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Original Research Article

To assess the effect of oral melatonin premedication on propofol requirement for induction in entropy guided general anaesthesia- A randomised double blind study

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Abstract

Introduction: Premedication plays an important role in providing anxiolysis prior to surgery, reduce the intraoperative requirement of intravenous anesthetics and manage perioperative pain. Melatonin premedication has been shown to allay pre-operative anxiety, produce postoperative sedation and reduce analgesic requirement. This study aims to assess the effect of oral melatonin premedication on propofol requirement for induction of anaesthesia.

Materials and Methods: A randomized double blind study was performed on 70 patients of American Society of Anaesthesiologists (ASA) I and II status after obtaining ethical committee clearance. Patients received 3 mg oral melatonin (group M) or placebo (group C) as premedication 60 min prior to surgery (n= 35 in each group). The requirement of propofol for induction was noted using entropy. Patients were assessed for preoperative anxiety using Hamilton anxiety rating scale (HAM) and peri-operative sedation using Ramsay sedation scale (RSS).

Results: The demographic variables were comparable between the 2 groups. There was significant difference between the mean propofol dose requirements for induction in group M and C i.e., 0.96 ± 0.1mg/kg and 2 ± 0.26 mg/kg respectively, with $p < 0.001$ using Mann Whitney U test.

Conclusion: Oral melatonin premedication reduces the induction dose of propofol.

Introduction

Premedication plays an important role in providing anxiolysis prior to surgery, reducing the intraoperative requirement of intravenous (IV) anaesthetics and managing perioperative pain.[1-4] Many drugs have been used for premedication including midazolam, dexmedetomidine, gabapentin and clonidine. Midazolam is known to cause postoperative cognitive and pschycomotor impairment.[5,6] Gabapentin causes nausea, vomiting and higher levels of sedation.[7] Clonidine is known to cause bradycardia.[8] Hence a drug without these side effects is preferred.

It has been more than 50 years since an American dermatologist, Dr. Aaron Bunsen Lerner, extracted a few milligrams of N-acetyl-5-methoxy-serotonin from more than 100,000 cattle pineal glands. It was called melatonin. Melatonin is a methoxyindole synthesized from tryptophan and secreted principally by the pineal gland. It has an endogenous circadian rhythm of secretion induced by the suprachiasmatic nuclei of the hypothalamus that is entrained to the light/dark cycle.[8,9] Melatonin premedication is known to significantly reduce the doses of propofol required for induction by acting on GABA-A receptor.[1,2] But there are relatively few studies on the use of melatonin for premedication and its effects on induction of anaesthesia.

Propofol, an alkyl phenol is most commonly used intravenous induction agent at a dose of 1.5-2.5 mg/kg.[10] Adequate preoperative anxiolysis through premedication is known to reduce anaesthetic requirement for induction.[1] Hence we conducted a randomized double blind control study to assess the efficacy of oral melatonin premedication on consumption of propofol for induction of general anaesthesia.

Materials and Methods

After obtaining approval from institutional ethical committee, the study was registered in clinical trial registry of India (CTRI NO: CTRI/2018/08/015537). A written informed consent was taken and we enrolled 70 patients aged 18-60 year, with basal mass index (BMI) 18-26 kg/m^2[11] of ASA I & II status. Patients on benzodiazepines or opioids, those with psychiatric illness, ischemic heart disease, hypertension & pregnant women were excluded from the study. Patients were randomly allocated in to one of the two groups M and C using numbers generated from www.random.org.

Group C- received placebo (sugar pellet) orally 60 min prior to surgery

Group M– received oral melatonin 3 mg 60 min prior to surgery

All patients were kept fasting overnight and were given Tablet Ranitidine 150 mg on the previous night of surgery. Inj.metaclopramide 10 mg was given to all patients 60 min prior to surgery.

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The study drug was given by a senior anaesthesiologist not involved in the study. Baseline vital parameters- Heart rate (HR), non-invasive blood pressure (NIBP), pulse oximetry (SpO_2) were noted. Patients and anaesthesia provider were not aware of the study drug. An 18G IV cannula was inserted and the study drug was orally administered with sips of water 60-90 mins prior to surgery. Heart rate (HR), non-invasive blood pressure (NIBP), pulse oximetry (SpO_2) were recorded every 20 mins till the patient was taken up for surgery. Questions relevant to Hamilton anxiety scale were asked to assess the degree of anxiety before shifting the patient to operation theatre at the end of 60 mins. Sedation was assessed at the end of 60 mins based on Ramsay sedation scale. Patients were pre-loaded with 10ml/kg body weight Ringer lactate. Any side effect like nausea, vomiting, headache, shivering, hypotension etc. were noted.

Intraoperative monitoring included electrocardiography (ECG), plethysmography (SpO_2), non-invasive blood pressure (NIBP), respiratory rate (RR), entropy, end tidal carbon-di-oxide($EtCO_2$), train-of-four (TOF). All patients were pre-medicated with inj. glycopyrrolate 0.005 mg/kg IV, inj.fentanyl 2µg/kg IV, inj. Ondansetron 4 mg, inj 2% preservative free lignocaine 2 ml and were pre-oxygenated with 100% oxygen for 3 min. Patients were induced with inj propofol 20mg every 10secs to reach entropy of (response entropy/state entropy) RE/SE 40-60. The consumption of propofol and mean time of induction (from the time propofol was given till entropy was reached) was noted. Patients were given inj. vecuronium 0.1 mg/kg. After 3 minutes of adequate ventilation, trachea was intubated with appropriate sized cuffed endotracheal tube. Anaesthesia was maintained with oxygen 33% and nitrous oxide 66%, isoflurane to maintain entropy between 40-60. Inj. Vecuronium 0.05mg/kg was used for maintenance of muscle paralysis.

At the end of surgery the time between cut off of isoflurane to extubation was noted (extubation time). Neuromuscular blockade was reversed using Inj neostigmine 0.05mg/kg with inj.glycoprrolate 0.01mg/kg and were extubated after TOF of 0.9 was achieved.

Sedation was assessed using Ramsay sedation scale (RSS) post-operatively at the end of 1hr and 4hrs.

Sample size was calculated based on a previous study conducted by Mohamed Naugib et al,[4] where the induction dose of propofol based on loss of eyelash reflex was found to be 0.9 mg/kg. With 95% confidence interval, α error of 0.05, standard deviation of 1.5 and power of study as 80%, a minimum sample size of 32 patients were required in each group. Assuming a dropout rate of 10%, we included 35 patients in each group for further validation. The data collected were tabulated using Microsoft Excel worksheet and the data were analyzed using Statistical Package for the Social Sciences version 20.0 Inc., Chicago, IL, US.

Results

A total of 70 patients were enrolled and randomly allocate into two groups of 35 each (group C n=35, group M n=35). No patients were excluded from the study and a total of 35 patients in each group were taken for the final analysis. (Fig. 1)

Demographic parameters were comparable in both the groups as shown in Table 1.

The mean dose of propofol consumption was 0.96mg/kg and 2mg/kg in the melatonin and placebo groups respectively which was statistically significant ($p<0.0001$) as shown in Table 2.

The mean induction time was 76±2.4 sec and 52±1.68 sec in the placebo and melatonin groups respectively which was statistically significant ($p<0.0001$) as shown in Table 2.

The depth of anesthesia measured by entropy was adequately maintained throughout the procedure as depicted in Fig. 2.

The sedation as assessed by Ramsay sedation scale was comparable between both the groups at baseline and till 10 min after giving melatonin, from 20 min onwards patients in melatonin group had higher sedation score compared to control group during pre-operative periods and also in post-operative till 4 hours (Table 3).

Patients who were premedicated with melatonin had lower anxiety score after 60 min of giving drug, as assessed by Hamilton anxiety scale which was statistically significant (Table 3).

The mean time for extubation in those patients who received placebo was 3.62±0.76 minutes and in those who received melatonin was 4.72±0.7 minutes with p-value of 0.48. Hence it was not significant.

None of patients had side effect nausea, headache, vomiting, bradycardia, hypotension.

Table 1: Comparison of demographic parameters between group C and group M.

Demographic data	**Group C**	**Group M**
Age(yrs)	41.26±9.98	41.17±12.08
Gender(M/F)	12/23	13/22
BMI (kg/m^2)	23.31±2.69	23.38±2.37
ASA grade(1:2)	21:14	20:15
Duration of surgery (minutes)	65.14±23.27	63.86±27.06

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Table 2: Comparison of Propofol consumption between group C and group M.

	Group C	**Group M**	**p value**
Mean dose of propofol consumption (mg/kg) Mean±SD	2±0.26	0.96±0.1	<0.0001
Mean induction time (seconds) Mean±SD	76±2.4	52±1.68	<0.0001

Table 3: Comparison of Ramsay sedation scale and Hamilton anxiety scale between group C and group M.

RSS (Ramsay sedation scale)		**group C**		**group M**		**P value**
		Mean	**SD**	**mean**	**SD**	
Pre op	Baseline	2	0	2	0	1.00
	5 min	2	0	2	0	1.00
	10 min	2	0	2	0	1.00
	20 min	2	0	2.3	0.5	<0.0001
	40 min	2	0	3	0	<0.0001
	60min	2	0	3	0	<0.0001
post op	1st hour	1.57	0.778	2	0	<0.0001
	4th hour	1	0	2	0	<0.0001
HAM (Hamilton anxiety scale)	Baseline	11.2	0.9	10.9	0.7	0.12
	At 60 min	10.89	2.27	1.43	0.502	<0.0001

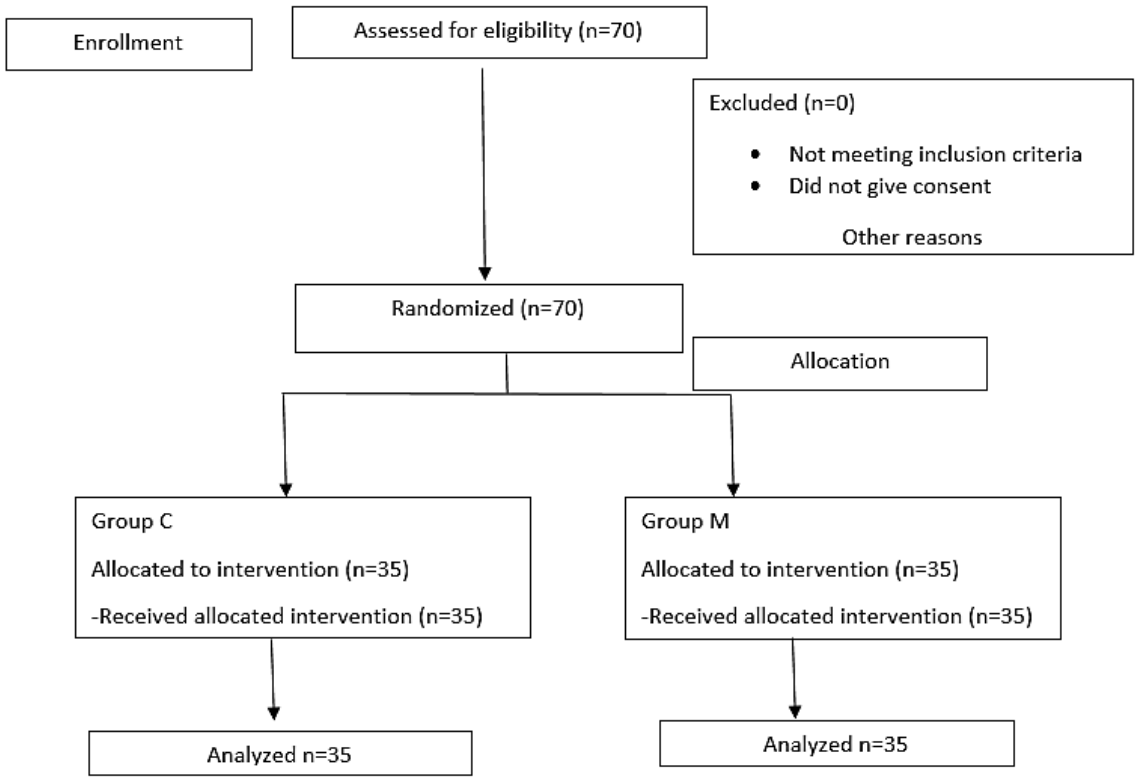

Fig. 1: Consort flow diagram

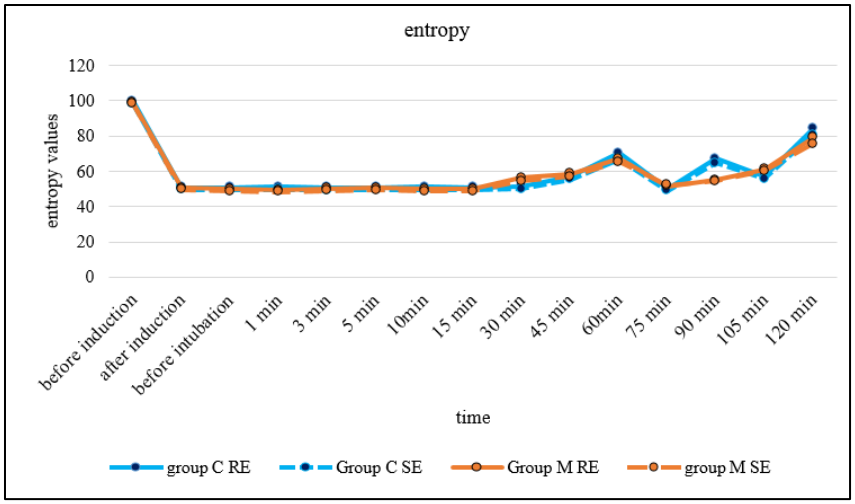

Fig. 2: Comparison of entropy between group C and group M

Discussion

Melatonin has a hypnotic/sedative effect when administered orally.[3] This may be due to its circadian rhythm regulation effect. The sedative effect of melatonin is due to modulation of gamma-aminobutyric acid (GABA-A) receptors in the brain through its action on melatonin receptors (MT1 and MT2). Binding of melatonin to the MT1 receptor appears to affect the GABA-A receptor through the G-coupled protein pathway. This enhances the binding of GABA to the GABA A receptor, which is similar to how other anesthetic drugs such as propofol and benzodiazepines exert their anesthetic effects.[4,12] Oral melatonin undergoes extensive first pass metabolism with varying bioavailability. It is a highly lipophilic substance with a consequent high volume of distribution. More than 90% of circulating melatonin is cleared by the liver. Exogenous melatonin is rapidly absorbed and peak plasma levels are reached in 60-150mins. The elimination half-life of melatonin is about 12-48 min. Hence we have given the drug 60 min before induction. Its bioavailability from an oral dose ranges from 10% to 56%.[13]

Our primary aim was to assess the consumption of propofol after pre-medicating with melatonin in patients undergoing surgery under general anesthesia.

Some studies have used two different dose of melatonin 6mg 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).[14] Hence in our study we have used 3 mg melatonin. None of the patients in our study had complaints of headache or other side-effects like nausea, bradycardia.

A study was conducted to evaluate the application of spectral entropy including response entropy (RE) and state entropy (SE) as a new electroencephalographic measure during induction period of general anaesthesia and compared it with bispectral-index (BIS), loss of eyelash reflex together with no responses to verbal commands and slight prodding or shaking which were considered to be unconscious. They concluded that entropy index seems to be better than BIS in predicting loss of consciousness.[15] Hence in our study we used entropy to assess the depth of anesthesia during induction and maintenance of anesthesia.

A study was conducted to assess the effect of two different dose of melatonin premedication on preoperative anxiety using modified Yale Preoperative Anxiety Scale and it was observed that oral melatonin (0.5 mg/kg and 0.75 mg/kg) in children decreases preoperative anxiety without impairing cognitive and psychomotor functions, the 0.75 mg/kg dose being most effective.[5] In our study we used Hamilton anxiety scale to assess the pre-operative anxiety. Patients premedicated with melatonin had better sedation compared to those who received placebo at 60 min after drug administration. Hence our result was consistent with the above study.

Some authors have observed that melatonin premedication decreased propofol ED50 values for loss of response to verbal command and eyelash reflex from 1.5 mg/kg (1.4–1.6 mg/kg) and 1.6 mg/kg (1.5–1.7 mg/kg) to 0.9 mg/kg (0.8–0.96 mg/kg) and 0.9 mg/kg (0.8–0.95 mg/kg), respectively (*P* 0.05).[1] Similarly in our study we observed the mean dose of propofol required for induction to be 0.96mg/kg and 2mg/kg in the melatonin and placebo groups respectively which was statistically significant (p<0.0001).

Some authors performed a clinical trial on 50 candidates undergoing general anesthesia and assessed the mean induction time (Time of bispectral index "BIS" to reach 60) for propofol induction in a control group vs those patients who received oral α_2 agonist (tizanidine). Induction time was 80.2±2.9 and 56.9±5.35 seconds in control and case group respectively (p value<0.009). This suggested that tizanidine prior to induction of anesthesia can lead to sedation and hence reduce the induction time and consumption of propofol for total intravenous anesthesia.[16] Our study demonstrates a similar result, patients who received melatonin premedication had shorter induction time compared to control group owing to the sedative effect of melatonin.

Some authors have compared the dose-response effects of melatonin and midazolam for premedication of adult patients, using different doses of melatonin and midazolam and concluded that patients who received 0.2 mg/kg

midazolam premedication had increased levels of sedation at 90 min compared with 0.05 and 0.1 mg/kg melatonin group. Patients who received midazolam had more sedation with reduced psychomotor performance.[12] In our study we observed that patients who received 3mg melatonin had better sedation compared to those who received placebo.

Our study has some limitations like sedation was monitored only for 4 hour postoperatively and we also did not observe the effect of melatonin on post-operative analgesia, hence further studies may be necessary.

Conclusion

Oral melatonin premedication reduces induction dose of propofol, reduces the pre-operative anxiety and improves peri-operative sedation.

Conflict of Interest: Nil.

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