ISSN- O: 2458 - 868X, ISSN–P: 2458 – 8687
National Library of Medicine - ID: 101731606

International Journal of Medical Science and Innovative Research (IJMSIR)
IJMSIR : A Medical Publication Hub
Available Online at: www.ijmsir.com
Volume – 6, Issue – 5, October – 2021 , Page No. : 75 - 84

Comparison of melatonin versus midazolam premedication on propofol induction dose, anxiety and emergence in paediatric patients undergoing elective surgery: a randomized, double blind, interventional study

[1]Dr Jyoti, Resident doctor, Department of Anaesthesiology, SMS Medical College Jaipur

[2]Dr Jitendra Mewara, Resident doctor, Department of Anaesthesiology, SMS Medical College Jaipur

[3]Dr Narayan V Kamath, Resident doctor, Department of Anaesthesiology, SMS Medical College Jaipur

[4]Dr Neelam Dogra, Senior professor, Department of Anaesthesiology, SMS Medical College Jaipur

Corresponding Author: Dr Neelam Dogra, Senior professor, Department of Anaesthesiology, SMS Medical College Jaipur

Citation this Article: Dr Jyoti, Dr Jitendra Mewara, Dr Narayan V Kamath, Dr Neelam Dogra, "Comparison of melatonin versus midazolam premedication on propofol induction dose, anxiety and emergence in paediatric patients undergoing elective surgery: a randomized, double blind, interventional study", IJMSIR- October - 2021, Vol – 6, Issue - 5, P. No. 75 – 84.

Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract

Background: We designed the present study to compare oral melatonin and midazolam premedication in term of effect onpropofol induction dose, anxiety and emergence in paediatric patients undergoing elective infraumbilical surgery.

Methods: This hospital based, randomized, double blind, interventional study was conducted in the Department of Anaesthesiology, SPMCHI, affiliated to SMS Medical College, Jaipur with due permission from institutional ethics committee and review board (EC No:47/MC/EC/2019)and after taking written informed consent from the parents, over duration of six months (October 2018- March 2019).80paediatric patients of American Society of Anesthesiologists I and II physical status aged between 2-6 years undergoing elective infraumbilical surgery under general anaesthesia were randomly allocated in two study groups using computerized random number table(40 patients in each group).

Results: Pain/ discomfort scale score 0 was seen in 19 (47.50%) patients of Group A and 18 (45%) patients of Group B. 14 (35%) patients in Group A and 13 (32.50%) patients in Group B showed score of 1. In 5 (12.50%) patients of Group A and 6 (15%) patients of Group B score of 2 was seen. Score 3 was seen in 2 (5%) patients of Group A and 3 (7.50%) patients of Group B. This difference in the Pain/ discomfort scale score was statistically insignificant among the groups (p=0.949).

Conclusion: We concluded that melatonin premedication, in comparison to midazolam, significantly reduced the dose of propofol required for induction of anaesthesia. Moreover, we found that melatonin is equally effective to midazolam in reducing the preoperative anxiety without causing postoperative emergence delirium.

Keywords: Pain. Melatonin, Midazolam

Introduction

Preoperative anxiety is described as a state of uneasiness or tension secondary to a disease, hospitalization, surgery or the presence of strange environment. Preoperative anxiety is frequently experienced by children undergoing surgery and is associated with a significant number of adverse outcomes.[1]Prevention of this anxiety is of utmost importance to provide a calm and pleasant anaesthetic experience and for preventing an adverse effect on the psychological development of the child in the future.[2]Several methods have been adopted to promote positive perioperative experience and lessen children's stress in preoperative settings among which pharmacologic premedication remains most effective. The goals for pharmacological premedication are the promotion of amnesia and anxiolysis, reduction of secretions and vagal reflexes after intubation, properly preparing patients for induction and enhancing the hypnotic effects of general anaesthesia [3] and preventing emergence agitation.

Midazolam, a fast-acting benzodiazepine with a short elimination half-life, is preferred treatment before induction of anaesthesia. [4] However, midazolam has several side effects. Because of these side effects, melatonin has been proposed as a premedication alternative to midazolam, before anaesthesia induction. Melatonin is an endogenous indoleamine produced and secreted by the pineal gland, mainly known as a regulator of circadian rhythms. [5] In addition to sleep promotion, melatonin exerts numerous other sedative and anti-excitatory effects that support use during anaesthetic procedures.[5], [6], [7]Melatonin acts because of the activation of the GABAergic system and exogenous administration produces a marked dose-dependent increase in GABA concentrations in the central nervous system.[8] This property of melatonin probably results from the mutual interaction between GABA and MT2 receptor systems. [3]

Propofol is an alkylphenol intravenous sedative-hypnotic agent and is commonly used in the induction of anaesthesia.It was seen in the previous studies [9], [10], [11], [12] that melatonin decreases the dose of propofol required for induction of anaesthesia because of its sedative and hypnotic properties. Most of these studies were comparing melatonin with placebo in adult patients. There are only a few published studies [3] on paediatric patients.

So we designed the present study to compare oral melatonin and midazolam premedication in term of effect onpropofol induction dose, anxiety and emergence in paediatric patients undergoing elective infraumbilical surgery.

Material and Methods

This hospital based, randomized, double blind, interventional study was conducted in the Department of Anaesthesiology, SPMCHI, affiliated to SMS Medical College, Jaipur with due permission from institutional ethics committee and review board (EC No:47/MC/EC/2019)and after taking written informed consent from the parents, over duration of six months (October 2018- March 2019).80paediatric patients of American Society of Anesthesiologists I and II physical status aged between 2-6 years undergoing elective infraumbilical surgery under general anaesthesia were randomly allocated in two study groups using computerized random number table(40 patients in each group). Patients in GROUP "A" (n=40): received 0.5 mg/kg oral melatonin premedication and in GROUP

"B"(n=40): received 0.5 mg/kg oral midazolam premedication. Melatonin and midazolam were prepared by mixing oral drops melatonin (0.5mg/kg) and Injmidazolam[13] (preservative free, 0.5 mg/kg) respectively in honey. Melatonin drops used were available in a concentration of 3 mg/0.9 ml. Both the drugs were expanded to a fixed volume of 5ml. The prepared drug was offered by spoon 60 min before induction. Patients undergoing emergency surgeries, having history of use of psychoactive medications, presence of neuromotor impairment, decompensated illness or history of previous surgery or patients whose parents refused to participate in the surgery were excluded from the study

On the day of surgery child was brought in preoperative play area and child's anxiety was assessed using **modified Yale Preoperative Anxiety Scale (m-YPAS)[14]**which was considered as baseline anxiety score of the child. [The m-YPAS is an observational state anxiety measure for children comprising 27 items in 5 domains that contemplate the child's relationship with its environment, namely, activity, state of arousal, vocalisation, expression of emotions and interaction with family members. The m-YPAS score ranges from 22.5 to 100, with higher scores indicating greater anxiety.]

After that the study drug was administered according to the group allocated to the child, 60 min before surgery. Anxiety score of the child was assessed at 10, 30, 45 and 60 minutes after administration of the study drug using m-YPAS. During this time child was allowed to play in the preoperative play area in parent's presence. 60 min after premedication, **separation anxiety score** of the child was recorded at the time of shifting to operation theatre.In operation theatre, standard patient monitoring devices (electrocardiogram, noninvasive blood pressure and pulse oximetry) were applied. Now child's compliance with induction using **induction compliance check list (ICC)[15]**was assessed and recorded. [The ICC is an observational checklist containing 10 negative behavioural groupings that describe a child's anxiety, fear, and negative behaviours during induction of anaesthesia, with good reliability. The ICC score is the sum of the items checked. Perfect induction is scored as 0, i.e. the child does not exhibit negative behaviours, fear, or anxiety. ICC $\geq$ 4 is considered poor behavioural compliance.] InjGlycopyrrolate (0.005 mg/kg) IV was given through already secured IV line (as per hospital protocols). After that an initial bolus dose of Inj Propofol mixed with Inj Lignocaine IV (10:1) 1 mg/kg IV was administered over 20 seconds, followed by similar bolus doses of propofol until the patient was anaesthetized. Patient was considered anaesthetized when asleep, not arousable and loss of eyelash reflex. This was used as end point of induction of anaesthesia. Total dose of propofol administered was recorded. InjFentanyl 2 mcg/kg IV and InjAtracurium (0.5mg/kg) IV were given and endotracheal intubation was done with appropriate size endotracheal tube. All the patients received caudal block with InjRopivacaine 0.2% (1 ml/kg) for postoperative analgesia. Thereafter, anaesthesia was maintained with O_2, N_2O and sevoflurane. At the end of anaesthesia Inj Neostigmine (0.06mg/kg) and InjGlycopyrrolate (0.005 mg/kg) IV given to reverse residual muscle blockade.10 minutes after extubation of the patient, **modified Aldrete score [16]** to a score of 8 and **post operative excitement and pain/ discomfort score [17]**were noted in the recovery room.

Results

Statistical analysis was performed with the SPSS, version 21 for Windows statistical software package (SPSS inc., Chicago, IL, USA). The Categorical data was presented as numbers (percent) and were compared among groups using Chi square test. The quantitative data was presented as mean and standard deviation and were compared by student's t-test. Probability was considered to be significant if less than 0.05.

Patients in the two study groups were comparable with respect to mean age, gender distribution, mean weight and mean duration of surgery.

Table 1

	Group A (Melatonin)		Group B (Midazolam)		P value
	Mean	SD	Mean	SD	
Age (years)	3.98	1.46	3.80	1.32	0.575 (NS)
Weight (kg)	14.27	4.34	14.26	3.35	0.990 (NS)
Duration of Surgery (minutes)	32.58	4.90	31.20	4.54	0.197 (NS)

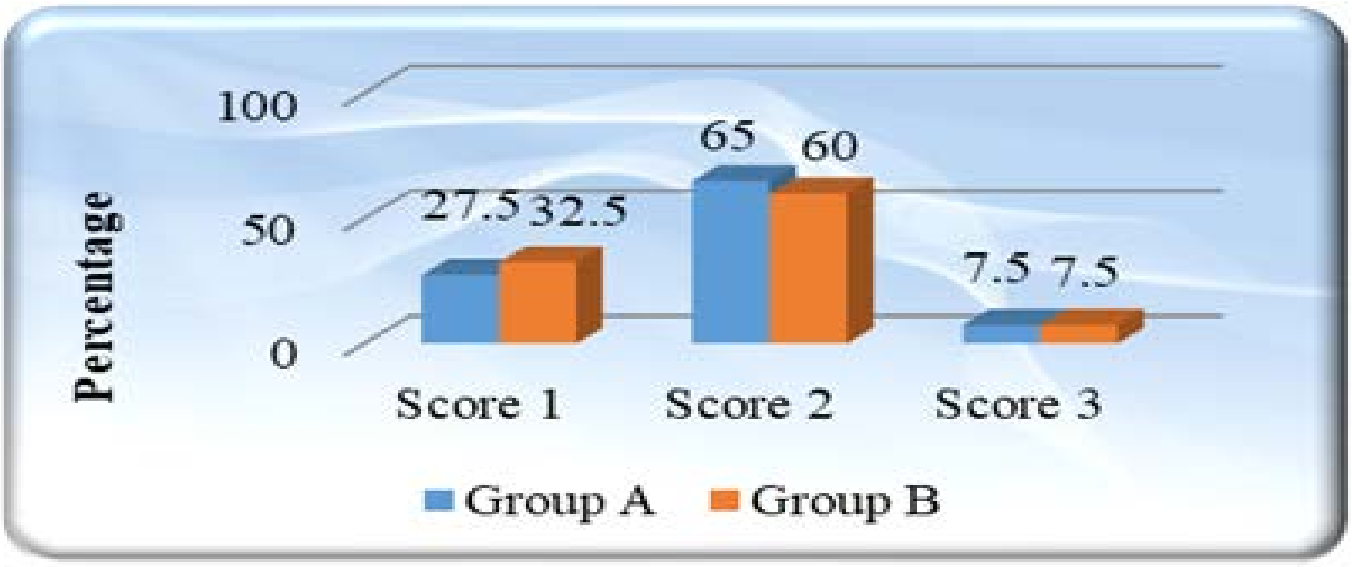
The **mean m-YPAS** score before giving the premedication in Group A was 58.56 and Group B was 58.23. This difference was not statistically significant (p=0.900).On intra-group comparison the mean m-YPAS score decreased significantly with time both in melatonin as well as in midazolam group (p<0.001). On intergroup comparison the difference in m-YPAS score was not statistically significant at any time point of observation. Lowest score in Group A was 29.49 and Group B was 30.68 at 60 minutes after premedication (p=0.344).

Table 2

	Group A			Group B			P value
	Mean	SD	Median [IQR]	Mean	SD	Median [IQR]	
Baseline	58.56	11.15	56.25[50.00-67.18]	58.23	12.47	54.12[50.00-68.75]	0.900 (NS)
10 min after premedication	52.49	11.22	50.00[45.75-61.44]	53.28	10.95	52.00[45.75-62.50]	0.753 (NS)
30 min after premedication	39.27	8.97	37.37[33.25-45.75]	39.42	8.90	39.25[33.25-45.75]	0.940 (NS)
45 min after premedication	33.01	6.78	33.25[27.56-35.50]	33.08	6.77	33.25[27.56-35.50]	0.960 (NS)
60 min after premedication	29.49	5.19	29.25[27.00-33.25]	30.68	6.02	29.25[27.00-33.25]	0.344 (NS)

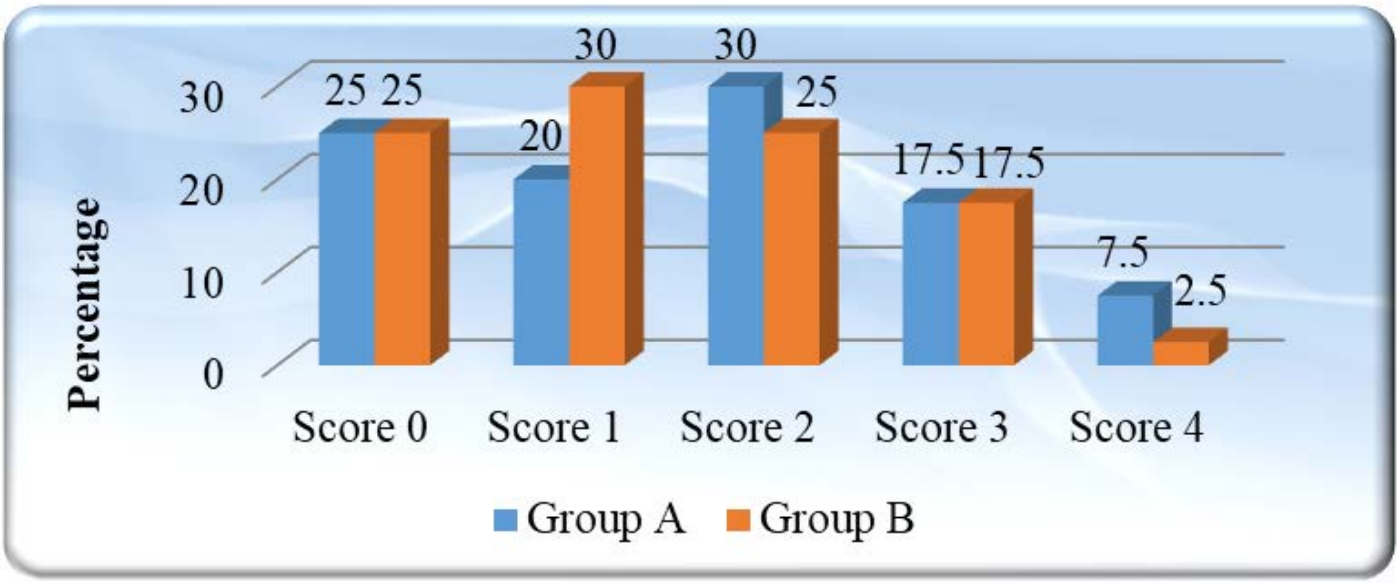
Separation anxiety score was 1 in 11 (27.50%) patients in Group A compared to 13 (32.50%) patients in Group B. The score 2 was observed in 26 (65%) patients of Group A whereas in 24 (60%) patients of Group B. In both the groups there were 3 (7.50%) patients who showed separation anxiety score 3. This difference in the score was found statistically insignificant (p=0.883).

Graph 1



Induction Compliance Checklist (ICC) score 0 was found in 10 (25%) patients in both the groups which represented perfect compliance. The score 1 was observed in 8 (20%) patients of Group A whereas in 12 (30%) patients of Group B. In both the groups there were 7 (17.50%) patients who showed ICC score 3. In 3 (7.5%) patients of Group A and 1 (2.5%) patient of Group B score 4 was observed. This difference in the score was found statistically insignificant (p=0.739).

Graph 2



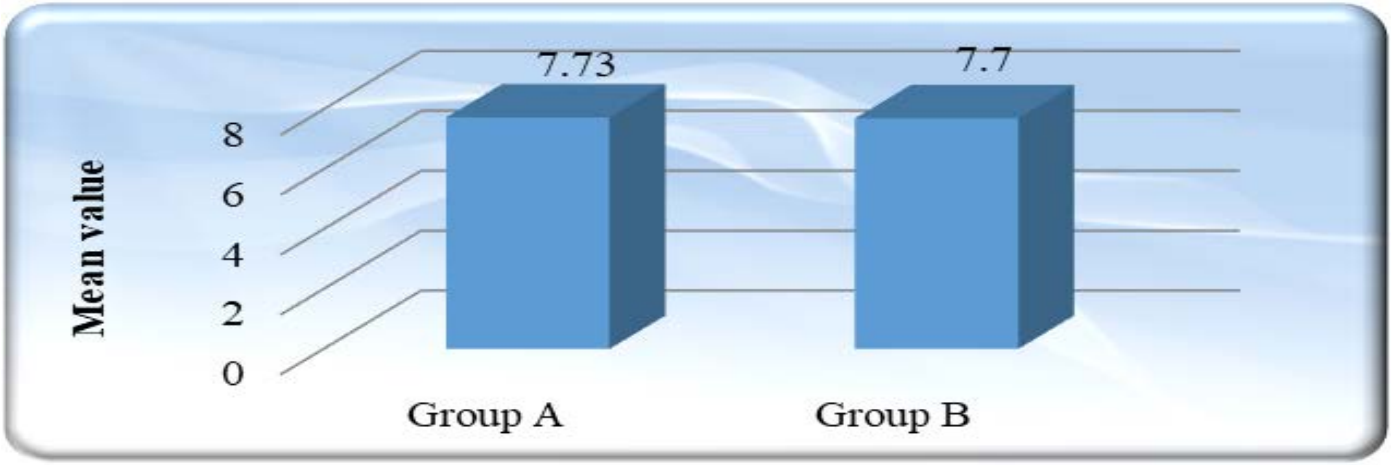
Mean total dose of propofol administered for induction of anaesthesia was 29.43 mg in Group A as compared to 40.50 mg in Group B and **mean dose of propofol administered per kg body weight** for induction of anaesthesia was 2.08 mg/kg in Group Aas compared to 2.83 mg/kg Group B. This difference was found to be statistically significant (p<0.001) among the groups.

Table 3

	Group A		Group B		P value
	Mean	SD	Mean	SD	
Total dose of propofol administered (mg)	29.43	8.39	40.50	10.97	p<0.001 (S)
Dose of propofol administered per kg body weight (mg/kg)	2.08	0.21	2.83	0.29	p<0.001 (S)

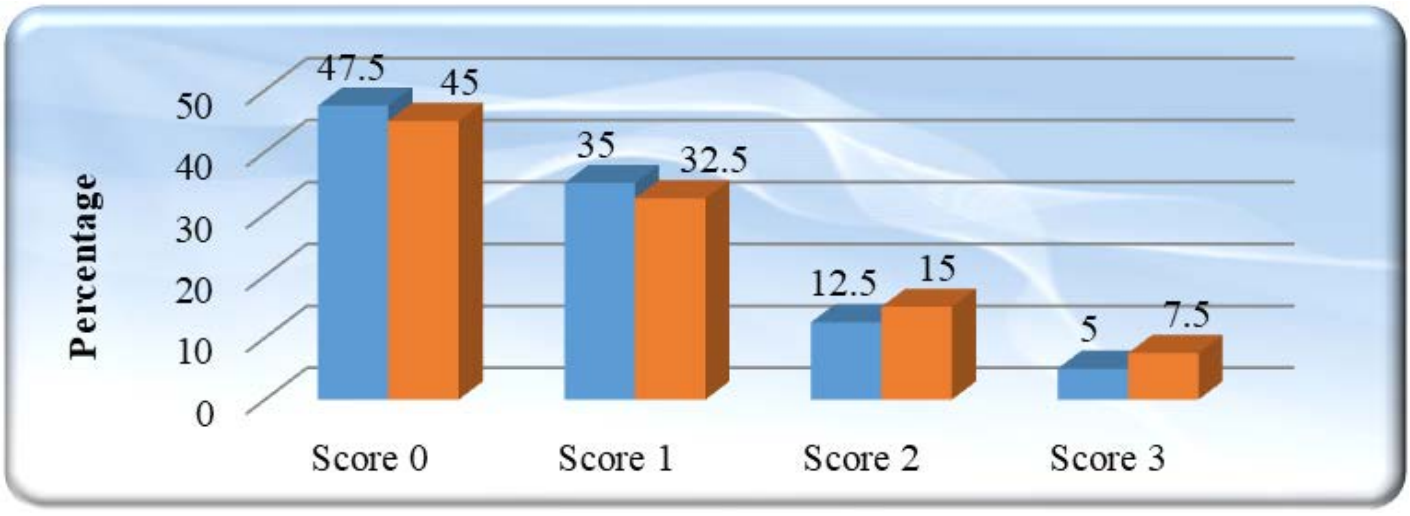
The **mean modified aldrete score** in Group A was 7.73 and Group B was 7.70. This difference in mean modified aldrete score between study groups was not statistically significant (p=0.807).

Graph 3



Pain/ discomfort scale score 0 was seen in 19 (47.50%) patients of Group A and 18 (45%) patients of Group B. 14 (35%) patients in Group A and 13 (32.50%) patients in Group B showed score of 1. In 5 (12.50%) patients of Group A and 6 (15%) patients of Group B score of 2 was seen. Score 3 was seen in 2 (5%) patients of Group A and 3 (7.50%) patients of Group B. This difference in the Pain/ discomfort scale score was statistically insignificant among the groups (p=0.949).

Graph 4



Discussion

UP to 65% of children experience intense anxiety throughout the perioperative period, especially in the preoperative holding area and during induction of anesthesia. [18] Intensity of perioperative anxiety is a predictor of both emergence delirium in the postanesthesia care unit and new-onset maladaptive behavioral changes (*e.g.*, nightmares, enuresis, separation anxiety etc). [19], [20]

Midazolam is one of the most commonly used drugs for anxiolytic premedication. Melatonin, because of its sedative and hypnotic properties, has been proposed as an alternative premedication to midazolam, as it has no adverse effects which limits the use of midazolam such as impaired psychomotor function, paradoxical reaction, interaction with opioids etc.

Propofol is commonly used intravenous induction agent because of its rapid onset (approximately 10–50 s) and short duration of action (approximately 3–10 min). Although a serious complication of propofol administration, that propofol-related infusion syndrome (which includes bradycardia, metabolic acidosis, liver enlargement, lipemic plasma, rhabdomyolysis and/or myoglobinuria and even death), may occur during prolonged administration, the bolus infusion is also not without adverse effects. Available experience would suggest that propofol, like most intravenous anaesthetics, may cause both cardiovascular and respiratory depression including bradycardia, hypotension and apnoea, necessitating close cardiorespiratory monitoring. [21]

It has been demonstrated in previous studies that melatoninis an effective premedication in term of anxiolysis both in adult as well as in paediatric patients, when compared to midazolam. It has been also demonstrated that melatonin decreases the dose of propofol required for induction of anaesthesia when compared with midazolam or placebo in adult patients.But there are only a few published studies [3] on paediatric patients.

So we designed the present randomized double blind study to compare oral melatonin and midazolam for premedication in paediatric patients aged 2-6 years posted for elective infraumbilical surgery under general anaesthesia. The primary objective of our study was to compare the effect of the study drugs on dose of propofol required for induction of anaesthesia in both the groups and secondary objective was to compare the effect on preoperative anxiety and postoperative emergence.

The peak effect of exogenous melatonin ranges from 60 to 150 min and of oral midazolam ranges from 30 to 90 min.[22]Hence, we gave both the drugs 60 min before induction.

Our results of effect of the two drugs on dose of propofol required for induction of anaesthesia are in concordance with study conducted by **Eloisa Gitto et al [3]**. In the literature search, no other studies are found comparing melatonin and midazolam in terms of their effect on dose of propofol required for induction of anaesthesia, both in children and adult population. However, there are some published studies which compared melatonin with placebo [9] – [12] and result of these studies also supported that melatonin decreased the induction dose of propofol.

Results of studies conducted by **Kurdi et al [2], Impellizzeri et al [5], Tushar Patel et al[22]D Ionescu et al [23],** and**Torun et al [24]**were similar to our study regarding effect on preoperative anxiety although age

of study population and doses of the study drugs varied with each study.

In our study we found that there was no significant difference in both the study drugs when compared in terms of post operative emergence and sedation. These results were found similar to the studies conducted by **Gitto et al** [3]and **zcengiz et al**[25]

Zeev N. Kain et al [26] found that incidence of emergence delirium was greatest in the midazolam groupwhen compared oral midazolam with different doses of oral melatonin. The disparity in the results regarding greater incidence of emergence delirium in their study may be due to use of sole sevoflurane anaesthesia from induction till end of surgery and also in our study caudal block was administered to all patients, thus the confounding effect of pain predisposing to emergence delirium was abolished.

Conclusion

The results of present study demonstrate that melatonin is an effective premedicant in paediatric patients. We observed that melatonin premedication, in comparison to midazolam, significantly reduced the dose of propofol required for induction of anaesthesia. Moreover, we found that melatonin is equally effective to midazolam in reducing the preoperative anxiety without causing postoperative emergence delirium.

References

1. Perry JN, Hooper VD, Masiongale J. Reduction of preoperative anxiety in pediatric surgery patients using age-appropriate teaching interventions. Journal of PeriAnesthesia Nursing. 2012 Apr 1;27(2):69-81.

2. Kurdi MS, Muthukalai SP. A comparison of the effect of two doses of oral melatonin with oral midazolam and placebo on pre-operative anxiety, cognition and psychomotor function in children: A randomised double-blind study. Indian journal of anaesthesia. 2016 Oct;60(10):744.

3. Gitto E, Marseglia L, D'Angelo G, Manti S, Crisafi C, Montalto AS, Impellizzeri P, Reiter RJ, Romeo C. Melatonin versus midazolam premedication in children undergoing surgery: A pilot study. Journal of paediatrics and child health. 2016 Mar;52(3):291-5.

4. Bajaj P. Melatonin for Anxiolysis in children. Indian Journal of Anaesthesia. 2009 Jul 1;53(4):504.

5. Impellizzeri P, Vinci E, Gugliandolo MC, Cuzzocrea F, Larcan R, Russo T, Gravina MR, Arena S, D'Angelo G, Gitto E, Montalto AS. Premedication with melatonin vs midazolam: efficacy on anxiety and compliance in paediatric surgical patients. European journal of pediatrics. 2017 Jul 1;176(7):947-53.

6. Acil M, Basgul E, Celiker V, Karagöz AH, Demir B, Aypar U. Perioperative effects of melatonin and midazolam premedication on sedation, orientation, anxiety scores and psychomotor performance. European journal of anaesthesiology. 2004 Jul;21(7):553-7.

7. Marseglia L, D'Angelo G, Manti S, Aversa S, Arrigo T, Reiter RJ, Gitto E. Analgesic, anxiolytic and anaesthetic effects of melatonin: new potential uses in pediatrics. International journal of molecular sciences. 2015 Jan;16(1):1209-20.

8. Naguib M, Gottumukkala V, Goldstein PA. Melatonin and anesthesia: a clinical perspective. Journal of pineal research. 2007 Jan;42(1):12-21.

9. Naguib M, Samarkandi AH, Moniem MA, Mansour EE, Alshaer AA, Al-Ayyaf HA, Fadin A, Alharby SW. The effects of melatonin premedication on propofol and thiopental induction dose–response curves: a prospective, randomized, double-blind study. Anesthesia & Analgesia. 2006 Dec 1;103(6):1448-52.

10. Turkistani A, Abdullah KM, Al-Shaer AA, Mazen KF, Alkatheri K. Melatonin premedication and the induction dose of propofol. European journal of anaesthesiology. 2007 May;24(5):399-402.

11. Norouzi A, Fateh S, Modir H, Kamali A, Akrami L. Premedication effect of melatonin on propofol induction dose for anesthesia, anxiety, orientation and sedation after abdominal surgery: a double-blinded randomized trial. Medical Gas Research. 2019 Apr 1;9(2):62.

12. Jain N, Tiwari T, Kohli M, Chandra G, Bhatia VK. Effect of oral melatonin on patients' anxiety scores and dose requirement of propofol during bispectral index-guided induction of general anesthesia. InThe Indian Anaesthetists Forum 2019 Jan 1 (Vol. 20, No. 1, p. 16). Medknow Publications.

13. Shrestha S, Shrestha BR. Oral administration of intravenous solution of midazolam mixed in syrup of paracetamol is an effective way of premedicating children undergoing surgery under general anaesthesia. Kathmandu University medical journal (KUMJ). 2007;5(4):449-55.

14. Kain ZN, Mayes LC, Cicchetti DV, Caramico LA, Spieker M, Nygren MM, Rimar S. Measurement tool for preoperative anxiety in young children: the Yale Preoperative Anxiety Scale. Child Neuropsychology. 1995 Dec 1;1(3):203-10.

15. Kain ZN, Mayes LC, Wang SM, Caramico LA, Hofstadter MB. Parental Presence during Induction of Anesthesia versus Sedative Premedication Which Intervention Is More Effective?. Anesthesiology: The Journal of the American Society of Anesthesiologists. 1998 Nov 1;89(5):1147-56.

16. Aldrete JA, Kroulik D. A postanesthetic recovery score. Anesthesia & Analgesia. 1970 Nov 1;49(6):924-34.

17. Hannallah RS, Broadman LM, Belman AB, Abramowitz MD, Epstein BS. Comparison of caudal and ilioinguinal/iliohypogastric nerve blocks for control of post-orchiopexy pain in pediatric ambulatory surgery. Anesthesiology: The Journal of the American Society of Anesthesiologists. 1987 Jun 1;66(6):832-3.

18. Kain ZN, Mayes LC, O'Connor TZ, Cicchetti DV. Preoperative anxiety in children: predictors and outcomes. Archives of pediatrics & adolescent medicine. 1996 Dec 1;150(12):1238-45.

19. Kain ZN, Caldwell-Andrews AA, Maranets I, McClain B, Gaal D, Mayes LC, Feng R, Zhang H. Preoperative anxiety and emergence delirium and postoperative maladaptive behaviors. Anesthesia & Analgesia. 2004 Dec 1;99(6):1648-54.

20. Kain ZN, Wang SM, Mayes LC, Caramico LA, Hofstadter MB. Distress during the induction of anesthesia and postoperative behavioral outcomes. Anesthesia & Analgesia. 1999 May 1;88(5):1042-7.

21. Wheeler DS, Vaux KK, Ponaman ML, Poss BW. The safe and effective use of propofol sedation in children undergoing diagnostic and therapeutic procedures: experience in a pediatric ICU and a review of the literature. Pediatric emergency care. 2003 Dec 1;19(6):385-92.

22. Patel T, Kurdi MS. A comparative study between oral melatonin and oral midazolam on preoperative anxiety, cognitive, and psychomotor functions. Journal of anaesthesiology, clinical pharmacology. 2015 Jan;31(1):37.

23. Ionescu D, Badescu C, Ilie A, Miclutia I, Iancu C, Ion D, Vasian H, Acalovschi I, Mocan T, Bondor C.

Melatonin as premedication for laparoscopic cholecystectomy: a double-blind, placebo-controlled study. Southern African Journal of Anaesthesia and Analgesia. 2008 Jul 1;14(4):8-11.

24. Torun AC, Yüceer E. Should Melatonin Be Used as an Alternative Sedative and Anxiolytic Agent in Mandibular Third Molar Surgery?. Journal of Oral and Maxillofacial Surgery. 2019 Mar 13.

25. Özcengiz D, Gunes Y, Ozmete O. Oral melatonin, dexmedetomidine, and midazolam for prevention of postoperative agitation in children. Journal of anesthesia. 2011 Apr 1;25(2):184-8.

26. Kain ZN, MacLaren JE, Herrmann L, Mayes L, Rosenbaum A, Hata J, Lerman J. Preoperative melatonin and its effects on induction and emergence in children undergoing anesthesia and surgery. Anesthesiology: The Journal of the American Society of Anesthesiologists. 2009 Jul 1;111(1):44-9.