and also by increasing the comfort and satisfaction for both the clinician and the patient. The minimum number of post operative complications and the maintenance of hemodynamic status in the normal physiological limits, govern the safety of the sedative drug in use.

The results in the present study showed that midazolam had a faster onset when compared to dexmedetomidine (Table 10 and Graph 10). **Zhou C and Zhao J. 2014**[57] also stated that the reason behind the faster onset of midazolam is its lipid solubility which enhances rapid absorption and penetration into CNS and because of its chemical structure, the drug is oxidized by liver much more rapidly. Similar findings were reported by **Surendar MN, Pandey RK, Saksena AK, Kumar R, Chandra G. 2014**[55]**,** they found that the onset of sedation was significantly faster with midazolam group than in dexmedetomidine group. **Musani IE, Chandan NV**.**2015**[85] also found that the the intranasal route of midazolam administration has a quick onset of action and a quick recovery of the patient from sedation as compared to the oral route of midazolam administration. **Yuen VM, Hui TW, Irwin MG, Yuen MK. 2008**[112] conducted a study to evaluate whether intranasal dexmedetomidine (on a dose 0.5mcg/kg and 1 mcg/kg) is as effective as oral midazolam(0.5 mg/kg) and it was concluded in their study of 96 chidren that an oral dose of 0.5mg/kg midazolam was satisfactory as a premedication and that the sedative effect associated more strongly with 1µg/kg dexmedetomidine rather than with 0.5 µg/kg dexmedetomidine intranasally. Midazolam also took a shorter time to achieve the peak level of sedation than dexmedetomidine. (Table 11 and Graph 11).

In the present study, the level of sedation was assessed by a 5 point scale given by AAPD 2006 modified by **Padmanabhan et al,**2009. The majority of the subjects in the midazolam group showed moderate sedation whereas the majority of the patients in the dexmedetomidine group showed minimal sedation(Table 7 and Graph 8). **Akin A, Bayram A, Esmaoglu A, Tosun Z, Aksu R, Altuntas R, et al. 2012**[113] compared the effects of intranasally administered midazolam(0.2 mg/kg) versus dexmedetomidine (1 mcg/kg) as premedication in children undergoing elective adenotonsillectomy. They concluded that both the drugs were equally effective in decreasing parent separation anxiety in children however midazolam was better in

providing satisfactory conditions during mask induction. Similarly, **Musani IE, Chandan NV**. **2015**[85] concluded that 0.1 mg/kg midazolam administered intranasally is as effective as the oral dose (0.2 mg/kg). Therefore, it is an effective substitute to oral route for a pediatric dental treatment .Contrary to above**, Fan TW, Ti LK, Islam I. 2013**[45]**; Sisi Li, Yang Y, Cong Y, Ying Y, Yujia W and Lian Q. 2015**[46] found that 4 mcg/ml dexmedetomidine provided better sedation and postoperative analgesia than 0.2 mg/ml midazolam intravenously during office-based artificial tooth implantation.**Zhou C and Zhao J. 2014**[57] conducted a meta-analysis and concluded that 0.2 – 0.7 mcg/kg dexmedetomidine administered orally was related with lower level of sedation and easier child-parent separation than children who received midazolam(0.14 mg/kg – 0.2 mg/kg orally).The meta-analysis also concluded that dexmedetomidine had many advantages over midazolam such as absence of respiratory depression and analgesic effects: but it has a major disadvantage that the onset time for sedation is longer in comparison with midazolam.

The ease of treatment completion was noted according to the five point scale given by AAPD 2006. Midazolam group showed better ease of treatment completion grading (Table 8 and Graph 9) than dexmedetomidine group but the acceptance of drug (Table 6 and Graph 7) were almost similar and had no significant difference when compared in both the groups. The acceptance of drug was noted according to a 4 point rating scale by Lochary and Co workers 1992 during the administration of drug intranasally. Similar to this study, **Mostafa G. M and Khaled M. 2013**[54] found better acceptance (in terms of alleviating stress and psychological trauma) of midazolam than dexmedetomidine intranasally in anxious children.. **Keles S and Kocaturk O. 2018**[114] compared the effects of 2 mcg/kg dexmedetomidine and 0.5 mg/kg midazolam administered orally on preoperative cooperation and emergence delirium among 52 children who underwent dental procedures. They concluded that dexmedetomidine provided satisfactory sedation levels, ease of parental separation, and mask acceptance in children in a manner similar to midazolam. Moreover, 26 children premedicated with dexmedetomidine experienced no emergence delirium .

The present study was also designed to evaluate the **safety** of midazolam in comparison with dexmedetomidine as a procedural sedation agent of pediatric patients. Both midazolam and dexmedetomidine did not show any post operative

complication in the present study (Table 9). **Waleed M. 2010[116]** compared the effect of 2 mcg/kg dexmedetomidine as a sedative in paediatric dental patients in comparison to the currently used combination of 0.05 mg/kg midazolam and 1 mg/kg propofol intravenously. They concluded that dexmedetomidine showed more analgesic effect than the other group. It also stated that dexmedetomidine is safe and effective when used for sedation in paediatric patients undergoing dental procedures. **Wood M. 2010 and 2011[80, 82]** concluded that intranasal midazolam (0.25 mg/kg) is a safe and effective agent for procedural sedation and can be used as an effective alternative for general anesthesia for dental treatments. **Primosch RE Bender F. 2001[110]** reported hypotension and bradycardia are most frequent adverse effects of 1mcg/kg of dexmedetomidine.

In both the experimental groups, the pulse rate (Table 2 and Graph 3), blood pressure (Table 3 & Table 4 and Graph 4 & Graph 5) and oxygen saturation(Table 4 and Graph 5), remained within acceptable physiological limits. In a retrospective study on 222 children in comparison to propofol, dexmedetodine(1mcg/kg) showed more stable hemodynamics status among 40 patients. **CJ Tsai et al.,2010**[109] **Shavit I, Feraru L, Miron D, Weiser G. 2012**[75] showed that sedation with intranasal midazolam was sufficient and did not causing serious adverse events. **Saad A, Sheta A,Maha A, Sarheed AL, Ashraf A. 2013[9]and Sheta MA. Al-Sarheed, Ashraf A. Abdelhalim. 2014[51]** compared the dexmedetomidine (1.5 mcg/kg) with midazolam (0.2mg/kg) administered intranasally for premedication and they found that intranasal dexmedetomidine was superior sedative and safe alternative for premedication in children than midazolam.

In the present study, dexmedetomidine showed higher recovery time (Table 13 and Graph 13) and longer discharge time (Table 13 and Graph 13) as compared with midazolam. **Zhou C and Zhao J. 2014[57]** also stated that midazolam is a lipid soluble drug therefore enhances rapid absorption and penetration into CNS and because of its chemical structure, the drug is oxidized by liver much more rapidly and consequently has a short duration of action.Similarly, **Makary L, Vornik V, Finn R, Lenkovsky F, McClelland AL, Thurmon J, Robertson B. 2010[96]** concluded that the prolonged recovery time of intranasal dexmedetomidine makes this drug unsuitable for busy

office-based practices.[96] **Hupp JR, Becker LE. 1988**[98] showed that midazolam produces at least 20 minutes of profound amnesia for all stimulis' and had a faster recovery time.

The results in the present study concluded that both intranasal midazolam (0.3 mg/kg) and intranasal dexmedetomidine (2.5 mcg/kg) produced sedation in children between 3 and 9 years of age with dexmedetomidine producing minimal sedation and midazolam producing moderate sedation in majority of children in the given doses. Midazolam had rapid onset time, early peak sedation time, faster recovery time and shorter discharge time as compared to dexmedetomidine.Hemodynamic parameters remained stable in both the groups and none of the patient suffered any drug related side effect which required any therapeutic intervention.

CONCLUSIONS

The present study was carried out in the Department of Pediatric and Preventive Dentistry, BBDCODS, Lucknow, after obtaining clearance from Institutional Ethical Committee.

This study was aimed to evaluate and compare the safety and efficacy of Midazolam (0.3 mg/kg) and Dexmedetomidine (2.5µg/kg) through intranasal route for procedural sedation in pediatric dental patients.

Based on the observations done during course of study, following conclusions were made:

- The intranasal route for administration of sedative drugs is a safe and effective method to control the behavior of uncooperative children who require comprehensive dental treatment.

- Both intranasal midazolam (0.3 mg/kg) and intranasal dexmedetomidine (2.5 mcg/kg) produced sedation in children between 3 and 9 years of age with dexmedetomidine producing minimal sedation and midazolam producing moderate sedation in majority of children in the given doses. The acceptance of drug was similar in both the groups.

- Midazolam had rapid onset time, early peak sedation time, faster recovery time and shorter discharge time as compared to Dexmedetomidine. The ease of treatment was also better with Midazolam.

- In both the experimental groups, the pulse rate, blood pressure and oxygen saturation remained within acceptable physiological limits and no post-operative complications was seen in either of the groups.

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ANNEXURES

ANNEXURE 1

BABU BANARASI DAS COLLEGE OF DENTAL SCIENCES (FACULTY OF BBD UNIVERSITY), LUCKNOW

INSTITUTIONAL RESEARCH COMMITTEE APPROVAL

The project titled **"Comparative Evaluation of Intranasal Midazolam and Dexmedetomidine for Procedural Sedation in Pediatric Dental Patients"** submitted by **Dr. Shubham Gupta** Post graduate student from the **Department of Paedodontics & Preventive Dentistry** as part of MDS Curriculum for the academic year 2017-2020 with the accompanying proforma was reviewed by the Institutional Research Committee present on **05th December 2017** at BBDCODS.

The Committee has granted approval on the scientific content of the project. The proposal may now be reviewed by the Institutional Ethics Committee for granting ethical approval.

8/12/17

Prof. (Dr) Vandana A Pant
Co-Chairperson

Prof. (Dr) B. Rajkumar
Chairperson

ANNEXURE 2

Babu Banarasi Das University
Babu Banarasi Das College of Dental Sciences,
BBD City, Faizabad Road, Lucknow – 226028 (INDIA)

Dr. Lakshmi Bala
Professor and Head Biochemistry and
Member-Secretary, Institutional Ethics Committee

Communication of the Decision of the VIth Institutional Ethics Sub-Committee

IEC Code: 16 **BBDCODS/01/2018**

Title of the Project: Comparative Evaluation of Intranasal Midazolam and Dexmedetomidine for Procedural Sedation in Pediatric Dental Patients.

Principal Investigator: Dr. Shubham Gupta **Department:** Pedodontics and Preventive Dentistry

Name and Address of the Institution: BBD College of Dental Sciences Lucknow.

Type of Submission: New, MDS Project Protocol

Dear Dr. Shubham Gupta,

The Institutional Ethics Sub-Committee meeting comprising following four members was held on 30th January 2018.

1.	Dr. Lakshmi Bala Member Secretary	Prof. and Head, Department of Biochemistry, BBDCODS, Lucknow
2.	Dr. Amrit Tandan Member	Prof. & Head, Department of Prosthodontics and Crown & Bridge, BBDCODS, Lucknow
3.	Dr. Rana Pratap Maurya Member	Reader, Department of Orthodontics & Dentofacial Orthopedics, BBDCODS, Lucknow
4.	Dr. Sumalatha M.N. Member	Reader, Department of Oral Medicine & Radiology, BBDCODS, Lucknow

The committee reviewed and discussed your submitted documents of the current MDS Project Protocol in the meeting.
The comments were communicated to PI thereafter it was revised.

Decisions: The committee approved the above protocol from ethics point of view.

Lakshmi Bala 05/02/18

(Dr. Lakshmi Bala)
Member-Secretary
IEC

Member-Secretary
Institutional Ethic Committee
BBD College of Dental Sciences
BBD University
Faizabad Road, Lucknow-226028

Forwarded by:

(Dr. B. Rajkumar)
Principal
BBDCODS

PRINCIPAL
Babu Banarasi Das College of Dental Sciences
(Babu Banarasi Das University)
BBD City, Faizabad Road, Lucknow-

ANNEXURE 3

Formula used for the analysis

Arithmetic Mean

The most widely used measure of central tendency is arithmetic mean, usually evaluated as

$$\bar{X} = \frac{\sum_{i=1}^{n} X_i}{n}$$

Standard deviation and standard error

The standard deviation (SD) is the positive square root of the variance, and calculated as

$$SD = \sqrt{\frac{\sum X_i^2 - \frac{(\sum X_i)^2}{n}}{n-1}}$$

and SE (standard error of the mean) is calculated as

$$SE = \frac{SD}{\sqrt{n}}$$

where, n= no. of observations

Minimum and Maximum

Minimum and maximum are the minimum and maximum values respectively in the measure data and denoted as below

Range = Min to Max

and also evaluated by subtracting minimum value from maximum value as

Range = maximum value-minimum value

Median

The median is generally defined as the middle measurement in an ordered set of data. That is, there are just as many observations larger than the median as there are smaller. The median (M) of a sample of data may be found by first arranging the measurements in order of magnitude (preferably ascending). For even and odd number of measurements, the median is evaluated as

$$M = [(n+1)/2]^{th} \text{ observation- odd number}$$

$$M = [n(n+1)/2]^{th} \text{ observation – even number}$$

Student's t-test

Student's t-test was used to calculate the differences between the means of two groups

$$t = \frac{\bar{X}_1 - \bar{X}_2}{SE}$$

.

$$SE = \sqrt{S^2 X \left(\frac{1}{n_1} + \frac{1}{n_2} \right)}$$

S^2 is the pooled variance and n_1 and n_2 are number of observations in group 1 and 2 respectively. The degrees of freedom (DF) is calculated as

$$DF = n1 + n2 – 2$$

Chi-square test

The chi-square (χ^2) test is used to compare the categorical data as

$$\chi^2 = \Sigma\Sigma \frac{(Fij - fij)^2}{fij}$$

where, F_{ij} is the observed frequency while f_{ij} the expected frequency. The degrees of freedom (DF) is calculated as

$$DF = (r-1)\,(c-1)$$

Analysis of Variance

Analysis of variance (ANOVA) is used when we compare more than two groups simultaneously. The purpose of one-way ANOVA is to find out whether data from several groups have a common mean. That is, to determine whether the groups are actually different in the measured characteristic. One way ANOVA is a simple special case of the linear model. For more than two independent groups, simple parametric ANOVA is used when variables under consideration follows Continuous exercise group distribution and groups variances are homogeneous otherwise non parametric alternative Kruskal-Wallis (H) ANOVA by ranks is used. The one way ANOVA form of the model is

$$Y_{ij} = \alpha_{.j} + \varepsilon_{ij}$$

Where;

Y_{ij} is a matrix of observations in which each column reSPO2esents a different group.

$\alpha_{.j}$ is a matrix whose columns are the group means (the "dot j" notation means that α applies to all rows of the j^{th} column i.e. the value α_{ij} is the same for all i).

ε_{ij} is a matrix of random disturbances.

The model posits that the columns of Y are a constant plus a random disturbance. We want to know if the constants are all the same.

Tukey's multiple comparison Test

After performing ANOVA, Tukey's HSD (honestly significant difference) post hoc test is generally used to calculate differences between group means as

where,

$$q = \frac{\bar{X}_1 - \bar{X}_2}{SE}$$

$$SE = \sqrt{\frac{S^2}{2}\left(\frac{1}{n_1} + \frac{1}{n_2}\right)}$$

S^2 is the error mean square from the analysis of variance and n_1 and n_2 are number of data in group 1 and 2 respectively.

Statistical significance

Level of significance "p" is the SPO2obability signifies level of significance. The mentioned p in the text indicates the following:

p>0.05- Not significant (ns)

p<0.05- Just significant (*)

p<0.01- Moderate significant (**)

p<0.001- Highly significant (***)

ANNEXURE 4

Sedation Case Sheets-

Name-

Age/Sex-

Weight –

Height-

Drug of choice-

	Pulse Rate	Blood Pressure	Oxygen Saturation
Before Administratiom			
5 minutes			
10 minutes			
15 minutes			
20 minutes			
25 minutes			
30 minutes			
35 minutes			
40 minutes			
45 minutes			
50 minutes			
55 minutes			
60 minutes			

Acceptance of drug rating-		
Crying and struggling	1	
Struggling	2	
Crying	3	
Quite	4	

Onset of sedation-

Sedation Rating Scale-			
1	No sedation	Typical Response /Cooperation	
2	Minimal sedation	Anxiolysis	
3	Moderate sedation	Purposeful response to verbal command	
4	Deep sedation	Purposeful respond after repeated verbal command or painful stimulation	
5	General anesthesia	Not arousable	

Ease of treatment completion-			
	Classification	Behavioral Sign	
5	Excellent	Quite and cooperative Treatment completed without difficulty	
4	Good	Mild objections or whimpering but the treatment was not interrupted. Treatment completed without difficulty	
3	Fair	Crying with minimal disruption to treatment . Treatment completed with minimal difficulty.	
2	Poor	Struggling that interfered with operative procedures. Treatment completed with difficulty	
1	Prohibitive	Active resistance and crying . Treatment cannot be rendered.	

Discharge criteria –Satisfied/Not satisfied

ANNEXURE 5

Babu Banarasi Das College of Dental Sciences

(Babu Banarasi Das University)

BBD City, Faizabad Road, Lucknow – 227105 (INDIA)

CONSENT FORM (ENGLISH)

Title of the Study- Comparative evaluation of intranasal midazolam and dexmedetomidine for procedural sedation in pediatric dental patients.

Study Number.....

Subject's Full Name.....

Date of Birth/Age .....

Address of the Subject.....

Phone no. and e-mail address.....

Qualification .....

Occupation: Student / Self Employed / Service / Housewife/ Other (Please tick as appropriate) Annual income of the Subject.....

Name and of the nominees(s) and his relation to the subject..... (For the purpose of compensation in case of trial related death).

1. I confirm that I have read and understood the Participant Information Document dated .....for the above study and have had the opportunity to ask questions. OR I have been explained the nature of the study by the Investigator and had the opportunity to ask questions.

2. I understand that my participation in the study is voluntary and given with free will without any duress and that I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected.

3. I understand that the sponsor of the project, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. However, I understand that my identity will not be revealed in any information released to third parties or published.

4. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s). 5. I permit the use of stored sample (tooth/tissue/blood) for future research. Yes [ ] No [ ] Not Applicable [ ]

6. I agree to participate in the above study. I have been explained about the complications and side effects, if any, and have fully understood them. I have also read and understood the participant/volunteer's Information document given to me. Signature (or Thumb impression) of the Subject/Legally Acceptable Representative:.....

Signatory's Name..... Date .....

Signature of the Investigator..... Date.....

Study Investigator's Name..... Date.....

Signature of the witness..... Date.....

Name of the witness..... Received a signed copy of the PID and duly filled consent form Signature/thumb impression of the subject or legally Date.....

Babu Banarasi Das College of Dental Sciences (Babu Banarasi Das University) BBD City, Faizabad Road, Lucknow – 227105 (INDIA)

ANNEXURE 6

DIETARY INSTRUCTION FOR THE DAY OF SEDATION (AMERICAN SOCIETY OF ANESTHESIOLOGISTS) 2019

Appropriate intake of food and liquids before elective sedation	
Ingested material	Minimal fasting period(hr)
Clear liquids(water, fruit juices without pulp ,clear tea ,black coffee)	2
Human milk	4
Infant formula	6
Non human milk	6
Light meal(toast and clear liquids)	6

ANNEXURE 7

Pulse rate

Normal values (Medline plus 2017)

Children 3 to 4 years -80 to 120 beats per minute

Children 5 to 6 years-75 to 115 beats per minute

Children 7 to 9 years – 70 to 110 beat per minute

Blood pressure (PALS GUIDELINES 2015)

Preschooler (3-5years) – Systolic pressure =89-112, Diastolic pressure=46-72

School age (6-9 years) – Systolic pressure =97-115, Diastolic pressure=57-76

Oxygen saturation

Normal level is 95-100 percenT

ANNEXURE 8

OHIO STATE BEHAVIOURAL RATING SCALE (OSBRS) by Lochary and co workers, 1992.

1	Crying and struggling
2	Struggling
3	Crying
4	Quiet

ANNEXURE 9

EASE OF TREATMENT COMPLETION SCALE (AAPD 2006 modified by **Padmanabhan et al 2009**)

Score	Classification	Behavioral Sign
5	Excellent	Quite and cooperative Treatment completed without difficulty.
4	Good	Mild objections or whimpering but treatment was not interrupted. Treatment completed without difficulty.
3	Fair	Crying with minimal disruption to treatment. Treatment completed with minimal difficulty.
2	Poor	Struggling that interfered with operative procedures. Treatment completed with difficulty.
1	Prohibitive	Active resistance and crying. Treatment cannot be rendered.

ANNEXURE 10

SEDATION RATING SCALE (AAPD 2006 modified by Padmanabhan et al 2009)

1	No sedation	Typical response/cooperation
2	Minimal sedation	Anxiolysis
3	Moderate sedation	Purposeful response to verbal command
4	Deep sedation	Purposeful response after repeated verbal command or painful stimulation
5	General anesthesia	Not arousable

ANNEXURE 11

(ALDRETE CRITERIA 2015 FOR DISCHARGE AND ASSESSMENT OF RECOVERY)

CRITERIA	POINT VALUE
OXYGENATION	
Spo2>92 on room temperature	2
Spo2>90 on oxygen	1
Spo2<90 on oxygen	0
RESPIRATION	
Breathes deeply and cough freely	2
Dyspnoiec –shallow or limited breathing	1
Apnoea	0
CIRCULATION	
Blood pressure ±20 mm hg of normal	2
Blood pressure ±20 – 50 mm hg of normal	1
Blood pressure more than ±50 mm hg of normal	0
CONSIOUSNESS	
Fully awake	2
Arousable on calling	1
No response	0
ACTIVITY	
Moves all extremities	2
Move two extremities	1
No movement	0

ANNEXURE 12

DISCHARGE CRITERIA (AAPD GUIDELINES 2016)

1. Cardiovascular function and airway patency are satisfactory and stable.
2. The patient is easily arousable and protective reflexes are intact.
3. The patient can talk.
4. The patient can sit up unaided.
5. For a very young or handicapped child incapable of usually expected responses, the presedation level of responsiveness or a level as close as possible to the normal level fro that child should be achieved.
6. The state of hydration is adequate.

FIGURES


5 ml
Cipla
NR
PHARMACY MEDICINE • THIS PRODUCT SHOULD BE USED ONLY IF PRESCRIBED BY YOUR PHYSICIAN
Midacip
Nasal Spray
0.5
CFC-FREE
Midazolam
Nasal Spray 5 mg/ml
Midacip
Nasal Spray


NEON
50 mcg
Rx
Dexmedetomidine
Injection USP
DEXTOMID* 50
For I.V. Infusion after dilution
डेक्सटोमिड 50
50mcg/0.5ml
One Ampoule of 0.5ml
SNAP-OFF AMPOULE


0.5
1.0
1.5
2.0
2.5
3.0
ml


Emeset