A Dissertation on

" A comparative study of oral midazolam and oral melatonin for premedication in Paediatric Anaesthesia "

Submitted to the

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

In partial fulfilment of the requirements

For the award of degree of

M.D. (Branch-X)

ANAESTHESIOLOGY

GOVERNMENT STANLEY MEDICAL COLLEGE & HOSPITAL,

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY,

CHENNAI, TAMILNADU

DECLARATION

I, **Dr.MALINI.P**, solemnly declare that the dissertation, titled "***A comparative study of oral midazolam and oral melatonin for premedication in Paediatric Anaesthesia",*** is a bonafide work done by me during the period of DECEMBER 2018 to MAY 2019 at Government Stanley Medical College and Hospital, Chennai under the expert guidance of **PROF.Dr.C.ANURADHA,M.D,** Professor and Head, Department Of Anaesthesiology, Government Stanley Medical College, Chennai.

This thesis is submitted to The Tamil Nadu Dr. M.G.R. Medical University in partial fulfilment of the rules and regulations for the M.D. degree examinations in Anaesthesiology to be held in May 2020.

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CERTIFICATE

This is to certify that the dissertation titled ***"A comparative study of oral midazolam and oral melatonin for premedication in Paediatric Anaesthesia"*** presented herein by **Dr.MALINI.P** is an original work done in the Department of Anaesthesiology, Government Stanley Medical College Hospital, Chennai for the partial fulfilment of the requirements M.D. Anaesthesiology (Branch X) Examination of The Tamilnadu Dr. M.G.R. Medical University to be held in May 2020 under my guidance and supervision.

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ACKNOWLEDGEMENT

I wish to express my sincere thanks to **Prof. Dr.SHANTHI M.D.,D.A., Dean,** Govt. Stanley Medical College and Hospital for having kindly permitted me to utilise the facilities of the hospital for the conduct of the study.

My heartfelt thanks to **Prof. Dr.C.ANURADHA M.D., Prof & HOD,** Department of Anaesthesiology, Govt. Stanley Medical college and Hospital for her motivation, valuable suggestions, constant supervision and for providing all necessary arrangements for conducting the study.

I wish to express my grateful thanks to **Prof. Dr.NAHEED AZHAR, M.D.,D.A.,DNB.,** for his valuable guidance, instructions and suggestions throughout the study.

My sincere thanks to my **Professor Prof. Dr.K.SEVAGAMOORTHY, M.D.,D.A.,** for his constant encouragement and suggestions.

My grateful thanks to **Prof. Dr.K.DHANASEKARAN,M.D.,D.A.,** for his constant guidance throughout the study.

My sincere thanks to **Prof. Dr.V.GOMATHI, MS, MCh (Paediatric Surgery)** Prof &HOD, Department of Paediatric Surgery, and her faculty for their kind co-operation and support.

My heartfelt thanks to my Assistant Professor **Dr.J.JAYAPRAKASH,M.D.,** for his constant guidance and suggestions throughout the study.

I thank my Assistant Professors **Dr.S.SARAVANA KUMAR,M.D.,DNB., Dr.K.SENTHILKUMAR,M.D.,D.A., Dr.J.ARUL,M.D.,** who were guiding me throughout the study and supervising periodically.

I thank **ALL ASSISTANT PROFESSORS** who evinced keen interest and gave support without which this study would not have been possible.

I thank **Dr.ASHOK,M.D.,** Assistant Professor of Anaesthesiology, SRM Medical college & Hospital, for helping me in the statistical analysis.

I thank all the post graduates for their valuable support during the study period.

I thank all the theatre personnel for their co-operation.

Finally, I thank all the patients and their parents without whose participation this study would not have been possible.

INTRODUCTION:

Pre-operative anxiety in children is associated with adverse post-operative outcomes. It includes increased distress in the recovery phase, post-operative regressive behavioural disturbances, separation anxiety. [1] Allaying this anxiety is of primary importance to prevent any adverse impact on the child [2] Premedication is not normally necessary for the average 6-month old infant but is warranted for a 10- to 12- month old who is afraid to be separated from his or her parents. Premedication can be administered orally, intramuscularly, intravenously, rectally, sublingually, or nasally. [3] An effective premedication may facilitate a smoother induction of GA with minimal hemodynamic alterations and minimize the emotional trauma in children undergoing surgery. Premedication is best given by an oral route in children, as children often exhibit an exaggerated psychological response to a needle, and it is easier to distribute a medication orally than to use nasal or rectal routes. Midazolam, with its rapid onset and relatively short duration of action, has proven to be a useful premedication.

Melatonin (MT) is a ubiquitous molecule. It is produced by the pineal gland at night. It has got sleep promoting and clock phase resetting functions in humans.[4] Melatonin and its analogues exert their sleep promoting effect by amplifying day/night differences in alertness.[5,6]

In this study, we planned to assess the efficacy of oral melatonin (0.5mg/kg) and compare it with that of oral midazolam (0.5 mg/kg).

AIM OF THE STUDY:

To compare the efficacy of oral midazolam and oral melatonin for premedication in paediatric anaesthesia.

OBJECTIVES OF THE STUDY:

PRIMARY OBJECTIVE:

To compare the effects of oral midazolam and oral melatonin in terms of sedation and anxiety scores at 15, 30, 45 and 60 minutes after premedication and at induction of anaesthesia.

SECONDARY OBJECTIVES:

To assess

1. Reaction to venipuncture
2. Wake-up behaviour score
3. Readiness to discharge from PACU at one hour post-operatively

LITERATURE

PREMEDICATION IN PAEDIATRICS

Premedication is a term applied to the use of drugs prior to the administration of an anaesthetic agent, with the important object of making anaesthesia safer and more agreeable to the patient.

The objectives of premedication are,

- To produce sedation, allay anxiety and reduce emotional trauma.
- Block unwanted (vagal) autonomic reflexes.
- Reduce volume and acidity of gastric contents.
- Facilitate a smoother and safer induction of anaesthesia.
- To provide amnesia.
- Supplement anaesthesia and reduce need for general anaesthetic drugs.
- Prevention of post-operative nausea and vomiting.

ANXIETY:

Few children are uncooperative at induction of anaesthesia unless they are anxious or stressed. In children, stress of hospitalization has been related to five general fears:

- fear of separation from their parents,
- fear of the strange hospital environment,
- fear of painful procedures,

- fear of the operation itself, or
- fear of anaesthesia.

Alleviating these fears forms much of the basis of reducing anxiety and non-compliance at induction of anaesthesia

The incidence of preoperative anxiety in paediatric population is shown to be more than 60% regardless of the country, procedure or health care system. Risk is greater in the following group of patients;

- Age >2 years
- Personality: children who are shy, inhibited, introverted are at increased risk
- Children who have anxious parents
- Prior upsetting hospital experience
- Only children (children without siblings)
- Children who did not attend pre-school

POSTOPERATIVE BEHAVIORAL CHANGES:

Postoperative behavioural changes related to stressful hospital experiences/induction of anaesthesia include general anxiety, enuresis, night-time crying, and temper tantrums. These changes are usually transient but may persist for up to 1 year. The incidence is greatest in preschool children in whom it can be reduced by psychological preparation, premedication, and the support of parents.[7]

COMMUNICATION:

The preoperative visit is both an opportunity to assess the child's fitness for anaesthesia and to provide reassurance to the child and their parents. Following are some of the useful strategies that may be used in this situation. [8]

Table**: Strategies for interviewing children before operation:**

1. Speak in a quiet, reassuring voice and get down to the child's eye level
2. Do not be condescending
3. Do not give the impression that the child's feelings are irrelevant
4. Do not laugh at the child unless you are sure they are being humorous
5. Do not tease the child unless you know them
6. Use age-appropriate language in discussing anaesthetic care with the child
7. Avoid using terms that may cause alarm or increase anxiety

DEVELOPMENTAL DIFFERENCES:

Children react to the stress of anaesthesia and surgery in an age-dependent manner. In addition, a minority of children display abnormal reactions related to behavioural and psychological disorders. A successful plan for induction of anaesthesia must take the following points into account.[8,9]

INFANTS:

Infants aged less than 9 months will readily accept parental surrogates and are less likely to experience anxiety on separation from parents. They respond to soothing voices, gentle rocking, and being held.[7]

1 TO 3 YEARS:

Separation anxiety is a problem in children of this age group, and is found to be reduced if a parent is usually allowed to be present during induction of anaesthesia. Children at this age are more at risk of a stormy induction as they are less likely to understand the proceedings. Toys and stories have been successfully used as distraction tools in these children.

3 TO 6 YEARS:

At this age, children can have concerns about bodily mutilation and may require reassurance. Simple explanations of surgical and anaesthetic procedures are usually effective in reducing anxiety and postoperative behavioural changes. Play therapy is especially useful in this age group.

7 TO 12 YEARS:

Children of this age feel the need to stay in control and hence need more explanation and participation. They may benefit from choosing an anaesthetic facemask or being allowed to hold the mask during induction. Play, storybooks, photographs, and videos/DVDs can all be useful.

ADOLESCENCE:

This group has increased body awareness, independence, and need for privacy. Adolescents may have better coping strategies but are still concerned about pain, awareness, and losing control. Their ability to understand explanations is variable. Involving this age group in the anaesthetic plan gives them a sense of control and reduces their anxiety.

MENTAL DISORDERS:

Establishing rapport with children having psychological, developmental, or behavioural disorders is difficult. They are more likely to be aggressive and combative at induction of anaesthesia requiring more extreme measures of sedation, restraint, or both.

IDENTIFYING THE ANXIOUS CHILD:

Some factors predicting anxiety and distress in the child at induction of anaesthesia are listed in the following table. Gender appears to have no influence on preoperative anxiety.

Factors predicting child anxiety and distress at induction of anaesthesia: [7,8]

Age	Children between the ages of 1 and 3 are more likely to experience separation anxiety and be distressed/less cooperative at induction of anaesthesia
Temperament	Shy, inhibited, dependent, and/or withdrawn children have higher levels of anxiety and are more likely to exhibit uncooperative/turbulent behaviour at induction
Parental anxiety	Children of anxious parents have higher levels of anxiety at induction of anaesthesia and are more likely to develop postoperative behavioural problems
Previous hospital/theatre experiences	Negative hospital experiences increase child anxiety and reduce cooperation at induction
Negative reaction to vaccination	Predicts non-compliance and a distressed state during induction of anaesthesia

METHODS OF PREMEDICATION :

PSYCHOLOGICAL INTERVENTIONS FOR PREOPERATIVE ANXIETY IN PAEDIATRICS:

PRE – HOSPITAL PROGRAMMES:

Tours of the hospital and theatre, videos, leaflets, and interactive books are used with the aim of reducing anxiety. If the programme is implemented 5–7 days before surgery in children age over 6 years, anxiety is lowered. The interventions tend to be more effective in children aged over 4 yr. [7,10]

PLAY THERAPY:

This is usually provided by trained play therapists using visual aids such as videos, interactive books, and dolls. It is useful in young children who have had repeated painful procedures or previous negative anaesthetic experiences. Play therapy can identify the patients who will benefit from sedative premedication.

PARENTAL PRESENCE AT INDUCTION:

A parent is usually invited to accompany their child at induction of anaesthesia to eliminate separation anxiety. Parental presence did reduce child anxiety, it did improve parental satisfaction with the separation process

In international practice, the parents of infants weighing 5 kg, children with potentially difficult airways, acutely ill children, and those requiring rapid sequence induction are discouraged from attending induction of anaesthesia.

OTHER INTERVENTIONS AT INDUCTION:

Hypnosis, music, and lighting can be used to provide a calm and soothing environment for the child in the anaesthetic room. Distraction methods (blowing bubbles, toys, action books) work best for children undergoing I.V. induction, while engagement with the anaesthetist and the anaesthetic process itself (choosing and handling the face mask, blowing up the 'balloon' etc.) work best with inhalation induction.

MANAGEMENT STRATEGIES FOR THE UNCOOPERATIVE CHILD:

From a management perspective, uncooperative children generally fall into one of two groups. [9] By far, the largest group consists of pre-school and young children who have an anxious temperament, anxious parents, or both. These patients may appear cooperative when interviewed in the surgical ward, but then become uncooperative in the anaesthetic room or at induction of anaesthesia. Fortunately, they are usually amenable to reasoning and encouragement possibly backed up by sedative premedication and minimal restraint. A second and smaller group consists of children who are uncooperative and combative from the outset and will resist any form of intervention. The underlying problems in these children may include neurological disability, developmental delay, behavioural disorders, autism, mental health, or personality problems.[11] In addition to the measures described for dealing with the anxious child, these patients often require more powerful sedative drugs before operation, more active restraint, or both.

RESTRAINT, HOLDING STILL, AND CONTAINING:

The use of physical restraint (overpowering), holding still (immobilizing),and containing (preventing escape or self-harm) in children raises ethical, legal, and practical problems.

STRATEGIES FOR ANXIOUS CHILDREN:

Distraction techniques such as books, music, or computer games can be used to calm this group of children. However, if the child is inconsolable, the urgency of the surgery and the patient's best interest have to be taken into account and the parents involved in further management.

STRATEGIES FOR AGGRESSIVE COMBATANT CHILDREN:

It is essential that parents and staff be involved in the preoperative plan for this group of children. Often these children have had previous anaesthetics and the parents can be extremely helpful in identifying what works best for them.
Frequently, oral premedication with midazolam will be rejected, in which case nasal midazolam may be tried. In the absence of I.V. access, the choice for induction of anaesthesia frequently lies between an I.M. injection of ketamine and inhalation of sevoflurane as these methods offer certainty of success with the application of effective restraint by parent, staff or both.[11]

PHARMACOLOGICAL PREMEDICATION:

Premedication drug choice and its dose are determined by:

- Patient's age and weight.
- Physical status.
- Level of anxiety.
- Tolerance for depressant drugs.
- Previous adverse experience with pre-medicant drugs.
- Elective or emergency surgery.
- Inpatient of outpatient surgery [12]

The various drugs, tried for premedication are barbiturates, narcotics, benzodiazepines, butyrophenones, antihistamines, anticholinergics, H2 receptor antagonists, antacids etc.

The ideal premedication for paediatric patients should have the following characteristics:

- Acceptable and atraumatic route of administration.
- Rapid and reliable onset.
- Minimum adverse effect.
- Rapid elimination

Premedication in children can be administered through different routes (intramuscular, intravenous, rectal, sublingual or intranasal). The different routes of administration or premedication drugs have their own advantages and disadvantages.

[13] Oral premedication is more preferred and injections for premedication are avoided in children. [14]

Recent studies have shown midazolam after oral administration is absorbed rapidly from GIT, peak plasma concentration is achieved easily and clinical effects are also rapidly obtained. It can be used as an effective premedicant in paediatric anaesthesia because of its hypnotic and sedative effect. [15]

PHARMACOLOGY OF MIDAZOLAM - INTRODUCTION:

Midazolam is an imidazo benzodiazepine derivative. It is water soluble, short acting newer drug with excellent sedative, hypnotic, amnestic properties and stable cardiorespiratory response

Fryer and Walser synthesised midazolam in 1976. It was the first clinically used water soluble benzodiazepine. It was the first benzodiazepine that was produced primarily for use in anaesthesia.

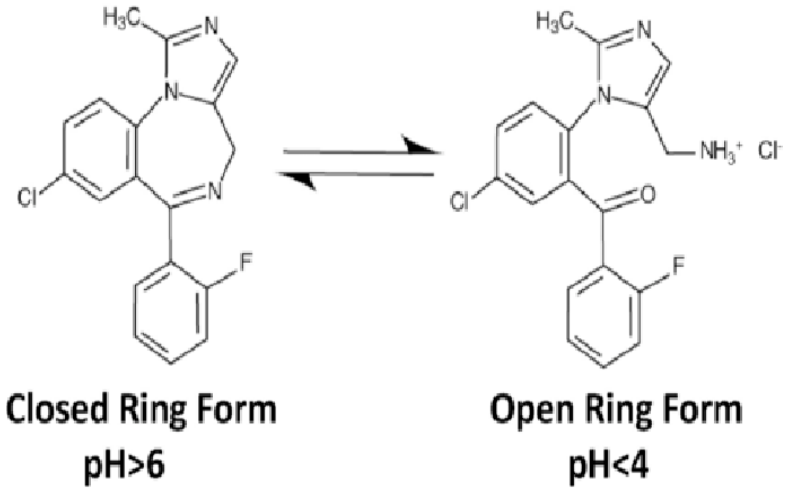
CHEMISTRY AND STRUCTURES:

Midazolam is 8-Chloro-6 (2-flurophenyl)-1-methyl- 4H- imidazo (1,5-a) (1,4)-benzodiazepine.

It's molecular weight is 362.

Midazolam has an unique chemical structure giving it distinct pharmacologic and pharmacokinetic properties. The imidazole ring is relatively basic, thus allowing the preparation of the salts, which are stable in aqueous solution. At pH < 4, part of the drug has an open benzepine ring and it imparts water solubility. At physiological pH,

drug is present in the ‘ring closed from’ and thus lipid solubility of the drug is increased.



Midazolam, an imidazobenzodiazepine derivative has a fused imidazole ring which accounts for the rapid metabolism.[16] The pKa of midazolam is 6.15, which allows preparation of water soluble salts. The parenteral preparation of midazolam is acidic in nature with a pH of 3.5 making it water soluble, thus avoiding the use of lipoidal constituents like propylene glycol. On the other hand, at physiologic pH, midazolam becomes highly lipid soluble and is one of the most lipid soluble benzodiazepines.[17] The high lipophilicity produces rapid absorption from gastrointestinal tract and entry into brain tissue after intravenous administration. Moreover, midazolam is compatible with 5% dextrose, Lactated Ringer’s solution, normal saline and can be mixed with acidic salts of other drugs. Midazolam is distributed with 0.8% sodium chloride and 0.01% disodium edetate with 1% benzyl alcohol as preservative.

Benzodiazepines exert their general effect by occupying BZD receptors which modulate GABA, which is the major inhibitory neurotransmitter in brain.[18] The

benzodiazepine receptors are found in highest densities in the olfactory bulb, cerebral cortex, cerebellum, hippocampus, substantia nigra and inferior colliculus. Decreased numbers are found in stratum, lower brain stem and spinal cord.

There are two types of GABA receptors. But it appears that the benzodiazepine receptor is a part of GABA-A receptor complex on the sub-synaptic membrane of effector neuron. This receptor complex is made up of three protein subunits α, β and γ and they are arranged in a pentameric aerolic glycoprotein complex. These proteins contain the various ligand binding sites of GABA-A receptor such as benzodiazepine, GABA and barbiturate binding sites. The BZD binding site is found on γ2 subunit and β subunit is thought to contain binding site for GABA. With activation of GABA-A receptor, gating of channel for chloride ions is triggered, after which the cells become hyperpolarized and resistant to neuronal excitation. The hypnotic effects of benzodiazepines are mediated by alternation in a potential dependent calcium ion flux. The degree of modulation of GABA receptor function has inbuilt limitation and this explains the relatively high degree of safety with benzodiazepines.
Benzodiazepine receptor occupancy of less than 20% is sufficient to produce anxiolytic effect. Sedation is observed with 30-50 % blockade of receptors and unconsciousness requires 60% or higher receptor blockade.

Long term administration of benzodiazepines produces tolerance. Although mechanism of chronic tolerance is not fully understood, it is probably due to down regulation of benzodiazepine GABA-A receptor complex. After cessation of use, there is up regulation of receptor complex, which could increase susceptibility to benzodiazepines.[19]

PHARMACODYNAMICS OF MIDAZOLAM:

Midazolam, similar to all benzodiazepines has anxiolytic, hypnotic, sedative, anticonvulsant, amnestic and centrally acting muscle relaxant properties. Midazolam is 3-6 times more potent than diazepam.

EFFECTS ON CNS:

Midazolam, in a dose related manner, is found to reduce the cerebral metabolic rate of oxygen consumption (CMRO2) and Cerebral Blood Flow (CBF) but it maintains a normal ratio of CBF to CMRO2. Midazolam is shown to increase the seizure initiation threshold to local anaesthetic drugs.[20]

The reduction in CMRO2 and CBF suggest that midazolam can protect against cerebral hypoxia and can be useful for patients who have increased Intracranial Pressure (ICP). This protection provided by midazolam is superior to diazepam but less than pentobarbital

EFFECTS ON RESPIRATORY SYSTEM:

Midazolam is found to produce central respiratory depression in a dose dependent manner, and is five to nine times more potent than diazepam. The rate of midazolam administration affects the onset of peak ventilatory depression. If the drug is given faster , the more quick will be the depression.

Apnoea can occur after midazolam administration. There is similar incidence of apnoea in patients who are induced by midazolam and thiopentone .[21] Apnoea is

related to doses of midazolam and is more likely to occur in presence of opioids, old age, other respiratory depressant drugs and debilitating diseases.

EFFECTS ON CARDIOVASCULAR SYSTEM:

Midazolam has a modest haemodynamic effect when it is used alone. There is a slight reduction in arterial blood pressure, resulting from a decrease in systemic vascular resistance. The relatively stable haemodynamics after midazolam administration are due to preservation of homeostatic reflex mechanisms, but the baroreceptor reflex maybe impaired by midazolam.[22]. The haemodynamic effects of midazolam is related to dose , however there is a plateau plasma drug level, above which little change in arterial blood pressure occurs. Heart rate, ventricular filling pressure and cardiac output are better maintained after induction with midazolam. In patients with raised left ventricular filling pressure, midazolam produces a 'nitroglycerine like' effect by lowering filling pressure and increasing cardiac output. It does not block the stress of endotracheal intubation and surgery.

STRESS RESPONSE:

Midazolam reduces the adrenergic but not the cortisol or renin response to the surgical stress. Premedication with midazolam has been found to lower antidiuretic hormone concentration in the plasma [23]

OTHER EFFECTS OF MIDAZOLAM:

ANXIOLYTIC EFFECT:

Midazolam has anxiolytic property. It exerts the anxiolytic effect by increasing the glycine inhibitory neurotransmitter. [24] Their affinity for glycine receptors in the brain stem correlates with their anti anxiety potency.

HYPNOTIC EFFECT:

The hypnotic effect of midazolam is by its accumulation in GABA receptors and by the occupation of the benzodiazepine receptors. Midazolam has a relatively high affinity for the benzodiazepine receptor, two times that of diazepam..

ANTICONVULSANT EFFECT:

This is because of enhanced action of GABA on motor circuits in the brain.

MUSCLE RELAXANT EFFECT:

It is mediated by glycine receptors found in the spinal cord. However, in anaesthetized humans, midazolam does not change requirement of succinylcholine or pancuronium needed to maintain muscle relaxation.

ANTEROGRADE AMNESTIC EFFECT:

The amnestic effect of an intravenous does of midazolam is 5 mg, ranges from 20 to 32 min. Intramuscular administration may prolong it. The amnestic effect of midazolam may be more intense than diazepam but shorter lasting than lorazepam.

Prolonged amnesia could be a problem in outpatients by interfering with their ability to recall oral instructions.

ANTI NOCICEPTIVE EFFECT:

Midazolam when given intrathecaly or epidurally injection can produce this effect which could be mediated by GABA receptors .[25]

PHARMACOKINETICS:

The high lipophilicity of midazolam at physiologic pH causes it to have very rapid onset of action after intravenous administration, the equilibrium between plasma and CSF occurs within few minutes of intravenous administration. The high lipophilicity of midazolam has both very high metabolic clearance and rapid elimination rate contributing to its short duration of activity. In healthy individuals, volume of distribution averages between 1- 205 litres/kg. Midazolam is bound extensively to plasma proteins. After the distribution equilibrium is achieved, elimination of midazolam proceeds rapidly, with half-life from one to four hours. The total clearance of midazolam depends predominantly on hepatic blood flow, approximately 50% . Midazolam is a widely distributed and very rapidly cleared benzodiazepine.

Table 3:

Comparison of pharmacokinetic variable of common Benzodiazepines

	Diazepam	**Midazolam**
t ½ α (min)	30-60	6-15
t½ β(h)	24-57	1.7-4
Vd (1/kg)	0.7-1.7	1.1-1.7
Cl (ml/min/kg)	0.24-0.53	6.4-11.1

The distribution half life of midazolam (t ½ α) is at least one half that of diazepam and elimination half life (t½ β) is tenfold less. The volume of distribution (Vd) is almost similar and the total body clearance (C1) of midazolam is much higher than diazepam. So midazolam is a short lived compound as compared to diazepam.

After oral administration, midazolam is absorbed rapidly from GIT, peak plasma concentration is generally achieved within 1 hour of ingestion and the clinical effects after oral administration are correspondingly rapid. Because of extensive first pass hepatic extraction, only 40- 50% of orally administered midazolam reaches plasma. The elimination half-life of oral midazolam, on the other hand is similar to that observed after intravenous administration.

The pharmacokinetics of midazolam are dependent on gender, age, race, enzyme induction, renal and hepatic function. Increasing age reduces the clearance of midazolam but to a lesser degree than diazepam.

METABOLISM:

Midazolam is bound extensively to plasma proteins, the degree of binding averages 96-97 % and is independent of the dose and plasma concentration of midazolam. Hepatic metabolism of midazolam involves hydroxylation by hepatic microsomal oxidative mechanism. The fused imidazole ring is oxidized rapidly in the liver, much more rapidly than the methylene group of the diazepine of other benzodiazepines producing quicker clearance. The principal metabolite is 1-hydroxyl midazolam, and the other metabolites are 4-hydroxyl midazolam and 1-4 dihydroxy midazolam, which are excreted in urine as glucuronide conjugates. The 1-hydroxy metabolite has a clinical potency of 20-30 % of the parent compound and can causes profound sedation in patients with renal impairment.

ROUTES OF ADMINISTRATION AND DOSAGES:

a) Preoperative sedation / Premedication:

0.07-0.08 mg/kg I.M

0.15-0.35 mg/kg I.V

0.5 mg/kg oral

0.3 mg/kg rectal

b) Induction of anaesthesia:

0.15-0.5 mg/ kg I.V

c) For I.V Sedation:

0.03-0.3 mg/ kg

USES / INDICATION:

- **Premedication:**

  Midazolam,is well suited for premedication because of its anxiolytic and hypnotic properties. When midazolam 5 mg is given as an intravenous premedication, the hypnotic and anxiolytic effects appeared within 1-2 minutes and memory picture shown at 4 minutes was not recalled by 78% of the patients. These effects persisted for 30 minutes. Midazolam has been used as a premedicant by intramuscular route. The intramuscular administration does not produce significant pain or local irritation. Oral midazolam for premedication has rapid onset and recovery and is being used for premedication in children, in a dose of 0.5 mg/ kg. In adults 15 mg per oral dose of midazolam is shown to be superior to placebo.

- **Induction and Maintenance of Anaesthesia**

It has faster onset of action, lack of pain and phlebitis after intravenous injection. It is the preferred induction agent among benzodiazepines. In a healthy, well premedicated patient midazolam 0.2 mg/kg given in 5-15 seconds will induce anaesthesia in 28 seconds. Patients above 55 years of age and those in physical statuses ASA III and above will require a 20% or more reduction in dose of midazolam for induction. When midazolam is used with other anaesthetic drugs for

induction (co-induction), there is a synergistic interaction, so that the induction dose of midazolam is reduced.

Awakening after midazolam anaesthesia is due to redistribution of drug from brain to other less well perfused tissues. The emergence time is related to the dose of midazolam used and administration of adjuvant anaesthesia.

- **Intravenous Sedation**

Midazolam is used for sedation pre-operatively as premedication, intra-operatively during regional or local anaesthesia. And, it is also used post operatively and in critical care. There exists slight synergistic action of midazolam and spinal anaesthesia with respect to ventilation.[26] So respiratory monitoring is mandatory when used with regional anaesthesia.

Midazolam should be given by titration for sedation, the end point being an adequate sedation and dysarthria. The peak effect of midazolam is reached within 2-3 minutes of administration. The degree of sedation and amnesia, maintenance of respiratory and haemodynamic functions are better with benzodiazepines.

- **ICU Sedation**

The main aim of sedation in critical care settings is to provide relief from anxiety and pain. Midazolam is safe and effective in these patients.

- **As an Adjunct to Local/Regional Anaesthesia**
- **Other Uses**

As an anticonvulsant especially in status epilepticus.

SIDE EFFECTS:

- Nausea and vomiting
- Respiratory depression is dose related and is common after intravenous administration and after opiate premedication.
- Negligible (<5%) local complications like pain on injection and thrombophlebitis
- Hiccough, bronchospasm, headache and emergence delirium which are rare

DRUG ABUSE AND DEPENDENCE:

Available data concerning drug abuse and dependence potential of midazolam suggest that the abuse potential of midazolam is equivalent to that of diazepam.

CONTRAINDICATION AND PRECAUTION:

.Hypersensitivity to benzodiazepines.

• Acute narrow angle glaucoma.

• There may be impairment of psychomotor skills following midazolam sedation or anaesthesia

• Elderly patients require lower doses whether premedicated or not.

• Patients with chronic obstructive pulmonary disease are usually sensitive to the respiratory depressant effects of midazolam.

• Midazolam should not be administered if resuscitation equipment and skilled personnel for airway management are not available.

• It is secreted in human milk, hence not recommended for use in nursing mothers.

• Paediatrics: No specific problem encountered till today.

DRUG INTERACTION:

- Sedation with midazolam is accentuated by premedication with morphine, meperidine and fentanyl.
- After I.M administration as premedication, dose of pentothal required for the induction is less and hence should be titrated.
- Hypotensive effects may be potentiated when medication viz. Beta-blockers, Calcium-channel blockers, Diuretics, Angiotensin converting enzyme inhibitors, nitrates are used concurrently.
- I. V. administration of midazolam decreases the MAC of halothane required for general anaesthesia.

OVERDOSE AND ITS TREATMENT:

The manifestation of midazolam over dose are sedation, confusion, impaired co-ordination, diminished reflexes, coma and untoward hemodynamic alterations.

Treatment:

- Most important is the maintenance of airway and support of ventilation.
- Haemodynamic support.

- “Flumazenil” is a specific BZD antagonist it is indicated for reversal of the effects of midazolam.[27]

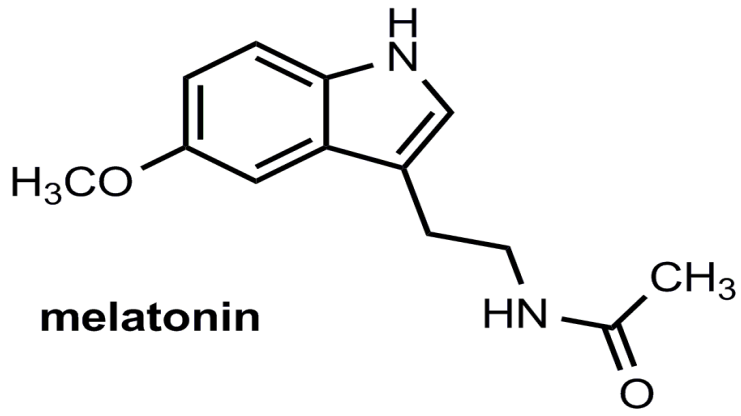
Action of flumazenil on intravenous administration starts in seconds and it lasts for 1 to 3 hours. The elimination half-life is one hour.

For reversal of benzodiazepine anaesthesia :0.3-1 mg I.V

Benzodiazepine over dose: 0.2 mg/min I.V. Patients usually respond within 5 minutes.

Side effects of Flumenazil include agitation, discomfort, tearfulness, anxiety and rarely withdrawal seizures.

MELATONIN:



melatonin

Melatonin was discovered in 1958. Molecular formula is C13H16N2O2. Molecular weight is 232.28 g/mol. Melatonin is a natural substance present in all major taxa of organisms. It is produced mainly in the pineal gland of all mammals and vertebrates. Its secretion is high during and low during day. Melatonin is also synthesized from tryptophan in other organs and peripheral tissues.

PHARMACOKINETICS:

Small amounts (0.3 mg) of melatonin when used several hours before sleep shift the circadian clock earlier according to the phase response curve for melatonin in humans thereby promoting earlier sleep onset and morning awakening. Melatonin is rapidly distributed and eliminated after intravenous administration. [28]After oral administration, plasma concentration peaks after 60 minutes and is then eliminated. [29] Melatonin has a half life of 35 to 50 minutes. In humans, 90% of orally administered exogenous melatonin is cleared in a single passage through the liver, a

small amount is excreted in urine, and a small amount is found in saliva. The bioavailability of melatonin is between 10 and 50%.

Melatonin is metabolised in the liver by cytochrome P450 enzyme CYP1A2 to 6-hydroxymelatonin. Metabolites are conjugated with sulphuric acid or glucuronic acid for excretion in the urine. 5% of melatonin is excreted in the urine as the unchanged drug.

Some of the metabolites formed via the reaction of melatonin with a free radical include cyclic 3-hydroxymelatonin, N-acetyl-N2-formyl-5-methoxy kynuramine (AFMK) and N1-acetyl-5-methoxykynuramine (AMK).

PHARMACODYNAMICS:

In humans, melatonin is a full agonist of melatonin receptor 1 (picomolar binding affinity) and melatonin receptor 2 (nanomolar binding affinity),[30,31] both of which belong to the class of G-protein coupled receptors (GPCRs). Melatonin receptors 1 and 2 are both $G_{i/o}$ - coupled GPCRs, although melatonin receptor 1 is Gq- coupled. Melatonin also acts as a high-capacity free radical scavenger within mitochondria which also promotes the expression of anti-oxidant enzymes such as superoxide dismutase, glutathione peroxidase, glutathione reductase, and catalase via signal transduction through melatonin receptors.

PHYSIOLOGICAL ROLES OF MELATONIN USEFUL TO THE ANAESTHESIOLOGIST:

1. SLEEP INDUCTION AND MAINTENANCE:

Many studies have showed the importance of melatonin for both initiation and maintenance of sleep. The hypnotic effects of melatonin are considered as an integral component of its physiological role.[32] It has been reported to improve sleep onset, duration and quality, suggesting a pharmacological hypnotic effect.[33] It exerts its effects through the activation of the MT1and MT2 melatonin receptors. Melatonin suppresses neuronal activity by which it contributes to regulation of sleep[34] . The central effects involve modulation of the GABA receptor activity thereby facilitating GABAergic transmission [35]. In humans, the peak values of melatonin concentration are seen in the evening and are associated with the lowest point in the rhythms of core body temperature, mental performance, metabolic functions, alertness and with maximum sleep propensity.[36] Melatonin and its analogues exert a sleep promoting effect. They amplify day/night differences in alertness and display a modest and mild sleep inducing effect.[37] Moreover, melatonin is devoid of hangover effects on the day following its intake. Melatonin and its analogues lack negative effects like addiction and dependence in contrast to BZDs[38]

2. ANALGESIC EFFECTS:

Melatonin has shown potent analgesic effects in a dose dependent manner in experimental studies.[39] But the physiological mechanism behind its analgesic effect has not been clarified.[40,41] It may be linked to Gi-coupled melatonin receptors,

GABA-B receptors or Gi- coupled opioid μ receptors. The exact site of action to induce anti-nociception is not clear.[42] Possibly, by augmenting GABA ergic systems and morphine anti-nociception, melatonin inhibits glycine effects and enhances GABA induced currents.[43] Melatonin could activate MT2 receptors in the dorsal horn of spinal cord and may also enhance the levels of β-endorphins and the anti-nociception induced by delta opioid receptor agonists. [44,45]

3. ANTI-INFLAMMATORY AND IMMUNOLOGICAL EFFECTS:

Melatonin has anti-corticoid and immune enhancing function. Possible mechanisms for melatonin's anti-inflammatory effects include

- Modulation of the pineal and pituitary / adrenal axis activity
- Lowering of corticoid levels by releasing vasotocin
- Inhibition of COX2 enzyme and iNOS enzyme
- Activation of **NF-kB**, inhibition of neutrophil infiltration
- Enhancement of thymocyte proliferation and IL2 production.

Melatonin exhibits immune modulatory properties. It has modulatory influence on the NO synthetase (NOS) and cytokine production in inflammatory and oncostatic processes [46]. It combats various bacterial and viral infections.

4. ANTI-OXIDATIVE EFFECTS:

Melatonin is a powerful antioxidant. It prevents the damage induced by free radicals and increases the activity of various antioxidant enzymes like catalase, glutathione reductase and glutathione S transferase.[47,48]

5. CHRONOBIOTIC PROPERTY:

Melatonin is an important regulator of the body circadian rhythm.[49, 50] The normal circadian rhythm of melatonin is acutely disturbed by anaesthesia and surgery because of the delay in the onset of nocturnal melatonin secretion.

6. ANTI HYPERTENSIVE PROPERTY:

Melatonin has a mild hypotensive effect. Melatonin may bind to specific melatonin receptors in the blood vessels and interfere with the vascular response to catecholamines. It may interfere with the peripheral and central autonomic system and cause a reduction in adrenergic outflow and catecholamine levels. Melatonin may induce relaxation of the arterial wall smooth muscle by increasing nitric oxide levels.

7. **OCULAR HYPOTENSIVE EFFECT:**

Melatonin has ocular hypotensive effect. It may have a complex undefined role in aqueous humour formation. Melatonin receptors (M2 and M3) were recognized in the ciliary body tissues in animals.

POTENTIAL CLINICAL APPLICATIONS OF MELATONIN IN ANAESTHESIA AND CRITICAL CARE:

PRE-MEDICATION BEFORE SURGERY:

Melatonin possesses analgesic, anti-inflammatory, sedative, hypnotic, chronobiotic and anti-oxidative properties.[5]

IN ADULT PATIENTS:

The analgesic effects in the perioperative period remain controversial.[5] Premedication with 0.05, 0.1 or 0.2 mg/kg sublingual/oral melatonin is associated with pre-operative anxiolysis and sedation without impairment of orientation, psychomotor skills or impact on quality of recovery.[51,52] Ismail and Mowafi et al[44] have found that 10 mg oral melatonin premedication 90 minutes before surgery provided anxiolytic effects and enhanced analgesia.

RanaAltaf Ahmed *et al.* [6] found that sublingual melatonin 0.5 mg/kg premedication in adults significantly decreased anxiety levels with no amnesia and next day hangover effects. Ionescu D *et al*[53]., successfully used 3 mg oral melatonin as premedication for laparoscopic cholecystectomy.

Naguib and Samarkandi et al [54] found that patients who received premedication with 5 mg melatonin 100 minutes pre-operatively had a significantly lower anxiety levels and increased sedation before surgery. They had no amnesia for pre-operative events.

IN CHILDREN:

In children younger than 3 years, the use of melatonin has decreased the number of patients undergoing GA for procedures like brainstem audiometry [56]. Clinical trials with melatonin as a premedication agent in anxious children under nitrous oxide-oxygen sedation for dental treatment have shown good results. Few clinical studies have shown that melatonin is as effective as midazolam in reducing preoperative anxiety in children. It is also associated with rapid recovery and reduced incidence of emergence delirium [51,57] .Melatonin dosing for children is reported to be between 0.3 and 20 mg. Patients on melatonin supplements can continue taking them perioperatively.

HYPNOSIS AND ANALGESIA AS AN ANAESTHETIC AGENT / ADJUVANT:

The hypnotic, anti-nociceptive properties of melatonin endow melatonin a novel hypnotic anaesthetic property. It significantly reduced the induction dose of propofol and thiopental in some studies. Melatonin and its analogues possess hypnotic properties when injected intravenously and they are comparable to the properties of propofol and thiopental.

MISCELLANEOUS PERIOPERATIVE USES:

IN PATIENTS WITH HYPERTENSION:

Ismail and Mowafi [44] showed that the mean arterial pressure decreased after melatonin premedication and it may be beneficial in elderly patients, particularly those at cardiovascular risk.

FOR NEUROPROTECTION AND AS AN ANTICONVULSANT:

Melatonin prevents neuronal damage associated with epilepsy and has putative neuro-protective effects and it can be used as an anticonvulsant.

TO REDUCE INTRAOCULAR PRESSURE:

10 mg oral melatonin 90 minutes before cataract surgery under topical anaesthesia has been reported to decrease intraocular pressure

TO IMPROVE SURGICAL OUTCOMES:

Melatonin in surgical neonates resulted in improvement of clinical outcomes by virtue of its ability to reduce oxidative stress related to surgical procedures.

POST OPERATIVE USE OF MELATONIN:

Anxiolytic and analgesic effects of melatonin may improve post-operative pain by controlling higher anxiety levels. Melatonin can regulate the disrupted sleep wake cycle after surgery. In a study by Kain ZN *et al*.,[58] children who received pre-

operative oral melatonin 0.05 mg/kg developed less emergence delirium when compared with those who received oral midazolam (0.5 mg/kg)

IN INTENSIVE CARE:

IN SEPSIS:

The anti-oxidative properties of melatonin are being investigated for use in sepsis and reperfusion injuries.

FOR PROTECTION AGAINST ORGAN INJURIES:

Melatonin has been shown to have protective effects against glycerol induced renal failure in rats. This is because of its antioxidant effects.

SLEEP DISORDERS IN CRITICALLY ILL PATIENTS:

Oral melatonin at 9 pm every night was associated with a 1 hour increase in nocturnal sleep and increased nocturnal sleep efficiency in critically ill patients.

TREATMENT AND PREVENTION OF STRESS INDUCED GASTRIC ULCERS:

Melatonin generated in the GIT serves as a local antioxidant. It has ulcer healing and gastro protective effects.

PAIN MANAGEMENT:

The dose of melatonin for analgesia is undefined. Melatonin has been associated with the relief of pain in patients with extensive tissue injuries. Disturbances in melatonin secretion have been proposed to be part of the pathophysiology leading to fibromyalgia. Melatonin alleviates abdominal pain in patients with inflammatory bowel syndrome (IBS). Trials have shown that melatonin may have both therapeutic and prophylactic role in patients suffering from migraine.

SAFETY OF MELATONIN:

Melatonin is reported to have an excellent safety profile and is remarkably well tolerated. Very high doses (300 mg/day) given orally for up to 2 years is found to be safe. The reported side effects of melatonin include 4% fatigue and 3% nausea. Doses as great as 20 mg were administered to children and there are no adverse side effects apart from sedation. Dizziness, headache and irritability may be other side effects that are seen only with very high doses. The interaction of melatonin with other drugs is yet to be systematically evaluated.

MELATONIN ANALOGUES:

There are two melatonin agonists, Ramelteon and Agomelatine. Ramelteon has been approved by the US FDA. Additionally, there are two melatonin agonists, Tasimelteon and TIK-301 and they have been granted orphan drug designation. They are going through clinical trials in the USA. Melatonin analogues have a good safety profile. Slow release forms of melatonin are being developed.

OTHER DRUGS USED FOR PREMEDICATION:

LORAZEPAM:

It can be administered orally, intravenously, or intramuscularly. It is metabolized by the liver to inactive metabolites. Lorazepam has a slower onset and offset of action, therefore is better used for inpatients. The usual dose is 0.05 mg/kg administered orally or intravenously to older children [59]

DIAZEPAM:

It has a greater fat solubility than midazolam. It has a faster CNS effect after intravenous administration (1.6 min). Its metabolite desmethyldiazepam has pharmacologic activity equal to the parent compound.[60] It is not used much in young children because they have immature liver function and that would lead to a prolonged half life. The average oral dose for premedication ranges from 0.1 to 0.3 mg/kg. Rectal diazepam appears to be less effective than rectal midazolam. The intramuscular route is painful and absorption is erratic and so is not recommended.

CHLORAL HYDRATE:

Chloral hydrate is an orally administered nonbarbiturate (20 to 75 mg/kg with a total maximum dose of 2 g). It has no analgesic properties. It has a bitter taste. It can be administered orally or rectally and has a relatively good sedation within 30 to 45 minutes. As it has a slow onset and long elimination half-life, its use is less frequent than midazolam as a premedicant. It is not recommended for use in neonates and patients with liver disease because of the potential accumulation of toxic metabolites and it may lead to metabolic acidosis, renal failure, and hypotonia. It’s active

metabolite trichloroethanol, has a long half life in toddlers and in preterm infants (39.8 ± 14.3 hours).

PHENOTHIAZINES:

Promethazine (0.25 to 0.5 mg/kg intravenously, intramuscularly, or orally) is an antihistaminic (H1blocker), antiemetic, anti-motion sickness, anticholinergic drug in addition to being a sedative. It is not a popular premedicant drug in pediatric anesthesia because of the reported dystonic reactions and it has long elimination half-life (8 to 12 hours). It has an insufficient effect when prescribed alone.

KETAMINE:

Ketamine has been administered via oral, nasal, and rectal routes. After oral and nasal administration, bioavailability is 17% and 50% respectively. Oral ketamine alone and in combination with midazolam has been used . Sedation is usually achieved after a dose of 5 to 6 mg/kg of oral ketamine in most children within 12 minutes. Larger doses may prolong recovery from anesthesia. The combination of oral midazolam and ketamine is synergistic.

OPIOIDS:

Neonates are very sensitive to the respiratory depressant effects of opioids. Fentanyl may be administered by parenteral, transdermal, nasal, and oral routes. A “lollipop” delivery system, oral transmucosal fentanyl citrate (OTCF) is more accepted by children than other routes. Fentanyl is strongly lipophilic. It is readily absorbed from the buccal mucosa and has an overall bioavailability of approximately 30-50%. The optimal dose as a preanesthetic medication appears to be 10 - 15 μg/kg.

Children begin to show signs of sedation within 10 minutes. Recovery from anesthesia after a premedication of 10 to 15 μg/kg of oral fentanyl is similar to that from a dose of 2 μg/kg intravenously.

CLONIDINE:

Clonidine is an α2 agonist. It causes dose-related sedation by its effect in the locus ceruleus through its inhibition of adenylatecyclase. The plasma concentration peaks at 60 to 90 minutes after oral administration and after rectal administration it peaks at 50 minutes. An oral dose of 3 μg/kg given 45 to 120 minutes before the surgery, produces comparable sedation to that of diazepam or midazolam.

REVIEW OF LITERATURE:

Anxiety in children coming for anaesthesia poses problems for the children, the parents and the anaesthesiologist. The long term implications of anxious child undergoing anaesthesia may be associated with long term adverse outcomes for the child. Several drugs through several different routes of administration have been used to overcome this problem. Latest is the armanetarium of premedicant drugs is the introduction of melatonin, which is known for its sleep producing effects. So this study was designed to compare the premedication effect of melatonin against the effects of midazolam. The study was designed to assess anxiety score at several points before induction and to study the impact of these drugs on the intra-operative haemodynamics and recovery characteristics of the child. To perform this study a diligent search was performed across various sources of published information to literature was reviewed to look at the related to this study. The relevant studies are presented below**.**

1. **NaguibM et al** [54] in 1999 evaluated the perioperative effects of melatonin vs midazolam in 75 adult women undergoing gynaecological laparoscopic procedures under general anaesthesia. Midazolam group received sublingual midazolam 15 mg from ampoule of IV preparation while melatonin group received 5 mg sublingually 2 hours before surgery.VAS scale was used to assess anxiety, orientation and sedation. Postoperatively psychomotor activity was evaluated. The findings in the study concluded that midazolam produced statistically significant sedation scores than melatonin at 30 and 60 mins(VAS score 5 vs 18). No significant difference was noted

in anxiety level either in the preoperative or recovery phase. Amnesia was noted only in the midazolam group.

2. **Tushar Patel et al**[64] in 2015 did a comparative study between oral melatonin and oral midazolam and placebo on preoperative anxiety, cognitive and psychomotor functions in patients aged 16-55 years posted for elective surgery. Patients were given either 0.4 mg/kg oral melatonin or 0.2 mg/kg oral midazolam or a placebo 60-90 minutes before induction. VAS scale was used to assess anxiety, orientation and sedation. Postoperatively psychomotor activity was evaluated. The findings in the study concluded that there was statistically significant difference in VAS anxiety score before and after premedication in all the 3 groups (VAS score 5.0±1.5vs 3.3 ± 1.3 in Melatonin group, 5.3±1.2 vs 3.1 ± 0.9 in Midazolam group and 5.0 ±1.2 vs 4.2 ±1.3 in placebo group) and also that midazolam and melatonin groups were comparable with respect to VAS scores(3.1± 0.9 vs 3.1 ± 1.3). Midazolam produced significantly more sedation compared with melatonin and placebo groups (1.3 vs 0.5 and 0.2 respectively). Orientation scores were comparable in all 3 groups. The Digit Symbol Substitution Test scores were increased in melatonin (25.28 ± 10.59 vs 27.22 ± 11.05) and placebo group (30.50 ± 11.38 vs 31.19 ±11.22) , while it was decreased in midazolam group after premedication (24.38 ± 5.46 vs18.75± 5.75) showing that psychomotor and cognitive functions were significantly affected in midazolam group patients.

3. **Reyhaneh et al** [62] in 2017 compared the effects of oral melatonin and oral midazolam as premedication in children undergoing general anaesthesia for dental

treatment . The study comprised of 132 children who were randomly assigned to one of 3 groups, oral midazolam group to receive 0.5mg/kg, oral melatonin group to receive 0.5 mg/kg, and placebo group to receive saline mixed with dextrose, all diluted to a volume of 15 ml. Patient's sedation score before GA (4 point sedation score), the ease of intravenous line establishment (4 point score), patient's need for pain killers and duration of recovery were evaluated. Patients in 3 groups were comparable in age, sex, and anaesthesia duration. The comparison showed statistically significant difference between midazolam and melatonin group as well as between midazolam and placebo groups in sedation score. 6.5% , 82.6%, 8.7%, and 2.2% of children in midazolam group were alert, awake, drowsy and asleep 40 minutes after premedication and 18.6%, 67.4%, 14.0% and 0.0% in melatonin group and 53.2%, 46.8%, 0.0%, and 0.0% in placebo group were alert, awake, drowsy and asleep at 40 minutes after premedication respectively. Its was shown that oral midazolam and oral melatonin were both effective to sedate patients than placebo administration. However, midazolam was more effective than melatonin. 15.2% of children showed no response to venepuncture in midazolam group compared with 2.3% and 2.1% in melatonin and placebo groups. The need for pain killer administration was observed in 31.9%, 8.8%, and 7% of placebo, melatonin, and midazolam groups respectively. Patients in the midazolam group exhibited faster recovery (79±29 minutes) than those in melatonin group (93±30 minutes) and the rate of recovery in melatonin group was comparable with that of placebo (78±30).

4. **Ionescu D et al** [53] in 2008 compared the effects of oral midazolam and oral melatonin administered as premedication in adult patients undergoing laparoscopic

cholecystectomy. The study comprised of 53 patients divided into 3 groups, oral melatonin (3mg), oral midazolam (3.75 mg), and placebo group. The trial drugs and placebo were prepared in a volume of 3 ml. The content of the syringe was given sublingually the night before surgery and 90 minutes before operation. Anxiety was evaluated by using CD Soielberger's questionnaire, STAI-S. Anxiety scores, the quality of preoperative sleep, and sedation scores were evaluated before the operation at patient arrival in the operation theatre and at 15 and 60 minutes and 6 and 24 hours postoperatively. Recovery time and the severity of postoperative pain (VAS score) was recorded. Preoperatively, there were no significant differences in sedation scores between the melatonin and midazolam groups and the placebo group. There was no significant difference between preoperative anxiety scores in the melatonin and midazolam groups; also this score was higher in the melatonin group (11.6 vs 10.5). The recovery time was shortest in the melatonin group (10.83 ± 5.36 min) compared with midazolam (13.18±4.73) and placebo groups (12.06 ±5.58) but it was not statistically significant. Postoperatively, the anxiety scores were significantly lower in the melatonin group (8.9, 8, 7.9, 7.2) at all time intervals , compared with midazolam (9.7, 10.4, 9.3, 9.3) and placebo groups (11.7, 11, 11.6,11.0) at 15min, 60 min, 6 hr, and 24 hrs after surgery. Postoperatively, sedation scores were significantly lower in the melatonin group compared to the midazolam group at 15 (1.6 vs 2.2) and 60 minutes (1.1 vs 1.6). The scores for remembered pictures was higher in the melatonin group at all time intervals. No side effects of melatonin was noted.

5. **RanaAltaf Ahmad et al** [6] conducted a study to evaluaten the sedation characteristics of sublingual melatonin and midazolam for premedication in 75 adult

patients aged 40-70 years undergoing cataract surgery under local anaesthesia. Group 1 received midazolam (sublingual, 0.5%, 0.1mg/kg), group 2 received melatonin (sublingual 0.05 mg/kg), group 3 received placebo (sublingual, saline). The Visual analogue scale was used to assess sedation and anxiety levels. Psychomotor activity was assessed using trigger dot test (TDT). There was no significant difference in VAS anxiety measurement between the groups after premedication and postoperatively. Orientation score was similar except at 15 and 30 min after premedication in midazolam group. At that time, only 20 patients were oriented to time and place compared to melatonin (24%) and placebo (23%) respectively. Regarding psychomotor function, there was significant difference in performing the TDT test for the midazolam group compared to melatonin and placebo ($p < 0.05$). 20% of patients in midazolam group and 22% of patients in melatonin group were satisfied with their premedication compared with 15% in the placebo group.

6. **Kain ZN et al** [58] in 2009 studied preoperative melatonin and its effects on induction and emergence in children aged 2-8 years scheduled for general anaesthesia and outpatient elective surgery by comparing oral midazolam 0.5 mg/kg with oral melatonin 0.05 mg/kg, 0.2 mg/kg or 0.4 mg/kg. Preoperative anxiety (Yale Preoperative Anxiety Scale), compliance with induction (Induction Compliance Checklist), emergence behaviour (Keegan Scale) and parental anxiety (State-Trait Anxiety Inventory) were studied. The groups did not differ in their anxiety in the holding area or at separation from parents. Child anxiety was less in midazolam group compared with the three melatonin groups at induction of anaesthesia. The proportion of high compliance rating (ICC score of 0) was significantly greater in the

midazolam group when compared with melatonin groups (73.3% vs 49.5%, P< 0.001). The incidence of emergence delirium was highest in the midazolam group (25.6%). Melatonin groups demonstrated a dose-response effect on emergence and incidence of emergence delirium was greatest after 0.05 mg/kg melatonin (25.0%) followed by 0.2 mg/kg (8.3%) and 0.4 mg/kg (5.4%).

7. **Eloisa Gitto et al** [63] in 2015 investigated the possible effect of melatonin premedication, in comparison to midazolam, on the required infusion of propofol in children undergoing surgery. The effect of oral melatonin on the preoperative sedation and post anaesthesia recovery score were also evaluated. 92 patients, 46 in each group were to receive either 0.5 mg/kg oral melatonin (max. 20 mg) or 0.5 mg/kg oral midazolam (max. 20 mg) before induction of anaesthesia with propofol. Sedation was assessed with University of Michigan Sedation Scale (UMSS) before and 40 minutes after premedication. Melatonin premedication significantly enhanced the effects of propofol, resulting in significantly lower administered drug doses. Children in the melatonin group received a mean dose of 2.08 ± 0.59 mg/kg propofol (95% CI: 1.91–2.25), while the mean dose was 2.85 ± 1.43 mg/kg propofol (95% CI: 1.02– 1.84) in the midazolam group ($P < 0.001$). Similarly, the mean total dose of propofol administered differed significantly: 69.2 ± 27.5 mg (95% CI: 61.2–77.1) in the melatonin group vs 100.8 ± 27.2 mg (95% CI: 92.9–108.6) in the midazolam group ($P < 0.001$). On arrival in the operating room, patients who had received melatonin premedication were equally sedated to those who received midazolam. The Aldrete score assessed after surgical procedures was similar between the two groups; they were orientated in both time or place. No reported side effects

were observed in either group.

8. **Kate Rempel et al** [69] in 2015 conducted a study for assessing the effect of supplemental melatonin on anxiety and pain levels of children . 60 children who required blood testing were randomized into two groups. Oral melatonin 0.5 mg/kg to a maximum of 5mg or placebo is given 30 minutes before the procedure. Pre-procedural anxiety was assessed using the scale from the Children's Anxiety and Pain Scales, while procedural pain used the Face, Legs, Activity, Cry and Consolabilityassessment tool for children under the age of 3 years, Faces Pain Scale Revised for children ages 3 to 8 years, and Numeric Rating Scale for children over the age of 8 years. Oral administration of melatonin before the blood withdrawal procedure significantly reduced both anxiety (P<0.0005) and pain levels compared to placebo (P<0.0002 for children under 3 years and P<0.0039 for children over 3 years).

9. **L.P.H. Andersen et al**[68] in 2014 published "A systematic review of peri-operative melatonin" which systematically included 24 studies of 1794 participants that reported 8 peri-operative outcomes: anxiety, analgesia, sleep quality, oxidative stress, emergence behaviour , anaesthetic requirements, steal induction, and safety. Compared with Placebo, melatonin reduced the standardised mean difference preoperative anxiety score by 0.88 and postoperative pain score by 1.06. The magnitude of effect was unreliable due to substantial statistical heterogeneity. Qualitative reviews suggested the melatonin improved sleep quality and emergence behaviour, and might be capable of reducing oxidative stress and anaesthetic requirements.

10. **ArvindKhare et al** [70] in 2018 compared the effects of oral melatonin with oral alprazolam used as a premedicant in 90 adult patients undergoing any surgical procedure under general anaesthesia. Patients were divided into 3 groups receiving oral melatonin 3mg, oral alprazolam 0.25 mg and oral low dose multi-vitamin tablets 120 minutes before induction of anaesthesia. Anxiety, sedation, orientation, and cognitive function were assessed before and 120 minutes after premedication using Visual analogue scale, Ramsay sedation score, orientation score and Digit symbol Substitution test (DSST). In melatonin group and alprazolam group, VAS score was significantly reduced (4.9 to 3.9) and (4.93 to 4.43) before and after premedication respectively and it was insignificant in the multi-vitamin group. The sedation scores were significantly more in alprazolam group compared to the other two groups (2.7 vs 2.0 and 1.5). No significant difference was noted in the 3 groups in orientation scores. DSST scores were increased (17.86 to 22.36) in melatonin group compared to alprazolam group in which it was reduced (19.3 to 15.7). No significant difference was noted between melatonin and placebo groups.

11. **Maurizia Capuzzo et al** [55] in 2006 conducted a study to compare preoperative anxiety in 150 elderly patients receiving either 10 mg of melatonin (M) or placebo (P). On the day of surgery, in a quiet room (T-basal), the study investigator, collected general data from the patients. Subsequently, anxiety and depression were measured, cognitive tests administered, and the study medication given to the patient. Ninety minutes after study medication administration, before surgery (T-pre), anxiety and depression were assessed. After surgery (T-post), the investigator measured anxiety, depression, and pain and administered cognitive tests. Seven days after hospital

discharge (T-fup), anxiety, depression, pain, and satisfaction with anesthesia were assessed, and cognitive tests were administered. The level of anxiety was measured using a numerical rating scale ranging from 0 to 10, where 0 means no anxiety and 10 means the maximum anxiety possible. The level of depression and pain was measured by a numerical rating scale (range, 0–10). Executive brain functions were explored with the Frontal Assessment Battery, with scores ranging from 0 to 18. Episodic memory was evaluated with the Babcock Story Recall Test, with scores ranging from 0 to 16 , by immediate and delayed recall .The anxiety level was 5 (2– 8) at T-basal and 3 (1–7) at T-pre in group P and 5 (3– 6) and 3 (1–5), respectively, in group M.. In each group, the anxiety levels showed a significant decrease from T-basal to T-pre, to T-post. The median score of satisfaction with anesthesia at T-follow-up was 100 (range, 76–100) in group P and 99 (range, 80–100) in group M. It was showed that melatonin, in comparison with placebo, does not significantly reduce anxiety in elderly patients undergoing elective surgery.

12. **Shrestha S, et al** [65] in 2007 evaluated the oral administration of intravenous solution of midazolam mixed in syrup of paracetamol in 60 children undergoing elective hernia repair under general anaesthesia. The study comprised of 2 groups- group A- oral midazolam 0.5 mg/kg, mixed in paracetamol syrup and group B – just the paracetamol syrup. In the study group, out of 30 patients, 22 patients (73.3%) showed excellent parent-child separation, 7 patients (23.3%) showed good separation, while only 1 patient (3.3%) had a poor separation. In the placebo group, only 6 patients (20.0%) showed excellent parent child separation, 10 patients (33.3%)

showed good separation and 11 patients (36.7%) had poor separation. The recovery time from general anaesthesia was not different in the two groups. No significant peri operative complications directly related to oral midazolam was noted.

13. **Binita Srivastava et al [61]** in 2014 compared the acceptability and efficacy of orally administered commercially available midazolam syrup and injection midazolam mixed in honey in 40 anxious and healthy children aged 2 to 6 years undergoing brief dental procedures under IV sedation. All subjects received either syrup midazolam or injection midazolam mixed in honey (0.5 mg/kg) per orally, prior to venepuncture. Acceptability of midazolam was 95% in the 1st group compared with 80% in the 2nd. Sedation scores measured with Houpt's scores for sleep, crying, movement and overall behaviour was not statistically significant between the two groups.Parental and observer satisfaction was higher in 1st group (100% vs 90%).

14. **L D Mishra et al** [71] in 2003 conducted a study to find out the acceptability, efficacy and safety of injectable midazolam as oral premedicant in 100 Paediatric neurosurgical patients aged 6 months to 6 years. The patients were randomly assigned to one of four groups receiving either saline or 0.5, 0.75 or 1.0 mg/kg midazolam in honey, 45 minutes before separation from parents. Age, sex, weight, heart rate, blood pressure, respiratory rate, saturation, reaction to parent's separation, sedation score, duration of anaesthesia, recovery conditions and side effects were assessed. The acceptance of the medication was 100% in groups A and C and 96% and 92% in groupsB and D respectively. More children were comfortable in midazolam groups B,C, and D (72%, 84% and 92%) respectively compared to placebo group (16%) during separation from parents. 4%, 8% and 24% of patients and 8%, 16% and 40% of

patients in groups B,C, and D showed increased ease of venepuncture and for induction respectively. Recovery of spontaneous ventilation and extubation was delayed over 5 minutes in 5 (20%) and 7 (28%) patients of groups C and D respectively. It was shown that injectable midazolam given orally as premedication scheduled for neurosurgical operations is acceptable, effective and safe in 0.75 mg/kg dose. While 0.5 mg/kg is less effective, 1.0 mg/kg does not offer any additional benefit over 0.75 mg/kg but does delay recovery and may compromise safety.

15. Keles .S et al [72] in 2018 compared oral dexmedetomidine with oral midazolam for premedication and emergence delirium in 52 children aged between 3-7 years after dental procedures under general anaesthesia. 26 children were given 2mcg/kg of oral dexmedetomidine and another 26 were given 0.5 mg/kg of oral midazolam. The Ramsay Sedation Scale, the Parental Separation Anxiety Scale, the Mask Acceptance Scale and the Paediatric Anaesthesia Emergence Delirium Scale were used for assessment. Both drugs provided effective sedation, satisfactory separation from parents, and satisfactory mask acceptance in children between 3 and 7 years of age. The mask acceptance scales and PSAS scores and RSS scores were not statistically different with $p>0.05$ in both groups, whereas the PAEDS scores were significantly lower in the DEXmed group with 100% absence of emergence delirium compared with 80.8% absence of emergence delirium in midazolam group.

16**. C.O McMillan et al**[66] in 1992 conducted a study on the safety, efficacy and feasibility of oral midazolam premedication in 80 children in an ambulatory surgery unit. The children were randomly assigned to 4 groups to receive midazolam – 0.5, 0.75, 1.0 mg/kg or a placebo 30 minutes before separation from parents. Sedation and anxiolysis were assessed using 4-point scale. Heart rate, systolic blood pressure, respiratory rate, and arterial oxygen saturation were assessed. Level of consciousness and agitation in PACU were assessed using 4-point scale. 40-60% of children who were given midazolam were drowsy but responsive to verbal/tactile stimuli (sedation score of 3) at time of separation and 80-90% of midazolam treated children had excellent anxiolysis (anxiety scores of 3 or 4) at the time of separation from their parents. Application of face mask at induction of anaesthesia was accepted more readily in midazolam group. Loss of balance and head control were observed in nine children; four in the 0.75mg/kg group (20%), and 5 in the 1mg/kg group (25%). It was concluded from the study that oral midazolam 0.5 mg/kg is a safe and effective premedication with $p>0.05$ and that 0.75 mg/kg and 1.0 mg/kg [$p=0.05$] while offering no additional benefit, may cause more side effects.

MATERIALS AND METHODOLOGY:

The Study was conducted in Govt. Stanley Medical College and Hospital in the Department of Paediatric Surgery from December 2018 to May 2019.

After institutional Ethics Committee approval and informed written consent from parents of the children, 72 ASA I-II children were enrolled for the study based on the inclusion and exclusion criteria. Patients were randomised into two groups i.e., group M & group MT using computer generated random numbers.

GROUPS:

Group M : Midazolam 0.5 mg/Kg reconstituted with honey to a volume of 5 ml

Group MT: Melatonin 0.5 mg/Kg as syrup reconstituted with honey to a volume of 5 ml

STUDY DESIGN:

A double blinded prospective randomized control study

INCLUSION CRITERIA:

- Patients aged between 2-8 years
- ASA Physical status I and II
- Undergoing elective surgery under general anaesthesia or general anaesthesia with regional anaesthesia
- Both sexes

EXCLUSION CRITERIA:

- History of psychiatric disorders, on antipsychotic drugs
- Sleep disorders
- Renal or hepatic derangement
- Mental retardation
- Known allergy to study drugs
- Color blindness
- Cardiovascular and respiratory dysfunction
- Obesity

PRIMARY OBJECTIVE:

To compare the effects of oral midazolam and oral melatonin as premedicant in paediatric patients undergoing elective surgical procedures under general anaesthesia with / without regional anaesthesia

Anxiety, and sedation scores are assessed at 15 mins, 30 mins, 45 mins and 60 mins after premedication and sedation and behaviour scores are assessed at separation from parents.

SECONDARY OBJECTIVES:

To assess

1. Reaction to venepuncture
2. Wake-up behaviour
3. Readiness to discharge from PACU at one hour postoperatively
4. Side effects, if any

PREOPERATIVE PREPARATION:

During pre-anaesthetic assessment, detailed clinical history was obtained, thorough general and systemic examination was carried out. Routine hematological and biochemical investigations were done as per institutional protocol.

Oral formulation was prepared by an independent anaesthesiologist not participating further in the observation or administration of anaesthesia.Children allotted to **Group M** received Midazolam 0.5 mg/Kg reconstituted with honey to a volume of 5 ml and children allotted to **Group MT** received Melatonin 0.5 mg/Kg as syrup reconstituted with honey to a volume of 5 ml, 60 minutes prior to surgery. After administration of the drug, anxiety score, sedation score and behaviour score was noted by a blinded observer every 10 minutes till separation from parent.

In operation theatre, the attending anaesthesiologist assessed the sedation status and behaviour at induction of anaesthesia using the same scales. IV access was obtained and a balanced salt solution infusion was started. All standard monitors and safety protocols recommended for paediatric anaesthesia were strictly adhered to.

Anaesthetic choice (intravenous vs inhalational / general anaesthesia with / without regional anaesthesia) was left to the discretion of the attending anaesthesiologist. Sedatives like benzodiazepines, drugs like ketamine were avoided.At the conclusion of surgery, anaesthesia was terminated and Behaviour of the child at awakening was recorded. Patient's vitals were monitored throughout the procedure by means of continuous ECG, non invasive blood pressure and pulse oximetry. Post operatively patients were assessed for wake up behaviour score upto 1 hour and postoperative recovery at one hour was assessed with Aldrete score.

EVALUATION SCALES:

RAMSAY Sedation Scale:

Response	Score
Awake and anxious,agitated, or restless	1
Awake, cooperative, accepting ventilation, oriented, tranquil	2
Awake; responds only to commands	3
Asleep; brisk response to light, glabellar tap or loud noise	4
Asleep; sluggish response to light, glabellar tap or loud noise	5
Asleep; no response to light, glabellar tap or loud noise	6

Behavior scores:

Calm and cooperative	1
Anxious but reassurable	2
Anxious and not reassurable	3
Crying, or resisting	4

Wake-up behavior scores:

Calm and cooperative	1
Not calm but could be easily calmed	2
Not easily calmed, moderately agitated or restless	3
Combative, excited, disoriented	4

Aldrete Scoring System:

Parameter		Score
ACTIVITY: Able to move voluntarily or on command	4 extremities	2
	2 extremities	1
	0 extremities	0
RESPIRATION	Able to take deep breath and cough freely	2
	Dyspnoeic , shallow or limited breathing	1
	Apnoeic	0
CIRCULATION	BP +/- 20 mmHg of preanaesthetic level	2
	BP +/- 20 – 50 mmHg of preanaesthetic level	1
	BP more than +/- 50 mmHg of preanaesthetic level	0
CONCIOUSNESS	Fully awake	2
	Arousable on calling	1
	Not responding	0

O2 SATURATION	Able to maintain O2 saturation >92% on room air	2
	Needs O2 inhalation to maintain O2 saturation >90%	1
	O2 saturation <90% even with O2 supplementation	0

RESULTS AND ANALYSIS:

DATA ANALYSIS:

The collected data were analyzed with IBM.SPSS statistics software 23.0 Version. To describe about the data descriptive statistics frequency analysis, percentage analysis was used for categorical variables and for continuous variables the mean and S.D were used.The mean values and standard deviation were calculated by using appropriate formula both for grouped and ungrouped data. To find the significant difference between the bivariate samples for Independent groups the Unpaired sample t-test was used. To find the association of significance in categorical data the Chi-Square test was used. In all the above statistical tools the probability value 0.05 was considered as significant level.

DEMOGRAPHIC DATA:

AGE DISTRIBUTION:

Crosstab

			GROUP		Total
			Midazolam 0.5 mg/Kg	Melatonin 0.5 mg/Kg	
AGE_GROUP	2-3 YEARS	Count	22	23	45
		% within GROUP	61.1%	63.9%	62.5%
	4 -5 YEARS	Count	5	5	10
		% within GROUP	13.9%	13.9%	13.9%
	6 - 7 YEARS	Count	3	6	9
		% within GROUP	8.3%	16.7%	12.5%
	8 YEARS	Count	6	2	8
		% within GROUP	16.7%	5.6%	11.1%
Total		Count	36	36	72
		% within GROUP	100.0%	100.0%	100.0%

Pearson Chi-Square=3.022 P=0.388

SEX DISTRIBUTION:

Crosstab

			GROUP		Total
			Midazolam 0.5 mg/Kg	Melatonin 0.5 mg/Kg	
SEX	FCH	Count	10	6	16
		% within GROUP	27.8%	16.7%	22.2%
	MCH	Count	26	30	56
		% within GROUP	72.2%	83.3%	77.8%
Total		Count	36	36	72
		% within GROUP	100.0%	100.0%	100.0%

Pearson Chi-Square=1.286 P=0.257

Demographic data like age and sex of the patients are comparable between the two groups and there is no statistically significant difference between the two.

CHOICE OF ANAESTHESIA:

GROUP Cross tabulation:

			GROUP		Total
			Midazolam 0.5 mg/Kg	Melatonin 0.5 mg/Kg	
GA	GA	Count	5	7	12
		% within GROUP	13.9%	19.4%	16.7%
	GA +RA	Count	31	29	60
		% within GROUP	86.1%	80.6%	83.3%
Total		Count	36	36	72
		% within GROUP	100.0%	100.0%	100.0%

Pearson Chi-Square=0.400 p=0.527

In M group and MT group, 5 (13.9%) and 7 (19.4%) patients underwent surgery under general anaesthesia respectively and, 31 (86.1%) and 29 (80.6%) patients underwent surgery under general anaesthesia with regional anaesthesia respectively. There is statistically no significant difference between the two groups in terms of choice of anaesthesia

ANXIETY SCORES AFTER PREMEDICATION:

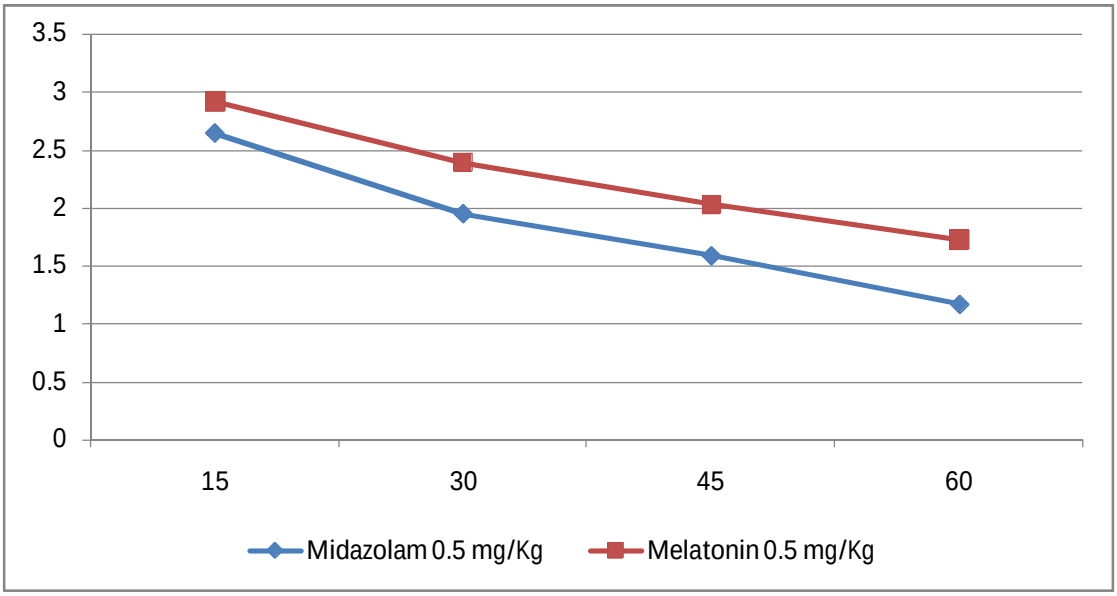
COMPARISON OF ANXIETY SCORE FOR GROUPS IN EACH PERIOD:

Descriptive Statistics	GROUP	Mean	Std. Deviation	N
15-MINUTES ANXIETY SCORE	Midazolam 0.5 mg/Kg	2.6389	.76168	36
	Melatonin 0.5 mg/Kg	2.9167	.73193	36
	Total	2.7778	.75475	72
30-MINUTES-ANXIETY-SCORE	Midazolam 0.5 mg/Kg	1.9444	.33333	36
	Melatonin 0.5 mg/Kg	2.3889	.59894	36
	Total	2.1667	.53074	72
45-MINUTES-ANXIETY-SCORE	Midazolam 0.5 mg/Kg	1.5833	.50000	36
	Melatonin 0.5 mg/Kg	2.0278	.37691	36
	Total	1.8056	.49330	72
60-MINUTES-ANXIETY-SCORE	Midazolam 0.5 mg/Kg	1.1667	.37796	36

	Melatonin 0.5 mg/Kg	1.7222	.56625	36
	Total	1.4444	.55383	72

COMPARISON OF INTRAGROUP ANXIETY SCORES WITH RESPECT TO TIME:

4. GROUP * TIME							
GROUP	TIME (in mins)	Mean	Std. Error	95% Confidence Interval		F value	
				Lower Bound	Upper Bound	Time	Group
Midazolam 0.5 mg/Kg	15	2.639	.124	2.391	2.887	127.036** **p<0.001	1.289 P=0.279
	30	1.944	.081	1.783	2.106		
	45	1.583	.074	1.436	1.731		
	60	1.167	.080	1.007	1.327		
Melatonin 0.5 mg/Kg	15	2.917	.124	2.668	3.165		
	30	2.389	.081	2.228	2.550		
	45	2.028	.074	1.881	2.175		
	60	1.722	.080	1.562	1.882		



The mean values of anxiety score in the M group were 2.639 ± 0.76, 1.944 ±0.33, 1.583 ±0.50 and 1.167 ± 0.378 and in the MT group were 2.917 ± 0.73, 2.389 ± 0.598, 2.028 ± 0.377, and 1.722 ± 0.567 at 15, 30, 45, and 60 minutes after premedication. Thus, anxiety scores are significantly lower with respect to time ($P < 0.001$) in both the groups.

Anxiety is decreasing in the same manner in both the groups and there is no statistically significant difference in the anxiety scores between the two groups ($P = 0.279$)

SEDATION SCORES AFTER PREMEDICATION:

COMPARISON OF SEDATION SCORE FOR GROUPS IN EACH PERIOD:

Descriptive Statistics	GROUP	Mean	Std. Deviation	N
@15-MINUTES-SEDATION-SCORE	Midazolam 0.5 mg/Kg	1.5556	.55777	36
	Melatonin 0.5 mg/Kg	1.2222	.42164	36
	Total	1.3889	.51882	72
@30-MINUTES-SEDATION-SCORE	Midazolam 0.5 mg/Kg	2.2222	.59094	36
	Melatonin 0.5 mg/Kg	1.6667	.53452	36
	Total	1.9444	.62549	72
@45-MINUTES-SEDATION-SCORE	Midazolam 0.5 mg/Kg	2.7500	.80623	36
	Melatonin 0.5 mg/Kg	2.0000	.23905	36
	Total	2.3750	.70085	72
@60-MINUTES-SEDATION-SCORE	Midazolam 0.5 mg/Kg	3.3889	.80277	36

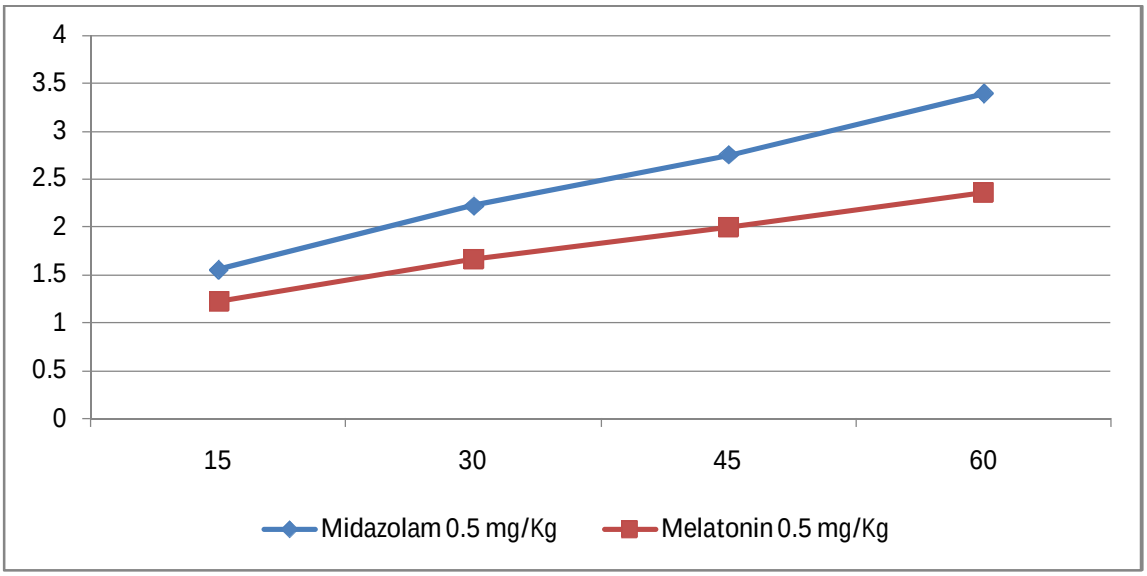
	Melatonin 0.5 mg/Kg	2.3611	.59295	36
	Total	2.8750	.87109	72

COMPARISON OF INTRAGROUP SEDATION SCORES WITH RESPECT TO TIME:

4. GROUP * TIME							
GROUP	TIME (in mins)	Mean	Std. Error	95% Confidence Interval		F value	
				Lower Bound	Upper Bound	Time	Group
Midazolam 0.5 mg/Kg	15	1.556	.082	1.391	1.720	145.216** **p<0.001	7.905** **p<0.001
	30	2.222	.094	2.035	2.410		
	45	2.750	.099	2.552	2.948		
	60	3.389	.118	3.154	3.623		
Melatonin 0.5 mg/Kg	15	1.222	.082	1.058	1.387		
	30	1.667	.094	1.479	1.854		
	45	2.000	.099	1.802	2.198		
	60	2.361	.118	2.127	2.596		

The mean sedation scores in the M group were 1.556 ± 0.557, 2.222 ± 0.590, 2.750 ± 0.806, 3.389 ± 0.803 at 15, 30, 45, and 60 minutes after premedication. In MT group,

the mean sedation scores were 1.222 ± 0.421, 1.667 ± 0.534, 2.00 ±0.239,and 2.361 ± 0.592 at 15, 30, 45, and 60 minutes respectively after premedication. Thus sedation scores increased significantly in both the groups with respect to time (P<0.001)



Sedation is increasing in the same manner in both the groups but sedation scores are significantly lower in the MT group when compared with the M group (P<0.001)

COMPARISON OF HEART RATE AFTER PREMEDICATION:

Descriptive Statistics

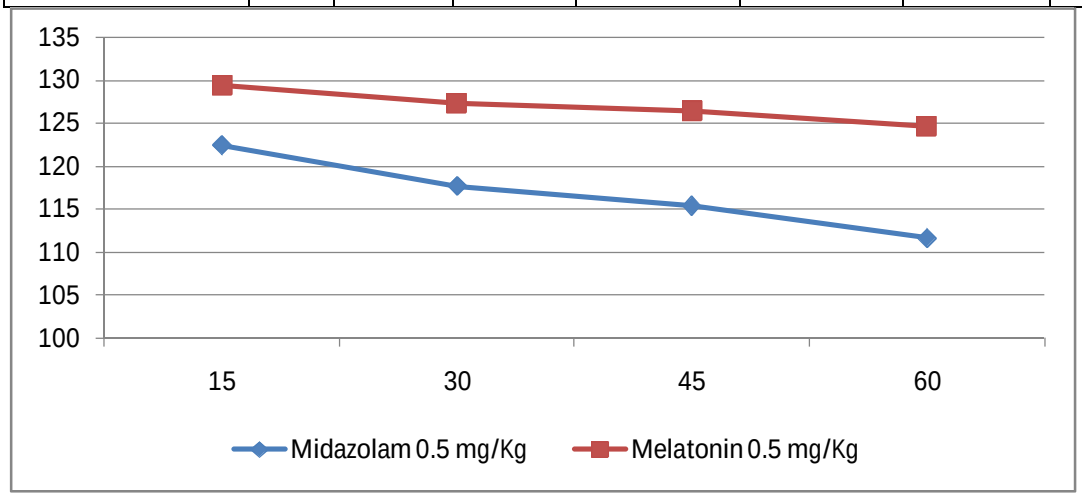
	GROUP	Mean	Std. Deviation	N
@15-MINUTES-HR	Midazolam 0.5 mg/Kg	122.4167	15.08145	36
	Melatonin 0.5 mg/Kg	129.3333	12.50600	36
	Total	125.8750	14.18980	72
@30-MINUTES-HR	Midazolam 0.5 mg/Kg	117.7222	14.08264	36
	Melatonin 0.5 mg/Kg	127.2500	11.56689	36
	Total	122.4861	13.66500	72
@45-MINUTES-HR	Midazolam 0.5 mg/Kg	115.4167	13.85718	36
	Melatonin 0.5 mg/Kg	126.4167	11.01784	36
	Total	120.9167	13.60794	72

	Midazolam 0.5 mg/Kg	111.6944	13.65874	36
@60-MINUTES-HR	Melatonin 0.5 mg/Kg	124.6111	10.94735	36
	Total	118.1528	13.90477	72

COMPARISON OF INTRAGROUP HEART RATE SCORES WITH RESPECT TO TIME:

GROUP * TIME							
GROUP	TIME (in mins)	Mean	Std. Error	95% Confidence Interval		F value	
				Lower Bound	Upper Bound	Time	Group
Midazolam 0.5 mg/Kg	15	122.417	2.309	117.812	127.022	39.04****p<0.001	6.074****p<0.001
	30	117.722	2.148	113.439	122.006		
	45	115.417	2.086	111.256	119.578		
	60	111.694	2.063	107.580	115.809		

Melatonin 0.5 mg/Kg	15	129.333	2.309	124.728	133.938		
	30	127.250	2.148	122.967	131.533		
	45	126.417	2.086	122.256	130.578		
	60	124.611	2.063	120.497	128.725		



The mean HR scores were 122.42 ± 15.08, 117.72 ± 14.08, 115.42 ± 13.85 and 111.69 ± 13.66 at 15, 30, 45, and 60 minutes respectively after premedication in M group. And in the MT group, the mean HR scores were 129.33 ± 12.50, 127.25 ± 11.57, 126.42 ±11.01, and 124.61 ± 10.95 at 15, 30, 45, and 60 minutes after premedication. Thus the HR scores decreased with time in both the groups and it is statistically significant (P<0.001). The mean HR scores were significantly lower in the M group (P<0.001) when compared with the MT group.

Comparison of SPO2 AFTER PREMEDICATION:

Descriptive Statistics

	GROUP	Mean	Std. Deviation	N
@15-MINUTES-SpO2	Midazolam 0.5 mg/Kg	99.3333	.58554	36
	Melatonin 0.5 mg/Kg	99.4444	.50395	36
	Total	99.3889	.54529	72
@30-MINUTES-SpO2	Midazolam 0.5 mg/Kg	96.8889	14.90307	36
	Melatonin 0.5 mg/Kg	99.5278	.50631	36
	Total	98.2083	10.55360	72
@45-MINUTES-SpO2	Midazolam 0.5 mg/Kg	99.3611	.48714	36
	Melatonin 0.5 mg/Kg	99.5833	.50000	36
	Total	99.4722	.50273	72
@60-MINUTES-SpO2	Midazolam 0.5 mg/Kg	99.3889	.49441	36

	Melatonin 0.5 mg/Kg	99.5833	.50000	36
	Total	99.4861	.50331	72

COMPARISON OF INTRAGROUP SpO2 SCORES WITH RESPECT TO TIME:

4. GROUP * TIME							
GROUP	TIME (in mins)	Mean	Std. Error	95% Confidence Interval		F value	
				Lower Bound	Upper Bound	Time	Group
Midazolam 0.5 mg/Kg	15	99.333	.091	99.152	99.515	0.988	0.970
	30	96.889	1.757	93.384	100.394		
	45	99.361	.082	99.197	99.525		
	60	99.389	.083	99.224	99.554		
Melatonin 0.5 mg/Kg	15	99.444	.091	99.263	99.626		
	30	99.528	1.757	96.023	103.033		
	45	99.583	.082	99.419	99.747		
	60	99.583	.083	99.418	99.749		

There is a mean decrease of SpO2 value to 96.89 ± 14.90 at 30 minutes after premedication in the M group. But there is statistically no significant decrease in the SpO2 scores with respect to time in both the groups (P=0.988). Also, there is no significant difference noted in the SpO2 scores between the two groups (P=0.970)

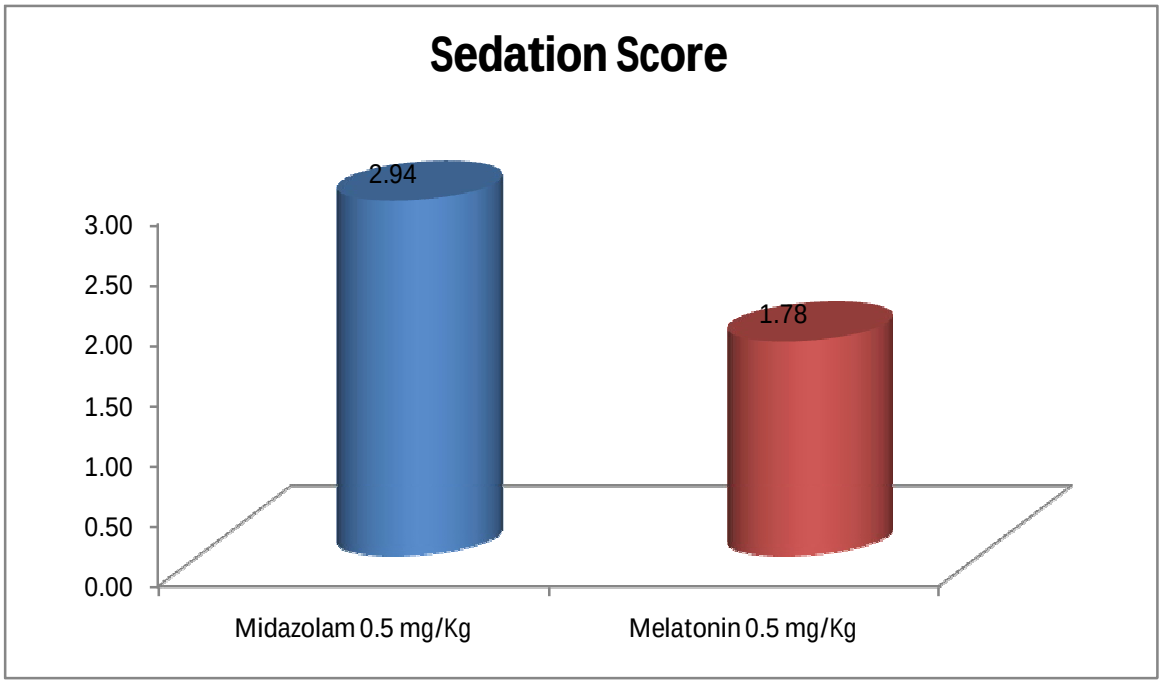
SCORES DURING SEPARATION FROM PARENTS AND AT VENEPUNCTURE:

Group Statistics						
	GROUP	N	Mean	Std. Deviation	Std. Error Mean	
SEDATION SCORE	Midazolam 0.5 mg/Kg	36	2.9444	.58282	.09714	7.547** (sig)
	Melatonin 0.5 mg/Kg	36	1.7778	.72155	.12026	
BEHAVIOUR SCORE	Midazolam 0.5 mg/Kg	36	3.0833	.73193	.12199	5.667** (sig)
	Melatonin 0.5 mg/Kg	36	2.0278	.84468	.14078	
HR	Midazolam 0.5 mg/Kg	36	112.5556	12.12894	2.02149	5.186** (sig)
	Melatonin 0.5 mg/Kg	36	126.4167	10.48911	1.74818	

SpO2	Midazolam 0.5 mg/Kg	36	99.4444	.50395	.08399	2.183* (sig)
	Melatonin 0.5 mg/Kg	36	99.6944	.46718	.07786	
REACTION TO VENEPUNC-TURE	Midazolam 0.5 mg/Kg	36	.9167	.84092	.14015	6.910** (sig)
	Melatonin 0.5 mg/Kg	36	2.2222	.76012	.12669	

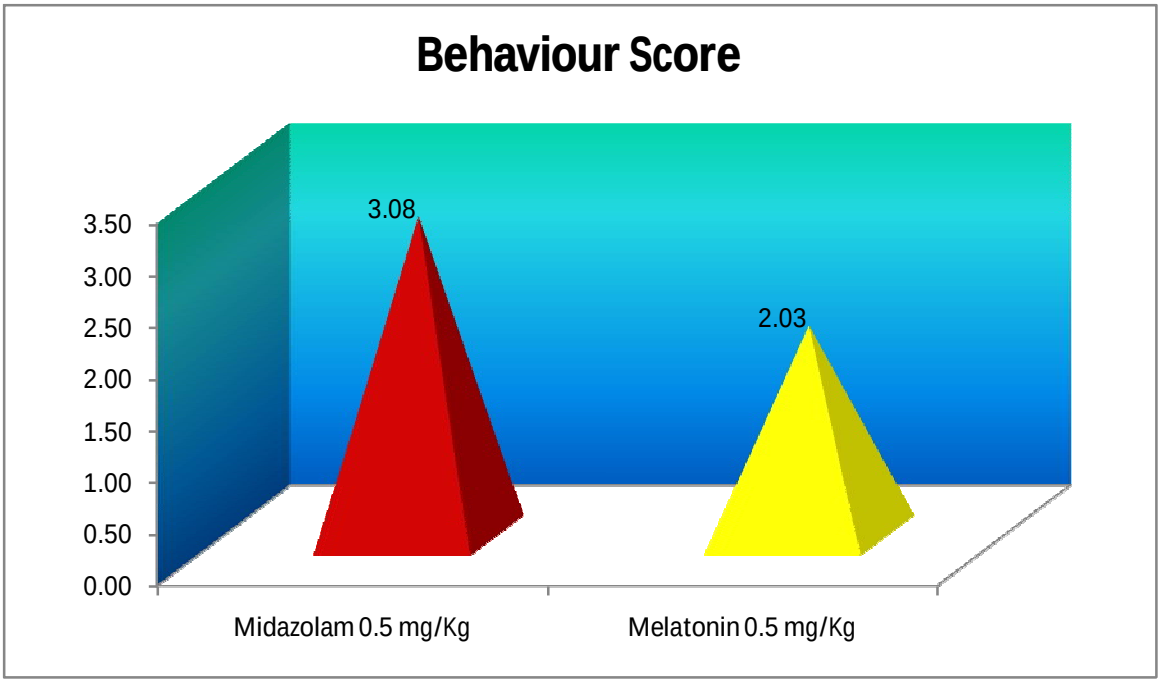
**p<0.001 *p<0.05

SEDATION SCORE DURING SEPARATION FROM PARENTS:



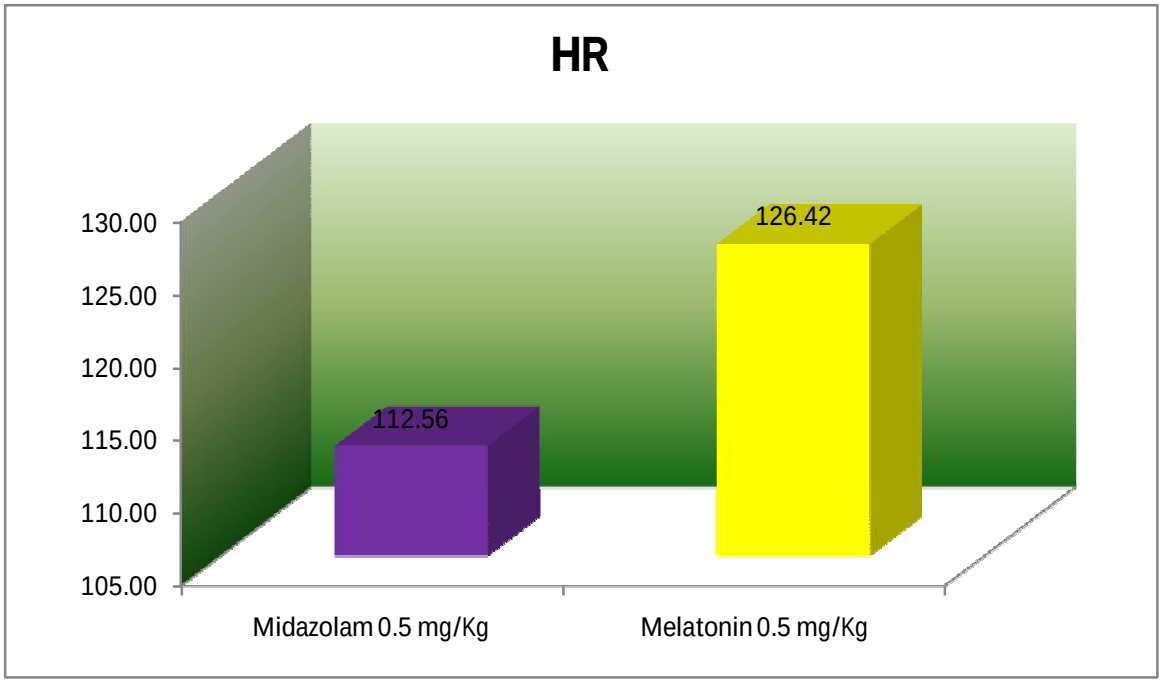
The mean sedation score during separation from parents in the M group was 2.94 ± 0.58 which is significantly higher when compared with the MT group 1.78 ±0.72 ($P<0.001$)

BEHAVIOUR SCORE DURING SEPARATION FROM PARENTS:



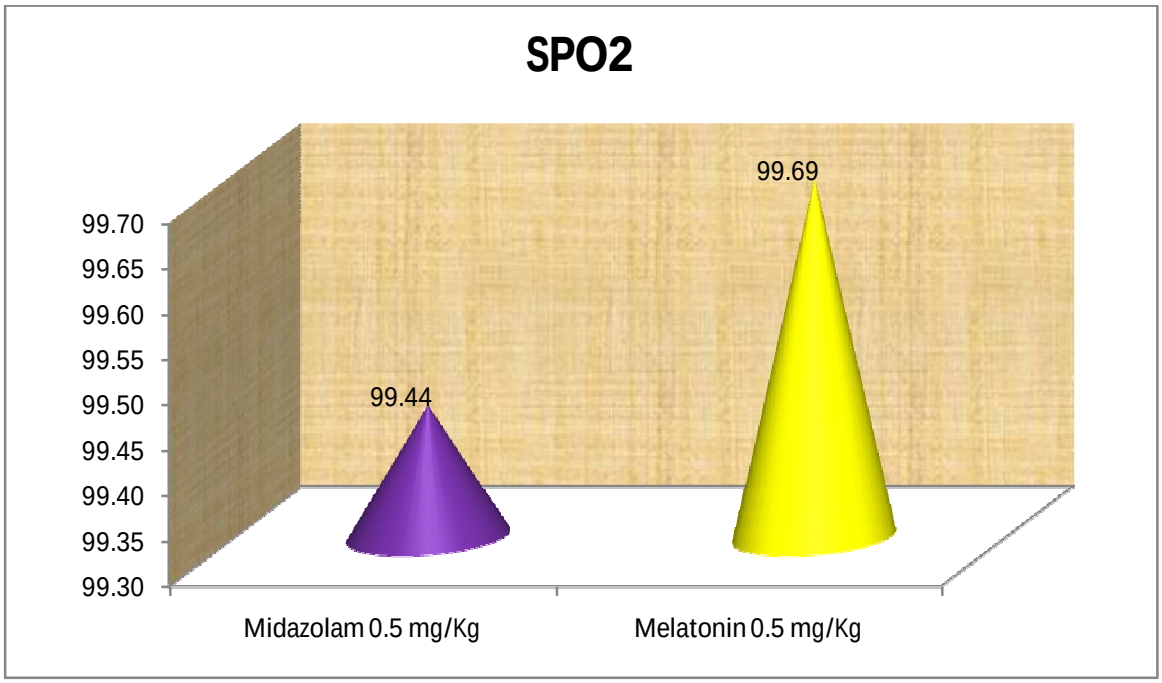
The mean behaviour score during separation from parents in the M group was 3.08 ±0.73 and in the MT group was 2.02 ± 0.84. Thus M group showed significantly better behaviour scores than MT group (P<0.001).

HEART RATE DURING SEPARATION FROM PARENTS:



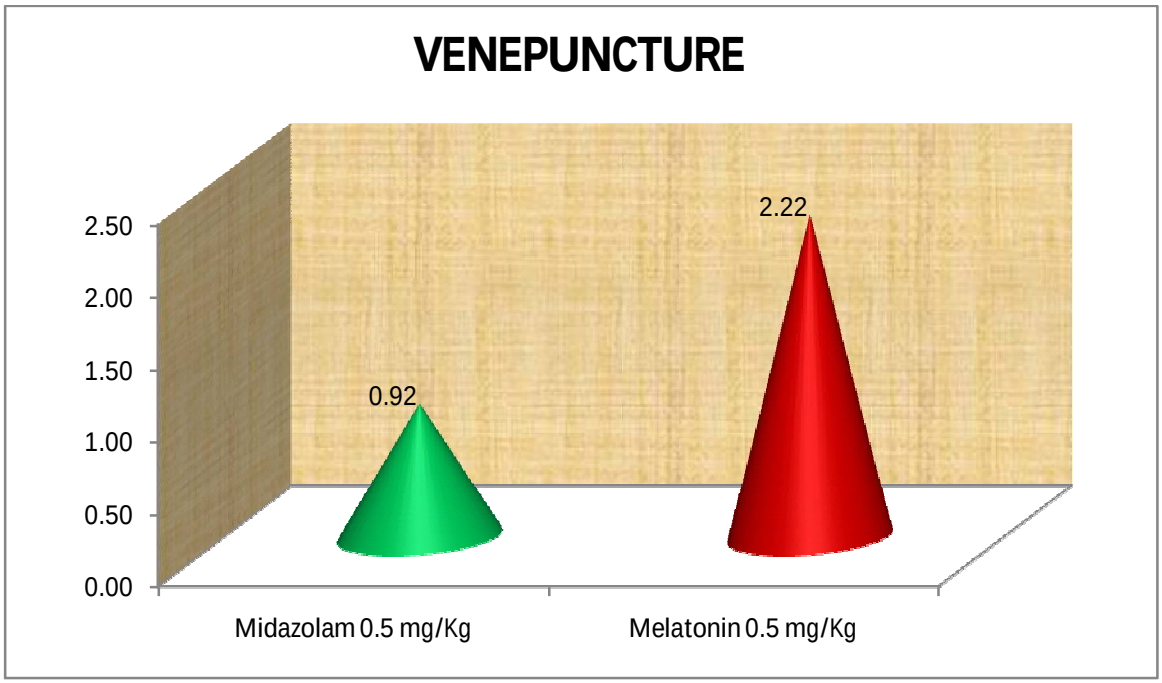
The mean HR scores during separation from parents in the M and MT groups were 112.56 ± 12.13 and 126.42 ± 10.49 respectively. Thus M group showed statistically significant decrease in HR scores compared with MT group ($P<0.001$)

SpO2 SCORE DURING SEPARATION FROM PARENTS:



The mean SpO2 score during separation from parents in M group was 99.44 ± 0.50 and in MT group was 99.69 ± 0.47. M group showed significantly lower SpO2 scores compared with MT group ($P<0.05$)

REACTION TO VENEPUNCTURE SCORE:

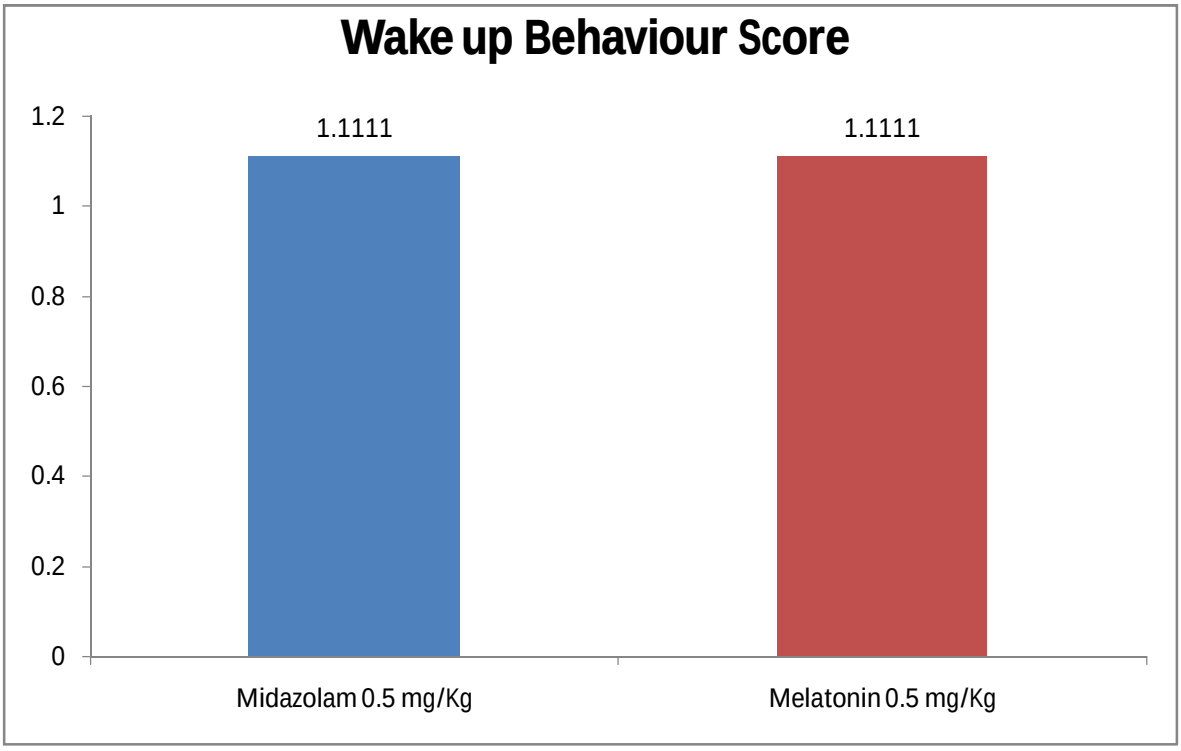


MT group showed a significantly more response to venepuncture (mean score of 2.22 ± 0.76) when compared with M group (mean score of 0.916 ± 0.84) (P<0.001)

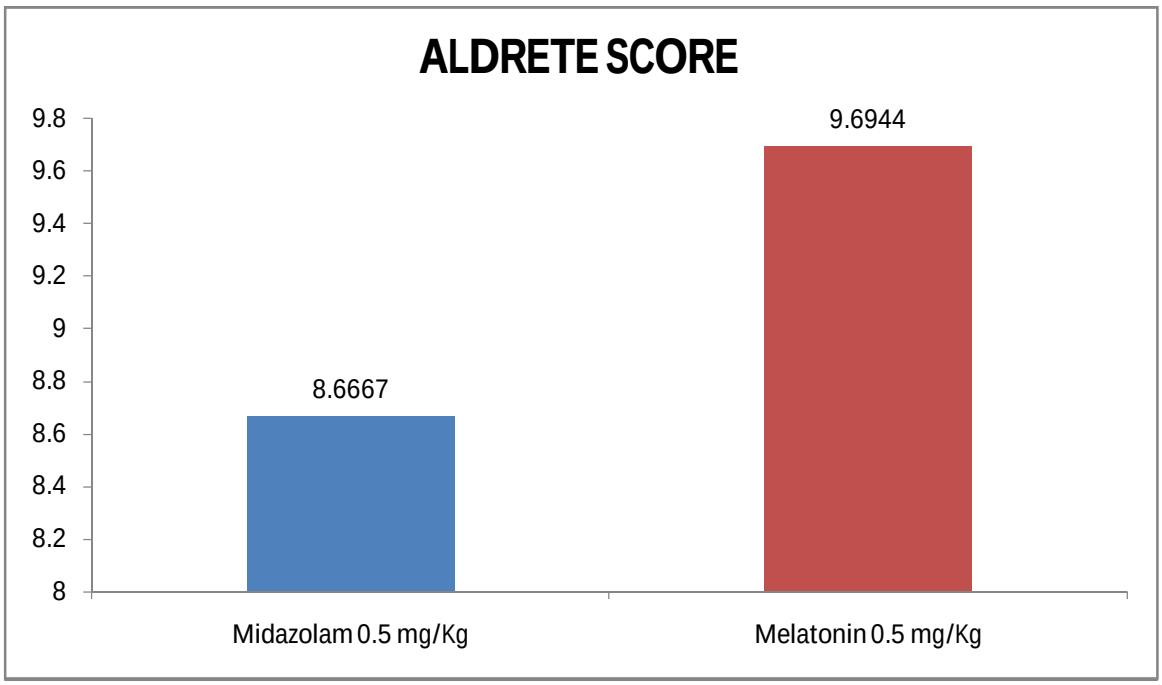
POST SURGICAL RECOVERY DATA:

Group Statistics						
	GROUP	N	Mean	Std. Deviation	Std. Error Mean	t value
WAKE-UP BEHAVIOUR SCORE	Midazolam 0.5 mg/Kg	36	1.1111	.31873	.05312	0.00
	Melatonin 0.5 mg/Kg	36	1.1111	.39841	.06640	
ALDRETE SCORE – ONE HOUR POSTOP	Midazolam 0.5 mg/Kg	36	8.6667	.58554	.09759	8.232**
	Melatonin 0.5 mg/Kg	36	9.6944	.46718	.07786	

**p<0.001



There is no statistically significant difference in the wake up behaviour score between the two groups.



The mean Aldrete score in M group was 8.667 ± 0.59 and in MT group was 9.69 ± 0.47 and there is a statistically significant difference between the two groups($P<0.001$) with the MT group showing better post operative recovery profile when compared with M group.

DISCUSSION :

Allaying preoperative anxiety and providing optimal and appropriate premedication in children has become the part and parcel of every paediatric anaesthesiologist. The goals of pharmacological premedication are the promotion of amnesia and anxiolysis, reduction of secretion and vagal reflexes after intubation, properly preparing patients for induction, and enhancing the hypnotic affect of general anaesthesia.

In this double – blinded randomised control study, we compared the effects of oral melatonin in dose of 0.5mg/kg on premedication in children aged between 2 – 8 years with that of oral midazolam in the same dose. The demographic profile (age and sex) had no statistically significant difference. So also is the choice of anaesthesia.

The primary purpose of this study is to assess and compare the sedative and anxiolytic effects of oral melatonin with that of oral midazolam in children undergoing elective surgical procedures. In the doses studied, we found that anxiety scores are significantly lower (M group- 2.639 ± 0.76, 1.944 ±0.33, 1.583 ±0.50 and 1.167 ± 0.378 and MT group - 2.917 ± 0.73, 2.389 ± 0.598, 2.028 ± 0.377, and 1.722 ± 0.567)and sedation scores are significantly higher(M group - 1.556 ± 0.557, 2.222 ± 0.590, 2.750 ± 0.806, 3.389 ± 0.80 and in MT group - 1.222 ± 0.421, 1.667 ± 0.534, 2.00 ±0.239,and 2.361 ± 0.592) at 15, 30, 45, and 60 minutes respectively after premedication in both the groups with respect to time.

A study by ZN Kain et al [58] compared different doses of oral melatonin with that of oral midazolam for premedicaton in children. They noted that melatonin was as effective an anxiolytic as midazolam after premedication, but not at induction of

anaesthesia. In our study,there is statistically no significant difference in anxiolysis between the two groups at 15, 30, 45, and 60 minutes after premedication, thus concurring with the findings of the above study.

Naguib et al [52] also showed that no significant difference was noted in anxiety level in the preoperative period between the two groups.

The sedation scores increased with respect to time in both the groups. However, the midazolam group showed a statistically significant increase in sedation scores at 15, 30, 45, and 60 minutes after premedication when compared with the melatonin group. This finding is similar to the results produced by Tushar Patel et al [64] who showed that midazolam produced more sedation compared with melatonin and placebo groups.

Similarly, Naguib et al[52] revealed increased levels of sedation in melatonin and midazolam groups versus placebo group at 60 and 90 minutes after premedication. The intergroup comparison revealed that midazolam provided the most favourable degree of sedation.

But, Eloisa et al[63] in their study revealed no significant difference in preoperative sedation levels in both melatonin and midazolam group.

With respect to the heart rate scores, both the groups showed a decrease in heart rate with time. But, the reduction in heart rate is significantly higher in the midazolam group when compared with the melatonin group. Regarding the SpO2 scores, there is no significant difference noted between the two groups; also, there is no significant decrease in SpO2 scores with respect to time in both the groups.

At the time of separation from parents, the midazolam group had significantly higher sedation scores (2.94 ± 0.58) and better behaviour scores (3.08 ± 0.73) when compared with the melatonin group (1.78 ± 0.72 and 2.02 ± 0.84). This finding of our study concurred with the results produced by Reyhaneh et al [92] who compared oral melatonin 0.5 mg/kg and oral midazolam 0.5 mg/ kg with that of placebo. It was shown in their study that midazolam was more effective than melatonin to sedate patients before induction of anaesthesia.

Midazolam group had a significantly lower heart rate profile when compared with the melatonin group. However, the fall in SpO2 scores are significantly higher in the midazolam group than in melatonin group.

Regarding the secondary outcome measures studied, the midazolam group showed a less response to venepuncture when compared with the melatonin group. The results are similar to those in the study conducted by Reyhaneh et al who showed better favourable response with midazolam group.

There is no significant difference noted in post operative wake up behaviour between the two groups. But the post operative recovery profile as studied with the Aldrete score was significantly better in melatonin group (9.69 ± 0.47) than in the midazolam group (8.67 ± 0.59). Similarly, Acil et al [67] declared that recovery after premedication with melatonin was faster than after premedication with midazolam. This is in contradiction tothe results produced by Ionescu D et al [53] who showed that the recovery times were shortest in the melatonin group compared with midazolam and placebo groups, but it was not statistically significant. The difference in results may be because we used drugs in per kg basis in our study, but in the above study, a

standard dose of midazolam (3.75mg), melatonin (3mg) were used and the sample size was also less (53 patients) when compared with our study. There were no reported side effects in both the groups during our study.

Thus, melatonin can be used as an acceptable alternative to midazolam for premedication in paediatric patients with good recovery profile and is also devoid of side effects. Though the sedative effects and response to venepuncture scores are not comparable with midazolam, melatonin deserves a better place in the premedication armamentarium in the near future. Further studies with larger sample size and varying doses of the trial drugs are needed.

SUMMARY:

Seventy two children in the age group of 2 – 8 years belonging to ASA PS I and II scheduled for elective minor surgical procedures under general anaesthesia or general anaesthesia with regional anaesthesia were enrolled in the study based on the inclusion and exclusion criteria. Patients were randomised into two groups i.e., group M & group MT using computer generated random numbers. Group M received oral midazolam in a dose of 0.5 mg/kg and Group MT received oral melatonin in a dose of 0.5 mg/kg. Anxiety and sedation scores were assessed every 15 minutes for 60 minutes after premedication .

1. Anxiety scores were significantly lower with respect to time in both the groups, though there were no significant difference in the intergroup comparison of anxiety scores.
2. The sedation scores were significantly higher in the Midazolam group after premedication when compared to Melatonin group.
3. During separation from parents, Midazolam group showed better sedation and behaviour scores when compared to the Melatonin group.
4. Reaction to venepuncture was found to be significantly better with Midazolam group.
5. Heart rate was lower and better controlled in the Midazolam group when compared to the Melatonin group.
6. Melatonin group showed a better SpO2 profile during separation from parents than Midazolam group.

7. Wake up behaviour which was assessed immediately after the surgical procedure was not significantly different between the two groups.
8. Aldrete score was used to assess the post operative recovery status of the children. Melatonin group showed better post operative recovery profile than Midazolam group.
9. No side effects were reported in either of the groups during the study.

CONCLUSION:

From our study, we concluded that oral midazolam (0.5 mg/kg) is superior to oral melatonin (0.5 mg/ kg) in premedication regarding the patients' sedation and behaviour score before anaesthesia and the ease of intravenous access establishment. The anxiety scores after premedication are similar between the two groups. However, postoperative recovery scores are better with melatonin group. There are no reported adverse effects of both the drugs during the study. Thus, melatonin can be used as an acceptable alternative to midazolam for premedication in paediatric patients without any adverse effects.

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ANNEXURES

ETHICAL COMMITTEE APPROVAL LETTER

GOVERNMENT STANLEY MEDICAL COLLEGE & HOSPITAL,CHENNAI -01

INSTITUTIONAL ETHICS COMMITTEE

TITLE OF THE WORK : A COMPARATIVE STUDY OF ORAL MIDAZOLAM AND ORAL MELATONIN FOR PREMEDICATION IN PAEDIATRIC ANAESTHESIA..

PRINCIPAL INVESTIGATOR : DR. P. MALINI
DESIGNATION : PG IN MD ANAESTHESIOLOGY,
DEPARTMENT : DEPARTMENT OF ANAESTHESIOLOGY, GOVT. STANLEY MEDICAL COLLEGE.

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 27.06.2018 at the Council Hall, Stanley Medical College, Chennai-1 at 10am.

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate from the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institution(s).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.

31/10/18

MEMBER SECRETARY,
IEC, SMC, CHENNAI

PATIENT INFORMATION SHEET

TOPIC: A comparative study of oral midazolam and oral melatonin for premedication in Paediatric anaesthesia

I Dr.MALINI.P, II year M.D post graduate in Anaesthesiology, Government Stanley medical college is going to undertake the study on above mentioned topic.

I request your co-operation and help for the study.

And there is absolutely no harm in this research.

Though you may not benefit directly from the study, it's possible that the findings of the study may be a great help in planning anaesthetic technique for other patients undergoing general anaesthesia in future.

I assure that all the information provided by you will be kept highly confidential and privacy is assured. The identity of your child won't be revealed to anyone. The study may be published in scientific Journal , but the identity will not be revealed.

Your consent for participation of your child in this study is voluntary and you can withdraw from this at any point of time.

Signature/left thumb impression of the Parent/Guardian

INFORMED CONSENT (PARENT/GUARDIAN)

Study number:

Participant identification number for this study:

Topic: A comparative study of oral midazolam and oral melatonin for premedication in Paediatric anaesthesia

Name of the Principal investigator : Tel no:

The content of the information sheet dated _____ that was provided have been read carefully by me/explained in detail to me, in a language that I comprehend, and fully understood the contents. I confirm that I have had opportunity to ask questions

The purpose of the study and its potential risks/benefit and expected duration of the study, and other relevant details of the study have been explained to me in detail. I understand that my child is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal right being affected.

I agree on behalf of my child (son/daughter) to take part in the study

(Signature/left thumb impression)

(Parent/guardian)

Name of the participant:

Son/daughter/under care of:

Complete postal address:

This is to certify that the above consent has been obtained in my presence;

Signature of the principal investigator:

Date:

Place:

Witness 1:	Witness 2:
Signature:	Signature:
Name :	Name:
Address:	Address:

PROFORMA **STUDY NO.**

Name: I.P NO:

Age: Duration:

Sex: Surgery:

Weight: Assigned group:

PREOPERATIVE ASSESSMENT:

Allergy to the study drug :

CVS:

RS:

Renal dysfunction:

Hepatic dysfunction:

Congenital heart disease:

Arrythmia:

Airway:

Assessed under ASA PS :

INVESTIGATIONS:

Hb:

TC:

DC:

BT:

CT:

Platelets:

Blood Urea

Serum Creatinine:

LFT:

Blood group:

PREMEDICATION:

BLINDED

Volume	Time

EVALUATION POST PREMEDICATION :

Time	Anxiety score	Sedation score	HR	SpO2
At 15 mins				
At 30 mins				
At 45 mins				
At 60 mins				

EVALUATION AT SEPARATION FROM PARENTS :

Sedation score	Behaviour score	HR	SpO2

REACTION TO VENEPUNCTURE:

Score	

ANAESTHETIC TECHNIQUE:

GA	
GA + RA	

INTRAOPERATIVE HEMODYNAMICS:

Time	HR	BP	SpO2	EtCO2	Temperature
At 0 mins					
At 15 mins					
At 30 mins					
At 45 mins					
At 60 mins					
At 75 mins					
At 90 mins					

EVALUATION AT AWAKENING:

Wake up behaviour score	HR	BP	SpO2

READINESS TO DISCHARGE FROM PACU AT ONE HOUR:

ALDRETE SCORE	

EVALUATION SCALES:

Anxiety SCALE:

Calm and sleepy	1
Apprehensive but not withdrawn from surrounding	2
Crying	3
Agitated and difficult to control	4

RAMSAY Sedation Scale:

Response	Score
Awake and anxious,agitated, or restless	1
Awake, cooperative, accepting ventilation, oriented, tranquil	2
Awake; responds only to commands	3
Asleep; brisk response to light, glabellar tap or loud noise	4
Asleep; sluggish response to light, glabellar tap or loud noise	5
Asleep; no response to light, glabellar tap or loud noise	6

Behaviour at the time of separation from parents (Separation score):

Poor (crying, clinging)	1
Fair (crying, not clinging)	2
Good (whimpers, easily reassured)	3
Excellent (easy separation)	4

Venipuncture score:

Crying or struggling	3
Wincing or vocalising	2
Moving the hand	1
None	0

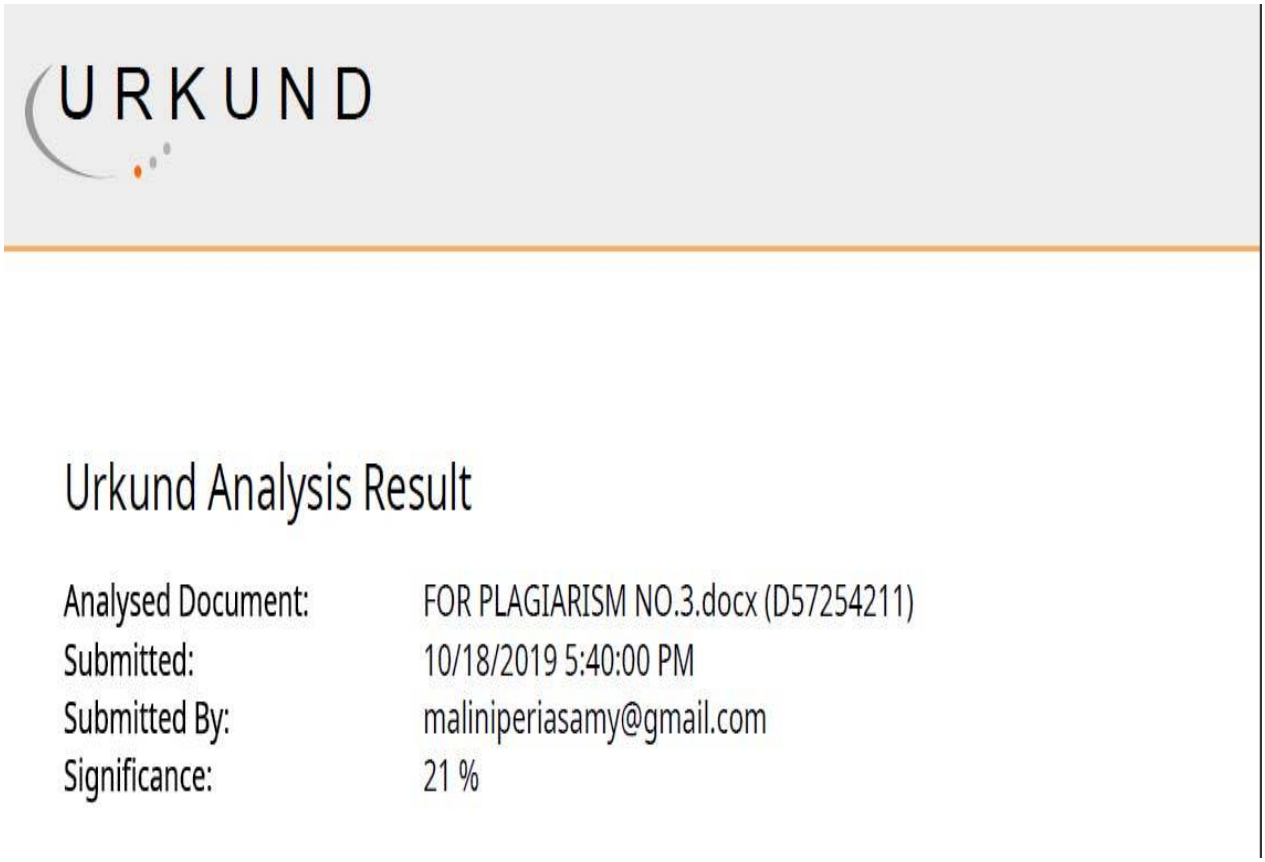
Wake-up behavior score:

Calm and cooperative	1
Not calm but could be easily calmed	2
Not easily calmed, moderately agitated or restless	3
Combative, excited, disoriented	4

Aldrete Scoring System:

Parameter		Score
Activity : Able to move voluntarily or on command	4 extremities 2 extremities 0 extremities	2 1 0
Respiration	Able to take deep breath and cough freely Dyspnoeic , shallow or limited breathing Apnoeic	2 1 0
Circulation	BP +/- 20 mmHg of preanaesthetic level BP +/- 20 – 50 mmHg of preanaesthetic level BP more than +/- 50 mmHg of preanaesthetic level	2 1 0
Consciousness	Fully awake Arousable on calling Not responding	2 1 0
O2 saturation	Able to maintain O2 saturation >92% on room air Needs O2 inhalation to maintain O2 saturation >90% O2 saturation <90% even with O2 supplementation	2 1 0

PLAGIARISM CERTIFICATE



ANTIPLAGIARISM CERTIFICATE

This is to certify that this dissertation work titled **"** *A comparative study of oral midazolam and oral melatonin for premedication in Paediatric Anaesthesia"* of the candidate **Dr.MALINI.P** with registration Number **201720052** for the award of **M.D.** in the branch of **ANAESTHESIOLOGY (BRANCH X)**. I personally verified the urkund.com website for the purpose of plagiarism Check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows **21%** percentage of plagiarism in the dissertation.

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