

Comparative Evaluation of Melatonin, Pregabalin and Alprazolam as Premedicants for Perioperative Anxiety and Post Operative Pain for Laparoscopic Surgeries

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Abstract

The present study was undertaken to compare the effects of Melatonin 3 mg, Pregabalin 75 mg and Alprazolam 0.5 mg as premedicant drugs for reduction in perioperative anxiety and post operative pain, assessment of level of sedation. 150 patients of ASA grade I and II, between 20 - 50 years, of either sex, undergoing laparoscopic surgery were divided into 3 groups of 50 patients each. Baseline anxiety level and level after 1hr of drug was assessed. Also postoperative anxiety at different intervals was assessed. Similarly postoperative pain and level of sedation at different intervals was assessed. Patients in group M were highly sedated as compared to group P and group A at all intervals and the difference was statistically significant. All the three groups were comparable regarding postoperative pain, perioperative anxiety and side effects at all intervals and the difference was statistically insignificant at all intervals.

Keywords

Premedication, Melatonin, Pregabalin, Alprazolam

Introduction

Premedication has some important goals like relief of anxiety, sedation and analgesia. Anxiety in surgical patients increases the need of anaesthetic drugs (1). It may also play a critical role in controlling pain responses with the help of pharmacological intervention (2). Thus multimodal approach has been used to improve postoperative analgesia, early mobilization and recovery (3). Benzodiazepines are important premedicant drugs used to produce anxiolysis, amnesia and sedation (4). Alprazolam, a benzodiazepine binds to GABA receptors and is more anxiolytic than other benzodiazepines.

Pregabalin is a structural derivative of inhibitory neurotransmitter GABA leading to anxiolysis and analgesia (5).

Melatonin (N acetyl 5, methoxytryptamine) is a hormone produced by pineal gland and when given orally

results in anxiolysis and sedation without interfering with cognitive or psychomotor skills and postoperative recovery (6).

The present study was conducted to compare Melatonin 3 mg, Pregabalin 75mg and Alprazolam 0.5 mg as premedicant drugs in laparoscopic surgeries.

Aim of study

To compare the effects of melatonin, pregabalin and alprazolam as premedicant drugs for reduction of perioperative anxiety, postoperative analgesia.

To assess the level of sedation and side effects postoperatively.

Methods

The current study was conducted in Department of Anaesthesiology in Govt Medical College Jammu. After obtaining approval from ethical committee, 150 patients of ASA grade 1 and 2, of either sex, aged be-

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tween 20 -50 yrs scheduled for laparoscopic surgery were included in study.

Following patients were excluded from study

1. Patients on long term analgesics and opioid containing drugs.
2. History of drug allergy to drugs involved.

During preanaesthetic visit detailed general physical, systemic examination was done. Informed consent taken and routine investigations advised.

Patients were kept fasting overnight and anxiety level was assessed before giving drugs by using Beck anxiety inventory score.

Beck score

0-21 Low anxiety

22-35 Moderate anxiety

>35 Severe anxiety

Patients were divided into 3 groups of 50 each

Group M received 3 mg of melatonin tablet orally 1 hr before induction. Group P received 75mg of pregabalin orally 1 hr before induction. Group A received 0.5mg of alprazolam orally 1 hr before induction.

Anxiety level was again assessed after 1 hr of premedication. Injection Glycopyrolate 0.005 mg /kg given to patients 45 mins before surgery. In operation theatre monitors (HR, BP, Spo2) were attached and i/v line started. Inj. Ondansetron 4 mg and Tramadol 1 mg/kg

Table.1 Showing Scale used

	Not At All	Mildly but it didn't bother me much.	Moderately - it wasn't pleasant at times	Severely – it bothered me a lot
Numbness or tingling	0	1	2	3
Feeling hot	0	1	2	3
Wobbliness in legs	0	1	2	3
Unable to relax	0	1	2	3
Fear of worst happening	0	1	2	3
Dizzy or lightheaded	0	1	2	3
Heart pounding/racing	0	1	2	3
Unsteady	0	1	2	3
Terrified or afraid	0	1	2	3
Nervous	0	1	2	3
Feeling of choking	0	1	2	3
Hands trembling	0	1	2	3
Shaky / unsteady	0	1	2	3
Fear of losing control	0	1	2	3
Difficulty in breathing	0	1	2	3
Fear of dying	0	1	2	3
Scared	0	1	2	3
Indigestion	0	1	2	3
Faint / lightheaded	0	1	2	3
Face flushed	0	1	2	3
Hot/cold sweats	0	1	2	3
Column Sum				

Table.2 Showing Score Level

Observation	Score level
Responds readily to name spoken in normal tone	5
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly and/or repeatedly	3
Responds only after mild prodding or shaking	2
Does not respond to mild prodding or shaking	1

was given to patient and induction done with Propofol 2-2.5 mg/kg. Tracheal intubation done with suxamethonium 1-2mg/ kg. Patient maintained on Oxygen, Nitrous oxide, Atracurium, Halothane. In intraoperative period Heart rate, ECG, SpO₂, Mean arterial pressure were recorded at 0,5,10,20,30,40,50,60,70 minutes. Patient reversed with Neostigmine 0.05mg/kg and Glycopyrrolate 0.01mg/kg i/v.

Postoperative anxiety assessed at 1 hr,2hr,6hr,12hr. Postoperative pain was assessed at 30min,2hr,4hr,6hr,8hr,12hr using VAS score on a scale of 0-10

where 0- no pain and 10- worst pain.

Level of sedation assessed postoperatively at 30 min.,2hr,6hr,8hr,12hr using Inverter Observer Assessment of alertness / sedation Score (OAA/S).

Side effects like headache and dizziness were reported with each drug in some patients.

Study was evaluated statistically using Student's independent t- test for intergroup comparison, Paired t test for intragroup comparison and Chi square test and Fischer exact test for comparison of categorial variables.

Table.3 Showing Age, Weight & Duration of Surgery among the Groups

Parameter		Mean	SD	Comparison	P-value
Age (years)	Group M	33.5	10.19	M vs P	0.511
	Group P	34.7	8.31	P vs A	0.190
	Group A	35.9	8.71	M vs A	0.191
Weight (Kgs)	Group M	63.5	7.65	M vs P	0.226
	Group P	61.6	7.96	P vs A	0.638
	Group A	62.7	7.31	M vs A	0.457
Duration of Surgery (Minutes)	Group M	67.3	18.07	M vs P	0.920
	Group P	67.7	16.59	P vs A	0.744
	Group A	68.4	12.60	M vs A	0.821

Discussion

The mean age of patients in group M ranges from 33.5 ± 10.19 , in Group P it is 34.7 ± 8.31 and in group A it is 35.9 ± 8.71 .

The near weight of patients in group M ranges from 63.5 ± 7.65 , in group P it ranges from 61.6 ± 7.96 and in group A it is 62.7 ± 7.31 .

Result

The demographic data regarding age, weight and duration of surgery was comparable in all groups and the difference among groups was statistically insignificant.

In Group M, %age decrease in anxiety was statistically significant as compared to baseline at all intervals.

In Group P, %age decrease in anxiety was statistically significant as compared to baseline at all intervals.

Anxiety score was statistically insignificant among three study groups at all intervals. (p value > 0.05)

Difference between mean pain scores amongst three groups was statistically insignificant at all intervals.

Comparison between sedation score of group M and group P was statistically significant at all intervals. Similarly comparison between sedation score of group M and group A was statistically significant at all intervals whereas comparison of sedation score between group P and group A was statistically insignificant at all intervals.

The duration of surgery for group M ranges from 67.3 ± 18.07 , in group P it is 67.7 ± 16.59 and in group A it is 68.4 ± 12.60 .

The age, weight and duration of surgery in all the three groups were comparable and the difference was statistically insignificant.

In group M baseline anxiety score was 35.26 which got reduced to 13.90 (60.6% decrease from

Table 4. Showing Intra Group Comparison of Changes in anxiety Score From Baseline Among Various Groups at Groups at Different Intervals of Time

Time Interval	Group M			Group P			Group A		
	Mean	%age	P-value	Mean	%age	P-value	Mean	%age	P-value
Before giving premedication	35.26	-	-	34.26	-	-	34.62	-	-
1 hour after premedication	13.90	60.6	<0.001*	14.76	56.9	<0.001*	14.40	58.4	<0.001*
1 hour after surgery	9.72	72.4	<0.001*	10.64	68.9	<0.001*	10.52	69.6	<0.001*
2 hour after surgery	4.74	86.6	<0.001*	5.56	83.8	<0.001*	5.32	84.6	<0.001*
6 hour after surgery	2.02	94.3	<0.001*	2.44	92.9	<0.001*	2.16	93.8	<0.001*
12 hour after surgery	0.58	98.4	<0.001*	0.74	97.8	<0.001*	0.76	97.8	<0.001*

Table 5 Showing Inter Group Comparison of Anxiety score Among Various Groups

Time Interval	M vs P	M vs A	P vs A
Before giving premedication	0.509	0.672	0.812
1 hour after premedication	0.087	0.318	0.472
1 hour after surgery	0.072	0.117	0.814
2 hour after surgery	0.071	0.201	0.596
6 hour after surgery	0.169	0.646	0.359
12 hour after surgery	0.258	0.203	0.887

baseline) 1 hour after premedication. 1 hour after surgery it was 9.72 (72.4% decrease from baseline). 2 hours after surgery it was 4.74 (86.6% decrease from baseline). 6 hours after surgery score was 2.02 (94.9% decrease from baseline). 12 hours after surgery the score was 0.58 (98.4% decrease from baseline). Our study is in

concordance with Caumo *et al*, 2009 (7) who reported that melatonin is associated with less perioperative anxiety as compared to placebo.

In group P baseline anxiety score was 34.26 which got reduced to 14.76 (56.9% decrease from baseline) after 1 hour of premedication. 1 hour after sur-

Table 6 Showing Pain Score Among Various Groups at different Intervals of Time

Time after surgery	Group M		Group P		Group A	
	Mean	SD	Mean	SD	Mean	SD
30 Minutes	1.68	0.71	1.36	0.90	1.48	0.68
2 Hours	2.82	0.83	2.50	0.89	2.72	0.78
4 Hours	2.96	1.59	2.82	1.27	2.92	1.61
6 Hours	3.60	1.46	3.42	1.50	3.54	1.51
8 Hours	2.58	1.33	2.32	1.30	2.62	1.37
12 Hours	2.56	1.07	2.44	0.99	2.72	0.99

Table 7. Showing Intergroup Comparison of Pain Score Among Various Groups

Time Interval	M vs P	M vs A	P vs A
30 Minutes	0.091	0.195	0.436
2 Hours	0.057	0.549	0.189
4 Hours	0.642	0.894	0.739
6 Hours	0.547	0.841	0.688
8 Hours	0.331	0.881	0.262
12 Hours	0.557	0.434	0.172

gery the score was 10.64 (68.9% decrease from baseline). 2 hours after surgery the score was 5.56 (83.8% decrease from baseline). 6 hours after surgery

the score was 2.44 (92.9% decrease from baseline). 12 hours after surgery the score was 0.74 (97.8% decrease from baseline).

Table -8 Showing Sedation Score among Various Groups at Different Intervals of Time

Time after surgery	Group M		Group P		Group A	
	Mean	SD	Mean	SD	Mean	SD
30 Minutes	2.36	0.60	2.46	0.76	2.89	0.96
2 Hours	1.84	0.51	1.96	0.60	2.25	0.75
4 Hours	1.60	0.53	1.68	0.62	1.98	0.75
6 Hours	1.24	0.48	1.28	0.45	1.57	0.63
8 Hours	1.06	0.31	1.12	0.39	1.31	0.49
12 Hours	0.98	0.25	1.04	0.35	1.18	0.45

Table.9 Showing Intergroup Comparison of Sedation Score among Various Groups

Time Interval	M vs P	M vs A	P vs A
30 Minutes	<0.001*	<0.001*	0.457
2 Hours	<0.001*	<0.001*	0.293
4 Hours	<0.001*	<0.001*	0.485
6 Hours	<0.001*	<0.001*	0.654
8 Hours	<0.001*	<0.001*	0.436
12 Hours	<0.001*	<0.001*	0.433

Our study is supported by Gonano *et al*, 2011(8) who found that pregabalin reduced perioperative anxiety. Spreng *et al*, 2011 (9) reported reduced perioperative anxiety with pregabalin whereas White *et al*, 2009(10) stated that no significant reduction in

perioperative anxiety was seen with pregabalin in minor elective procedures.

In group A the baseline anxiety score was 34.62 which got reduced to 14.40 (58% decrease from baseline) after 1 hour of premedication. 1 hour after surgery score

was 10.52 (69.9% decrease from baseline). 2 hours after surgery score was 5.32 (84.6% decrease from baseline). 6 hours after surgery score was 2.16 (93.8% decrease). 12 hours after surgery score was 0.76 (97.8% decrease from baseline). Our study is supported by Meletzky *et al.*, (11) who reported anxiolysis with Alprazolam as compared to placebo. Peak plasma concentration of Melatonin ranges from 0.25 hours – 6 hours (12) and that of pregabalin peak plasma concentration reaches at 1 hour (13) whereas Benzodiazepines are most common anxiolytic agents with peak plasma conc. at 1-2 hours (4).

In our study all the three groups M, P and A were comparable regarding perioperative anxiety at all intervals and the difference at all intervals was statistically insignificant. Our study is supported by Nasr *et al.*, (14) who reported similar anxiolysis with Melatonin and Pregabalin and the inter group comparison at all intervals was statistically insignificant. Rickels *et al.*, (15) compared Pregabalin with Alprazolam and reported more effective anxiolysis with chronic use of pregabalin as compared to alprazolam. Pokharel *et al.*, (16) reported that combination of melatonin and alprazolam was more anxiolytic than either of drug alone.

Pain score in group M at 30 min, 2 hours, 4 hours, 6 hours, 8 hours and 12 hours after surgery was 1.68 ± 0.71 , 2.82 ± 0.83 , 2.96 ± 1.59 , 3.60 ± 1.46 , 2.58 ± 1.33 and 2.56 ± 1.07 . Our study is in accordance with Mowafi *et al.*, (17) who reported postoperative analgesic effect with Melatonin. Kim *et al.*, (18) reported dose dependent antinociception.

Pain score in Pregabalin group at 30 min, 2 hours, 4 hours, 6 hours, 8 hours and 12 hours was 1.36 ± 0.90 , 2.50 ± 0.89 , 2.82 ± 1.27 , 3.42 ± 1.50 , 2.32 ± 1.30 , 2.44 ± 0.99 respectively. Our study is supported by White *et al.*, (10) who reported that single dose of Pregabalin reduced postoperative pain and opioid consumption.

Pain score in group A at 30 mins, 2 hours, 4 hours, 6 hours, 8 hours and 12 hours after surgery was 1.48 ± 0.68 , 2.72 ± 0.78 , 2.92 ± 1.67 , 3.54 ± 1.51 , 2.62 ± 1.37 and 2.72 ± 0.99 . Our study is in accordance with Yilmaz *et al.*, (19) who reported analgesic effects of Alprazolam. In Melatonin there is interplay of melatonergic and GABAergic systems leading to endorphin release whereas Pregabalin is a potent ligand.

Pain score of all the three groups M, P and A was comparable at all intervals and the intergroup comparison at all intervals was statistically insignificant.

Sedation score of group M at 30 min, 2 hours, 4 hours, 6 hours, 8 hours and 12 hours were 2.36 ± 0.60 , 1.84 ± 0.51 , 1.60 ± 0.53 , 1.24 ± 0.48 , 1.66 ± 0.31 , 0.98 ± 0.25 respectively. In group P sedation score at 30 min, 2 hours, 4 hours, 6 hours, 8 hours and 12 hours was 2.46 ± 0.76 , 1.96 ± 0.60 , 1.68 ± 0.62 , 1.28 ± 0.45 , 1.12 ± 0.39 and 1.04 ± 0.35 respectively. In group A the sedation score at 30 min, 2 hours, 4 hours, 6 hours, 8 hours and 12 hours was 2.89 ± 0.96 , 2.25 ± 0.75 , 1.98 ± 0.75 , 1.57 ± 0.63 , 1.31 ± 0.49 , 1.18 ± 0.45 respectively.

In our study we found that patients in group M were more sedated as compared to group P or group A at all intervals and the difference at all intervals was statistically significant whereas sedation score in patients of group P and group A was comparable at all intervals and the difference at all intervals was statistically insignificant. Our study is in accordance to Nasr *et al.*, (14) who reported more sedated patients in group M. Nutt D *et al.*, (20) reported more sedation in group P as compared to group A. This may be due to higher dose of Pregabalin used –150mg.

Side effects like headache, dizziness were comparable in all groups and the study is supported by Pokharel *et al.*, (16) who reported safety of melatonin and alprazolam in terms of adverse effects. Nasr *et al.*, (14) reported comparable side effects between melatonin and pregabalin. Heart Rate, Mean Arterial Pressure, Oxygen Saturation were comparable in all groups at all intervals.

Conclusion

We concluded that 3mg melatonin was more sedative than 75 mg of Pregabalin and 0.5 mg of alprazolam in patients undergoing laparoscopic surgery but all the three groups M, P and A had comparable perioperative anxiety, postoperative analgesia and adverse effects.

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