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Indian Journal of Clinical Anaesthesia

Journal homepage: www.ipinnovative.com

Original Research Article

Efficacy of preoperative melatonin and ramelteon (melatonin agonist) therapy on dose requirement of propofol for induction of general anaesthesia: A comparative prospective study

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ARTICLE INFO

Article history:
Received 15-11-2019
Accepted 18-11-2019
Available online 28-02-2020

Keywords:
General anesthesia
Melatonin
Ramelteon
Propofol
Post-operative sedation

ABSTRACT

Introduction: General anesthesia is a medically induced coma with loss of protective reflexes resulting from the administration of one or more general anesthetic agents our study is to compare the role and efficacy of preoperative oral Melatonin, Ramelteon, and Midazolam therapy on the dose requirement of induction agent (Propofol).

Materials and Methods: Were divided into Case and Control Group. Case group of people were given Oral Melatonin (6mg)/Ramelteon (8mg) as premedication 2 to 3 hours before induction in OT and the control group were given oral Midazolam (5mg). After checking all the parameters, the induction process Total number of 60 people was randomly selected from ASA grade I & grade II, aged between 20 to 50 years, started with injection Propofol slowly in intravenous route and subsequently the BIS level up 60 was noted. After complete reversal of General Anesthesia, post-operative sedation level of the patient was measured using Ramsey sedation scale.

Result: Melatonin and Ramelteon shows significant reduction in preoperative anxiety state of the patient in comparison to Midazolam, measured by Hamilton Anxiety rating scale. The sedation status was measured by Ramsey Sedation Scale for each drug and it shows no significant difference between the drugs.

Conclusion: Considering absolute values and statistical values, all three drugs are potent premedication in general anesthesia. Among them, Melatonin is most potent in reducing the induction dose of injection Propofol. Ramelteon is also effective in reducing induction dose of Propofol. Along with, both are potent anxiolytic agent in pre-operative state.

1. Introduction

General anesthesia is a medically induced coma with loss of protective reflexes resulting from the administration of one or more general anesthetic agents. It is carried out to allow medical procedures that would otherwise be intolerably painful for the patient; or where the nature of the procedure itself precludes the patient being awake.

A variety of drugs may be administered, with the overall aim of ensuring unconsciousness, amnesia, analgesia, loss of reflexes of the autonomic nervous system, and in some cases paralysis of skeletal muscles. The optimal combination of drugs for any given patient and procedure is typically selected by an anesthetist.

Benzodiazepines are widely used as premedication in General anesthesia. Few studies recently done showing that Oral Melatonin therapy, preoperatively have significant role in General anesthesia. Exogenous preoperative Melatonin is as effective as benzodiazepines in reducing preoperative anxiety with minimal action on psychomotor performance and sleep wake cycle. It may be considered as a safe and effective alternative of benzodiazepines as preoperative anxiolytic. It may have opioid sparing effect, may reduce intraocular pressure, and have role in prevention of

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https://doi.org/10.18231/j.ijca.2020.030

postoperative delirium. The short-term administration of melatonin is free from significant adverse effects also. Our study is to compare the role and efficacy of preoperative oral Melatonin, Ramelteon, and Midazolam therapy on the dose requirement of induction agent (Propofol).

Melatonin is a hormone found in all living creatures, from algae to humans. In humans, Melatonin is mainly produced by the Pineal gland and to a lesser extent, by the gastrointestinal tract and Retina. These sites synthesize Melatonin from the amino acid Tryptophan, via the 5-hydroxyindole-o-methyl transferase enzyme pathway.[1,2] The pathway is under the influence of Hypothalamus. Melatonin is produced in the Pineal gland, acts as an endocrine hormone since it is released into the blood. The biological effects are produced through the activation of Melatonin receptors, MT1 and MT2 and are due to its role as a powerful antioxidant, which specially protects nuclear and mitochondrial DNA.

It was only recently that Naguib et al and other have demonstrated that Melatonin can be used effectively as premedication for anesthesia and for the induction of general anaesthesia.[3] Oral premedication with 0.2 mg/Kg Melatonin significantly reduces the Propofol and Thiopental doses required for loss of responses to verbal commands and eyelash stimulation.[4]

2. Aim

The goal of our study is to compare the effects of Melatonin, Melatonin analogue Ramelteon and Midazolam used as premedication, on dose requirement of Inducing agent (Propofol) for General anesthesia and simultaneously the Bispectral index at the time of induction.

3. Materials and Methods

Randomized Comparative Prospective Study with study population Age between 20-50 years, both Male & Female ASA Group 1 and Group II at ESI PGIMSR, Manicktala, Kolkata. Sample size Total number of 60 people

3.1. Inclusion criteria

1. Age between 20-50 years
2. Normotensive, Non-Diabetic or controlled Diabetic
3. ASA grade I and grade II
4. Fit for General Anesthesia.

3.2. Exclusion criteria

1. Age <20 and >50 years
2. ASA grade II onwards
3. Allergic to any of the selected drugs
4. Contraindicated for general anesthesia
5. Previous history of compromise of any organ like hepatic, renal, metabolic function, cardiovascular, neurological etc.

3.3. Study method

After getting approval from Ethical Committee at ESI PGIMSR, Manicktala the study started. Total number of 60 people was randomly selected from ASA grade I & grade II, aged between 20 to 50 years. They were randomly divided into Case and Control Group. Case group of people were given Oral Melatonin (6mg)/Ramelteon (8mg) as premedication 2 to 3 hours before induction in OT and the control group were given oral Midazolam (5mg). On the morning of the day of operation both group of people were given Injection Ranitidine (50) along with Injection Metoclopramide (10). Just before taking the patient to OT table, Anxiety scoring was done by HAM-A Scoring questioner. Then the patient was taken to OT table and attached to various monitoring device like Pulse Oxymeter, NIBP monitor, BIS monitor etc. After checking all the parameters, the induction process started with injection Propofol slowly in intravenous route and subsequently the BIS measured. The total dose of injection Propofol needed to bring down the BIS level at 60 was noted. Hemodynamic parameters like Pulse, BP and Oxygen saturation level (SpO2) was noted from monitor before and after intubation. In the same way Hemodynamic parameters was noted before & after Extubation also. After complete reversal of General Anesthesia, post-operative sedation level of the patient was measured using Ramsey sedation scale.

3.4. Analysis of data

Statistical analysis has been performed using SPSS software (version 23.0; IBM Inc., Chicago, IL, USA, 2015). Continuous variables were compared between the two groups by unpaired Student's t-test. Ordinal data were analyzed using the Mann–Whitney non-parametric test. For qualitative data, either chi-square test or Fisher's exact test was used. Two factor, repeated measures ANOVA with one factor as a fixed group and the other as a repeated factor (i.e. time) was used to compare the variability between the subjects. Mauchly's test was used for checking sphericity. If found significant, the Greenhouse Geisser correction was used to find the p-value within time points. The value of $p < 0.05$ was considered significant.

4. Result

There are total of 30 male and 30 females were selected for the study and were equally distributed between each drug. We found, mean age are 36.8, 39.65 and 38.5 accordingly in case of Melatonin, Ramelteon and Midazolam. Applying statistical analysis P-value was calculated, and it was found not significant. The Mean weight was calculated and then applied in statistics. The P-Value shows no significance in weight distribution. Tables 1 and 2 shows the mean of total

Propofol dose needed in each group and statistical analysis applied. The P-value was measured, and it was significant as it is <0.00001. Also, the distributions of Propofol dose according to per kg body weight in each study group, the P-value we got is statistically significant. Mean of Pulse rate measured, in different time for every drug and the value before and after intubation statistically analyzed by T test and compared, there is no significant changes in Pulse rate during Intubation in case of Oral Melatonin and Ramelteon, but there is a significant change in Pulse rate in case of Midazolam during intubation. When it comes about BP, there are significant changes in Systolic BP during intubation in case of Melatonin and Midazolam, but in case of Ramelteon, the change is not significant. In case of Diastolic BP, there are no significant changes in case of Melatonin and Ramelteon, but there is significant change in case of Midazolam. About peripheral capillary Oxygen saturation (SpO2), we can say, good preoxygenation makes no difference in SpO2 during intubation for all drugs we used. Melatonin and Ramelteon shows significant reduction in preoperative anxiety state of the patient in comparison to Midazolam, measured by Hamilton Anxiety rating scale Tables 3 and 4. The sedation status was measured by Ramsey Sedation Scale for each drug and it shows no significant difference between the drugs Tables 5 and 6.

Mean of HAM-A Score measured and statistically analyzed, P value measured to compare between the Study groups.

4.1. Ramsey Ssedation scale score

Ramsey Sedation Scale score of study groups statistically analyzed by Anova and P value measured to compare between study groups.

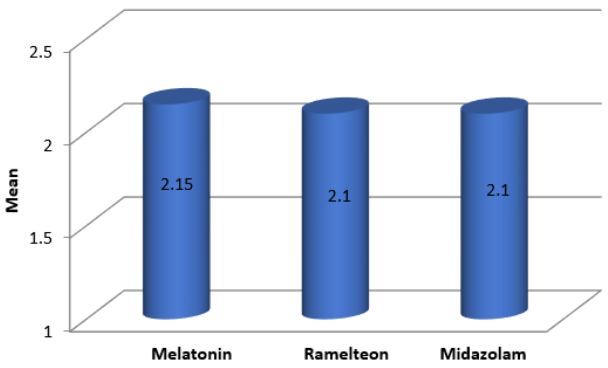

Fig. 1: Mean sedation score

5. Discussion

Since the time of introduction, Propofol is a very well-known and efficient induction agent in General anesthesia. Propofol is generally known for its hemodynamic depressant effects. The most prominent effect of Propofol is a decrease in arterial blood pressure during induction of anesthesia. Induction of anesthesia with Propofol is often associated with pain on injection, apnea, hypotension, and, rarely, thrombophlebitis of the vein into which Propofol is injected.[3] Several studies have been focused on the effects of various premedication on the induction and maintenance Propofol dose in the human body.[5] We are trying to reduce the induction dose needed for injection Propofol and subsequently its side effect. In our study, we have used Oral Melatonin and Ramelteon (Melatonin agonist) as premedication and compared with oral Midazolam. A dose range of melatonin premedication is used to provide sedation and analgesia without cognitive impairment and psychomotor skills, and without any increase in recovery time.[5,6] Laryngoscopy and endotracheal intubation are considered potent noxious stimuli which provoke hemodynamic responses leading to a marked increase in heart rate and blood pressure. These events are especially detrimental in individuals who have limited myocardial reserve due to coronary artery disease, cardiac dysrhythmias, congestive heart failure, hypertension, cardiomyopathy and geriatric age group.[7] Hence, it is mandatory to take measures to attenuate these pressure responses. The mechanisms of these hemodynamic alterations are somato visceral reflexes due to sympathetic stimulation. During intubation of trachea, the laryngeal and tracheal sensory receptors are stimulated which result in the release of endogenous catecholamine resulting in tachycardia and hypertension.[8]

Since the invention of laryngoscopy and endotracheal intubation, various drug regimens and techniques have been used from time to attenuate these stress responses. Some of these agents are opioids like fentanyl, alfentanil; some are calcium channel blockers like verapamil, diltiazem, sympatholytic agents like clonidine, dexmedetomidine and methyldopa, some beta blockers like esmolol, propranolol, and benzodiazepines like midazolam, alprazolam, and peripheral vasodilators like sodium nitroprusside, nitroglycerine.[9] However, each agent has some limitations such as respiratory depression, hypotension, tachycardia, bradycardia, rebound hypertension or allergic reactions. Hence, there is always need for a better agent as premedication during induction of general anesthesia for all anesthesiologist till date. Exogenous administration of melatonin facilitates sleep onset and improves the quality of sleep. It is different from benzodiazepines and their derivatives; it produces natural sleep pattern and does not lead to impairment of cognitive functions.[10] Various researchers have used this drug in different dose patterns as premedication in both adults as well as children. It has been mainly studied in view of pre-operative anxiolysis, pre-operative cognitive and psychomotor functions.[11] We

Table 1: Total propofol dose distributions in study groups

Drug	Mean	St deviation	St Error	N	P Value
Melatonin	71	14.1049	3.15394	20	
Ramelteon	75.5	19.0498	4.25966	20	<0.00001
Midazolam	99	16.5116	3.6921	20	

Table 2: Anova result

Source	Sum of Squares	df	Mean Square	F	P Value
Between Treatments	9043.3333	2	4521.6667		
Within Treatments	15855	57	278.1579	16.25576	<0.00001
Total	24898.3333	59			

Table 3: Pre-operative Anxiety status by HAM-A Score in Study Groups

	Mean	St deviation	St Error	N	P Value
Melatonin	10.3	2.6577	0.59427	20	
Ramelteon	9.5	2.1643	0.48395	20	0.005706
Midazolam	11.95	2.1879	0.48923	20	

Table 4: Anova result

Source	Sum of Squares	df	Mean Square	F	P Value
Between Treatments	62.4333	2	31.2167		
Within Treatments	314.15	57	5.5114	5.66401	0.005706
Total	376.5833	59			

Table 5: Post-operative sedation status by Ramsey Sedation Scale in Study Groups

	Mean	St deviation	St Error	N	P Value
Melatonin	2.15	0.3663	0.08192	20	
Ramelteon	2.1	0.3078	0.06882	20	0.857225
Midazolam	2.1	0.3078	0.06882	20	

Table 6: Anova result

Source	Sum of Squares	df	Mean Square	F	P Value
Between Treatments	0.0333	2	0.0167		
Within Treatments	6.15	57	0.1079	0.15447	0.857225
Total	6.1833	59			

assumed that its inhibitory actions on central nervous system responsible for sedation and anxiolysis may have role in attenuating hemodynamic responses to laryngoscopy and intubation. Based on this, we made a hypothesis that melatonin can provide hemodynamic stability during laryngoscopy and intubation when given 2 to 3 hours before the procedure. The primary objective was to study the changes in blood pressure during laryngoscopy and intubation.

Studies have shown that melatonin can reduce anxiety. In comparison to the widely used benzodiazepines in treating anxiety, melatonin produces no ' hang-over effects' and has no known serious side effects and could therefore be a worthy alternative.[12] What we have seen in our study, there is significant dose reduction at the induction dose of injection Propofol (P<0.00001) by using oral Melatonin or oral Ramelteon as premedication compared with oral benzodiazepine, Midazolam. There is no significant change in age, sex and weight distribution. Therefore, we can say that, Melatonin and Ramelteon might be a good premedication before general anesthesia to maintain a stable hemodynamics.

In our study, Melatonin and Ramelteon shows significant reduction in preoperative anxiety state of the patient in comparison to Midazolam, measured by Hamilton Anxiety rating scale. So, it can be said that Melatonin and Ramelteon are potent anxiolytic agent in preoperative state.

6. Conclusion

Considering absolute values and statistical values, all three drugs are potent premedication in general anesthesia. Among them, Melatonin is most potent in reducing the induction dose of injection Propofol. Ramelteon is also

effective in reducing induction dose of Propofol. Along with, both are potent anxiolytic agent in pre-operative status. However, in post-operative state the sedation status almost same for all three drugs.

7. Source of funding

None.

8. Conflict of interest

None.

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Cite this article: Roy K, Panigrahi MR, Mukhopadhyay B, Bisak S, Biswas BK. Efficacy of preoperative melatonin and ramelteon (melatonin agonist) therapy on dose requirement of propofol for induction of general anaesthesia: A comparative prospective study. *Indian J Clin Anaesth* 2020;7(1):172-176.