Egypt. J. Chem. **Vol. 64,** No. 1 pp. 431 - 436 (2021)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

Adjuvent Effect of Melatonin Premedication on Propofol Induction Dose

Eman E. Mohamed[1*], Nagia M. Abdelmoeti[2], Sawsan G. Mohamed [2]

[1] *M.B.B.ch Faculty of Medicine for Girls AL-Azhar University*

[2] *Intensive Care and Pain Management, Faculty of Medicine for Girls Al-Azhar University*

Abstract

This study investigated the role of melatonin different doses as a premedication in decreasing the induction dose of propofol for anesthesia, preoperative anxiety, pain and sedation after abdominal surgery. This study was conducted on 60 patients scheduled for elective abdominal surgery under general anesthesia. The sixty patients included in this study were randomly divided into three equal groups(n=20)for each group: Control (C Group), melatonin 3mg (M3 Group) were received 3mg oral melatonin 100 min preoperative and melatonin 5mg (M5 Group) were received 5mg oral melatonin 100 min preoperative. The results revealed that mean induction dose of propofol was significantly higher in group C than in M3, M5 groups .Although the dose of propofol that result in loss of response to verbal commands and loss of eye lash reflex. VAS anxiety score preoperative and VAS pain score postoperative were statistically significant higher in C group than both melatonin groups. Time taken before the first dose of analgesia was significantly higher in both melatonin group than the control group.

Keywords: Melatonin Premedication; Propofol dose; Anesthesia

Introduction

Millions of patients receive sedatives to reduce anxiety before surgery, but the choice of premedication is often determined by habit and tradition, rather than by any scientific evidence (1). Although the use of preoperative benzodiazepines is the most common practice, the potential clinical benefits of new therapeutic options in this setting remain to be investigated (2).

Melatonin (N-acetyl-5-methoxytryptamine) is a neurohormone secreted mainly from the pineal gland. Its main function is regulation of sleep and circadian rhythm (3). Recently melatonin is discovered to have a promising role in anesthesia as antinociceptive, analgesic, anxiolytic and hypnotic agent (4). These possible clinical effects and the general safety of melatonin make melatonin a potential future Supplement to other drugs used in anesthesia.

Aim we have conducted the study is to evaluate and compare the role of melatonin different doses as a premedication in decreasing the induction dose of propofol for anesthesia, anxiety, pain and sedation after abdominal surgery.

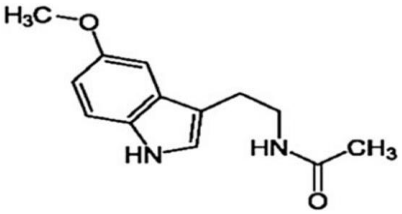

Figure (1): Chemical structure of melatonin.

Patient and method

After obtaining approval of the research ethics committee and patients' written informed consents, this randomized double-blinded and controlled study was conducted on 60 patients scheduled for elective abdominal surgery under general anesthesia in El-Zahraa Hospital-AlAzhar University. Inclusion criteria include American Society of Anesthesiologists status I–II, age 22-55 years, surgery time from 30 minutes to 120 minutes, body mass index > 19 to < 25 kg/m2.

*Corresponding author e-mail: emanelnagar93aneth@gmail.com.; (Eman E. Mohamed).
Receive Date: 06 September 2020, Revise Date: 08 September 2020, Accept Date: 09 September 2020
DOI: 10.21608/EJCHEM.2020.42023.2844

Exclusion criteria include that lack of patient cooperation, use of benzodiazepine-derived drugs within the past 72 hours and use of narcotics or sedatives during the previous week.

The sixty patients included in this study were randomly divided into three equal groups (n=20) for each group Control (C Group), melatonin 3mg (M3 Group) and melatonin 5mg (M5 Group).

On arrival to the operating theatre; 3mg and 5mg were given to patients of M3 andM5 group respectively. In operating room standard monitoring electrocardiogram, pulse oximetry, noninvasive blood pressure and End tidal CO2 were applied in addition to BIS monitor.

All patients operated upon under general anesthesia after preoxygenation an anesthesiologist who was blinded to the premedication will inject propofol 1mg/kg in the start then10 mg over 5 seconds every 15 s until the bispectral index (BIS) score fall to 45.

When a BIS score of 45 reached, tracheal intubation was accomplished after administration of a narcotic (fentanyl citrate 1-2μg/kg) and muscle relaxant (atracurium besylate).General anesthesia was maintained by isoflurane in100% oxygen and muscle relaxant on need. All patients in all groups received their intravenous fluid requirement. Intravenous fluids were warmed to 37 C.Both of MAP and HR were maintained within 20%of measured baseline values.

At the end of surgery, patients were allowed to recover spontaneously and extubation was done once the patient regained consciousness. Patients in all groups were transferred to the post- anesthesia care unit (PACU) and observed for 2 hours after the end of surgery for possible residual drug effects. After that, they were transferred to the intensive care unit (ICU) for 24 hours for proper observation and to determine the time of first dose of analgesia.

The parameters were recorded in three groups are the total dose of propofol required to achieve a BIS score of 45. Response to verbal commands was evaluated at induction and correlated to the BIS score and propofol dosage. Loss of eyelash reflex was evaluated at induction and correlated to the BIS score and propofol dosage. Preoperative anxiety was measured using the visual analog scale for anxiety (VAS-A) ranging between 0 and 10 (0=completely calm, 10 = the worst possible anxiety) as in. Sedation level was assessed and scored according to (Ramsay sedation score). Postoperative pain assessed according to the visual analog scale for pain (VAS-A) ranging between 0 and 10 (0=no pain, 10 = worst pain imaginable).Time of first dose of analgesia was recorded.

Statistical analysis

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage. The following tests were done: 1-A one-way analysis of variance (ANOVA) when comparing between more than two means. 2-Post Hoc test. To assess individual differences after a significant ANONA. 3-Chi-square (x2) test of significance was used in order to compare proportions between qualitative parameters. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following: Probability (P-value)

–P-value <0.05 was considered significant–P-value <0.001 was considered as highly significant–P-value >0.05 was considered insignificant.

Results and Discussion

There was no statistically significant difference between groups according to their demographic data (Age, sex, ASA classification and BMI) and hemodynamics (SBP, DBP, MABP, and HR) even before administration of melatonin or after induction of anesthesia.

The results from table (1) and figures (2-6) showed the mean induction dose of propofol was significantly higher in control group 144.70± 16.03 than in M3 and M5 groups (128.6±11.9 and 124.55±15.8 respectively).Although the dose of propofol that result in loss of response to verbal commands was more in control group 124.1±15.18 than in M3 and M5 groups (114.95±10.03 and 111.95±15.08 respectively). Also, the dose of propofol that result in loss of eye lash reflex was more in control group 135.55±17.12 than M3 and M5 groups (118.30±12.47 and 113.20±16.98 respectively). The BIS value at eye lash reflex and loss of response to verbal commands show no significant difference between all groups.

VAS anxiety score preoperative were (4-9), (1-7) and (2-7) for control group, M3 and M5 groups respectively (p- value<0.001), which showed statistically significant difference between the control group and both melatonin groups. VAS pain score postoperative were (1-4), (1-3) and (1-3) for control group, M3and M5 groups respectively (p-value<0.001), which showed statistically significant difference between the control group and both melatonin groups. Ramsay Sedation score postoperative were (1-5), (1-4) and (1-5) for control group, M3 and M5 groups respectively (p-value 0.127), which showed no statistically significant difference between all groups.

Table (1): Comparison between groups according to Propofol dose (mg) to loss of eye lash reflex, Propofol dose (mg) to loss of verbal contact, Propofol dose (mg) to reach BIS45, BIS score at loss of eye lash reflex, BIS score at loss of verbal contact and Ramsay Sedation Score.

	Control Group (n=20)	**M3 Group (n=20)**	**M5 Group (n=20)**	**ANOVA**	**p-value**
PD(ELR)					
Mean±SD	135.55±17.12	118.30±12.47a	113.20±16.98a	11.166	<0.001**
Range	117-165	98-140	90-145		
PD(LVC)					
Mean±SD	124.10±15.18	114.95±10.03a	111.95±15.08a	4.304	0.018*
Range	105-150	103-138	97-140		
PD(BIS45)					
Mean±SD	144.70±16.03	128.60±11.90a	124.55±15.80a	10.512	<0.001**
Range	125-170	112-151	105-156		
BIS(ELR)					
Mean±SD	55.45±4.81	53.95±4.45	53.70±4.54	0.845	0.435
Range	50-63	46-62	48-62		
BIS(IVC)					
Mean±SD	58.60±2.96	59.05±4.82	59.30±4.39	0.147	0.863
Range	53-63	53-67	50-67		
VAS(Anxiety)#					
Range	4-9	1-7a	2-7a	-4.197	<0.001**
VAS(Pain)#					
Range	1-4	1-3a	1-3a	-3.331	<0.001**
RSS#					
Range	1-5	1-4	1-5	0.115	0.127

F-One Way Analysis of Variance; p-value>0.05 NS; *p-value <0.05 S; **p-value <0.001 HS

#Kruskal Wallis test; data are expressed [Median (Interquartile range)]

Post HOC test: a: significant difference with control group

PD(ELR)= Propofol dose to loss of eye lash reflex (mg); PD(LVC)= Propofol dose to loss of verbal contact (mg)

PD(BIS45)= Propofol dose to reach BIS45 (mg); BIS(ELR)= BIS score at loss of eye lash reflex

BIS(LVC)= BIS score at loss of verbal contact; RSS= Ramsay Sedation Score

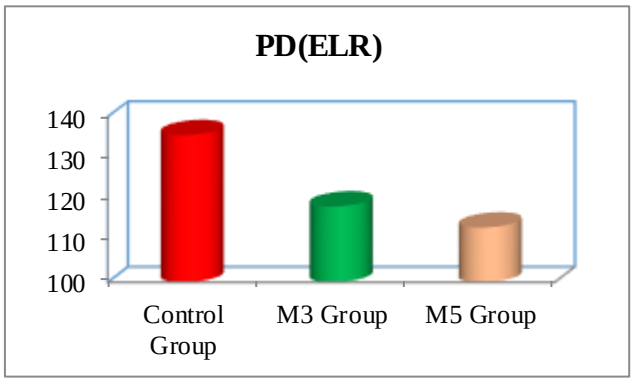

Fig. (2): Bar chart between groups according to their PD (ELR).

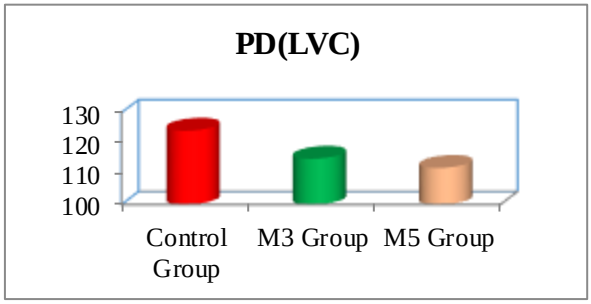

Fig. (3): Bar chart between groups according to their PD (LVC).

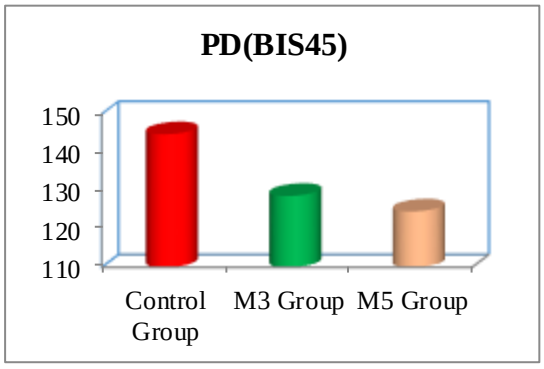

Fig. (4): Bar chart between groups according to their PD (BIS45).

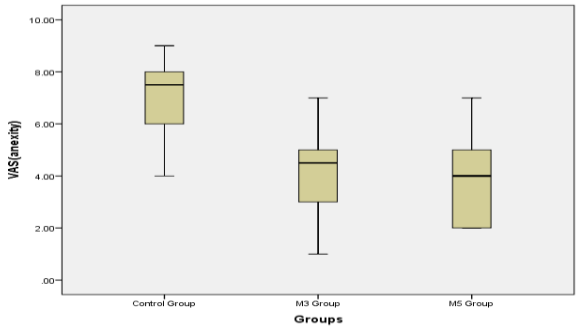

Fig. (5): Bar chart between groups according to their VAS (anxiety).

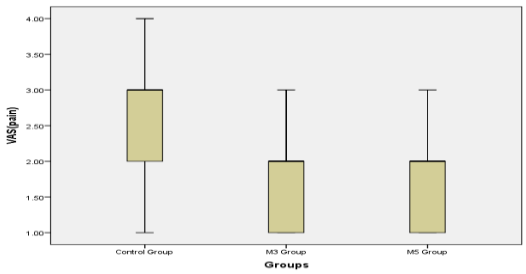

Fig. (6): Bar chart between groups according to their VAS (pain).

In table (2)and figure (7)as regard time of administration of first dose of analgesia postoperative there was statistically significant decrease mean in control group 141.00±47.56 compared to M3 group and M5group (171.75±49.24 and 181.25±33.12 respectively). This indicates that the control group needs to be drugged faster than the rest of the groups.

As regard assessment of preoperative anxiety we used the VAS anxiety score as it is very simple, fast, and manageable calling for only few seconds to be administrated and scored. Our results shows that melatonin is useful in reducing preoperative anxiety regardless the dose used in this study even 3mg or 5mg as there is no significant difference between the two groups but there is significant difference with control group.

In agreement with the result of the current study Ionescu et al., (5)in which 3mg oral melatonin was used successfully as premedication for laparoscopic cholecystectomy and at this dose it produced

anxiolysis. Also, in a study on 75 women Naguib and Samarkandi (6) found that premedication with 0.05 mg/kg sublingual melatonin was associated with preoperative anxiolysis without impairment of cognitive and psychomotor skills or affecting the quality of recovery. In contrast, Capuzzo et al., (7) said that melatonin doesn't reduce anxiety more than placebo in the elderly undergoing surgery. As regard propofol induction dose we used the BIS monitor which is validated for measuring the depth of anesthesia. And according to manufacturer's guidelines, a BIS value should be kept between 40 and 60 in general anesthesia we randomly select the values of 45 as an end point for propofol injection. We also record the propofol dose needed to loss of verbal contact and loss of eye lash reflex and correlate the two points with BIS score to enhance the result and in trial to overcome machine and human error.This study revealed that the mean induction dose of propofol was significantly higher in control group than in the 3 and 5mg melatonin groups. The dose of propofol at which the eye lash reflex was lost was significantly higher in control group than in the melatonin groups. Although the dose of propofol that resulted in loss of response to verbal commands was more in control group than in both melatonin groups, the difference was statistically significant. That prove the role of melatonin in reducing propofol induction dose. Like this study Turkistani et al., (8) found that melatonin premedication, in an oral dose of either 3 or 5 mg reduced the required dose of propofol to achieve BIS score of 45. Also, Norouzi et al., (9) did their study on 100 patients had abdominal surgery by dividing them into two groups melatonin 3mg who received melatonin 3mg 50 min before surgery and placebo group and reveal that propofol dose used was lower in the melatonin group than the placebo group.

As regard postoperative pain score according to VAS this study shows no significant difference between M3 and M5 groups but there is significant difference between the two groups and control group this result may be due to the effect of melatonin in reducing anxiety and pain related to it. It is also proved that melatonin interacts with multiple receptors including opioidergic, serotonergic and MT1/MT2 melatonergic receptors present in the dorsal horn of spinal cord as well in central nervous system (10). In agreement with the results of the current study the study was done by, Dubey et al., (11) found that premedication with oral 3mg melatonin significantly reduced fentanyl requirement in the postoperative period without any untoward effect in patients undergoing laparoscopic cholecystectomy. Also, Radwan et al., (12) showed that premedication oral dose of 6 mg of melatonin reduces the pain scores and pethidine requirements in the first postoperative 24 hours in patients undergoing abdominal surgery. Other study done by Caumo et al., [13] found that 5mg oral melatonin the night before and 1 hour before surgery in patients undergoing abdominal hysterectomy decrease pain and anxiety during the first day postoperative.In contrast, Acil et al. [14] did not observe any significant difference in pain scores in melatonin versus placebo groups during the stay in the postanesthesia care unit.

Table (2): Comparison between groups according to 1st dose of analgesia (min).

1st dose of analgesia (min)	Control Group (n=20)	M3 Group (n=20)	M5 Group (n=20)	ANOVA	p-value
Mean±SD	141.00±47.56	171.75±49.24a	181.25±33.12a	4.592	0.014*
Range	90-240	100-265	120-280		

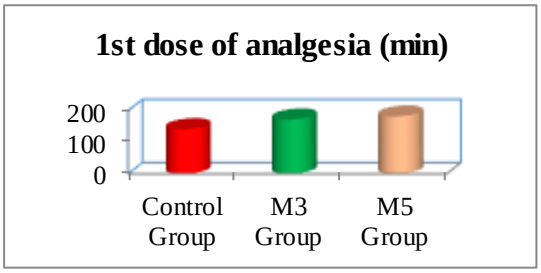

Fig. (7): Bar chart between groups according to their 1st dose of analgesia.

Conclusion

Our study demonstrated that premedication with melatonin in an oral dose of either 3 or 5 mg reduced the required dose of propofol to achieve a BIS score of 45. They also decrease preoperative anxiety score and postoperative pain score. Although, melatonin has no effect on postoperative sedation.

References

1. Hidalgo MPL, Auzani JAS, Rumpel LC, Moreira Jr NL, Cursino AW C, Caumo W (2005): The clinical effect of small oral clonidine doses on perioperative outcomes in patients undergoing abdominal hysterectomy. Anesthesia & Analgesia, 100(3), 795-802.
2. Weinbrown AA, Szold O, Ogorek D (2001): The midazolam-induced paradox phenomenon is reversible by flumazenil. Epidemiology, patient chageneral anaesthesia: a randomized controlled trial. British journal of Anaesthesia, 112(6):1055-1064.
3. Zawilska JB, Skene DJ, Arendt J (2009): Physiology and pharmacology of melatonin in relation to biological rhythms. Pharmacological reports, 61(3), 383-410.
4. Kurdi MS, Muthukalai SP (2016): The efficacy of oral melatonin in improving sleep in cancer patients with insomnia: a randomized double-blind placebo-controlled study. Indian journal of palliative care, 22(3), 295.
5. Ionescu D, Badescu C, Ilie A, Miclutia I, Iancu C, Ion D, Bondor C (2008): Melatonin as premedication for laparoscopic cholecystectomy: a double-blind, placebo-controlled study. Southern African Journal of Anaesthesia and Analgesia, 14(4), 8-11.
6. Naguib M, Samarkandi AH (2000): The comparative dose-response effects of melatonin and midazolam for premedication of adult patients: a double-blinded, placebo-controlled study. Anesthesia & Analgesia, 91(2), 473-479.
7. Capuzzo M, Zanardi B, Schiffino E, Buccoliero C, Gragnaniello D, Bianchi S, Alvisi R (2006): Melatonin does not reduce anxiety more than placebo in the elderly undergoing surgery. Anesthesia & Analgesia, 103(1), 121-123.
8. Turkistani A, Abdullah KM, Al-Shaer AA, Mazen KF, Alkatheri K (2007): Melatonin premedication and the induction dose of propofol. European Journal of Anaesthesiology (EJA), 24(5), 399-402.
9. Norouzi A, Fateh S, Modir H, Kamali A, Akrami L (2019): 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, 9(2), 62.
10. Tarocco A, Caroccia N, Morciano G, Wieckowski MR, Ancora G, Garani G, Pinton P (2019): Melatonin as a master regulator of cell death and inflammation: molecular mechanisms and clinical implications for newborn care. Cell death & disease, 10(4), 1-12.
11. Dubey RK, Srivastava S, Gupta PK (2017): Effect of Melatonin Premedication on Postoperative Analgesic Requirement in Laparoscopic Cholecystectomy Surgery. (e)-ISSN: 2250-3013, (p)-ISSN: 2319-4219 Volume 7, Issue 8 Version. 1, PP. 10-15.
12. Radwan K, Youssef M, El-Tawdy A (2010): Melatoninversus Gabapentin. A comparative study of preemptive medications. The Internet Journal of Anaesthesiology, DOI: 10.5580/265.
13. Caumo W, Torres F, Moreira NL, Auzani JA, Monteiro CA, Londero G, Hidalgo MPL (2007): The clinical impact of preoperative melatonin on postoperative outcomes in patients undergoing abdominal hysterectomy. Anesthesia & Analgesia, 105(5), 1263-1271.

Andersen LPH, Werner MU, Rosenberg J, Gögenur I (2014): A systematic review of peri-operative melatonin. Anaesthesia, 69(10), 1163-1171.