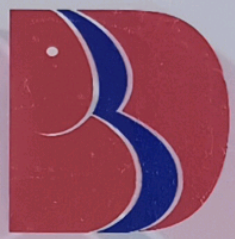
A COMPARATIVE EVALUATION OF INTRANASAL KETAMINE WITH INTRANASAL MIDAZOLAM AND DEXMEDETOMIDINE COMBINATION FOR PROCEDURAL SEDATION IN PEDIATRIC DENTAL PATIENTS

BABU BANARASI DAS UNIVERSITY, LUCKNOW

Thesis submitted in partial fulfilment of the requirements for degree of

MASTER OF DENTAL SURGERY



In the subject of

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DEPARTMENT OF PEDIATRIC AND PREVENTIVE DENTISTRY

BABU BANARASI DAS OF DENTAL SCIENCES,
LUCKNOW, UTTAR PRADESH- 227105

BATCH- 2020-2023

GUIDE: DR. NEERJA SINGH

DR. BIBHAV DUBEY

ENOROLLMENT NO:
12003270336

DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation entitled **"A COMPARATIVE EVALUATION OF INTRANASAL KETAMINE WITH INTRANASAL MIDAZOLAM AND DEXMEDETOMIDINE COMBINATION 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,** Department of Paediatric and Preventive Dentistry, Babu Banarasi Das College of Dental Sciences, Babu Banarasi Das University, Lucknow, Uttar Pradesh.

Date: 24-02-2023

Place: Lucknow

DR. BIBHAV DUBEY

CERTIFICATE

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GUIDE
DR. NEERJA SINGH
M.D.S, PhD
PROFESSOR

DEPARTMENT OF PAEDIATRIC AND PREVENTIVE DENTISTRY
BABU BANARASI DAS COLLEGE OF DENTAL SCIENCES,
BBDU, LUCKNOW (U.P.)

DEPARTMENT OF PEDIATRIC AND PREVENTIVE DENTISTRY

BABU BANARASI DAS COLLEGE OF DENTAL SCIENCES, LUCKNOW, UTTAR PRADESH-227105

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RECOMMENDATION OF HEAD OF DEPARTMENT

DR. MONIKA RATHORE

PROFESSOR & HEAD

DEPARTMENT OF PEDIATRIC AND PREVENTIVE DENTISTRY

BABU BANARASI DAS COLLEGE OF DENTAL SCIENCES.

BBDU, LUCKNOW (U.P.)

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LUCKNOW, UTTAR PRADESH-227405

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DR. PUNEET AHUJA

PRINCIPAL

Babu Banarasi Das College of Dental Sciences

BBDU, Lucknow (U.P.)

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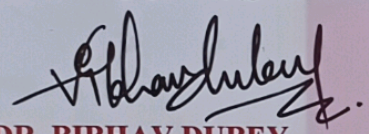

DR. BIBHAV DUBEY

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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 efficacy, safety and acceptability of intranasal ketamine (INK) with intranasal midazolam and dexmedetomidine (INM_zD) combination for procedural sedation in pediatric dental patients.

MATERIALS AND METHOD:

Subjects were randomly divided into two groups for different drugs to be administered in crossover manner.

- **Group INK** for administration of intranasal ketamine (7mg/kg) in first visit.
- **Group INMzD** for administration of midazolam (0.3mg/kg) dexmedetomidine combination (3µg/kg) on second visit.

RESULTS

This study was aimed to evaluate efficacy, safety and acceptability of intranasal ketamine (INK) with intranasal midazolam and dexmedetomidine (INMzD) combination for procedural sedation in pediatric dental patients.

- Considering the efficacy parameters, INK had rapid onset time, early peak sedation time, faster recovery time and shorter discharge time as compared to INMzD combination.

- 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 drug acceptance was better with INK.as compared with INMzD combination

CONCLUSION

- Intranasal ketamine was better than intranasal midazolam dexmedetomidine combination for procedural sedation in terms of efficacy, safety and acceptability.

INTRODUCTION

There is famous saying by McElroy (1895), “Although the operative procedures may be perfect but appointment is failure if the child departs in tears”. Children might experience anxiety when interacting with dental healthcare professionals. These interactions are required for the prevention and treatment of orofacial diseases, infection, and pain in children, as well as the restoration of dentition form and function. Providing dental care to uncooperative and struggling paediatric patients may endanger both clinicians and patients. To protect children from negative consequences, restraint, including restraint of the limbs and head, are frequently required, whether mediated by a device or a pharmacologic agent.

An effective behavior management system is a must for complex procedures that provide safe and painless treatment while minimizing potential psychological trauma. Non-pharmacological behavior guidance techniques are frequently used to relieve anxiety and provide quality oral health care for infants, children, adolescents, and patients with special health care needs, but in some cases, these are insufficient to effectively reduce anxiety and as a result make the treatment unpleasant. A traumatic dental experience can cause children to develop a lifelong fear of dentists. As a result, pharmacological methods of behavior management are being considered.

In recent years, procedural sedation and analgesia (PSA) has been developed for the management of pain, anxiety, and unwanted movements in children undergoing dental treatment, which has reduced the need for general anesthesia. **[1]**

The American College of Emergency Physician (ACEP) defines procedural sedation as “a technique of administering sedatives or dissociative agents with or without analgesics to induce a state that allow” the patient to tolerate unpleasant procedures while 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. Pediatric dentists all over the world have been searching for the ideal agents and route to provide procedural sedation for decades. There is a long list of drugs that have been used for procedural sedation via various routes over the years, but none have been proven to be ideal.

Ketamine (K) is a rapid acting non-narcotic, non-barbiturate drug with a wide safety margin, protective reflexes and dissociative anesthetic property with a powerful analgesic effect. The psycho mimetic effects of the drug do not appear to be a serious problem in children, when used in low, "sub anesthetic" doses. [2]

The use of midazolam for conscious sedation in paediatric dentistry has sparked a lot of interest. Midazolam HCl was first synthesised in 1976 by Fryer and Walser; it is a water-soluble, short-acting benzodiazepine that works on GABA- (y-amino butyric acid) associated benzodiazepine receptors in the same way that diazepam does. **[3]** It has anticonvulsant, anxiolytic, sedative, hypnotic, muscle relaxant, and anterograde amnesia properties. In the past, the medication was used as a pre-anaesthetic sedative.

The Food and Drug Administration (FDA) approved dexmedetomidine for short-term sedation procedures in 1999. In paediatric anesthesia, it has emerged as an alternative to premedication. Dexmedetomidine is an advanced drug used for procedural sedation that has been used sparingly in our country (Prakhar G et al., 2013). **[4]** It is an alpha-2 agonist with sedative and anxiolytic properties and with few side effects. Dexmedetomidine sedation is characterized by easy and quick arousal similar to natural sleep, making it an effective agent for providing procedural sedation. **[5]**

Sedatives can be administered through a variety of routes (oral, intranasal, submucosal, transmucosal, intramuscular, intravenous, and rectal). The intranasal route has several advantages, including the absence of first-pass metabolism, a shorter duration of action, a painless technique, and ease of administration. Intranasal administration is accomplished through the use of a Mucosal Atomizer Device (MAD), a nasal spray, or a nasal drop. The use of MAD or nasal spray for administration eliminates the need for intravenous access, which is often painful and depressing for the child, with the added risk of needle stick injury. **[6]** Delivery of Intranasal medication administration is relatively painless, inexpensive, and simple to perform with minimal training.

Ketamine has the advantage of being one of the most potent dissociative drugs, with both analgesic and sedative properties. Midazolam is a good sedative but does not provide analgesia, whereas Dexmedetomidine has gained popularity as a drug used for procedural sedation because it has both sedative and anxiolytic effects as well as the ability to produce dose-dependent milder analgesia without respiratory depression.

Hence, this crossover randomized study aimed to compare intranasal ketamine with intranasal midazolam and dexmedetomidine combination for the procedural sedation of uncooperative paediatric dental patients.

AIM

- To evaluate efficacy, safety and acceptability of intranasal ketamine (INK) with intranasal midazolam and dexmedetomidine (INM_zD) combination for procedural sedation in pediatric dental patients.

OBJECTIVES

1. To evaluate the efficacy, safety and acceptability of intranasal ketamine (INK) for procedural sedation in uncooperative pediatric dental patients.

2. To evaluate the efficacy, safety and acceptability of intranasal midazolam and dexmedetomidine (INM_zD) combination for procedural sedation in uncooperative pediatric dental patients.

3. To compare efficacy, safety and acceptability of intranasal ketamine (INK) with intranasal midazolam and dexmedetomidine (INM_zD) combination for procedural sedation in uncooperative pediatric dental patients.

REVIEW OF LITERATURE

Dental pain and anxiety are very common among paediatric patients. However, both these symptoms have been underestimated and undertreated in pediatric settings due to the inability of children to express their fears and concerns, and ignorance about the procedures that will be performed. Patients avoid making dental visits because of their fear, resulting in worsening of problems, that in future may require more intensive and potentially traumatic treatment, which then reinforces or exacerbates the fear, which leads to continued avoidance with the possibility to establish what has been referred to as a vicious cycle of dental fear for the child.

Among the various branches of dentistry, pediatric dentistry faces the most difficult challenge in providing dental care without having a negative psychological impact on the child. Pediatric dentistry as a specialty recognizes that child behavioral management cannot be separated from the quality of dental care.[7] Furthermore; the majority of the children have age-appropriate anxiety and fears, such as being afraid of the dentist and dental treatment. Fearful, disruptive children are among the most difficult problems encountered by practicing dentists in their clinical work. In order for the treatment to be completed, the child must cooperate or at least passively comply with the dentist's procedures. The most unpleasant aspect of pediatric dentistry is minimized by reducing disruptive patient behavior such as crying, screaming children whose peripheral and gross motor movements frequently make direct contact with the dentist or his equipment.

Most of the time, traditional behavior modification techniques overcome children's fear and anxiety. However, a significant proportion of children may still experience fear or anxiety, necessitating a more intensive intervention. According to the study by **De Jongh A et al., (2005)** [8] different anxiety management approaches are dictated by dental practitioners based on different levels, types, and characteristics of dental anxiety and fear among patients.

Where there is a high level of urgency for treatment, as well as high levels of anxiety, possible approaches to patient management may include intravenous sedation, conscious sedation, or general anesthesia (GA).[9]

In contrast to procedural sedation, which aims to change patient behaviour and make the patient cooperative by reducing dental fear and anxiety, treatment under general

anaesthesia should be considered the last treatment option because there is no evidence that it benefits the highly anxious patient beyond meeting their immediate treatment needs.

The credit for the introduction of sedation in dentistry goes to Horace Wells, who used nitrous oxide as a sedative for dental extractions. However, it was William T. G. Morton (1819-1868) a Massachusetts dentist who successfully demonstrated the anesthetic property of ether on October 16, 1846 for pain-free extraction of tooth.

Pharmacological agents may be used in addition to behavioral techniques to help manage anxiety in some pediatric dental patients. They may also be particularly useful in children with disabilities. These medications are typically sedatives or analog sedatives that do not remove anxiety but rather improve patient acceptance by reducing arousal and modifying anticipation of danger. The agents used vary and include nitrous oxide, benzodiazepines, and opioid congeners. Nitrous oxide has proven to be particularly valuable, but it poses a risk to operating personnel and is a weaker agent in terms of providing an adequate sedative effect. Midazolam has become more popular among benzodiazepines in recent years. It may be given by a variety of routes, including intranasal (IN).**[10]** Dentists who employ such analog-sedative agents and techniques should be familiar with the pharmacology of the agents selected, be familiar of the risks and benefits of the technique employed and be able to manage any adverse events that may arise through their use.**[10]**

Sedation for dental procedures (with or without local anesthesia) can be obtained by administering drugs that cause central nervous system depression. “Procedural sedation and analgesia (PSA) is defined as the technique of administering sedatives or dissociative agents with or without analgesics to induce an altered state of consciousness that enables” a patient to tolerate a painful or unpleasant procedure (Godwin, et.al. 2005).” **[1, 11]**

This technique causes drug induced depression of consciousness, during which patients respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation. No interventions are required to maintain a patent airway, and spontaneous ventilation is sufficient. Cardiovascular function is usually maintained. [11]

While performing urgent PSA procedures, there are numerous pharmacological options. The drug chosen will be determined by the type of procedure to be performed, whether

painful or non-painful, the patient's characteristics, such as age, attitude, and the experience of the responsible physician.

Anxiolytic drugs are usually used for non-painful procedures where the goal is only to reduce the child's anxiety and avoid movements, but for painful techniques where the goal is analgesia as well as sedation, inhaled nitrous oxide or the various sedative agents with alone or in combination which not only provides a level of anxiolysis but also the analgesic and amnestic effect which may be desirable in some cases.

Since then, dentistry has witnessed the use of numerous pharmacological agents which allay pain and anxiety without complete loss of consciousness, to facilitate dental procedures even in anxious and uncooperative pediatric patients. To achieve this, hundreds of compounds have been synthesized and tested through various route of administration in dentistry as well as in other field for sedation. But none of the sedative agent and administration route has proved to be an ‘ideal’ agent and route.

INTRANASAL (IN) MODE OF ADMINISTRATION:

Among the various sedative administration routes, the intranasal route is most preferred in sedating pediatric dental patients because it is non-invasive and facilitates in rapid drug absorption. Moreover, this route is highly acceptable by paediatric dental patients also **(Wolfe** and **Bernstone 2004).** [12] In addition, the nasal mucosa has a large absorptive surface with high blood flow, allowing drugs to be absorbed quickly into the bloodstream and cerebral spinal fluid. Intranasal drugs can bypass the blood-brain barrier via olfactory and trigeminal extracellular pathways, eliciting biological effects at multiple sites throughout the brain and spinal cord **(Thorne RG et al., 2005).** [13] Intranasal drug administration results in direct medication absorption, avoids gastrointestinal destruction, and hepatic first-pass metabolism (i.e., drug destruction by liver enzymes), allowing more drug to be available for rapid action than if administered orally. The result is that many medications delivered through intranasal route achieve absorption rates and plasma concentrations comparable with that obtained by intravenous administration. **(ChienYW *et al.*, (1987)**; **Aggarwal V *et al.*, (1999)**; **Pir esA *et al.*, (2009)**. [14] However, there are relatively fewer studies with this route in our country.

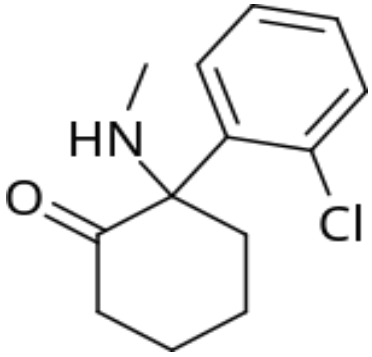
Hence, this crossover randomized study aimed to evaluate and compare intranasal ketamine with intranasal midazolam and dexmedetomidine combination for the procedural sedation of uncooperative pediatric dental patient.

Among the vast and extensive literature on historical aspects, regarding these agent, a brief pharmacokinetic and pharmacodynamic profile are given below-

KETAMINE:

Ketamine is an arylcycloalkylamine, a phencyclidine derivative. It is a water soluble compound which has been in clinical use since many years as a premedicant, analgesic, sedative, and an induction agent administered via several routes. It was first synthesized in 1962 by an American pharmacist Calvin Stevens **(Kelly K. 1999)** [15]**.** Ketamine was discovered to be a useful anesthetic in 1965 when Edward Domino described it as a potent psychedelic drug and coined the term 'dissociative anesthetic' and was first used in clinical practice in 1970s**(Craven R.2007)**[16] **.** Ketamine role in clinical anesthesia is changing as a result of the evolving concepts of its mechanism of action and the advantages of alternative routes of administration.

CHEMICAL STRUCTURE:



MECHANISM OF ACTION:

Ketamine hydrochloride is a dissociative nonbarbiturate anaesthetic. It is a rapidly acting cyclohexanone derivative that causes profound anaesthesia and analgesia. It has the structural formula CHClNO and the chemical formula 2-(o-chlorophenyl)-2-(methylamino) cyclohexanone hydrochloride. [17] Ketamine is a noncompetitive N-methyl-D-aspartate (NMDA) and glutamate receptor antagonist. [18] It blocks HCN1 receptors. The unique dissociative action and partial agonism on opiate mu-receptors,

painful procedures can be performed in a consistent state of sedation and patient comfort. [19]

Ketamine effects in chronic pain and as an antidepressant are likely mediated by a secondary increase in structural synaptic connectivity mediated by a neuronal response to the ketamine-induced hyper-glutamatergic state." Sleigh (2014). [18]

The N-methyl-D-aspartate (NMDA) receptor plays an important role in the etiology of depression. [18] Ketamine works quickly to control symptoms of depression and acute suicidal ideation due to its NMDA antagonistic action. [18] Ketamine may cause synaptogenesis and in Ketamine may interact with sigma receptors. It reduces central sensitization, the wind-up phenomenon (the development of ongoing, worsening, or chronic pain), and pain memory.[18] In both sedation and analgesia, cholinergic, aminergic, and opioid systems appear to play a positive and negative modulatory role.[20] Ketamine reverses opioid tolerance. The hepatic system metabolises it via N-dealkylation, hydroxylation, conjugation, and dehydration.[18] Ketamine has a half-life of about 45 minutes creased levels of brain-derived neurotrophic factor by increasing glutamate levels (BDNF).

Ketamine generally maintains normal pharyngeal and laryngeal reflexes and, therefore, permits spontaneous respiration.[18] It slightly enhances or maintains normal skeletal muscle tone and is associated with cardiovascular and respiratory stimulation.[18] These characteristics make it particularly useful in the emergency department setting for short-term procedures, especially as is often the case when a patient has not been "prepped" for an emergency procedure.[18] Since there is no guarantee of maintenance of the pharyngeal and laryngeal reflexes, there can be no assumption that they will "protect" the airway.[18] Additionally, there may be transient minimal respiratory depression if the medication is administered too rapidly or in too high a dose.[18] Therefore, the physician must be ready to perform emergency intubation.[18]

PHARMACOKINETICS:

Ketamine is rapidly absorbed when administered through the intramuscular (Tmax 5-15 min) Nasal (Tmax 20 min) or oral route as a solution (Tmax 30min). [17] It has a high

bioavailability following IV or IM administration. First pass metabolism and lower absorption necessitate higher doses when ketamine is administered by the oral or rectal routes. Only about 16% of oral ketamine is bioavailable as opposed to 93% with parenteral routes **(Grant *et al.*, 1981).** [21] Extensive bio-transformation takes place in the liver, and multiple metabolites have been described. The most important pathways involve N-demethylation by cytochrome P_{450} to nor-ketamine, an active metabolite with an anesthetic potency one third that of ketamine **(Clement** and **Nimmo 1981)** [21] contributing significantly to the analgesic effects of ketamine. Nor-ketamine is then hydroxylated and finally conjugated forming a water soluble compound that is excreted in the urine. It has got relatively short distribution and elimination half-lives i.e. α-elimination phase last only a few minutes and the β-elimination half-life is 2-3 hours.

Pharmacokinetics properties were similar in children, except that absorption was more rapid following intramuscular administration, and higher concentration of nor-ketamine is present **(Grant *et al.*, 1981).**[21]

PHARMACODYNAMICS:

A Mechanism of action:

Ketamine's neuropharmacology is complex as it shows interaction with multiple binding sites. Excitatory amino acid neurotransmitters (EAA) are the most prevalent excitatory neurotransmitters in the brain. Ketamine acts on one of these EAA receptors, specifically at the phencyclidine site of N-methyl-D-Aspartate (NMDA) receptor and in this respect mimic other dissociative anesthetics such as nitrous oxide **(Jevtovic-Todorovic *et al.*, 2001).**[22] Here it acts as a non-competitive NMDA antagonist. However the full range of effects induced by ketamine cannot be explained by its action on the NMDA receptor alone, although it is the most important mechanism. Analgesic, anesthetic and sympathomimetic effects are mediated by different sites of action. Effects on opioid receptors may contribute to the analgesic state as well as to dysphoric reactions **(Ulugol *et al.*, 2000).** [23] Sympathomimetic properties are mediated by enhanced central peripheral monoaminergic transmission. Inhibition of central and peripheral cholinergic

transmission may contribute to the induction of anesthetic effects and hallucination **(Adams H.A. 1988).** [24]

The most common commercial preparation of ketamine is a recemic mixture of two enantiomers, S (+) ketamine and R (-) ketamine. R (-) ketamine is bound approximately 7-10 times more strongly than the S-isomer **(Ebert *et al*., 1997).** [25]

Classical ketamine effects are best described as a dose-dependent central nervous system depression that leads to so- called dissociative state, characterized by profound analgesia and amnesia but not necessarily loss of consciousness. Thus, clinically it produces dissociation between the mind/thought processes and own body/surroundings which results from electrophysiological inhibition of thalamo-cortical pathways and the stimulation of the limbic system **(Flood** and **Krauss 2003).** [26]

B. Pharmacological effects

The effects of ketamine are apparently due to the CNS activity of the parent compound. It produces dissociative anesthetic state **(Domino *et al*., 1965).** [27] This is a state of catalepsy in which eyes remains open with a slow nystagmus, while light and corneal reflexes remain intact. Ketamine when used as an anesthetic produces profound anesthesia, analgesia, amnesia and catalepsy. It is also a potent analgesic even at subanesthetic dose, when given by IV route **(Correll *et al*., 2004).** [28] It causes loss of skin and musculoskeletal sensation, resulting in a reduced ability to feel gravity and a sensation of bodily detachment or floating in space. This ability of ketamine to allow the user to separate perceptions from sensation has sparked an interest in using low doses of the drug to treat chronic pain.

Ketamine has effects other than analgesia and amnesia. The effects on the respiratory system are generally beneficial. It is a bronchodilator; it causes minimal respiratory depression, and compared with other anesthetic agents it preserves protective airway reflex more **(Reich** and **Silvay 1989, Craven R. 2007).** [16, 29] Dose-related respiratory depression with incremental doses is demonstrated by **Bourke *et al*., 1987**. [30] Its bronchodilator property is probably by two different mechanisms- firstly, via a central effect inducing catecholamine release, thereby stimulating β_2 adrenergic receptors, resulting in bronchodilation, and secondly, via inhibition of vagal pathways to produce an

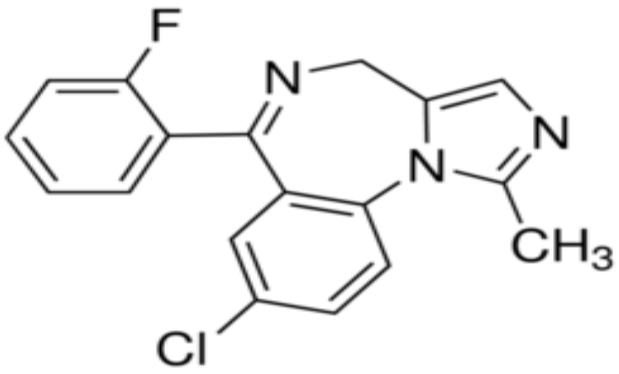
anticholinergic effect acting directly on bronchial smooth muscle **(Lau** and **Zed 2001).**[31,32]

"Ketamine differs from most anesthetic agents in that it appears to stimulate the cardiovascular system, producing changes in heart rate, cardiac output and blood pressure **(Haas** and **Harper 1992)**." [33] Possibly re-uptake inhibition of circulating catecholamines may contribute to this phenomenon. On the other hand cardio-depressant effects have been noted in critically ill patients. This may be due to chronic catecholamine depletion preventing any sympathomimetic effects of ketamine and unmasking negative inotropic effects, which is usually overshadowed by sympathetic stimulation **(Reich** and **Silvay 1989)**.[29,33] The cardiovascular effects of ketamine usually do not pose a problem, but its use is contraindicated in patients with significant heart disease and should be avoided in patients with a history of high blood pressure and cerebrovascular accidents **(Haas** and **Harper 1992).**[33]

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 and adverse effects are due to its effects on the $GABA_A$ receptors; midazolam does not directly activate $GABA_A$ receptors, 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. [34] 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-amino butyric 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 shown to be 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 GABA's inhibitory action. [35] 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. [35]

The hypnotic effect of midazolam appears to be related to GABA accumulation and occupation of the benzodiazepine receptor. Midazolam has a relatively high affinity (twice as 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. [35]

PHARMACOKINETICS:

Absorption- Bioavailability oral 40% intramuscular 90%.

Metabolized 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.[36] 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 1 hr. Midazolam metabolic turnover in children is more rapid than in adults due to children's more active fiver metabolism. [37] The elimination half-life is approximately 45-60 min since a child as compared with 2-6 hr in an adult. [38, 39] Midazolam is eliminated significantly faster when compared with diazepam's elimination half-life of 24-57 hr. [40]

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. [41]

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. [41] Midazolam, like other benzodiazepines, may have anticholinergic effects on patients with glaucoma (angle-closure, acute).

Respiratory depression is produced however; the respiratory depressant effect of midazolam is dose-related. [41, 42]

Midazolam appears to have minimal cardiovascular effects. 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. [43] 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. [44] 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. [40]

USE OF MIDAZOLAM AS A SEDATIVE AGENTIN DENTAL FIELD:

Singh N, Pandey RK, Saksena AK, Jaiswal JN (2002)[45] 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)[46] 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) [47] carried out a study to 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.

Wood M (2010) [48] 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) [49] 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)[50] 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.

Ghajari MF et al (2016) [51] the efficacy of two oral midazolam dosages (0.3 mg/kg and 0.5 mg/kg) for conscious sedation of children having dental treatment was compared. Half of the children received 0.5mg/kg oral midazolam plus 1mg/kg hydroxyzine orally in the first session and 0.3mg/kg oral midazolam plus 1mg/kg hydroxyzine in the next session. The other half received the drugs on a reverse order and concluded that the overall success

rate of the two drug combinations was not significantly different for management of pediatric patients.

Ghajari MF et al (2019) [52] in uncooperative paediatric dental patients, researchers compared the sedative effect of Midazolam Elixir to Vial through Oral Route. At their first appointment, Group I received 0.5 mg/kg Midazolam Vial and 1 mg/kg Hydroxyzine oral, and at their second visit, they received 0.5 mg/kg Midazolam Elixir and 1 mg/kg Hydroxyzine oral. The medication order was reversed in group II. The level of sedative success between the two groups was not statistically different and was nearly identical. In some circumstances of impaired collaboration, this could suggest a successful use of the vial for oral application.

Manso MA, Guittet C, Vandenhende F, Granier LA (2019)[53] 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)[54] 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)[55] 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)[56] 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 Frankl'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 acceptance of drug through buccal route was significantly better than the intranasal route ($p < 0.05$) but no statistically significant difference was found in the behaviour scores for the two routes of administration ($p > 0.05$).

Musani IE, Chandan NV (2015)[57] 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 efficiency, acceptance and safety in controlling the behavior 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.

Shanmugaavel AK et al., (2016)[58] conducted research to see how anxiety levels and drug acceptability differed following 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.

Peerbhay F et al., (2016)[59] compared the effectiveness and recovery times of 0.3 and 0.5 mg/kg intranasal midazolam administered with a mucosal atomizer device (MAD) in a pediatric emergency dental hospital clinic. 118 children aged from 4 to 6 years were randomly administered either 0.3 or 0.5 mg/kg INM via an MAD. They reported no post operative complications. The recovery time of the 0.5 mg/kg group was statistically longer than that of the 0.3 mg/kg group but the difference was not clinically significant. The findings of this study also showed that 0.3 or 0.5 mg/kg doses of INM resulted in safe and

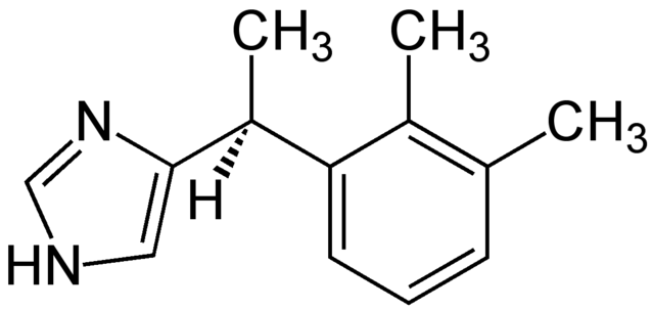
effective sedation. The 0.5 mg/kg dose was more effective than the 0.3 mg/kg dose in reducing anxiety.

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 et al., 2013).** [60]

CHEMICAL STRUCTURE:

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



MECHANISM OF ACTION:

The hypnotic effect of (D) 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 et al., (2014)** [61] 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. **(Khan ZP et al., 1999)**. [62]

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 and Maze M et al., 2000)**[63]

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 not 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 L et al., 2001)** [64]

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 (d) is (84%), intranasal (65%) and intramuscular (100%) offering a potential role in pediatric sedation and premedication**.** 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%)

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 et al., (1992)** [65] .The rise in blood pressure can be attenuated by a slow infusion and by avoiding bolus administration of the drug **(Haselman M.A et al., 2008)**.[66] 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).**[67]

Central nervous system

The amnestic effects of (d) 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 (d) only at high plasma levels (≥ 1.9 ng.mL-1), without retrograde amnesia.(D) may also provide antinociception through non-spinal mechanisms– in addition to it intraarticular administration during knee surgery improves postoperative analgesia 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, 2008)**[68]

Respiratory System

Dexmedetomidine does not suppress respiratory function, even at high doses (**Hsu YW et al., 2004)** [69]. 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.

USE OF DEXMEDETOMIDINE AS A SEDATIVE AGENT IN DENTAL FIELD

Makary et al., (2010) [70] 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..

Yuen V et al., (2012) [71] concluded that intranasal dexmedetomidine in a premedication dose of 2 µg/kg was more efficacious than 1 µg/kg in children. Similarly**,** Kawaai H et al., (2010) 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 et al., (2012) , 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 et al., (2014) [72] 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 faster with midazolam and ketamine group as compared to two different doses of dexmedetomidine group .There was no significant adverse effects with any group.

Mohite V et al., (2019) [73] 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:

Cimen Z.S. et al., (2010)[74] 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**.**

Vinod P et al., (2018) [75] 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 intranasal and orally. It was concluded that dexmedetomidine is a safe and efficient drug for with intranasal route having many advantages over oral route.

MATERIALS AND METHODS

The current study was carried out at the BBDCODS Department of Pediatric and Preventive Dentistry in Lucknow. The study aimed to evaluate and compare intranasal ketamine with a combination of intranasal midazolam and dexmedetomidine for the procedural sedation of uncooperative paediatric dental patients. After receiving approval from the BBDCODS, Lucknow, institutional ethical committee, 47 patients who met the inclusion and exclusion criteria was enrolled in the study. A written assent form from the child and a written informed consent form from the parents/guardians were obtained before starting treatment.

SAMPLE SIZE CALCULATION:

GPower software (version 3.0) was used to estimate the sample size. Sample size was estimated for Paired t test (Cross over trial)

A minimum total sample size of 47 was found to be sufficient for an alpha of 0.05, power of 95 %, 0.05 as effect size (assessed from a similar study).

Wilcoxon signed-rank test (matched pairs) t tests

Options: A.R.E. method

Analysis: A priori: Compute required sample size

Input: Tail(s) = One

Parent distribution = Normal

Effect size dz = 0.5005558

α err prob = 0.05

Power (1-β err prob) = 0.95

Output: Non-centrality parameter = 3.3534136

Critical t = 1.6803274

Df = 43.8816940

Total sample size = 47

Actual power = 0.9511571

Thus, a total of 47 patients were required for the study.

ELIGIBILITY CRITERIA:

Inclusion criteria

- Children aged between 3 to 7 years
- The patient should belong to criteria of American Society of Anaesthesiologists (ASA) classification- I
- The patients for whom the basic behaviour guidance techniques have not been successful.
- The patients undergoing dental procedures which need more than one appointment.

Exclusion Criteria

- Patients not willing to submit their consent in written.
- Definitively Negative patients as on Frankl's behaviour rating scale.
- Patients who are sensitive or allergic to the drugs being administered.
- Patients taking any other sedative medications.
- Children who were given analgesics six hours before the procedure.
- Patients with nasal infections and nasal pathologies.

MATERIALS AND INSTRUMENTS USED:

Material and equipment used in the study with specifications and company.

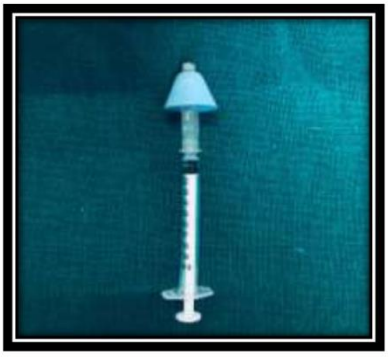
- Ketamine vial - Qualket 50mg/1ml (Taj Pharmaceutical Ltd)
- 5ml bottle of midazolam spray with a 0.5mg dosage per puff (Midacip, Neon Pharmaceuticals)
- 100 mcg/ml of dexmedetomidine hydrochloride injection in a 0.5 ml ampule. (Neon Pharmaceuticals, Dextomid)
- Glycopyrrate HCl injection
- MAD Nasal (Mucosal atomizer device, LMA MAD nasal limited).

- 1ml syringe
- Multipara monitor(Planet 50 n Lifecare)
- Oxygen cylinder(B2 type)
- Pulse oximeter
- Emergency drugs
- Reversal agent

KETAMINE 50 mg/ml

MIDAZOLAM NASAL SPRAY 5mg/ml

DEXMEDETOMIDINE 100mg/ml



MUCOSAL NASAL ATOMIZER

DRUG DELIVERY THROUGH MUCOSAL NASAL ATOMIZER

STUDY DESIGN:

The present study enrolled 47 children with ASA grade-1 between the ages of 3 and 7 years old, of both genders, for whom basic behaviour modification techniques had failed to provide dental treatment. The patients were then managed using pharmacological method of behaviour modification.

The children who required dental treatment were randomly assigned to receive (INK) Intranasal Ketamine (atomized spray) through a MAD device and a combination of (INMzD) Intranasal Midazolam (Intranasal spray) and Dexmedetomidine (atomized spray) in one of the subsequent visits. The current study was a two-stage cross-over trial in which each child received ketamine and a combination of midazolam and dexmedetomidine through intranasal route. During each visit, the vital signs were continuously monitored. The atomized dose for the intranasal ketamine was 7mg/kg body weight, midazolam spray (Midcap, Cipla pharmaceutical) was 0.3mg/kg body weight and the dose for the atomized dexmedetomidine was 3mcg/kg body weight. For the excessive salivation caused by ketamine, 0.1ml/kg body weight intramuscular (IM) glycopyrrate HCl injection was given.

METHODOLOGY:

Forty-seven healthy children (ASA 1) between the ages of 3 and 7 years were recruited into the study for whom basic behaviour modification techniques had failed to provide dental treatment, which was approved by the institutional Ethics Committee of BBDCODS, Lucknow, India. The parent/guardian was asked to fill out a written informed consent form, and children 8 years of age and above were asked to fill out an assent form. At the initial appointment, the parent/guardian was informed of the risks and benefits of the sedation. A comprehensive dental and medical history was obtained. To assess the risk of airway obstruction, the airway was thoroughly examined (tonsillar hypertrophy, abnormal anatomy, ability to visualize only the hard palate or tip of the uvula). A systemic review was performed, with a focus on abnormalities in cardiac, pulmonary,

renal, or hepatic functions that could alter the child's expected responses to sedating medication.

The patient was given pre-sedation dietary instructions according to the American Society of Anesthesiologists guidelines. An experienced anesthesiologist performed a comprehensive preanesthetic assessment of the patient at the Babu Banarasi Das College of Dental Sciences in Lucknow. The blood tests (CBC), chest X-ray and Sodium Potassium test were advised to the patient before the day of sedation. Sedation was only carried out when all of the parameters were within normal range.

The anesthesiologist reassessed patients on the day of dental treatment. With the help of a multi-para monitor, the vital signs (pulse rate and blood pressure) and peripheral oxygen saturation levels were examined and recorded.

The body weight was measured prior to the administration of a drug, and the drug was calibrated based on the body weight. With the patient in a semi-recumbent position, half the required amount of drug was administered into each nostril using a nasal spray or an atomizer device for intranasal administration.

The purpose of this study was to compare the efficacy, safety, and acceptability of intranasal ketamine (INK) with intranasal midazolam and dexmedetomidine (INMzD) combination for sedation in pediatric dental patients while delivering dental treatment to uncooperative children. The enrolled patient was given atomized ketamine spray (7mg/kg) during first visit and the same patient during subsequent visit was given combination of midazolam spray (0.3mg/kg) with atomized spray of dexmedetomidine (3mcg/kg). During each sedation session, the children were evaluated for their behavior response to drug acceptance during drug administration, while after drug administration, they were evaluated for the time of onset, depth of sedation, and duration of sedation., behavioral response during the treatment, the ease with which treatment can be completed, the recovery from sedation, and the drug side effects.

In the presence of an anesthesiologist, all dental procedures were performed by a single operator. The vital signs (pulse rate, blood pressure, and oxygen saturation) were recorded before the drug was administered and every 5 minutes afterward for a total duration of 60 minutes.

The Ohio State Behavioral Rating Scale (OSBRS), as described by Lochary and colleagues in 1992, was chosen for each patient's drug acceptance and was noted down. The time for onset of sedation was recorded. The onset of sedation was identified when the patient's level of sedation was equivalent to a score of 2 on the sedation rating scale (AAPD 2006 modified by Padmanabhan et al 2009). Similarly, the peak of sedation was observed when the patient's level of sedation corresponded to a score of 3 on the sedation rating scale. The level of sedation was assessed using a 5-point scale by University of Michigan Sedation Scale (UMSS) Scoring and the ease with which treatment could be completed was scored by AAPD 2006 modified by Padmanabhan et al 2009.

The patient was transferred to the recovery room after the treatment was completed. If there were any post-sedation side effects, they were also noted. The time required to recover completely was recorded. The patient was declared fully recovered after meeting certain criteria using the Aldrete Recovery Scoring 2015. Vital signs were re-evaluated, and the patient was discharged once the AAPD sedation guidelines for discharge were met. The discharge time was calculated from the end of the procedure until the patient left the hospital. Both the parents and the patient received post-discharge instructions.

RESULTS AND OBSERVATIONS

The present study evaluated and compared intranasal ketamine with intranasal midazolam and dexmedetomidine combination for procedural sedation in uncooperative paediatric dental patients. 47 study subjects in age range from 3-7 years were required to carry out the study, with a 10% loss to follow up, 53 study participants in total was enrolled for the completion of study. Each subject were recruited and randomized equally into two interventions on the basis of drug administered. Ketamine 7 mg/kg (n=47) was administered in first visit and on subsequent visit the combination of midazolam (0.3mg/kg) and dexmedetomidine (3mcg/kg) were given in cross over manner. The outcome measures of the study were hemodynamic parameters (pulse 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 hour.

Table 1: Distribution of study subjects

Total recruited N (%)	**Estimated Loss to follow up**	**Sample size**
53 (100%)	6 (11.3%)	47 (88.6%)

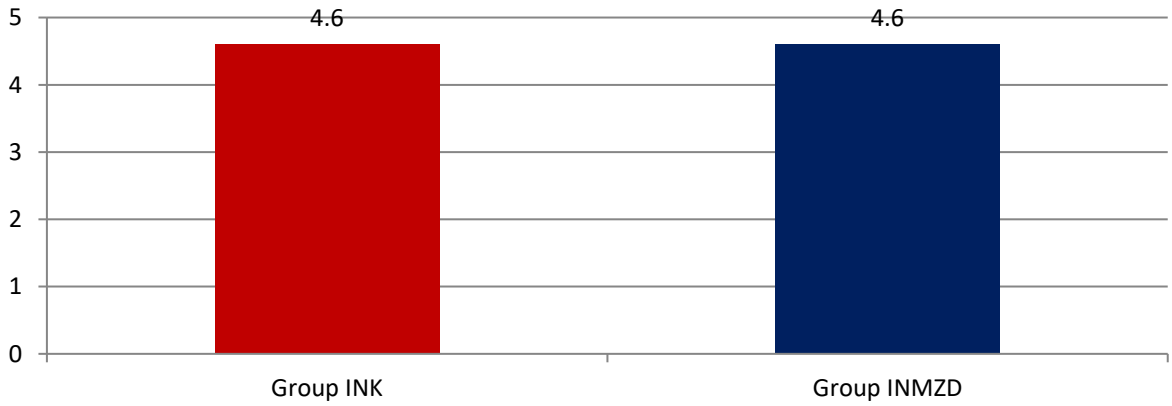
DEMOGRAPHIC CHARACTERISTICS

The total age of participants in both the groups (INK and INMZD) are summarized in Table 2 and Graph 1. In both the groups' age ranged from 3 to 7 yrs, respectively with a mean (± SD) of 4.6 ± 1.13 yrs respectively. Comparing the mean age, subjects in both groups were age-matched.

Table 2: The mean age of subjects in both the groups.

Demographic characteristics	**Group INK (n=47) (%)**	**Group INMzD (n=47) (%)**	**t value**	**p value**
Age (yrs): Mean ± SD Range (minutes to max) Median	 4.6±1.13 3 to 7 years 4.5	 4.6±1.13 3 to 7 years 4.5	0.00	1.000 (Non-Sig)

The age in both the groups were summarized and compared by Student's t test



Graph 1 :The mean age of subjects in both the groups

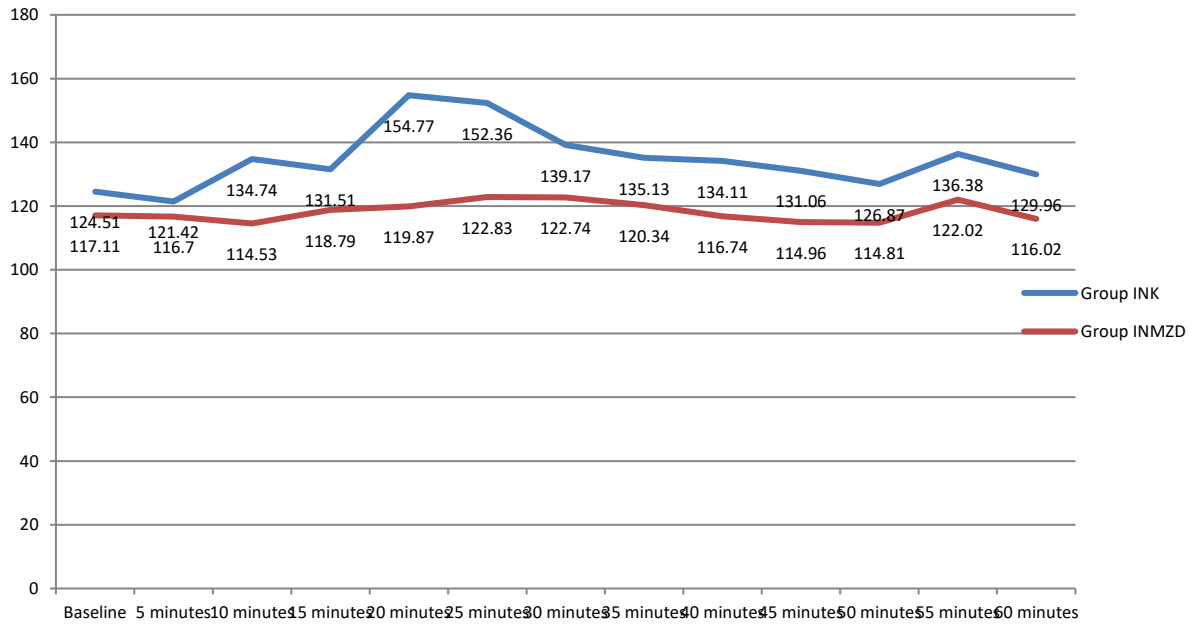
HEMODYNAMIC PARAMETERS

I. Pulse rate: The pulse rate (PR) in both the groups over a period of 60 minutes is summarized in Table 3 and Graph 2. 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 all the intra operative time periods, it was comparatively higher with INK as compared to INMzD.

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 at 20,25,30,35 and 55 minutes in INMzD combination group. Similarly in the INK, the Tukey test showed significantly higher PR as compared to baseline at 10 minutes onwards till 60 minuets

Table 3: Pulse rate of both the groups over a period of 60 minutes

Time period	Group INK (n=47)	Group INMzD (n=47)	p value
Baseline	124.51±10.34	117.11±21.10	0.033
5 minutes	121.42. ±18.39 ns	116.70±14.36ns	0.127
10 minutes	134.74±11.99*	114.53±13.66 ns	0.001
15 minutes	131.51±14.51*	118.79±21.65 ns	0.001
20 minutes	154.77±30.93*	119.87±30.52*	0.001
25 minutes	152.36±20.52*	122.83±30.12*	0.001
30 minutes	139.17±19.24*	122.74±31.78*	0.003
35 minutes	135.13±15.45*	120.34±25.73*	0.001
40 minutes	134.11±20.29*	116.74±10.77 ns	0.001
45 minutes	131.06±17.64*	114.96±15.38 ns	0.001
50 minutes	126.87±15.49 ns	114.81±12.76 ns	0.001
55 minutes	136.38±19.96*	122.02±26.79*	0.004
60 minutes	129.96±18.43*	116.02±20.15	0.001



Graph 2:Pulse rate of both the groups over a period of 60 minutes

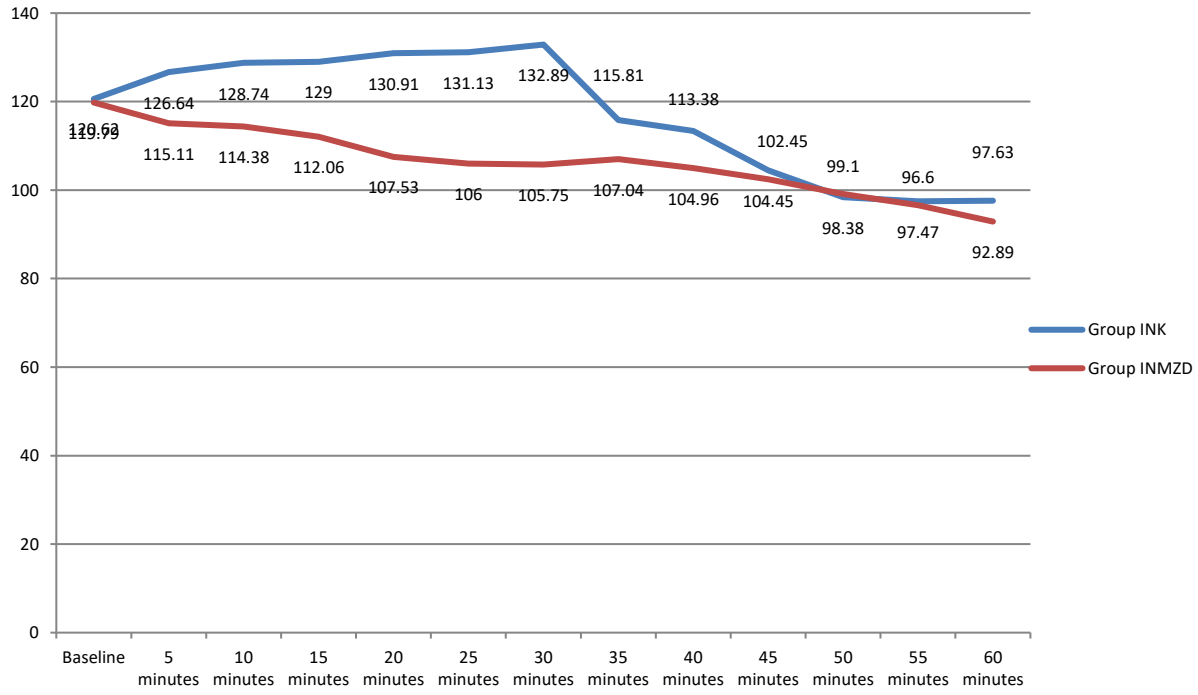
II. Systolic Blood Pressure:

The systolic blood pressure (SBP) of both groups over a period of one hour is summarized in Table 4 and Graph 3. In the INK, the mean SBP increased after drug administration till 30 minutes and then there was a gradual reduction in the blood pressure till 60 minutes. In the INMzD combination, there was a reduction in the Blood pressure from baseline to 60 minutes. Further, at most of the intra operative time period, it was comparatively higher in INK as compared to the INMZD combination.

On intra-group comparison, the difference in mean SBP between baseline and intra operative time periods, Tukey test showed significantly higher SBP as compared to baseline in INK till 30 minutes and lower SBP from 35 minutes to 60 minutes. In the INMzD combination, the intragroup reduction in blood pressure from baseline to 60 minutes was statistically significant

Table 4: Systolic Blood Pressure of both the groups over a period of 60 minutes

Time period	Group INK (n=47)	Group INMzD (n=47)	p value
Baseline	120.62±22.21	119.79±17.89	0.942
5 minutes	126.64±15.01*	115.11±17.59*	<0.001
10 minutes	128.74±14.17*	114.38±16.51*	0.001
15 minutes	129.00±15.91*	112.06±12.32*	0.001
20 minutes	130.91±9.11*	107.53±10.88*	0.001
25 minutes	131.13±20.65*	106.00±12.94*	0.001
30 minutes	132.89±14.09*	105.75±15.001*	0.001
35 minutes	115.81±18.43*	107.04±20.83*	0.001
40 minutes	113.38±22.04*	104.96±15.03*	0.001
45 minutes	104.45±13.61*	102.45±18.86*	0.144
50 minutes	98.38±8.78*	99.10±9.87*	0.708
55 minutes	97.47±14.11*	96.60±11.52*	0.624
60 minutes	97.63±7.91*	92.89±11.32*	0.021



Graph 3 : Systolic Blood Pressure of both the groups over a period of 60 minutes

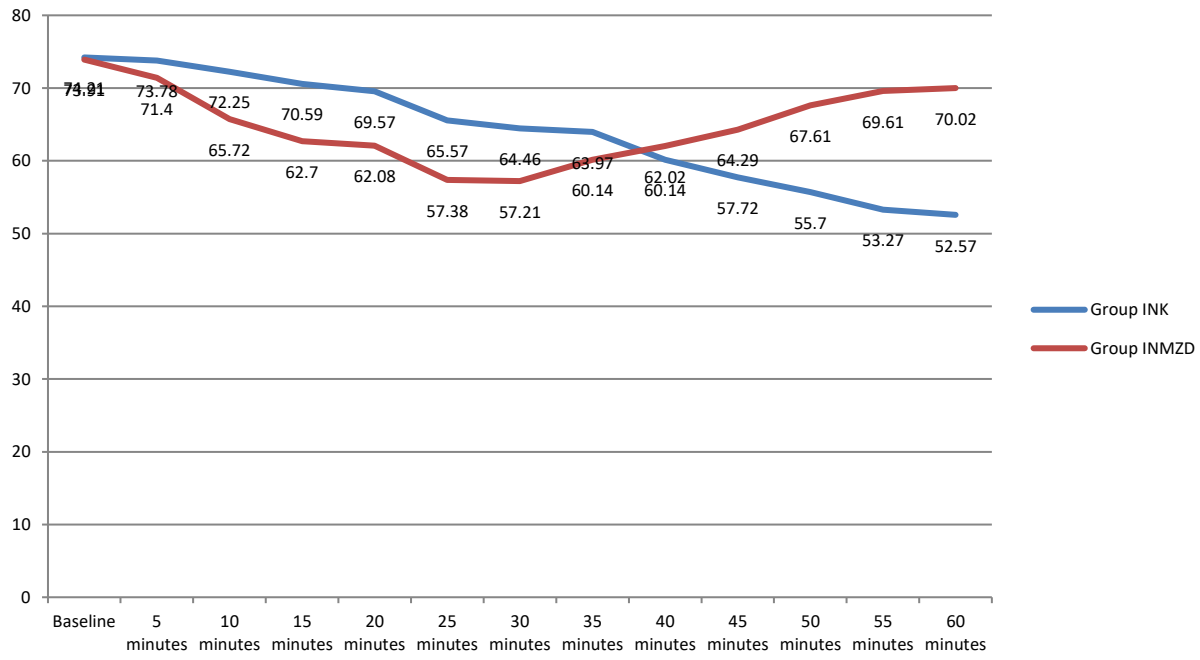
III. Diastolic Blood Pressure

The diastolic blood pressure (DBP) of both groups over the period of 60 minutes is summarized in Table 5 and Graph 4. In INK, the mean DBP decreased after drug administration and remained lower till the end of the 60-minute session as compared to the baseline. While, in INMzD combination, it decreased after the drug administration to 30 minutes and then gradually increased to 60 minutes. Till 35 minutes, the DBP remained higher in INK as compared to the INMzD combination and thereafter the DBP was higher in the INMzD as compared to the INK intervention.

For intra group comparison, the difference in mean DBP between baseline and intra-operative time periods, Tukey test showed significantly lower DBP from 10 minutes to 60 minutes as compared to baseline in both INK and INMzD combination.

Table 5: Diastolic Blood Pressure of both the groups over a period of 60 minutes

Time period	Group INK (n=47)	Group INMZD (n=47)	p value
Baseline	74.21±9.01	73.91±7.76	0.864
5 minutes	73.78±17.20	71.40±12.22	0.243
10 minutes	72.25±12.38*	65.72±7.58*	0.001
15 minutes	70.59±13.87*	62.70±19.84*	0.683
20 minutes	69.57±12.42*	62.04±18.92*	0.04
25 minutes	65.57±13.70*	57.38±9.90*	0.001
30 minutes	64.46±8.95*	57.21±11.29*	0.001
35 minutes	63.97±8.91*	60.14±11.28*	0.071
40 minutes	60.14±11.28*	62.02±7.83*	0.001
45 minutes	57.72±10.61*	64.29±17.23*	0.002
50 minutes	55.70±8.67*	67.61±7.05*	0.001
55 minutes	53.27±7.43*	69.61±5.45*	0.001
60 minutes	52.57±9.64*	70.02±7.53*	0.001



Graph 4: Diastolic Blood Pressure of both the groups over a period of 60 minutes

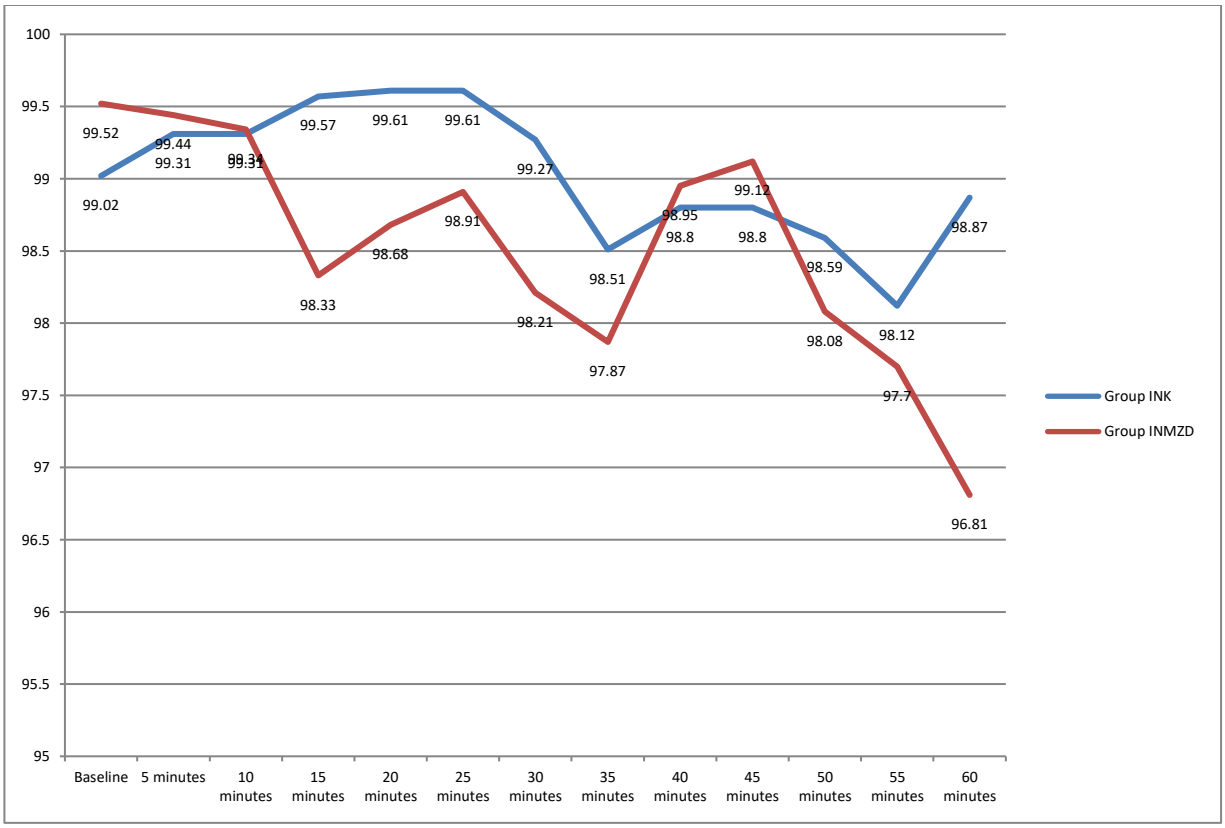
IV. Oxygen Saturation

The oxygen saturation (SPO2) of both groups over a period of 60 minutes is summarized in Table 6 and Graph. 5. After administration of the drug, the mean SPO2 remained slightly higher as compared to baseline till 30 minutes and thereafter oxygen saturation (SPO2) was slightly lower as compared to baseline in INK. In contrast, in INMzD oxygen saturation (SPO2) was slightly lower as compared to baseline at all the time intervals. On Intra group comparison, the difference in mean SPO2 between baseline and intra operative time periods for each group was taken out. The Tukey test showed a non-significant difference from baseline at all the time intervals in both groups.

Similarly, in intergroup comparison for each period, the difference in mean SPO2 between both groups was taken out. The results of the Independent t-test showed that oxygen saturation (SPO2) was found significantly higher in INK as compared to INMzD at most of the time interval

Table 6: Oxygen Saturation of both the groups over a period of 60 minutes

Time period	**Group INK (n=47)**	**Group INMzD (n=47)**	**p value**
Baseline	99.02±1.62	99.52±0.80 ns	0.847
5 minutes	99.31±0.95ns	99.44±0.81 ns	0.485
10 minutes	99.31±0.81 ns	99.34±0.93 ns	0.907
15 minutes	99.57±1.24 ns	98.33±1.91 ns	0.01
20 minutes	99.61±1.01 ns	98.68±0.79 ns	0.001
25 minutes	99.61±0.71 ns	98.91±0.77 ns	0.001
30 minutes	99.27±0.86 ns	98.21±1.31 ns	0.001
35 minutes	98.51±1.94 ns	97.87±1.76 ns	0.047
40 minutes	99.48±1.02 ns	98.95±0.97 ns	0.011
45 minutes	98.80±1.12 ns	99.12±0.72 ns	0.102
50 minutes	98.59±1.17 ns	98.08±1.62 ns	0.239
55 minutes	98.12±3.21 ns	97.70±2.05 ns	0.148
60 minutes	98.87±1.77 ns	96.81±3.97 ns	0.001



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

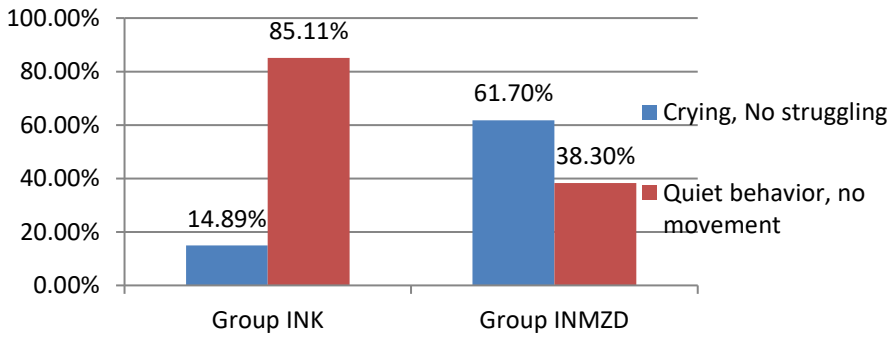
ACCEPTANCE OF DRUG

The drug acceptance for both interventions is summarized Table 7 and Graph 6. The acceptance of drugs showed significant difference between both the groups. The majority of patients in INK accepted the drug with quiet behavior and no movement (85.11%), whereas the majority of patients in INMzD accepted it with crying and no struggling (61.70%).

Table 7: Acceptance of drug between both the groups.

Score	Acceptance of drug rating:	Group INK(n=47) %	Group INMZD(n=47) %	χ^2 value	p value
4	Quiet behavior, no movement	40 (85.11)	18 (38.30)	21.789	0.001
3	Crying, No struggling	07 (14.89)	29 (61.70)		
2	Struggling movement without Crying,	0	0		
1	Struggling movement with Crying,	0	0		

Acceptance of drug in both the groups were summarized and compared by χ2 test.



Graph 6:Acceptance of drug between both the group

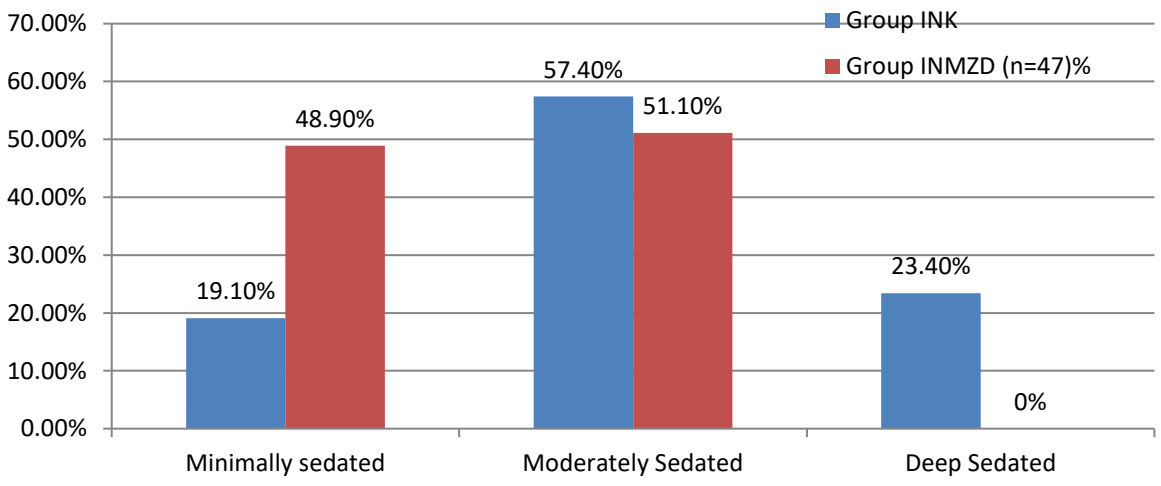
LEVEL OF SEDATION

The Level of Sedation of both the groups is summarized in Table 8 and Graph.7. The level of sedation in both groups showed significant difference. The level of sedation rating in majority of patients in INK was moderate (57.4%) and deep (23.4%) where as in INMzD combination the rating was minimal (48.9%) and moderate (51.1%).

Table 8 : Level of sedation scale between both groups.

Sedation rating scale	**Group INK (n=47) %**	**Group INMzD (n=47)%**	**χ^2 value**	**p value**
Minimally sedated	9 (19.1%)	23 (48.9%)	17.301	0.001 (Sig)
Moderately Sedated	27(57.4%)	24 (51.1%)		
Deep Sedated	11(23.4%)	0(0.0%)		

Level of sedation in both the groups were summarized and compared by χ2 test.



Graph 7: Level of sedation scale between both the groups.

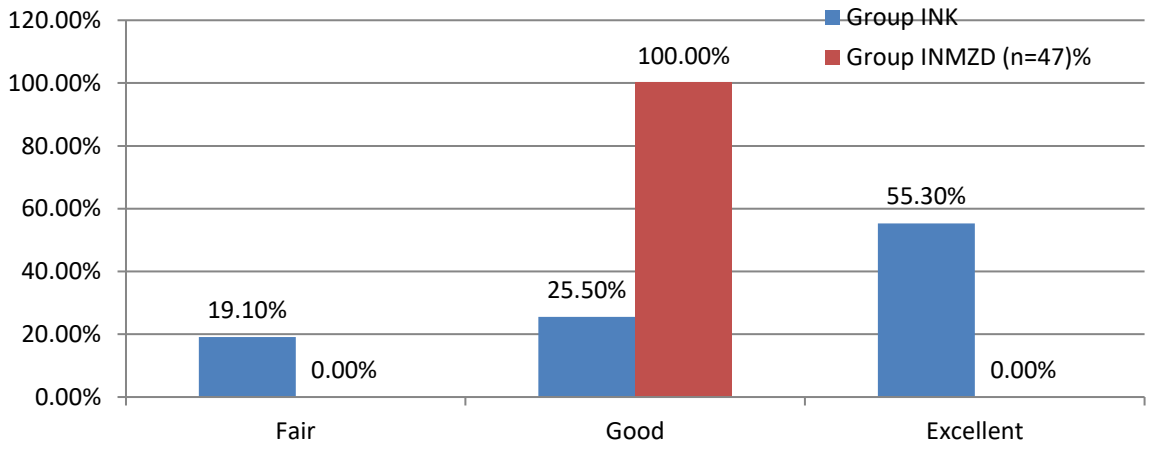
EASE OF TREATMENT COMPLETION

The Ease of treatment completion between both the groups is summarized in Table 9 and Graph 8. On comparing, ease of treatment completion it was found significantly better for the intranasal midazolam and dexmedetomidine combination (INMzD), 100% of the results were in good category while for the intranasal ketamine (INK) 53.2% results were found to be Excellent, 27.7% were good and 19.1 % were fair

Table 9: Ease of treatment completion between both the groups

Ease of treatment completion:	**Group INK (n=47) %**	**Group INMzD (n=47)%**	**χ^2 value**	**p value**
Fair	9 (19.1%)	0 (.0%)	55.764	0.001 (Sig)
Good	12 (25.5%)	47 (100.0%)		
Excellent	26 (55.3%)	0 (.0%)		

Ease of treatment completion in both the groups were summarized and compared by χ2 test. NA: not applicable.



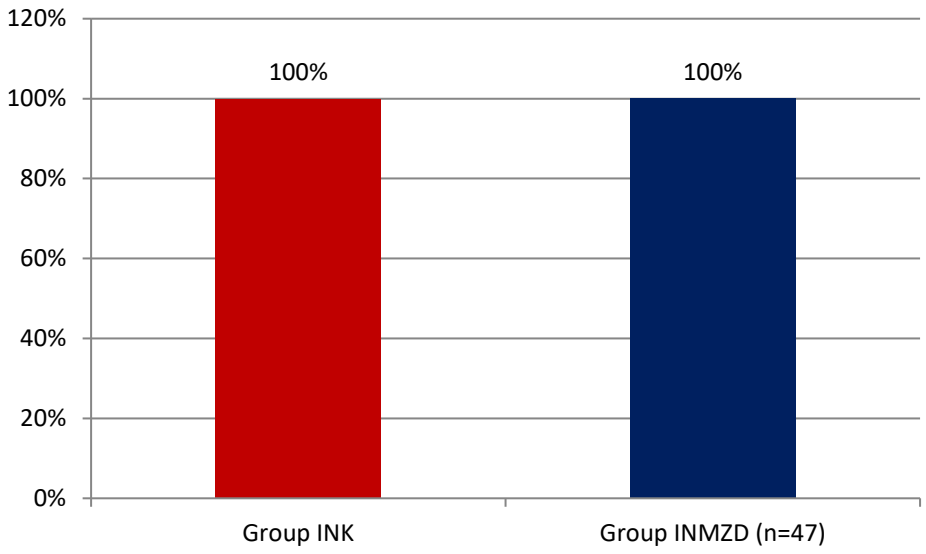
Graph 8: Ease of treatment completion between both the groups

POST OPERATIVE COMPLICATION

There were no post operative complications in both the groups. (Table 10, Graph 9)

Table 10: Post operative complications between both the groups

Post operative complications	Group INK (n=47)	Group INMzD (n=47)	χ^2 value	p value
No	47 (100.0%)	47 (100.0%)	NA	-



Graph 9: Post operative complications between both the groups

OUTCOME MEASURES

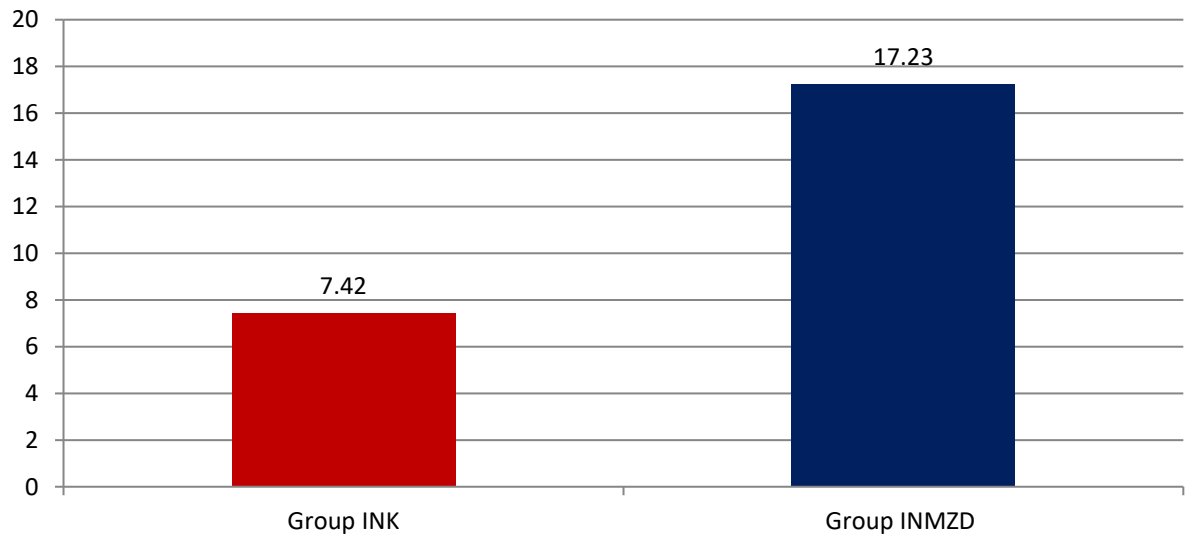
1.ONSET TIME

Onset time of both the groups is summarized in Table 11 and Graph 10. On comparing the mean, Student's t test showed significantly faster onset time in INK as compared to INMzD combination.

Table 11: Onset time of the both groups

Parameter	**Group INK (n=47)**	**Group INMzD (n=47)**	**t value**	**p value**
Onset Time	7.42 ± 2.33	17.23 ± 2.40	20.665	<0.001

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



Graph 10 : Onset Time of the both groups

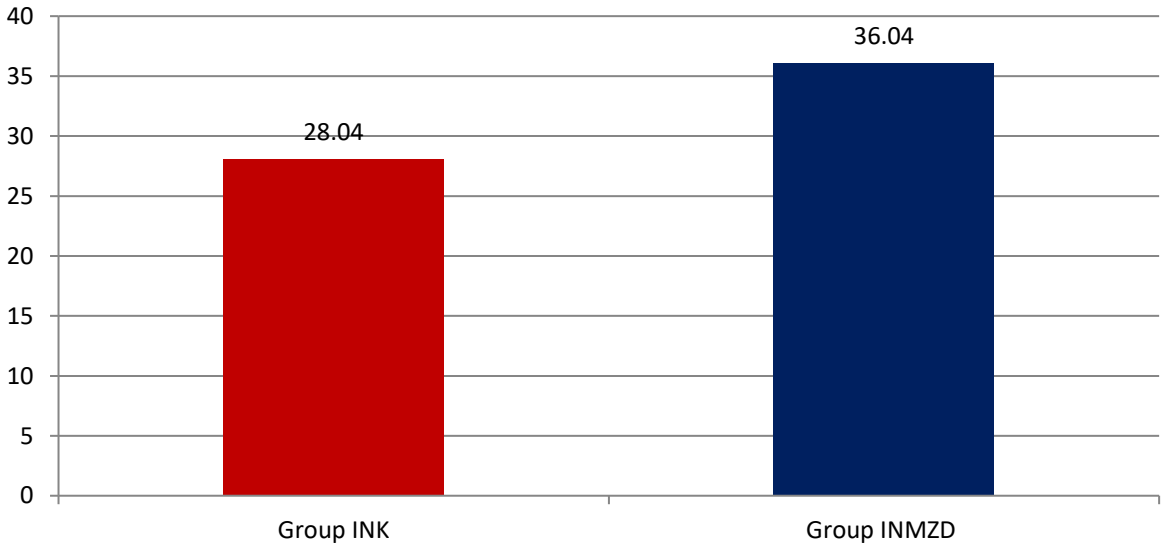
2. PEAK SEDATION TIME

Peak sedation time of both the groups is summarized in Table 12 and Graph 11. On comparing the mean of peak sedation time, Student's t test showed significantly higher peak sedation time in INMzD combination as compared to INK.

Table 12: Peak sedation time between both the groups

Parameter	Group INK (n=47)	Group INMzD (n=47)	t value	p value
Peak sedation time (minutes)	28.04 ± 2.97	36.04 ± 3.60	11.727	<0.001

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



Graph 11: Peak sedation time between both the groups

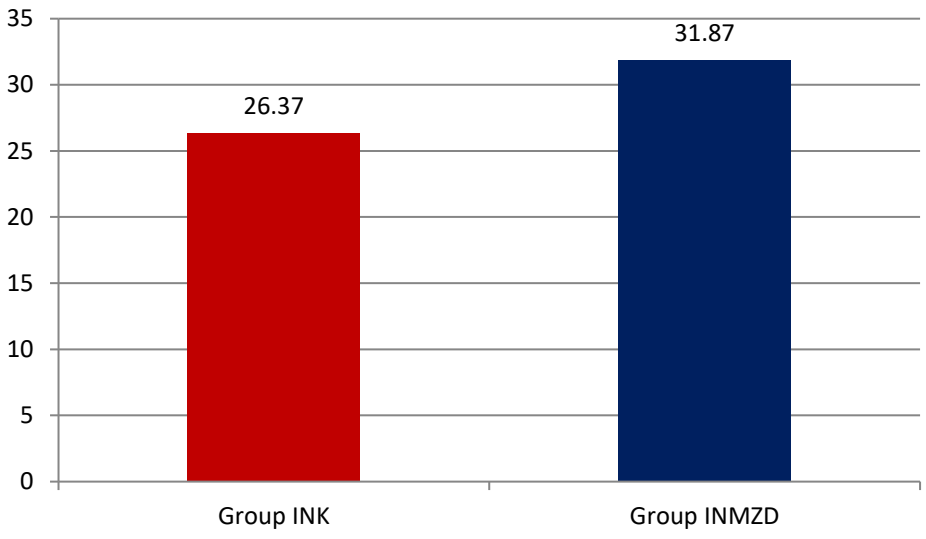
3. RECOVERY TIME

Recovery time of both the groups is summarized in Table 13 and Graph 12. On comparing the mean, Student's t test showed significantly higher recovery time in Group INMZD as compared to Group INK.

Table 13 : Recovery time of both the groups after 30 minutes from treatment completion.

Parameter	Group INK (n=47)	Group INMZD (n=47)	t value	p value
Recovery time (minutes)	26.37 ± 3.64	31.87 ± 2.26	8.809	<0.001

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



Graph 12: Recovery time of both the groups after 30 minutes from treatment completion.

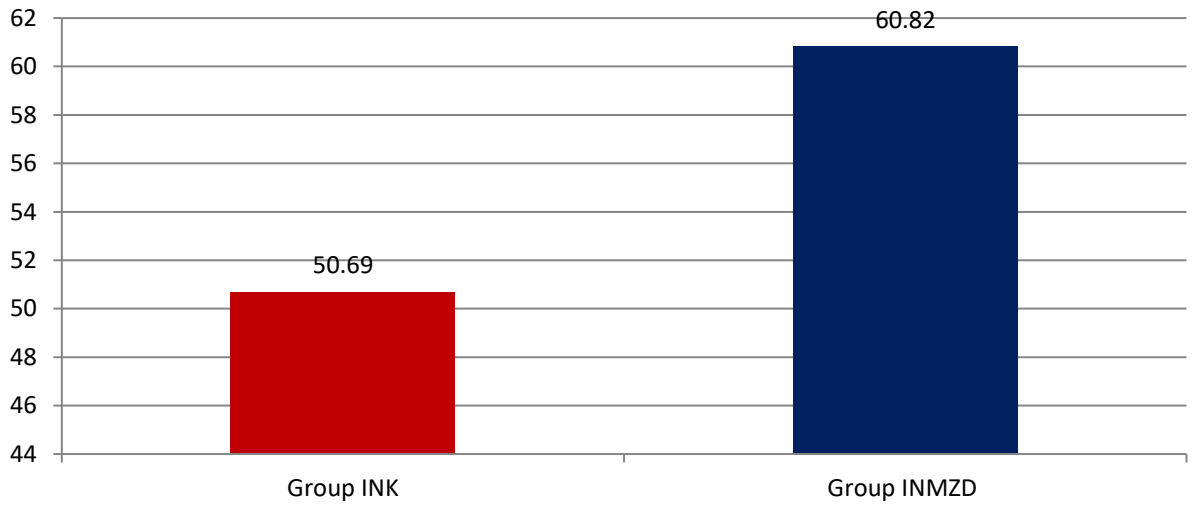
4. DISCHARGE TIME

Discharge time of both the groups is summarized in Table 14 and Graph 13. On comparing the mean, Student's t test showed significantly higher discharge time in INMzD as compared to INK.

Table 14: Discharge time of both the groups after 60 mins from recovery

Parameter	**Group INK (n=47)**	**Group INMzD (n=47)**	**t value**	**p value**
Discharge time (minutes)	50.69 ± 6.65	60.82 ± 4.99	8.359	<0.001

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



Graph 13: Discharge time of both the groups after 60 mins from recovery

DISCUSSION

Pediatric patients frequently have poor oral health due to a lack of knowledge about dental treatment. There are various reasons for ignorance toward dental treatment, but the most common reason for ignorance of dental treatment in this age group may be anxiety or fear of pain. Therefore, it is the primary duty of a paediatric dentist to carry out dental procedures with such care that the procedure is painless, any existing anxiety is relieved, and the child does not recall any unpleasant experiences on subsequent visits.

One option for treating unmanageable paediatric patients is to use general anesthesia. However, it is considered the last treatment option because it is a less acceptable choice for providing dental treatment as a behavior management tool due to its high cost, questionable parental acceptability, and associated complications, as well as no evidence that it provides any benefit to the highly anxious patient other than meeting their immediate treatment needs. Conscious sedation has been regarded as one of the most reliable options for overcoming high levels of interfering dental anxiety while maintaining acceptable levels of patient health and safety when used by skilled paediatric dentists. According to **Jorgensen et al. (1992),** [75] another option for the pharmacological management of apprehensive children is moderate sedation (conscious sedation, procedural sedation). In addition, **Hazha Ibrahim (2019)** [76] contended that conscious sedation is a more cost-effective alternative to general anesthesia for children with limited treatment needs and temperament. Sedation in paediatric anesthesia has the goal of reducing pre and post-operative anxiety, allowing for good child-parent separation, and making procedures easier to complete. According to **Litke J et al. (2012),** [77] pre-operative anxiety in children can result in aggressive reactions, increased distress, increased postoperative pain, behavioral changes, and agitation.

For many years, paediatric dentists have researched the best ways to administer sedative drugs. Among the various sedation routes in children, the oral route is the most commonly used and widely accepted. The main disadvantage of oral sedation, according to **Fallahinejad Ghajari M (2014)**, [52] is the delayed onset, as well as the long recovery period and high first-pass metabolism. In addition, **Kramer N et al., (1990)**[78] discovered in their study that rectal application is frequently painful, and medications administered through this route may be easily expelled from the rectum in younger

children and can be embarrassing in older children. Further, intramuscular pre-medications have been used, but injections are invasive procedures resulting in pain, bruises, and fear in children. As a result, non-invasive routes such as oral and transmucosal administration of sedative drugs in children are preferred. Intranasal administration is a simple and noninvasive technique for avoiding inadvertent intravenous or arterial injection, nerve injury, or infection associated with intramuscular injections. A survey of paediatric dentistry advanced education programmes in the United States found an increase in the use of intranasal administration of sedatives for the sedation of young, uncooperative pediatric dental patients. Intranasal drugs have primarily been used in pediatrics to avoid the need for injection or bitter-tasting oral drugs in children, particularly in unwilling patients. **Primosch RE et al (2001)** [79] in their study concluded that transmucosal routes, such as intranasal, sublingual, and buccal administration, were effective because of the rich mucosal blood supply. In addition, as stated by **Primosch RE and Bender F (2001)**, [79] they also concluded that the compliance with nasal sedation is easier to achieve in younger children than compliance with oral sedation. **Lowhagen et al. (2002)**,[80] in their study found that intranasal route has a quicker onset, which may be because the drugs quickly reach adequate levels of cerebrospinal fluid and are able to communicate with the subarachnoid space via the olfactory nerve and its sheath. The oral route bypasses first-pass metabolism, so the intranasal route has gained traction in the field of sedation for paediatric dental patients in recent years. **Wood M et al (2010),**[48] in their study found that intranasal administration of drug to be safe and effective method of procedural sedation also **Vinod P et al. (2018)**[74] demonstrated in their study that dexmedetomidine administered intranasally acted as a safe and effective agent for procedural sedation in pediatric dental patients.

Several authors have previously used drops for intranasal sedation of uncooperative paediatric dental patients, but atomized intranasal administration has recently gained popularity. According to **Primosch RE et al (2005)**[81] and **Griffith N et al (2005)**[82], using an atomizer instead of drops improved patient tolerance. **Pandey et al. (2011)** [83] found that using an atomizer for procedural sedation analgesia in uncooperative pediatric dental patients was an effective alternative. Based on previous research, we chose an atomizer for intranasal administration of ketamine and dexmedetomidine in our study.

Dentists have used a variety of pharmacological agents to provide sedation, but none have been proven to be the best. Ketamine, which has been in use since 1970, is known as a dissociative agent because it causes a functional and electro physiologic dissociation between the thalamocortical and limbic areas of the brain, resulting in a “trancelike cataleptic” state characterized by profound analgesia and amnesia, with retention of protective airway reflexes, spontaneous respiration, and cardiopulmonary stability." It is especially well” suited to paediatric procedures and offers better sedation with fewer respiratory complications than midazolam/fentanyl, making it an excellent agent for paediatric dental sedation. [9]

Furthermore, several studies showed that it has a wide margin of safety. It has been used successfully by few researchers for pediatric dental sedation. Despite the fact that clinical trials of intranasal ketamine in medicine have been well documented; its use in paediatric dentistry has received little attention. **Pandey Rk et al (2011)** [83] Dexmedetomidine, the first alpha 2-adrenoceptor agonist, was synthesized in the 1960s for use as a nasal decongestant. The sedative and analgesic properties provided are useful for pre-anesthetic medication. When used intranasally, the drug was found to be a safe and effective substitute for premedication in children. **(Saad A. Et al., 2013).**[60] Midazolam is a short-acting benzodiazepine that has therapeutic and adverse effects due to its effects on $GABA_A$ receptors, resulting in sedation, sleep induction, anxiety reduction, anterograde amnesia, muscle relaxation, and anticonvulsant effects. **Malika A. et al (2023)** [84] in their study found that the use intranasal midazolam route was effective in providing minimal to moderate sedation for paediatric dental patients undergoing procedural sedation.

Hence, the purpose of this study was to compare and evaluate the efficacy and safety of intranasal ketamine with intranasal midazolam and dexmedetomidine combination as a behavior modification technique for providing comprehensive oral care to young, uncooperative pediatric dental patients.

Several studies on the use of intranasal ketamine at various doses to produce a sedative and analgesic effect in children undergoing procedural sedation have been published in the literature. The literature revealed variations in the frequency and dose of intranasal ketamine as monotherapy drug. The single atomized dose for intranasal ketamine ranged from 2 to 10 mg/kg body weight. **Abrams et al (1993)**, [85] in their study

with 3-6mg/kg body weight intranasal dose of ketamine found that the depth of sedation was minimal. **Tsze et al. (2012)** [86] used three different doses of intranasal ketamine in their study i.e., 3, 6, and 9 mg/kg body weight of the participants; they found that 9 mg/kg provided adequate depth of sedation versus all other doses. Furthermore, they concluded that 6% of sedation failures occurred at doses of 3 mg/kg and 6 mg/kg. Based on previous research and the drug's safety margin, we chose a dose of 7mg/kg intranasal ketamine for our study. The dose for midazolam and dexmedetomidine combination therapy was 0.3mg/kg body weight for midazolam spray and 3mcg/kg body weight for dexmedetomidine via the atomizer. According to **James et al (2014)**, [87] intranasal dexmedetomidine alone did not produce sufficient sedation and analgesia, whereas dexmedetomidine when combined with opioid/ sedatives offered the potential for increased sedation efficacy. The current study was a crossover study in which patients were given intranasal ketamine on their first visit and then a combination of midazolam and dexmedetomidine for dental treatment on their second visit.

To alleviate ketamine-induced excessive salivation prior to administering intranasal ketamine, the patient was given 0.1ml per kg body weight of glycopyrrolate injection I.M. In our study dexmedetomidine was administered 30 minutes before entering into operatory because of its delayed onset of action and also to achieve desired level of sedation. It is also expected to reduce the burning sensation caused by midazolam due to its acidic nature, allowing for better drug acceptance.

The current study was completed with 47 study subjects in the age range from 3-7 years. Anticipating a 10% loss to follow-up, 53 study participants in total were enrolled for the completion of the study. Each subject was recruited and randomized equally into two groups (Group INK and Group INMzD) based on the drug administered. Ketamine 7 mg/kg (n=47) was administered on the first visit and in the subsequent visits, the combination of midazolam (0.3mg/kg) and dexmedetomidine (3mcg/kg) was given in a cross-over manner. As a result, a total of 94 sedation sessions were carried out.

In present study Table 2 and Graph 1 summarizes the demographic characteristics of both the groups (INK and INMzD). The age range for both the groups was 3 to 7 years, with a mean (SD) of 4.6 ± 1.13 yrs. The age group between 3 to 7 years was chosen for our study because children of this age group may have a poor understanding of dental treatment and

may exhibit anxiety and fear when visiting the dental clinic. In addition, to predict the behavior of children in the dental clinic, we used Frankl's behavior rating scale, which was modified by Wright with symbolic representation. The children who had failed to be managed by basic behavior guidance techniques (non pharmacological) were included in our study with a Frankl's scale rating II, i.e. negative (-,-).

The acceptability of intranasal ketamine (INK) was significantly higher in the current study than the combination of intranasal midazolam and dexmedetomidine (INMzD).This could be because midazolam, when administered intranasally, causes a burning sensation in the nasal mucosa. To support the aforementioned statement, **Lee-Kim SJ et al (2004)** [88] and **Peerbhay F et al (2016)** [59] concluded in their studies that the only disadvantage of administering intranasal midazolam was that children reported a burning sensation of nasal mucosa. To mask the effect, **Chiaretti et al (2011)** anaesthetized the nasal mucosa with intranasal lidocaine prior to the administration of midazolam and found effective for drug acceptance. In another study, **Wood et al. (2011)** [48] found that even after prior administration of intranasal lidocaine, 9% of children experienced a burning sensation of the nasal mucosa. In our study, dexmedetomidine was administered intranasally prior to the administration of midazolam spray in order to mask the effect of burning sensation caused by midazolam spray and to achieve a successful depth of sedation with combination therapy. (Table 7, Graph 6).

The current study found that intranasal ketamine (INK) had a faster onset time with a mean value of 7.40 minutes, whereas intranasal Midazolam Dexmedetomidine Combination (INMZD) had a longer onset time with a mean value of 17.11 minutes (Table 11 and Graph 10). **Pandey Rk et al (2011)**[83] found that intranasal ketamine had a rapid onset of action with a mean value of 5.13 minutes, whereas **Li L et al (2018)**[89] in their study found that intranasal dexmedetomidine plus buccal midazolam had an onset time of 15 minutes in children for auditory brainstem response testing. **Gu et al (2022)** [90] used two regimes with the combination of intranasal dexmedetomidine with oral midazolam in their study, and the results for the onset time for both regimes were 24.97 to 27.92 minutes. **James et al (2014)**[87] administered intranasal dexmedetomidine 45 minutes prior to the procedure start time because intranasal dexmedetomidine is associated with

an onset of sedation 45 to 60 minutes after administration **(Yuen, V.M et al 2007)**.[70] **Zhou C. and Zhao J, (2014)** [91] performed a meta-analysis of studies conducted by **Cho et al** [92] and **Aydogan et al** [93].The meta-analysis concluded that dexmedetomidine had many advantages over midazolam such as analgesic effects and absence of respiratory depression; but it has a major disadvantage that the onset time for sedation is longer in comparison with midazolam. Considering that in present study, dexmedetomidine was administered 30 minutes prior to midazolam.

When comparing the mean peak sedation time, the Student's t test revealed that INMzD had significantly longer peak sedation time than INK. **Yuen, V.M. et al. (2007)** [70] found that the peak sedation effect occurred between 90 and 105 minutes in their study with intranasal dexmedetomidine. Although it has been established that intranasal dexmedetomidine is an effective sedative for premedication in children; to the best of our knowledge no data on its onset and peak sedation time in the paediatric population have been published. Furthermore, **Yuen, V.M. et al. (2010)** [70] also discovered that the pharmacodynamic and pharmacokinetic response of dexmedetomidine may vary with age. According to **Vilo S et al 2008**, [94] children under the age of 2 years require a higher initial dose than older children. According to **Markku A. et al.**[95] **(2003)**, transmucosal dexmedetomidine has a bioavailability of approximately 80%, and dexmedetomidine appears to be well absorbed systemically through the oral mucosa, with buccal bioavailability as high as 82% and the maximum concentration in serum reaching in 1.5 h. (Table 12 and Graph 11).

The Ease of Treatment Completion **(AAPD 2006, modified by Padmanabhan et al 2009)** for the intranasal midazolam and dexmedetomidine combination (INMzD) was significantly better with 100% of the participants being positive and falling in the good category whereas the results for the intranasal ketamine (INK) ranged from excellent to fair.(Table 9 and Graph 8).

The sedation levels in both groups were compared, (Table 8, Graph 7) intranasal ketamine (INK) was found to cause moderate to deep sedation. Some of our study participants experienced deep sedation because ketamine (7mg/kg) alone was potent

enough to induce deep sedation whereas INMzD the level of sedation was minimal to moderate. **Bergese DS et al (2009)[96]** in their study found similar results that subjects receiving a combination of midazolam and dexmedetomidine were significantly more cooperative and calmer during the procedure than those receiving midazolam alone. **Sago T et al (2018) [97]** in their case study combined dexmedetomidine with midazolam for paediatric dental surgery and concluded that the combination therapy provided adequate level of sedation.

The current study also aimed to evaluate the safety of intranasal ketamine (INK) and the combination of midazolam and dexmedetomidine (INMzD) as a procedural sedation agent for uncooperative paediatric patients. There were no major adverse effects reported with either group. **Bergese DS et al (2009) [96]** sedated 31 study subjects with a combination of dexmedetomidine and midazolam and found no complications during or after intubation with combination therapy, whereas **Pandey Rk (2011) [83] and Bahetwar SK (2011) [98]** found vomiting as a post-operative complication with monotherapy with intranasal ketamine. Furthermore, he stated that vomiting could occur if the participants did not maintain NPO status whereas ketamine was found to cause deep sedation in 23.4% of participants in our study

In present study, the pulse rate and blood pressure were significantly higher in INK than in INMzD. The possible reason for this is that ketamine is a cardio stimulant drug that causes a mild to moderate transient increase in blood pressure, pulse rate, and cardiac output due to an increase in sympathetic activity, and ketamine also has direct negative inotropic effects according to **Kongsayreepong S et al (1993)[99]** in their animal study. (Table 3, 4, 5, and Graph2, 3, 4). Similarly, oxygen saturation (SPO2) was found significantly higher in INK as compared to INMzD at all the time intervals because ketamine does not affect protective reflexes and minimal effect on breathing and airway. It also acts as moderate bronchodilator. The reason for the lower oxygen saturation for INMzD could be that midazolam being a benzodiazepine produces mild respiratory depression. However, dexmedetomidine has no significant effect on respiration. (Table 6, Graph 5)

Although, emergence reactions are well reported in case of ketamine; these were not detected in any of our patients. **Gutstein HB et al (1992) [100], and Hannallah R.S. et al (1989) [101],** in their study did not detect emergence reactions among child patients receiving either low dose intramuscular or oral K for pre-anesthetic sedation. **Keles S and Kocaturk O et al (2018)[102]** 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. Furthermore, children premedicated with dexmedetomidine had lesser incidence of emergence delirium than children premedicated with midazolam. In contrast to the literature reviewed above, none of our study subjects experienced an emergence reaction to the INMzD combination therapy.

In the current study, we found that INMzD had a longer recovery and discharge time (Table 13,14 and graph 12,13). **Markary et al. (2010) [69]** with a similar finding stated that intranasal dexmedetomidine had a long recovery time, making it unsuitable for busy office-based practices. **Li L et al. (2018) [89]** observed that when intranasal dexmedetomidine was combined with buccal midazolam and administered to children for auditory brainstem response testing, the average discharge time was of 80 minutes. In addition to our study, the findings were similar to the above discussed literature that dexmedetomidine caused longer recovery time as in INMzD combination therapy. Further, the recovery time for intranasal ketamine in our study showed early recovery and discharge time than combination therapy with INMzD. **Bahetwar SK et al. (2011)[98]** found that ketamine had a longer mean recovery time, with a mean value ranging from 34 to 46 minutes when compared to children sedated with midazolam. **Koirala B (2006) [103]** found a similar result, concluding that ketamine, alone or in combination with midazolam, had a longer recovery time than midazolam.

The three major aspects of procedural sedation and analgesia for the paediatric dentist to perform successful dental treatment in children undergoing procedural sedation are the onset, depth, and recovery of sedation. An ideal agent and route would be one that has a rapid onset of action, provides an adequate level of sedation, and has a rapid recovery of sedation, avoiding unnecessary stay of children in the dental office. Therefore, we can say that 7mg/kg intranasal ketamine and combination therapy of midazolam (0.3mg/kg) and dexmedetomidine (3mcg/kg) provided significant level of sedation in children between 3 to 7 years of age. Moreover, the findings of current study showed intranasal Ketamine (INK) had rapid onset, early peak sedation, provides adequate depth of sedation and in addition better acceptability of drug as compared to combination therapy with midazolam and dexmedetomidine (INMzD).

CONCLUSIONS

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

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

- Intranasal ketamine (7mg/kg) and combination of midazolam (0.3mg/kg) with dexmedetomidine (3mcg/kg) are safe and effective agents to provide procedural sedation to uncooperative children requiring comprehensive dental treatment.

- Intranasal ketamine has rapid onset of action, early peak sedation, and greater depth of sedation in comparison to the intranasal midazolam and dexmedetomidine combination.

- The acceptability of the drug was better with intranasal ketamine as compared to midazolam dexmedetomidine combination.

- 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 group.

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ANNEXURES

ANNEXURES I

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

INSTITUTIONAL RESEARCH COMMITTEE APPROVAL

The project titled "**A Comparative Evaluation of Intranasal Ketamine with Intranasal Midazolam and Dexmedetomidine Combination for Procedural Sedation in Pediatric Dental Patients**" submitted by **Dr Bibhav Dubey** Post graduate student from the **Department of Pediatric and Preventive Dentistry** as part of MDS Curriculum for the academic year 2020-2023 with the accompanying proforma was reviewed by the Institutional Research Committee present on **12th October 2021** 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.

Prof. Vandana A Pant
Co-Chairperson

Prof. B. Rajkumar
Chairperson

ANNEXURES II

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 IXth Institutional Ethics Sub-Committee

IEC Code: 16 **BBDCODS/04/2022**

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

Principal Investigator: Dr Bibhav Dubey **Department:** Pediatric and Preventive Dentistry

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

Type of Submission: New, MDS Project Protocol

Dear Dr Bibhav Dubey,

The Institutional Ethics Sub-Committee meeting comprising following four members was held on 07th April, 2022.

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, BBDCODS, Lucknow
4.	Dr. Akanksha Bhatt Member	Reader, Department of Conservative Dentistry & Endodontics, 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.

Forwarded by:

(Dr. Lakshmi Bala)
Member-Secretary
IEC

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

(Dr. Puneet Ahuja)
Principal
PRINCIPAL
BBDCODS
Babu Banarasi Das College of Dental Sciences
(Babu Banarasi Das University)
BBD City, Faizabad Road, Lucknow-226028

ANNEXURES III

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: A COMPARATIVE EVALUATION OF INTRANASAL KETAMINE WITH INTRANASAL MIDAZOLAM AND DEXMEDETOMIDINE COMBINATION 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 beenexplained 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 sucha 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 andside 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……..

ANNEXURES IV

Babu Banarasi Das College of Dental Sciences

(Babu Banarasi Das University)

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

PARTICIPANT INFORMATION DOCUMENT

1. Study Title A COMPARATIVE EVALUATION OF INTRANASAL KETAMINE WITH INTRANASAL MIDAZOLAM AND DEXMEDETOMIDINE COMBINATION FOR PROCEDURAL SEDATION IN PEDIATRIC DENTAL PATIENTS.

2. Invitation Paragraph

You are being invited to take part in a research study. Before you decide it is important for you to understand why the study is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your treating physician/family doctor if you wish. Ask us for any clarifications or further information. Whether or not you wish to take part is your decision.

2. What is the purpose of the study?
   To evaluate efficacy, safety and acceptability of Intranasal ketamine (INK) with intranasal midazolam and dexmedetomidine combination for procedural sedation in pediatric dental patients

.

4**. Why have I been chosen?**

You have been chosen for this study as you are fulfilling the required criteria for this study.

5. **Do I have to take part?**

Your participation in the research is entirely voluntary. If you do, you will be given this information sheet to keep and will be asked to sign a consent form. During the study you are still free to withdraw at any time and without giving a reason.

6. **What will happen to me if I take part?**

The participant will be benefited as the required dental treatment will be carried out once the local anaesthesia is effective. This will also help the patients to get the treatment done without pain, fear and anxiety.

7**. What do I have to do?**

This study requires treatment to be carried out only after the patient has been thoroughly examined by complete blood investigations and PA chest done before the visit. On the day of sedation, the fasting for solid food should be at least 4 hours and for liquids it should be 2 hours. The guardian should make sure about the above mentioned details. The participant should report to the institute at 9.00 am in the morning. He/she will be discharged in the afternoon once the discharge criteria are met. The guardian will be instructed not to leave the child alone for that day and even inform the doctor in case of any unusual behaviour or post-operative complications.

8. What is the procedure that is being tested?

The study will be carried out to evaluate and compare the safety and efficacy of midazolam,dexmedetomidine and ketamine administered through intranasal for procedural sedation in pediatric dental patients. Patient selection will be done on basis of Behaviour Ranting scale. The drugs will be administered through either of the route and onset of action, duration, efficacy of the drug will be assessed on short intervals.

9. What are the interventions for the study?

Restorative and minimum invasive procedures will be carried out on the participants.

10. What are the side effects of taking part?

Although there are no reports of serious side effects of the procedure, but the participant may have minimum side effects of the drugs like nausea or post-operative vomiting. If anything happens during the procedure we have skilled personnel and specialized equipments to manage any emergency.

If the participant suffers any other symptom post operatively, the guardian should immediately talk to the doctor.

11. What are the possible disadvantages and risks of taking part?

There are no disadvantages of taking part in this study, there can be minimum side effects of the drug.

12. What are the possible benefits of taking part?

The participant will be benefited as the required dental treatment will be carried out once the participant goes into conscious sedation. This will also help the patients to get the treatment done without fear and anxiety.

13. What if new information becomes available?

If additional information becomes available during the course of the research you will be told about these and you are free to discuss it with your researcher, your researcher will tell you whether you want to continue in the study. If you decide to withdraw, your researcher will make arrangements for your withdrawal. If you decide to continue in the study, you may be asked to sign an updated consent form.

14. What happens when the research study stops?

Nothing will happen to the participants.

15. What if something goes wrong?

The problems/complaint will be handled by the HOD or the IRC. If something serious happens the institute will take care of the problems.

16. Will my taking part in this study be kept confidential?

Yes it will be kept confidential.

17. What will happen to the results of the research study?

The results of the study will be used to compare the safety and efficacy of ketamine, dexmedetomidine and midazolam administered through intranasal route.Your identity will be kept confidential in case of any report/publications.

18. Who is organizing the research?

The research is been done in the DEPARTMENT OF PEDIATRIC AND PREVENTIVE DENTISTRY, BBDCODS. The research is self -funded. The participants will have to pay for procedural charges as given by the institution.

19. Will the results of the study be made available after study is over?

Yes

20. Who has reviewed the study?

The HOD and the members of IRC/ IEC of the institution has reviewed and approved the study.

21. Contact for further information

Dr. Bibhav Dubey

Department of Pediatric and Preventive Dentistry

Babu Banarasi College of Dental Sciences.

Lucknow-227105

Mob- 9555442753

Dr. LaxmiBala

Member Secretary of Ethics Committee of the institution,

Babu Banarasi College of Dental Sciences.

Lucknow

bbdcods.iec@gmail.com

THANK YOU FOR TAKING OUT YOUR PRECIOUS TIME FOR READING THE DOCUMENTS AND PARTICIPATING IN THE STUDY.

Signature of PI……
Name…….
Date……..

ANNEXURES V

बाबू बनारसी दास कॉलेज ऑफ डेंटल साइंसेज

(बाबू बनारसी दास विश्वविद्यालय)

बीबीडी सिटी, फैजाबाद रोड, लखनऊ - 227105 (भारत)

प्रतिभागी सूचना दस्तावेज

1. अध्ययन शीर्षक

बाल चिकित्सा दंत रोगियों में प्रक्रियात्मक बेहोश करने के लिए इंट्रानासल मिडाज़ोलम और डेक्समेडिटोमिडाइन संयोजन के साथ इंट्रानासल केटामाइन का तुलनात्मक मूल्यांकन।

2. आमंत्रण पैराग्राफ

आपको एक शोध अध्ययन में भाग लेने के लिए आमंत्रित किया जा रहा है। निर्णय लेने से पहले आपके लिए यह समझना महत्वपूर्ण है कि अध्ययन क्यों किया जा रहा है और इसमें क्या शामिल होगा। कृपया निम्नलिखित जानकारी को ध्यान से पढ़ने के लिए समय निकालें और यदि आप चाहें तो मित्रों, रिश्तेदारों और अपने इलाज करने वाले चिकित्सक/पारिवारिक चिकित्सक के साथ इस पर चर्चा करें। किसी भी स्पष्टीकरण या अधिक जानकारी के लिए हमसे पूछें। आप भाग लेना चाहते हैं या नहीं, यह आपका निर्णय है।

2. अध्ययन का उद्देश्य क्या है?

बाल चिकित्सा दंत रोगियों में प्रक्रियात्मक बेहोश करने की क्रिया के लिए इंट्रानैसल मिडाज़ोलम और डेक्समेडेटोमिडाइन संयोजन के साथ इंट्रानैसल केटामाइन (आईएनके) की प्रभावकारिता, सुरक्षा और स्वीकार्यता का मूल्यांकन करने के लिए

.

4. मुझे क्यों चुना गया है?

आपको इस अध्ययन के लिए चुना गया है क्योंकि आप इस अध्ययन के लिए आवश्यक मानदंडों को पूरा कर रहे हैं।

5. क्या मुझे भाग लेना है?

शोध में आपकी भागीदारी पूरी तरह से स्वैच्छिक है। यदि आप ऐसा करते हैं, तो आपको यह सूचना पत्रक रखने के लिए दिया जाएगा और सहमति प्रपत्र पर हस्ताक्षर करने के लिए कहा जाएगा। अध्ययन के दौरान आप किसी भी समय और बिना कोई कारण बताए वापस लेने के लिए स्वतंत्र हैं।

6. यदि मैं भाग लेता हूँ तो मेरा क्या होगा?

प्रतिभागी को लाभ होगा क्योंकि स्थानीय संज्ञाहरण प्रभावी होने के बाद आवश्यक दंत चिकित्सा उपचार किया जाएगा। इससे मरीजों को बिना दर्द, भय और चिंता के इलाज कराने में भी मदद मिलेगी।

7. मुझे क्या करना होगा?

इस अध्ययन के लिए आवश्यक है कि उपचार तभी किया जाए जब रोगी की पूरी रक्त जांच और दौरे से पहले किए गए पीए चेस्ट द्वारा पूरी तरह से जांच की गई हो। वशीकरण के दिन ठोस आहार का उपवास कम से कम 4 घंटे और तरल पदार्थ के लिए 2 घंटे का होना चाहिए। अभिभावक को उपर्युक्त विवरणों के बारे में सुनिश्चित करना चाहिए। प्रतिभागी को सुबह 9 बजे संस्थान में रिपोर्ट करना होगा। छुट्टी के मानदंड पूरे होने के बाद दोपहर में उन्हें छुट्टी दे दी जाएगी। अभिभावक को निर्देश दिया जाएगा कि वह उस दिन बच्चे को अकेला न छोड़ें और यहां तक कि किसी भी असामान्य व्यवहार या ऑपरेशन के बाद की जटिलताओं के मामले में डॉक्टर को सूचित करें।

8. किस प्रक्रिया का परीक्षण किया जा रहा है?

बाल चिकित्सा दंत रोगियों में प्रक्रियात्मक बेहोश करने की क्रिया के लिए इंट्रानैसल के माध्यम से प्रशासित मिडाज़ोलम, डेक्समेडिटोमिडाइन और केटामाइन की सुरक्षा और प्रभावकारिता का मूल्यांकन और तुलना करने के लिए अध्ययन किया जाएगा। मरीज का चयन बिहेवियर रेंटिंग स्केल के आधार पर किया जाएगा। दवाओं को किसी भी मार्ग के माध्यम से प्रशासित किया जाएगा और कार्रवाई की शुरुआत, अवधि, दवा की प्रभावकारिता का मूल्यांकन थोड़े अंतराल पर किया जाएगा।

9. अध्ययन के लिए क्या हस्तक्षेप हैं?

प्रतिभागियों पर पुनर्स्थापनात्मक और न्यूनतम आक्रामक प्रक्रियाएं की जाएंगी।

10. भाग लेने के दुष्प्रभाव क्या हैं?

यद्यपि प्रक्रिया के गंभीर दुष्प्रभावों की कोई रिपोर्ट नहीं है, लेकिन प्रतिभागी को मतली या पोस्ट-ऑपरेटिव उल्टी जैसी दवाओं के न्यूनतम दुष्प्रभाव हो सकते हैं। यदि प्रक्रिया के दौरान कुछ भी होता है तो हमारे पास किसी भी आपात स्थिति को प्रबंधित करने के लिए कुशल कार्मिक और विशेष उपकरण हैं।

यदि ऑपरेशन के बाद प्रतिभागी को कोई अन्य लक्षण दिखाई देता है, तो अभिभावक को तुरंत डॉक्टर से बात करनी चाहिए।

11. भाग लेने के संभावित नुकसान और जोखिम क्या हैं?

इस अध्ययन में भाग लेने के कोई नुकसान नहीं हैं, दवा के न्यूनतम दुष्प्रभाव हो सकते हैं।

12. भाग लेने के संभावित लाभ क्या हैं?

प्रतिभागी को लाभ होगा क्योंकि एक बार प्रतिभागी के होश में आने के बाद आवश्यक दंत चिकित्सा उपचार किया जाएगा। इससे मरीजों को बिना किसी डर और चिंता के इलाज कराने में भी मदद मिलेगी।

13. क्या होगा यदि नई जानकारी उपलब्ध हो जाती है?

यदि शोध के दौरान अतिरिक्त जानकारी उपलब्ध हो जाती है तो आपको इनके बारे में बताया जाएगा और आप अपने शोधकर्ता के साथ इस पर चर्चा करने के लिए स्वतंत्र हैं, आपका शोधकर्ता आपको बताएगा कि क्या आप अध्ययन जारी रखना चाहते हैं। यदि आप वापस लेने का निर्णय लेते हैं, तो आपका शोधकर्ता आपकी वापसी की व्यवस्था करेगा। यदि आप अध्ययन जारी रखने का निर्णय लेते हैं, तो आपसे एक अद्यतन सहमति फॉर्म पर हस्ताक्षर करने के लिए कहा जा सकता है।

14. जब शोध अध्ययन बंद हो जाता है तो क्या होता है?

प्रतिभागियों को कुछ नहीं होगा।

15. अगर कुछ गलत हो जाए तो क्या होगा?

समस्याओं/शिकायतों को एचओडी या आईआरसी द्वारा नियंत्रित किया जाएगा। अगर कुछ गंभीर होता है तो संस्थान समस्याओं का ध्यान रखेगा।

16. क्या इस अध्ययन में मेरे भाग लेने को गोपनीय रखा जाएगा?

हां इसे गोपनीय रखा जाएगा।

17. शोध अध्ययन के परिणामों का क्या होगा?

अध्ययन के परिणामों का उपयोग इंट्रानैसल मार्ग के माध्यम से प्रशासित केटामाइन, डेक्समेडिटोमिडाइन और मिडाज़ोलम की सुरक्षा और प्रभावकारिता की तुलना करने के लिए किया जाएगा। किसी भी रिपोर्ट/प्रकाशन के मामले में आपकी पहचान को गोपनीय रखा जाएगा।

18. शोध का आयोजन कौन कर रहा है?

यह शोध बाल चिकित्सा और निवारक दंत चिकित्सा विभाग, बीबीडीसीओडीएस में किया गया है। शोध स्व-वित्त पोषित है। प्रतिभागियों को संस्था द्वारा दिए गए प्रक्रियात्मक शुल्क का भुगतान करना होगा।

19. क्या अध्ययन समाप्त होने के बाद अध्ययन के परिणाम उपलब्ध कराए जाएंगे?

हां

20. अध्ययन की समीक्षा किसने की है?

संस्थान के एचओडी और आईआरसी/आईईसी के सदस्यों ने अध्ययन की समीक्षा की और उसे मंजूरी दी।

21. अधिक जानकारी के लिए संपर्क करें

डॉ. विभव दुबे

बाल चिकित्सा और निवारक दंत चिकित्सा विभाग

बाबू बनारसी कॉलेज ऑफ डेंटल साइंसेज।

लखनऊ-227105

मोब- 9555442753

डॉ. लक्ष्मीबाला

संस्था की आचार समिति के सदस्य सचिव,

बाबू बनारसी कॉलेज ऑफ डेंटल साइंसेज।

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

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

$M = [n(n+1)/2]^{th}$ 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)

$p<0.05$- Significant (*)

$p<0.01$- Highly significant (**)

ANNEXURES VII

NAME –

AGE/SEX –

WEIGHT –

HEIGHT –

DRUG OF CHOICE –

	Pulse Rate	Blood Pressure	Oxygen Saturation
Before Administration			
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	Score	
Quiet behavior , no movement (Q)	1	
Crying , no struggling (C)	2	
Struggling movement without crying (Sc)	3	
Struggling movement with crying (S)	4	

Onset of Sedation: Sedation Rating Scale

1	No sedation	Typical /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	

UMSS Score	Description	
0	Awake/alert	
1	Minimally sedated: tired/sleepy, appropriate response to verbal conversation and or sound (calling child's name)	
2	Moderately sedated: somnolent/sleeping, easily aroused with light tactile stimulation (light touching arm, face, or leg)	
3	Deeply sedated: deep sleep arousal only with significant physical stimulation (tickling their feet)	
4	Unarousable:unresponsive to foot tickle	

DISCHARGE CRITERIA –SATISFIED / NOT SATISFIED

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.	

ANNEXURES VIII

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**

ANNEXURES IX

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

ANNEXURES X

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

1	Crying with struggling movement
2	Struggling movement without crying
3	Crying,no struggling
4	Quiet,no movement

ANNEXURES XI

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.

ANNEXURES XII

UMSS Score	Description	
0	Awake/alert	
1	Minimally sedated: tired/sleepy, appropriate response to verbal conversation and or sound (calling child's name)	
2	Moderately sedated: somnolent/sleeping, easily aroused with light tactile stimulation (light touching arm, face, or leg)	
3	Deeply sedated: deep sleep arousal only with significant physical stimulation (tickling their feet)	
4	Unarousable:unresponsive to foot tickle	

ANNEXURES XIII

(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

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 of consciousness of that child should be achieved.
6. The state of hydration is adequate.

ANNEXURES XV

MIDAZOLAM DOSE per kg

Weight in kg	Dose in mg (0.3 mg/kg)	Dose in ml	No. of puff.	Dose in mg (0.5 mg/kg)	Dose in ml	No. of puff.
10	3	0.6	6	5	1	10
11	3.3	0.66	6.6	5.5	1.1	11
12	3.6	0.72	7.2	6	1.2	12
13	3.9	0.78	7.8	6.5	1.3	13
14	4.2	0.84	8.4	7	1.4	14
15	4.5	0.9	9	7.5	1.5	15
16	4.8	0.96	9.6	8	1.6	16
17	5.1	1.02	10.2	8.5	1.7	17
18	5.4	1.08	10.8	9	1.8	18
19	5.7	1.14	11.4	9.5	1.9	19
20	6	1.2	12	10	2	20
21	6.3	1.26	12.6	10.5	2.1	21
22	6.6	1.32	13.2	11	2.2	22
23	6.9	1.38	13.8	11.5	2.3	23
24	7.2	1.44	14.4	12	2.4	24
25	7.5	1.5	15	12.5	2.5	25
26	7.8	1.56	15.6	13	2.6	26
27	8.1	1.62	16.2	13.5	2.7	27
28	8.4	1.68	1.68	14	2.8	28
29	8.7	1.74	17.4	14.5	2.9	29
30	9	1.8	18	15	3	30
31	9.3	1.86	18.6	15.5	3.1	31
32	9.6	1.92	19.2	16	3.2	32

ANNEXURESXVI

KETAMINE DOSE per kg			
S.NO	weight (kg)	DOSE IN ML(6mg/kg) 1kg /(6mg/kg)=0.12ml	DOSE IN ML(9mg/kg) 1kg /(9mg/kg=0.18ml
1	10	1.2	1.8
2	11	1.32	1.98
3	12	1.44	2.16
4	13	1.56	2.34
5	14	1.68	2.52
6	15	1.8	2.7
7	16	1.92	2.88
8	17	2.04	3.06
9	18	2.16	3.24
10	19	2.28	3.42
11	20	2.24	3.6
12	21	2.52	3.78
13	22	2.64	3.96
14	23	2.76	4.14
15	24	2.88	4.32
16	25	3	4.5
17	26	3.12	4.68
18	27	3.24	4.86
19	28	3.36	5.04
20	29	3.48	5.22
21	30	3.6	5.4
22	31	3.72	5.58
23	32	3.84	5.76

ANNEXURE XVIII

DEXMEDETOMIDINE DOSE Per Kg		
Weight in kg	**Dose in mg (3 mcg/kg)**	**Dose in ml**
10	3 0	0.3
11	33	0.33
12	36	0.36
13	39	0.39
14	42	0.42
15	45	0.45
16	48	0.48
17	51	0.51
18	54	0.54
19	57	0.57
20	60	0.60
21	63	0.63
22	66	0.66
23	69	0.69
24	72	0.72
25	75	0.75

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