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**Original Research Article**

# To observe the effect of oral melatonin premedication on induction doses of propofol and pentothal sodium

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**Abstract:**

**Background & Method:** The aim of this study is to observe the effect of oral melatonin premedication on induction doses of propofol and pentothal sodium. The patients was examined clinically a day before the surgery to note demographic data, baseline heart rate, blood pressure, respiratory rate, oxygen saturation of Hb. Biochemical tests were done to rule out co-morbid condition associated. ECG and X –Ray chest was done ASA grade 1 and 2 patients of either gender, 18 - 60 years old, scheduled to undergo elective surgical procedures under general anesthesia will be assigned into equal groups- group (P+M), group (P), group (PS+M) and group (PS).

**Result:**

In P Group, the mean Pulse 120 minutes after drugs (mean± s.d.) of patients was 91.6774± 11.5741. In P + M Group, the mean Pulse 120 minutes after drugs (mean± s.d.) of patients was 82.0968± 7.4938. In PS Group, the mean Pulse 120 minutes after drugs (mean± s.d.) of patients was 90.1613± 10.2538. In PS + M Group, the mean Pulse 120 minutes after drugs (mean± s.d.) of patients was 80.4516± 7.9282. Distribution of mean Pulse 120 minutes after drugs with Group was statistically significant (p=<0.0001).

In P Group, the mean MAP 120 minutes after drugs (mean± s.d.) of patients was 99.9677± 6.4626. In P + M Group, the mean MAP 120 minutes after drugs (mean± s.d.) of patients was 89.1290± 7.4420. In PS Group, the mean MAP 120 minutes after drugs (mean± s.d.) of patients was 100.0000± 7.0475. In PS + M Group, the mean MAP 120 minutes after drugs (mean± s.d.) of patients was 86.0968± 8.0056. Distribution of mean MAP 120 minutes after drugs with Group was statistically significant (p=<0.0001).

In P Group, the mean Dose calculated as mg/kg (mean± s.d.) of patients was 1.9529± .1710. In P + M Group, the mean Dose calculated as mg/kg (mean± s.d.) of patients was 1.0932± .0754. In PS Group, the mean Dose calculated as mg/kg (mean± s.d.) of patients was 4.6161± .3666. In PS + M Group, the mean Dose calculated as mg/kg (mean± s.d.) of patients was 2.6835± .3678. Distribution of mean Dose calculated as mg/kg with Group was statistically significant (p=<0.0001).

In P Group, the mean Dose required (mg) (mean± s.d.) of patients was 107.7419± 19.0979. In P + M Group, the mean Dose required (mg)(mean± s.d.) of patients was 72.2581± 14.3084. In PS Group, the mean Dose required (mg) (mean± s.d.) of patients was 295.1613± 40.5274. In PS + M Group, the mean Dose required (mg) (mean± s.d.) of patients was 186.2903± 42.7389. Distribution of mean Dose required (mg) with Group was statistically significant (p=<0.0001).

**Conclusion:** We concluded that the significant effect was found in oral melatonin on induction doses of propofol and Pentothal sodium and changes in vital parameters before and after 90-120 minutes of oral administration of study drug.
Melatonin premedication significantly decreased the doses of both propofol and pentothal sodium required to induce anesthesia.

**Keywords:** General anesthesia, oral melatonin , propofol and pentothal sodium.

**Study Designed:** Observational Study.

## 1. INTRODUCTION

Melatonin is a hormone secreted by pineal gland which regulates cardiovascular, circadian cycle, reproductive, neuro-endocrine function and immune system. Hypnotic effect of oral premedication with melatonin reduces dose of i/v induction agents in pediatric and adult patients. As a premedication administered orally about 90 – 120 minutes prior to induction of anaesthesia reduces anxiety and offer adequate sedation.[1]
Commonly used drugs like benzodiazepins, gabapentin, clonidine has been used as premedication are associated with psychomotor, cognitive impairment, nausea-vomiting and bradycardia in postoperative period.
Melatonin is a methoxy indole derivative, synthesized from tryptophan and is secreted by pineal gland. Melatonin as a premedication reduces the required dose of Propofol for induction. Besides melatonin receptors, it also acts on GABA-A receptor. Similarly Melatonin premedication also reduces dose of pentothal sodium during induction. Very few studies are available related to oral melatonin as premedication and Propofol and pentothal sodium required as induction dose.[2]
Exogenous melatonin has been studied for various indication such as hypnosis, anxiolysis, sedation and analgesia. It facilitates sleep onset and improves the quality of sleep.[3]
Endogenous melatonin is mainly metabolized by hydroxylation [approx.90%] to 6-hydroxymelatonin in liver and excreted urine.[4]
End points for Propofol and pentothal sodium induction are sharp, loss of response to verbal commands and abolition of eyelash reflex. Melatonin premedication is used as a sedative and analgesic without causing impairment of cognitive and psychomotor skill.
Melatonin (N-acetyl-5-methoxytryptamine) is a hormone naturally produced in the brain, secreted by the pineal gland, whose receptors are found throughout the central nervous system and other body tissues. It is known to be an effective hormone in sleep disorders, anxiety, and pain, as well as an anti-inflammatory antioxidant, used as a premedication[5].
Melatonin interacts with multiple receptors, including opioidergic, benzodiazepinergic, muscarinic, nicotinic, serotonergic, α1- and α2-adrenergic, and melatonergic receptors found in the spinal cord in the central nervous system. Premedication reduces the need for anaesthetic induction agents during surgery. Melatonin, an effective hypnotic drug, is

revealed to have the effect on both the onset and maintenance of sleep, while it is known as a natural hypnotic agent whose actions are activated by MT1 and MT2 receptors and a yet-unclarified physiologic mechanism underlying the analgesic actions of melatonin[6].

## 2. MATERIAL & METHOD

The study was completed in one year after the approval from ethics committee and research guidance committee of the institution.

The patients was examined clinically a day before the surgery to note demographic data, baseline heart rate, blood pressure, respiratory rate, oxygen saturation of Hb. Biochemical tests were done to rule out co-morbid condition associated. ECG and X –Ray chest was done ASA grade 1 and 2 patients of either gender, 18 - 60 years old, scheduled to undergo elective surgical procedures under general anesthesia will be assigned into equal groups- group (P+M), group (P), group (PS+M) and group (PS).

Patients of group (P+M) and group (PS+M) shall be receiving oral 10 mg mouth dispersible tablet melatonin and shall be included either with propofol or pentothal sodium, group (P) and group (PS) shall be receiving placebo drug orally.

End point of induction are sharp for both drugs, the patients was considered induced with propofol or pentothal sodium upon loss of verbal contact and disappearance of eyelash reflex respectively.

**Inclusion criteria**

- Patients belonging to ASA I and II
- Age group – 18 to 60 years of age
- All patients scheduled for routine elective surgeries to be performed under general anesthesia.

**Exclusion criteria**

- Patient refusal for inclusion in study.
- Patients belonging to American Society of Anaesthesiologists grade 3 and 4.
- Patients with severe systemic disease like respiratory, cardiac, hepatic, renal and neurological disorders, diabetes and hypertension.
- Pregnant and lactating patients.
- Age group of patients <18 and >60 years.

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## 3. RESULTS

**Table 1: Association between Sex: Group**

| | GROUP | | | | |
|---|---|---|---|---|---|
| **Sex** | **P** | **P + M** | **PS** | **PS + M** | **TOTAL** |
| **Female** | 17 | 21 | 16 | 14 | 68 |
| Row % | 25.0 | 30.9 | 23.5 | 20.6 | 100.0 |
| Col % | 54.8 | 67.7 | 51.6 | 45.2 | 54.8 |
| **Male** | 14 | 10 | 15 | 17 | 56 |
| Row % | 25.0 | 17.9 | 26.8 | 30.4 | 100.0 |
| Col % | 45.2 | 32.3 | 48.4 | 54.8 | 45.2 |
| **TOTAL** | 31 | 31 | 31 | 31 | 124 |
| Row % | 25.0 | 25.0 | 25.0 | 25.0 | 100.0 |
| Col % | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 |

In P Group, 17 (54.8%) patients were Female and 14 (45.2%) patients were Male. In P + M Group, 21 (67.7%) patients were Female and 10 (32.3%) patients were Male. In PS Group, 16 (51.6%) patients were Female and 15 (48.4%) patients were Male. In PS + M Group, 14 (45.2%) patients were Female and 17 (54.8%) patients were Male. Association of Sex with Group was not statistically significant (p=0.3358).

**Table 2: Distribution of mean SBP just before drugs: Group**

| | | Number | Mean | SD | Minimum | Maximum | Median | p-value |
|---|---|---|---|---|---|---|---|---|
| SBP just before drugs | P | 31 | 124.6774 | 8.8219 | 108.0000 | 145.0000 | 128.0000 | 0.1434 |
| | P + M | 31 | 120.0000 | 10.5293 | 100.0000 | 140.0000 | 118.0000 | |
| | PS | 31 | 124.1613 | 8.0337 | 110.0000 | 140.0000 | 124.0000 | |
| | PS + M | 31 | 122.0645 | 7.4830 | 110.0000 | 140.0000 | 120.0000 | |

In P Group, the mean SBP just before drugs (mean± s.d.) of patients was 124.6774± 8.8219. In P + M Group, the mean SBP just before drugs (mean± s.d.) of patients was 120.0000± 10.5293. In PS Group, the mean SBP just before drugs (mean± s.d.) of patients was 124.1613± 8.0337. In PS + M Group, the mean SBP just before drugs (mean± s.d.) of patients was 122.0645± 7.4830. Distribution of mean SBP just before drugs with Group was not statistically significant (p=0.1434).

**Table 3: Distribution of mean SBP 120 minutes after drugs: Group**

| | | Number | Mean | SD | Minimum | Maximum | Median | p-value |
|---|---|---|---|---|---|---|---|---|
| SBP 120 minutes after drugs | P | 31 | 130.1935 | 11.2351 | 109.0000 | 163.0000 | 130.0000 | 0.0001 |
| | P + M | 31 | 115.9032 | 9.7924 | 98.0000 | 130.0000 | 116.0000 | |
| | PS | 31 | 129.7097 | 9.0892 | 108.0000 | 148.0000 | 130.0000 | |
| | PS + M | 31 | 115.7742 | 8.4250 | 100.0000 | 132.0000 | 114.0000 | |

In P Group, the mean SBP 120 minutes after drugs (mean± s.d.) of patients was 130.1935± 11.2351. In P + M Group, the mean SBP 120 minutes after drugs (mean± s.d.) of patients was 115.9032± 9.7924. In PS Group, the mean SBP 120 minutes after drugs (mean± s.d.) of patients was 129.7097± 9.0892. In PS + M Group, the mean SBP 120 minutes after drugs (mean± s.d.) of patients was 115.7742± 8.4250. Distribution of mean SBP 120 minutes after drugs with Group was statistically significant (p=0.0001).

**Table 4: Distribution of mean SBP pre-induction: Group**

| | | Number | Mean | SD | Minimum | Maximum | Median | p-value |
|---|---|---|---|---|---|---|---|---|
| SBP pre induction | P | 31 | 126.4516 | 9.2334 | 111.0000 | 151.0000 | 127.0000 | 0.3169 |
| | P + M | 31 | 123.0000 | 12.7462 | 104.0000 | 160.0000 | 126.0000 | |
| | PS | 31 | 127.7742 | 8.5973 | 108.0000 | 150.0000 | 128.0000 | |
| | PS + M | 31 | 124.4516 | 11.6814 | 106.0000 | 160.0000 | 124.0000 | |

In P Group, the mean SBP pre induction (mean± s.d.) of patients was 126.4516± 9.2334. In P + M Group, the mean SBP pre induction (mean± s.d.) of patients was 123.0000± 12.7462.

In PS Group, the mean SBP pre induction (mean± s.d.) of patients was 127.7742± 8.5973. In PS + M Group, the mean SBP pre induction (mean± s.d.) of patients was 124.4516± 11.6814. Distribution of mean SBP pre induction with Group was not statistically significant (p=0.3169).

**Table 5: Distribution of mean Dose calculated as mg/kg: Group**

| | | Number | Mean | SD | Minimum | Maximum | Median | p-value |
|---|---|---|---|---|---|---|---|---|
| Dose calculated as mg/kg | P | 31 | 1.9529 | .1710 | 1.6600 | 2.4000 | 1.9500 | <0.0001 |
| | P + M | 31 | 1.0932 | .0754 | 0.9000 | 1.2000 | 1.1000 | |
| | PS | 31 | 4.6161 | .3666 | 4.0100 | 5.2600 | 4.6400 | |
| | PS + M | 31 | 2.6835 | .3678 | 2.0000 | 3.1600 | 2.7700 | |

In P Group, the mean Dose calculated as mg/kg (mean± s.d.) of patients was 1.9529± .1710. In P + M Group, the mean Dose calculated as mg/kg (mean± s.d.) of patients was 1.0932± .0754. In PS Group, the mean Dose calculated as mg/kg (mean± s.d.) of patients was 4.6161± .3666. In PS + M Group, the mean Dose calculated as mg/kg (mean± s.d.) of patients was 2.6835± .3678. Distribution of mean Dose calculated as mg/kg with Group was statistically significant (p=<0.0001).

**Table 6: Distribution of mean Dose required (mg): Group**

| | | Number | Mean | SD | Minimum | Maximum | Median | p-value |
|---|---|---|---|---|---|---|---|---|
| Dose required (mg) | P | 31 | 107.7419 | 19.0979 | 80.0000 | 140.0000 | 100.0000 | <0.0001 |
| | P + M | 31 | 72.2581 | 14.3084 | 40.0000 | 100.0000 | 80.0000 | |
| | PS | 31 | 295.1613 | 40.5274 | 225.0000 | 375.0000 | 300.0000 | |
| | PS + M | 31 | 186.2903 | 42.7389 | 125.0000 | 275.0000 | 175.0000 | |

In P Group, the mean Dose required (mg) (mean± s.d.) of patients was 107.7419± 19.0979. In P + M Group, the mean Dose required (mg)(mean± s.d.) of patients was 72.2581± 14.3084. In PS Group, the mean Dose required (mg) (mean± s.d.) of patients was 295.1613± 40.5274. In PS + M Group, the mean Dose required (mg) (mean± s.d.) of patients was

186.2903± 42.7389. Distribution of mean Dose required (mg) with Group was statistically significant (p=<0.0001).

**Table 7: Distribution of mean Pulse 120 minutes after drugs: Group**

| | | Number | Mean | SD | Minimum | Maximum | Median | p-value |
|---|---|---|---|---|---|---|---|---|
| Pulse 120 minutes after drugs | P | 31 | 91.6774 | 11.5741 | 60.0000 | 122.0000 | 93.0000 | <0.0001 |
| | P + M | 31 | 82.0968 | 7.4938 | 66.0000 | 98.0000 | 82.0000 | |
| | PS | 31 | 90.1613 | 10.2538 | 68.0000 | 118.0000 | 92.0000 | |
| | PS + M | 31 | 80.4516 | 7.9282 | 66.0000 | 98.0000 | 80.0000 | |

In P Group, the mean Pulse 120 minutes after drugs (mean± s.d.) of patients was 91.6774± 11.5741. In P + M Group, the mean Pulse 120 minutes after drugs (mean± s.d.) of patients was 82.0968± 7.4938. In PS Group, the mean Pulse 120 minutes after drugs (mean± s.d.) of patients was 90.1613± 10.2538. In PS + M Group, the mean Pulse 120 minutes after drugs (mean± s.d.) of patients was 80.4516± 7.9282. Distribution of mean Pulse 120 minutes after drugs with Group was statistically significant (p=<0.0001).

**Table 8: Distribution of mean MAP 120 minutes after drugs: Group**

| | | Number | Mean | SD | Minimum | Maximum | Median | p-value |
|---|---|---|---|---|---|---|---|---|
| MAP 120 minutes after drugs | P | 31 | 99.9677 | 6.4626 | 87.0000 | 117.0000 | 100.0000 | <0.0001 |
| | P + M | 31 | 89.1290 | 7.4420 | 73.0000 | 99.0000 | 92.0000 | |
| | PS | 31 | 100.0000 | 7.0475 | 88.0000 | 114.0000 | 99.0000 | |
| | PS + M | 31 | 86.0968 | 8.0056 | 67.0000 | 99.0000 | 85.0000 | |

In P Group, the mean MAP 120 minutes after drugs (mean± s.d.) of patients was 99.9677± 6.4626. In P + M Group, the mean MAP 120 minutes after drugs (mean± s.d.) of patients was

89.1290± 7.4420. In PS Group, the mean MAP 120 minutes after drugs (mean± s.d.) of patients was 100.0000± 7.0475. In PS + M Group, the mean MAP 120 minutes after drugs (mean± s.d.) of patients was 86.0968± 8.0056. Distribution of mean MAP 120 minutes after drugs with Group was statistically significant (p=<0.0001).

## 4. DISCUSSION

The present study was an Observational study conducted for a period of one year after the approval from ethics committee and research guidance committee of the institution. Total 124 patients were included in this study. The findings of the present study was compared with the similar other studies as follows:

Sivakumar S et al[7](2017) studied the dose of thiopentone required for induction of general anesthesia following administration of oral melatonin compared to that of placebo found that melatonin has some unique properties like anxiolysis, hypnosis and analgesia without impairment of psychomotor skills. This study included 44 patients of ASA status I and II in the age group of 16 to 55 years who had undergone elective surgical procedures under general anesthesia.

Ali M et al [8] (2018) examined that Reducing anxiety is an important goal in good anaesthesia management. Preoperative anxiety can be reduced with certain pharmacological interventions. The present study was carried to assess the potential role of oral Melatonin as a pre-medicant to general anaesthesia and its effect on induction dose of Propofol. A prospective randomized double blind placebo controlled study was planned on 80 patients of ASA I & II physical status aged between 18- 55 yrs. scheduled to undergo different elective surgeries and satisfying all the inclusion criteria. Oral melatonin 3mg can be an effective premedication for preoperative anxiolysis and sedation and an adjuvant to induction drug Propofol.

**Kumar R et al[9] (2021)** showed that melatonin has been studied to have anxiolytic, sedative, and analgesic effects. Maximum percentage increase in systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean blood pressure (MBP) was lesser in melatonin group than placebo group (SBP 9.25% vs. 37.73%, DBP 10.58% vs. 35.51%, MBP 9.99% vs. 36.45% at 1 min post-intubation respectively) ($p < 0.0001$). Induction dose of propofol (1.42 mg/kg vs. 2.01 mg/kg) and the number of patients requiring additional fentanyl intraoperatively (3 vs. 11) were also significantly reduced in the melatonin group. Pre-medication with 6 mg of oral melatonin resulted in significant attenuation of post-intubation rise in HR, SBP, DBP, and MBP.

Our study showed that, the mean Weight (kg) was significantly more in [69.4194± 12.5373] PS + M Group compared to [65.6774± 12.0841] P + M Group, [63.9032± 7.4492] PS Group and [55.1613± 9.5642] P Group (p<0.0001). And the mean SBP just before drugs was not significantly more in [124.6774± 8.8219] P Group compared to [124.1613± 8.0337] PS Group, [122.0645± 7.4830] PS + M Group and [120.0000± 10.5293.] P + M Group (p=0.1434).

**Hadavi MR et al[10] (2019)** found that although regional anesthesia is the most frequently used method for selected surgical approaches, general

anesthesia (GA) is still common. All patients were evaluated for recall of the events. No patient recalled the peri-operative events during the follow up period. BIS scores were significantly lower in group P compared with group T after induction of GA until

discontinuation of volatile anesthetics ($p < 0.001$). IFT values were significantly higher in thiopental group in time interval of induction to skin incision comparing to propofol group ($p<0.050$). The current study suggests regarding better effect of propofol on decreasing of awareness during anesthesia and surgery, it seems to be better to use propofol in cases where they are forced to use GA in cesarean section.

## 5. CONCLUSION

In our study, out of 124 patients, most of the patients were 21-30 years old. We found that, female population was higher than the male population and female: male ratio was 1.21:1 but this was not statistically significant. Our study showed that, the mean Weight (kg) was significantly more in PS + M Group compared to P + M Group, PS Group and P Group. And the difference of mean SBP just before drugs was not significantly significant in P Group compared to PS Group, PS + M Group and P + M Group and the mean SBP 120 minutes after drugs was significantly less in PS + M Group compared to P + M Group, PS Group and P Group. The mean SBP pre induction was not significantly less in P + M Group compared to PS + M Group, P Group and PS Group.

We observed that, the mean Dose required (mg) was more in PS Group compared to PS + M Group, P Group and P + M Group which was statistically significant. We observed that, the mean Dose calculated as mg/kg was lower in P + M Group compared to P Group, PS + M Group and PS Group which was statistically significant. We concluded that the significant effect was found in oral melatonin on induction doses of propofol and Pentothal sodium and changes in vital parameters before and after 90-120 minutes of oral administration of study drug.

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