Journal of Cardiovascular Disease Research

ISSN:0975 -3583,0976-2833 VOL13, ISSUE 01, 2022

Original research article

MELATONIN PREMEDICATION ON PREOPERATIVE ANXIOLYSIS AND SEDATION: HEMODYNAMIC CHANGES

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Abstract

Informational interventions designed to minimize anxiety may have limited use in clinical practice where cost and time are major factors. Such interventions may also increase distress for patients who have an avoidance coping style for dealing with a threat such as surgery. Hospital ethical committee clearance was obtained for this study. Informed consent was taken from all the patients. Patients included in study were posted for general anesthesia from department of general surgery, orthopaedics, obstetrics and gynaecology and ENT. The baseline mean arterial pressures were compatible. The maximum drop was seen at 15 min after pre-medication and the maximum change was at 60 min in melatonin group. Though there was decrease in MAP in control group the change was clinically not significant. Between the groups the decrease in MAP was significantly strongly significant (p<0.001). The time to recovery score of 9 on modified recovery scale of aldrete is comparable (p=0.194).

Keywords: Melatonin, anxiolysis and sedation, hemodynamic changes

Introduction

Most patients awaiting elective surgery experience preoperative anxiety. This anxiety is influenced by the uncertainty of impending surgical procedure, past experience and a patient's personality and coping styles. Anxiety is an unpleasant emotion and may cause patient to avoid a planned operation. It may also adversely influence anaesthetic induction and patient recovery as well as decrease patients satisfaction with perioperative experience [1].

The natural course of anxiety before and after surgery was examined using the State-Trait Anxiety Inventory in 4 studies involving 136 surgical patients. The results

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suggested that high levels of anxiety were experienced before admission to hospital, between admission and surgery and following surgery, and were not restricted to the immediate preoperative period. Only a small percentage of patients reached their maximum level of anxiety on the morning of surgery [2].

Christoph H. Kindler *et al's*. study of qualitative aspects of anxiety reveals three distinct dimensions of preoperative fear.

1. Fear of the unknown.
2. Fear of feeling ill.
3. Fear of one's life.

Young patients, female patients, and patients with no previous anesthesia experience and previous negative anesthetic experience had higher anxiety scores. Patients worried most about the waiting period, preceding surgery and were least concerned about possible awareness intraoperatively. Overall, well-informed patients tend to recover faster and experience less pain and fewer postoperative complications. Operations associated with high preoperative anxiety include thoracic and otorhinolaryngological surgery [3].

Raised anxiety has important clinical implications since it has been demonstrated to adversely impact on anaesthetic requirements, postoperative pain and post-operative recovery, for example slow respiration, which increases pulmonary risk, decreasing activity which increases the risk of thrombosis. Several studies, as well as reported clinical experience, suggest that the anxious patient requires increased doses of anaesthetic agents in order to establish and maintain an anaesthetized state. Numerous studies have demonstrated a positive correlation between anxiety and pain with those less anxious patients experiencing less pain. It has also been shown that the anxious patient tends to require a longer post-operative hospital stay. Additionally, raised anxiety can result in behavioral and cognitive sequelae that can also have far reaching, effect on recovery [4, 5].

Informational interventions designed to minimize anxiety may have limited use in clinical practice where cost and time are major factors. Such interventions may also increase distress for patients who have an avoidance coping style for dealing with a threat such as surgery [6].

Methodology

Hospital ethical committee clearance was obtained for this study. Informed consent was taken from all the patients. Patients included in study were posted for general anesthesia from department of general surgery, orthopaedics, obstetrics and gynaecology and ENT.

Sample size

Keeping the power of study at 80% and alpha error (confidence intervals) at 95%, the minimal sample size in each group is 20. However we included 30 patients in each group to make up for possible drop outs and better validation of results.

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Study design

A prospective randomized control study was conducted on 60 patients scheduled to undergo different elective surgical procedures under GA and satisfying all the inclusion criteria.

Inclusion criteria

1. Patient with ASA physical status grade I & II
2. Patients aged between 18-55, Ts of either sex.
3. Patients weighing between 40-80 kgs.
4. Patients giving valid informed consent.

Exclusion criteria

1. Pregnant and lactating woman.
2. Patients with psychiatric disorders or on antipsychotic drugs.
3. Patients with sleep disorders.
4. Patients with language or communication difficulties.

Pre anaesthetic examination and preparation

Patients were randomly assigned to 2 groups M and C (n=30 patients per group), according to a computer-generated random number.

Group M received Tab Melatonin 0.2mg/kg orally and Group C is control group.

The patients and Anaesthesiologist recording the observations were blinded to the drug administered.

Preanaesthetic assessment was done one day prior to the surgery. A detailed history of present and past medical illness, past h/o of anaesthetic exposure, concomitant history of drug allergy and any medications in preoperative period was recorded. General physical examination and systemic examination of the patients was carried out. Routine investigation and relevant specific investigations were done. ASA Physical status was evaluated. Weight in kgs was recorded. An informed and written consent was taken after explaining the anaesthetic procedure in detail.

Results

Table 1: Age distribution of patients studied

Age in yrs	**Melatonin group**		**Placebo group**	
	No	**%**	**No**	**%**
18-30	9	30	8	26.66
31-40	12	40	10	33.3
41-50	8	26.66	10	33.3
51-60	1	3.33	2	6.66
Total	30	100	30	100
Mean + SD	37.26±9.74		36.63±9.4	

Samples were age matched with P=0.501

Mean age was37.26±9.74 yrs in group M and 36.63±9.4 in control group and was comparable.

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Table 2: Comparition of spo2 in the groups studied

Spo2	Melatonin group	Control group	P value
Day before surgery (PAE)	98.05±0.39	97.95±0.32	0.211
Before premedication	97.83±0.96	97.73±0.64	0.585
0 min	97.85±0.83	97.62±0.77	0.215
15 min	96.46±1.32	97.18±1.01	0.005**
30min	95.80±1.22	97.48±0.88	<0.001**
45 min	95.60±1.39	97.53±0.85	<0.001**
60 min	96.43±1.41	98.00±0.82	<0.001**
Before induction	98.10±0.87	98.53±0.85	0.030*
After induction	99.90±0.38	100.00±0.00	0.099

There is decreased in SpO_2 from baseline in melatonin group and decreased at 15 min minute was significant P=0.005 and statistically strongly significant (p<0.001) when compared to control group, there was no significant decrease from baseline in control group.

Table 3: Comparison of SBP (mmhg) between groups studied

SBP (mmhg)	Melatonin group	Control group	P value
Day before surgery (PAE)	126.63±10.69	126.88±11.46	0.920
Before premedication	133.28±14.86	132.55±10.70	0.803
0 min	132.93±14.81	131.20±10.67	0.552
15 min	114.80±10.79	129.20±10.23	<0.001**
30min	113.18±10.45	126.13±8.42	<0.001**
45 min	111.00±10.17	126.20±7.58	<0.001**
60 min	109.68±9.18	127.05±7.92	<0.001**
Before induction	118.43±11.44	140.10±9.99	<0.001**
After induction	108.78±13.13	116.93±9.83	0.002**

The mean base line systolic blood pressure (SBP) is comparable. SBP at 15,30,45 and 60 minutes decreased in melatonin group and statistically strongly significant (p<0.001) compared to control group. Before induction the SBP was high in both group, but less than the baseline in melatonin group and more than baseline in control group.

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Table 4: Comparison of DBP (mmhg) in the groups of patient studied

DBP (mmhg)	Melatonin group	Control group	P value
Day before surgery (PAE)	80.90+8.54	79.20+9.29	0.397
Before premedication	83.70+9.22	83.50+7.18	0.914
0 min	82.75+9.31	83.03+7.06	0.885
15 min	73.53+8.26	80.05+6.71	<0.001**
30min	70.88+8.66	78.90+5.93	<0.001**
45 min	70.23+8.35	77.93+7.16	<0.001**
60 min	70.13+10.15	79.25+7.07	<0.001**
Before induction	73.73+8.68	87.65+5.94	<0.001**
After induction	66.95+8.34	70.18+8.19	<0.001**

The mean base line diastolic blood pressure (DBP) is comparable. DBP at 15,30,45 and 60 minutes decreased in Melatonin group and statistically strongly significant (p<0.001) compared to control group. Before induction the DBP was high in both groups, but less than the baseline in melatonin group and more than baseline in control group.

Table 5: Comparison of MAP (mmhg) between the groups

MAP (mmhg)	Melatonin group	Control group	P value
Day before surgery (PAE)	95.70±9.38	94.45±9.35	0.552
Before premedication	100.00±9.55	99.60±7.99	0.839
0 min	98.93±9.36	98.68±7.74	0.897
15 min	87.10±8.14	95.95±6.37	<0.001**
30min	84.85±8.32	94.45±6.47	<0.001**
45 min	83.55±8.24	94.20±5.86	<0.001**
60 min	83.28±9.34	94.68±6.63	<0.001**
Before induction	88.20±10.09	104.35±7.28	<0.001**
After induction	80.55±9.43	85.20±8.07	<0.001**

The baseline mean arterial pressures were compatible. The maximum drop was seen at 15 min after pre-medication and the maximum change was at 60 min in melatonin group. Though there was decrease in MAP in control group the change was clinically not significant. Between the groups the decrease in MAP was significantly strongly significant (p<0.001). Before induction the MAP was high in both the group, but less than the baseline in melatonin group and more than baseline in control group.

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Table 6: Time to recovery score 9 on Aldrete scale

Time to recovery score 8 on Aldrete scale	Melatonin group		Control group	
	No	%	No	%
1-5	12	40	17	56.66
6-10	18	60	13	43.33
Total	30	100	30	
Mean + SD	6.25±1.37		5.88±1.18	100

The time to recovery score of 9 on modified recovery scale of aldrete is comparable (p=0.194).

Discussion

The level of oxygen saturation (SpO_2) was assessed to determine if melatonin had any impact on oxygen saturation over time if used as a premedication. The baseline values were comparable (P=0.585), and there was statistically significant difference at 15 minutes (P=0.005) and strongly statistically significant (P<O01) difference at 30, 45, 60 minutes after premedication between the two groups. The difference was not clinically significant.

In the melatonin group, the difference in Spa) from baseline (97.83±0.96%) and at 15, 30, 45, 60 minutes (97.85%, 96.43%, and 95.80%, 95.60%, 96.43%, 98.10% respectively). was very small and not clinically significant. This was may be due to the sedative effect of melatonin.

In placebo group, the baseline $Sp0_2$ value was 97.73±0.64%. The difference in baseline Sp02 and that at 0,15,30,45, and 60minutes were not significant.

Therefore, it appears that the use of melatonin as an oral premedication did not affect the patient's oxygen saturation levels clinically.[7]

Other indirect methods of determining anxiety reduction are to examine changes in heart rate and blood pressure. With increasing anxiety, a subject's heart rate and blood pressure (especially systolic) tend to increase as well, and vice-versa. This is because fear and anxiety elicits the sympathetic nervous system, or the so-called "fight-or - flight" system. One of the effects of the sympathetic nervous system is to increase heart rate and systolic blood pressure. In fact, increases in heart rate and blood pressure are among the signs used to detect inadequate depth of anesthesia by anesthesiologists. Therefore, the difference in heart rate and blood pressure at the different time intervals of the study compared to the baseline value would be an indication of a subject's level of anxiety, with higher levels being related to higher degrees of anxiety [8].

In our study, each subject's heart rate, blood pressure was measured on the day before surgery, before premedication and at 0, 15, 30, 45. 60 min after premedication and at induction.

The mean basal heart rate on day before surgery, on the day of surgery were comparable between the two group (P=0.203 and P=0.359 respectively). Inter group comparison shows statistically highly significant (p<0.001) difference in the heart rate measured at different intervals. Within the melatonin group the maximum change in the heart rate was seen at 15 min from baseline and maximum decrease was seen at 60

ISSN:0975 -3583,0976-2833 VOL13, ISSUE 01, 2022

minutes. Within the placebo group there was no significant change in heart rate. Both the group showed increase in heart rate just before induction and after induction. In melatonin group the increase was below the baseline heart rate. In placebo group the increase in heart rate was more than baseline heart rate. This decrease in the heart rate correlated with the decrease in anxiety in melatonin group [9, 10].

The comparison of systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial blood pressure (MAP) between the two groups respectively.

The mean systolic blood pressure, diastolic blood pressure and the mean arterial pressure were comparable between the two groups on the day before surgery, before premedication and at 0 min after premedication (P>0.5).

There was statistically significant difference (p<0.001) in SBP. DBP and MAP at 15, 30, 45, 60 minutes. before induction and significant difference after induction in between the group.

In melatonin group, the decrease in blood pressures from base line was seen at 15 min and the maximum decrease was at 60 minute. The change may be due to the anxiolytic and sedative effect of melatonin. These changes at different interval after premedication correlates well with the decrease in anxiety scores and increase in sedation scores after premedication.

In the placebo group the decrease in blood pressure from the baseline was seen at different time interval after premedication, but vas not clinically significant as seen in melatonin group.

It was noted that there was increase in blood pressures just before induction in both the group. This could be due to shifting of patient from quite premedication room to noisier operating room and the operating room environment. However, in melatonin group the increase in blood pressures was well below the baseline blood pressures and in placebo group, the increase in blood pressures was well above the base line blood pressures.

Our observation shows that melatonin, by decreasing anxiety and inducing sedation as an impact on the heart rate and blood pressures significantly compared to placebo.

Conclusion

The mean systolic blood pressure, diastolic blood pressure and the mean arterial pressure were comparable between the two groups on the day before surgery, before premedication and at 0 min after premedication (P>0.5).

There was statistically significant difference (p<0.001) in SBP. DBP and MAP at 15, 30, 45, 60 minutes before induction and significant difference after induction in between the group.

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ISSN:0975 -3583,0976-2833 VOL13, ISSUE 01, 2022

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Accepted on 28/05/2022