A COMPARATIVE EVALUATION OF INTRANASAL MIDAZOLAM - KETAMINE COMBINATION WITH MIDAZOLAM - FENTANYL 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

PEDIATRIC AND PREVENTIVE DENTISTRY

DEPARTMENT OF PEDIATRIC AND PREVENTIVE DENTISTRY

BABU BANARASI DAS OF DENTAL SCIENCES,

LUCKNOW, UTTAR PRADESH- 227105

BATCH: 2021-2024   **DR. SARWANI MISHRA**

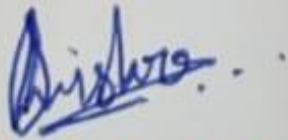**GUIDE: DR. NEERJA SINGH**   **ENROLLMENT NO: 12103272947**

DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation entitled **"A COMPARATIVE EVALUATION OF INTRANASAL MIDAZOLAM - KETAMINE COMBINATION WITH MIDAZOLAM - FENTANYL 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: 10-02-2024

Place: Lucknow

DR. SARWANI MISHRA

DEPARTMENT OF PEDIATRIC AND PREVENTIVE DENTISTRY

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

CERTIFICATE

This is to certify that the dissertation entitled "A COMPARATIVE EVALUATION OF INTRANASAL MIDAZOLAM - KETAMINE COMBINATION WITH MIDAZOLAM - FENTANYL COMBINATION FOR PROCEDURAL SEDATION IN PEDIATRIC DENTAL PATIENTS" is an original bonafide research work done by **DR. SARWANI MISHRA,** in partial fulfilment of the requirement for the degree of **MASTER OF DENTAL SURGERY (M.D.S)** in the speciality of **PEDIATRIC AND PREVENTIVE DENTISTRY** under our supervision.

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

CERTIFICATE

This is to certify that the dissertation entitled **"A COMPARATIVE EVALUATION OF INTRANASAL MIDAZOLAM - KETAMINE COMBINATION WITH MIDAZOLAM - FENTANYL COMBINATION FOR PROCEDURAL SEDATION IN PEDIATRIC DENTAL PATIENTS"** is an original bonafide research work done by **DR. SARWANI MISHRA,** under the supervision of **DR. SANTOSH KUMAR** M.B.B.S, M.D Anesthesia, Reader as co-guide, Department of Oral And Maxillofacial Surgery, Babu Banarasi Das College of Dental Sciences, BBDU, Lucknow (U.P.)

CO-GUIDE

DR. SANTOSH KUMAR

M.B.B.S, M.D ANESTHESIA, READER
DEPARTMENT OF ORAL MAXILLOFACIAL SURGERY
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

CERTIFICATE

This is to certify that the dissertation entitled "A COMPARATIVE EVALUATION OF INTRANASAL MIDAZOLAM - KETAMINE COMBINATION WITH MIDAZOLAM - FENTANYL COMBINATION FOR PROCEDURAL SEDATION IN PEDIATRIC DENTAL PATIENTS" 'has been undertaken by the candidate **DR. SARWANI MISHRA**, herself in this department. The candidate fulfills all the conditions necessary for the submission of this thesis.

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.)

BABU BANARASI DAS COLLEGE OF DENTAL SCIENCES

LUCKNOW, UTTAR PRADESH-227105

CERTIFICATE

This is to certify that the dissertation entitled "A COMPARATIVE EVALUATION OF INTRANASAL MIDAZOLAM - KETAMINE COMBINATION WITH MIDAZOLAM - FENTANYL COMBINATION FOR PROCEDURAL SEDATION IN PEDIATRIC DENTAL PATIENTS" has been undertaken by the candidate DR. SARWANI MISHRA, under direct supervision and guidance of DR. NEERJA SINGH, Professor in the Department of PEDIATRIC AND PREVENTIVE DENTISTRY, Babu Banarasi Das College of Dental Sciences, Babu Banarasi Das University, Lucknow, Uttar Pradesh

DR. PUNEET AHUJA

PRINCIPAL

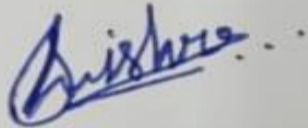## BABU BANARASI DAS COLLEGE OF DENTAL SCIENCES

BBDU, LUCKNOW (U.P.)

COPYRIGHT

I hereby declare that the **BABU BANARASI DAS UNIVERSITY** shall have the right to preserve, use and disseminate this dissertation in print or electronic format for academic / research purpose.

Date: 10-02-024

Place: Lucknow

DR. SARWANI MISHRA

ACKNOWLEDGEMENT

TABLE OF CONTENT

LIST

OF

TABLES

&

GRAPHS

ABSTRACT

BACKGROUND

In pediatric dental practice, managing uncooperative and anxious children poses a significant challenge, with factors like parental anxiety and unfamiliar environments exacerbating the situation. Traditional methods such as behavioral modification and physical restraints are not universally successful. Consequently, procedural sedation emerges as a crucial clinical need, offering a well-tolerated, safe, and effective alternative. This minimally invasive and economical approach not only facilitates dental procedures in children but also alleviates parental anxiety, reduces emotional trauma, and shortens procedural duration. By addressing both the child's discomfort and the challenges faced by dental practitioners, procedural sedation emerges as a valuable tool in pediatric dentistry.

AIM

To evaluate and compare, efficacy and safety of intranasal midazolam-ketamine combination with intranasal midazolam- fentanyl combination for procedural sedation in uncooperative pediatric dental patients.

MATERIALS AND METHOD

Sixty children, aged 3-7 years, with Frankel behavior rating II (Negative) were randomly assigned to either of the following groups for the administration of different drugs via the intranasal route.

Group I INMK for administration of intranasal midazolam (0.3mg/kg) ketamine (7mg/kg).

Group II INMF for administration of intranasal midazolam (0.3mg/kg) fentanyl (1.5 mcg/kg)

Throughout the sedation session, the children were assessed for behavioral responses. Various parameters including drug acceptance, onset and peak sedation time, hemodynamic parameters, level of sedation, ease of treatment completion, postoperative complications, recovery, and discharge time were also systematically evaluated.

RESULTS

This study aimed to evaluate and compare the efficacy and safety of intranasal midazolam-ketamine combination with intranasal midazolam-fentanyl combination for procedural sedation in uncooperative pediatric dental patients.

➢ Intranasal midazolam-ketamine combination and intranasal midazolam-fentanyl combination provided sedation and were deemed safe in uncooperative pediatric dental patients.

➢ The intranasal midazolam-ketamine combination demonstrated notably greater efficacy, achieving moderate sedation in the majority of participants whereas the combination of intranasal midazolam-fentanyl resulted in minimal sedation in all the participants.

➢ Intranasal midazolam-ketamine combination reported rapid onset, early peak sedation accompanied by favorable drug acceptability while intranasal midazolam-fentanyl combination reported faster recovery and shorter discharge time.

➢ In both the experimental groups the hemodynamic parameters which were the pulse rate, blood pressure, and oxygen saturation remained within acceptable physiological limits, and no postoperative complications were seen.

CONCLUSION

The study highlighted the efficacy and safety of both intranasal midazolam (0.3 mg/kg) – ketamine (7 mg/kg) and intranasal midazolam (0.3 mg/kg) – fentanyl (1.5 mcg/kg) combinations for procedural sedation in uncooperative pediatric dental patients. While midazolam-ketamine demonstrated superior efficacy, rapid onset and early peak of sedation, midazolam-fentanyl showed faster recovery and shorter discharge times. Both combinations maintained hemodynamic parameters within acceptable limits, suggesting their suitability for procedural sedation in uncooperative pediatric dental patients.

INTRODUCTION

Pediatric healthcare requires a specialized approach, acknowledging that children are not miniature adults; their distinctive needs demand attention, and nurturing their emotional well-being is just as crucial as addressing their physical health. Especially in the context of day-case surgeries and dental procedures, the emotional impact on young children is of paramount concern. The prospect of hospitalization, separation anxiety from parents, and unfamiliar environments can induce substantial emotional distress. Explaining the necessity of treatment is challenging due to their limited understanding, making it essential to find effective modalities beyond conventional methods. Dental anxiety and phobia are prevalent in children, often compounded by parental apprehension and the anticipation of pain. Recognizing the limitations of traditional approaches like behavior modification and physical restraints, there is a pressing need for a well-tolerated, efficient, and compassionate method, such as procedural sedation, to mitigate anxiety and facilitate essential medical and dental interventions without resorting to general anesthesia.[1]

Addressing the unique challenges of pediatric care, procedural sedation emerges as a vital component, particularly in the dental setting where uncooperative behavior among younger children is common. Procedural sedation, being minimally invasive and cost-effective compared to general anesthesia not only aids in reducing patient anxiety and emotional trauma but also alleviates parental discomfort, facilitating the completion of procedures while minimizing stress for healthcare providers and shortening the overall duration of the medical or dental intervention. The ultimate goal is to create a positive and comfortable healthcare experience for children, recognizing that a traumatic encounter at a young age can lead to a lasting fear of medical and dental professionals. Therefore, the thoughtful implementation of procedural sedation becomes essential to ensure both the physical and emotional well-being of pediatric patients during medical and dental procedures.

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]

For decades, pediatric dentists worldwide have actively sought optimal agents and administration routes for procedural sedation in their practice. While a variety of drugs have been utilized through different pathways, none have definitively emerged as the ideal solution. It's well-established that sedation effectively reduces fear, anxiety, or apprehension in pediatric patients. However, a notable limitation is that it does not inherently provide analgesia for painful procedures. Addressing this gap, the current study introduces a novel approach by combining a sedative, such as midazolam, with an analgesic—either ketamine or fentanyl—each known for their potent analgesic effects. This innovative combination aims to act as a double-edged tool in procedural sedation, not only managing fear and anxiety but also addressing pain during procedures. By providing simultaneous sedation and analgesia, this approach strives to enhance the overall experience for young patients, aligning with the ongoing commitment to advancing safety and comfort in pediatric dental care.

Midazolam is a water-soluble, short-acting benzodiazepine that acts on GABA-associated receptors, similar to diazepam.[2] It possesses anticonvulsant, anxiolytic, sedative, hypnotic, muscle relaxant, and amnesic properties. With a short half-life of 1-2 hours, high potency, and rapid onset, it was historically used for pre-anaesthetic sedation. It is a safe and effective choice for pediatric preprocedural sedation, providing anxiolysis and amnesia.[3]

Ketamine is a rapid-acting, non-narcotic anesthetic with a broad safety margin and dissociative properties, providing powerful analgesia. In low, "sub-anesthetic" doses, its psycho-mimetic effects pose minimal concern in children.[4] Derived from phencyclidine, it acts as a sedative and analgesic [5], preserving cardiac output and maintaining respiratory function even in patients with hypovolemia or hemodynamic issues [6].

Fentanyl stands out as a potent opioid known for its rapid onset of action, delivering minimal sedation effects and maintaining hemodynamic stability.[7] This makes it particularly effective in addressing acute, moderate to severe pain in pediatric patients. Its efficient absorption through the nasal mucosa is attributed to its high lipophilicity and low molecular weight, further enhancing its utility in pediatric pain management.[8]

In pediatric care, various routes for analgesia and anxiolysis exist, including oral, intranasal, submucosal, transmucosal, intramuscular, intravenous, and rectal administration. The intranasal (IN) route is particularly valuable for children due to its painless, needle-free nature,

eliminating the need for intravenous catheters. The nasal mucosa provides a large absorptive surface with significant blood flow, facilitating rapid drug absorption into the bloodstream and cerebral spinal fluid. Intranasal delivery ensures direct medication absorption, bypassing hepatic first-pass metabolism, leading to quicker drug availability compared to other routes. Intranasal sedatives can be administered as drops or through a sprayed/atomized system, offering a safe, rapid, and well-tolerated method for achieving almost immediate analgesia in children.[9]

Pediatric procedural sedation is rapidly advancing, offering a vital solution for treating anxious children while research in this area is still relatively recent. Hence, this simple randomized study is aimed to evaluate and compare intranasal ketamine-midazolam with intranasal fentanyl-midazolam combination for the procedural sedation of uncooperative pediatric dental patients.

AIM

To evaluate and compare intranasal midazolam- ketamine combination with intranasal midazolam- fentanyl combination for procedural sedation in uncooperative pediatric dental patients.

OBJECTIVES

1. To evaluate the efficacy and safety of midazolam and ketamine combination administered through the intranasal route for the drug acceptance and for the procedural sedation of uncooperative pediatric dental patients.

2. To evaluate the efficacy and safety of midazolam and fentanyl combination administered through intranasal route for the drug acceptance and for the procedural sedation of uncooperative pediatric dental patients

3. To compare the efficacy and safety of ketamine and midazolam combination with fentanyl and midazolam combination administered through intranasal route for the drug acceptance and for the procedural sedation of uncooperative pediatric dental patients.

REVIEW OF LITERATURE

Dental pain and anxiety are prevalent in pediatric patients, often underestimated and undertreated due to children's difficulty expressing fears and unfamiliarity with procedures. Fear leads to avoidance, worsening issues, potentially requiring traumatic treatments, reinforcing anxiety and perpetuating a cycle of dental fear in children.

Pediatric dentistry presents a unique set of challenges, requiring a delicate balance between providing effective dental care and ensuring a positive psychological experience for the child. Recognizing that child behavioral management is integral to quality dental care, practitioners in this field must navigate age-appropriate anxieties and fears that many children naturally harbor towards dental visits and procedures.[10] The management of fearful and disruptive children stands out as a particularly formidable task for dentists, as successful treatment relies on the child's cooperation or, at the very least, passive compliance.

Moreover, a significant number of children exhibit age-appropriate anxiety and fears, particularly in relation to dental visits and treatments. Managing fearful and disruptive behavior in children poses a considerable challenge for dentists in their clinical practice. Successful completion of treatment hinges on the child's ability to cooperate or, at the very least, passively comply with the dentist's procedures.

The most challenging aspect of pediatric dentistry involves mitigating disruptive patient behavior, particularly in instances where children express their fears through crying and screaming. These behaviors, often accompanied by peripheral and gross motor movements, can result in direct contact with the dentist or their equipment. Effectively minimizing such disruptive behaviors is crucial to creating a more positive and comfortable environment for both the child and the dental practitioner.

While traditional behavior modification techniques are often effective in alleviating children's fears and anxieties, there remains a subset of cases where a more intensive intervention is necessary. A study by **De Jongh et al. (2005)** highlights the varied approaches dental practitioners employ in managing dental anxiety and fear, taking into account the diverse levels, types, and characteristics observed among patients.[11] This recognition underscores the need for tailored strategies to address the specific needs of each child, ensuring a positive dental experience while prioritizing their emotional well-being. In situations characterized by a pressing need for treatment coupled with elevated levels of anxiety, various approaches to patient management become viable options. These may encompass intravenous sedation, conscious sedation, or the use of general anesthesia (GA).[12]

While procedural sedation is geared towards modifying patient behavior, fostering cooperation by alleviating dental fear and anxiety, the consideration of treatment under general anesthesia should be approached with caution. It should be viewed as a last resort due to the lack of evidence supporting its long-term benefits for highly anxious patients beyond addressing their immediate treatment requirements. The decision to employ general anesthesia should be carefully weighed, recognizing that alternative approaches that address anxiety and encourage patient cooperation may be more appropriate whenever feasible.

The inception of sedation in dentistry is attributed to **Horace Wells**, who utilized nitrous oxide as a sedative during dental extractions. However, it was **William T. G. Morton,** a Massachusetts dentist, who successfully showcased the anesthetic properties of ether on October 16, 1846, revolutionizing pain-free tooth extraction.

In the realm of pediatric dentistry, pharmacological agents are often employed alongside behavioral techniques to alleviate anxiety in young patients, including those with disabilities. These medications typically fall into the category of sedatives or analog sedatives, aiming not to eliminate anxiety entirely but to enhance patient acceptance by diminishing arousal and altering the anticipation of potential discomfort. The range of agents used encompasses nitrous oxide, benzodiazepines, and opioid congeners. While nitrous oxide has proven to be valuable, its use comes with risks for operating personnel, and it is considered a relatively milder sedative. In recent years, midazolam has gained popularity among benzodiazepines, and it can be administered through various routes, including intranasally.[13]

Dentists utilizing analog-sedative agents and techniques should possess a comprehensive understanding of the pharmacology of the selected agents. Additionally, they must be well-versed in the associated risks and benefits of the employed techniques.[13] Equally important is the ability to proficiently manage any adverse events that may arise as a result of their use. This ensures a safe and effective application of sedation in dental procedures, prioritizing both patient well-being and the successful outcome of the treatment.

"Procedural sedation and analgesia (PSA)[1] 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). This approach induces a drug-induced depression of consciousness, characterized by patients being responsive to verbal commands, either independently or in conjunction with light tactile stimulation. Importantly, maintaining a patent airway does not necessitate interventions, and spontaneous ventilation is generally adequate. The cardiovascular function is typically preserved throughout this process. In the context of PSA, the choice of pharmacological options is influenced by several factors. The selection of a specific drug is guided by the nature of the procedure, whether it involves pain or not, as well as patient characteristics such as age, disposition, and the expertise of the attending physician. For non-painful procedures, anxiolytic drugs are typically employed to alleviate a child's anxiety and minimize movements. However, in the case of painful techniques requiring both analgesia and sedation, inhaled nitrous oxide or a combination of various sedative agents is often utilized. This approach not only achieves a level of anxiolysis but also provides analgesic and amnestic effects, which can be advantageous in certain situations.

Over the years, dentistry has embraced a variety of pharmacological agents designed to alleviate pain and anxiety during dental procedures, particularly in pediatric patients who may be anxious or uncooperative. Extensive research has led to the synthesis and testing of numerous compounds, administered through various routes, with the goal of achieving sedation without inducing complete loss of consciousness. Despite these efforts, no single sedative agent or administration route has been universally recognized as the 'ideal' solution, emphasizing the ongoing pursuit of optimal approaches to enhance patient comfort and cooperation during dental treatments.

INTRANASAL (IN) MODE OF ADMINISTRATION

The intranasal route stands out as the preferred method for sedating pediatric dental patients due to its non-invasive nature and the swift absorption of drugs. This approach is well-received by pediatric patients, as highlighted by **Wolfe** and **Bernstone** (2004) .[14] The nasal mucosa, with its expansive absorptive surface and high blood flow, facilitates rapid drug absorption into both the bloodstream and cerebral spinal fluid. Notably, intranasal administration allows drugs to bypass the blood-brain barrier through olfactory and trigeminal extracellular pathways, exerting biological effects at various sites in the brain and spinal cord (**Thorne RG et al., 2005**).[15]

The direct absorption of medication via intranasal administration offers advantages such as avoiding gastrointestinal degradation and hepatic first-pass metabolism, where liver enzymes may break down the drug. This results in a higher amount of drug available for prompt action compared to oral administration. Importantly, studies by **Corbo DC et al**. **(1989)**[16], and **Pires A et al. (2009)** [17] demonstrate that many medications administered intranasally achieve absorption rates and plasma concentrations comparable to those obtained through intravenous administration. Despite these benefits, it's noteworthy that there is a relatively limited number of studies exploring this route.

Within the expansive domain of historical literature concerning these agents, concise descriptions of their pharmacokinetic and pharmacodynamic profiles are provided below.

MIDAZOLAM

Midazolam, categorized as a short-acting benzodiazepine, exhibits an elimination half-life spanning 1.5-2.5 hours. In the elderly, as well as in young children and adolescents, the elimination half-life tends to be prolonged. The therapeutic and adverse effects of midazolam are attributed to its influence on GABAA receptors. Although midazolam doesn't directly activate GABAA receptors, it, akin to other benzodiazepines, augments the impact of the neurotransmitter GABA on GABAA receptors, specifically by increasing the frequency of Cl channel opening, leading to neural inhibition.[17] Almost all of its properties can be elucidated by the actions of benzodiazepines on GABAA receptors, resulting in pharmacological attributes such as sedation, sleep induction, anxiety reduction, anterograde amnesia, muscle relaxation, and anticonvulsant effects.

CHEMICAL STRUCTURE:
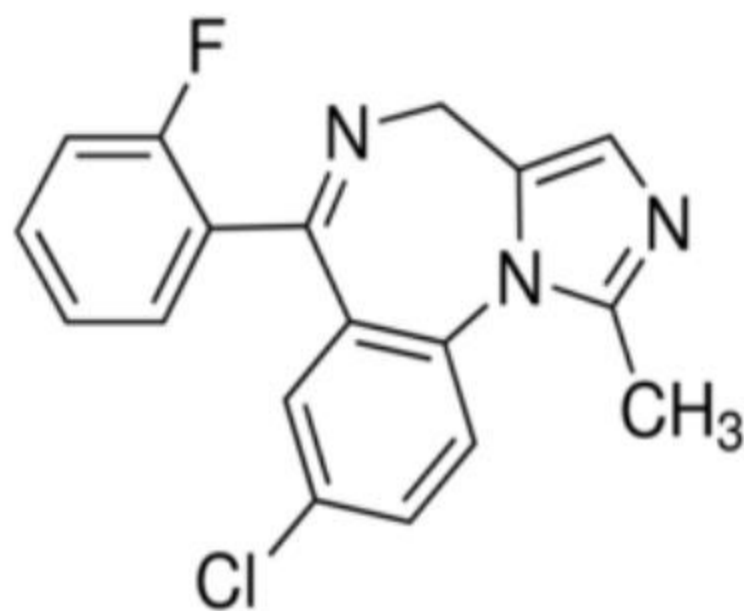
MECHANISM OF ACTION:

Benzodiazepines are thought to exert their effects by modulating the activity of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), a key player in the brain's inhibitory signaling. By increasing GABA activity, benzodiazepines induce a calming effect, relax skeletal muscles, and, in higher doses, promote sleep. These drugs act as agonists at benzodiazepine receptors, integral components of the benzodiazepine-GABA receptor-chloride ionophore complex. Most anxiolytic medications operate through one or more elements of this complex to enhance the inhibitory actions of GABA.[18] Additionally, benzodiazepines may elicit sedative, anticonvulsant, and muscle relaxant effects through a comparable mechanism, although distinct receptor subtypes could be involved.[18]

The hypnotic effects of midazolam seem to be linked to the accumulation of gamma-aminobutyric acid (GABA) and the occupation of benzodiazepine receptors. Midazolam exhibits a relatively high affinity for the benzodiazepine receptor, approximately twice that of diazepam. It is theorized that there are distinct benzodiazepine and GABA receptors, both connected to a shared ionophore (chloride) channel. The occupation of both receptors by midazolam results in membrane hyperpolarization and neuronal inhibition. Additionally, midazolam disrupts the reuptake of GABA, leading to the accumulation of this inhibitory neurotransmitter.[18]

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

Following absorption from the administration site, midazolam is transported to its site of action via blood plasma. Within the plasma, the drug extensively binds to plasma proteins, with only the unbound fraction exhibiting pharmacological activity. Metabolically, midazolam is transformed into alpha-hydroxy-midazolam, which is promptly conjugated by glucuronic acid, resulting in the formation of a pharmacologically inactive end product that is excreted in the urine. Two other metabolites are excreted in negligible amounts.[19]

Peak serum concentrations of midazolam in children vary depending on the administration method: for intramuscular (IM) and rectal routes, peaks occur at 15 and 30 minutes after administration, respectively, while the oral route shows serum concentration peaks in less than 1 hour. The metabolic turnover of midazolam in children is more rapid than in adults due to the heightened metabolic activity in children.[20] Consequently, the elimination half-life is approximately 45-60 minutes in children compared to 2-6 hours in adults.[21,22] This rapid elimination contrasts with diazepam, which has an elimination half-life of 24-57 hours, highlighting midazolam's significantly faster elimination rate.[23]

PHARMACODYNAMICS:

Midazolam induces a moderate reduction in cerebrospinal fluid pressure, as observed in lumbar puncture measurements. This effect is akin to the decrease produced by thiopental when midazolam is employed for anesthesia induction in patients without intracranial lesions. In the case of intracranial surgical patients with normal intracranial pressure but reduced compliance (measured through subarachnoid screw measurements), midazolam mitigates the rise in intracranial pressure associated with intubation. This attenuation is comparable to the effect achieved with thiopental in similar situations.[24]

When utilized for anesthesia induction in patients without eye disease, midazolam has been demonstrated to moderately lower intraocular pressure; however, there is a lack of studies examining its effects in patients with glaucoma.[24] It's important to note that midazolam, like other benzodiazepines, may exert anticholinergic effects on individuals with glaucoma, particularly those with angle-closure or acute glaucoma.

Respiratory depression is an outcome associated with midazolam use, but the degree of respiratory depression is dose-dependent.[25,26] Midazolam's impact on the cardiovascular system appears to be minimal. Cardiac hemodynamic studies reveal a slight to moderate decrease in mean arterial pressure, cardiac output, stroke volume, and systemic vascular resistance when midazolam is employed for anesthesia induction.[27]

In a comparison of the systemic vascular effects of midazolam and lorazepam in patients undergoing cardiopulmonary bypass, midazolam was found to be more effective than lorazepam in mitigating the increase in systemic vascular resistance associated with cardiopulmonary bypass.[28]

Additionally, midazolam may cause a slight elevation in slow heart rates (less than 65 per minute), especially in individuals taking propranolol for angina, while it may lead to a slight reduction in faster heart rates (e.g ., 85 per minute).[23]

USE OF MIDAZOLAM AS A SEDATIVE AGENT IN DENTISTRY:

Singh N, Pandey RK, Saksena AK, Jaiswal JN (2002)[29] 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 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)[30] 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)[31] carried out a study to assess the sedative effect of oral ketamine and oral midazolam before general anesthesia. Twenty uncooperative children in the 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)[32] 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.

Ransford NJ, Manley MC, Lewis DA, Thompson SA, Wray LJ, Boyle CA, Longman LP (2010)[33] carried out a study to evaluate the combined intranasal/intravenous midazolam sedation technique. This study included patients with severe disabilities who were not able to cooperate with dental treatment. It was concluded that this study provided a sufficient basis to justify its use by properly qualified dental practitioners in primary care.

Shavit I, Feraru L, Miron D, Weiser G (2012)[34] 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.

Chopra R, Mittal M, Bansal K, Chaudhuri P (2013)[35] performed a study to evaluate the acceptance of midazolam spray through the buccal route as compared to the intranasal route and compare the efficacy of the drug through both 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 ($p > 0.05$).

Sheta SA, Al Sarheed MA, Abdelhalim AA (2014)[36] 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.

Musani IE, Chandan NV (2015)[37] 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, Asokan S, John JB, Priya PR, Raaja MT (2016)[38] conducted a study to compare the difference in anxiety level and acceptance of drugs 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)[39] studied the efficacy of two oral midazolam dosages (0.3 mg/kg and 0.5 mg/kg) for conscious sedation of children having dental treatment and 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 in reverse order and concluded that the overall success rate of the two drug combinations was not significantly different for the management of pediatric patients.

Peerbhay F et al., (2016)[40] 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 a 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.

Manso MA, Guittet C, Vandenhende F, Granier LA (2019)[41] conducted a review to check the 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.

KETAMINE:

Ketamine, categorized as an arylcycloalkylamine and a derivative of phencyclidine, is a water-soluble compound that has served various clinical purposes for many years. Originally synthesized in 1962 by American pharmacist Calvin Stevens[42], its potential as an anesthetic and its dissociative psychedelic properties were discovered by Edward Domino in 1965. The term 'dissociative anesthetic' was coined to describe its unique effects. Introduced into clinical practice in the 1970s, ketamine has been employed as a premedicant, analgesic, sedative, and induction agent through different administration routes.[43] Over time, the role of ketamine in clinical anesthesia has evolved, driven by changing perceptions of its mechanism of action and the recognition of the benefits associated with alternative administration methods.

CHEMICAL STRUCTURE:
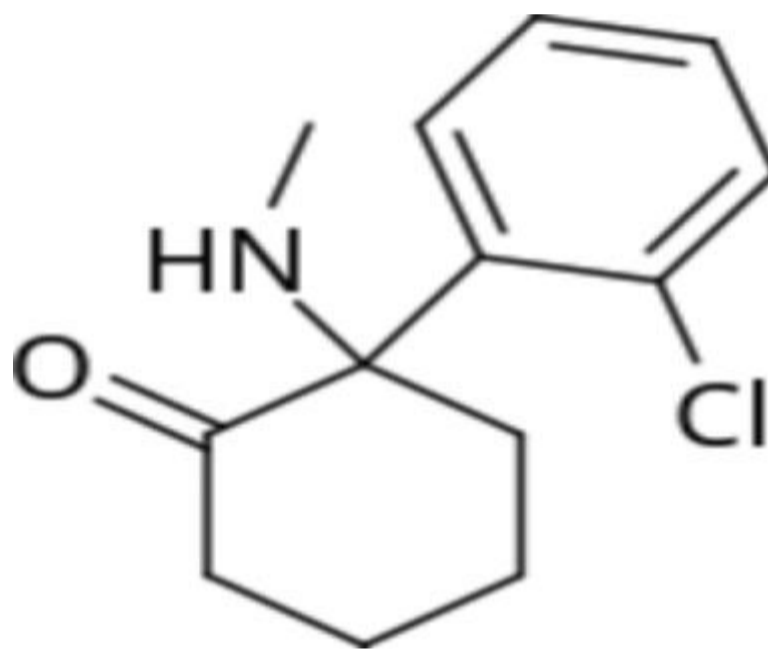
MECHANISM OF ACTION:

Ketamine hydrochloride, classified as a dissociative nonbarbiturate anesthetic, belongs to the rapidly acting cyclohexanone derivative category. With a structural formula of CHClNO and a chemical formula of 2-(o-chlorophenyl)-2-(methylamino) cyclohexanone hydrochloride[44], ketamine induces profound anesthesia and analgesia. Acting as a noncompetitive N-methyl-D-aspartate (NMDA) and glutamate receptor antagonist, it also blocks HCN1 receptors.[45] Its distinctive dissociative action and partial agonism on opiate mu-receptors enable the performance of painful procedures in a consistent state of sedation, ensuring patient comfort.[46]

The therapeutic effects of ketamine in chronic pain and its antidepressant properties are likely attributed to a secondary enhancement in structural synaptic connectivity, induced by the neuronal response to the ketamine-induced hyper-glutamatergic state (Sleigh, 2014).[45]The N-methyl-D-aspartate (NMDA) receptor, pivotal in the etiology of depression, is rapidly modulated by ketamine, effectively managing symptoms and acute suicidal ideation.[45] Ketamine's actions extend to synaptogenesis, potential interaction with sigma receptors, and reduction of central sensitization, wind-up phenomenon, and pain memory.[45] In sedation and analgesia, positive and negative modulatory roles are played by the cholinergic, aminergic, and opioid systems, with ketamine exhibiting the ability to reverse opioid tolerance.[47] Metabolized by the hepatic system through processes like N-dealkylation, hydroxylation, conjugation, and dehydration, ketamine has a half-life of approximately 45 minutes.[45] Additionally, ketamine increases brain-derived neurotrophic factor (BDNF) levels by elevating glutamate levels.

Ketamine generally preserves normal pharyngeal and laryngeal reflexes, allowing for spontaneous respiration.[45] It mildly enhances or sustains typical skeletal muscle tone and is linked with cardiovascular and respiratory stimulation. These attributes render it particularly valuable in the emergency department for brief procedures, especially when a patient is unprepared for an urgent intervention.[45] While

the maintenance of pharyngeal and laryngeal reflexes is not guaranteed, precluding assumptions of airway protection, there may be momentary, minimal respiratory depression if the drug is administered too rapidly or in excessive amounts.[45] Consequently, the physician must be prepared to perform emergency intubation as needed.

PHARMACOKINETICS:

Ketamine exhibits rapid absorption through intramuscular (Tmax 5-15 min), nasal (Tmax 20 min), or oral solution (Tmax 30 min) administration.[44] It demonstrates high bioavailability with intravenous (IV) or intramuscular (IM) delivery. Oral or rectal administration requires higher doses due to first-pass metabolism and lower absorption, resulting in only about 16% oral bioavailability compared to 93% with parenteral routes (Grant et al., 1981).[48] Extensive liver biotransformation produces multiple metabolites, with N-demethylation by cytochrome P450 yielding nor-ketamine, an active metabolite contributing significantly to ketamine's analgesic effects.[48] Nor-ketamine undergoes hydroxylation and conjugation, forming a water-soluble compound excreted in the urine. The distribution and elimination half-lives are relatively short, with an α-elimination phase lasting only a few minutes and a β-elimination half-life of 2-3 hours. Pharmacokinetic properties in children are similar, except for more rapid absorption following intramuscular administration and higher concentrations of nor-ketamine (Grant et al. 1981).[48]

PHARMACODYNAMICS:

The neuropharmacology of ketamine is intricate, involving interactions with multiple binding sites. Predominantly, ketamine influences excitatory amino acid neurotransmitters (EAA), which are the primary excitatory neurotransmitters in the brain. Specifically, it acts on the phencyclidine site of the N-methyl-D-Aspartate (NMDA) receptor, akin to other dissociative anesthetics like nitrous oxide, functioning as a non-competitive NMDA antagonist (Jevtovic-Todorovic et al., 2001).[49]

While its primary mechanism involves the NMDA receptor, the comprehensive spectrum of effects induced by ketamine goes beyond this singular action. Different sites of action contribute to its analgesic, anesthetic, and sympathomimetic effects. The involvement of opioid receptors may play a role in the analgesic state and contribute to dysphoric reactions (Ulugol et al., 2000) .[50] Furthermore, sympathomimetic properties are facilitated by an augmented central peripheral monoaminergic transmission. The induction of anesthetic effects and hallucination may involve the inhibition of central and peripheral cholinergic transmission (Adams H.A., 1988).[51]

Ketamine, in its most prevalent commercial form, consists of a racemic mixture comprising two enantiomers: S (+) ketamine and R (-) ketamine. Notably, R (-) ketamine exhibits a binding strength approximately 7-10 times greater than the S-isomer **(Ebert et al., 1997)** .[52]

The classical effects of ketamine can be aptly characterized as a dose-dependent depression of the central nervous system, culminating in a dissociative state. This state is marked by profound analgesia and amnesia, without necessarily inducing loss of consciousness. Clinically, ketamine induces a dissociation between the mind/thought processes and the individual's own body/surroundings. This effect arises from the electrophysiological inhibition of thalamo-cortical pathways and the simultaneous stimulation of the limbic system **(Flood and Krauss, 2003)** .[53]

The effects of ketamine primarily stem from the central nervous system (CNS) activity of the parent compound. It induces a dissociative anesthetic state, as observed in studies such as that by **Domino et al. in 1965** .[54] This state manifests as catalepsy, characterized by open eyes with slow nystagmus while maintaining intact light and corneal reflexes. As an anesthetic, ketamine elicits profound effects encompassing anesthesia, analgesia, amnesia, and catalepsy. Even at subanesthetic doses administered intravenously, ketamine exhibits potent analgesic properties **(Correll et al., 2004)** .[55]

Beyond analgesia and amnesia, ketamine's impact extends to the respiratory system, generally yielding favorable effects. It acts as a bronchodilator with minimal respiratory depression, preserving protective airway reflexes more effectively than other anesthetic agents **(Craven R. 2007, Reich and Silvay 1989).**[43,56] Research by Bourke et al. in 1987 demonstrates dose-related respiratory depression with incremental doses.[57] Ketamine's bronchodilator properties likely result from two mechanisms: first, a central effect inducing

catecholamine release, stimulating β2 adrenergic receptors and causing bronchodilation; second, inhibition of vagal pathways, producing an anticholinergic effect that acts directly on bronchial smooth muscle **(Lau and Zed, 2001).**[58]

"Ketamine distinguishes itself from most anesthetic agents by its propensity to stimulate the cardiovascular system, leading to alterations in heart rate, cardiac output, and blood pressure, as observed in studies such as those by **Haas and Harper in 1992**".[59] This cardiovascular stimulation is thought to be potentially linked to the re-uptake inhibition of circulating catecholamines. Conversely, in critically ill patients, cardio-depressant effects have been documented. This phenomenon may arise from chronic catecholamine depletion, preventing the sympathomimetic effects of ketamine and revealing negative inotropic effects, typically overshadowed by sympathetic stimulation, as noted by **Reich and Silvay in 1989** .[56]

While the cardiovascular effects of ketamine generally do not pose significant issues, caution is advised in its use. Ketamine is contraindicated in patients with significant heart disease and should be avoided in those with a history of high blood pressure and cerebrovascular accidents, as outlined by Haas and Harper in 1992.[59]

USE OF KETAMINE AS A SEDATIVE AGENT IN DENTISTRY:

Fallahinejad Ghajari M, Ansari G, Soleymani AA, Shayeghi S, Fotuhi Ardakani F.(2015)[60] carried out a study to compare the effect of intranasal and oral midazolam plus ketamine in children with high levels of dental anxiety. 23 uncooperative children aged 3-6 who required at least two similar dental treatments were randomly given ketamine (10 mg/kg) and midazolam (0.5 mg/kg) through oral or intranasal routes in each visit. It concluded that the Intranasal midazolam/ketamine combination was more satisfactory and effective than the oral route when sedating uncooperative children based on Houpt's scale for sedation.

Malhotra PU, Thakur S, Singhal P, Chauhan D, Jayam C, Sood R, Malhotra Y.(2016)[61] Comparative evaluation of intranasal dexmedetomidine and midazolam-ketamine combination as sedative agents in pediatric dentistry.36 children of 3-9 years old with ASAs-I status presenting early childhood caries were randomly assigned to one of three groups: Group MK received intranasal saline and oral midazolam (0.5 mg/kg) with ketamine (5 mg/kg) mixed in mango juice; Group DX received intranasal dexmedetomidine (1 μg/kg) and oral mango juice; and Group C received intranasal saline and oral mango juice.It concluded that 75% patients in Group MK were successfully sedated as compared to 53.9% Group DX and none of the patients in Group C.

Mehran M, Tavassoli-Hojjati S, Ameli N, Zeinabadi MS.(2017)[62] performed a study to compare the effects of intranasal ketamine and midazolam on behavior of 3-6 year-old children during dental treatments.17 uncooperative children requiring at least two dental treatments were selected and randomly received ketamine (0.5mg/kg) or midazolam (0.2mg/kg) before treatment and other medication were used in the next visit. It concluded that Ketamine reported higher success of sedation with fewer movements, and less crying along with some unwanted effects like more sleepiness, higher heart rate, and blood pressure compared to midazolam .

Poonai N et al.(2017)[63] conducted a systematic review of randomized trials of IN ketamine in PSA that reported any sedation-related outcome in children 0 to 19 years. The review included 7 studies (n = 264) of children ranging from 0 to 14 years. In four of seven studies, IN ketamine provided superior sedation and resulted in adequate sedation for 148/175 (85%) of participants with vomiting as the most common adverse effect reported by 9/91 (10%) of participants. It concluded that IN ketamine administration is well tolerated and without serious adverse effects precluding a recommendation for PSA in children.

Ilasrinivasan, Setty JV, Shyamachalam, Mendiretta P. (2018)[64] performed a study to compare nitrous oxide-oxygen inhalation and low-dose oral midazolam-ketamine combination for anxiolysis in the management of children aged between 3 to 10 years for dental treatment. A total of 30 children were equally divided into 2 groups, oral midazolam-ketamine (MK) group which received 0.25mg/ kg midazolam with 3mg/kg ketamine in combination and the Nitrous oxide-oxygen (N) group which received nitrous oxide-oxygen inhalation.It concluded no statistically significant differences between the groups in all the parameters that are drug/ mask acceptance, need for the use of a physical restraint, Houpt's sedation scale, faces pain score, except for the duration of sedation and the time taken to achieve maximum sedation which were higher in oral MK group than the Nitrous-oxide oxygen inhalation group.

Sado-Filho J, Viana KA, Corrêa-Faria P, Costa LR, Costa PS.(2019)[65] evaluated the efficacy of intranasal ketamine and midazolam as the main component of the behavioral guidance approach for preschoolers during dental treatment.84 Children with a mean age of 3.1 years, with caries and non-cooperative behavior, were randomized into three groups: (KMIN) intranasal ketamine and midazolam; (KMO) oral ketamine and midazolam; or (MO) oral midazolam.It concluded, the success of the treatment as assessed by 'quiet behavior for at least 60% of the session length' was: KMIN 50.0%,KMO 46.4% and MO 32.1%.

Yongping Z, Xinyi L, Aming S, Qiang X, Tianqi Z, Mengmeng S, Xiong C, Xuemin S. (**2021)[66]** conducted a study to compare the effect of intranasal Dexmedetomidine (D) and esketamine (K) in producing moderate sedation for uncooperative pediatric dental patients. One hundred and fifty American Society of Anesthesiologists (ASA) grade I and II patients aged 3-10 years were included and classified into four groups, Group K esketamine (0.5 mg/kg), and group D was given D1 (1 μg/kg), D2 (1.5 μg/kg), or D3 (2.0 μg/kg) intranasally respectively.It concluded that there was not significant difference between the groups in terms of the sedation level, changes in vital signs, sedation onset and recovery times, analgesia, behavior, and overall success addressing Intranasal D and K are effective in producing moderate sedation for uncooperative pediatric dental patients.

Rathi GV, Padawe D, Takate V, et al.(2022)[67] performed a study to assess and compare the effectiveness of midazolam vs midazolam and ketamine combination in the management of young uncooperative pediatric patients. Three hundred forty-six uncooperative children were included with a mean age of 5.8 years.It concluded that Midazolam with ketamine was the most successful combination for delivering rapid and sufficient analgosedation with overall success rate of 84% when compared to ketamine and midazolam alone.

Wang J, Zeng J, Zhao N, Chen S, Chen Z, Liao J, Ran H, Yu C (2023)[68] conducted a study with intranasal esketamine combined with oral midazolam that provides adequate sedation for outpatient pediatric dental procedures. A total of 60 children were enrolled and intranasal esketamine with 0.5 mg/kg -1 midazolam orally was given. It concluded that 53 children were successfully sedated considering using midazolam oral solution combined with esketamine nasal drops for noninvasive sedation in pediatric dentistry for moderate sedation.

FENTANYL

Fentanyl, a potent synthetic opioid, surpasses morphine in analgesic efficacy by a factor of 50 to 100, with a mere 100 micrograms yielding analgesia equivalent to approximately 10 mg of morphine. Despite sharing analgesic properties, fentanyl differs significantly in its pharmacokinetics. Predominantly eliminated by the liver, it finds common clinical application as a sedative for intubated patients and for managing severe pain in individuals with renal failure.[69] Additionally, fentanyl may be prescribed for chronic pain patients who have developed opiate tolerance. When employed as a sedative, it is typically administered through an intravenous drip.[70] Notably, fentanyl extends its utility to epilepsy treatment when combined with specific neuroleptic medications in therapeutic neuroleptanalgesia.[71]

CHEMICAL STRUCTURE
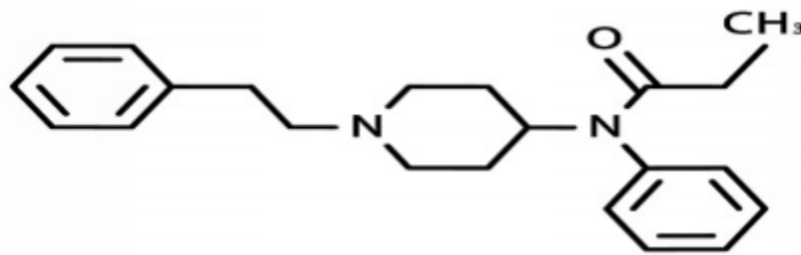
MECHANISM OF ACTION

Fentanyl, akin to other opioid drugs, interacts with a specific subclass of opioid receptors in the body, predominantly located in specialized neuroanatomical structures within the brain that regulate emotions, pain, and the reward system, contributing to its notorious addictive properties.[72] Biochemically classified as a Mu-selective opioid agonist, fentanyl also has the potential to activate delta and kappa-receptors. The activation of these receptors, especially the Mu-receptors, results in analgesic effects. Additionally, fentanyl induces an increase in the neurotransmitter dopamine in the brain's reward areas, leading to the characteristic feelings of exhilaration and relaxation associated with drug addiction.[72] The hepatic metabolism of fentanyl occurs through the CYP450 enzyme system, primarily CYP3A4, with a half-life ranging from 3 to 7 hours. The drug is predominantly excreted through the urine (75%) and to a lesser extent in feces (9%).

PHARMACOKINETICS

The pharmacokinetics of fentanyl refers to the processes that govern the absorption, distribution, metabolism, and excretion of the drug in the body.

Fentanyl's pharmacokinetics involve its absorption, distribution, metabolism, and excretion. It is administered via various routes, with rapid and complete absorption intravenously and slower release from transdermal patches. With high lipid solubility, it crosses the blood-brain barrier, distributing extensively, especially in the brain. Metabolism primarily occurs in the liver through CYP3A4, leading to nor fentanyl as the major metabolite. Fentanyl and its metabolites are excreted mainly in urine. The elimination half-life ranges from 2 to 4 hours, but analgesic effects may persist longer, particularly with transdermal administration. Understanding these dynamics is essential for dosing, onset, duration of action determination, and managing potential interactions or accumulation, guiding clinicians in optimizing therapeutic benefits while minimizing adverse effects.

PHARMACODYNAMICS

The pharmacodynamics of fentanyl involves its effects on the body's opioid receptors, particularly the mu-opioid receptors in the central nervous system. Fentanyl, being a potent opioid agonist, binds to these receptors and activates them. This activation leads to various physiological responses, both therapeutic and adverse.

The primary therapeutic effect of fentanyl is profound analgesia or pain relief. Mu-opioid receptors play a crucial role in modulating the perception of pain, and fentanyl's activation of these receptors inhibits the transmission of pain signals in the spinal cord and brain. This results in a powerful and rapid relief of severe pain, making fentanyl especially valuable in medical settings such as surgery or management of chronic pain conditions. However, the activation of mu-opioid receptors by fentanyl also produces side effects. One significant concern is respiratory depression, where the drug suppresses the respiratory drive, potentially leading to decreased breathing rates and oxygen saturation. Sedation and euphoria are other common central nervous system effects associated with opioid receptor activation. These side effects, along with the risk of dependence and addiction, underscore the need for careful dosing and monitoring when using fentanyl.

In summary, the pharmacodynamics of fentanyl involve its binding to mu-opioid receptors, resulting in potent analgesia but also carrying the risk of respiratory depression and other central nervous system effects. Balancing the therapeutic benefits with potential side effects is crucial in the clinical use of fentanyl.

USE OF FENTANYL AS A SEDATIVE AGENT IN DENTISTRY:

Jaikaria A, Thakur S, Singhal P, Chauhan D, Jayam C, Syal K.(2018)[73] conducted a study to compare Sedative Agents in Pediatric Dentistry. In this study 36 children who were 3-9 year old with American Society of Anesthesiologists -I status and presenting early childhood caries were randomly assigned to oral combinations of midazolam-ketamine (MK), dexmedetomidine-fentanyl (DF), and dexmedetomidine-ketamine (DK) respectively into three groups. It concluded that the oral dexmedetomidine-fentanyl(DF) group promises to be a potential sedative agent for children due to its successful anxiolysis.

Chatrath V, Kumar R, Sachdeva U, Thakur M.(2018)[74] conducted a study to compare the efficacy of intranasal fentanyl, midazolam, and dexmedetomidine as premedication in pediatric patients. 75 patients in the age group of 2-6 years of either sex of the American Society of Anesthesiologists physical Class I or II were divided into three groups of 25 each and were scheduled to undergo surgery under general anesthesia.It concluded that onset of action of fentanyl and midazolam is early as compared to that of dexmedetomidine along with fentanyl providing better conditions for induction and emergence.

Cheng C, Tabbara N, Cheng C, Shah V.(2022)[75] carried out a study to evaluate the effectiveness and safety of IN fentanyl for procedural pain in preterm infants. Thirteen infants received IN fentanyl in neonatal intensive care unit and response was evaluated in terms of pain responses, physiological parameters before and up to 60 min after administration, and adverse events.It concluded that IN fentanyl appears to be an alternative pharmacotherapy for procedural pain management in the absence of intravenous access in preterm infants as there was no significant difference in physiological parameters before and up to 60 of administration with beneficial effect in pain profile scores.

Alhaidari RI, AlSarheed MA.(2022)[76] Carried out a study to evaluate the post-discharge effects of oral midazolam with intranasal fentanyl sedation in pediatric patients who had dental treatment and to evaluate parents' preference regarding sedation visits. A total of 32 uncooperative healthy pediatric patients aged 3-6 years were included among which in the first visit, one group received oral midazolam (0.7 mg/kg) with intranasal fentanyl (1 μg/kg) sedation (M/F) and the other group received oral midazolam with intranasal placebo (M), and in the second visit each group received the other type of sedation in a cross-over type. It concluded that children sedated with midazolam/fentanyl encountered prolonged sleeping, and prolonged recovery time with no difference in parents' preferences regarding the any of two sedation regimens.

Agarwal A et al. (2023)[77] performed a study to assess the effectiveness of various analgesia-sedative combinations for pain relief and sedation in pediatric dental patients. A total of 128 healthy, uncooperative pediatric dental patients were randomly allocated to receive one of the four combinations of drugs via the intranasal (IN) route: Group I received midazolam-ketamine (MK), Group II received dexmedetomidine-ketamine (DK), Group III received midazolam-fentanyl (MF), and Group IV received dexmedetomidine-fentanyl (DF). It concluded that DK and DF groups showed potential as analgesia-sedative with significantly higher depth of sedation.

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, efficacy and safety of intranasal ketamine-midazolam combination with intranasal fentanyl-midazolam combination for procedural sedation in uncooperative pediatric dental patients. After receiving approval from the BBDCODS, Lucknow, institutional ethical committee, 30 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

Healthy subjects aged between 3-7 years will be included in the study.

Sample size estimation was done by using nMaster2.0 (CMC, vellore)

A minimum total sample size of 28 was found to be sufficient for an alpha of 0.05, power of 95. Sample size was further rounded off to 30 i.e. 15 in each group.

Two Means - Estimating the difference between two means

Standard deviation in group I = 2.92

Standard deviation in group II = 7.49

Estimated difference between means = 3

Desired confidence level (%)= 95

Required sample size = 28

Formula

$$n = \frac{Z^2_{1-\alpha/2}\left[2S^2_p\right]}{d^2}$$

Where,

$$S^2_p = \frac{S^2_1 + S^2_2}{2}$$

S^2_1 : Standard deviation in the first group

S^2_2 : Standard deviation in the second group

S^2_p : Pooled standard deviation

d   : Precision

α   : Significance level

Thus, a total of 30 patients will be required for the study. However, in this study, we enrolled more than the calculated sample size; therefore, the experimental sample size consisted of 60 patients (n = 30).

The data collected from the study will be subjected for statistical analysis.

ELIGIBILITY CRITERIA:

INCLUSION CRITERIA

I.   Children aged between 3 to 7 years

II.   The patient should belong to the criteria of the American Society of Anaesthesiologists (ASA) classification- I.

III. The patient is depicting a negative (score 2) on Frankel's behavior rating scale.

IV. The patients for whom the basic behavior guidance techniques have not been successful.

V.   The patients undergoing dental procedures which need more than one appointment like multiple extractions, pulpectomy, restorations, crown placement, requiring the administration of local anesthetic, etc.

EXCLUSION CRITERIA

I. Patients are not willing to submit their consent in writing.

II. Definitively Negative patients as on Frankl's behavior rating scale.

III. Patients who are sensitive or allergic to the drugs being administered.

IV. Patients taking any other sedative medications.

V. Children who were given analgesics six hours before the procedure.

VI. 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)

- ➢ Fentanyl vial - 50 mcg/2ml (Neon Pharmaceuticals)

- ➢ 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

STUDY DESIGN:

The present study enrolled 60 children, aged between 3 to 7 years, of both genders, classified as ASA Grade-1. These children had previously undergone basic behavior modification techniques that were insufficiently effective in providing dental treatment. Subsequently, the patients were subjected to a pharmacological approach for behavior modification.

The patients were randomly allocated into two groups, with each group comprising 30 participants.

Group I (INMK): Intranasal midazolam- ketamine combination

Group II (INMF): Intranasal midazolam- fentanyl combination

In this randomized controlled trial, each child in the respective group was administered a combination of midazolam-ketamine and a combination of midazolam-fentanyl via the intranasal route. Throughout the entire procedure, vital signs were continuously monitored, spanning from the preadministration (baseline) of the drug to a comprehensive sixty-minute observation period. The intranasal dosage parameters were configured as follows: 7mg/kg body weight for atomized ketamine, 0.3mg/kg body weight for midazolam spray, and 1.5 mcg/kg body weight for atomized fentanyl. To address excessive salivation induced by ketamine, an intramuscular (IM) injection of glycopyrrolate HCl 0.1ml/kg body weight was administered in the INMK Group.

METHODOLOGY:

The study included sixty systemically healthy children (ASA type I) aged between 3 to 7 years, for whom basic behavior modification techniques had proven ineffective in facilitating dental treatment. During the initial appointment, the potential risks and benefits of the sedation were thoroughly explained to the parent or guardian.

60 participants meeting the eligibility criteria were randomly divided into two groups: Group I (INMK) and Group II (INMF), each consisting of 30 individuals. The allocation process employed a sealed envelope randomization method. Participants were allowed to select a sealed envelope, with each envelope corresponding to one of the two groups. These envelopes, containing the group assignments, were then handed over to the anesthesiologist. This method was chosen to maintain blinding throughout the allocation process, ensuring that neither the participants nor other personnel were aware of the group assignments. Only the anesthesiologist possessed knowledge of each participant's intervention group, allowing for prompt action in the event of any unforeseen reactions to the administered drugs. This allocation process will continue until both groups reach their predetermined size of 30 participants each.

The study is designed to maintain a triple-blind approach, ensuring that parents, care providers, and outcome assessors remain unaware of the group assignments. Meanwhile, the anesthesiologist remains the only individual aware of this information, maintaining the integrity of the blinding process.

A comprehensive dental and medical history were gathered, including a detailed assessment of the airway to evaluate the risk of obstruction (considering factors such as tonsillar hypertrophy, abnormal anatomy, and visibility of the hard palate or uvula tip). A systematic review of systems was conducted, focusing on potential abnormalities in cardiac, pulmonary, renal, or hepatic functions that could impact the child's response to sedative medications. Pre-sedation dietary instructions were provided per the guidelines of the American Society of Anesthesiologists.

An experienced anesthesiologist at Babu Banarasi Das College of Dental Sciences, Lucknow, conducted a thorough pre-anesthetic assessment. Blood investigations and chest X-rays were recommended to the patient before the sedation day. The sedation procedure was implemented only when all parameters fell within normal ranges.

On the day of dental treatment, a re-evaluation was conducted by the anesthesiologist. Vital signs, including pulse rate and blood pressure, along with peripheral oxygen saturation levels, were meticulously examined and recorded using a multi-para-monitor. Before drug administration, the patient's body weight was measured, and the drug dosage was calibrated based on body weight. The required amount of drug was then administered, with half the volume introduced into each nostril while the patient was in a semi-recumbent position, employing either a nasal spray or an atomizer device for intranasal administration.

The purpose of this study was to evaluate and compare the efficacy and safety of intranasal midazolam-ketamine (INMK) combination with intranasal midazolam-fentanyl (INMF) combination for sedation in pediatric dental patients while delivering dental treatment to uncooperative children.

In Group A, patients received a combination of midazolam spray (0.3mg/kg) along with an atomized spray of ketamine (7mg/kg). Subsequently, in Group B, patients were administered a combination of midazolam spray (0.3mg/kg) with an atomized spray of fentanyl (1.5 mcg/kg).

Throughout each sedation session, the children's response to drug acceptance during administration was assessed. Subsequently, after drug administration, evaluations were conducted to determine the onset time, depth of sedation, and duration of sedation. This comprehensive assessment included the examination of behavioral responses during treatment, the ease with which the treatment could be completed, the recovery from sedation, and the occurrence of any drug-related side effects.

Under the supervision of an anesthesiologist, a single operator conducted all dental procedures. Vital signs, including pulse rate, blood pressure, and oxygen saturation, were documented before drug administration and subsequently at five-minute intervals for a total duration of 60 minutes.

The Ohio State Behavioral Rating Scale (OSBRS), as detailed by Lochary and colleagues in 1992, was employed to assess each patient's drug acceptance and duly documented. The time for the onset of sedation was recorded, with the onset being recognized when the patient's sedation level reached a score of 2 on the sedation rating scale (AAPD 2006 modified by Padmanabhan et al., 2009). Similarly, the peak

of sedation was identified when the patient's sedation level corresponded to a score of 3 on the sedation rating scale. The level of sedation was evaluated using a 5-point scale by the University of Michigan Sedation Scale (UMSS) Scoring, and the ease with which treatment could be completed was scored based on AAPD 2006 modified by Padmanabhan et al., 2009.

Following the completion of the treatment, the patient was transferred to the recovery room. Any post-sedation side effects were carefully observed and documented. The duration needed for full recovery was noted, and the patient was deemed fully recovered upon meeting specific criteria outlined in the Aldrete Recovery Scoring 2015. Vital signs were reassessed, and discharge took place once the criteria for discharge outlined in the AAPD sedation guidelines were satisfied. The discharge time was calculated from the completion of the procedure until the patient departed from the hospital. Both the parents and the patient were provided with post-discharge instructions

MIDAZOLAM NASAL SPRAY 5 mg/ml
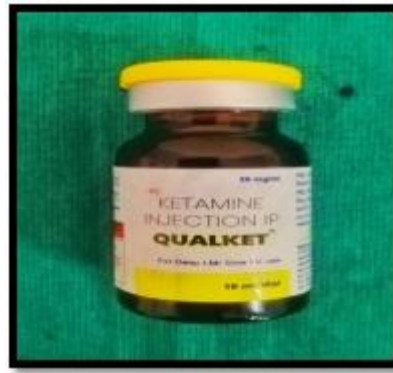
FENTANYL CITRATE IP 50 mcg/2 ml

KETAMINE 50 mg/ml

NASAL SPRAY

MUCOSAL ATOMIZER DEVICE
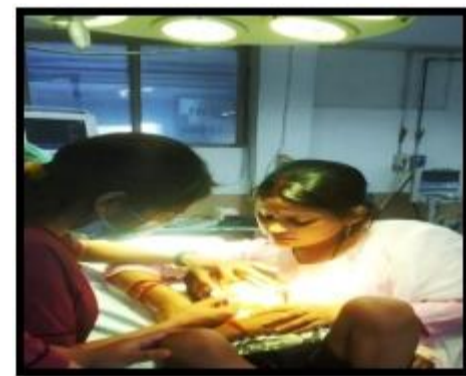
DRUG DELIVERY THROUGH INTRANASAL ROUTE

RESULTS AND OBSERVATIONS

The present study evaluated and compared intranasal ketamine-midazolam combination with intranasal fentanyl-midazolam combination for procedural sedation in uncooperative pediatric dental patients.

Thirty participants meeting eligibility criteria in the age range of 3-7 years were required to carry out the study. However, in this study, we enrolled more than the calculated sample size, therefore, the experimental sample size consisted of 60 study participants in total (n=30). Each subject was recruited randomly in either group, Group I INMK [Midazolam (0.3mg/kg) and Ketamine 7 mg/kg (n=30) combination] and Group II INMF [Midazolam (0.3mg/kg) and Fentanyl 1.5 mcg/kg (n=30) combination] through permuted block randomization method. The outcome measures of the study were hemodynamic parameters (pulse rate, SBP, DBP, and oxygen saturation), acceptance of the 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 intervals up to 1 hour.

DISTRIBUTION OF STUDY SUBJECTS

Based on the distribution of study subjects 50% of the subjects were allocated to Group I INMK and 50% of the subjects were allocated to Group II INMF.

Group	N	Percentage
Group I INMK	30	50%
Group II INMF	30	50.0%

Table 1: Distribution of study subjects

DEMOGRAPHIC CHARACTERISTICS

The ages of participants in both groups (INMK and INMF) are summarized in Table 2 and Graph 1. In both the groups, age ranged from 3 to 7 years, with a mean of 4.105 years. The mean age of the study subjects in the Group I INMK was 4.06 years and the mean age of the study subjects in the Group II INMF was 4.15 years. Comparing the mean age, subjects in both groups were age-matched.

	N	Mean Age	SD
Group I INMK	30	4.06 years	1.21
Group II INMF	30	4.15 years	1.04

Table 2: Mean age of study subjects
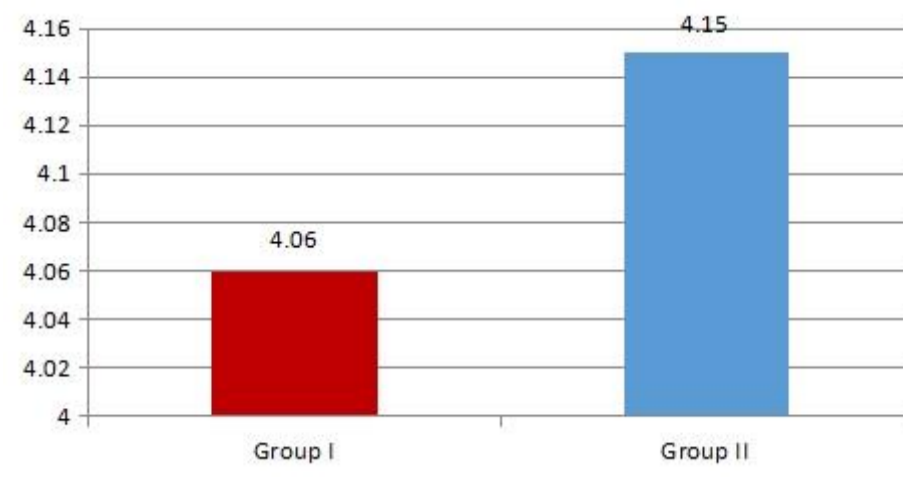
Graph 1: The mean age of subjects in both the groups

ACCEPTANCE OF DRUG

The intergroup comparison of ease of drug acceptance between the groups is described in Table 3 and Graph 2 respectively. The majority of patients in Group I INMK accepted the drug with quiet behavior and no movement (86.7%), whereas the majority of patients in Group II INMF accepted it with crying and no struggling (66.7%). The intergroup comparison between the two groups was statistically significant when analyzed using Chi Square test.

Score	Acceptance of drug rating	Group I INMK (n=30) %	Group II INMF (n=30)%	P value
4	Quiet behavior, no movement	26 (86.7%)	10 (33.3%)	
3	Crying, No struggling	04 (13.3%)	20 (66.7%)	
2	Struggling movement without Crying,	0	0	0.001*
1	Struggling movement with Crying,	0	0	

Chi Square test with p value less than 0.05 is significant

Table 3: Acceptance of drug for both the groups.
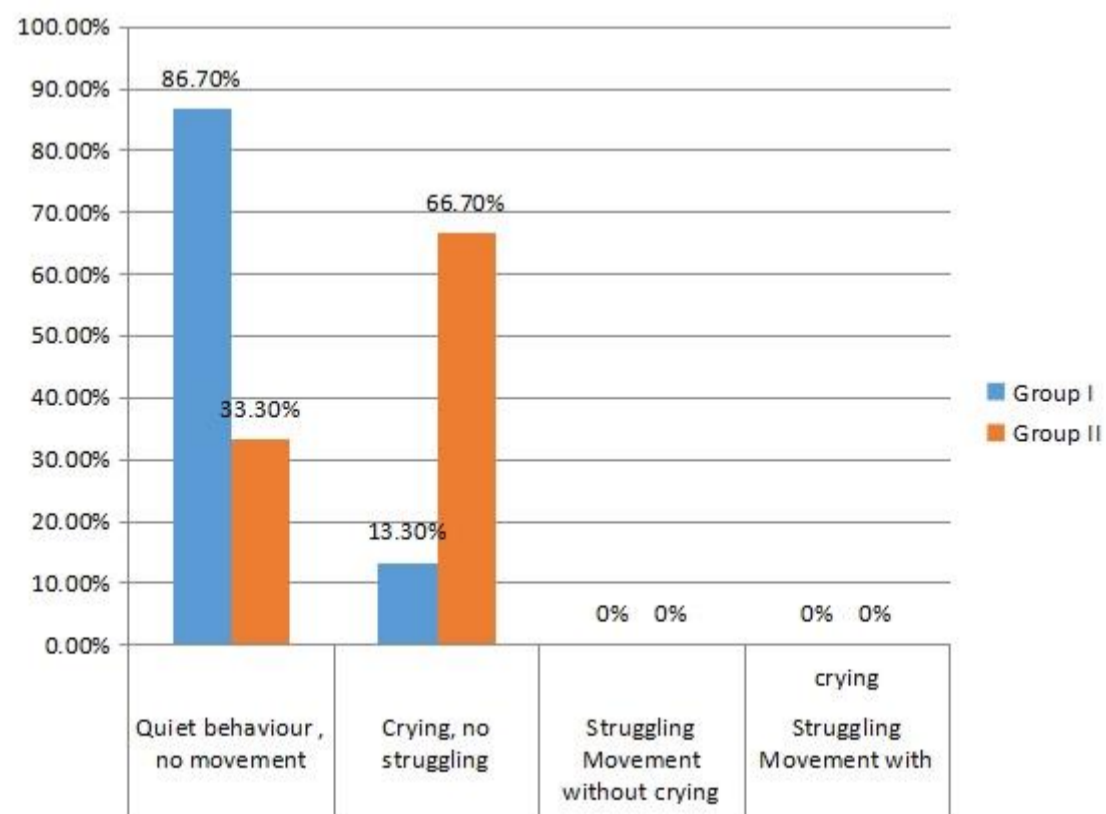
Graph 2: Acceptance of drug for both the groups

ONSET TIME

The time of onset for both groups is summarized in Table 4 and Graph 3. On comparing the mean, the independent t-test showed a significantly faster onset time in Group I INMK (7.40 min) as compared to Group II INMF (12.46 min).

	Mean (min)	Std Dev	Std Error	P value
Group I INMK	7.4000	2.29285	.59201	0.001*
Group II INMF	12.4667	2.41622	.62386	

Independent t-test with p value less than 0.05 is significant

Table 4: Time of onset for both groups
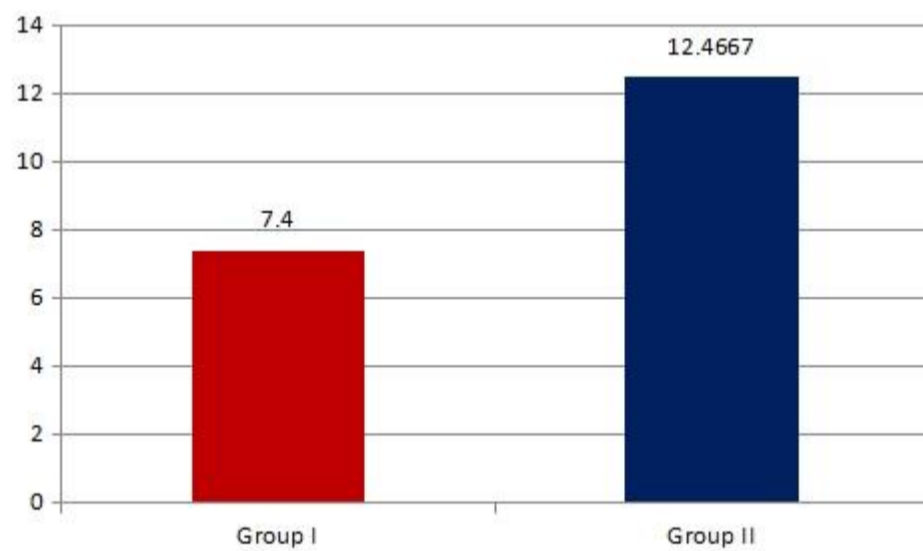
Graph 3: Time of onset for both the groups

PEAK SEDATION TIME

The peak sedation time of both groups is summarized in Table 5 and Graph 4. On comparing the mean, the independent t-test showed significantly higher peak sedation time in the Group I INMK (21.33 min) as compared to Group II INMF (28.14 min).

	Mean	Std Dev	Std Error	P value
Group I INMK	21.3333	3.33095	.86005	

Group II INMF	28.1400	2.32404	.60006	0.001*

Independent t-test with p value less than 0.05 is significant

Table 5: Peak sedation time for both the groups
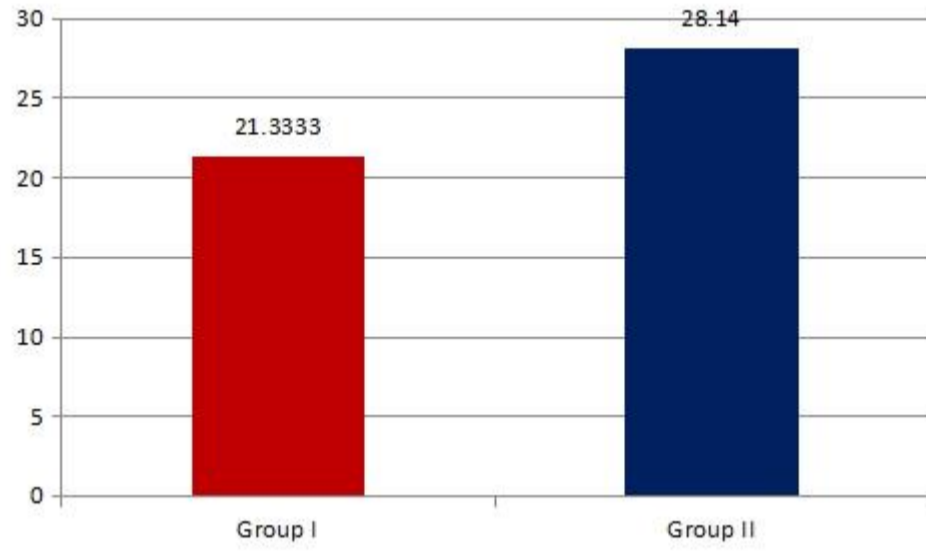
Graph 4: Peak sedation time for both the groups

HEMODYNAMIC PARAMETERS

I.   Pulse rate:

The pulse rate (PR) in both groups for 60 minutes is summarized in Table 6 and Graph 4. The mean pulse in the Group I INMK at the baseline was 123.27 and in the Group II INMF was 124.33.

On intra-group comparison, in Group I INMK PR was significantly higher than baseline from 10 minutes to 45 minutes and a gradual decrease close to baseline by the end of sixty minutes. In Group II INMF, PR was significantly lower than baseline from 5 minutes to 40 minutes with a slight increase close to baseline by the end of 60 minutes.

On inter-group comparison, the PR was significantly higher in Group I INMK than in Group II INMF from 10 minutes to 40 minutes. On all other points of time, there was no significant difference between both the groups.

	GP	Mean	Std. Deviation	Std. Error Mean	P value
0 Minutes	Group I	123.27	7.43	3.12	0.876
	Group II	124.33	7.42	3.56	
5 minutes	Group I	121.53	7.12	3.67	0.812
	Group II	121.33	7.19	3.98	
10 Minutes	Group I	126.07	6.97	3.13	0.001*
	Group II	119.80	6.78	3.45	
15 Minutes	Group I	127.47	6.45	3.61	0.001*
	Group II	117.53	6.13	2.98	
20 Minutes	Group I	127.53	6.57	3.45	0.001*
	Group II	117.27	6.75	3.89	
25 Minutes	Group I	126.60	6.56	3.04	0.001*
	Group II	117.87	6.86	2.78	
30 Minutes	Group I	126.53	6.89	2.89	0.001*
	Group II	119.60	6.94	3.01	
35 Minutes	Group I	125.60	7.12	3.12	0.032*
	Group II	119.73	7.08	3.32	
40 Minutes	Group I	124.40	7.01	2.96	0.049*
	Group II	120.73	6.96	2.99	
45 Minutes	Group I	124.60	6.90	3.12	0.253
	Group II	121.40	6.89	3.41	
50 Minutes	Group I	123.60	6.55	3.53	0.457
	Group II	122.20	6.61	2.99	
55 Minutes	Group I	122.87	6.98	3.17	0.912
	Group II	122.20	7.03	3.43	
60 Minutes	Group I	122.00	7.12	3.36	0.923
	Group II	122.73	7.16	3.39	

Table 6: Pulse rate for both the groups over 60 minutes
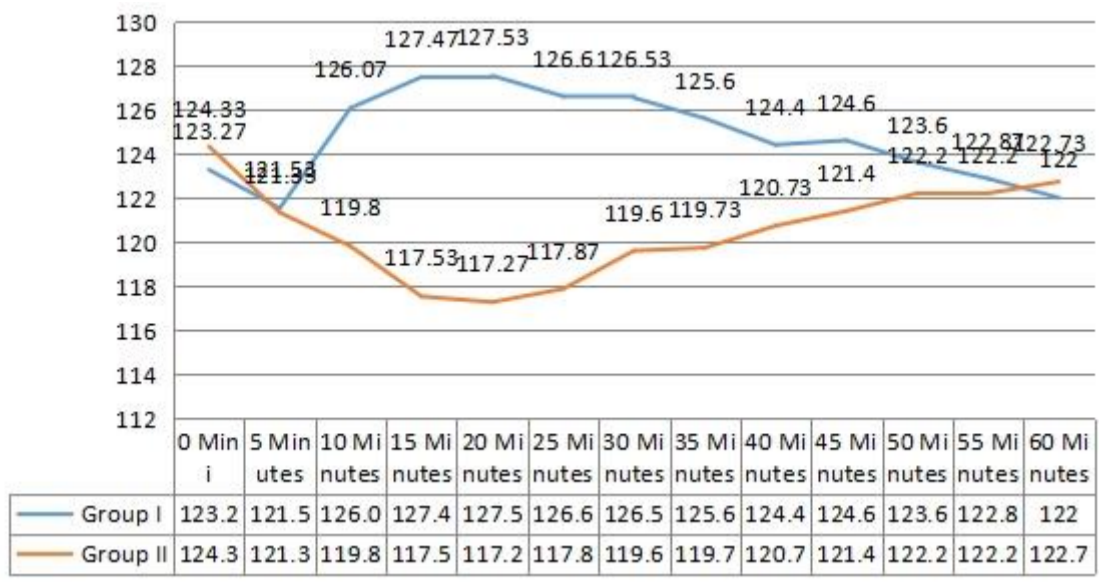
Graph 5: Pulse rate for both the groups over 60 minutes

	0 Min i	5 Min utes	10 Mi nutes	15 Mi nutes	20 Mi nutes	25 Mi nutes	30 Mi nutes	35 Mi nutes	40 Mi nutes	45 Mi nutes	50 Mi nutes	55 Mi nutes	60 Mi nutes
Group I	123.2	121.5	126.0	127.4	127.5	126.6	126.5	125.6	124.4	124.6	123.6	122.8	122
Group II	124.3	121.3	119.8	117.5	117.2	117.8	119.6	119.7	120.7	121.4	122.2	122.2	122.7

II. Oxygen Saturation

The oxygen saturation (SPO2) of Group I (INMK) and Group II (INMF) over 60 minutes is summarized in Table 7 and Graph. 6.

On intra-group comparison, the difference in mean SPO2 between baseline and intra-operative periods for each group was taken out. The Independent t-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 statistically non-significant between the two groups (Group I and Group II).

	GP	Mean	Std. Deviation	Std. Error Mean	P value
0 Minutes	Group I	99.2667	1.53375	.39601	0.661
	Group II	99.4667	.83381	.21529	
5 minutes	Group I	99.3333	.97590	.25198	0.857
	Group II	99.2667	1.03280	.26667	
10 Minutes	Group I	99.3333	.81650	.21082	0.582
	Group II	99.1333	1.12546	.29059	
15 Minutes	Group I	98.9333	1.22280	.31573	0.378
	Group II	98.3333	2.28869	.59094	
20 Minutes	Group I	99.6000	1.05560	.27255	0.036*
	Group II	98.8667	.74322	.19190	
25 Minutes	Group I	99.6000	.73679	.19024	0.015*
	Group II	98.8000	.94112	.24300	
30 Minutes	Group I	99.1333	.91548	.23637	0.009*
	Group II	97.9333	1.38701	.35813	
35 Minutes	Group I	98.5333	1.95911	.50584	0.049*
	Group II	97.1333	1.95911	.50584	
40 Minutes	Group I	99.4000	1.05560	.27255	0.859
	Group II	99.3333	.97590	.25198	
45 Minutes	Group I	98.7333	1.16292	.30026	0.059
	Group II	99.4667	.51640	.13333	
50 Minutes	Group I	98.4667	1.06010	.27372	0.269
	Group II	97.8667	1.76743	.45635	
55 Minutes	Group I	98.0000	3.33809	.86189	0.541
	Group II	97.3333	2.49762	.64488	
60 Minutes	Group I	98.8667	1.72654	.44579	0.618
	Group II	97.8000	4.64758	1.20000	

Independent t-test with p value less than 0.05 is significant

Table 7: Oxygen Saturation for both groups over 60 minutes

	0 Minutes	5 minutes	10 Minutes	15 Minutes	20 Minutes	25 Minutes	30 Minutes	35 Minutes	40 Minutes	45 Minutes	50 Minutes	55 Minutes	60 Minutes
Group I	99.26	99.33	99.33	98.93	99.6	99.6	99.13	98.53	99.4	98.73	98.46	98	98.86
Group II	99.46	99.26	99.13	98.33	98.86	98.8	97.93	97.13	99.33	99.46	97.86	97.33	96.8

Graph 6: Oxygen Saturation for both the groups over 60 minutes

III. Systolic Blood Pressure:

The systolic blood pressure (SBP) of both groups over one hour is summarized in Table 8 and Graph 7. The mean systolic blood pressure (SBP) in the Group I INMK at the baseline was 123.27 and in the Group II INMK was 119.33.

On intra-group comparison, the difference in mean SBP between baseline and intra-operative periods, there was significantly higher SBP as compared to baseline in Group I INMK till 15 minutes while the decrease from 20 minutes to 35 minutes followed by gradual increase till 60 minutes. In the Group II INMF, there was a fall in SBP from baseline (0 minutes) to 30 minutes and afterward a steady increase from 30 minutes to 60 minutes. Hence, the intragroup rise and fall in SBP from baseline to 60 minutes was statistically significant.

On inter-group comparison, there was a significant rise in SBP in Group I INMK till 15 minutes while a significant fall in SBP in Group II INMF till 30 minutes. There was a gradual rise in SBP in both groups from 40 minutes onwards till 60 minutes restoring SBP near to baseline.

	GP	Mean	Std. Deviation	Std. Error Mean	P value
0 Minutes	Group I	123.27	6.91	1.52868	0.224
	Group II	119.33	6.96	1.71741	
5 minutes	Group I	125.73	7.21	1.33162	0.041*
	Group II	118.87	7.75	1.89733	
10 Minutes	Group I	127.13	7.71	1.41128	0.001*
	Group II	115.27	7.39	1.03388	
15 Minutes	Group I	128.13	6.72	1.28324	0.001 *
	Group II	112.07	6.24	1.42696	
20 Minutes	Group I	125.53	5.46	1.13556	0.001*
	Group II	112.67	7.57	1.48538	
25 Minutes	Group I	122.80	7.34	1.15031	0.001*
	Group II	110.40	7.14	1.50619	
30 Minutes	Group I	121.27	6.78	1.22066	0.001*
	Group II	108.47	7.06	1.13485	
35 Minutes	Group I	119.00	6.41	1.99238	0.034*
	Group II	110.40	7.15	1.21350	
40 Minutes	Group I	120.00	7.47	1.52828	0.001*
	Group II	111.27	6.94	1.42984	
45 Minutes	Group I	121.00	6.61	1.73656	0.058
	Group II	114.93	7.3	1.34161	
50 Minutes	Group I	121.13	7.09	1.51441	0.057
	Group II	114.53	6.57	1.46880	
55 Minutes	Group I	121.93	7.12	1.89684	0.074
	Group II	115.40	6.95	1.02232	
60 Minutes	Group I	122.47	6.91	1.90466	0.090
	Group II	116.87	6.96	1.63410	

Table 8: Systolic Blood Pressure of both the groups over a period of 60 minutes
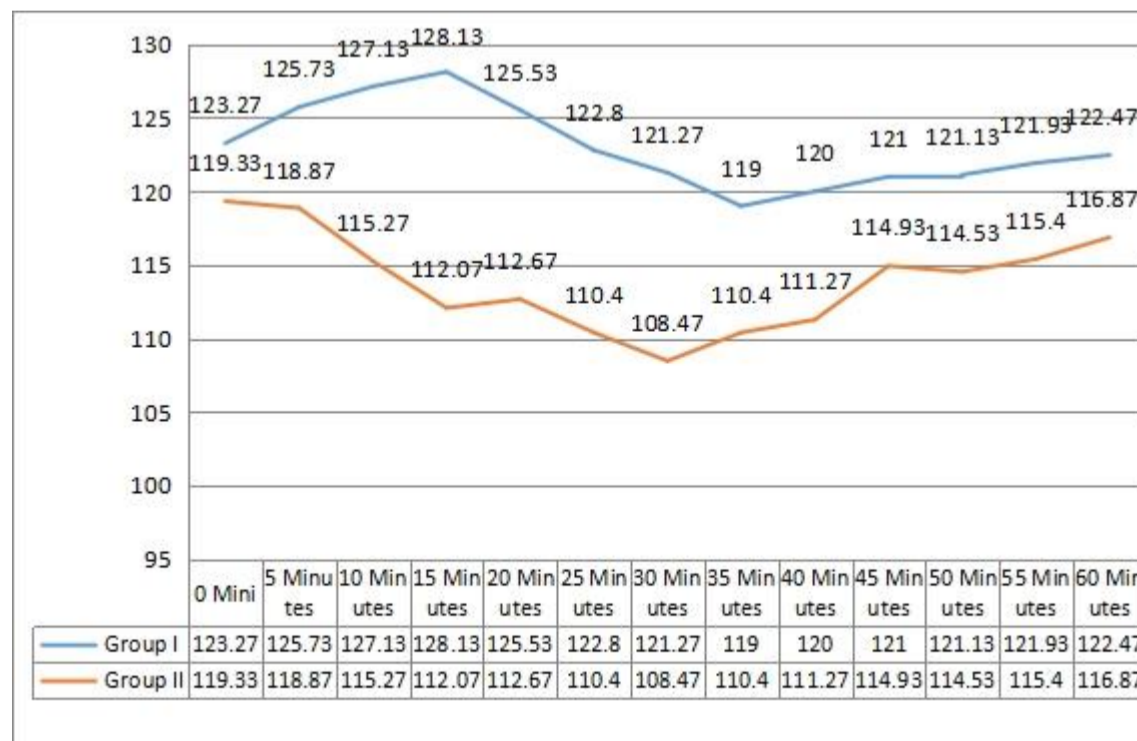
Graph 7: Systolic Blood Pressure of both the groups over a period of 60 minutes

IV. Diastolic Blood Pressure

The diastolic blood pressure (DBP) of both groups over 60 minutes is summarized in Table 9 and Graph 8. The mean diastolic blood pressure in the Group I INMK at the baseline was 74.60 and in the Group II INMF was 74.80.

For intra-group comparison, Group I INMK showed a transient increase in DBP till 15 minutes followed by a decrease till 40 minutes, then again a gradual increase till 60 minutes towards the baseline. In Group II INMF, there was a significant decrease in DBP till 40 minutes followed by a gradual increase till 60 minutes near baseline.

On inter-group comparison, there was an increase in the diastolic blood pressure from baseline (0 minutes) to 15 minutes in the Group I INMK and a fall in the blood pressure from 15 minutes to 40 minutes. From 40 minutes to 60 minutes, there was an increase in blood pressure. In Group II INMF there was a fall in blood pressure from 0 minutes to 30 minutes and afterwards a steady increase in blood pressure from 30 minutes to 60 minutes. The statistically significant difference in the DBP was there from 5 minutes to 40 minutes between Group I and Group II.

	GP	Mean	Std. Deviation	Std. Error Mean	P value
0 Minutes	Group I	74.6000	2.47	1.254	0.741
	Group II	74.8000	2.85	1.176	
5 minutes	Group I	75.3333	2.37	1.143	0.001*
	Group II	69.0000	2.96	1.172	
10 Minutes	Group I	76.4000	2.57	1.114	0.001 *
	Group II	68.6000	2.39	1.033	
15 Minutes	Group I	76.3333	2.72	1.283	0.001*
	Group II	66.7333	2.24	1.434	
20 Minutes	Group I	72.5333	2.49	1.045	0.001*
	Group II	66.0667	2.51	1.045	
25 Minutes	Group I	72.7333	2.36	1.150	0.001*
	Group II	64.1333	2.21	1.506	
30 Minutes	Group I	71.2000	2.75	1.220	0.001*
	Group II	63.2667	2.18	1.135	
35 Minutes	Group I	70.0667	2.45	1.98	0.001*
	Group II	64.0000	2.56	1.350	
40 Minutes	Group I	68.6000	2.49	1.528	0.110
	Group II	66.6000	2.99	1.484	
45 Minutes	Group I	70.8667	2.61	1.656	0.087
	Group II	67.9333	2.14	1.161	
50 Minutes	Group I	71.1333	2.06	1.231	0.091
	Group II	69.0000	2.58	1.480	
55 Minutes	Group I	71.7333	2.14	1.884	0.445
	Group II	70.8000	2.58	1.022	
60 Minutes	Group I	70.1333	2.78	1.046	0.914
	Group II	70.0000	2.96	1.103	

Table 9: Diastolic Blood Pressure for both the groups over 60 minutes

	0 Min i	5 Min utes	10 Mi nutes	15 Mi nutes	20 Mi nutes	25 Mi nutes	30 Mi nutes	35 Mi nutes	40 Mi nutes	45 Mi nutes	50 Mi nutes	55 Mi nutes	60 Mi nutes
Group I	74.6	75.33	76.4	76.33	72.53	72.73	71.2	70.06	68.6	70.86	71.13	71.73	70.13
Group II	74.8	69	68.6	66.73	66.06	64.13	63.26	64	66.6	67.93	69	70.8	70
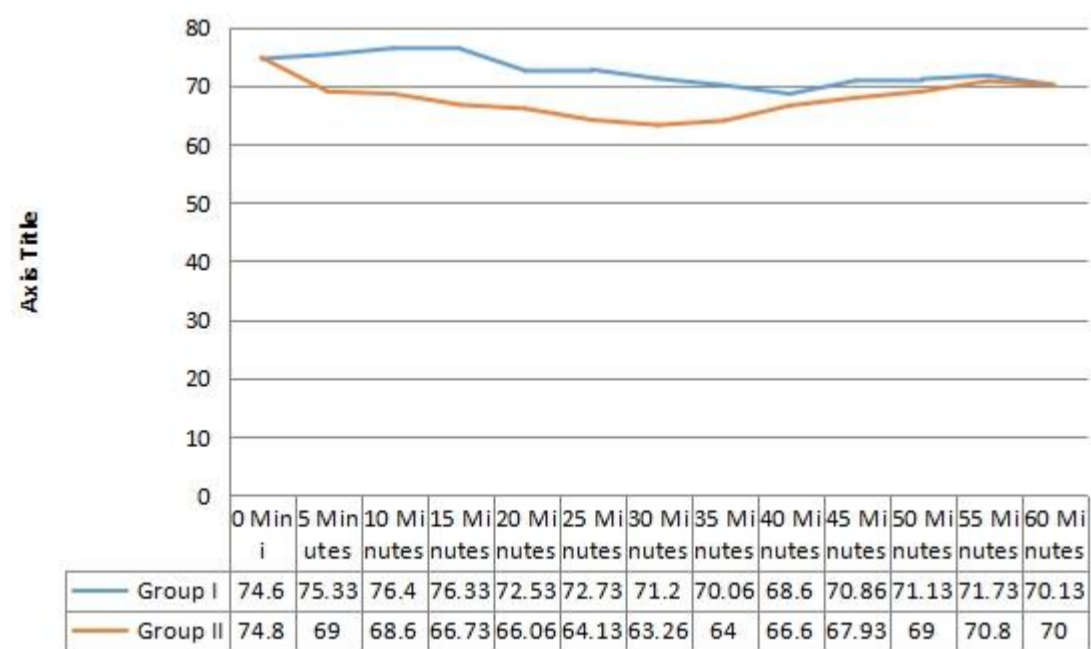
Graph 8: Diastolic Blood Pressure for both the groups over 60 minutes

LEVEL OF SEDATION

The Level of Sedation of both groups is summarized in Table 10 and Graph.9. The level of sedation in both groups showed significant differences. The level of sedation rating in the majority of patients in Group I INMK was minimal (26.7%) to moderate (66.7%) whereas in Group II INMF the rating was exclusively minimal (100.0%). Hence, the intergroup comparison between the two groups was statistically significant.

	Minimally Sedated	Moderately Sedated	Deep Sedated	P value
Group I INMK	8	20	02	
	26.7%	66.7%	6.6%	0.001*
Group II INMF	30	0	0	
	100.0%	.0%	.0%	

Chi Square test with p value less than 0.05 is significant

Table 10: Level of sedation scale for both groups.
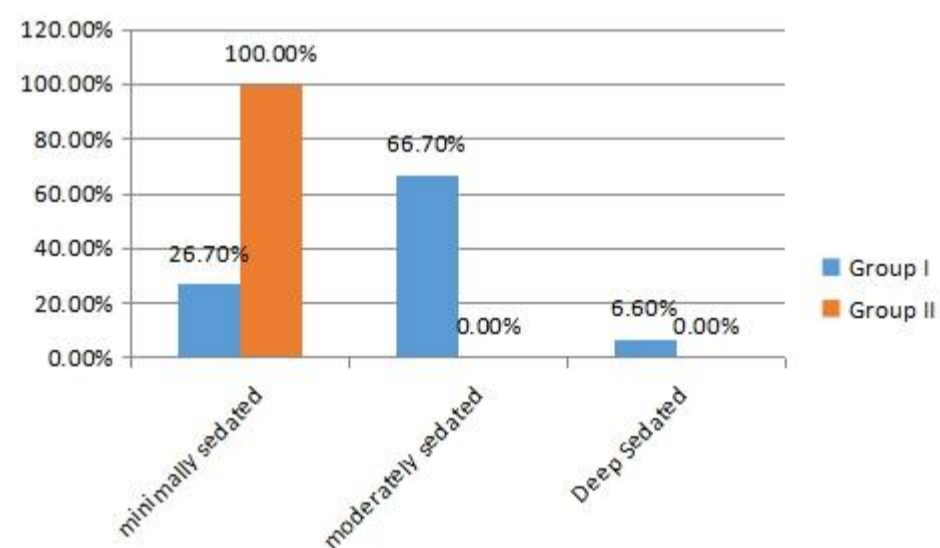
Graph 9: Level of sedation scale for both the groups.

EASE OF TREATMENT COMPLETION

The Ease of treatment completion between both groups is summarized in Table 11 and Graph 10. Among the subjects in the Group I INMK, 46% had good ease of treatment completion and 53.3%. had excellent ease of treatment completion. In the Group II INMF, 66.7% had good ease of treatment completion and 33.3%. had fair ease of treatment completion. The intergroup comparison between the two groups was statistically significant when analysed using the Chi Square test showing Group I INMK was excellent in ease of treatment complication while Group II INMF good in respect to ease of treatment complication.

	Fair	Good	Excellent	P value
Group I INMK	0	14	16	
	.0%	46.7%	53.3%	0.001*
Group II INMF	10	20	0	
	33.3%	66.7%	.0%	

Chi Square test with p value less than 0.05 is significant.

Table 11: Ease of treatment completion for both the groups
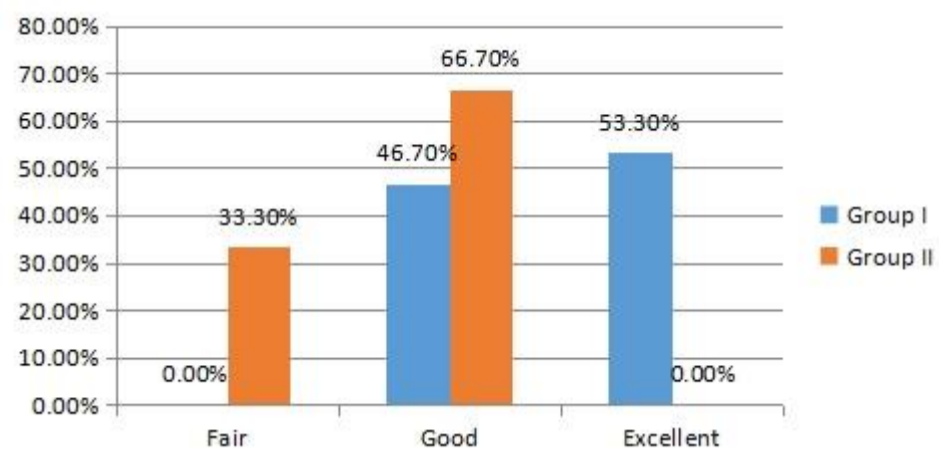
Graph 10: Ease of treatment completion for both groups

POSTOPERATIVE COMPLICATION

Post-operative complications between the groups are summarised in Table 12 and Graph 11. Among the subjects in the Group I INMK, 100% of the subjects had no complications. In the Group II INMF, 100% of the subjects had no complications. The intergroup comparison between the two groups was statistically non-significant when analysed using Chi-Square test.

	No Complication	Complication Present	P value
Group I	30	0	
INMK	100.0%	0%	1.000
Group II	30	0	
INMF	100.0%	0%	

Chi Square test with p value of more than 0.05 is non-significant.

Table 12: Post-operative complications for both groups
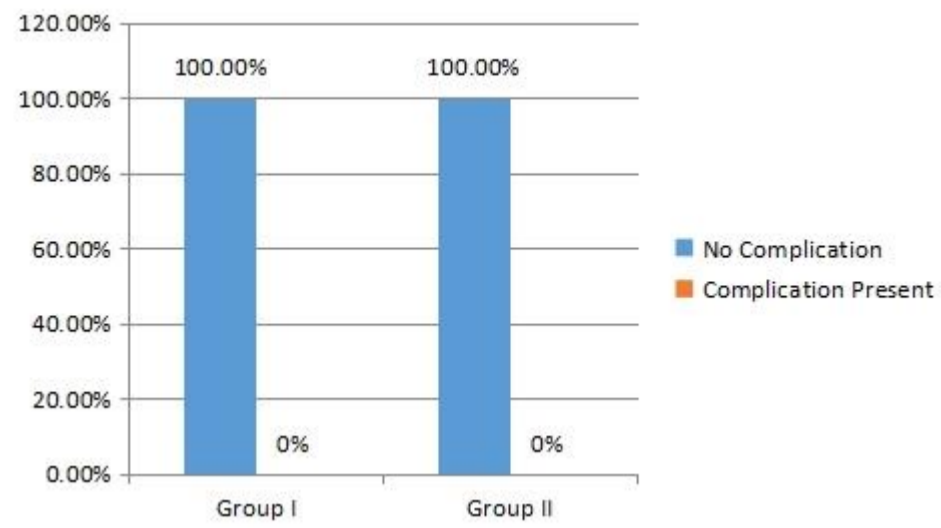
Graph 11: Post-operative complications for both the groups

RECOVERY TIME

The recovery time of both groups is summarized in Table 13 and Graph 12. Comparing the mean independent t-test showed, that the recovery time was significantly higher in the Group I INMK (36.93 min) as compared to Group II INMF (31.86 min).

	Mean	Std Dev	Std Error	P value
Group I INMK	36.9333	3.34806	.86447	0.001*
Group II INMF	31.8667	2.03072	.52433	

Independent t test with p value less than 0.05 is significant.

Table 13: Recovery time for both the groups after 30 minutes from treatment completion.
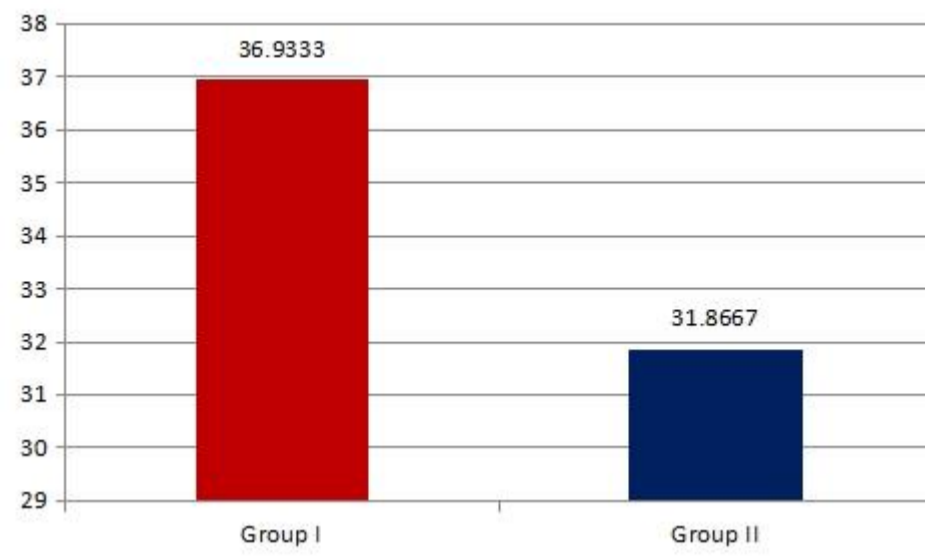
Graph 12: Recovery time for both the groups after 30 minutes from treatment completion.

DISCHARGE TIME

The discharge time of both groups is summarized in Table 14 and Graph 13. Comparing the mean independent t-test showed, that the discharge time was significantly higher in the Group I INMK (49.20 min) as compared to Group II INMF (25.46 min).

	Mean (min)	Std Dev	Std Error	P value
Group I INMK	49.2000	6.78444	1.75173	0.001*
Group II INMF	25.4667	5.02660	1.29786	

Independent t-test with p value less than 0.05 is significant

Table 14: Discharge time for both the groups after 60 minutes from recovery
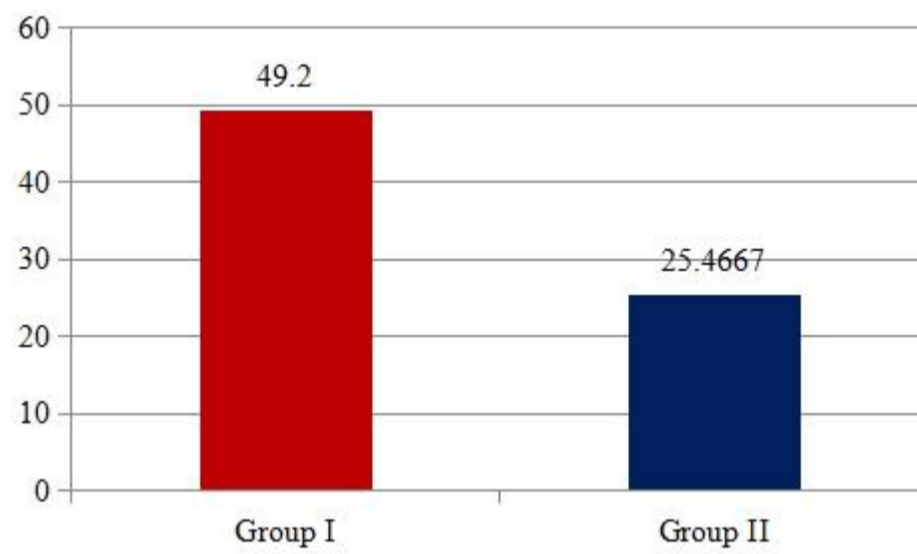
Graph 13: Discharge time for both the groups after 60 minutes from recovery

DISCUSSION

Pediatric healthcare necessitates a specialized approach that emphasizes the emotional well-being of children alongside addressing their physical health, particularly in the context of dental treatments and day-case surgeries. Poor oral health in children often results from a lack of awareness and avoidance driven by anxiety and fear of pain during procedures. Pre-operative anxiety in children, as noted by Litke J et al. (2012)[78], can lead to various adverse outcomes, making effective communication of treatment necessary and challenging.

Pediatric dentists play a crucial role in minimizing discomfort and anxiety during procedures to ensure positive experiences and prevent recall of unpleasant encounters. While physical restraints and behavior modification have long been used as traditional methods in an attempt to manage uncooperative children, conscious sedation administered by skilled pediatric dentists is considered a safe and reliable alternative. Procedural sedation, as suggested by Jorgensen et al. (1992)[79] and Hazha Ibrahim (2019)[80], is well-tolerated, efficient, and a more cost-effective alternative, offering a practical solution for managing apprehensive children without resorting to general anesthesia. This approach proves minimally invasive, effective, and not only reduces patient anxiety but also alleviates parental discomfort. By addressing the unique challenges in pediatric care, procedural sedation aims to create a positive and comfortable healthcare experience, recognizing the lasting impact of early traumatic encounters on a child's physical and emotional well-being.

For years, pediatric dentists have explored optimal methods for administering sedative drugs. Non-invasive drug delivery systems, such as oral, transdermal, and transmucosal systems, offer several potential advantages compared to invasive alternatives like intravenous and intramuscular routes. In the realm of sedation routes for children, the oral route emerged as the most frequently employed and broadly accepted. Despite being regarded as the oldest and most readily accepted method among children, Silver T. et al. (1994)[81] and Davies FC (1998)[82], noted that the reliability of the oral route is compromised due to first-pass metabolism, resulting in a longer recovery time and reported efficacy ranging from 60% to 76%.[82,83] This viewpoint is reinforced by Fallahinejad G M (2017)[83], highlighting the main drawbacks of oral sedation, including its delayed onset, extended recovery period, and high first-pass metabolism.[83]

Consequently, transdermal and transmucosal systems bypass hepatic first-pass metabolism and the gastrointestinal degradation associated with oral drug administration. As suggested by Ashburn M.A. (1991), transdermal and transmucosal drug delivery systems allow for "titration to effect," facilitating rapid cessation of drug administration in case of toxicity.[84] Primosch RE et al. (2001) concluded in their study that transmucosal routes, including intranasal, sublingual, and buccal administration, were effective due to the rich mucosal blood supply. Additionally, they noted that compliance with nasal sedation is easier to achieve in younger children compared to oral sedation.[85]The rising popularity of the intranasal route for procedural sedation can be attributed to its swift onset, potentially facilitated by the rapid drug access to cerebrospinal fluids and interaction with the subarachnoid space via the olfactory nerve and its sheath [87]. Intranasal administration is a simple and noninvasive technique, avoiding potential complications associated with intramuscular injections, such as inadvertent intravenous or arterial injection, nerve injury, or infection. Wood M et al. (2010) found intranasal drug administration to be a safe and effective method of procedural sedation.[31] Despite several advantages, as reported by Klein EJ et al. (2011), a few drugs administered nasally may not be well-tolerated due to their acidic potential, causing a burning sensation and pain during administration.[87]Traditionally, drops have been favored by several authors for intranasal sedation in uncooperative pediatric dental patients, but there has been a surge in popularity for atomized intranasal administration. Primosch RE et al. (2005) and Griffith N et al. (2005) reported that using an atomizer instead of drops enhanced patient tolerance.[88,89] Pandey et al. (2011) found that employing an atomizer for procedural sedation analgesia in uncooperative pediatric dental patients proved to be an effective alternative.[90] Based on this precedent, we opted for an atomizer for the intranasal administration of ketamine and fentanyl in our study.Over the decades, pediatric dentists worldwide have actively sought the most effective agents for procedural sedation in their practice. While various drugs have been used via different pathways, none have definitively emerged as the ideal solution. Although many sedative drugs effectively reduce fear and anxiety in pediatric patients, they fall short of providing adequate analgesia for painful procedures. To address this limitation, an effective analgesio-sedative combination is required, acting as a dual-purpose tool in procedural sedation—managing both fear/anxiety and addressing pain during procedures.Folayan MO et al. (2002) suggested that different available agents, such as chloral hydrate, promethazine, hydroxyzine, midazolam, ketamine, nitrous oxide, sevoflurane, propofol, and opioids, can be administered alone or in combination.[91] Our study introduces a novel approach by combining a sedative, like midazolam, with an analgesic—either ketamine or fentanyl—both known for their potent analgesic effects. Through simultaneous sedation and analgesia, this analgesia-sedative combination aims to enhance the overall experience for young patients, aligning with the ongoing commitment to enhancing safety and comfort in pediatric dental care.

Midazolam, a short-acting benzodiazepine, exerts therapeutic and adverse effects by acting on GABA receptors. It produces anterograde amnesia, relaxation of the muscles, drowsiness, induction of sleep, reduction of anxiety, and anticonvulsant properties. It is generally administered in combination with opioids for painful procedures as it does not have any inherent analgesic properties.[92] Rech et al. (2017) recommended an intranasal dosage range of 0.1 to 0.5 mg/kg of midazolam in pediatric patients to achieve sufficient anxiolysis during procedural sedation while minimizing the risk of adverse drug reactions.[93] Studies by Johnson et al. (2010) , Tavassoli et al. (2014) and Mahdavi A. et al. (2018) have specifically identified 0.3 mg/kg as an effective dose in reducing anxiety.[94,95,96]

Ketamine, utilized since 1970, functions as a dissociative agent by inducing a functional and electrophysiological dissociation between the thalamocortical and limbic brain areas. This results in a "trance-like cataleptic" state characterized by profound analgesia and amnesia while maintaining protective airway reflexes, spontaneous respiration, and cardiopulmonary stability. According to Armfield J. and Heaton L. (2013), ketamine is particularly well-suited for pediatric procedures, offering superior sedation with fewer respiratory complications.[12] Numerous studies have investigated the use of intranasal ketamine at various doses to induce sedative and analgesic effects in children undergoing procedural sedation. The literature demonstrates variations in the frequency and dosage of intranasal ketamine, with single-atomized doses ranging from 2 to 10 mg/kg body weight. In the study conducted by Abrams et al. (1993), administering a 3-6 mg/kg body weight intranasal dose of ketamine resulted in minimal sedation depth.[97] Tsze et al. (2012) investigated three different doses (3, 6, and 9 mg/kg body weight), determining that 9 mg/kg provided sufficient sedation depth compared to other doses, with 6% of sedation failures observed at 3 mg/kg and 6 mg/kg doses.[98] Ibrahim M. (2014) found that a 7 mg/kg intranasal ketamine dose was both safe and effective in inducing moderate sedation and facilitating parental separation. [99]

Fentanyl, a potent opioid, is known for its rapid onset of action and has minimal sedation effects while maintaining hemodynamic stability. This makes it highly effective in managing acute, moderate to severe pain in pediatric patients. Its efficient absorption through the nasal mucosa is attributed to its high lipophilicity and low molecular weight, enhancing its utility in pediatric pain management. Mace SE (2004) proposed that when combined with a sedative, fentanyl can provide mild sedative and anxiolytic effects. [100] Williams JM et al. (2019) suggested intranasal fentanyl is recommended to be dosed at 2 to 5 mcg/kg. [101] However, studies conducted by researchers such as Raynolds et al. (2017), Quinn et al. (2018) and Seiler et al.(2019) have found that 1.5 mcg/kg body weight of intranasal fentanyl is potent in providing analgesia. [102,103,104]

The insights from the aforementioned studies contribute to a comprehensive understanding of the optimal therapeutic doses for each necessary drug, thereby ensuring their safety and efficacy when administered independently. Considering the synergistic effects arising from the combination of these drugs, we meticulously selected a dosage that not only resides comfortably within the therapeutic range but also accentuates their collective potency. This strategic dosage selection not only achieves the dual outcome of analgesia and sedation in concert but does so within the well-defined boundaries of safety and effectiveness. Thus, our approach capitalizes on the symbiotic interactions between these drugs, harmonizing analgesic and sedative effects seamlessly, all while upholding a delicate equilibrium of safety and efficacy.

Therefore, in our current study, we opted for a dosing regimen: Group I INMK (0.3 mg/kg of midazolam spray and 7 mg/kg of intranasal ketamine administered via mucosal atomizer device (MAD) and Group II INMF (0.3 mg/kg of midazolam spray and 1.5 mcg/kg of intranasal fentanyl administered via MAD). To address potential ketamine-induced excessive salivation beforehand, we preemptively administered glycopyrrolate intramuscularly at 0.1 ml per kg body weight in Group I INMK.

This study aimed to assess the safety and effectiveness of two intranasally administered analgesia-sedative combinations in children aged 3 to 7 years, with a mean age of 4.10 years (refer to Table 2 and Graph 1). Children in this age group, especially those between the ages of 3 and 5, may go through periods of severe emotional distress due to hospital stays, separation anxiety, and unfamiliar environments.[105] Factors such as the fear of separation from parents and discomfort in unusual setting contribute to heightened emotional responses. Additionally, children within this age range may lack a complete understanding of the necessity of their surgical procedure.The present study observed a markedly higher level of acceptability during administration for intranasal midazolam-ketamine (INMK) compared to intranasal midazolam-fentanyl (INMF), as evident in the data presented in Table 3 and Graph 2. This preference can be attributed to a notable distinction: unlike opioids, ketamine administration does not elicit the release of histamine. This absence of histamine release is crucial as it mitigates nasal itching and congestion, a factor highlighted by White PF (1982).[106] Moreover, both combinations include midazolam, which, when administered intranasally, is known to induce a burning sensation in the nasal mucosa. This observation finds support in the works of Lee-Kim SJ et al. (2004) and Peerbhay F et al. (2016), whose respective studies concluded that the primary drawback of intranasal midazolam administration was the reported burning sensation in the nasal mucosa. [107,108]

In our investigation, the intranasal midazolam-ketamine (INMK) combination exhibited a swifter onset time, registering a mean value of 7.40 minutes, in contrast to the intranasal midazolam-fentanyl (INMF) combination, which demonstrated a more prolonged onset time with a mean value of 12.46 minutes (refer to Table 4 and Graph 3). The onset times referenced in the literature are 5.13 minutes for intranasal ketamine (AlSarheed MA. 2016), 5 minutes for intranasal midazolam, and up to 10 minutes for intranasal fentanyl (Hudson, 2017).[109,110] Our study validates these established onset times, noting a slightly longer onset time in the INMF group at 12.46 minutes while emphasizing the comparative advantage of the INMK Group with a faster onset time. This finding aligns with Agrawal et al.'s (2023) research, which similarly reported a quicker onset time for INMK (0.2 mg/kg midazolam and 4 mg/kg ketamine) compared to INMF (0.2 mg/kg midazolam and 2 mcg/kg fentanyl).[77]

This extended onset time observed in the INMF group in our study, and a slightly longer onset time when compared with similar studies, can likely be attributed to specific characteristics of the fentanyl administration in our protocol. The use of a lower dose (1.5 mcg/kg) of fentanyl in the INMF group in our study likely contributed to the delayed onset compared to the INMK group and other studies where fentanyl is typically administered at a dose of 2 mcg/kg, as opioids often exhibit dose-dependent effects.[111] Moreover, the decision to dilute the fentanyl with normal saline to achieve the necessary volume for delivery via MAD might have impacted the pharmacokinetics. Dilution can potentially slow the absorption rate of the drug, resulting in a delayed onset of action.[111] This combination of fentanyl dose and its dilution could explain the observed differences in onset times between the INMF and INMK groups within our study, as well as the variations when compared to similar studies, highlighting the importance of dose considerations and drug formulation in intranasal drug delivery. The explanation provided corresponds to demonstrated early peak of sedation (Table 5 and Graph 4) observed in the INMK group when compared to the INMF group in our study.[111]

In the current study, hemodynamic parameters such as pulse (Table 6, Graph 5), blood pressure (Table 7,8, Graph 6,7), and oxygen saturation (Table 9, Graph 8), remained within 10% of baseline values. Consequently, the observed changes were deemed insignificant and did not necessitate intervention.

During the intra-operative period, a comparative analysis of hemodynamic parameters revealed that the INMK group exhibited a transient elevation in both pulse rate and blood pressure compared to the INMF group. This phenomenon can be attributed to the well-documented tendency of ketamine to induce a mild to moderate, temporary surge in blood pressure, heart rate, and cardiac output, primarily through its impact on sympathetic activity.[112] Moreover, studies conducted by Stanley TH (1978) and Webster LR (1978) have underscored the occurrence of bradycardia following fentanyl administration, elucidating its mechanism as stimulation of the vagal nucleus in the medulla, thereby influencing heart rate and cardiac functions.[113] In contrast, intranasal midazolam, as suggested by Narendra PL et al (2015), Fei J et al (2017), and Lang B et al (2022), tends to exert minimal fluctuation or a minor influence on respiratory and cardiovascular parameters.[114,115,116] This implies that intranasal midazolam administration results in comparatively steadier effects on these hemodynamic aspects during the intra-operative period.

Moreover, the analysis of oxygen saturation (SPO2) revealed a non-significant difference from baseline at all the observed time intervals in both groups. This observation may be attributed to the well-documented property of ketamine, highlighted by Suleiman Z (2012), in preserving normal pharyngeal-laryngeal reflexes and respiratory stimulation.[117] In contrast, Clavijo CF et al. (2012) reported respiratory depression associated with fentanyl due to its action on mu-opioid receptors (MORs) expressed in brainstem regions controlling breathing.[118] Despite the acknowledged potential of benzodiazepine-opioid combinations to induce respiratory depression, our study did not detect any such events. This corresponded with the findings of the study conducted by Agrawal A et al. (2023), who administered doses of 0.2 mg/kg midazolam and 2 mcg/kg fentanyl and Lobb D et al. (2018), who utilized concentrations of 1mg/ml midazolam and 5mcg/ml fentanyl, both of which did not report any episodes of respiratory depression. [77,119]

In the comparison of sedation levels between the two groups (refer to Table 10 and Graph 9), intranasal midazolam-ketamine (INMK) achieved a range of minimal to moderate sedation. In contrast, intranasal midazolam-fentanyl (INMF) exclusively induced minimal sedation in all participants. This discrepancy likely arises from the robust combination dose of ketamine (7mg/kg) and midazolam (0.3 mg/kg) in INMK, synergizing their effects to produce varied levels of sedation. In contrast, the midazolam (0.3 mg/kg) combined with fentanyl (1.5 mcg/kg) in INMF was found to primarily geared toward providing analgesia, resulting in insufficient sedation for most participants. Thus, while INMK offered a spectrum of sedation, INMF predominantly yielded minimal sedation outcomeIn our study, it was evident that some participants in the INMK group experienced instances of deep sedation. This can be attributed to the synergistic effect of the sedative properties of midazolam and the dissociative anesthetic effect of ketamine. This observation resonated with Ibrahim M's 2014 study, where the administration of ketamine at 7 mg/kg, coupled with the addition of midazolam at a dose insufficient for

independent sedation, achieved a profound level of sedation.[99] The assessment of Ease of Treatment Completion, as per the modified AAPD 2006 criteria by Padmanabhan et al. (2009), revealed a significant superiority in Group INMK compared to INMF. The majority of participants in the INMK group were notably quiet and cooperative, leading to a treatment process completed without difficulty, as indicated in Table 11 and Graph 10. This aligned with findings from Agrawal A et al. (2023), who similarly reported a higher frequency of ease of treatment completion in the INMK group compared to the INMF group.[77] One of the objectives of our study was to assess the safety (table 12 and Graph 11) of intranasal midazolam-ketamine (INMK) and intranasal midazolam-fentanyl (INMF) as procedural sedation agents for uncooperative pediatric patients. Notably, there were no major adverse effects reported in either group during both the intraoperative and postoperative periods. This observation correlated with Ibrahim M.'s 2014 study, demonstrating that the administration of intranasal ketamine at 7 mg/kg, combined with 0.2mg/kg IV midazolam, attained a profound level of sedation without any noted adverse effects, highlighting a favorable safety profile.[99] Moreover, the safety profile of the intranasal midazolam-ketamine combination is supported by the work of Roelofse J. A et al. (2004), who used a combination of intranasal midazolam and ketamine in 25 children and observed no adverse effects, affirming the safety and efficacy of this combination.[105] Consequently, no evidence of emergence and excitatory phenomena was observed both intra and post-operatively. This absence of adverse reactions is likely due to the combined effects of midazolam and ketamine, with midazolam, a benzodiazepine, potentially counteracting and mitigating the emergence of excitatory effects typically associated with ketamine administration (Suleiman Z 2012).[117] Our study aligned with the findings of Kaur T et al. (2023), supporting the safety and efficacy of the intranasal midazolam-fentanyl combination in sedating 50 children aged 3-8 years [midazolam (0.2 mg/kg)-fentanyl (2 µg/kg)], with no observed adverse effects.[120] Following the recommendations of Williams JM et al. (2019) to minimize adverse drug reactions (ADRs) while ensuring sufficient analgesia and anxiolysis during procedural sedation, our selected dosages for fentanyl (1 to 2 mcg/kg) and midazolam (0.1 to 0.5 mg/kg) in pediatric patients fell within these established limits.[101] This strategic dosage selection further contributes to the safety profile of the sedation protocol employed in our study. Our investigation demonstrated that the intranasal midazolam-ketamine (INMK) group exhibited a longer recovery time (refer to Table 13 and Graph 12) and discharge time (refer to Table 14 and Graph 13) compared to the intranasal midazolam-fentanyl (INMF) group. This aligns with the findings of Agrawal A et al. (2023), who similarly reported a faster recovery with the midazolam-fentanyl combination compared to midazolam-ketamine.[77] Additionally, the findings of Koirala B (2006) also support our results, concluding that ketamine, whether administered alone or in combination with midazolam is associated with a longer recovery time compared to midazolam alone.[121] These consistent findings underscore the impact of the specific sedative agents on recovery times, emphasizing the importance of considering these factors when selecting an intranasal sedation approach for pediatric patients. In conclusion, this study underscores the efficacy and safety of the intranasal midazolam-ketamine and midazolam-fentanyl combination for procedural sedation in pediatric dental care. The study highlights the reliability, success, and invaluable role of the intranasal route of sedation administration, particularly for managing anxious and uncooperative children requiring dental procedures. The optimal sedation agent and route should exhibit rapid onset, maintain adequate sedation levels, and facilitate swift recovery to minimize the unnecessary duration of children's stay in the dental office. In light of our findings, the combinations of intranasal midazolam (0.3 mg/kg) - ketamine (7 mg/kg) and intranasal midazolam (0.3 mg/kg) - fentanyl (1.5 mcg/kg) stand out as promising, safe, and effective analgesio-sedative options. Both combinations played a significant role in rapidly achieving successful anxiolysis and analgesia, emphasizing their potential as valuable choices for procedural sedation in pediatric dental care. Furthermore, our study demonstrated that intranasal midazolam-ketamine exhibits a rapid onset, and early peak sedation, and provides moderate sedation, accompanied by favorable drug acceptability. On the other hand, intranasal midazolam-fentanyl induces minimal sedation with faster recovery and discharge. These nuanced differences in the profiles of the two combinations provide valuable insights into tailoring sedation approaches based on specific patient needs and procedural requirements.

CONCLUSIONS

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

Through the course of our study, based on the observations, the following conclusions were derived:

- Intranasal midazolam-ketamine combination and intranasal midazolam-fentanyl combination, both provided sedation and were deemed safe in managing uncooperative pediatric dental patients.

- The intranasal midazolam-ketamine combination demonstrated notably greater efficacy, achieving moderate sedation in the majority of participants whereas the combination of intranasal midazolam-fentanyl resulted in minimal sedation in all the participants.

- Intranasal midazolam-ketamine combination reported rapid onset, early peak sedation accompanied by favorable drug acceptability while intranasal midazolam-fentanyl combination reported faster recovery and shorter discharge time.

- In both the experimental groups the hemodynamic parameters such as pulse rate, blood pressure, and oxygen saturation remained within acceptable physiological limits, and no postoperative complications were seen.

REFERENCES

American Academy of Pediatric Dentistry. Policy on medically necessary care. Pediatr Dent 2015; 37(special issue):18-22.

Milnes AR, Maupomé G, Cannon J. Intravenous sedation in paediatric dentistry using midazolam, nalbuphine and droperidol: Department of Oral Health Sciences, Faculty of Dentistry, University of British Columbia, Vancouver,Canada.Paediatric Dentistry. 2000; 22(2):113-119

Lane RD, Schunk JE. Atomized intranasal midazolam use for minor procedures in the pediatric emergency department. Pediatr Emerg Care 2008;24:300-3.

Natarajan Surendar, M., Kumar Pandey, R., Kumar Saksena, A., Kumar, R., & Chandra, G. (2014). A Comparative evaluation of Intranasal Dexmedetomidine, Midazolam and Ketamine for their sedative and analgesic properties: A Triple Blind Randomized Study. Journal of Clinical Pediatric Dentistry, 38(3), 255–261.

Green SM, Johnson NE. Ketamine sedation for pediatric procedures: Part 2, Review and implications. Ann Emerg Med 1990;19:1033-46.

Liu J, Du M, Liu L, et al. Sedation effects of intranasal dexmedetomidine combined with ketamine and risk factors for sedation failure in young children during transthoracic echocardiography. Paediatr Anaesth 2019;29:77-84.

Cole J, Shepherd M, Young P. Intranasal fentanyl in 1-3-year-olds: a prospective study of the effectiveness of intranasal fentanyl as acute analgesia. Emerg Med Australas 2009;21:395-400.

Kress HG, Orońska A, Kaczmarek Z, et al. Efficacy and tolerability of intranasal fentanyl spray 50 to 200 microg for breakthrough pain in patients with cancer: a phase III, multinational, randomized, double-blind, placebo controlled, crossover trial with a 10-month, open-label extension treatment period. Clin Ther 2009;31:1177-91.

Del Pizzo J, Callahan JM. Intranasal medications in pediatric emergency medicine. Pediatr Emerg Care 2014;30:496-501.

Greenbaum P .E, Melamed B.G.Pretreatment Modelling: A technique for reducing children's fear in dental operatory. Dental Clinics of North AmericaVolume 32, Issue 4, October 1988, Pages 693-704.

De Jong, Jeroen R et al. "Reduction of pain-related fear in complex regional pain syndrome type I: the application of graded exposure in vivo." Pain vol. 116, 3 (2005): 264-275.

Armfield, J., & Heaton, L. (2013). Management of fear and anxiety in the dental clinic: a review. Australian Dental Journal, 58(4), 390–407.

Folayan, M. O., Faponle, A., & Lamikanra, A. (2002). A review of the pharmacological approach to the management of dental anxiety in children. International Journal of Paediatric Dentistry, 12(5), 347–354.

Wolfe, Timothy R, and Tony Bernstone. "Intranasal drug delivery: an alternative to intravenous administration in selected emergency cases." Journal of emergency nursing vol. 30,2 (2004): 141-7.

Thorne, R., Hrabětová, S. & Nicholson, C. Diffusion measurements for drug design. Nature Mater 4, 713 (2005).

Corbo DC, Liu JC, Chien YW. Drug absorption through mucosal membranes: effect of mucosal route and penetrant hydrophilicity. Pharm Res. 1989 Oct;6(10):848-52.

Pires, Anaísa et al. "Intranasal drug delivery: how, why and what for?" Journal of pharmacy & pharmaceutical sciences : a publication of the Canadian Society for Pharmaceutical Sciences, Societe canadienne des sciences pharmaceutiques vol. 12,3 (2009)

Current DJ.Pharmacology for anesthesia. Google book results.p-245. https://books.google.com/books?id=_Du2bfrO9FwC.

Paul S, Marangos P, Skolnick P. The benzodiazepine-GABA-chloride ionophore receptor complex: common site of minor tranquilizer action. Biol Psychiatry 1981; 16: 213-29.

Heizmann P, Eckert M, Ziegler WH: Pharmacokinetics and bioavailability of midazolam in man. Br J Clin Pharmaco116(Suppl 1):43S-49S, 1983.

Kupietzk A, Houp IM, Midazolam: a review of its use for conscious sedation of children. Pediatric Dentistry: July/August 1993 - Volume 15, Number 4 237.

Greenblatt DJ, Abernethy DR, Locniskar A, Harmatz JS, Limjuco RA, Shader RI: Effect of age, gender, and obesity on midazolam kinetics. Anesthesiology 61:27-35, 1984.

AllonenH, Ziegler G, Klotz U: Midazolam kinetics. Clin Pharmacol Ther 30:653-61, 1981.

Reves JG, Fragen RJ, Vinik HR, Greenblatt DJ: Midazolam: Pharmacology and uses. Anesthesiology 62:310-24, 1985.

Versed package insert (Roche—US), Rev 4/97, Rec 8/97

Kanto J. Midazolam: the first water-soluble benzodiazepine. Pharmacology, pharmacokinetics and efficacy in insomnia and anesthesia. Pharmacotherapy 1985; 5: 138-55.

Messina A, Paranicas M, Yao F, et al. The effect of midazolam on left ventricular pump performance and contractility in anesthetized patients with coronary artery disease: effect of preoperative ejection fraction. Anesth Analg 1995; 81: 793-9.

McNulty S, Gratch D, Kim J. Comparative vascular effects of midazolam and lorazepam administered during cardiopulmonary bypass. Anesth Analg 1994; 79: 675-80.

Singh N, Pandey RK, Saksena AK, Jaiswal JN. A comparative evaluation of oral midazolam with other sedatives as premedication in pediatric dentistry. J Clin Pediatr Dent. 2002 Winter;26(2):161-4.

Pisalchaiyong T, Trairatvorakul C, Jirakijja J, Yuktarnonda W Comparison of the effectiveness of oral diazepam and midazolam for the sedation of autistic patients during dental treatment. Pediatr Dent. 2005 May-Jun;27(3):198-206.

Damle SG, Gandhi M, Laheri V .Comparison of oral ketamine and oral midazolam as sedative agents in pediatric dentistry. J Indian Soc Pedod Prev Dent. 2008 Sep;26(3):97-101.

Wood M The safety and efficacy of using a concentrated intranasal midazolam formulation for paediatric dental sedation.SAAD Dig. 2011 Jan; 27:16-23.

Ransford NJ, Manley MC, Lewis DA, Thompson SA, Wray LJ, Boyle CA, Longman LP. Intranasal/intravenous sedation for the dental care of adults with severe disabilities: a multicentre prospective audit. Br Dent J. 2010 Jun;208(12):565-9.

Shavit I, Feraru L, Miron D, et al. Midazolam for urethral catheterisation in female infants with suspected urinary tract infection: a case-control study.Emerg Med J 2014;31:278–280.

Chopra R, Mittal M, Bansal K, Chaudhuri P. Buccal midazolam spray as an alternative to intranasal route for conscious sedation in pediatric dentistry. J Clin Pediatr Dent. 2013 winter; 38(2):171-3.

Sheta SA, Al-Sarheed MA, Abdelhalim AA. Intranasal dexmedetomidine vs midazolam for premedication in children undergoing complete dental rehabilitation: a double-blinded randomized controlled trial. Paediatr Anaesth. 2014 Feb;24(2)

Musani IE, Chandan NV. A comparison of the sedative effect of oral versus nasal midazolam combined with nitrous oxide in uncooperative children. Eur Arch Paediatr Dent. 2015 Oct;16(5):417-24.

Shanmugaavel AK, Asokan S, John JB, Priya PR, Raaja MT Comparison of Drug Acceptance and Anxiety Between Intranasal and Sublingual Midazolam Sedation. Pediatr Dent. 2016 Mar-Apr;38(2):106-11.

Ghajari MF, Ansari G, Hasanbeygi L, Shayeghi S. Conscious Sedation Efficacy of 0.3 and 0.5 mg/kg Oral Midazolam for Three to Six Year-Old Uncooperative Children Undergoing Dental Treatment: A Clinical Trial. J Dent (Tehran). 2016 Mar;13(2):101-107.

Peerbhay F, Elsheikhomer AM. Intranasal Midazolam Sedation in a Pediatric Emergency Dental Clinic. Anesth Prog. 2016 Fall;63(3):122-30.

Manso MA, Guittet C, Vandenhende F, Granier LA. Efficacy of oral midazolam for minimal and moderate sedation in pediatric patients: a systematic review. Paediatr Anaesth. 2019 Sep 20.

Kelly K., A little book of ketamine. Ronin publishing group. Edi 1st. 1999. www. roninpub.com.

Craven, R. "Ketamine." Anaesthesia vol. 62 Suppl 1 (2007): 48-53.

Report on the risk assessment of ketamine in the framework of the joint action on new synthetic drug, Luxembourg: Office for Official Publications of the European Communities, 2002. http://www.emcdda.org

Rosenbaum SB, Gupta V, Patel P, et al. Ketamine. [Updated 2022 Nov 24]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan.

Juels NA, Windle LM, Talavera F, Schraga DE, Lovato ML, Orlewicz SM, Coleman EA, Dudley MR, Bailey RA.Procedural Sedation: Overview, Sedation Definitions, Pharmacologic Options for Procedural Sedation and Analgesia.Updated: Dec 20, 2022

Sleigh, J., Harvey, M., Voss, L., & Denny, B. (2014). Ketamine – More mechanisms of action than just NMDA blockade. Trends in Anaesthesia and Critical Care, 4(2-3), 76-81.

S. Grant, M.B., Ch.B.., Fs.A.R.C.S., W. S. Nimmo, M.B., Ch.B., M.R.C.P., F.F.A.R.C.S., J. A. Clements, Pharmacokinetics And Analgesic Effects Of I.M. And Oral Ketamine, Bja: British Journal Of Anaesthesia, Volume 53, Issue 8, August 1981, Pages 805–810,

Jevtovic-Todorovic, V., Wozniak, D. F., Benshoff, N. D., & Olney, J. W. (2001). A comparative evaluation of the neurotoxic properties of ketamine and nitrous oxide. Brain Research, 895(1-2), 264-267.

Ulugol, A., Dost, T., Dokmeci, D. et al. Involvement of NMDA receptors and nitric oxide in the thermoregulatory effect of morphine in mice. J Neural Transm 107, 515–521 (2000).

Adams HA, Biscoping J, Russ W, et al. [Sedative-analgesic medication in intensive care patients needing ventilator treatment]. Der Anaesthesist. 1988 Apr; 37(4):268-276.

Ebert, B et al. "Norketamine, the main metabolite of ketamine, is a non-competitive NMDA receptor antagonist in the rat cortex and spinal cord." European journal of pharmacology vol. 333,1 (1997): 99-104.

Flood, R. and Krauss, B. (2003) Procedural sedation and analgesia for children in the emergency department. Emergency Medicine Clinics of North America, 21, 121- 139.

Domino, E F Et Al. "Pharmacologic Effects of Ci-581, A New Dissociative Anesthetic, In Man." Clinical Pharmacology and Therapeutics Vol. 6 (1965): 279-91.

Graeme E. Correll, BE, Jahangir Maleki, Edward J. Gracely, P Jesse J. Muir, Ronald E. Harbut, Subanesthetic Ketamine Infusion Therapy: A Retrospective Analysis of a Novel Therapeutic Approach to Complex Regional Pain Syndrome, Pain Medicine, Volume 5, Issue 3, September 2004, Pages 263–275.

Reich, D L, and G Silvay. "Ketamine: an update on the first twenty-five years of clinical experience." Canadian journal of anaesthesia = Journal canadien d'anesthesie vol. 36,2 (1989): 186-97.

Bourke DL, Malit LA, Smith TC. Respiratory interactions of ketamine and morphine. Anesthesiology. 1987 Feb; 66(2):153-156.

Lau, T T, and P J Zed. "Does ketamine have a role in managing severe exacerbation of asthma in adults?" Pharmacotherapy vol. 21, 9 (2001): 1100-6.

https://legal-high-inhaltsstoffe.de/sites/default/files/uploads/ketamine.pdf

Fallahinejad Ghajari M, Ansari G, Soleymani AA, Shayeghi S, Fotuhi Ardakani F. Comparison of Oral and Intranasal Midazolam/Ketamine Sedation in 3-6-year-old Uncooperative Dental Patients. J Dent Res Dent Clin Dent Prospects. 2015 Spring;9(2):61-5.

Malhotra PU, Thakur S, Singhal P, Chauhan D, Jayam C, Sood R, Malhotra Y. Comparative evaluation of dexmedetomidine and midazolam-ketamine combination as sedative agents in pediatric dentistry: A double-blinded randomized controlled trial. Contemp Clin Dent. 2016 Apr-Jun;7(2):186-92.

Mehran M,Tavassoli-Hojjati S,Ameli N,Zeinabadi MS. Effect of Intranasal Sedation Using Ketamine and Midazolam on Behavior of 3-6 Year-Old Uncooperative Children in Dental Office: A Clinical Trial. Journal of Dentistry (Tehran, Iran), Jan 2017, 14(1):1-6

Poonai N, Canton K, Ali S, Hendrikx S, Shah A, Miller M, Joubert G, Rieder M, Hartling L. Intranasal ketamine for procedural sedation and analgesia in children: A systematic review. PLoS One. 2017 Mar 20;12(3):e0173253.

Ilasrinivasan, V Setty J, Shyamachalam, Mendiretta P. A Comparative Evaluation of the Sedative Effects of Nitrous Oxide-oxygen Inhalation and Oral Midazolam-Ketamine Combination in Children. Int J Clin Pediatr Dent. 2018 Sep-Oct;11(5):399-405

Sado-Filho J, Viana KA, Corrêa-Faria P, Costa LR, Costa PS. Randomized clinical trial on the efficacy of intranasal or oral ketamine-midazolam combinations compared to oral midazolam for outpatient pediatric sedation. PLoS One. 2019 Mar 11;14(3):e0213074.

Yongping Z, Xinyi L, Aming S, Qiang X, Tianqi Z, Mengmeng S, Xiong C, Xuemin S. The safety and efficacy of esketamine in comparison to dexmedetomidine during drug-induced sleep endoscopy in children with obstructive sleep apnea hypopnea syndrome: A randomized, controlled and prospective clinical trial. Front Pharmacol. 2022 Dec 1;13:1036509.

Rathi GV, Padawe D, Takate V, Dighe K, Bansode KK, Narwade AU. Comparative Evaluation of Ease of Dental Treatment and Clinical Efficiency of Midazolam vs Midazolam and Ketamine Combination for Sedation in Young Uncooperative Pediatric Patients: A Systematic Review. Int J Clin Pediatr Dent. 2022 Nov-Dec;15(6):680-686.

Wang J, Zeng J, Zhao N, Chen S, Chen Z, Liao J, Ran H, Yu C. Intranasal esketamine combined with oral midazolam provides adequate sedation for outpatient pediatric dental procedures: a prospective cohort study. Int J Surg. 2023 Jul 1;109(7):1893-1899.

Glick JL, Christensen T, Park JN, McKenzie M, Green TC, Sherman SG. Stakeholder perspectives on implementing fentanyl drug checking: Results from a multi-site study. Drug Alcohol Depend. 2019 Jan 01;194:527-532.

Wakeman SE, Chang Y, Regan S, Yu L, Flood J, Metlay J, Rigotti N. Impact of Fentanyl Use on Buprenorphine Treatment Retention and Opioid Abstinence. J Addict Med. 2019 Jul/Aug;13(4):253-257.

Hagedorn H, Kenny M, Gordon AJ, Ackland PE, Noorbaloochi S, Yu W, Harris AHS. Advancing pharmacological treatments for opioid use disorder (ADaPT-OUD): protocol for testing a novel strategy to improve implementation of medication-assisted treatment for veterans with opioid use disorders in low-performing facilities. Addict Sci Clin Pract. 2018 Dec 13;13(1):25.

Comer SD, Cahill CM. Fentanyl: Receptor pharmacology, abuse potential, and implications for treatment. Neurosci Biobehav Rev. 2019 Nov;106:49-57.

Jaikaria A, Thakur S, Singhal P, Chauhan D, Jayam C, Syal K. A Comparison of Oral Midazolam-ketamine, Dexmedetomidine-fentanyl, and Dexmedetomidine-ketamine Combinations as Sedative Agents in Pediatric Dentistry: A Triple-Blinded Randomized Controlled Trial. Contemp Clin Dent. 2018 Sep;9(Suppl 2):S197-S203.Chatrath V, Kumar R, Sachdeva U, Thakur M. Intranasal Fentanyl, Midazolam and Dexmedetomidine as Premedication in Pediatric Patients. Anesth Essays Res. 2018 Jul-Sep;12(3):748-753.

Chatrath V, Kumar R, Sachdeva U, Thakur M. Intranasal Fentanyl, Midazolam and Dexmedetomidine as Premedication in Pediatric Patients. Anesth Essays Res. 2018 Jul-Sep;12(3):748-753.

Cheng C, Tabbara N, Cheng C, Shah V. Intranasal Fentanyl for Procedural Analgesia in Preterm Infants. Front Pain Res (Lausanne). 2022 Jan 24;2:815014.

Alhaidari RI, AlSarheed MA. Post-Discharge Effects and Parents' Opinions of Intranasal Fentanyl with Oral Midazolam Sedation in Pediatric Dental Patients: A Cross-Sectional Study. Children (Basel). 2022 Jan 22;9(2):142.

Agarwal A, Ansari AA, Nath R, Chak RK, Singh RK, Khanna R, Singh PR. Comparative evaluation of intranasal midazolam-ketamine, dexmedetomidine-ketamine, midazolam-fentanyl, and dexmedetomidine-fentanyl combinations for procedural sedation and analgesia in pediatric dental patients: a randomized controlled trial. J Dent Anesth Pain Med. 2023 Apr;23(2):69-81.

Litke J, Pikulska A, Wegner T. Management of perioperative stress in children and parents. Part II--anaesthesia and postoperative period: Anaesthesiol Intensive Ther. 2012 Jul-Sep; 44(3):170-4.

Jorgensen, N.B. Local anesthesia and intravenous premedication. Anesth Prog, 13.1966; 168–169.

Hazha Ibrahim. Cost and Time Analysis of Procedural Sedation versus General Anesthesia in a Pediatric. University of Washington Committee: Travis Nelson, Chair Zheng Xu Sarat Thikkurissy 2019.

Silver T, Wilson C, Webb M. Evaluation of two dosages of oral midazolam as a conscious sedation for physically and neurologically compromised pediatric dental patients. Pediatric Dentistry. 1994; 16:350-359.

Davies FC, Waters M. Oral midazolam for conscious sedation of children during minor procedures. Emerg Med J. 1998; 15:244- 248.

Fallahinejad Ghajari, Masoud & Ansari, Ghassem & Zomorrodian, Sarira & Shayeghi, Shahnaz. (2017). Sedative Effect of Midazolam Elixir Compare to Vial Through Oral Route in Uncooperative Pediatric Dental Patients. J of Islamic Dental Association of IRAN. 29. 64-69.

Ashburn M.A., Stanley T.H. Non-Invasive Drug Delivery Systems for the Management of Postoperative Pain. In: Stanley T.H., Ashburn M.A., Anesthesiology and Pain Management. Developments in Critical Care Medicine and Anesthesiology, Springer, Dordrecht. 1991;24.

Primosch RE, Bender F. Factors associated with administration route when using midazolam for pediatric conscious sedation. ASDC J Dent Child. 2001 Jul-Aug; 68(4):233-8, 228.

Löwhagen,G. Granerus, H. Wetterqvist. Studies on Histamine Metabolism in Intrinsic Bronchial Asthma:1111/j.1398-9995.1979;tb 02009.

Klein EJ, Brown JC, Kobayashi A, Osincup D, Seidel K. A randomized clinical trial comparing oral, aerosolized intranasal, and aerosolized buccal midazolam. Ann Emerg Med. 2011 Oct;58(4):323-9.

Primosch RE, Guelmann Marcio. Comparison of Drops Versus Spray Administration of Intranasal Midazolam in Two-and Three-year old Children for Dental Sedation. Pediatr Dent, 27:5: 401–8, 2005.

Griffith N, Howell S, Mason DG. Intranasal midazolam for premedication of children undergoing day-case anaesthesia: Comparison of two delivery systems with assessment of intra-observer variability. Br J Anaesth, 81: 865–69, 1998.

Pandey RK ,Bahetwar SK ,Saksena AK, Girish Chandra. A Comparative Evaluation of Drops versus Atomized Administration of Intranasal Ketamine for the Procedural Sedation of Young Uncooperative Pediatric Dental Patients: A Prospective Crossover Trial. J Clin Pediatr Dent 36(1): 79–84 2011.

Folayan MO, Faponle A, Lamikanra A. Seminars on controversial issues. A review of the pharmacological approach to the management of dental anxiety in children. Int J Paediatr Dent 2002; 12: 347-54.

Kain ZN, Hofstadter MB, Mayes LC, Krivutza DM, Alexander G, Wang SM, et al. Midazolam: effects on amnesia and anxiety in children. Anesthesiology 2000; 93: 676-84.

Rech MA, Barbas B, Chaney W, Greenhalgh E, Turck C. When to Pick the Nose: Out-of-Hospital and Emergency Department Intranasal Administration of Medications. Ann Emerg Med. 2017 Aug;70(2):203-211.

Johnson E, Briskie D, Majewski R, Edwards S, Reynolds P. The physiologic and behavioral effects of oral and intranasal midazolam in pediatric dental patients. Pediatr Dent. 2010 May-Jun;32(3):229-38.

Tavassoli-Hojjati S, Mehran M, Haghgoo R, Tohid-Rahbari M, Ahmadi R. Comparison of oral and buccal midazolam for pediatric dental sedation: a randomized, cross-over, clinical trial for efficacy, acceptance and safety. Iran J Pediatr. 2014 Apr;24(2):198-206.

Mahdavi A, Fallahinejad Ghajari M, Ansari G, Shafiei L Intranasal Premedication Effect of Dexmedetomidine Versus Midazolam on the Behavior of 2-6-Year-Old Uncooperative Children in Dental Clinic. J Dent (Tehran). 2018 Mar;15(2):79-85.

Abrams, R et al. "Safety and effectiveness of intranasal administration of sedative medications (ketamine, midazolam, or sufentanil) for urgent brief pediatric dental procedures." Anesthesia progress vol. 40,3 (1993): 63-6.

Tsze S. D, Dale W. Steele, Jason T. Machan, Fatemeh Akhlaghi, and James G. Linakis, Intranasal Ketamine for Procedural Sedation in Pediatric Laceration Repair. Pediatric Emergency Care & Volume 28, Number 8, August 2012

Ibrahim M. A prospective, randomized, double blinded comparison of intranasal dexmedetomodine vs intranasal ketamine in combination with intravenous midazolam for procedural sedation in school aged children undergoing MRI. Anesth Essays Res. 2014 May-Aug;8(2):179-86.

Mace SE, Barata IA, Cravero JP, Dalsey WC, Godwin SA, Kennedy RM, et al. Clinical policy: evidence-based approach to pharmacologic agents used in pediatric sedation and analgesia in the emergency department. Ann Emerg Med 2004; 44: 342-77.

Williams JM, Schuman S, Regen R, Berg A, Stuart L, Raju J, Mabry W, Kink RJ. Intranasal Fentanyl and Midazolam for Procedural Analgesia and Anxiolysis in Pediatric Urgent Care Centers. Pediatr Emerg Care. 2020 Sep;36(9):e494-e499.

Reynolds SL, Bryant KK, Studnek JR, et al. Randomized Controlled Feasibility Trial of Intranasal Ketamine Compared to Intranasal Fentanyl for Analgesia in Children with Suspected Extremity Fractures. Acad Emerg Med 2017;24:1430-40.

Quinn K, Kriss S, Drapkin J, et al. Analgesic Efficacy of Intranasal Ketamine Versus Intranasal Fentanyl for Moderate to Severe Pain in Children: A Prospective, Randomized, Double-Blind Study. Pediatr Emerg Care 2018.

Seiler M, Staubli G, Landolt MA. Combined nitrous oxide 70% with intranasal fentanyl for procedural analgosedation in children: a prospective, randomised, double-blind, placebo-controlled trial. Emerg Med J 2019;36:142-7.

Roelofse JA, Shipton EA, de la Harpe CJ, Blignaut RJ. Intranasal sufentanil/midazolam versus ketamine/midazolam for analgesia/sedation in the pediatric population prior to undergoing multiple dental extractions under general anesthesia: a prospective, double-blind, randomized comparison. Anesth Prog. 2004;51(4):114-21..

White PF, Way WL, Trevor AJ. Ketamine–its pharmacology and therapeutic uses. Anesthesiology 1982;56:119-36.

Lee-Kim SJ, Fadavi S, Punwani I, Koerber A. Nasal Versus oral midazolam sedation for pediatric dental patients. J dent child (chic), MayAug, 71(2): 135–138, 2004.

Peerbhay F, Ahmed M. Intranasal Midazolam Sedation in aPediatric Emergency Dental Clinic. Anesth Prog (2016) 63 (3): 122–130.

AlSarheed MA. Intranasal sedatives in pediatric dentistry. Saudi Med J. 2016 Sep;37(9):948-56.

Hudson ,OH .Fentanyl. Pediatric and Neonatal Lxi-Drugs. Lexicomp, Inc,; 2017

Tripathi KD, In:General Pharmacological Principles. Essentials of medical pharmacology, ,8th Ed.. Pg.15-71.Jaypee Brothers Meical Publishers,2023

Goddard K, Sampson C, Bedy SM, Ghadban R, Stilley J. Effect of Ketamine on Cardiovascular Function During Procedural Sedation of Adults. Cureus. 2021 Mar 31;13(3):e14228.

Stanley TH, Webster LR. Anesthetic requirements and cardiovascular effects of fentanyl-oxygen and fentanyl-diazepam-oxygen anesthesia in man. Anesth Analg. 1978 Jul-Aug;57(4):411-6.

Narendra PL, Naphade RW, Nallamilli S, Mohd S. A comparison of intranasal ketamine and intranasal midazolam for pediatric premedication. Anesth Essays Res. 2015 May-Aug;9(2):213-8.

Fei J, Tang X, Liang H, Li Y, Tang J, Deng Y, et al. The preoperative sedation comparison of dexmedetomindine, midazolam, and ketamine on children with the pediatric tumor after surgery by nasal medicine delivery. Anti-tumor Pharmacy. 2017;7(6):702–707.

Lang B, Wang H, Fu Y, Zeng L, Huang L, Zhang Q, Chen S, Jia ZJ, Zhang L. Efficacy and safety of intranasal midazolam versus intranasal ketamine as sedative premedication in pediatric patients: a meta-analysis of randomized controlled trials. BMC Anesthesiol. 2022 Dec 22;22(1):399.

Suleiman Z, Ik K, Bo B. Evaluation of the cardiovascular stimulation effects after induction of anaesthesia with ketamine. J West Afr Coll Surg. 2012 Jan;2(1):38-52.

Clavijo CF, Rachael Rzasa Lynn, Uwe Christians and Jeffrey L. Galinkin. Intranasal Fentanyl for Breakthrough Pain Control. Clinical Medicine Insights: Therapeutics 2012:4

Lobb D, Clarke A, Lai H. Administration order of midazolam/fentanyl for moderate dental sedation. J Dent Anesth Pain Med. 2018 Feb;18(1):47-56.

Kaur T, Kumar P, Kundra TS, Kaur I. Comparison of intranasal midazolam-fentanyl with dexmedetomidine-fentanyl as pre-medication in the paediatric age group. Indian J Med Res. 2023 Jan;157(1):51-56.

Koirala B, Pandey RK, Saksena AK, Kumar R, Sharma S. A comparative evaluation of newer sedatives in conscious sedation. Journal of Clinical Pediatric Dentistry, 30: 273–276, 2006.
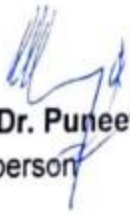
BABU BANARASI DAS UNIVERSITY

BBD COLLEGE OF DENTAL SCIENCES, LUCKNOW

INSTITUTIONAL RESEARCH COMMITTEE APPROVAL

The project titled "**A Comparative Evaluation Of Intranasal Ketamine-Midazolam Combination With Fentanyl-Midazolam Combination For Procedural Sedation In Pediatric Dental Patients: A Simple Randomised Sampling**" submitted by **Dr Sarwani Mishra** Postgraduate student in the **Department of Pediatric & Preventive Dentistry** for the Thesis Dissertation as part of MDS Curriculum for the academic year 2021-2024 with the accompanying proforma was reviewed by the Institutional Research Committee in its meeting held on **14th September, 2022** 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. Dr. Puneet Ahuja
Chairperson

Dr. Mona Sharma
Co-Chairperson

BABU BANARASI DAS UNIVERSITY
BBD COLLEGE OF DENTAL SCIENCES, LUCKNOW

BBDCODS/IEC/09/2022   Dated: 16th September, 2022

Communication of the Decision of the Xth Institutional Ethics Sub-Committee Meeting

IEC Code: 28

Title of the Project: A Comparative Evaluation Of Intranasal Ketamine- Midazolam Combination With Fentanyl-Midazolam Combination For Procedural Sedation In Pediatric Dental Patients: A Simple Randomised Sampling.

Principal Investigator: Dr Sarwani Mishra   **Department:** Pediatric & Preventive Dentistry

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

Type of Submission: New, MDS Project Protocol

Dear Dr Sarwani Mishra,

The Institutional Ethics Sub-Committee meeting comprising following members was held on 15th September, 2022.

1.	Dr. Lakshmi Bala Member Secretary	Prof. and Head, Department of Biochemistry
2.	Dr. Praveen Singh Samant Member	Prof. & Head, Department of Conservative Dentistry & Endodontics
3.	Dr. Jiji George Member	Prof. & Head, Department of Oral Pathology & Microbilogy
4.	Dr. Amrit Tandan Member	Professor, Department of Prosthodontics and Crown & Bridge
5.	Dr. Rana Pratap Maurya Member	Reader, Department of Orthodontics & Dentofacial Orthopaedics

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:

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

Dr. Lakshmi Bala
Member-Secretary
Institutional Ethics Sub-Committee (IEC)
BBD College of Dental Sciences
BBD University, Lucknow

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

BABU BANARASI DAS COLLEGE OF DENTAL SCIENCES

(Babu Banarasi Das University)

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

CHILD INFORMATION DOCUMENT

Study title: — **A COMPARATIVE EVALUATION OF INTRANASAL MIDAZOLAM – KETAMINE COMBINATION WITH MIDAZOLAM - FENTANYL COMBINATION FOR PROCEDURAL SEDATION IN PEDIATRIC DENTAL PATIENTS: A SIMPLE RANDOMISED SAMPLING**

Introduction

1. To evaluate the efficacy and safety of ketamine and midazolam combination with fentanyl and midazolam combination administered through intranasal route for the drug acceptance and for the procedural sedation of uncooperative pediatric dental patients.

What will you have to do?

To participate in this research study, you will be interviewed/ examined by complete Blood Investigations and PA chest and if found to fulfill pre-specified criteria, you will be eligible to be enrolled in this research study.

Since you are in the age group of 3-14 years we ask your accompanying parent / guardian will also sign a similar form called as the Parent Informed Consent Form.

Risks and discomforts

There is no foreseen significant risk / hazard to your health, if you wish to participate in the study. If you follow the directions of the dentist in charge of this study and you are injured due to any procedure given under the study plan, the institute will take care.

Benefits

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

Confidentiality

Your existing medical records may be accessed; personal health information about you may be collected and processed by study investigators for the purpose of performing the study.

Information about you will be collected and stored in files with an assigned number, and not directly with your name. All documents related to the study will only be accessed by the study investigator, sponsor, the Ethics Committee and the Regulatory authority.

Your parent / guardian will have the right to access personal information about you at any time with the study doctor and the right to correct this personal information. Your parent / guardian can take away your authorization to collect process and disclose data about you at any time.

Right to refuse or withdraw

You do not have to take part in this research if you do not wish to do so. You may stop participating in the research at any time you wish. The study investigator may decide to withdraw you from the study if he/she considers it is in your best interest.

You will be informed of important new findings developed during the course of the study so you will be able to consider your participation in the study in light of new information.

Parents responsibilities

It is the responsibility of your parent / guardian to come along with you to the centre during the study period for all the visits unless you withdraw or are prematurely discontinued from the study. It is also your responsibility and your parent / guardian to report any expected or unexpected reactions (side effects) that you notice during the study period.

We expect your co-operation throughout the study.

ANNEXURES IV

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 MIDAZOLAM- KETAMINE COMBINATION WITH MIDAZOLAM- FENTANYL COMBINATION FOR PROCEDURAL SEDATION IN PEDIATRIC DENTAL PATIENTS: A SIMPLE RANDOMISED SAMPLING**

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 such a use is only for scientific purpose(s).
5. I permit the use of stored sample (tooth/tissue/blood) for future research. **Yes [ ]   No [ ]**
   Not Applicable [ ]
6. I agree to participate in the above study. I have been explained about the complications 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 AcceptableRepresentative:.................
Signatory's Name...............   Date ....
Signature of the Investigator.....................   Date..........
Study Investigator's Name..........................   Date..........
Signature of the witness.......................   Date...........
Name of the witness..............................
Received a signed copy of the PID and duly filled consent form
Signature/thumb impression of the subject or legally   Date......
Acceptable representative

ANNEXURES V

BABU BANARASI DAS COLLEGE OF DENTAL SCIENCES

PARTICIPANT INFORMATION DOCUMENT

1. Study Title: A COMPARATIVE EVALUATION OF INTRANASAL MIDAZOLAM- KETAMINE COMBINATION WITH MIDAZOLAM- FENTANYL COMBINATION FOR PROCEDURAL SEDATION IN PEDIATRIC DENTAL PATIENTS: A SIMPLE RANDOMISED SAMPLING

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.

3. **What is the purpose of the study?**

To evaluate efficacy, safety, and acceptability of intranasal midazolam- ketamine combination with midazolam- fentanyl 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 anesthesia 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- ketamine combination with midazolam-fentanyl combination combination administered through intranasal route 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 equipment's 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- midazolam combination with fentanyl-midazolam combination 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 being 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. Sarwani Mishra

Department of Pediatric and Preventive Dentistry

Babu Banarasi Das College of Dental Sciences.

Lucknow-227105

Mob- 8340379722

Dr. Laxmi Bala

Member Secretary of Ethics Committee of the institution,

Babu Banarasi Das 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 VI

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 मिडाजोलैम-केटामाइन संयोजन के साथ इंट्रानासल मिडाजोलैम-फेंटनाइल संयोजनका 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।

3. 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. सरवानी मिश्र

बाल चिकित्सा और निवारक दंत चिकित्सा विभाग

बाबू बनारसी कॉलेज ऑफ डेंटल साइंसेज

लखनऊ-227105

मोब- 8340379722

डॉ. लक्ष्मीबाला

संस्था की आचार समिति के सदस्य सचिव,

बाबू बनारसी कॉलेज ऑफ डेंटल साइंसेज

ANNEXURES VII

<u>STATISTICAL ANALYSIS</u>

The data for the present study was entered in the Microsoft Excel 2007 and analyzed using the SPSS statistical software 23.0 Version. The descriptive statistics included frequency and percentage. Some of the intra-operative and post-operative parameters were measured in terms of mean and standard deviation The level of the significance for the present study was fixed at 5%.

The intergroup comparison of the ordinal variable like score of debris removal will be compared using Chi Square test. The intergroup comparison of continuous variables was done using the independent t test depending upon the normality of the data

Chi Square Test

Chi-square is a statistical test commonly used to compare observed data with data we would expect to obtain according to a specific hypothesis. When an analyst attempts to fit a statistical model to observed data, he or she may wonder how well the model actually reflects the data. How "close" are the observed values to those which would be expected under the fitted model? One statistical test that addresses this issue is the chi-square goodness of fit test. This test is commonly used to test association of variables in two-way tables, where the assumed model of independence is evaluated against the observed data. In general, the *chi-square test statistic* is of the form

$$X^2 = \sum \frac{(\text{observed} - \text{expected})^2}{\text{expected}}$$

If the computed test statistic is large, then the observed and expected values are not close and the model is a poor fit to the data

Independent t-test

Independent t Test can be used to determine if two sets of data are significantly different from each other, and is most commonly applied when the test statistic would follow a normal distribution. The independent samples *t*-test is used when two separate sets of independent and identically distributed samples are obtained, one from each of the two populations being compared

$$t = \frac{\overline{X}_1 - \overline{X}_2}{\sqrt{\left(\frac{(N_1 - 1)s_1^2 + (N_2 - 1)s_2^2}{N_1 + N_2 - 2}\right)\left(\frac{1}{N_1} + \frac{1}{N_2}\right)}}$$

Where X1 =Mean of the first Group, X2 =Mean of the Second Group

ANNEXURES VIII

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	

ANNEXURES IX

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 X

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 XI

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 XII

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 XIII

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

ANNEXURES XIV

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

ANNEXURES XV

DISCHARGE CRITERIA (AAPD GUIDELINES 2016)

ANNEXURES XVI

Cardiovascular function and airway patency are satisfactory and stable.

The patient is easily arousable and protective reflexes are intact.

The patient can talk.

The patient can sit up unaided.

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.

The state of hydration is adequate.

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

ANNEXURES XVII

| 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

FENTANYL DOSE per Kg

Weight Estimate (Kg)	Initial Dose (1.5 mcg/kg)	Volume – Initial Dose (mL)	Top–up Dose (0.75 – 1.5 mcg/kg)	Volume – Top-up Dose (mL)
7	10 mcg	0.2	5	0.1
10	15	0.3	7.5 – 15	0.15-0.3
12	18	0.35	9-18	0.2-0.35
14	20	0.4	10-20	0.2-0.4
16	24	0.5	12-24	0.25-0.5
18	27	0.55	13.5-27	0.25-0.55
20-24	30	0.6	15-30	0.3-0.6
25-29	37.5	0.75	18.75-37.5	0.35-0.75
30-34	45	0.9	22.5-45	0.45-0.9
35-39	52.5	1.05	26.5-52.5	0.5-1.05
40-44	60	1.2	30-60	0.6-1.2
45-49	67.5	1.35	67.5	0.65-1.35
>50	75	1.5	37.5-75	0.75-1.5

Note : Volumes have been rounded to the nearest 0.05 mL
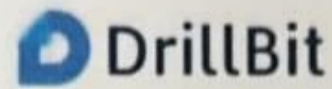
DrillBit

The Report is Generated by DrillBit Plagiarism Detection Software

Submission Information

Author Name	SARWANI MISHRA
Title	A COMPARATIVE EVALUATION OF INTRANASAL MIDAZOLAM - KETAMINE COMBINATION WITH MIDAZOLAM - FENTANYL COMBINATION FOR PROCEDURAL SEDATION IN PEDIATRIC DENTAL PATIENTS
Paper/Submission ID	1416543
Submitted by	amarpal.singh056@bbdu.ac.in
Submission Date	2024-02-09 14:40:47
Total Pages	19
Document type	Dissertation

Result Information

Similarity **4 %**

Internet 1.08%

Journal/Publication 2.92%

Quotes 0.11%

Words < 14, 7.5%
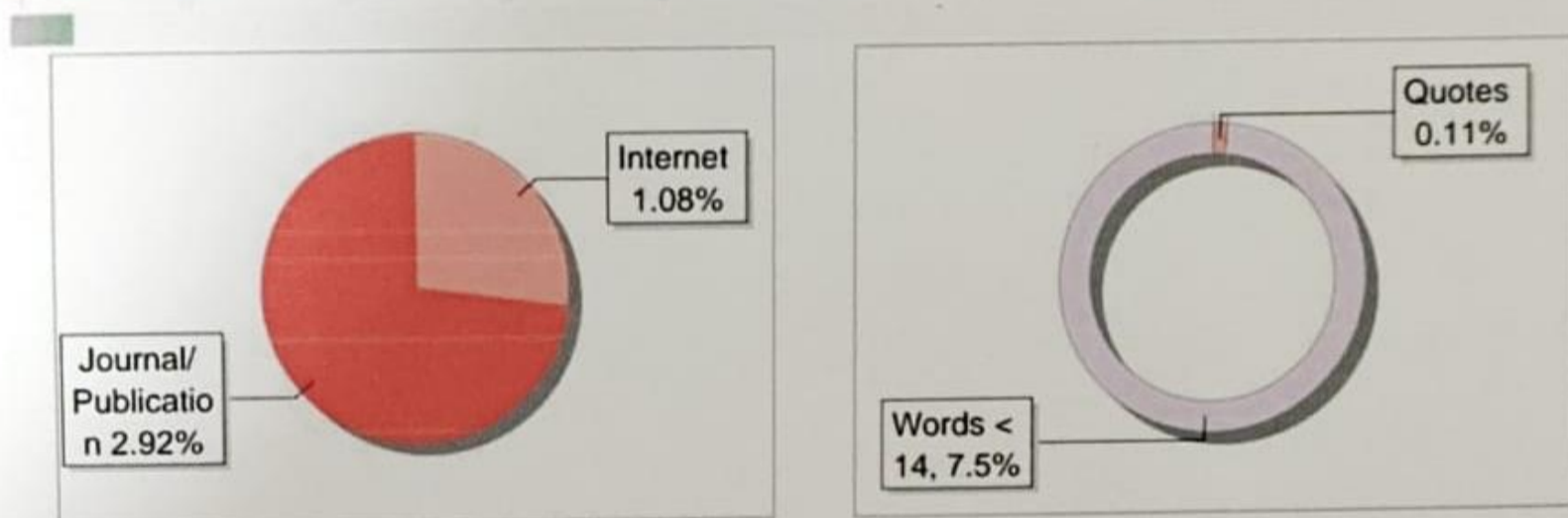
Exclude Information

Quotes	Excluded
References/Bibliography	Excluded
Sources: Less than 14 Words %	Excluded
Excluded Source	**0 %**
Excluded Phrases	Not Excluded

Database Selection

Language	English
Student Papers	Yes
Journals & publishers	Yes
Internet or Web	Yes
Institution Repository	Yes