IF : 4.547 | IC Value 80.26 VOLUME-6, ISSUE-5, MAY-2017 • ISSN No 2277 - 8160

Original Research Paper Anaesthesiology

"ORAL MELATONIN TO REDUCE STRESS HORMONE PERIOPERATIVELY"

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ABSTRACT

AIM - To study any change in Stress Hormone before Oral Melatonin, after 2 hrs of tablet intake and after the induction of General Anaesthesia by withdrawing blood for Serum Cortisol levels. To determine the Haemodynamic stability Intraoperatively. **MATERIALS AND METHODS-** Sixty adult patients of class ASA 1&2 of either sex in age groups 20 to 50 years having surgeries under General Anesthesia were selected for the study. Patients were randomly divided into three groups of 20 in each group. Group "L" – Patient were given Melatonin 3mg. Group "M" – Patient were given Melatonin 5mg. Group "N" –patient were given Fourts-B tablet (placebo). **RESULTS-** Based on the finding of this study, compared to placebo, Melatonin at doses does not reduce the serum Cortisol levels Peri-operatively. There was no significant reduction in serum Cortisol levels after administration of Melatonin compared to placebo. The patient's heart rate and blood pressure, which is expected to change with different time of observation. Therefore, the null hypothesis(H_o) for this study was accepted; Melatonin produces only sleepiness and arousal effects after administration and does not produce sedative or amnesic properties as the benzodiazepines class of drugs.

KEYWORDS : .

INTRODUCTION

Preoperative anxiety is described as an unpleasant state of mind and anxiety that's secondary to patient being concerned about a disease, hospitalisation, Anaesthesia and Surgery or the unknown. (TUSHAR et al., 2015) Anxiety in response to impending surgery is a common emotional phenomenon, but also leads to Pre-operative Physiological and Psychological changes. The major goal of premedication is to allay anxiety. An ideal pre-medication should have a non-invasive route of administration, rapid and reliable onset, rapid elimination, consistent and predictable result and good patient acceptance. At the same time, it should be free of side effects, Haemodynamic variations, Respiratory depression and delayed recovery.(Rakhi et al., 2015). Melatonin has also been reported to cause preoperative anxiolytic and increase in level of sedation without impairing orientation.(Tushar et al 2015).Various studies have shown that Melatonin has the potential to be as good an anxiolytic as Benzodiazepines but without most of their side effects (Naguib et al., 1999)[1]. Premedication with 0.05mg/kg or 5mg of Melatonin sublingually was shown to be associated with preoperative anxiolysis in adults without psychomotor impairment or impact on recovery(Acil et al., 2004)[2].

OBJECTIVES

1) To study any change in Stress Hormone before Oral Melatonin, after 2 hrs of tablet intake and after the induction of General Anaesthesia by withdrawing blood for Serum Cortisol levels

2) To determine the Haemodynamic stability Intraoperatively.

MELATONIN

Melatonin is a substance found in animals, plants and bacteria. Melatonin was isolated and characterized by from the Bovine pineal by the Dermatologist Aaron Lerner as early in 1958. (Claustrat et al., 2005)[3]. It is a main Hormone secreted by Pineal gland. Secondary sources are retina, Gut, Skin, Platelet, Bone marrow and probably other structures, whose systemic contribution is insignificant. Melatonin (N-acetyl -5-Methoxytryptamine) is one such a powerful Hormone derived from an essential Amino acid Tryptophan. (Chava et al., 2012).

Melatonin is rapidly metabolized, primarily in liver to 6-HydroxyMelatonin. A series of reactions next yield N-acetyl-5-Methoxy-6-Hydroxytryptamine that depending upon the chemical environment is conjugated to either sulphate or glucuronide (Naguib et al.,2007)[4].

The calculated serum half-life of Melatonin is about 30-50minutes. "Dark" and "light" – induced neural and Endocrine signals co-ordinately regulate Melatonin, it is inhibited by light and permitted by darkness peaking in the middle of the night in both diurnal and nocturnal animals.(Souvik et al.,2013)[5].

Melatonin rhythm is generated by a endogenous clock located in the suprachiasmatic nuclei of the Hypothalamus, like other circadian rhythms in the mammals (drinking and feeding, sleep wake cycles, temperature, Cortisol or corticosterone, etc..). In human, 1mg Melatonin decreased ABP and plasma Norepinephrine concentration after standing and 3mg attenuated reflux sympathetic increases that respond to orthostatic stress. (jiyon et al.,2015).Melatonin action mediated by Neurohormone,pineal gland also include its role in reducing blood pressure and decreasing Catecholamine level. Moreover, Melatonin is reported to be associated with Analgesic effect in patient with Major Tissue injury (Marzieh et al., 2011).

SERUM CORTISOL

The Adrenal cortex synthesizes dozen of different Steroid molecules, but only few of these have biological activity. These are classified into three classes of hormones: Glucocorticoids, Mineralocorticoids and Androgens. Cortisol level measurement is used in the assessment of Adrenal Pituitary and Hypothalamic function and is especially important in the diagnosis of Cushing's syndrome and Addison's disease. The hormone of the Adrenal cortex particularly the Glucocorticoids, are an essential component of adaptation to severe stress. In particular, many Glucocorticoids analogues are potent anti-inflammatory agents.

The adult cortex has three distinct layers as zones. The Subcapsular area is called the Zonaglomerulosais associated with production of Mineralocorticoids. Next is the zonafasciculata, which, with the Zonareticularis produces Glucocorticoids and also Androgens. The Glucocorticoids are 21-carbon steroid with many actions, the most important of which is to promote Gluconeogenesis.(Harper's Biochemistry)[8].

Cortisol is the predominant glucocorticoid in humans and is made in zona fasciculate (Half-Life70-90mins).Daily output 10 µg/dL. Plasma level-13.9 µg/dL.

Cortisol is one of several end product of a process called Steroidogenesis. This process start with the synthesis of Cholesterol, which then proceeds through a series of modification in the Adrenal gland (Suprarenal) to become any one of many steroid hormones. One end product of this pathway is Cortisol. For Cortisol to be released from the Adrenal gland, a cascade of signalling occurs. Corticotropin releasing hormone released from the Hypothalamus stimulates Corticotrophes in the Anterior Pituitary to release capsular ACTH, which relays the signal to the Adrenal cortex. Here, the Zonafasciculata and ZonaReticularis in response to capsular ACTH, secrete Glucocorticoids, in particular Cortisol. In peripheral tissue Cortisol is converted to Cortisone by the enzyme 11-beta steroid dehydrogenase (Mohammed et al., 2013)[6].

LABORATORY CORTISOL ASSAY:
SERUM CORTISOL TOTAL ASSAY:
- Radio immunoassay
- Liquid chromatography
- HPLC
-Fluroscence polarization immune assay

SERUM FREE CORTISOL ASSAY:
- Coolen's method
- Ultra filtration

URINE FREE CORTISOL ASSAY:
- RIA
- Immunoassays
- Liquid chromatography

SALIVARY CORTISOL ASSAYS:
- RIA
- Immunoassays
- Liquid chromatography.

MATERIAL AND METHOD

This study **"ORAL MELATONIN TO REDUCE STRESS HORMONE PREOPERATIVELY"** a clinical study was carried out at **MEENAKSHI MEDICAL COLLEGE HOSPITAL AND RESEARCH INSTITUTE**, Enathur, Kancheepuram

Sixty adult patients of class ASA 1&2 of either sex in age groups 20 to 50 years having surgeries under General Anesthesia were selected for the study. Patients were randomly divided into three groups of 20 in each group.

Group"L"– Patient were given Melatonin 3mg
Group"M"– Patient were given Melatonin 5mg
Group"N"–patient were given Fourts-B tablet (placebo)

INCLUSION CRITERIA:
1. ASA I and II
2. Not taking Benzodiazepines or Barbiturates
3. Age 20-50 years inclusive
4. Body weight between 40-120 kg
5. No seizure disorder
6. Not taking Anticoagulant Medication

EXCLUSION CRITERIA:
1. ASA III and above
2. Taking Benzodiazepines or Barbiturates
3. Age less than 20 and more than 50
4. Body weight less than 40 and more than 120 kg
5. Pregnancy
6. Seizure disorder
7. On Anticoagulant medication
8. Patient not willing for the study

During the Anesthesia Consultation session, eligible subjects were asked to volunteer for this study and those who agreed to do were chosen. After explaining the procedure and the effects of the drug informed consent was taken from each subject (see appendix), Patient were explained about the procedure of General Anesthesia. Blood samples was taken the night before the day of Surgery, (Before Ingestion of tablet and two hours after ingestion of tablet in the night) on the day of Surgery in the morning, (Before Ingestion of tablet and two hours after ingestion of tablet in the morning)and after the induction of General Anesthesia. Basic investigations were done (HB%, BT, CT, Blood grouping, urine routine, CXR, ECG, BUN, Serum creatinine and Blood sugar).

The drug used in our study oral Melatonin5mg liquid softgel and oral Melatonin 3mg tablet from nature's bounty, Bohemia,NY 11716 U.S.A and FOURTS-B film-coated tablet from fourts (premiere).

The study was carried out and blood samples were taken for serum Cortisol levels estimation the night before the day of Surgery (before ingestion of Melatonin 3mg or 5mg or placebo tablet and after 2hrs of intake of tablet). On the day of surgery morning blood samples were taken (before ingestion of tablet and after 2hrs of medication). After induction of General Anesthesia the last blood sample was taken. Totally five blood samples were collected from every patient undergoing surgery, samples were immediately sent to the Biochemistry lab for serum Cortisol levels estimation.

In the operating room, IV assess were secured with 18Gvenflon, an infusion of lactated Ringer's solution was started. Baseline Heart rate, SBP, DBP, MAP, SPO2 was recorded prior to induction. All patient were pre-oxygenated for 3 minutes and Anesthesia induced with 1µg/kg Fentanyl, 2mg/kg Propofol and 0.1mg/kg Vecuronium, after Tracheal intubation, Anesthesia was maintained with 50% Oxygen and 50% Nitrous oxide and Sevoflurane. Gas analyser was used throughout the surgical procedure.

Intra operative blood sampling was done immediately after Tracheal intubation and before the surgical incision was made.

Anesthesia continued with O2, N2o, Sevoflurane and Vecuronium. Analgesia and IV fluids administered based on the requirement. SPB, DBP, MAP, Heart rate, SPO2 were recorded throughout the surgical procedure. At the end of the surgery, sevoflurane and N2O were discontinued and when respiratory attempts were present, residual neuromuscular blockage was reversed with Inj.Neostigmine 0.05mg/kg and Inj.Glycopyrrolate0.01mg/kg recovery assessed and extubation done after through throat suctioning. After adequate clinical recovery patient shifted to post Anesthesia case unit, observed for one hour for nausea, vomiting, bradycardia, hypotension and sedation.

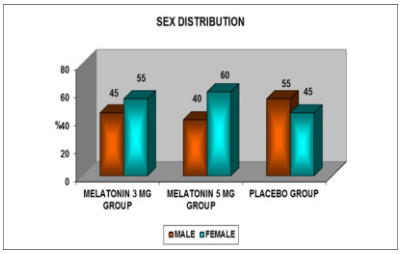
OBSERVATION & RESULT
STATISTICS AND ANALYSIS

Sample size of 20 per group was taken for this study. Data was expressed mean ± standard deviation (SD) or absolute values. Qualitative data were compared with the chi square test and Fisher´s exact test. Quantitative variables were compared with student 't'test. The level of statistical significance was set at $P < 0.05$.

DEMOGRAPIC VALUES
TABLE: 1

SEX * GROUP Crosstabulation

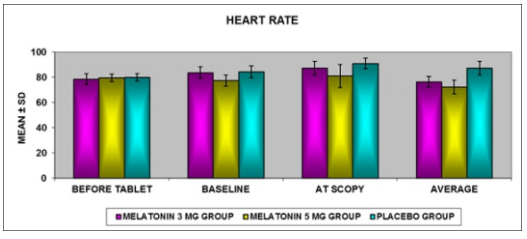
			GROUP			
			MELATONIN 3 MG GROUP	MELATONIN 5 MG GROUP	PLACEBO GROUP	Total
SEX	MALE	Count	9	8	11	28
		% within GROUP	45.0%	40.0%	55.0%	46.7%
	FEMALE	Count	11	12	9	32
		% within GROUP	55.0%	60.0%	45.0%	53.3%
Total		Count	20	20	20	60
		% within GROUP	100.0%	100.0%	100.0%	100.0%



INTERPRETATION:
The gender distribution of the cases is graphically shown in Fig-I. In total there were 9, 8 and 11 male Patients in the Melatonin 3mg Melatonin 5mg group and the placebo group. There were 11, 12 & 9 female Patients in the Melatonin 3mg, Melatonin 5mg group and placebo group.

HEAMODYNAMICS PARAMETERS:
HEART RATE (HR)
TABLE: 2

S.NO	TIME OF OBSERVATION	HR (Bt/Min)	SD	P VALUE
1	Before tablet			
	Melatonin 3mg	78.35	4.380	
	Melatonin 5mg	79.45	2.911	
	Placebo	79.23	3.024	0.361
2	Baseline			
	Melatonin 3mg	83.65	4.637	
	Melatonin 5mg	77.35	4.246	
	Placebo	84.30	4.769	0.000
3	At scopy			
	Melatonin 3mg	87.10	5.370	
	Melatonin 5mg	80.95	8.941	
	Placebo	90.95	4.097	0.000
4	Average			
	Melatonin 3mg	76.30	4.181	
	Melatonin 5mg	72.30	5.440	
	Placebo	87.25	5.379	0.000



INTERPRETATION:
Mean values of heart rate were taken before ingestion of tablet, at baseline, at laryngoscopy and average.

The p values have been calculated on comparing three groups at each stage and the result are significant except during values taken before intake of tablet.

This shows that Melatonin group show definite reduction in heart rate than the placebo group.

TABLE: 3

HEART RATE (HR) BETWEEN GROUPS					
S.NO	TIME OF OBSERVATION			MEAN DIFFERENCE	P VALUE
1	HR-before tablet	Melatonin 3mg	Melatonin 5mg	-1.100	0.584
			Placebo	-1.550	0.348
		Melatonin 5mg	Melatonin 3mg	1.100	0.584
			Placebo	-0.450	0.913
		Placebo	Melatonin 3mg	1.550	0.348
			Melatonin 5mg	0.450	0.913
2	HR-baseline	Melatonin 3mg	Melatonin 5mg	6.300	0.000
			Placebo	-0.650	0.894
		Melatonin 5mg	Melatonin 3mg	-6.300	0.000
			Placebo	-6.950	0.000
		Placebo	Melatonin 3mg	0.650	0.894
			Melatonin 5mg	6.950	0.000
3	HR- at scopy	Melatonin 3mg	Melatonin 5mg	6.150	0.011
			Placebo	-3.850	0.153
		Melatonin 5mg	Melatonin 3mg	-6.150	0.011
			Placebo	-10.000	0.000
		Placebo	Melatonin 3mg	3.850	0.153
			Melatonin 5mg	10.000	0.000
4	HR-average	Melatonin 3mg	Melatonin 5mg	4.000	0.039
			Placebo	-10.950	0.000
		Melatonin5mg	Melatonin3mg	-4.000	0.039
			Placebo	-14.950	0.000
		Placebo	Melatonin 3mg	10.950	0.000
			Melatonin 5mg	14.950	0.000

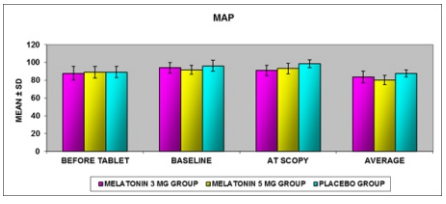
INTERPRETATION:
Mean values of heart rate were taken before ingestion of tablet, at baseline, at scopy and average.

The p values have been calculated on comparing three groups at each stage between groups and the result showed statistical significance during the baseline between Melatonin5mg to Melatonin 3mg & placebo, at scopy between Melatonin 5mg & placebo and during average between Melatonin 5mg & 3mg to placebo values.

This shows that Melatonin group has definite reduction in heart rate than the placebo group. Thus all other mean result shows non-significant values.

MEAN ARTERIAL PRESSURE (MAP)
TABLE: 4

S.NO	TIME OF OBSERVATION	MAP(mm/Hg)	SD	P VALUE
1	Before tablet			
	Melatonin 3mg	87.60	7.625	
	Melatonin 5mg	88.90	6.561	
	Placebo	88.95	6.761	0.780
2	Baseline			
	Melatonin 3mg	94.00	5.982	
	Melatonin 5mg	91.80	4.927	
	Placebo	96.15	6.158	0.063
3	At scopy			
	Melatonin 3mg	91.00	5.885	
	Melatonin 5mg	93.15	5.941	
	Placebo	98.45	4.430	0.000
4	Average			
	Melatonin 3mg	83.65	6.483	
	Melatonin 5mg	80.20	5.357	
	Placebo	87.70	3.854	0.000



INTERPRETATION:
Mean values of mean arterial pressure were taken before ingestion of tablet, at baseline, at scopy and at average.

The p value have been calculated on comparing three groups at each stage and the result are significant except during the before intake of tablet and at baseline.

This shows Melatonin group show definite reduction when compared with placebo.

TABLE: 5

MEAN ARTERIAL PRESSURE (MAP) BETWEEN GROUPS					
S.NO	TIME OF OBSERVATION			MEAN DIFFERENCE	P VALUE
1	MAP- before tablet	Melatonin 3mg	Melatonin 5mg	-1.3	0.821
			Placebo	-1.35	0.808
		Melatonin 5mg	Melatonin 3mg	1.3	0.821
			Placebo	-0.05	1.000
		Placebo	Melatonin 3mg	1.35	0.808
			Melatonin 5mg	0.05	1.000
2	MAP- baseline	Melatonin 3mg	Melatonin 5mg	2.2	0.448
			Placebo	-2.15	0.464
		Melatonin 5mg	Melatonin 3mg	-2.2	0.448
			Placebo	-4.35	0.050
		Placebo	Melatonin 3mg	2.15	0.464
			Melatonin 5mg	4.35	0.050
3	MAP- at scopy	Melatonin 3mg	Melatonin 5mg	-2.15	0.432
			Placebo	-7.45	0.000
		Melatonin 5mg	Melatonin 3mg	2.15	0.432
			Placebo	-5.3	0.009
		Placebo	Melatonin 3mg	7.45	0.000
			Melatonin 5mg	5.3	0.009
4	MAP- average	Melatonin 3mg	Melatonin 5mg	3.45	0.111
			Placebo	-4.05	0.051
		Melatonin5mg	Melatonin3mg	-3.45	0.111
			Placebo	-7.5	0.000
		Placebo	Melatonin 3mg	4.05	0.051
			Melatonin 5mg	7.5	0.000

INTERPRETATION:

Mean values of mean arterial pressure were taken before ingestion of tablet, at baseline, at scopy and at average.

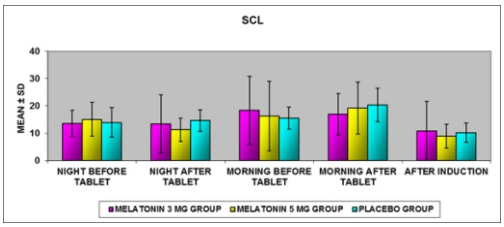
The p value have been calculated on comparing three groups at each stage and the result are significant between Melatonin3mg & placebo group during scopy and between Melatonin 5mg & placebo group during average.

This shows Melatonin group has definite reduction when compared with placebo. Thus all other mean result shows non-significant values.

SERUM CORTISOL LEVELS (SCL)

TABLE: 6

S.NO	TIME OF OBSERVATION	MEAN	SD	P VALUE
1	SCL- before tablet night			
	Melatonin 3mg	13.510	4.8235	
	Melatonin 5mg	15.045	6.2387	
	Placebo	13.965	5.3486	0.665
2	SCL- after tablet night			
	Melatonin 3mg	13.35	10.638	
	Melatonin 5mg	11.24	4.258	
	Placebo	14.63	3.984	0.309
3	SCL- before tablet morning			
	Melatonin 3mg	18.35	12.488	
	Melatonin 5mg	16.28	12.750	
	Placebo	15.47	4.091	0.675
4	SCL- after tablet morning			
	Melatonin 3mg	16.94	7.632	
	Melatonin 5mg	19.14	9.476	
	Placebo	20.26	6.136	0.405
5	SCL- Induction			
	Melatonin 3mg	10.180	10.812	
	Melatonin 5mg	8.880	4.309	
	Placebo	10.150	3.518	0.669



INTERPRETATION:

Mean values of serum Cortisol levels were taken at before intake of tablet & 2hrs after tablet at night, before intake of tablet & 2hrs after tablet in morning and after induction of General Anaesthesia.

The p values have been calculated on comparing three groups at each stage and the result showed no statistical significance.

This shows Melatonin and placebo group has no definite reduction or elevation on serum Cortisol levels.

TABLE: 7

MEAN ARTERIAL PRESSURE (MAP) BETWEEN GROUPS					
S.NO	TIME OF OBSERVATION			MEAN DIFFERENCE	P VALUE
1	MAP- before tablet	Melatonin 3mg	Melatonin 5mg	-1.3	0.821
			Placebo	-1.35	0.808
		Melatonin 5mg	Melatonin 3mg	1.3	0.821
			Placebo	-0.05	1.000
		Placebo	Melatonin 3mg	1.35	0.808
			Melatonin 5mg	0.05	1.000
1	SCL- night before tablet	Melatonin 3mg	Melatonin 5mg	-1.535	0.654
			Placebo	-0.455	0.963
		Melatonin 5mg	Melatonin 3mg	1.535	0.654
			Placebo	1.08	0.809
		Placebo	Melatonin 3mg	0.455	0.963
			Melatonin 5mg	-1.08	0.809
2	SCL- night after tablet	Melatonin 3mg	Melatonin 5mg	2.12	0.607
			Placebo	-1.275	0.283
		Melatonin 5mg	Melatonin 3mg	-2.12	0.607
			Placebo	-3.395	0.283
		Placebo	Melatonin 3mg	1.275	0.834
			Melatonin 5mg	3.395	0.283
3	SCL- Morning before tablet	Melatonin 3mg	Melatonin 5mg	2.07	0.810
			Placebo	2.885	0.666
		Melatonin 5mg	Melatonin 3mg	-2.07	0.810
			Placebo	0.815	0.968
		Placebo	Melatonin 3mg	-2.885	0.666
			Melatonin 5mg	-0.815	0.968
4	SCL- Morning after tablet	Melatonin 3mg	Melatonin 5mg	-2.195	0.654
			Placebo	-3.315	0.383
		Melatonin 5mg	Melatonin 3mg	2.195	0.654
			Placebo	-1.12	0.895
		Placebo	Melatonin 3mg	3.315	0.383
			Melatonin 5mg	1.12	0.895
5	SCL- Induction	Melatonin 3mg	Melatonin 5mg	1.97	0.650
			placebo	0.7	0.947
		Melatonin 5mg	Melatonin 3mg	-1.97	0.65
			placebo	-1.27	0.835
		Placebo	Melatonin 3mg	-0.7	0.947
			Melatonin 5mg	1.27	0.835

INTERPRETATION:

Mean values of serum Cortisol levels were taken before ingestion of tablet in night, after 2hrs tablet intake at night, before intake of tablet in morning, after 2hrs of tablet intake at morning and after induction of General Anaesthesia.

The p values have been calculated on comparing three groups at

each stage between the groups and the result shows no statistical significance.

This shows Melatonin group comparing with placebo group has no definite reductionor elevation in serum Cortisol levels.

DISCUSSION:

This study attempted to examine Melatonin's potential for stress level during before & after intake and perioperative period by taking blood samples for serum Cortisol levels, in adult patients undergoing general anaesthetic surgical procedure.

In this study, stress response was assessed using serum Cortisol levels where the subjects assessed before the day of surgery night, the day of surgery morning and intra-operatively. Blood sample were collected before the administration of Melatonin or placebo, 2hrs after tablet intake at night and morning before ingestion of Melatonin or placebo, 2hrs after ingestion of tablet on the day of surgery and after induction of Anaesthesia. There were no significant changes in serum Cortisol levels over different time of observation between Melatonin 5mg, Melatonin 3mg and placebo group. Therefore, it appears to be no significant decrease or increase in serum Cortisol levels occurred after or before administration of Melatonin.

Other indirect methods of determining anxiety or stress reduction are to examine changes in heart rate and blood pressure. With increasing anxiety or stress, 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 response. One of the effects of sympathetic nervous system is to increase heart rate and systolic blood pressure. In fact, increase in heart rate and blood pressures are among the signs used to detect inadequate depth of Anaesthesia by Anaesthesiologists. Therefore, the difference in heart rate, systolic & diastolic blood pressure and mean arterial pressure at four time intervals of the study compared to before tablet intake would be an indication of a subject's level of anxiety or stress, with higher levels being related to higher degrees of anxiety or stress.

The change in heart rate relative to before administration for Melatonin was statistically and clinically mild reduction for heart rate at base line, at scopy and at average time intervals; for systolic blood pressure at scopy and at average time intervals; diastolic blood pressure at average time interval and mean arterial pressure at scopy and average time intervals, which suggested that Melatonin may possess anxiolylic properties. However, the difference in heart rate, SBP, DBP and MAP were statistically significant. Thus, although the results of the Melatonin trial indicated its potential to be used for anxiolysis, Melatonin been appeared to decrease anxiety to a mild significant extent when compared to placebo during General Anaesthetic surgical procedure, based on heart rate and blood pressure.

Furthermore, changes in heart rate and blood pressure between the time of observation for both Melatonin and placebo were also very small definite reduction found. This showed that Melatonin had little effect on heart rate and blood pressure changes relative to throughout the different time of observation. This further indicated that at doses used in this study, Melatonin appeared to have little effect in claiming the subjects and reducing anxiety or stress compared to placebo. This finding is especially worth nothing due to the currently understanding of the placebo effect. Traditionally, the placebo that is used to study drugs has been considered to have little or no efficacy and that the real drug to which it was being compared to had to be superior relative to placebo in order for it to be considered effective in its therapeutic effect (Greene et al., 2009)[7]. This is because placebo was believed to represent psychological phenomenon and not considered to be biologically real. However, as reported by Greene et al. (2009)[7], placebos do in fact elicit biological and behavioural responses in humans. Therefore, the use of a placebo itself can be considered therapeutic and an effective method of treatment.

CONCLUSION

In this study, Melatonin was used at doses of 3mg and 5mg to determine its reduction of stress response of Cortisol perioperative period to alleviate stress hormone in anxious patient undergoing General Anaesthetic surgical procedure.

Based on the finding of this study, compared to placebo, Melatonin at doses does not reduce the serum Cortisol levels Peri-operatively. There was no significant reduction in serum Cortisol levels after administration of Melatonin compared to placebo. The patient's heart rate and blood pressure, which is expected to change with different time of observation.

Therefore, the null hypothesis(H_o) for this study was accepted; Melatonin produces only sleepiness and arousal effects after administration and does not produce sedative or amnesic properties as the benzodiazepines class of drugs.

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