Original Article

Efficacy of Perioperative Low dose Oral Gabapentin with Melatonin on Postoperative Delirium and Cognition Status of the Patients Undergoing Non-Cardiac Surgery

Ankur Upadhyay, Jyoti Pathania, Arti Sharma, Arvind Sethi

Department of Anaesthesia, Indra Gandhi Medical College, Shimla, Himachal Pradesh, India.

ABSTRACT

Introduction: Various pharmacological and non-pharmacological strategies are advocated, without definitive results, to ameliorate stress induced post-operative cognitive disorder (POCD).

Objective: To target the disturbed sleep component of patients perioperatively with melatonin and gabapentin combination.

Methods: This prospective, double blind, randomized study was done on 130 patients of >50 years age, of either sex undergoing routine surgery under entropy guided general anesthesia. Melatonin 3mg and gabapentin 300mg orally was used in the perioperative periodin group 1 and placebo drugs in group 2 patients. Confusion assessment method (CAM score), mini mental state examination (MMSE) and Stanford sleepiness scale was used to assess the POCD of patients.

Results: Incidence of delirium was 0% in group 1 and 27.69% in group 2 (p<0.0001). Low baseline cognition status represented by <25 MMSE score was seen in [89.23% (58 patients) of group, 92.3% (60 patients) of group 2] and was 96% (63 patients) in both the groups at time of discharge. The cognition decline (moderate and severe) was significantly higher in group 2 at all times (p≤0.003). The subjective sleep quality of group 1 patients was significantly better over control group (p<0.0001). Educational status, serum electrolytes, perioperative hemoglobin and serum sugar were not factors for its occurrence (p>0.05).

Conclusion: Low dose melatonin with gabapentin significantly decreased the incidence of delirium, the severity of ognition status decline and improved the sleep quality of patients in the perioperative period.

Key Words: Cognition, Dementia, General Surgery, Sleep.

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Corresponding Author: Jyoti Pathania, MD, Department of Anesthesia Indra Gandhi Medical College, Shimla, Himachal Pradesh, India, **Tel.:** +91-9418120659, **E-mail:** pathaniajyoti7@gmail.com

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INTRODUCTION

Neurological disturbances with impaired cognitive performance like POCD, delirium and dementia manifesting usually as hallucinations, fluctuating state of consciousness, and impaired memory are commonly observed in the immediate and late postoperative period[1].

The etiology of these neurological manifestations is largely not defined but some risk factors like increased age, major joint replacements or cardiovascular surgery, low education status, premorbid conditions with hypoxemia, hypotension, inadequate depth of anesthesia and analgesia, electrolyte derangements, hypo or hyper glycemia and increased blood loss in surgery are commonly implicated in its development[2-6]. The disturbed circadian sleep rhythm and anxiety are also known to modify its occurrence in patients[7,8]. The study was planned to target the disturbed sleep component of patients perioperatively with melatonin and gabapentin combination, as various studies have stressed upon the varying degree of efficacy of these drugs when used in such scenario[9,10].

METHODS

After approval from the institutional ethics committee (Indra Gandhi Medical college) a prospective randomized controlled double-blind study conforming with consort 2010 statement and the principles of the Declaration of Helsinki, (2013) was conducted at (Indra Gandhi Medical college) from february 2022 to Dec. 2022. The study was registered with the national trial registry. (CTRI No: :http://ctri.icmr.org.in 2022/02/039963) The study protocol were explained and patients' written informed consent was taken to be part of the study and to use the data thus obtained for research and publication.

The study was conducted on 130, ASA I-II patients, aged 50 years and above of either sex, undergoing elective

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non-cardiac surgery under general anesthesia where enteral feeding could be started in <12hrs in the postoperative period.

Patients in which gastric surgery was done and patients who were to be kept nil orally for >12hrs. ASA grade III and IV, patients with history of schizophrenia, epilepsy or parkinsonism disease, obstructed sleep apnea, those having Visual, hearing, language or other barriers which could hampers communication or preoperative delirium assessment, neurosurgery or traumatic brain injury patients or those with severe hepatic dysfunction, renal failure and patients whose baseline CAM score was ≥3 were excluded from the study.

Sample size was calculated through openepi software. by taking confidence level at 95%, power of study as 80%. Campbell A. *et al.,* used oral melatonin and reported 10% delirium as outcome in intervention group and 32% in the control group, that is 22% difference in percentage, Accordingly the final sample size was 104 patients. Since we expected some loss of cases in both the groups thus 130 patients were included in the study with 65 patients in each group[9].

The guide, patient, surgeon and observer were blind to the drugs used and the co-guide did the randomization of patients by computer generated software, maintained the record and ensured the dispensing of the drugs to the patients. All the records of coded drugs used were opened at the end of study and appropriate statistical test were applied.

Group 1 patients received tab gabapentin 300mg (tab Gaba neuron) and tab melatonin 3mg (tab Melo set) at bed time preoperatively and for 5 days in the postoperative period.

Group 2 patients received tab B- complex and tab alprazolam 0.5mg at bed time for these times.

All patients underwent a routine pre-anesthetic checkup, one day prior to surgery. Study protocol was explained to all the patients during pre-anesthetic evaluation and they were familiarized with the scale and baseline readings were recorded. If CAM (Confusion assessment method) was positive (≥3) then those patients were excluded from the study. The observer examined the patient preoperatively one day before surgery and followed up the patients subsequently till day of discharge post operatively to assess the CAM and MMSE score and sleep quality of the patients by Stanford sleepiness scale[7,11,12]. The patients were instructed for a minimum fasting period of 6hrs. preoperatively. In the operation theatre, after obtaining baseline vital data (ECG, heart rate, blood pressure, SpO2), 18G intravenous cannula was secured and intravenous fluid of either normal saline or ringer lactate was started. According to the disease and anesthetic choice epidural anesthesia if required was allowed in conjunction with general anesthesia and was activated intraoperatively and noted. Entropy electrodes (GE entropy disposable sensors which were PVC and latex free, were applied on the forehead of the patient in the glabella, temporal line and baseline values were recorded by Carescape GE monitor B650.

General anesthesia was given as per the institutional protocol with fentanyl 2µg/kg, propofol 2mg/kg and atracurium 0.5mg/kg and maintained with 1% isoflurane with 33% oxygen and 66% nitrous oxide. The intraoperative parameters like HR, MAP and SPO2 were noted every 15 minutes by the observer. The mean arterial pressure was maintained within 20% from baseline or MAP >65mmhg with fluids, blood or blood products or vasopressors as required and was noted. The depth of anesthesia was maintained by entropy and the values were kept between 40-60 by varying the volatile anesthetic concentration or by using paracetamol, fentanyl or activating the epidural dose if present. Prior to extubation residual neuromuscular blockade was reversed with intravenous neostigmine 0.05mg/kg and glycopyrrolate 0.01mg/kg. Random blood sugar level was taken with available glucometer at extubation.

When the patient was shifted to the respective ward MMSE and CAM scoring were done at 6hrs. post operatively. If oral sips were allowed the necessary instructions was given to give the drugs with a sip of water to the patient or the same was given through the ryles tube. If by any chance the study drugs could not be given till 12hrs. postoperatively then such patients were excluded from the study.

Delirium diagnosis and severity assessment was done in pre and postoperative period by CAM scoring and MMSE score at 6hrs. postoperative period and on subsequent days (1-5 days) and on the day of discharge. Day time alertness and the subjective sleep quality of the patients was inquired from the patient, attendants or nurse as per the Stanford sleepiness scale at 9am and 9pm daily and the mean value was taken.

The data was entered in Microsoft Excel spreadsheet and analysis was done using SPSS software, IBM manufacturer, Chicago Ver 25. Normality was checked by Kolmogorov-Smirnov test. The presentation of categorical variable was in percentage and of quantitative data was in mean±Sd (median, quartile range). Mann-Whitney test was used for quantitative data not normally distributed and student *t* test was used for normally distributed data. Chi-square and Fischer test were used for qualitative data as applicable.

RESULTS

We assessed 150 patients for the study but 10 patients were excluded at the preoperative examination as their CAM score was >3. five patients were excluded later in each group as they were not allowed orally for 12hrs. in the postoperative period or they were shifted to ICU and hence not extubated. Thus 130 patients were analyzed in both the groups at the end of study. we included patients undergoing nephrectomy, ureter lithotomy, urethroplasty ,mastectomy, open gall bladder surgery and hydatid cyst liver in our study.

The mean age of patients was 61.79±8.12 years. There were 65% females and 35% males included in the study. The mean weight in kg of the patients was 71.92±14.37 and they were comparable in ASA physical status distribution. The mean duration of surgery was 2.19±0.51 hrs. (p>0.05) (Table 1).

At majority of times, statistically insignificant results for serum electrolytes (Na,K,Cl), hemoglobin, intraoperative blood transfusion used and postoperative blood sugar were seen in patients during postoperative period. (p>0.05) (Table 2). The patients in group 1 were CAM negative (score <3) at all times in the postoperative period till discharge. In group 2, 18(28%) patients were CAM positive (score ≥3) on postoperative period and the incidence of delirium decreased over the days till discharge (p<0.0001) (Table 3).

Cognition status of patients as assessed by serial MMSE score estimations showed that 12(9.23%) patients had normal ≥25 score at baseline. rest 113(87%) patients had mild cognition decline and 5(4%) patients were having moderate dementia. Over the days this decline continued and baseline values were not obtained in either of the groups till discharge though the severity of this decline (MMSE score ≤20) was significantly more in group 2 (p<0.0001) (Table 4).

We did not find any significant correlation between the <25 MMSE score and CAM ≥3 measurements, except on the first postoperative day when out of three positive patients in group 2, two patients were having MMSE score <25 (p= 0.02) (Table 5).

The quality of sleep as assessed by Stanford sleepiness scale was significantly good (score 1-2) at all recorded times in group 1 over group 2 (p≤0.033) (Table 6).

None of our patient had any side effect like respiratory depression or drowsiness in the postoperative period.

Table 1: Demographic parameters:

Age (years)	Group 1 (n= 65)	Group 2 (n= 65)	Total	P value
50-60	33(50.77%)	26(40%)	59(45.38%)	
61-70	21(32.31%)	29(44.62%)	50(38.46%)	0.241*
71-80	9(13.85%)	10(15.38%)	19(14.62%)	
81-90	2(3.08%)	0(0%)	2(1.54%)	
Mean±SD	61.26±8.51	62.32±7.75	61.79±8.12	
Median (25^{th}-75^{th} percentile)	60(55-65)	63(56-68)	62(55-67)	0.458‡
Range	50-84	50-80	50-84	
Gender (Females)	44(67.69%)	41(63.08%)	85(65.38%)	0.58†
Males	21(32.31%)	24(36.92%)	45(34.62%)	
ASA grade I	32(49.23%)	31(47.69%)	63(48.46%)	0.861†
ASA grade II	33(50.77%)	34(52.31%)	67(51.54%)	
Weight(kg) mean±SD	72.03±14.19	71.82±14.66	71.92±14.37	0.932‡
Duration of surgery(hours) mean±SD	2.24±0.45	2.14±0.57	2.19±0.51	0.252‡

‡: Independent t test; *: Fisher's exact test; †: Chi square test.

Table 2: Measurements of other known risk factors of delirium in the patients:

	Group 1 (*n*= 65)	**Group 2 (*n*= 65)**	**Total**	***P* value**
Serum electrolytes(mEq/L)	Mean±SD Median (25th-75th percentile)			
Day 1. Serum sodium	137.51±5.37[138(135-142)]	137.31±5.34[136(134-142)]	137.41±5.33[138(134-142)]	0.832‡
Day 3 Serum sodium	135.6±4.16[135(132-138)]	134.85±5.4[135(131-138)]	135.22±4.82[135(132-138)]	0.374‡
Day 1 Serum potassium	4.24±0.52[4.2(4-4.5)]	4.01±0.7[4(3.6-4.4)]	4.12±0.62[4(3.8-4.5)]	0.039‡
Day 3 Serum potassium.	4.17±0.54[2(3.8-4.5)]	4.02±0.68[4(3.7-4.6)]	4.09±0.6[4.1(3.725-4.5)]	0.172‡
Day 1Serum Chloride	97.68±3.13[98(96-99)]	97.09±3.08[97(96-98)]	97.38±3.11[98(96-99)]	0.285‡
Day 3 Serum Chloride	97.88±3.11[98(96-99)]	96.06±2.88[97(95-98)]	96.97±3.12[97(95.25-98)]	0.0007‡
Hemoglobin(g/dL)				
preoperative	12.17±1.33	12.12±1.61	12.15±1.47	0.845‡
On day 1	11.43±1.08	11.53±1.33	11.48±1.21	0.655‡
On day 3	11.6±1.24	11.36±1.24	11.48±1.24	0.284‡
Education				
5th class	18(27.69%)	18(27.69%)	36(27.69%)	0.996†
8th class	15(23.08%)	16(24.62%)	31(23.85%)	
10th class	14(21.54%)	14(21.54%)	28(21.54%)	
12th class	18(27.69%)	17(26.15%)	35(26.92%)	
Intra-operative blood transfusion (mean±SD)	32(49.23%)	34(52.31%)	66(50.77%)	0.726†
Post-operative blood sugar (mg/dL)mean±SD	102.83±15.64	104.25±19.51	103.54±17.63	0.649‡

‡: Independent *t* test; †: Chi square test 2.

Table 3: Comparison of CAM scoring between group 1 and 2:

CAM scoring	**Group 1 (*n*= 65)**	**Group 2 (*n*= 65)**	**Total**	***P* value**
Pre-operative baseline				
Normal{0-2}	65(100%)	65(100%)	130(100%)	NA
Mean±SD	1.18±0.39	1.2±0.4	1.19±0.4	
Median (25th-75th percentile)	1(1-1)	1(1-1)	1(1-1)	0.825§
Range	1-2	1-2	1-2	
Post-operative 6 hours				
Normal{0-2}	65(100%)	47(72.31%)	112(86.15%)	<.0001*
Moderate delirium{3-5}	0(0%)	18(27.69%)	18(13.85%)	
Mean±SD	1.35±0.51	2.28±0.45	1.82±0.67	
Median (25th-75th percentile)	1(1-2)	2(2-3)	2(1-2)	<.0001§
Range	0-2	2-3	0-3	
Post-operative 1 day				
Normal{0-2}	65(100%)	62(95.38%)	127(97.69%)	0.244*
Moderate delirium{3-5}	0(0%)	3(4.62%)	3(2.31%)	
Mean±SD	0.83±0.55	1.92±0.41	1.38±0.73	
Median (25th-75th percentile)	1(1-1)	2(2-2)	1(1-2)	<.0001§
Range	0-2	1-3	0-3	
Post-operative 2 days				
Normal{0-2}	65(100%)	62(95.38%)	127(97.69%)	0.244*
Moderate delirium{3-5}	0(0%)	3(4.62%)	3(2.31%)	
Mean±SD	0.52±0.5	1.62±0.58	1.07±0.77	
Median (25th-75th percentile)	1(0-1)	2(1-2)	1(1-2)	<.0001§
Range	0-1	1-3	0-3	
Post-operative 3 days				
Normal{0-2}	65(100%)	64(98.46%)	129(99.23%)	1*
Moderate delirium{3-5}	0(0%)	1(1.54%)	1(0.77%)	

CAM scoring	Group 1 (*n*= 65)	Group 2 (*n*= 65)	Total	*P* value
Mean±SD	0.22±0.41	1.31±0.56	0.76±0.73	
Median (25^{th}-75^{th} percentile)	0(0-0)	1(1-2)	1(0-1)	<.0001§
Range	0-1	0-3	0-3	
Post-operative 4 days				
Normal{0-2}	65(100%)	64(98.46%)	129(99.23%)	1*
Moderate delirium{3-5}	0(0%)	1(1.54%)	1(0.77%)	
Mean±SD	0.08±0.27	1.25±0.59	0.66±0.74	
Median (25^{th}-75^{th} percentile)	0(0-0)	1(1-2)	1(0-1)	<.0001§
Range	0-1	0-3	0-3	
Post-operative 5 days				
Normal{0-2}	65(100%)	65(100%)	130(100%)	NA
Mean±SD	0±0	0.88±0.67	0.44±0.65	
Median (25^{th}-75^{th} percentile)	0(0-0)	1(0-1)	0(0-1)	<.0001§
Range	0-0	0-2	0-2	
Day of discharge				
Normal{0-2}	65(100%)	65(100%)	130(100%)	NA
Mean±SD	0±0	0.6±0.61	0.3±0.52	
Median (25^{th}-75^{th} percentile)	0(0-0)	1(0-1)	0(0-1)	<.0001§
Range	0-0	0-2	0-2	

§: Mann Whitney test; *: Fisher's exact test.

Table 4: Comparison of MMSE between group 1 and 2:

MMSE	Group 1 (*n*= 65)	Group 2 (*n*= 65)	Total	*P* value
Pre-operative baseline				
>=25{Normal}	7(10.77%)	5(7.69%)	12(9.23%)	0.06*
21 to 24 {Mild Dementia (Cognitive impairment)}	53(81.54%)	60(92.31%)	113(86.92%)	
10 to 20 {Moderate Dementia (Cognitive impairment)}	5(7.69%)	0(0%)	5(3.85%)	
Mean±SD	23.15±1.51	22.86±1.26	23.01±1.39	
Median (25^{th}-75^{th} percentile)	24(22-24)	23(22-24)	23(22-24)	0.234‡
Range	20-26	21-26	20-26	
Post-operative 6 hours				
>=25{Normal}	1(1.54%)	0(0%)	1(0.77%)	
21 to 24 {Mild Dementia (Cognitive impairment)}	37(56.92%)	22(33.85%)	59(45.38%)	0.008*
10 to 20 {Moderate Dementia (Cognitive impairment)}	27(41.54%)	43(66.15%)	70(53.85%)	
Mean±SD	20.97±1.52	20.45±1.58	20.71±1.57	
Median (25^{th}-75^{th} percentile)	22(20-22)	20(20-22)	20(20-22)	0.057‡
Range	18-25	18-24	18-25	
Post-operative 1 day				
>=25{Normal}	0(0%)	1(1.54%)	1(0.77%)	
21 to 24 {Mild Dementia (Cognitive impairment)}	41(63.08%)	24(36.92%)	65(50%)	0.005*
10 to 20 {Moderate Dementia (Cognitive impairment)}	24(36.92%)	40(61.54%)	64(49.23%)	
Mean±SD	21.62±1.98	20.29±1.9	20.95±2.05	
Median (25^{th}-75^{th} percentile)	22(20-24)	20(18-22)	21.5(20-22)	0.0002‡
Range	18-24	18-25	18-25	
Post-operative 2 days				
21 to 24 {Mild Dementia (Cognitive impairment)}	54(83.08%)	28(43.08%)	82(63.08%)	<.0001†
10 to 20 {Moderate Dementia (Cognitive impairment)}	11(16.92%)	37(56.92%)	48(36.92%)	

MMSE	Group 1 (*n*= 65)	Group 2 (*n*= 65)	Total	*P* value
Mean±SD	22.37±1.64	20.37±1.76	21.37±1.97	
Median (25th-75th percentile)	22(22-24)	20(18-22)	22(20-22)	<.0001‡
Range	18-24	18-24	18-24	
Post-operative 3 days				
>=25{Normal}	0(0%)	1(1.54%)	1(0.77%)	
21 to 24 {Mild Dementia (Cognitive impairment)}	58(89.23%)	29(44.62%)	87(66.92%)	<.0001*
10 to 20 {Moderate Dementia (Cognitive impairment)}	7(10.77%)	35(53.85%)	42(32.31%)	
Mean±SD	22.82±1.43	20.97±1.58	21.89±1.77	
Median (25th-75th percentile)	24(22-24)	20(20-22)	22(20-24)	<.0001‡
Range	19-24	18-25	18-25	
Post-operative 4 days				
>=25{Normal}	0 (0%)	2 (3.08%)	2 (1.54%)	
21 to 24 {Mild Dementia(Cognitive impairment)}	61 (93.85%)	40 (61.54%)	101 (77.69%)	<.0001*
10 to 20 {Moderate Dementia(Cognitive impairment)}	4 (6.15%)	23 (35.38%)	27 (20.77%)	
Mean ± SD	23.18 ± 1.24	21.22 ± 1.75	22.2 ± 1.81	
Median(25th-75th percentile)	24(22-24)	22(20-22)	22(22-24)	<.0001‡
Range	20-24	18-26	18-26	
Post-operative 5 days				
>=25{Normal}	3 (4.62%)	1 (1.54%)	4 (3.08%)	
21 to 24 {Mild Dementia(Cognitive impairment)}	61 (93.85%)	47 (72.31%)	108 (83.08%)	<.0001*
10 to 20 {Moderate Dementia(Cognitive impairment)}	1 (1.54%)	17 (26.15%)	18 (13.85%)	
Mean ± SD	23.52 ± 1	21.62 ± 1.32	22.57 ± 1.51	
Median(25th-75th percentile)	24(24-24)	22(20-22)	22(22-24)	<.0001‡
Range	20-25	18-25	18-25	
Day of discharge				
>=25{Normal}	2 (3.08%)	2 (3.08%)	4 (3.08%)	
21 to 24 {Mild Dementia(Cognitive impairment)}	63 (96.92%)	54 (83.08%)	117 (90%)	0.003*
10 to 20 {Moderate Dementia(Cognitive impairment)}	0 (0%)	9 (13.85%)	9 (6.92%)	
Mean ± SD	23.6 ± 0.86	21.94 ± 1.16	22.77 ± 1.32	
Median(25th-75th percentile)	24(24-24)	22(22-22)	22(22-24)	<.0001‡
Range	22-25	18-25	18-25	

‡: Independent *t* test; *: Fisher's exact test: †: Chi square test.

Table 5: Relation Between CAM Score and MMSE score:

		Group 1		Group 2		Total		* *P* value
MMSE score		**<25**	**≥25**	**<25**	**≥25**	**<25**	**≥25**	
Baseline	CAM<3	58	7	60	5	118	12	0.763
Postoperative 6 hrs.	CAM ≥3	0	0	18	0	18	0	1
	CAM<3	64	1	47	0	111	1	
1 day	CAM ≥3	0	0	2	1	2	1	0.0231
	CAM<3	65	0	62	0	127	0	
2 Day	CAM ≥3	0	0	3	0	3	0	1
	CAM<3	65	0	62	0	127	0	
3Day	CAM ≥3	0	0	1	0	1	0	1
	CAM<3	65	0	63	1	128	1	
4Day	CAM3	0	0	1	0	1	0	1
	CAM<3	65	0	62	2	127	2	
5 Day	CAM<3	62	3	64	1	126	4	1
Discharge	CAM<3	63	2	63	2	126	4	1

*: Fisher's exact test.

Table 6: Comparison of Stanford sleepiness scale between group 1 and 2:

Stanford sleepiness scale	Group 1 (*n*= 65)	Group 2 (*n*= 65)	Total	*P* value
Post-operative 6 hours				
Good sleep{1-2}	60(92.31%)	29(44.62%)	89(68.46%)	<.0001†
Poor sleep{>2}	5(7.69%)	36(55.38%)	41(31.54%)	
Mean±SD	1.8±0.56	2.55±0.5	2.18±0.65	
Median (25^{th}-75^{th} percentile)	2(1-2)	3(2-3)	2(2-3)	<.0001‡
Range	1-3	2-3	1-3	
Post-operative 1 day				
Good sleep{1-2}	65(100%)	52(80%)	117(90%)	0.0001*
Poor sleep{>2}	0(0%)	13(20%)	13(10%)	
Mean±SD	1.15±0.36	2±0.64	1.58±0.67	
Median (25^{th}-75^{th} percentile)	1(1-1)	2(2-2)	1(1-2)	<.0001‡
Range	1-2	1-3	1-3	
Post-operative 2 days				
Good sleep{1-2}	65(100%)	60(92.31%)	125(96.15%)	0.058*
Poor sleep{>2}	0(0%)	5(7.69%)	5(3.85%)	
Mean±SD	1.05±0.21	1.78±0.57	1.42±0.57	
Median (25^{th}-75^{th} percentile)	1(1-1)	2(1-2)	1(1-2)	<.0001‡
Range	1-2	1-3	1-3	
Post-operative 3 days				
Good sleep{1-2}	65(100%)	59(90.77%)	124(95.38%)	0.028*
Poor sleep{>2}	0(0%)	6(9.23%)	6(4.62%)	
Mean±SD	1±0	1.6±0.66	1.3±0.55	
Median (25^{th}-75^{th} percentile)	1(1-1)	2(1-2)	1(1-1.75)	<.0001‡
Range	1-1	1-3	1-3	
Post-operative 4 days				
Good sleep{1-2}	65(100%)	64(98.46%)	129(99.23%)	1*
Poor sleep{>2}	0(0%)	1(1.54%)	1(0.77%)	
Mean±SD	1±0	1.32±0.5	1.16±0.39	
Median (25^{th}-75^{th} percentile)	1(1-1)	1(1-2)	1(1-1)	<.0001‡
Range	1-1	1-3	1-3	
Post-operative 5 days				
Good sleep{1-2}	65(100%)	63(96.92%)	128(98.46%)	0.496*
Poor sleep{>2}	0(0%)	2(3.08%)	2(1.54%)	
Mean±SD	1±0	1.22±0.48	1.11±0.36	
Median (25^{th}-75^{th} percentile)	1(1-1)	1(1-1)	1(1-1)	0.0006‡
Range	1-1	1-3	1-3	
Day of discharge				
Good sleep{1-2}	65(100%)	64(98.46%)	129(99.23%)	1*
Poor sleep{>2}	0(0%)	1(1.54%)	1(0.77%)	
Mean±SD	1±0	1.09±0.34	1.05±0.24	
Median (25^{th}-75^{th} percentile)	1(1-1)	1(1-1)	1(1-1)	0.033‡
Range	1-1	1-3	1-3	

‡: Independent *t* test; *: Fisher's exact test; †: Chi square test.

DISCUSSION

Perioperative nausea and vomiting in nearly 66% of woAmerican society for enhanced recovery and perioperative quality initiative joint consensus statement on post-operative deliriumhave identified sleep disturbance, pain, inadequate depth of anesthesia, hypotension, blood transfusion, anemia and mechanical ventilation as some of the modifiable factors associated with delirium and have strongly recommended multicomponent interventions for the prevention of delirium[1]. Radtke FM. Huang, and Chan MT. *et al.,*[5,6] have labelled inadequate depth of anesthesia

as a risk factor for POD, so the depth of anesthesia was controlled using entropy guided anesthesia in our patients.

Sadaf Farasat *et al.,*[7] concluded in their study that sleep deprivation and delirium are closely linked. Jacqueline M. *et al.,*[8] observed that sleep disruption was more severe before surgery in the patients who experienced postoperative delirium. The incidence of POD has also been linked to postoperative stress in a study by Deiner S. *et al.,*[13], where they found significantly increased noradrenaline levels in patients who develop POD and Pak Victoria *et al.,*[14] have also stressed upon the association of sleep disturbances and brain and cognition integrity. Qingyu Zhang *et al.,*[15] in clinical practice guidelines about preventing and managing pain, agitation, and delirium in adult patients in the ICU recommended optimized environment, decreased stimuli, and low level of noise in ICU and have reported the beneficial effect of exogenous administration of melatonin and melatonin receptor agonists for improving sleep and delirium in subjects in intensive care units.

No drug alone or in combination is known to abolish its incidence completely. Some of the studies have used gabapentin in single 900-1200mg preoperative dose for control of anxiety but recently FDA has issued warnings about the use of gabapentin in patients as serious respiratory depression occurred in few patients[16-18]. In literature the dose of melatonin used for control of delirium is also variable ranging from 3mg to 50mg[9,10]. We used melatonin 3mg and 300mg Gabapentin once daily at bed time in our patients Since both these drugs are used for sleep regulation hence we used them at lower dose and used Stanford sleepiness score to assess quality of sleep of the patients.

The incidence of delirium was 0% in group 1 and was 27.69% in group 2 in immediate postoperative period which thereby decreased from 2.31% to 0.7% over next 2 days. Thus the severity of CAM decreased over the days in our study in both interventional and control group.

Our results were in accordance with the results observed Heymann *et al.,* and De johnge *et al.,* who too observed similar incidence of delirium ranging from 20-30% in the postoperative period[3,19].

When we searched the literature for studies where melatonin and gabapentin was used alone or in combination to control delirium we obtained varying results due to different subset of patients and tolls taken for measuring the delirium. Similar to our study Nishikimi M. *et al.,* and Nickkholgh *et al.,*[20,21] have observed low to 0% incidence of delirium with melatonin or melatoninergic drugs use. Artemiou *et al.,* reported 8.4% incidence of delirium after 5mg melatonin in patients undergoing cardiac surgery[22]. Leung *et al.,* in his 2006 study observed 0% incidence with the use of 900mg gabapentin and Dighe *et al.,* reported 9-12% incidence after 600mg gabapentin use[16,17]. Javaher *et al.,*[23] used 6mg melatonin or 600mg gabapentin and found better results with gabapentin use. where as Khezri *et al.,*[24] used both the drugs in combination in patient undergoing cataract surgery under retrobulbar block and obtained good control of anxiety in patients. In contrast Wang *et al.,* in a metanalysis of 15 studies found inconclusive evidence on delirium control by use of melatonin. They did not find any improvement in sleep quality and thereby no decrease in delirium incidence in their patients[25].

Zhang Y. *et al.,*[26] reported beneficial effect of dexmedetomidine whereas Yong Liu *et al.,*[27] in their metanalysis concluded that there are no drugs that show an ability to prevent postoperative delirium. Dexmedetomidine and two atypical antipsychotic drugs (olanzapine and risperidone) showed some prophylactic effect but there was not enough evidence to support the use of atypical antipsychotics for preventing delirium. Thus, the crux of the management of delirium lies on use of both pharmacological and non-pharmacological interventions based on individual patients need. Since sleep augmentation and control of anxiety are the basic requirement in such scenario hence the use of melatonin and gabapentin to improve the sleep cycle is warranted.

Some amount of preoperative cognition decline (10–15%) is seen in patients aged >65 years on hospitalization prior to surgery and it can coexist and modify the delirium. We used MMSE score to identify its presence in our patients. As the majority of studies have taken >24 MMSE value as normal thus we also categorized our patients as normal (≥25), mild dementia (21-24) and moderate dementia (<21)[28-30]. In our study the baseline MMSE score was <25 in 91% of the patients (89% in group 1and 92% in group 2). Over the days the MMSE score values further decreased similarly in both the groups till discharge. When we studied the correlation between the <25 MMSE score and CAM ≥3. amounting to delirium, we did not find any significant association between these two values. As majority of the patients of group 1 and 2 had score <25 yet they were not having delirium.

Ringdal *et al.,* and Radtke *et al.,*[5,12] found poor specificity of <24 MMSE score as a screening tool for delirium and concluded that it may have high false positives with a specificity of 54%. On the contrary Tsui A. *et al.,* and Kalisvaart *et al.,*[31,2] found significant association between MMSE score and development of delirium. They took different cut off values between 18 to 24 as a risk factor for delirium with a sensitivity ranging from 60% and 83.8% and specificity of 92.5% and 62.8%. Alex Tsui *et al.,*[31] in their studyconcluded that better baseline cognition was associated with a lower risk of delirium (odds ratio 0•63, 95% CI 0•45 to 0•89) and with less severe delirium (−1•6 MDAS point, 95% CI –2•6 to –0•7). In 2021 the delirium and cognitive impact in dementia

(DECIDE) study it was observed that delirium leads to cognition decline as seen by 1.8 point reduction on the MMSE score (95% CI -3.5 to -0.2) and new dementia diagnosis in patients with delirium at 12 month follow up (OR 8.8, 95% CI 1.9 -41.4)[32].

Most of the studies have reporting this correlation between CAM and MMSE score have studied the results over over six months to one year period. Thus they have reported varying degree of association between the two entities whereas we followed the association in immediate postoperative period till discharge only[29,32].

Unlike our results some researchers have reported anemia, excessive blood transfusion, blood sugar levels, deranged serum electrolytes and low educational status as risk factors for POD Behrends Matthias *et al.,* and Christina AM. *et al.,*[33,30] found low hemoglobin and blood transfusion of more than 1000ml was a strong predictor of POD in early postoperative day. (OR, 3.68; 95% CI, 1.32 -10.94; $p<0.01$). Heymann A. *et al.,*[3] concluded that hyperactive delirium was associated with elevated blood glucose greater than 130mg/dl and. Martocchia A. *et al.,*[4] observed that both hyperglycemia and hypoglycemia extremes worsened delirium [HbA1c levels between 6.9 -10.3% (mean 8.3%)]. Li-Hong Wang *et al.,*[34] concluded that serum sodium and calcium disorders were higher in patients of POD (OR, 2.38). Morley JE. *et al.,*; Koizumi J.; Shiraishi H. *et al.,*[35,36] concluded that restoring sodium and volume status to normal can reduce its incidence of delirium in older patients of hip fractures.

Strengths of the study were that we did the preoperative MMSE score of our patients to know their cognation status prior to surgery and tested its correlation with the POD. We used melatonin which is a naturally occurring hormone and low dose gabapentin to target the normal sleep rhythm, anxiety of the patient which is disturbed in such scenario. We also recorded the postoperative sleep pattern for initial 3 days in the postoperative period to know whether the drugs we were using produced normal sleep or led to decreased alertness in the recovery.

Limitations of the study were that the mean age of our patients was 61.79 years which is lower than seen in most of the studies where the age is above 70. We used a lower age for inclusion criteria as we specifically wanted patients who could be given oral medications 6hrs. after surgery and we wanted not only patients of hip fracture but also of general surgery to make wider recommendations about the use of melatonin and gabapentin in future. Secondly we studied the patients till discharge. Late cognation decline and dementia over 3 months to 1 year was not studied as the total duration of the study was for a period of 1 year only. Finally we did not check the levels of serum inflammatory markers like IL-6 and TNF because they are not available in our hospital. We recommend more studies with these biomarkers and drugs which will specifically decrease the neuroinflammation and thereby could decrease the cognition decline in patients.

CONCLUSION

Perioperative use of low dose melatonin with gabapentin significantly decreased the incidence of delirium, the severity of the cognition status decline and improved the subjective sleep quality of the patients. Hence its use is recommended in the peri operative period to decrease the morbidity associated with surgery.

LIST OF ABBREVIATIONS

ASA: American society of Anaesthesiologist physical status classification.
CAM: Confusion assessment method.
MMSE: Mini Mental scale examination.
POCD: Post operative cognitive dysfunction.
POD: Post operative delirium.
DSM: Diagnostic and statistical manual of mental disorder.
Et al.: Et alia.
Gm: gram.
ICD-10: International classification of diseases 10th edition.
IL: Interleukin.
µgm: Microgram.
TNF: Tumour necrosis factor.
CI: Class index.
OR: Odd ratio.
MAP: Mean arterial pressure.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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