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Efficacy of Melatonin as an adjuvantin lower limb surgeries performed under spinal anaesthesia and its role in preventing post- operative delirium.

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Abstract : *Introduction: Postoperative delirium (POD) is usually seen in patients of any age and even upto5 days after surgery. Melatonin (N-acetyl-5-methoxytryptamine) is pineal hormone used in sleep disorders and for anxiolysis. It has a curative effect on POD.Aims & objectives: To study the efficacy of melatonin in reducing the incidence of POD in patients undergoing lower limb surgeries under spinal anaesthesia. Alsoto study the haemodynamic variables, analgesic effects and complications.Material & Methods: This prospectivedouble-blind control study was conducted on 60 patients, randomized into two groups.Group P(n=30): Received two tablets of placeboat 9.00 PM and 90 minutes before surgery orally. Group M(n=30): Received two tablets of melatonin (3mg each) at 9.00 PM and 90 minutes before surgery orallySpinal anaesthesia was administered in sitting position at L3-L4 lumbar space. Intraoperatively vital parameters were monitored at regular intervals of 15 minutes. Sedation score and Abbreviated Mental Test {AMT} were noted prior to administration of morning dose of melatonin. AMT repeated on the same day and three days postoperatively. Patients having scores lesser than 8 were considered to develop postoperative delirium, were further administered melatonin & assessed (AMT) for three days. Data wereanalysed by two-way analysis of variance (ANOVA) and t-test as applicable. P values <0.05 were considered significant. Results & Conclusion: Melatonin was effective in preventing post- operative delirium in patients undergoing lower limb surgery under spinal anaesthesia. It also prolonged the requirement of first rescue analgesia.*

Keywords : *Analgesia,delirium, melatonin, post- operative,sedation, spinal anaesthesia.*

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I. Introduction

Postoperative delirium (POD) is an adverse complication usually seen at all ages. Major predisposing risk factors including cognitive deficits, sensorineural impairment, malnutrition, comorbidity, poly-medication, impairment in functional status etc. accumulate and overlap with aging, thus posing elderly patients at higher risk of POD[1]. Delirium leads to acute and fluctuatingdisturbance in mental state leading to reduction in awareness and attention disturbances. POD can occur in recovery room which can further continue for 5 days[2].Investigations reveal that patients have POD in peripheral ward which is usually a sequel of POD in the recovery room[3]. Emergence delirium is early onset of POD in immediate post-anaesthesia period or on arrival at the recovery room[4].

Delirium usually presents as hypoactive (decreased alertness, motor activity and anhedonia), hyperactive (agitated and combative) or as mixed forms[5,6]. Prognosis is often worse with hypoactive delirium due to under-detection by staff and consequently delayed treatment[5].Increasing age is predisposing factor for the hypoactive form[7].Incidence of POD is 10% to 61% in patients aged 65 or older[8].Orthopedic patients have higher risk of delirium than those undergoing general surgery. Delirium is seen in 44% to 55% of hip surgery patients whereas it is 10% to 14% in general surgery patients[9].A meta-analysis done in 26 studies regarding POD

concluded that there was incidence of 4.0 to 53.3% in patients undergoing hip fracture surgery [10]. Delirium leads to 10% to 75% mortality, although death is seen more in advanced age and severely ill patients[11].
Melatonin (N-acetyl-5-methoxytryptamine) is a hormone produced by pineal gland. It is composed of amino acid tryptophan. It is used in variety of medicalconditions, mostly disorders related to sleep. It is also used as premedicant to decrease anxiety in patients with excellent cognitive profile[12].Moreover, it is proved to have a curative effect on postoperative delirium[13].

II. Aims& Objectives

To study the efficacy of melatonin as adjuvant to spinal anaesthesia and in reducing the incidence of postoperative delirium in patients undergoing lower limb surgeries.Also to study the haemodynamic variables and complications viz.respiratory depression, impairment of cognitive function or others, if any.

III. Material & Methods

This prospective randomized double-blind control study was conducted on 60 patients at the Department of Anaesthesiology,Mahatma Gandhi Medical College Jaipur over a period of six months extending from June 2017 -November 2017.Prior permission was attained from institutional ethical committee. All patients were explained about the anaesthesia technique and written informed consent was obtained.Patients were randomly divided into two groups of 30 each with the help of a chit in the box method.
Group P - (30 patients): Received two tablets of placebo at night before and 2 tablets
90 minutes before surgery orally.
Group M - (30 patients): Received two tablets of melatonin (3mg each) at 9.0 PM
night prior to surgery and another two tablets given 90 minutes before surgery orally.
Inclusion Criteria: ASA grade I and II patients, age between 50-65 years, scheduled for lower limb surgeries under spinal anaesthesia. Exclusion Criteria: ASA grade III and IV patients, history of alcohol abuse, sensory impairment (blindness, deafness), dementia, severe infections (especially respiratory, urinary), severe anaemia (haematocrit <30%), intracranial events (stroke, bleeding, infection),fluid or electrolyte disturbances including dehydration, hyponatremia, hypernatremia. Anticonvulsants especially phenytoin, antidepressants especially the tertiary amine tricyclic agents: amitriptyline, imipramine, doxepin; antihistaminic including diphenhydramine; antiparkinsonian agents: levodopa-carbidopa, dopamine agonists, amantadine; antipsychotics especially low-potency anticholinergic agents and atypical agents (clozapine); benzodiazepines especially long-acting including diazepam, flurazepam, chlordiazepoxide or ultra-short-acting benzodiazepines including triazolam, alprazolam.
Pre-anaesthetic evaluation was done a day prior to surgery. The patients were administeredmelatonin/ placebo in the dose of 6 mg orally at 9 pm night prior to surgery and 6 mg 90 minutes before surgery. On the day of surgery after receiving the patient in operating room, confirmation of patient's identity, fasting status, review of pre-anaesthetic evaluation was done and informed consent was checked. Anaesthetist giving the spinal and conducting the case was blinded to the drug used as premedication. In the operating room standard 5 leads ECG, non-invasive blood pressure and pulse oximetry was attached and base line parameters were noted. Venous access was secured using an 18 G cannula on the dorsum of the non- dominant hand. Spinal anaesthesia was administered to all patients using the standard technique in sitting position at L3-L4 lumbar space. Intraoperatively vital parameters viz. heart rate(HR),non- invasive blood pressure(NIBP) and arterial oxygen saturation(SpO2)were monitored at regular intervals of 15 minutes. In the recovery room sedation score and Abbreviated Mental Test {AMT} was noted prior to administration of morning dose of melatonin. AMT repeated on the same day of operation (D-0) and in the three postoperative days followed (D-1, D-2 and D-3). Patients having scores lesser than 8 were considered to develop postoperative delirium. Patient of either group who developed delirium were further administered melatonin and further assessed for AMTfor three days.
Statistical Analysis: Data were expressed as Mean+_SD. Intragroup difference was evaluated by two-way analysis of variance (ANOVA), and intergroup difference was assessed using t-test. P value of <0.05 was considered significant.

IV. Results

All study groups were comparable with respect to distribution of age, gender, weight. (Table1) There was no significant difference found among group P& group M with respect to change in intraoperative haemodynamic parameters like heart rate and blood pressure. (Fig.1,2,3,4) Patients who were given Melatonin tablets had higher sedation scores than those who were given placebo.(Fig.6,7,8)However there was no incidence of respiratory depression as per SpO2 values (Fig5). None of the patients developed delirium during immediate postoperative period in both the groups. Post-operatively onD1:in group P,3 patients and in group M, 1 patient; onD2:in group P, 4 patients and in group M, 2 patients;on D3:in group P, 3 patients and in group M none developed delirium. Overall33.3% patients in group P and only 10% in group M developed delirium.

Moreover, these could be successfully treated with melatonin.(Table2, Fig9).Requirement of first rescue analgesic dose was significantly earlier in the placebo group(p=0.002)(Table3)

There was no bradycardia, hypotension or respiratory depression observed in either groups at any given time interval and also there was no complication observed related to spinal block in any patient.

V. Conclusion

On the basis of results obtained in our study, we concluded that Melatonin in a dose of 6 mg administeredorally the night before surgery and in the morning, 90 minutes before surgery prolonged the time to first rescue analgesia and devoid of any complicationsin patients undergoing lower limb surgery under spinal anaesthesia.Although it seemed to be effective in preventing post- operative deliriumbut the values were not statistically significant.

VI. Limitations

Further studies may be conducted using higher doses and in larger number of patients so as to study its role in preventing postoperative delirium.

VII. Discussion

Although postoperative delirium is seen at all ages, its prevalence is more in patients of65 years or more age[14,15]. Aging involves a continuum of changes in biological and functional parameters that increase vulnerability and reduce functional reserve[16]. Number of diseases (chronic organic diseasessuch as hypertension) increases with age in general population which may lead to increase in prevalence of delirium[17]. The present study suggested that none of the patients developed delirium in immediate postoperative period in both groups. However, it was observed on first, second and third days post operatively. There was significant difference between placebo and melatonin group with less patients developing delirium in melatonin group. Also, these could be treated successfully. The cause of postoperative delirium is still not well defined. Some studies show that number of drugs lead to delirium.Geriatric patients undergoing surgery have pre-existing factors as well as intraoperative and postoperative reasons of delirium. Most of the preoperative patient related factors are usually not modifiable. This becomes reason for developing "preoperative" delirium and also for delirium in medical wards of hospitals[18].

POD leads to temporary attenuation of brain function which is usually followed by a full remission. POD is associated with long term cognitive and noncognitive morbidity and reduced quality of life. Cognitive impairment at any time during surgical stay, including preoperative delirium, is usually a risk factor in hip fracture patients for poor functional outcome[19].Any cognitive impairment before hospital admission is an independent risk factor for poor long term cognitive impairment[19]. As described by Maldonado in his landmark review, potential mechanisms can be grouped into categories including neuroinflammation and oxidative stress[20]. These two are likely interact to cause delirium by promoting neurotransmitter dysregulation and network disconnection causing an imbalance in activation or inhibition of neural networks (in specific cholinergic and GABAergic systems)[21,22]. Bruce AJ et al observed that delirium was more common in patient undergoing hip surgeries than other elective surgeries and was usually preoperative when associated with trauma[8].

Sherif S. Sultan used melatonin for three consecutive days postoperatively, he was successful in reducing post-operative delirium and also treating more than half of the patients developing postoperative delirium[23]. In another study, it was concluded that melatonin used exogenously in low dose at night, to elderly patients admitted for acute care was potent in preventing delirium[24].

In our study, the comparison of heart rate and mean blood pressure was done at different time intervals. Compared with the baseline values, the change in heart rate between the study groups were found to be nonsignificant at any given time interval ($p > 0.05$). This is similar with results of Yildiz et al who also did not find statistically significant change in heart rate after oral administration of melatonin[25]. Intra-operatively there was no bradycardia recorded in both groups at any given time interval.

In present study the overall mean arterial pressures were found to be on higher side in group P as compared to Group M. Mean arterial pressure were found to be more stable throughout the surgery in group M as compare to group P. However, the difference in mean arterial pressure was found statisticallynon-significant among different study groups at any given time intervals ($p>0.05$).Melatonin has sedative, analgesic, hypnotic, anti-oxidative, anti-inflammatory and chrono biotic properties which are useful as alternative pre-medication[26].Melatonin binds to particular melatonin receptors inside blood vessels which interfere with the vascular response to catecholamines and also with the peripheral and central autonomic system, causing a reduction in adrenergic outflow and catecholaminelevels which lead to relaxation of smooth muscles of the arterial walls by increasing nitric oxide availability ultimately leading to decrease in blood pressure[27].This is in

conflict with findings of Frank et al, who observed significant reduction of mean blood pressure after administration of 2.5 mg melatonin 1 hour before bedtime for 3 weeks[28].

In our study the difference in SpO2 was not found to be statistically significant among different study groups at any given time intervals ($p>0.05$). Throughout the intraoperative period, the SpO_2 was maintained at 96-100% with no episode of fall in saturation at any point of time.

Patients in the melatonin group had higher sedation scores at 60 and even upto130 minutes but they were arousable(scores1-2) than those who were given placebo. This is comfortable recovery for patients. None had respiratory depression. This finding is in accordance with other researcherswho found that sedation score was markedly higher in the melatonin group than in control group[29,30].

The present study showed that the requirement of first rescue analgesia was earlier in group P than group M (P=0.0020)(Table3). Inan experimental study, it was found that melatonin is a good analgesic in a dose dependent manner[31]. Melatonin is useful as an analgesic in preventing chronic pain in various diseases viz. fibromyalgia, irritable bowel syndrome, migraine as stated in clinical studies. The physiology behind the analgesic actions of melatonin is linked to G(i) -coupled melatonin receptors, to G(i) -coupled opioid μ-receptors or GABA-B receptors leading to downstream changes which further leads to decrease in anxiety and pain. Subsequent dose of melatonin leads to improvement in sleep and reduction in anxiety.

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Table 1: Demographic Variables

Age (yrs.)	**Group P**	**Group M**	**P Value**
Mean± SD	65.67±8.88	66.50±7.38	0.694
Weight (Kg)			
Mean± SD	59.40±3.97	61.83±6.29	0.078
Gender			
Male	19	15	
Female	11	15	0.434

Table 2: Number of Patients Developing Delirium in Different Postoperative Days

Post-operative Day(D)	**Group P**	**Group M**
D -0	0	0
D -1	3	1
D -2	4	2
D-3	3	0
Total	10 (33.3%)	3 (10%)
No. of patients cured with melatonin	5 (50%)	3 (100%)

Table 3: Comparison of Mean Time to First Rescue Analgesia in Different Group

Time to first rescue analgesia(seconds)	**Group P**	**Group M**	**Pvalue**
Mean±SD	287.0±58.80	326.0±38.18	0.0020

Table4 Sedation Score

Score	**Variable**
0	**Alert**
1	**Arousal to voice**
2	**Arousal with gentle tactile stimulation**
3	**Arousal with vigorous tactile stimulation**
4	**Unarousable**

Table 5 Abbreviated Mental Test

Score	**Variable**
1	**Age**
2	**Time**
3	**Address to recall at the end of test**
4	**Year**
5	**Name of the hospital**
6	**Recognition of the two persons**
7	**Date of birth**
8	**Year of the start of first world war**
9	**Name of the monarch**
10	**Count backwards from 20 to 1.**

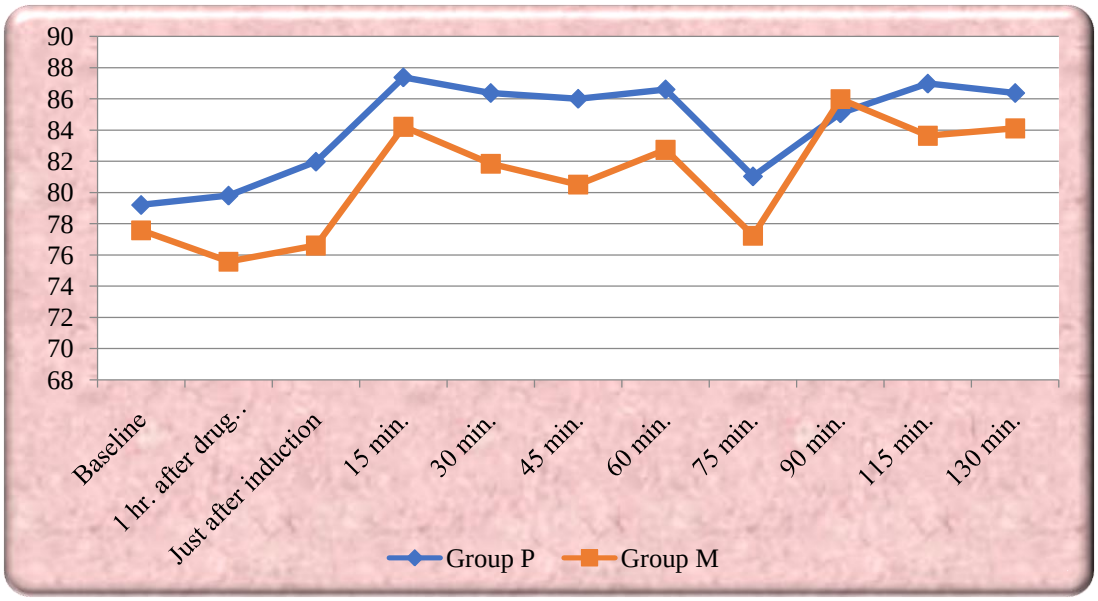

Fig.1: Comparison of Heart Rate at Different Time Intervals in Between Groups(p>0.05)

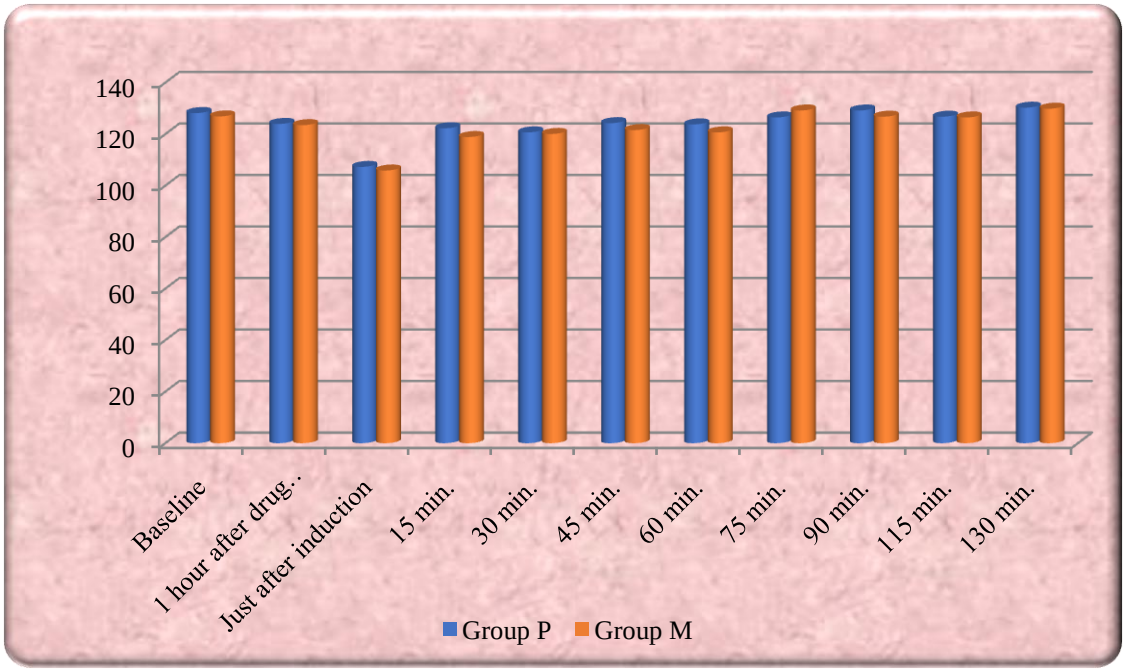

Fig.2 Comparison of SBP at Different Time Intervals in Between Groups(p>0.05)

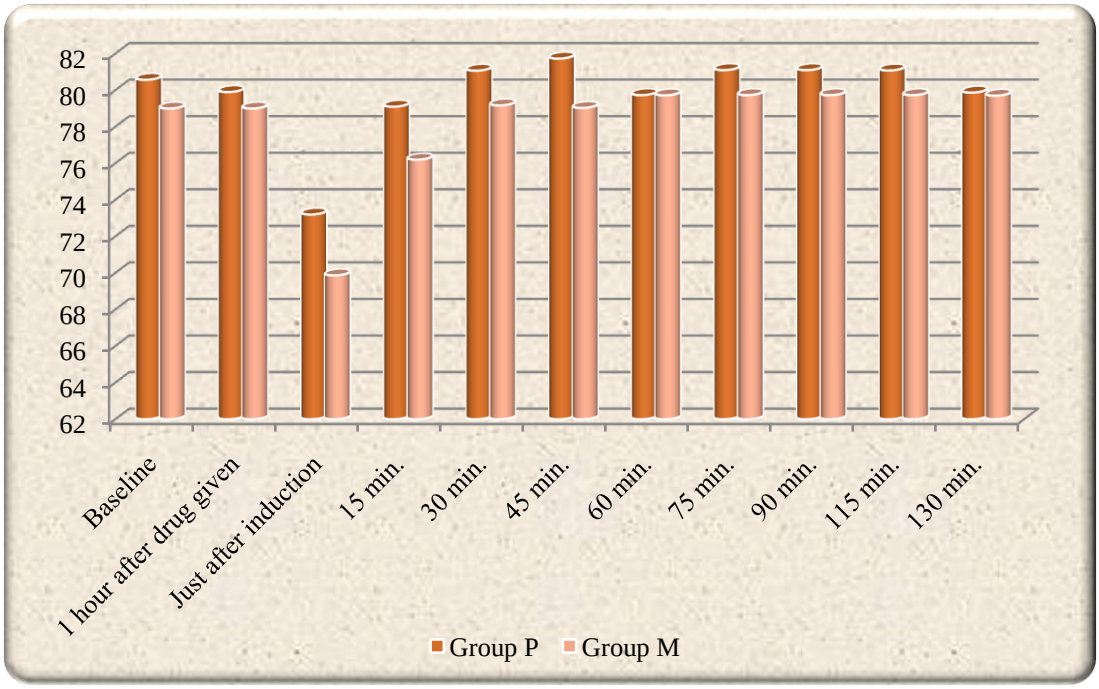

Fig.3 Comparison of DBP in Different Time Interval in Between Groups(p>0.05)

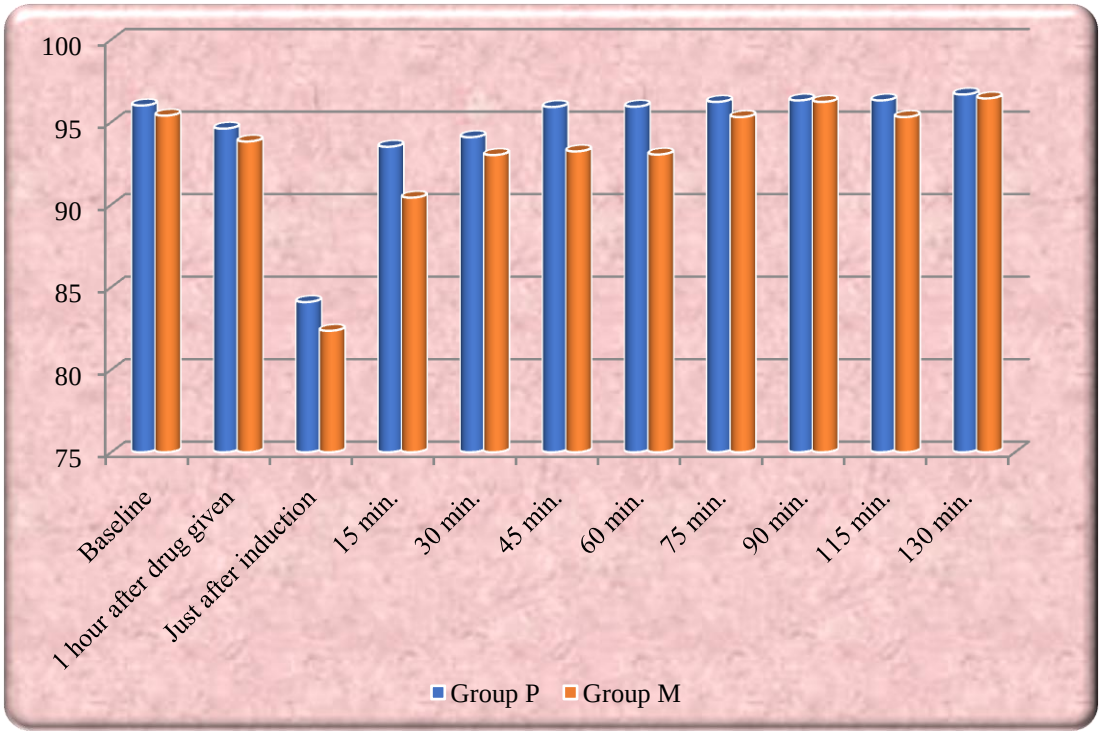

Fig.4 Comparison of Mean Arterial Pressure (MAP) at Different Time Intervals in Between Groups(p>0.05)

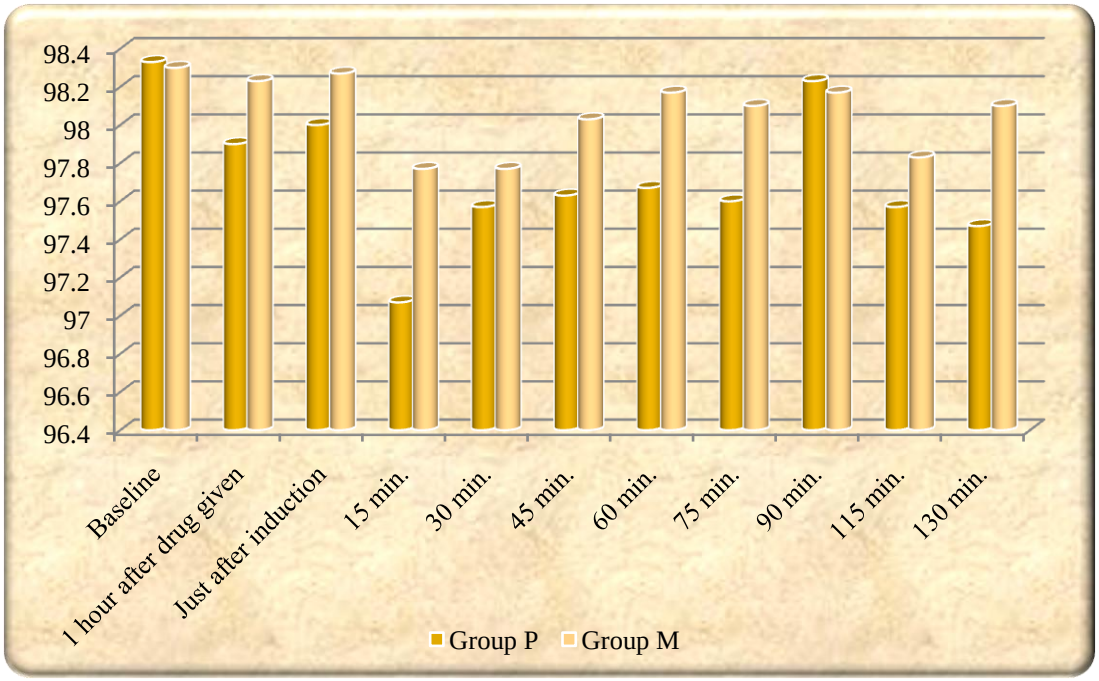

Fig.5 Comparison of SPO2 at Different Time Intervals in Between Groups(p>0.05)

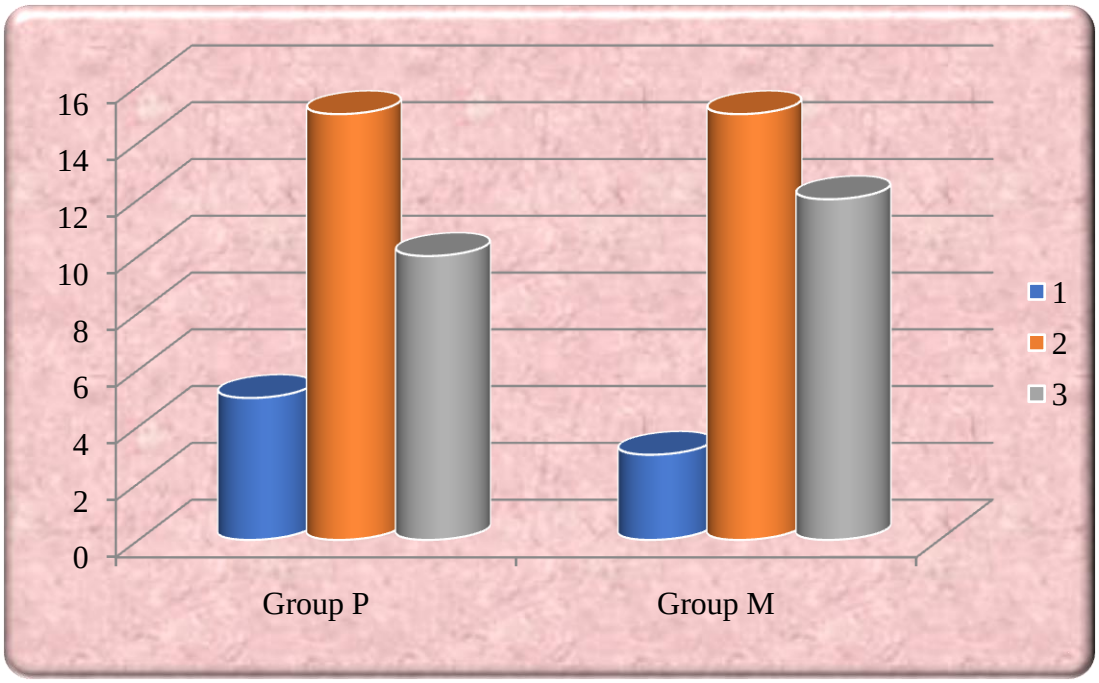

Fig.6 Sedation Score (SS) at Baseline in Between Groups(p=0.711)

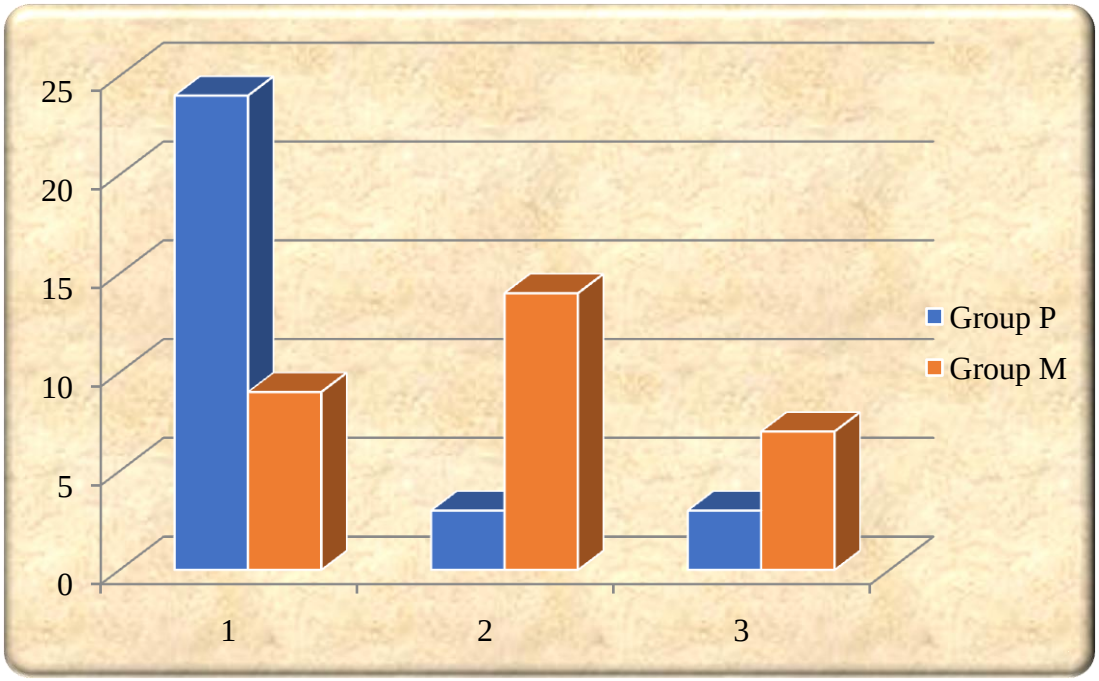

Fig.7 Sedation Score (SS) After 60 Minutes in Between Groups(p=0.0004)

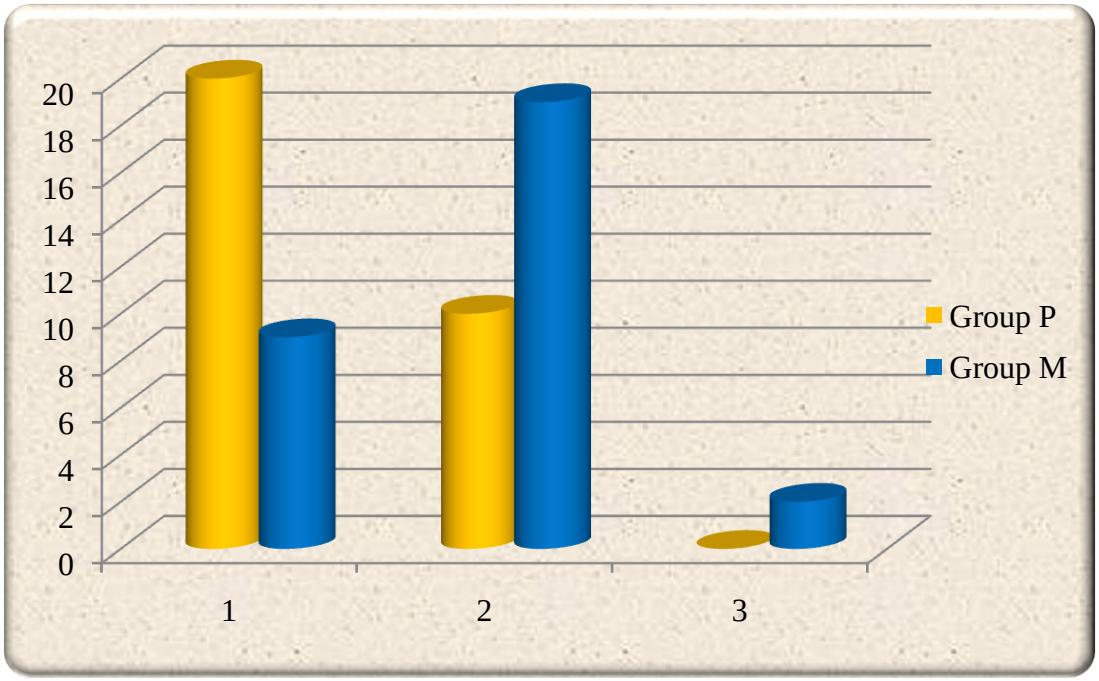

Fig.8 Sedation Score (SS) After 130 Minutes in Between Groups(p=0.0113)

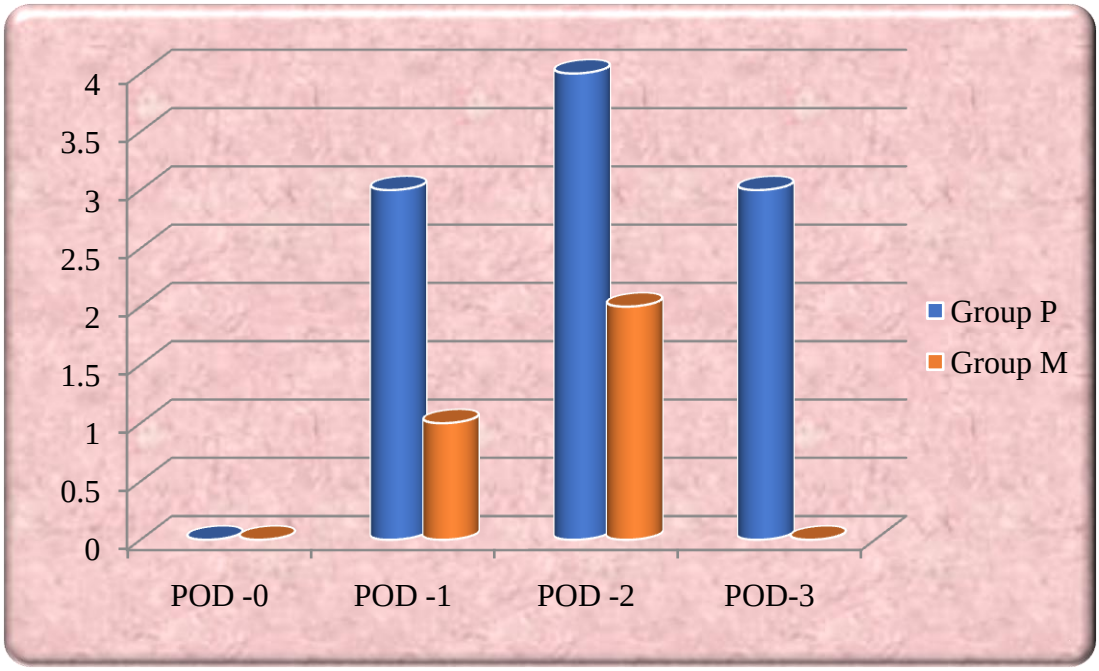

Fig.9 Number of Patients Developing Delirium in Different Postoperative Days

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