A comparison between the effect of Oral Melatonin and Hydroxyzine for preventing preoperative Anxiety in Pediatric Patients undergoing Adenotonsillectomy: A randomized, double-blinded controlled study

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Abstract

Background: Induction of anesthesia is one of the most anxiety-provoking factors of preoperative anxiety in children. Melatonin is a safe drug used in the management of anxiety. Hydroxyzine is a first-generation antihistaminic that crosses the blood-brain barrier, causing sedation.

Objectives: Our study aimed to estimate the effect of a single preoperative oral melatonin versus hydroxyzine to prevent preoperative pediatric anxiety in adenotonsillectomy children.

Patients and methods: In a randomized, double-blinded, prospective study, 90 children of both sexes aged 3 to 10, were divided into three equal groups, all the patients received 10 ml of apple juice 2 hours preoperatively. In group M 0.1mg/kg of melatonin syrup was added, group H 1mg/kg of crushed hydroxyzine tablet was added, while group C received the juice alone. The primary outcome was the preoperative anxiety evaluated by the ease of parenteral separation scale, and the secondary outcomes were the compliance with the anesthesia induction mask assessed by the modified preoperative anxiety scale of Yale, the preoperative sedation evaluated by the Ramsay scale, and postoperative pain.

Results: The hydroxyzine group showed the best cooperation during parenteral separation and the least anxiety (P =0.001), then melatonin (P =0.01) compared to the placebo. Pre-operative anxiety was measured before and during induction, hydroxyzine was better than melatonin and placebo. There were statistically insignificant differences between the study groups regarding preoperative sedation and postoperative pain.

Conclusion: Hydroxyzine is more effective than melatonin and placebo for easiness of parenteral separation, reducing anxiety in the operative room, and increasing compliance with the mask in pediatric patients without causing sedation. Melatonin was superior to placebo.

Keywords: Adenotonsillectomy; Anxiety; Hydroxyzine; Melatonin.

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Introduction

Pre-operative anxiety is manifested with numerous postoperative adverse outcomes such as tachycardia, hypertension, agitation on recovery, and increased post-operative pain. Premedication for preventing preoperative anxiety is linked to better preoperative outcomes in surgical patients; however, it can be difficult to find an effective safe drug **(Ni et al., 2023).**

Melatonin is a methoxy indole secreted mainly by the pineal gland at night, it modulates the circadian rhythms **(Vasey et al., 2022).**

Melatonin as a premedication has sedative and anti-anxiety effects, without postoperative impairment of psychomotor performance **(Mellor et al., 2022).**

Hydroxyzine is a first-generation histamine blocker (H1-receptor) of the diphenylmethane and piperazine classes that has an anxiolytic, and sedative properties **(Gober et al., 2022).** It is used with or without other medications in adults and children as a sedative premedication. Unlike other antihistaminics, Hydroxyzine has a lower risk of anticholinergic adverse effects **(Nathan, 2022).**

The study highlighted the effectiveness of administrating melatonin versus hydroxyzine orally on decreasing preoperative anxiety in pediatric patients scheduled for adenotonsillectomy, evaluated by the ease of parental separation. The compliance with anesthesia induction mask, postoperative pain scores, requesting analgesia, and sedation score were also assessed.

Patients and methods

Eligibility of the study

After obtaining the Faculty of Medicine, El Minia University's ethical committee approval **(505:2022)**, this study was registered at Clinical Trial Gov. **(NCT05680584).** Written consents were obtained from all patients' guardians. The study was conducted on 92 pediatric patients of both sexes 3 to 10 years old, ASA I, underwent adenotonsillectomy in the period from March 2023 to September 2023 at El Minia University Hospital. Two patients were excluded from the study because their parents refused to sign the consent.

Children with a history of, developmental delay, acute porphyria, chronic illness, or autoimmune disease were excluded from this study. Sleep disturbances, speech, or communication problems were also exclusion criteria. Patients with allergies to the studied drugs were also excluded.

Study design, randomization, and blinding

The pediatric patients were allocated into 3 equal groups of 30 each in this prospective randomized, double-blinded study by a randomization table using Microsoft Excel by a statistician. The grouping papers were put in sealed dark envelopes to cover the allocation. The study medications were prepared and offered to the children in the preparation room 2 hours before surgery by an anesthesiologist other than the study investigator, who was completely blinded to the study medications. The patients and their parents were also blind to the study drugs. After the study had ended, it was revealed that M was the melatonin group (the patients received 0.1mg/kg of melatonin syrup orally in 10 ml apple juice). Group H was the hydroxyzine group (received 1mg/kg of crushed hydroxyzine tablet in 10 ml apple juice), while group C was the control group in which the patients received 10 ml of apple juice only.

Technique

In the preparation room, the studied medications were introduced to the children two hours before the induction of anesthesia by an anesthesiologist other than the investigator, 10 ml of apple juice was offered to the children either free of any medications (control group), or containing melatonin syrup at a dose 1 mg/kg

(Melatonin, Nutraceutical Company), or hydroxyzine crushed tablets at a dose 1 mg/kg (Atarax, Chemical Industries Development "CID" Company).

Vital parameters were recorded every 15 minutes after administration of the syrup until the start of anesthesia; the sedation status was measured using the Ramsey Sedation Scale (from 1 to 8) **(Lozano -Díaz et al., 2021)**:

1- Awake with no cognitive dysfunction.
2- Awake and drowsy with purposeful responses to verbal orders.
3- Appears asleep with purposeful responses to verbal orders.
4- Appears asleep with purposeful responses to verbal orders but at louder than usual or requiring a slight glabellar tap.
5 – Asleep with sluggish purposeful responses only to loud verbal orders or strong glabellar taps.
6- Asleep with sluggish purposeful responses only to pain.
7- Asleep with reflex withdrawal to pain only (no purposeful response).
8- Unresponsive to pain.

During the operative room's entrance, the ease of separation was evaluated by the Ease of separation score (Méndez et al., 2022) as excellent, good, fair, and poor (from 1 to 4)

1- Patient is fearless, cooperative, or asleep (Excellent)
2- Slightly afraid or crying, but quiet with reassurance (Good)
3- Moderately afraid and crying, and not quite with reassurance (Fair)
4- Crying, restraining is required (poor)

In the operative room, during induction of anesthesia by oxygen-sevoflurane administered via an anesthesia mask, the behavior of the children was evaluated by the modified Yale Preoperative Anxiety Scale (mYPAS**) (Table.1)**. Five categories of behavior were assessed **(Kain et al, 1995)** for detecting anxiety level.

Table 1. Modified Yale scale (Kain et al, 1995).

Category of behavior	
Activity	1. Looking around, curious, playing with toys, reading; moving around the holding area. 2. Not playing may look down, fidget with hands, or suck thumb; may sit close to parent while waiting. 3. Moving from toy to parent in an unfocused manner may push the mask away. 4. Actively trying to get away, pushing with extremities, can move the whole body; will not separate from the parent.
Vocalizations	1. Reading, answering questions but generally quiet. 2. Responding but whispering, or only head nodding. 3. Quiet, no responses to adults. 4. Whimpering, moaning, and silently crying. 5. Crying with or without screaming. 6. Crying, screaming audible through a mask.
Emotional expressivity	1. Happy or concentrating on play. 2. Neutral, no expression. 3. Sad to frightened, with or without tearful eyes. 4. Distressed, crying.
State of apparent	1. Alert or relaxed. 2. Withdrawn, sitting still and quiet.

arousal	3. Vigilant, may startle to sounds, eyes wide, body tense. 4. Crying or pushing others away.
Use of parents	1. Busy playing or engaged and doesn't need a parent. 2. Reaches out to a parent and may lean against the parent. 3. Looks to parent quietly, doesn't need contact or comfort. 4. Keeps parent at a distance or actively withdraws from a parent.

All patients received 0.5 mg/kg atracurium for muscle relaxation, the endotracheal tube (ETT) was inserted orally at a lower, central position. Anesthesia was maintained by sevoflurane and increments of atracurium 0.1mg/kg; after the operation was completed, the inhalational anesthetic was discontinued, the muscle relaxant was reversed by 0.05 mg/kg neostigmine and the patient was securely extubated in the post-tonsillectomy position, all patients admitted to Post Anesthesia Care Unit (PACU). At the PACU, heart rate, arterial blood pressure, oxygen saturation, and respiratory rate were recorded every hour for the first three hours after the procedure. Post-operative pain was assessed every hour during the first three hours in children aged 3 to 7 using the FLACC scale (Face, Legs, Activity, Cry, and Consolability scale) **(Table.2)**: **(Crellin et al., 2018)**

Table 2. FLACC scale (Crellin et al., 2018)

Face	Leg	Activity	Cry	Consolability
0- Expressionless or smile 1- Grimace 2- Frequent clenched jaw	0- Relaxed 1- Restless 2- Kicking	0- Lying in a normal position 1- Shifting back and tense 3- Arched, or jerking	0- No cry 1- Moans 2- Difficult to comfort	0- Relaxed 1-Reassured by hugging 2- Difficult to comfort

For older children aged 8 to 10, postoperative pain was measured by the numerical rating pain scale **(Fig.1),** the kids rated their pain level on a scale of zero indicating no pain, to ten indicating the severest pain **(Wang et al., 2020).**

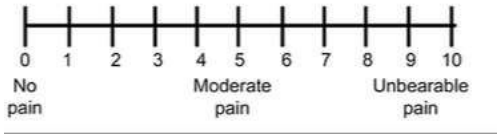

Fig.1. Numerical rating pain scale (Wang et al., 2020)

Sample size calculation

The number of patients required in the groups was determined after the data was taken from a previous study (**Impellizzeri et al., 2017)**. The primary outcome of that study was the ease of parental separation. The effect size was calculated as 0.36 (moderate effect size), the alpha error was 0.05, and a power of 0.85 was used. The sample size was calculated as 80 patients in the 3 groups; it was increased to 90 patients for better accuracy. The sample size was calculated using the PASS program (Power Analysis and Sample Size Calculation) by NCSS, LLC, USA.

Statistical analysis

All data were collected, tabulated, and statistically analyzed using SPSS 26 for

Windows (SPSS Inc., Chicago, IL, USA), data were evaluated for normal distribution using the Shapiro Walk test; Qualitative data were expressed as frequencies and relative percentages, Chi-square test (χ^2) and Fisher exact was used to detect the difference between qualitative variables as indicated.

Quantitative data were shown as mean ± SD (Standard deviation), median, and range for parametric and non-parametric data, ANOVA and Kruskal Wallis tests were used to detect the difference between quantitative data in three groups for parametric and non-parametric variables, respectively. All statistical comparisons were two-tailed with a significance level of P value equal to or less than 0.05 indicating significance.

Results

The current study included 92 patients, 2 patients' parents refused consent, and 90 patients were randomly divided into 3 equal groups of 30 patients each, as appears in the Consort flow chart of the study in (**Fig.2**). There were statistically insignificant differences between the three study groups as regards demographic data as shown in (**Table.3**). The patients in the study groups showed no statistically significant differences as regards hemodynamic data throughout the recorded period.

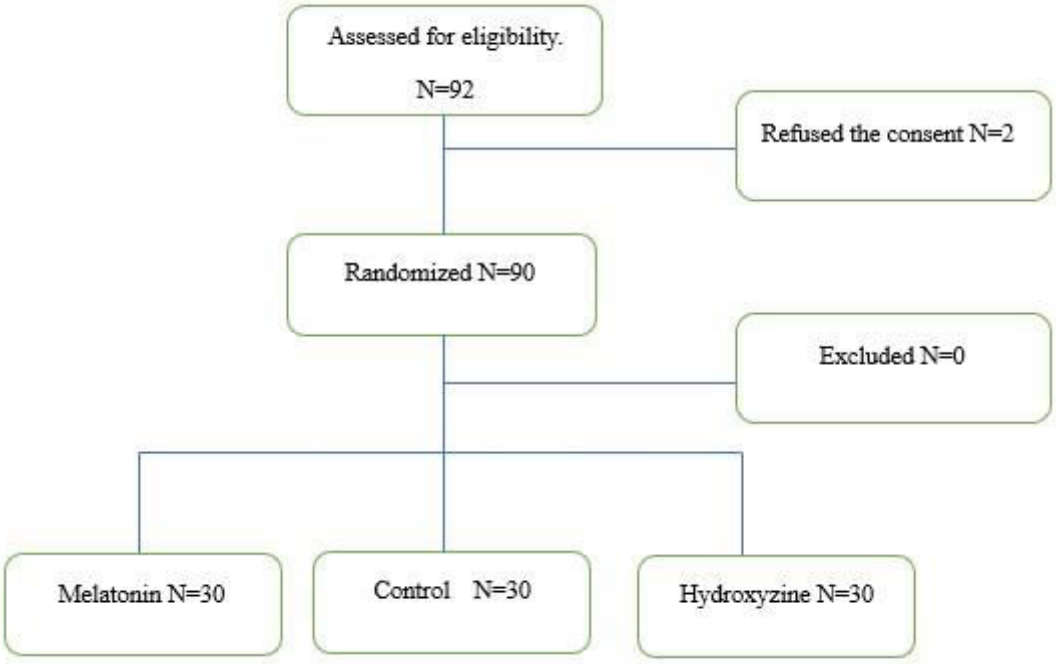

Fig.2. Consort flow chart

Table 3. Demographic Data of the patients

Variables	Group M N=30	Group H N=30	Group C N=30	P value
Age (y)				0.64
Median (range)	8 (4:10)	7 (3.5-10)	7 (3.5-10)	
Mean±SD	7.3±2.1	6.8±2.2	7.1±2	
Age distribution (n %)				0.4
Children aged 3- 7	14 (46.66%)	19 (63.3%)	17 (56.7%)	
	16 (53.33%)	11 (36.7%)	13 (43.3%)	

Children aged 8-10				
Sex distribution (n %) Male Female	17(56.7%) 13(43.3%)	15(50.0%) 15(50.5%)	11(36.7%) 19(63.3%)	0.33

Significant p-value < 0.05, Y: year, N: number, SD: Standard Deviation. Numerical data are expressed as mean ± standard deviation (SD) and range. Categorical data are presented as numbers (percentages). Chi-square test ($\chi 2$) test for categorical variables.

(**Table.4 & Fig.3**) compar the three groups in terms of how easy it was to separate the children from their parents assessed by the ease of parental separation scale. There was a statistically significant difference between the three groups. Compared to melatonin and placebo, hydroxyzine exhibited the lowest mean, indicating a cooperative and fearless separation. There was a significant difference favoring melatonin in comparison to placebo too.

Table 4. Ease of parental separation in the studied groups

Variables	**Group M N= 30**	**Group H N= 30**	**Group C N= 30**	**P value**		
Ease of parenteral separation score Median(range) Mean± SD	1 (1:3) 1.3±0.6	1(1:2) 1±0.25	1(1:4) 1.7±0.8	0.001*		
				P1	**P2**	**P3**
				0.01*	0.03*	0.001*

* significant< 0.05. P1: p-value between groups M and H, P2: p-value between M and C, P3: p-value between H and C

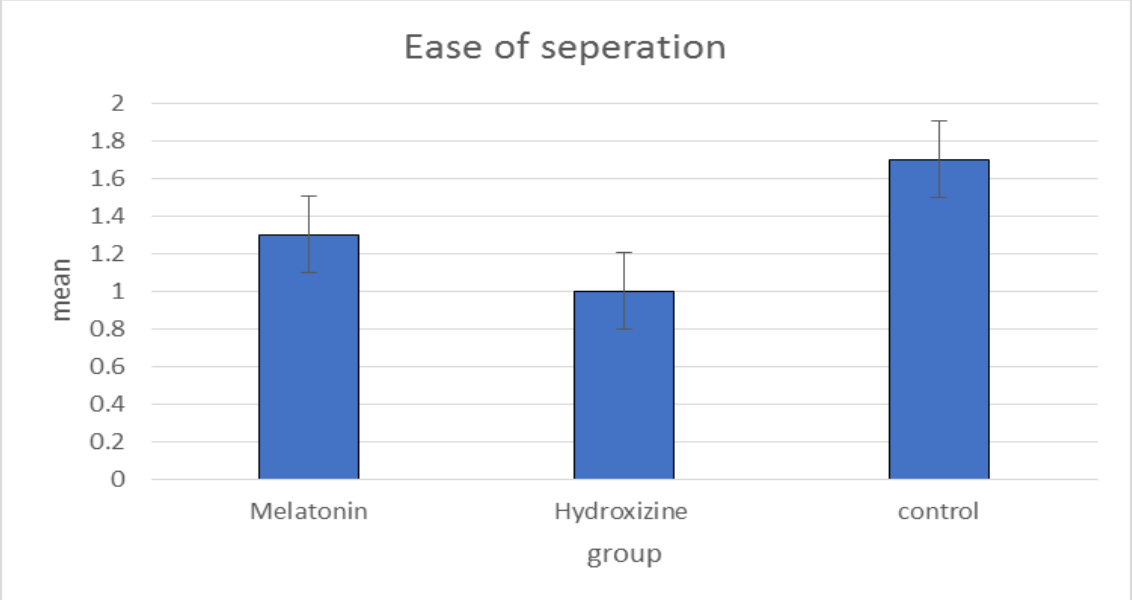

Fig.3. Ease of parenteral separation in the studied groups

(**Table.5& Fig.4**) show the mYPAS scores, comparing the 3 groups before and during mask induction, there was a statistically significant difference between the 3 groups before and at induction of anesthesia. Hydroxyzine had the lowest mean anxiety degree on the mYPAS scores, with a p-value of 0.001 when compared to the control group and a p-value <0.05 when compared to melatonin. There was also a statistically significant difference between the melatonin and control groups.

Table 5. Modified Yale preoperative anxiety score

Variables	Group M N= 30	Group H N= 30	Group C N= 30	P value		
Before induction		5 (5:8)		<0.001*		
Median (range)	6 (5:10)	5.4±	8 (5:18)	**P1**	**P2**	**P3**
mean± SD	6.1± 1.3	0.72	8.3± 3.4	0.049*	0.01*	0.001*
At induction	10		15	<0.001*		
Median (range)	(5:18)	8 (5:17)	(5:22)	**P1**	**P2**	**P3**
mean± SD	10± 3.7	8± 1.4	14± 3.8	0.048*	0.001*	0.001*

Mean significant< 0.05.P1: p-value between groups M and H, P2: p-value between M and C, P3: p-value between H and C

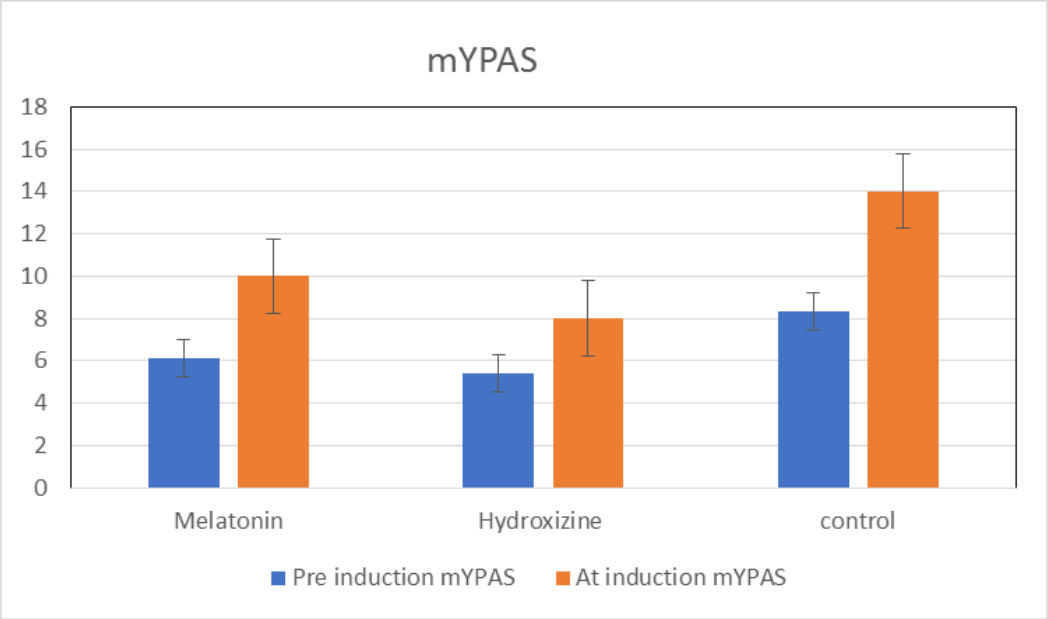

Fig.4. Modified Yale Preoperative Anxiety Scale

(**Fig.5**) shows that there was no statistically significant difference in the mean scores of the Ramsay sedation scale between the melatonin, hydroxyzine, and control groups from the time of juice administration and for one hour.

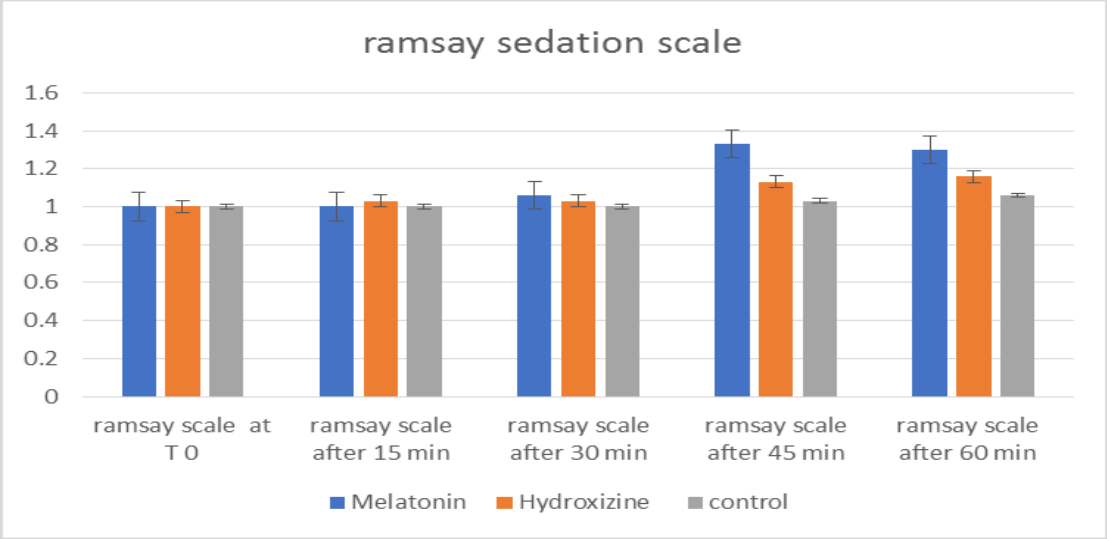

Fig.5. Ramsay sedation

(**Fig.6**) presents the comparison of the three groups of children aged 3-7 years old (50 children) using the FLACC scale. No statistical significance had been demonstrated between the groups.

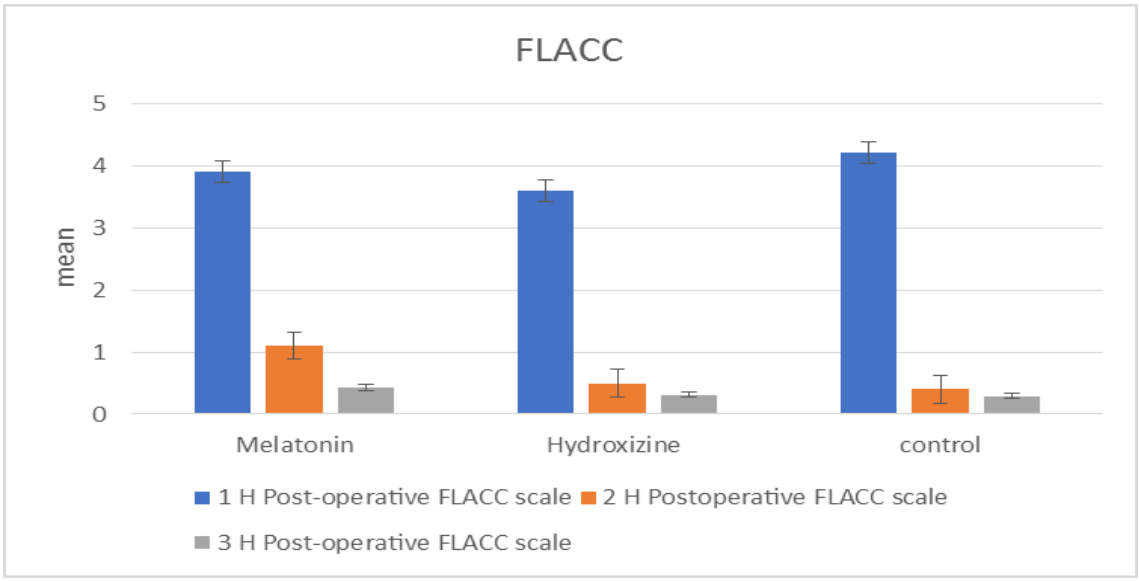

Fig.6. FLACC scale

(**Fig.7**) compares the groups on the numerical pain rating scale in patients aged 8 to 10 years (40 children). As stated below, no statistically significant differences existed between melatonin, hydroxyzine, and placebo.

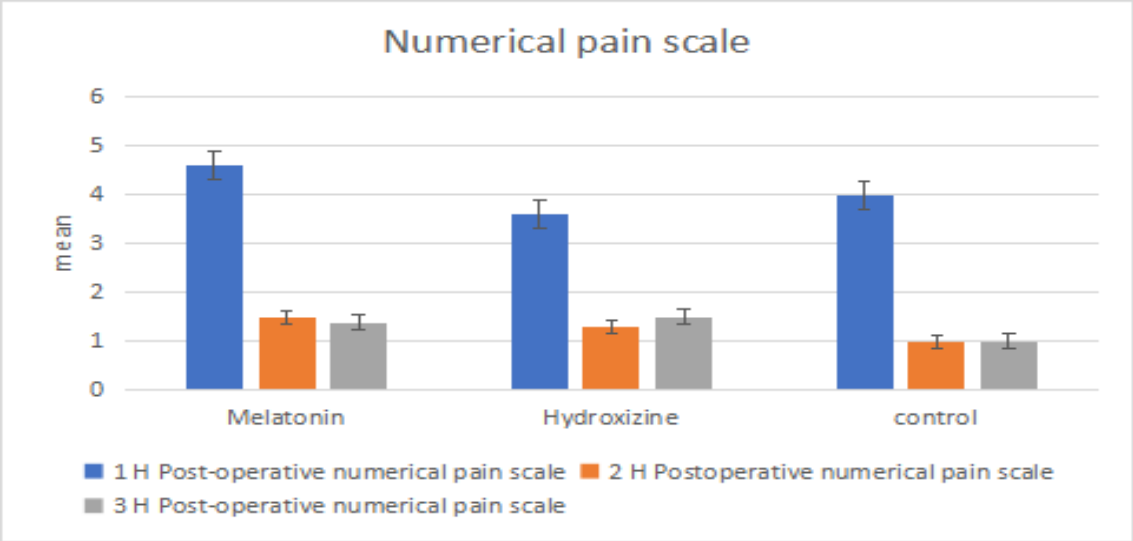

Fig.7. Numerical pain rating scale

Regarding the request for post-operative analgesics within the first three hours after surgery. As shown in (**Fig.8**), there was no statistically significant difference between the three groups; the average time of analgesic request was within the first hour in all three groups.

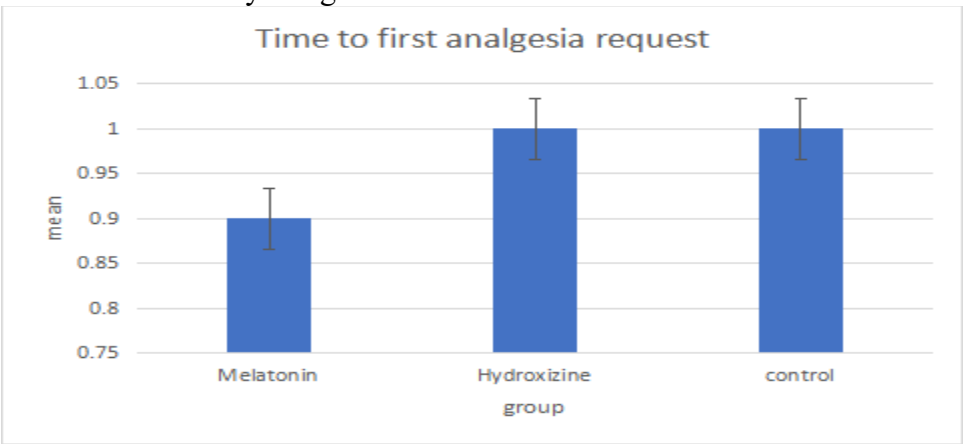

Fig.8. Time of first analgesic request

Discussion

The results of our study demonstrated that oral 1 mg/kg hydroxyzine and 0.1 mg/kg melatonin, administered one hour before induction of anesthesia were more effective than placebo in facilitating separating the children from their parents, reducing anxiety in the operative room, and improving the compliance in accepting anesthesia mask without sedation. Hydroxyzine was statistically better than melatonin.

Aleo and his colleagues in their study on 188 children aged 2-6 years old underwent outpatient surgery, anxiety attempted to be relieved with either oral hydroxyzine 2mg/kg, clowns, or both hydroxyzine and clowns in comparison to a placebo juice. The Hydroxyzine group was superior to placebo and clowns regarding alleviating anxiety in children before the entrance of the operative room and during induction of anesthesia. This study aligns with what we concluded in our study hydroxyzine is effective in reducing pre-operative fear in children **(Aleo et al., 2020)**.

Melatonin was assessed for preoperative anxiety **(Kurdi and Muthukalai, 2016)**, the study was

conducted on 100 patients from 5 to 15 years old, and they either received oral melatonin 0.75mg/ kg, melatonin 0.5 mg/kg, midazolam 0.5mg/kg or a placebo 45-60 minutes before anesthesia induction. Oral melatonin 0.75, 0.5 mg/kg showed significant results in the context of preoperative anxiety during the parental separation and in the operative room in comparison to placebo. This study backs up our findings.

Moreover, a study utilized either melatonin 0.2 mg/kg, clonidine 5ug/kg, or dexmedetomidine 3ug/kg in 105 children aged 3-8 years old prepared for infra umbilical surgeries, there was no statistically profound difference between the three medications according to child-parent separation score, melatonin was equally beneficial as clonidine and dexmedetomidine in parental separation management **(Ali et al.,2020)**.

As regards preoperative sedation measured by the Ramsay sedation scale, there was no significant difference between hydroxyzine and melatonin in comparison to placebo.

Güler in his study used hydroxyzine 1 mg/kg and chloral hydrate 50mg/kg in 60 children aged 6 months to 12 years old before EEG, the findings showed that the hydroxyzine group showed significantly less sedation scores measured by the Ramsay sedation scale and higher failure rates of sedation **(Güler et al., 2021).**

However, premedication for pediatric patients scheduled for strabismus surgery involved two doses of hydroxyzine, added to 0.5 mg/kg of midazolam. The findings confirm that improved sedation is produced by adding hydroxyzine. This runs counter to the findings of our results; this could be explained by the sedative enhancement effect of adding midazolam to hydroxyzine. (**Kartufan et al., 2022).**

On the opposite side, a study done by **Cevizci and Uçarin** on 87 children from 3 to 14 years old, aimed to evaluate the impact of oral hydroxyzine. premedication on pre-operative Ramsay sedation scale before an outpatient surgery (inguinal hernioplasty or circumcision), results showed that there was a significant difference between hydroxyzine and placebo in terms of Ramsay sedation scale p value<0.001. This study deviates from our findings that hydroxyzine does not cause preoperative sedation despite using the same dose as ours 1mg/kg, which can be explained by delaying the evaluation of the sedation score for two hours following premedication **(Cevizci and Uçarin, 2020)**.

Consistent with our findings that premedication with either melatonin or hydroxyzine has no benefit in reducing postoperative pain; a study used hydroxyzine by a dose of 0.6 mg/kg alone or with adding topical anesthetic cream and chloral hydrate 50 mg in 70 leukemic children from 3-11 years old before lumbar puncture, the study declared that neither hydroxyzine nor chloral hydrate with or without local anesthetic cream was effective in relieving the pain of lumbar puncture measured by the visual analog scale, hydroxyzine just acted as a calming agent **(Esfahani et al.,2022)**.

Regarding the role of melatonin in post-operative pain, research done by **Saleh and Hassan** concluded that oral 0.5mg/kg melatonin administration given before thoracotomy in 50 pediatric patients markedly reduced post-operative pain and pethidine consumption in the first 24 hours postoperatively in comparison to placebo. Perhaps since they utilized a higher dose of melatonin, there is a difference between their results and ours **(Saleh and Hassan, 2022)**.

Limitations: It is a Single-center clinical trial. The brief post-operative

hospital stays, which impede post-operative pain and sedation monitoring.

Conclusion

Hydroxyzine (1 mg/kg) is superior to Melatonin (0.1 mg/kg) in easing children's separation from parents, lowering anxiety in the operating room, and improving mask anesthesia compliance in pediatric patients without causing sedation. Melatonin was also effective in comparison to the control group. Both hydroxyzine and melatonin are ineffective in alleviating postoperative pain in adenotonsillectomy.

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Not applicable.

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