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Original article

Effect of melatonin on postoperative delirium in patients with heart valve replacement on cardiopulmonary bypass

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ABSTRACT:

INTRODUCTION- Patients undergoing heart valve replacement on cardiopulmonary bypass (CPB) frequently develop postoperative delirium in intensive care unit (ICU) which increases morbidity and longer ICU stay. This is attributed by microemboli and disturbed circadian rhythm with sleep disturbances.

AIMS AND OBJECTIVE- We studied the effect of exogenous Melatonin supplementation on occurrence and severity of postoperative delirium in these patients.

PATIENTS AND METHODS- From April 2021 to March 2022, with total 60 patients were included in this study divided into Melatonin & placebo group. Perioperative Melatonin was supplemented till 3days after extubation in Melatonin group and both the groups were compared in terms of delirium occurrence and severity along with duration of mechanical ventilation. Statistical analysis was done significance was defined with p-value <0.05.

RESULTS- Within 12 hours of surgery, 1 (3.3%) patient in Melatonin group and 2 (6.7%) patients in placebo group developed delirium which was statistically insignificant (p-value >0.005). Within 12-24 hours, 6 (20%) patients in Melatonin group and 11(36.7%) patients in placebo group developed delirium which was statistically significant (p-value <0.05). Within 24-48 hours, 4 (13.3%) patients in Melatonin group and 9 (30%) patients in placebo group developed delirium which was statistically significant (p-value<0.05). Significant difference was found in duration of mechanical ventilation, with mean durations of 10±5.6 hours and 14±5.1 hours in Melatonin and placebo group respectively.

CONCLUSION- Melatonin supplementation is effective in reducing occurrence and postoperative delirium. It can be considered for the patients undergoing heart valve replacement surgery under CPB.

KEY WORDS- Melatonin, postoperative delirium, heart valve surgery, cardiopulmonary bypass.

BACKGROUND-

The current diagnosis of delirium is based on criteria described in the Diagnostic and Statistical Manual of mental disorders, 5th edition (DSM-5) from American Psychiatric Association.[1] It includes acute onset and fluctuating course, inattention, impaired consciousness, and disordered cognition. The subtypes of delirium are hyperactive, hypoactive and mixed type though they are ill defined.[2] The hypoactive subtype delirium is predominantly observed in medical and cardiac surgical intensive care units (ICUs) accounting about 92% cases.[3] Patients showing symptoms of delirium but not fulfilling DSM-5 criteria, are categorized as subsyndromal delirium and it has been associated with poor outcomes in ICUs.[4] Delirium is commonly seen among post cardiac surgery patients in ICU

with an prevalence of 50-67% as compared to 10-46% in noncardiac surgery patients and it causes longer period of mechanical ventilation, increased morbidity, increased mortality, decreased functional status, cognitive decline etc.[5.6]

Melatonin (N-acetyl-5-methoxytryptamine) is a serotonin derived neurohormone, primarily in the pineal gland and its secretion into the blood stream is regulated by the environmental light/dark cycle via the suprachiasmatic nucleus.[7] It induces sleep by acting on prefrontal cortex and regulates sleep-wake cycle. Its secretion is stimulated by low exposure to light and the peak level corresponds to main sleep period. It also acts as powerful antioxidant, antihypertensive and hypolipidemic agent.[8] At lower concentrations it protects against myocardial and cerebral iscaemia-reperfusion injury and also has protective effect against hyperglycemia.[9, 10, 11]

Older age, preexisting cognitive impairment, dehydration, malnutrition, complexity of surgery, cardiopulmonary bypass (CPB), hemofiltration, microemboli, reperfusion injury, sleep deprivation in ICU and disturbances in melatonin level regulation predispose the patients for psychosis and delirium after cardiac surgery.[12,13] Owing to the pleiotropic, beneficial effect of melatonin in reducing post operative delirium has been established many non cardiac surgery patients and its beneficial role against delirium in post cardiac surgery patients has been analyzed in few studies showing mixed results. Here we prospectively evaluated the effect of Melatonin on delirium in post cardiac surgery patients.

PATIENTS AND METHODS-

This prospective observational study was conducted at G.B. Pant institute of postgraduate medical education and research (GIPMER) from April 2021 to March 2022, with total 60 patients excluding the patients as per exclusion criteria. Patients ≥ 18 years of age, with minimum ejection fraction (EF > 30%), valve replacement surgery done on cardiopulmonary bypass (CPB), with no contraindication to Melatonin and who gave verbal and written consent were included in the study. Patients with low EF ≤30%, deranged renal or hepatic function, with diagnosed psychiatric illness, taking psychiatric treatment, allergy to Melatonin or any other psychiatric medication, preexisting respiratory disease, preexisting neurological illness, addiction to alcohol or not willing to participate and patients who expired during postoperative course in ICU, were excluded from the study. This was a prospective randomized double blinded study conducted with clearance from institutional ethical committee. The patients who participated in the study gave written consent after being well explained about the objectives, risks and benefits from the study.

The patients were alternately allotted supplementation with Melatonin or placebo and the investigator was blinded to the study. The patients were divided in 2 groups, one supplemented with Melatonin and the other with placebo. Starting from a day before the surgery, the Melatonin group patients received Melatonin 5mg at night till 3rd day after extubation. The other group received corn starch powder placebo tablet. Proper hydration was maintained preoperatively. All the patients had different valve replacement surgeries for on cardiopulmonary bypass. General anesthesia was established with Fentanyl, Thiopentone, and muscle relaxants Vecuronium or Pancuronium. Throughout the surgeries activated clotting time (ACT was maintained > 480 seconds with heparin and after being weaned off from CPB, the heparin reversal was done with protamine. After the surgery, all patients were monitored

in cardiac surgery ICU with required inotropic support. Proper sedation, analgesia and mechanical ventilation was maintained in the ICU, extubation was done as per eligibility parameters for extubation.

The occurrence of delirium was assessed by confusion assessment method for intensive care unit (CAM-ICU) and the intensity of delirium was assessed by Memorial delirium assessment scale (MDAS) up to 48 hours of extubation, every 8 hourly[14]. These assessment tools used multiple step algorithm based on diagnostic and statistical manual of mental disorder criteria. The MDAS is a 4-point, 10 item (range 0–30) clinician-rated scale designed to quantify the severity of delirium in a medically ill patient population. The surgeon and intensivist on duty were well trained to assess the patients with help from psychiatrist. The patients who exhibited standard features of delirium, were classified as delirious (CAM positive). The other demographic parameters were analyzed as per described in table 1. Primary outcome was analysis of delirium in the postoperative patients and secondary outcomes were measured in terms of duration of mechanical ventilation support and length of ICU stay. Any association of other preoperative or postoperative parameters were analyzed.

The statistical analyses were performed using SPSS Software, version 20. The quantitative variables were described as mean±SD and the qualitative variables as frequencies and percentages. The continuous variables were compared using the unpaired *t* - test or a nonparametric equivalent (Mann–Whitney *U* test). Comparisons between the 2 groups were performed using the *t*- test and the Chi-square tests. Statistical significance was defined as a p-value of less than 0.05.

RESULTS-

During the period April 2021 to March 2022, total 60 patients were enrolled for this study as per the inclusion and exclusion criteria. They were divided into two groups as 30 patients in Melatonin group and 30 patients in placebo group. The basic demographic characteristics, intraoperative and postoperative parameters were compared among the two group as shown in table 1 in which no significant difference was found. The occurrence of postoperative delirium in ICU in both the groups was divided as occurring within 12 hours, 12-24 hours, 24-48 hours and after 48 hours. It was assessed every 8 hourly till 48 hours of extubation. Within 12 hours of surgery, 1 (3.3%) patient in Melatonin group and 2 (6.7%) patients in placebo group developed delirium which was statistically insignificant (p-value >0.005). Within 12-24 hours, 6 (20%) patients in Melatonin group and 11(36.7%) patients in placebo group developed delirium which was statistically significant (p-value <0.05). Within 24-48 hours, 4 (13.3%) patients in Melatonin group and 9 (30%) patients in placebo group developed delirium which was statistically significant (p-value<0.05). After 48 hours, 4 (13.3%) patients in Melatonin group and 5 (16.7%) patients in placebo group developed delirium which was statistically insignificant (p-value >0.05). The duration of mechanical ventilation among both the groups was compared and significant difference was found with mean durations of 10±5.6 hours and 14±5.1 hours in Melatonin and placebo group respectively. No serious adverse effect was observed during treatment of patients with Melatonin and no mortality was observed in any of both the groups.

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Table 1. Baseline characteristics of patients in melatonin and placebo group-

Parameters	**Melatonin group (n=30)**	**Placebo group (n=30)**	**p- value**
Age (years) mean ±SD	39.2±16.6	40.8±15.2	0.142
Sex			
Male, n (%)	18 (60)	22 (73.3)	0.273
Female, (%)	12 (40)	08 (26.7)	0.242
Euro SCORE, % (mean ±SD)	5.13±2.1	4.98±2.3	0.365
Diabetes, n (%)	8 (26.7)	7 (23.3)	0.184
Hypertension, n (%)	13 (43.3)	17 (56.7)	0.654
Smoking, n (%)	17 (56.7)	13 (43.3)	0.433
Cardiopulmonary bypass time, mean ±SD (min)	88±19.8	94±16.5	0.211
Type of valve replacement surgery			
MVR, n (%)	11 (36.7)	15 (50)	0.273
MVR + AVR, n (%)	07 (23.3)	08 (26.7)	0.312
MVR/AVR + TV annuloplasty, n (%)	11 (36.7)	06 (20)	0.091
MVR + AVR + TV annuloplasty, n (%)	01 (3.3)	01 (3.3)	0.553
Postoperatively deranged renal function, n (%)	12 (40)	09 (30)	0.144
Postoperatively deranged hepatic function, n (%)	13 (43.3)	15 (50)	0.226

MVR- Mitral valve replacement, AVR- Aortic valve replacement, TV- Tricuspid valve

Table 2. Comparison of occurrence of delirium between patients in melatonin group and placebo group

Post-operative period	**Melatonin group**	**Placebo group**	**p- value**
Within 12 hours, n (%)	01 3.3)	02 (6.7)	0.067
12- 24 hours, n (%)	06 (20)	11 (36.7)	0.044
24-48 hours, n (%)	04 (13.3)	9 (30)	0.039
After 48 hours, n (%)	04 (13.3)	05 (16.7)	0.056
Duration of mechanical ventilation, hours (mean ±SD)	10±5.6	14±5.1	0.047

DISCUSSION-

In this study we observed that Melatonin decreases the postoperative delirium occurrence (assessed by CAM-ICU) and severity (MDAS) in patients undergone valve replacement under cardiopulmonary bypass. The occurrence and severity of delirium was significantly lesser in the group of patients who received perioperative and postoperative Melatonin. Similar results were observed by Martinez et al[15] which showed Melatonin (dose 4mg) was effective in preventing delirium in 850 postoperative patients in ICU. Our study results are consistent with that even with a

smaller sample size. Al Aama et al[16] reported significant reduction in delirium in 72 elderly postoperative patients (>65 years), with injectable Melatonin (0.5mg) for longer period of treatment. De Jonhge et[17] al found that Melatonin (3mg) was effective in decreasing incidence but did not decrease the severity and duration of delirium in 378 patients undergone surgery for hip fracture. This discordance in results might be due to use of dissimilar assessment criteria.

The Healthy Heart and Mind trial by Ford et al, [18] reported that Melatonin (3mg) significantly reduced postoperative delirium in cardiac surgery patients. Artemiou et al[19] studied the effect of Melatonin (5mg) in 250 patients undergone various cardiac surgery. They reported that Melatonin administration significantly decreased the incidence of delirium after cardiac surgery, shortened the duration of mechanical ventilation with shortened postoperative ICU stay. Their result is consistent with our findings in this study. In a meta-analysis of 16 trials (1634 patients), Ng KT et al[20] did not find significant reduction in postoperative delirium by treatment with Melatonin though they found significantly shorter length of ICU stay which is consistent with our results in terms of occurrence of delirium. Javaherforoosh et al[21] reported reduced occurrence and severity of delirium in 100 postoperative CABG patients which is consistent with our result. Dianatkhah et al[22] reported significantly disturbed sleep pattern after CABG but the lower occurrence of postoperative delirium with Melatonin administration was not statistically significant as compared with that of Oxazepam. Abnormally low levels of serum Melatonin was reported after thoracic esophagectomy and abdominal surgery by Miyagawa et al[23] and Shen et al[24] respectively. This emphasizes the disturbance of circadian rhythm, sleep pattern and development of delirium which possibly can be lowered by supplemental Melatonin and stimulation of endogenous Melatonin secretion. Andrejaitiene et al[25] have described increased CPB time and aortic cross clamp time are risk factors for development of postoperative delirium in patients with cardiac surgery. Also higher doses of intraoperative administration of Fentanyl appears to be a risk factor for delirium.[26] Various cardiac surgeries have been reported to be associated with postoperative delirium, most likely due to air embolism of the air trapped in cardiac chambers intraoperatively.

Our study has few limitations. Firstly, it is an observational prospective study. Secondly, we did not assess the preoperative baseline psychiatric and cognitive baseline characteristics which are risk factors for postoperative delirium. We did not take other postoperative factors into consideration, which might be involved in development of delirium. Also we analyzed only the early postoperative delirium in a small sample size. Hence, more powerful, randomized, multicenter, placebo controlled and double blinded studies are required for validation of the results of this study and standardization of the dose of Melatonin.

CONCLUSION-

Postoperative supplementation with Melatonin significantly decreases the occurrence and severity of delirium in patients in ICU undergone different valve replacement surgeries. It also significantly reduces the duration of mechanical ventilation. Other perioperative strategies are to be developed along with administration of Melatonin for maintenance of the circadian rhythm, reduction in postoperative delirium after valve replacement surgeries. Also prophylactic, perioperative and postoperative Melatonin administration can be considered for patients undergoing cardiac surgery.

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