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Original Research Paper

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COMPARISON OF EFFECT OF PREOPERATIVE MELATONIN AND CLONIDINE ON POSTOPERATIVE PAIN IN PATIENTS UNDERGOING CRANIOTOMY FOR SUPRATENTORIAL TUMOURS

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ABSTRACT

Background: Patients undergoing neurosurgeries suffer from pain after the surgery and anxiety before the surgery but the incidence, magnitude and duration of the pain is not precisely known. Preoperative anxiety is known to cause abnormal haemodynamics as a consequence of sympathetic and endocrine stimulation. Pain results in sympathetic stimulation which leads to hypertension which may precipitate secondary intracranial haemorrhage. Oral melatonin as premedication before induction, helps in appropriate anxiolysis, provides analgesia, has anti-inflammatory, anti-oxidative properties and maintains circadian rhythm. Clonidine reduces sympathetic activity, shivering and oxygen consumption during recovery from anesthesia and lowers the requirement of anaesthetic drugs. **Aims And Objectives :** The primary objective is to assess difference between melatonin versus clonidine as oral premedicants in craniotomies for supratentorial tumors based on 100 point VAS score postoperatively, fentanyl consumption in the postoperative period, comparison in perioperative state anxiety and sedation, haemodynamic stability and adverse effects between the two groups. **Methods:** This is a randomized controlled triple-blinded study. Ethical permission has been sought from the institutional ethical committee before commencing the study. The study drugs were given to the study groups the night before surgery and 1 hour before inducing. Perioperative haemodynamics, sedation score, anxiety score and pain scores were noted. **Results:** Anxiety and pain scores were less in the group receiving melatonin. Sedation scores and haemodynamics were comparable in both the groups. **Conclusion :** Oral melatonin plays a superior and important role as a premedication in craniotomies for supratentorial tumours.

KEYWORDS : melatonin, clonidine, supratentorial tumours, postoperative pain, anxiety

INTRODUCTION :

Patients undergoing neurosurgeries suffer from pain after surgery and anxiety before surgery. Pain occurs mostly after subtemporal and suboccipital craniotomies[1] whereas patients undergoing frontal craniotomy undergo lesser pain and thus require less opioid analgesics.[2] Pain is mostly present within 48 hours after surgery. Patients who are more anxious preoperatively require more analgesics postoperatively.[3] Pain results in sympathetic stimulation which leads to hypertension which may precipitate secondary intracranial haemorrhage.[4] Scalp block and infiltration of wound margins with local anaesthetics before surgery starts and repeated at the end of surgery, opioids, non opioid analgesics (paracetamol, NSAIDs, COX-2 inhibitors), NMDA receptor antagonists, gabapentin, alpha 2 adrenoreceptor agonists, etcetra.are used. Literature has shown that oral melatonin as premedication before induction, helps in appropriate anxiolysis, provides analgesia, has anti-inflammatory, anti-oxidative properties and maintains circadian rhythm.[5] Clonidine reduces sympathetic activity, shivering and oxygen consumption during recovery from anaesthesia and lowers the requirement of anaesthetic drugs. Clonidine stimulates alpha2 receptors in the central nervous system, thus plays a role in sedation and thus it is widely used as an adjunct to anaesthesia and pain medicine.[6]

MATERIALS AND METHODS :

Objectives: to assess difference between melatonin versus clonidine as oral premedication in craniotomies for supratentorial tumours based on

a) 100 point VAS score postoperatively (pain assessment)
b) systemic rescue analgesic consumption in the postoperative period,
comparison in perioperative state
a) Anxiety And Sedation
b) haemodynamic stability and
c) adverse effects between the two groups.

The study was conducted at Operation theatre (O.T.), Post anaesthesia care unit (PACU), HDU and ITU, Institute of Neurosciences, Kolkata. The study population constituted patients with intact mentation undergoing craniotomies for excision of supratentorial tumours. This is a randomized controlled triple-blinded study.

Inclusion Criteria :

1. Aged 20–60 years
2. Either gender
3. Patients with intact higher mental functions
4. Scheduled for elective craniotomies for supratentorial tumours
5. Patients who had signed informed consent form

***Exclusion Criteria*:**

1. Patients with hypersensitivity to any drug
2. History of congestive heart failure, valvular heart disease
3. History of renal or hepatic disease
4. History of neuropsychiatric disorders
5. Pregnancy
6. Patients on beta blockers, antiplatelet drugs, anticoagulants, extended release formulation of any analgesic or any psychotropic drugs in the present or in the past.
7. Patients not getting extubated immediately after surgery

***Statistical Analysis*:**

The sample size was calculated at clinicalc.com. The 100

point VAS score was considered 55 and 77 respectively for melatonin and clonidine groups with a standard deviation (S.D.) of 25 based on a previous publication[7].The alpha error and power of the study was 5% and 80% respectively. Expecting a drop-out rate of 20%, we recruited 25 patients in each group. Thus the total sample size will be 50 patients. The categorical variables have been presented as % and numerical variables as mean and S.D. The difference between two unpaired groups have been assessed using unpaired t-test/ Mann Whitney U test (whichever was applicable) for numerical data. The categorical data between two groups has been compared using Fisher's exact test.

***Study Variables*:**
mean arterial blood pressure (MAP), heart rate (HR), oxygen saturation (spo2), sedation score (by Ramsay sedation assessment scale), anxiety score (by Amsterdam preoperative anxiety and information scale) and pain (by Visual Analogue Scale).

***Randomization*:**
After getting institutional ethics committee approval and written consent of patients, total 50 patients undergoing craniotomy were included in the study. In this prospective randomized controlled trial study the patients were allocated in two groups using a computer generated random number table. Group A received 5 mg oral melatonin the night before surgery and 1 hour prior to induction of anaesthesia while group B was given 50 mcg oral clonidine the night before surgery and 100 mcg 1 hour prior to induction of anaesthesia.

***Blinding*:**
The blinding was conducted by using SNOSE (Sequentially Numbered Opaque Sealed Envelope) method. The randomization group was written on a paper and kept in an opaque sealed envelope. The envelope was labelled with a serial number. The unblinded anesthesiologist knew which envelope contained which drug (without the drug packaging). The investigator , the nurse who gave the drug to the patient and the patient – all three were blinded and did not know which drug was being administered. The nurse opened the sealed envelope once the patient had consented to participate.

***Ethical Consideration*:**
Ethical permission was sought from the institutional ethical committee before commencing the study.

***Procedure*:**
The study drugs were given to the groups A and B the night before surgery and 1 hour before inducing. Prior to this, the HR, MAP, spo2, sedation score, and anxiety score were noted. After 1 hour of drug administration, the HR, MAP, spo2, sedation score, and anxiety score were noted. ASA standards for basic anaesthetic monitoring were attached to all the patients. Anaesthesia was induced with propofol 2 mg/kg body weight i.v., lidocaine 1.5 mg/kg body weight i.v. and fentanyl @ 2mcg/kg body weight i.v. Immediately after induction, MAP & HR were documented. Endotracheal intubation was facilitated with rocuronium bromide 0.9 mg/kg body weight and patient positioned with all precautionary measures. We documented patient's MAP & HR after induction, during application of pins, during incision, 30 minutes, 60 minutes,120 minutes,180 minutes and 240 minutes after incision (if surgery continued till that time). Anaesthesia was maintained with sevoflurane and 50% air in oxygen. Intravenous paracetamol 15 mg/kg and fentanyl as required were given for analgesia and cisatracurium infusion for muscle relaxation. Upon completion of surgery, the neuromuscular blockade was reversed with neostigmine 0.04μg/kg i.v. and glycopyrolate 0.01mg/kg i.v. Immediately after extubation, MAP, HR, sedation score, anxiety score, and pain score were documented and the patient was shifted to post-anaesthesia care unit. At 6 hours, 12 hours, 24 hours & 48 hours post-extubation MAP, HR, sedation score, and VAS were documented. The patient was given the 1st dose of analgesic (i.v. fentanyl 1mcg/kg) when the VAS score was ≥ 50/100. The time duration of receiving the 1st dose of analgesic since the time of extubation was documented. Incidence of any adverse effect (bradycardia , hypotension, over-sedation, delayed awakening, etcetra) was noted.

Table 1 Depicts The Ramsay Sedation Scale.

If awake	
Ramsay 1	Anxious, agitated, restless
Ramsay 2	Cooperative, oriented, tranquil
Ramsay 3	Responsive to commands only
If Asleep	
Ramsay 4	Brisk response to light glabellar tap or loud auditory stimulus
Ramsay 5	Sluggish response to light glabellar tap or loud auditory stimulus
Ramsay 6	No response to light glabellar tap or loud auditory stimulus

Table 2 Depicts The Amsterdam Preoperative Anxiety And Information Scale(APAIS).

Questions		APAIS 1	APAIS 2	APAIS 3	APAIS 4	APAIS 5
1	I am worried about the anesthetic					
2	The anesthetic is on my mind continually					
3	I would like to know as much as possible about the anesthetic					
4	I am worried about the procedure					
5	The procedure is on my mind continually					
6	I would like to know as much as possible about the procedure					

1: not at all, 2: somewhat, 3: moderate, 4: moderately high, 5: extremely

Ethics committee approval was received from the institutional ethics committee of Institute of Neurosciences Kolkata.

RESULTS:
In this study, the group which received clonidine is the control group and the other which received melatonin is the test group. Gender distribution was comparable among the study groups. p value is 0.56. Mean age in melatonin and clonidine group was 48.8 ± 9.40 and 51.12 ± 8.5 years respectively. p value is 0.37. Mean weight (kg) in melatonin and clonidine group was 66.84 ± 6.87 and 63.32 ± 8.18 kg respectively, p value being 0.10. Hypertension was reported among 60% and 48% of the subjects in melatonin and clonidine groups respectively, p value being 0.39.

Table 3 Shows The Anxiety Score Before And One Hour After Giving The Study Drug.

Group	Anxiety Score					
	Before		After 1 Hr of Drug		Mean Difference	SD
	Mean	SD	Mean	SD		
Drug A	10.12	3.87	7.40	2.16	2.72	0.96
Drug B	10.12	3.38	8.76	3.09	1.36	0.89
t test					3.41	
p value					0.027*	

Anxiety score before giving the drugs was same in the two groups. After 1 hour of giving the drug, it was found to be

decreased more in melatonin group as compared to clonidine group with statistically significant difference as p value is 0.027 ($p<0.05$).

Sedation score was found to be 2 (Ramsay sedation scale) in both the groups.

MAP was found to be comparable among both the groups at all the time points as $p>0.05$.

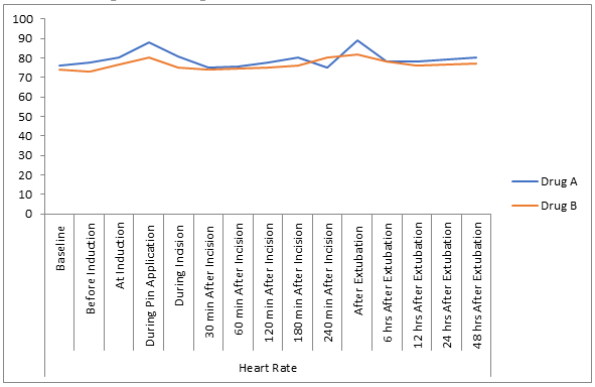

Figure 1 : Comparison Of Heart Rate At Different Intervals Among The Study Groups

Drug A : melatonin
Drug B : clonidine
Mean heart rate was found to be comparable among both the groups at all the intervals as $p>0.05$ except during pin application and after extubation where mean heart rate was lower in clonidine group, and 4 hours after incision where it was lower in melatonin group.

Table 4 Compares VAS At Different Intervals Among The Study Groups.

VAS	Drug A		Drug B		T Test	p value
	Mean	SD	Mean	SD		
After Extubation	9.60	13.06	9.20	10.38	0.01	0.91
6 hrs After Extubation	12	9.57	24.80	11.59	18.12	<0.01*
12 hrs After Extubation	6.80	8.02	21.60	14.34	20.28	<0.01*
24 hrs After Extubation	1.20	3.32	12.80	16.71	11.59	0.001*
48 hrs After Extubation	0	0	7.20	10.61	11.50	0.001*

Mean VAS score after extubation in melatonin and clonidine group was 9.6 and 9.2 respectively. After 6 hrs of extubation, VAS score increased to 12 and 24.80 in melatonin and clonidine group respectively. After 12, 24 and 48 hrs of extubation, VAS score decreased more in melatonin group as compared to clonidine group. When VAS score was compared after 6, 12, 24 and 48 hrs of extubation using t test, statistically significant difference was found.

There was reduction in fentanyl consumption perioperatively in both the groups, melatonin group did not require postoperative fentanyl.

DISCUSSION :

Melatonin produces significant anxiolysis and thus useful in anxious patients who will be undergoing surgeries.[5] Melatonin reduces anxiety and fatigue, while improving self-perceived vitality and mental function.[8] Melatonin has hypnotic and anaesthetic sparing properties also.[9] Premedication orally with 0.2 mg/kg melatonin dramatically lowers the amount of propofol needed for induction.[10] During anaesthesia for craniotomies, cardiovascular stability is therefore important in preventing rise in ICP and reduction in cerebral perfusion pressure (CPP).[11] Clonidine acts predominantly by a reduction in centrally mediated sympathetic activity due to its effect on the lateral reticular nucleus.[12] It has been demonstrated that taking clonidine orally at a dose of 3 mcg/kg an hour before inducing anaesthesia is safe.[13] Clonidine has been investigated in a number of studies and has been found to reduce hypertensive reactions to intubation and the use of pin head holders.[11,14]

In this study, we have compared the effects of melatonin with clonidine on preoperative anxiety, perioperative pain, sedation and haemodynamics.

In our study, the anxiety score (mean value) before giving the morning dose of drug was 10.12 in both the groups. But after one hour of administering the morning dose of drug, the mean anxiety score decreased to 7.40 in the melatonin receiving group and 8.76 in the clonidine receiving group. There has been a statistically significant difference between the two. Farhanah Y et al. performed a qualitative systematic review of the literature and found that there was significant reduction in preoperative anxiety with oral melatonin given as premedication in nine out of ten studies.[5] Ionescu et al.'s study revealed that melatonin had superior perioperative anxiolysis and a better recovery profile as evaluated by sedation and memory.[15] In a research by Naguib M, compared to control participants, patients who were administered midazolam or melatonin prior to surgery showed a substantial decrease in anxiety and an increase in sedation. Melatonin premedication did not impair cognitive or psychomotor abilities or have an impact on the degree of recovery.[16] In a study conducted by M Acil, those who received melatonin had less anxiety and more sedation before surgery compared to placebo.[17] Thus oral melatonin as a premedication before craniotomy is effective in reducing anxiety scores more than clonidine.

MAP was comparable in both the groups. The blood pressure decreased from the baseline blood pressure and there was no rise in BP during various stimuli for craniotomy except during pin head-holder application where the BP rose in both the groups.

Mean heart rate stayed more controlled and stable in the group which received clonidine during various sympathetic stimuli.

Roger Traill premedicated patients undergoing elective craniotomies with 4 mcg/kg oral clonidine 90 minutes before induction of anaesthesia.[11] It curtailed any rise in SBP after intubation, though it did not reduce the requirement of isoflurane intraoperatively.[11] Postextubation MAP was also reduced , thus it was concluded that clonidine might be useful in suppressing any sympathetic surge after induction of anaesthesia.[11] Similarly, Tim G. Costello [18] and R. Chadha [14] found that premedication with clonidine reduced hypertensive reactions on applying a pin head-holder or during intubation. M. M. Rifat Chowdhury conducted a study in which patients scheduled to undergo craniotomies for supratentorial lesions were premedicated with oral clonidine 3 mcg/kg 90 minutes before induction of anaesthesia. Clonidine reduced any sympathetic surge and prevented dural swelling intraoperatively.[19]

VAS decreased more in the melatonin receiving group implying melatonin to be playing an important role in providing analgesia in the intraoperative and postoperative period.

In a research by Farshad H. Kiabi[20], patients who got 10 mg of melatonin as a premedication experienced significantly reduced mean pain intensity following surgery than patients

who received 5 mg of melatonin plus a placebo. With 10 mg of melatonin, the mean dosage of opioid needed was at its lowest. Five studies evaluated scores related to postoperative pain. In the two studies that Naguib et al. carried out, there was no discernible change in the melatonin group's pain scores at 15, 30, 60, and 90 minutes after surgery.[16,21]Moreover, Acil et al. found no discernible variation in pain ratings between the melatonin and placebo groups for the duration of their stay in the postanaesthesia care unit.[17] On the other hand, melatonin-treated patients' pain scores decreased statistically significantly after 6, 12, 18, 24, 36, and 48 hours after surgery, according to two studies by Caumo et al.[7,22] It is significant to remember that in the two studies by Naguib et al. and the one by Acil et al. that shown melatonin's lack of analgesic effects, melatonin was given as a single dose. However, melatonin was administered using a dual-dosing strategy in the two studies by Caumo et al. where its analgesic effects were clearly shown. In two studies by Caumo and colleagues, the analgesic use was lower in the melatonin group compared with placebo at 6, 12, 18, 24, 42, 48, and 54 hours postoperatively.[7,22]

The sedation score was comparable in both the groups and the patients were cooperative, oriented and tranquil postextubation.

In the study conducted by Caumo W et al[11], anxiety levels significantly decreased in the melatonin and clonidine groups at 6, 24, and 48 hours; melatonin patients also scored lower on postoperative pain questionnaires; and both melatonin and clonidine patients consumed less morphine after surgery.

In this study, 3 patients who received clonidine required postoperative fentanyl as rescue analgesic after 12, 24 , and 48 hours of surgery.

Three patients who received clonidine had intraoperative hypotension. There was no other adverse effect in any other patient. In the study conducted by Kiabi FH [20], few patients who received melatonin had headache, nausea and vomiting. In the clinical report by Traill R[11], the patients had perioperative hypotension due to clonidine premedication. In the study by Caumo W et al[7], some of the patients who received clonidine had decreased heart rate perioperatively.

Both the groups had decreased requirement of inhalational agents for maintenance of anaesthesia.

It can be concluded that oral melatonin decreases perioperative pain, requirement of fentanyl and anaesthetic agents more effectively as a premedication in craniotomies for supratentorial tumours as compared to oral clonidine.

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