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Comparison of Oral Melatonin and Clonidine Premedication on Isoflurane Consumption and Postoperative Analgesia

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Abstract

Background: Premedication with oral melatonin and clonidine reduces anxiety and prolongs the postoperative analgesia. But there are few studies that have observed the isoflurane consumption when they are given as premedication, hence this study was conducted to compare the isoflurane consumption and duration of analgesia when oral melatonin and clonidine is given as premedication. *Methods:* Eighty-four patients whose aged between 18 and 60 years of American Society of Anesthesiologists one and two, undergoing surgery under general anesthesia were randomly allocated into three groups of 28 each. Group C received placebo (sugar pellet), Group M melatonin 3 mg orally and Group Cl clonidine 100 µg orally 60 min before surgery. *Results:* The end tidal isoflurane concentration at 30 min [Group C 0.78 (0.21), Group M 0.48 (0.15), Group Cl 0.64 (0.16) ($p < 0.001$)], at 60 min [Group C 0.75 (0.16), Group M 0.53 (0.2), Group Cl 0.64 (0.12) ($p < 0.001$)] was lower in Group M compared to Group Cl and C. Isoflurane consumption at 30 min [Group C 6.24 (1.3), Group M 3.84 (0.75), Group Cl 4.96 (0.98) ($p < 0.001$)] and at 60 min [Group C 10.8 (2.18), Group M 7.65 (1.11), Group Cl 9 (2.45) ($p < 0.001$)] was lower in Group M compared to Group Cl and C. Duration of analgesia was 267.60 ± 81.66 min in Group C, 507.00 ± 136.11 min in group M and 438.60 ± 111.01 min in Group Cl ($p < 0.001$). *Conclusion:* Premedication with oral melatonin resulted in lower end tidal isoflurane concentration and isoflurane consumption, however it did not prolong the duration of analgesia when compared with oral clonidine.

Keywords: Analgesia; Clonidine; Isoflurane; Melatonin.

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Introduction

Pain is the most feared discomfort in all perioperative patients. Although there are significant improvements in perioperative pain management, fear and anxiety are still the major hurdles that prevent several patients from undergoing surgical interventions. There are many drugs used orally to reduce anxiety preoperatively like midazolam, clonidine, melatonin, gabapentin, etc.

Melatonin is a hormone secreted by the pineal gland.[1] Melatonin has several functions that make it an attractive option for premedication including the regulation of circadian rhythm, sedative, analgesic, anti-inflammatory and antioxidant effects.[2] Clonidine is an α-2 adrenoreceptor agonist which produces analgesia by its central action.[3]

Some studies have shown that melatonin has similar efficacy compared to clonidine in reducing postoperative pain and narcotic consumption.[4]

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There are many studies which have inferred that clonidine reduces the requirement of isoflurane concentration,[5] but there are very few studies which have compared the anesthetic consumption when melatonin and clonidine are given as premedication.

Hence the present study was conducted to compare the effects of oral melatonin 3 mg and clonidine 100 μg as premedication on isoflurane consumption and postoperative analgesia in patients undergoing general anesthesia. The isoflurane consumption was considered as the primary outcome measure. The end tidal isoflurane concentration and postoperative analgesia were considered as the secondary outcome measures.

Materials and Methods

This prospective, randomized, double-blind control trial study was conducted from February 2018 to June 2018. Approval from the institutions ethical committee was obtained. The study was approved by Bangalore medical college and research institute ethical committee (BMCRI/PS/197/2017-18 dated 29/12/2017) and is registered in www.ctri.nic.in (CTRI/2018/02/012032). Eighty-four patients aged between 20 and 60 yrs of American Society of Anesthesiologists grade 1 and 2, who were undergoing surgery under general anesthesia, were randomly allocated into three groups of 28 each using a computer generated randomization sequence (www.random.org). Group C was considered as control and received placebo (sugar pellet), Group M received oral melatonin 3 mg and Group Cl received oral clonidine 100 μg. All the study drugs were given 60 min prior to surgery. Patients with systemic disorders (cardiovascular, respiratory, renal and central nervous system disorders), psychiatric illness, on chronic sedatives, opioid use or those with known drug allergies and duration of surgery more than 3 hours or less than 30 min were excluded from the study.

After obtaining informed written consent from patients, preanesthetic evaluation was performed. All patients were educated about the use of visual analog scale (VAS).[6] Preoperative investigations were performed as per the institutional protocol. Patients were fasted for 8 hr prior to surgery and were premedicated with 150 mg ranitidine and 0.25 mg alprazolam the night before surgery.

Patient's basal parameters like heart rate, non-invasive blood pressure (NIBP) and peripheral oxygen saturation were recorded. Based on the computer generated random list, patients were allocated randomly into Group C, Group M and Group Cl. The allocation based on the randomization sequence was concealed using sequentially numbered opaque sealed envelopes. The study drug was enclosed in opaque sealed envelopes and were opened by the principle investigator just before giving the study drug. The drug was given to the patient by an anesthesiologist not involved in the study. The group allocation was not revealed to any of the attending anesthesiologists until the end of the study. An 18G intravenous cannula was inserted and the study drug was orally administered with sips of water 60 min prior to surgery. Vital parameters were recorded every 20 min till the patient was taken up for surgery. Sedation was assessed at 60 min based on Ramsay sedation scale.[7] Questions relevant to the Hamilton anxiety scale[8] were asked to assess the degree of anxiety before giving the study drug and 60 min later. Patients were pre-loaded with 10 ml/kg body weight Ringer lactate. Any side effect like nausea, vomiting, headache, shivering, giddiness, etc. were noted. Once the patient was shifted to the operation theater, monitors like electrocardiogram, noninvasive blood pressure, pulse oximeter, entropy (Response Entropy/State Entropy) were connected and the basal parameters recorded. Patients were preoxygenated with 100% oxygen for 3 min and premedicated with glycopyrrolate 0.2 mg, ondansetron 4 mg, fentanyl 2 μg/kg and inj 2% preservative free lignocaine 3 ml (63.9 mg). Patient was induced with Inj propofol 10 mg every 5 sec till entropy was less than 60. The consumption of propofol and mean time of induction (from the time propofol was given till entropy of 60 was reached) was noted. Inj vecuronium 0.1 mg/kg was given and the patient was ventilated for 3 min. Under direct laryngoscopy trachea was intubated with appropriate size endotracheal tube. After confirming the proper position of the endotracheal tube, the agent gas monitoring line was connected and ventilation continued with Datex Ohmeda Avance S5™ GE healthcare, Finland (with an inbuilt software to calculate anesthetic consumption) anesthesia workstation ventilator. Anesthesia was maintained with 50% oxygen and air and isoflurane. Vital parameters were recorded before induction, after induction, after intubation and every 5 min thereafter till the end of surgery. Initial flows of 4l/min was kept till a minimum alveolar concentration of 1 or entropy RE/SE less than 60 was achieved and then flows were reduced to 1.5l/min. Isoflurane concentration was adjusted to maintain state entropy of 40–60. The depth of neuromuscular monitoring was monitored using

train of four (TOF), which was connected after the patient was induced but before the administration of muscle relaxant. TOF was maintained below a count of 2 with vecuronium increments. The end tidal isoflurane, end tidal oxygen and end tidal carbon dioxide were recorded every 5 min till the end of surgery. Isoflurane consumption was recorded every 30 min using a patented formula inbuilt in the software of the agent gas module of the anesthesia workstation. Any additional requirement of rescue propofol (10 mg) to maintain state entropy of less than 60, despite adequate administration of isoflurane (Minimum alveolar concentration of 1.5) was noted. Hypertension was defined as a rise in basal mean arterial pressure (MAP) more than 20% and tachycardia was defined as heart rate more than 100 bpm. Fentanyl 0.5 microg/kg was administered intravenously if tachycardia or hypertension persisted despite adequate depth of anesthesia (entropy <60). Intraoperatively, side effects like hypotension (defined as a fall in basal mean arterial pressure (MAP) more than 20%) and bradycardia (defined as heart rate less than 60 bpm) if any, were noted.

At the end of surgery, isoflurane was discontinued and muscle relaxation was reversed with Inj neostigmine 0.05 mg/kg and glycopyrollate 0.008 mg/kg and trachea extubated when the TOF > 0.8 with sustained head lift and hand grip. Extubation time defined as the time between discontinuation of isoflurane to extubation was recorded.

Postoperatively side effects like nausea, vomiting, shivering, headache, etc. if any were noted. Vital parameters were monitored every 15 min for half an hour, then every 30 min for 2 hr and hourly till 6 hr. Sedation was assessed using Ramsay sedation scale and pain was assessed using VAS postoperatively at the end of 1 hr and 4 hr. When the VAS > 3, rescue analgesia was given using Inj Paracetamol 1g IV infusion. The time from the start of surgery to the first requirement of analgesia, i.e. duration of analgesia was recorded.

Statistical method and analysis: Sample size was calculated using www.openepi.com. Sample size was based on the pilot study, where the mean isoflurane consumption at 1 hr was 8 ml, assuming a standard deviation of 1.5 and normal distribution of values to detect a minimum of 15% difference in isoflurane consumption between 2 drugs, a minimum of 25 patients were required in each group. For further validation of the study we have taken 28 patients in each group assuming a dropout rate of 10%.

The Statistical software namely SPSS 18.0, and R environment ver. 3.2.2 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables, etc.

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean and standard deviation (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance.

Analysis of variance (ANOVA) has been used to find the significance of study parameters between three or more groups of patients, chi-square/ Fisher exact test has been used to find the significance of study parameters on categorical scale between two or more groups, non-parametric setting for Qualitative data analysis. Intergroup analysis has been done using the student *t* test.

Results

A total of 84 patients were enrolled and randomly allocated into three groups (Group C n=28, Group M n=28 and Group Cl n=28) [Fig. 1]. However 9 patients (Group C n=4, Group M n=3, Group Cl n=2) were excluded from the study due to protocol violation, prolonged duration of surgery > 3 hr and duration of surgery < 30 min due to inoperable tumor. A total of 24 patients in Group C, 25 patients in Group M and 26 patients in Group Cl were included for the final analysis.

Demographic parameters such as age, sex, weight and duration of surgery were comparable in all the three groups as shown in Table 1.

The mean dose of propofol consumption was significantly lower in Group M and Cl when compared to Group C as shown in Table 2. Intergroup analysis showed no significant difference in mean dose of propofol consumption (p value 0.528) between group M and group Cl.

The mean induction time was significantly lower in Group M and Group Cl when compared to Group C as shown in Table 2. Intergroup analysis showed no significant difference in mean induction time (p value 0.088) between Group M and Group Cl.

Intraoperative heart rate was higher in control group when compared to the clonidine and melatonin group as shown in Figure 2. There was an increase in heart rate after intubation which subsided 3 min after intubation in all the three groups.

The MAP was comparable in all the three groups of patients as shown in Figure 3. The MAP increased after intubation and subsided 3 min after intubation in all the three groups. All patients in melatonin group and clonidine group had a sedation score of 2, whereas in control group, 3 patients had a sedation score of 2 and 22 patients had a sedation score of 1 which was statistically significant with *p* value < 0.001. Intergroup analysis showed that the sedation score was similar in Group M and Group Cl (*p* value 0.9978). The anxiety score at 60 min after oral administration of the drug was 19.96 in the control group, 6.72 in the melatonin group and 7.4 in the clonidine group with a *p* value <0.001. Intergroup analysis showed that the anxiety score was similar in Group M when compared to Group Cl (*p* value 0.1172).

The end tidal isoflurane concentration in % at 30 min and 60 min was significantly lower in Group M and Cl compared to Group C as shown in Table 2 and Figure 4. Intergroup analysis showed that end tidal isoflurane concentration was lower in Group M compared to Group Cl at 30 min (*p* value <0.001) and at 60 min (*p* value 0.022). Isoflurane consumption at 30 min and 60 min was significantly lower in Group M and Cl compared to Group C as shown in Table 2. Intergroup analysis showed that isoflurane consumption was lower in Group M when compared to Group Cl at 30 min (*p* value <0.001) and at 60 min (*p* value 0.015). The

Table 1: Demographic parameters

	Group C n=24	**Group M n=25**	**Group Cl n=26**	***p* value**
Age (mean ± SD *) in yrs	37.4 ± 11.9	43.8 ± 12.0	38 ± 12.5	
Sex (M/F)	5/19	14/11	14/12	
Weight (mean ± SD) in kg	58.6 ± 9.7	59.9 ± 7.3	63.2 ± 7.3	
Duration of Surgery (mean ± SD) in mins	77.60 ± 11.62	75.13 ± 13.41	76.56 ± 12.52	0.944
Type of surgery (number of cases)				
Breast surgery	9	11	12	0.855
Upper abdominal surgery	4	5	5	0.914
lower abdominal surgery	3	3	5	0.662
Scalp and face surgery	8	6	4	0.426

*SD: standard deviation

Table 2: Comparison of end tidal isoflurane concentration, isoflurane consumption, propofol consumption, induction time, duration of analgesia, peripheral oxygen saturation, end tidal carbon dioxide, response entropy, state entropy and extubation time between the three groups.

	Group C	**Group M**	**Group Cl**	***p* value**
Endtidal Isoflurane Concentration (%)				
30 min [mean (SD)] (95% CI† of means)	0.78 (0.21) (0.69–0.86)	0.48 (0.15) (0.42–0.53)	0.64 (0.16) (0.57–0.70)	<0.001
60 min [mean (SD)] (95% CI of means)	0.75 (0.16) (0.68–0.81)	0.53 (0.2) (0.45–0.60)	0.64 (0.12) (0.59–0.68)	<0.001
Isoflurane Consumption (ml)				
30 min [mean (SD)] (95% CI of means)	6.24 (1.3) (5.73–6.74)	3.84 (0.75) (3.54–4.13)	4.96 (0.98) (4.57–5.34)	<0.001
60 min [mean (SD)] (95% CI of means)	10.8 (2.18) (9.94–11.65)	7. 65 (1.11) (7.21–8.08)	9 (2.45) (8.04–9.96)	<0.001
Mean dose of propofol consumption (mg) [mean (SD)] (95% CI of means)	96.40 (14.97) (90.53–102.26)	74.00 (13.84) (68.57–79.43)	76.40 (12.87) (71.35–81.44)	<0.001
Mean induction time (seconds) (95% CI of means)	76 (2.2) (75.14–76.86)	52 (1.66) (51.35–52.65)	53 (1.5) (52.41–53.59)	<0.001
Duration of Analgesia (mins) [mean (SD)] (95% CI of means)	267.60 (81.66) (235.59–299.61)	507.00 (136.11) (453.65–560.35)	438.60 (111.01) (395.08–482.11)	<0.001
Peripheral 02 saturation (%) [mean (SD)]	99.33 (0.51)	99.33 (0.51)	99.5 (0.54)	0.401
End tidal carbon dioxide (mm Hg) [mean (SD)]	33.96 (1.19)	34.26 (0.66)	33.98 (0.87)	0.524
End tidal oxygen (mm Hg) [mean(SD)]	38.9 (1.59)	39.69 (2.36)	39.6 (2.27)	0.068
Response entropy [mean(SD)]	55.4 (1.17)	55.2 (1.13)	55.5 (2.63)	0.845
State entropy [mean (SD)]	52.4 (0.84)	52.5 (1.08)	52.8 (1.61)	0.688
Extubation time (secs)	389.6 (39.63)	382.6 (30.8)	379.2 (31.61)	0.552

† Cl : Confidence interval

duration of analgesia was significantly prolonged in Group M and Cl compared to Group C as shown in Table 2. Intergroup analysis showed that the duration of analgesia was not statistically significant in Group M when compared to Group Cl (p value 0.0576).

Peripheral oxygen saturation, end tidal carbon dioxide, response entropy and state entropy are comparable between the three groups as shown in Table 2. Response entropy was maintained between 40–60 throughout the surgery as shown in Table 2. One patient in Group M, 6 patients in Group C and no patients in Group Cl received 20 mg of rescue propofol. Two patients had shivering in Group M which was treated with Inj Tramadol 100 mg IV. The extubation time was comparable between the three groups.

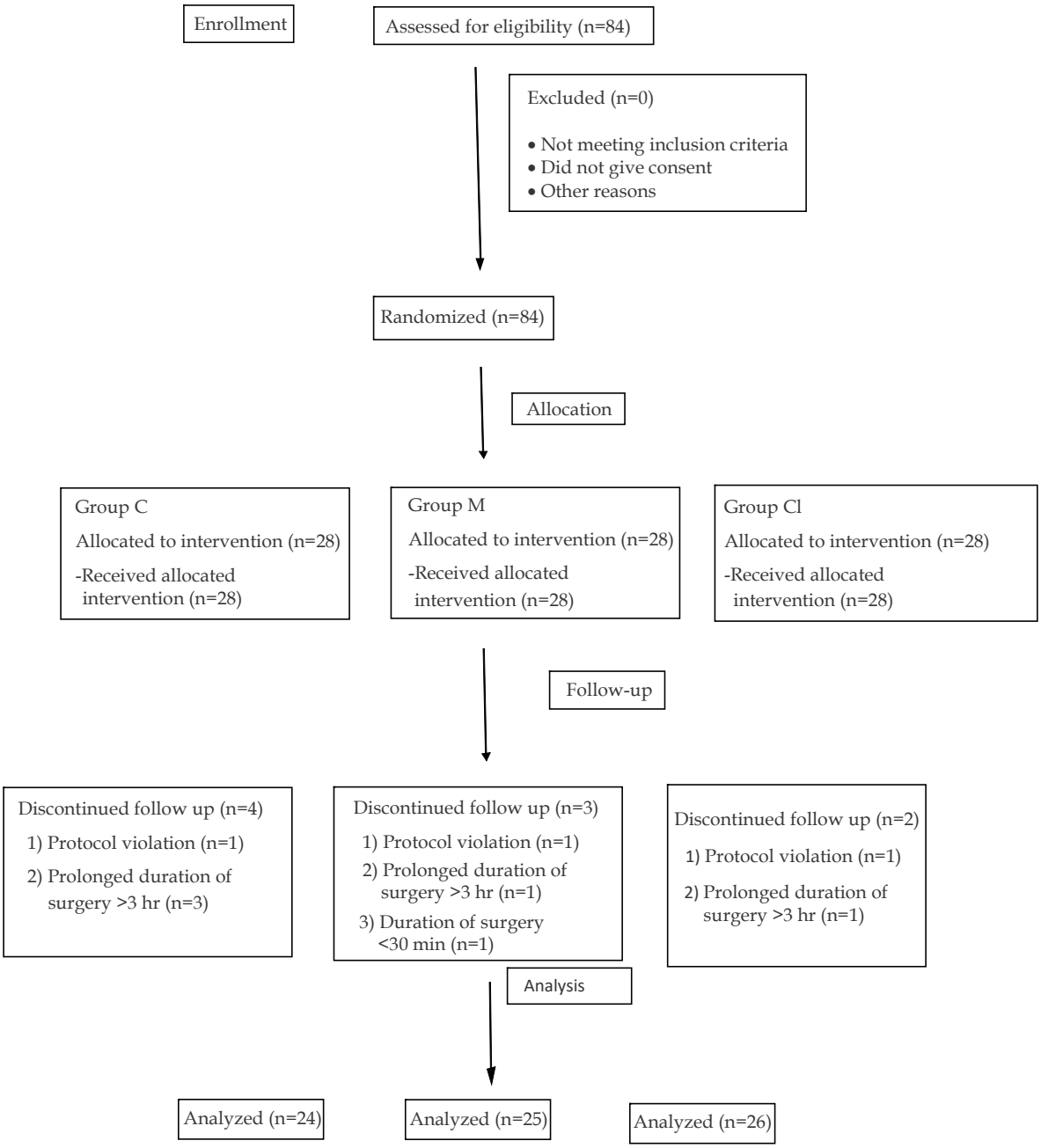

Fig. 1: Consort flow diagram

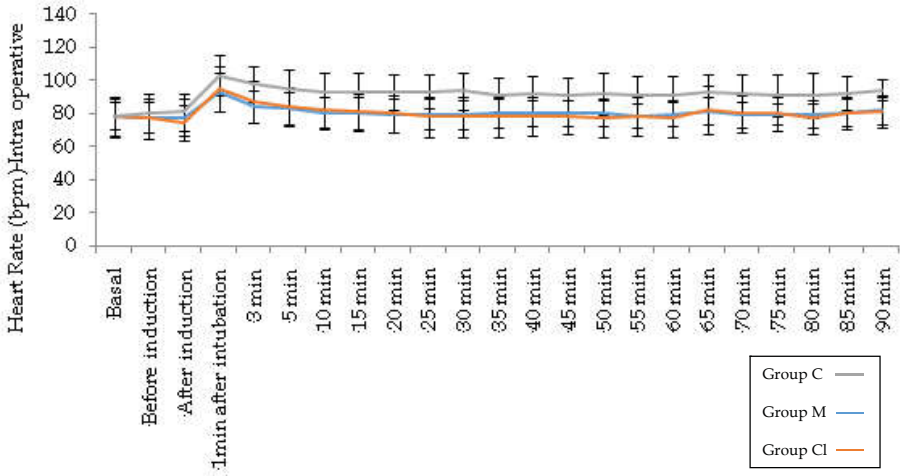

Fig. 2: Comparison of the trends of Preoperative and intraoperative heart rate between the three groups

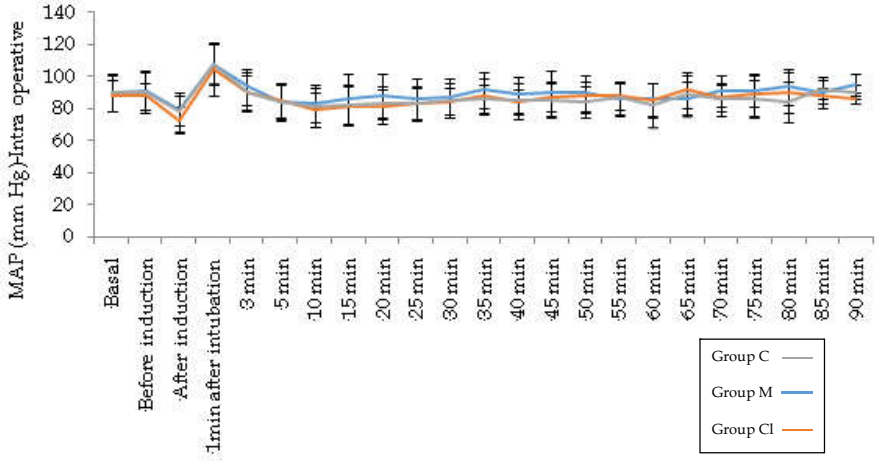

Fig. 3: Comparison of the trends of Mean arterial blood pressure between the three groups

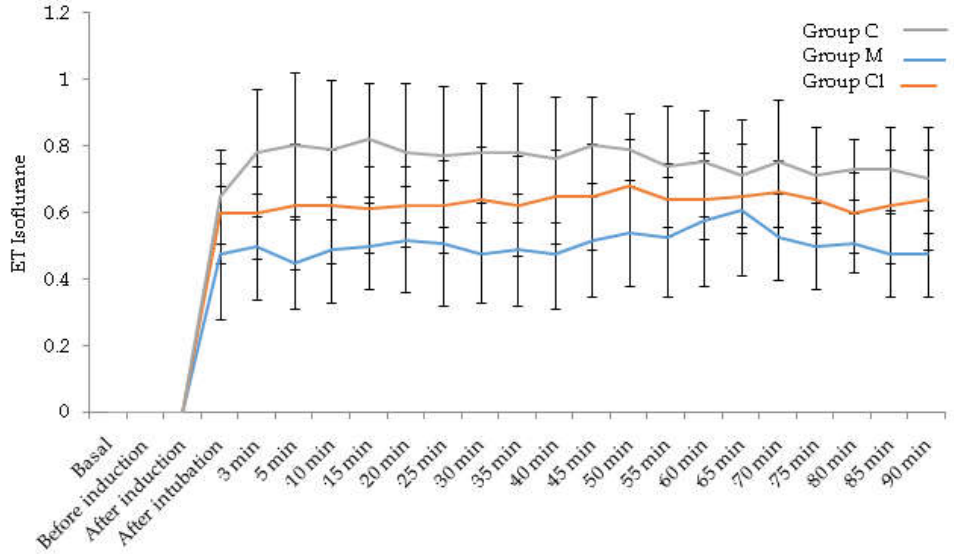

Fig. 4: Comparison of end tidal isoflurane concentration between the three groups.

Discussion

In this study it was observed that premedication with oral melatonin resulted in lower end tidal isoflurane concentration and lower isoflurane consumption, however it did not prolong the duration of analgesia when compared with oral clonidine.

There are many drugs used orally to reduce anxiety preoperatively like midazolam, clonidine, melatonin, gabapentin, etc. Midazolam is known to cause postoperative cognitive and psychomotor impairment.[9] Gabapentin causes nausea, vomiting and higher levels of sedation.[10] Hence a drug without these side effects is preferred.

Melatonin (*N*-acetyl-5-methoxytryptamine), discovered about half a century ago, is a hormone produced chiefly by the pineal gland[11] but also in much smaller amounts by the gastrointestinal tract, retina, platelets, respiratory epithelium, bone marrow, thymus, and skin. Melatonin has several functions that make it an attractive option for premedication including the regulation of circadian rhythm, sedative, analgesic, anti-inflammatory and antioxidant effects.[2] It interacts with multiple receptor sites including opioidergic, benzodiazepinergic, muscarinic, nicotinic, serotonergic, α_1, α_2 adrenergic and most importantly MT1/MT2 melatonergic receptors present in the dorsal horn of the spinal cord as well in the central nervous system.[12] The calculated serum half-life of melatonin is about 30–50 minutes.[13]

In a study the effect of melatonin 6 mg and pregabalin 150 mg as premedication on perioperative anxiety and postoperative pain was assessed and the authors concluded that both the drugs reduce preoperative anxiety and increase the postoperative duration of analgesia, but melatonin caused more sedation than pregabalin.[14] This sedation could be due to the higher dose of melatonin used.

Some studies have used two different doses of melatonin 6 mg and 3 mg to assess the efficacy of analgesia in patients undergoing cesarean section under spinal anesthesia. The incidence of headache in patients given 6mg was significantly higher than others ($p < 0.001$).[15] Hence in our study we have used 3 mg melatonin. None of the patients in our study had complains of headache or other side-effects like nausea or bradycardia.

Clonidine is an α_2 adrenoreceptor agonist which produces analgesia by its central action.[3,16] It is rapidly absorbed after oral administration and reaches a peak plasma concentration within 60–90 min. Clonidine stimulates alpha-2 adrenergic neurons in the medullary vasomotor center causing a decrease in the sympathetic nervous system outflow from the central nervous system to the peripheral tissues and central activation of non-adrenergic imidazoline preferring receptors. Decreased sympathetic activity is manifested as peripheral vasodilatation, hypotension, decrease in heart rate and cardiac output.

Some authors have studied the effect of oral clonidine 100 μg on postoperative pain and concluded that clonidine significantly reduces the severity of postoperative pain without any side effects.[17] Hence we have also used oral clonidine 100 μg as premedication in our study.

Studies have compared the effect of oral clonidine 3 μg/kg on propofol requirements during lower extremity vascular surgery and concluded that clonidine reduces the requirement for propofol.[18] Few authors have assessed the efficacy of oral melatonin 5 mg and clonidine 150 μg on pharmacodynamics and pharmacokinetics of propofol target controlled infusions and have inferred that there was no significant differences in the pharmacokinetics and pharmacodynamics of propofol infusion due to premedication with clonidine or melatonin.[19] Whereas in our study we observed that oral melatonin 3 mg and clonidine 100 μg premedication reduces the total requirement of propofol when compared to placebo.

Some authors performed a clinical trial and concluded that the induction time with sevoflurane was significantly longer in the placebo group compared to those who received clonidine 150 μg and 300 μg as oral premedication.[20] Our study demonstrates a similar result where patients who received melatonin and clonidine premedication had shorter induction time with propofol when compared to control group owing to their sedative effects.

In a study the role of oral melatonin 6 mg as premedication on attenuation of pressor response to laryngoscopy and intubation was studied and they concluded that melatonin 6 mg effectively attenuated the cardiovascular responses to laryngoscopy and intubation.[21] Whereas in our study we did not observe any attenuation of pressor response to intubation, which may be due to the lower dose of melatonin that we have used.

Some authors have studied the effect of oral clonidine 200 μg as premedication and concluded that it reduces the pressor response to intubation and laryngoscopy.[22] We did not observe any

attenuation of pressor response to intubation and laryngoscopy which could be due to the lower dose of clonidine used in our study.

In a study, the effect of oral clonidine 100 µg and melatonin 5 mg on postoperative pain and morphine consumption was compared and they concluded that their effect was greater than placebo and was equivalent between these two drugs.[23] There are studies which have assessed the efficacy of melatonin 6 mg, clonidine 200 µg and gabapentin 600 mg in reducing preoperative anxiety and postoperative pain in patients undergoing laparoscopic cholecystectomy and have found that the use of melatonin had an efficacy similar to that of clonidine and gabapentin in reducing preoperative anxiety, postoperative pain and narcotic consumption.[4] They have observed few cases of decreased blood pressure in those patients given clonidine, though it was not significant. We did not observe any such difference in MAP in all the three groups which could be because of the lower dose of clonidine used. In our study both melatonin and clonidine had lower anxiety scores and sedation scores compared to control. The basal heart rate was lower in the melatonin and clonidine group when compared to placebo, probably due to decreased anxiety. We also observed increased duration of analgesia in melatonin and clonidine group when compared to the control group.

Some authors have concluded that clonidine 2 µ/kg and 4 µ/kg, given as premedication reduces the MAC of sevoflurane in paediatric patients.[24] The effect of oral clonidine 150 µg premedication on perioperative hemodynamic response and postoperative analgesic requirement for patients undergoing laparoscopic cholecystectomy has been studied and inferred that clonidine 150 µg results in improved perioperative hemodynamic stability and a reduction in the intraoperative isoflurane concentration and postoperative analgesic requirements.[5] In our study melatonin 3 mg reduced the end tidal isoflurane concentration and isoflurane consumption significantly when compared to clonidine 100 µg.

In our study we observed two cases of shivering in patients who received melatonin. This may be due to the hypothermic properties of melatonin[25] or reduced operation theater temperature as the patient temperature was not monitored and the theater temperature was not kept constant in all the cases.

There are certain limitations in our study. We have not observed the effects of oral clonidine and melatonin on the recovery profile of the patients. The effect of melatonin on the sleep quality was also not assessed. The pain score was not analyzed as we have studied different varieties of cases with varied pain threshold. We did not find any literature, to the best of our knowledge and resources available, regarding the equipotent doses of melatonin and clonidine which could be because they belong to different groups of pharmacological classification.

To conclude premedication with oral melatonin 3 mg resulted in lower end tidal isoflurane concentration and lower isoflurane consumption, however it did not prolong the duration of analgesia when compared with oral clonidine 100 µg.

Conflict of interest: Nil declared.

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References

1. Marcus R, David M G, Steven K H, *et al.* Human performance and patient safety. Miller's anesthesia, 8th edition. Philadelphia, Elsevier Inc; 2015.p.168.
2. Eadi M, Govitrapong P, Phansuwan-Pujito P, *et al.* Pineal opioid receptors and analgesic action of melatonin. J Pineal Res. 1998;24:193–200.
3. Joel G H. Pharmacological basis of therapeutics. Goodman and Gilman, 10th edition; 2001.pp.233–34.
4. Vahide SH, Reza AY, Shaqayeq M, *et al.* The efficacy of Melatonin, Clonidine and Gabapentin in reducing preoperative anxiety and postoperative pain in patients undergoing laparoscopic cholecystectomy: a randomized clinical trial. Archives of Anesthesiology and critical care. 2015;1(4):120–25.
5. Shivinder S, Kapil A. Effect of oral clonidine premedication on perioperative hemodynamic response and postoperative analgesic requirement for patients undergoing laparoscopic cholecystectomy. Indian Journal of Anaesth. 2011 Jan-Feb;55(1):26–30.
6. EC Huskisson. Measurement of pain. The Lancet. 1979;9(2):1127–31.
7. Ramsay MA, Savege TM, Simpson BR, *et al.* Controlled sedation with alphaxalone – alphadolone, Br Med J. 1974 Jun 22;2(5920):656–9.
8. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol. 1959;32:50–55.

9. Tushar P, Madhuri SK. A comparative study between oral melatonin and oral midazolam on preoperative anxiety, cognitive, and psychomotor functions. Journal of Anesthesiology Clinical pharmacology. 2015 Jan-Mar;13(1):37–43.
10. Karthik S, Mandeep G, Ashok G. Protective premedication: a comparative study of Acetaminophen, Gabapentin and combination of acetaminophen with gabapentin for postoperative analgesia. Journal of Anesthesiology Clinical Pharmacology, 2010 Oct-Dec;26(4):531–36.
11. Lionel H O, Sandrine L. Melatonin has multiorgan effects. European Heart Journal–Cardiovascular Pharmacotherapy, Oct 2016;2(4):258–65.
12. Srinivasan V, Lauterbach EC, Ho KY, *et al.* Melatonin in antinociception: its therapeutic applications. Curr Neuropharmacol, 2012;10:167–78.
13. Souvik M, Dalim KB, Puneet K. Melatonin in perioperative medicine: Current perspective. Saudi Journal of Anesthesia. 2013 Jul-Sep;7(3): 315–21.
14. Dalia AN, Ayman AA. Efficacy of preoperative melatonin versus pregabalin on perioperative anxiety and postoperative pain in gynecological surgeries. Egyptian Journal of Anesthesia. 2014 Jan;30(1);89–93.
15. Marzeih Beigom K, Morteza Delkhosh R, Sonia Oveisy *et al.* Evaluation of analgesic efficacy of melatonin in patients undergoing caesarean section under spinal anesthesia. Iran J Pharm Res. 2016;15(4):963–71.
16. Yukio H. Drugs affecting adreneceptors: alpha-2 agonists. The pharmacological basis of Anesthesiology-Kharasch. 1994; Chapter 27:607–23.
17. Behdad S, *et al.* Effect of oral low dose clonidine premedication on postoperative pain in patients undergoing abdominal hysterectomy: a randomized placebo controlled clinical trial. Rev Med Chir Soc Med Nat Lasi. 2013 Oct-Dec; 117(4):934–41.
18. Morris J, Acheson M, Reeves M, *et al.* Effect of clonidine premedication on propofol requirements during lower extremity vascular surgery: a randomized controlled trial. British Journal of Anesthesia. 2005;95(2):183–8.
19. Agnieszka B, Katarzyna W, Pawel W, *et al.* Melatonin and Clonidine Premedication Has Similar Impact on the Pharmacokinetics and Pharmacodynamics of Propofol Target Controlled-Infusions. Journal of Clinical Pharmacology. 2015;55(3):307–16.
20. Watanabe T, Inagaki Y, Ishibe Y. Clonidine premedication effects on inhaled induction with sevoflurane in adults: a prospective, double blind, randomized study. Acta Anesthesiologica Scandinavica. 2006 Feb;50(2):180–7.
21. Priyamvada G, Durga J, Dharam D J. Role of melatonin in attenuation of haemodynamic responses to laryngoscopy and intubation. Indian Journal of Anesthesia. 2016 Oct;60(10):712–18.
22. Nagol Shekharappa S, Nongthombam Ratan S, Haorongbam Shanti S, *et al.* A comparative study of clonidine and gabapentin for attenuating hemodynamic responses to laryngoscopy and tracheal intubation. Journal of Medical Society. 2014;28(2):94–98.
23. Wolnei C, Rosa L, Maria P L, Hidalgo. Preoperative anxiolytic effect of Melatonin and Clonidine on postoperative pain and morphine consumption in patients undergoing abdominal hysterectomy: a double blind, randomized, placebo controlled study. The Journal of Pain. 2009 Jan;10(1):100–8.
24. Mikawa, Katsuya, Nishina, Kahoru. Oral clonidine and postoperative pain. Anesthesia and analgesia. 1997 Jan;84(1):229.
25. Cagnacci A, Elliot JA, Yen SS. Melatonin: a major regulator of the circadian rhythm of core temperature in humans. The Journal of Clinical Endocrinology and Metabolism. 1992 Aug; 75(2):447–52.