

A Comparative Study of the Efficacy of Oral Gabapentin and Melatonin on Post Operative Pain and Analgesic Consumption in Patients Undergoing Modified Radical Mastectomy

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Abstract

High levels of post operative pain and anxiety increases patient discomfort and post operative morbidity. Anxiolytic and analgesic effects of melatonin improves control of post operative pain by controlling higher anxiety that accompanies surgical intervention. This study compares antinociceptive effects of both melatonin and gabapentin premedication on post operative pain and analgesic requirement. *Methods:* Ninety female patients undergoing modified radical mastectomy were randomly divided into three groups of 30 each where Group G given Gabapentin 600 mg, Group M given Melatonin 6 mg, Group C given placebo tablet 90 minutes before surgery. Post operative pain, sedation scores and post operative analgesic consumption was assessed for 24 hrs. *Results:* Visual analogue scale (VAS) score were lower in the group G and group M as compared to group C. Sedation score recorded highest in Group M followed by Group G and least in Group C. Time to first analgesic requirement was 16.58±4.47 hrs in Group G, 6.09±5.12 hrs in Group M and 2.80±0.83 hr in Group C ($p<0.0001$). Total 24 hr post operative diclofenac requirement in Group G (96.77±34.60) was significantly lower than Group C (166.93±31.87) and M (142.74±44.81) ($p<0.0001$). *Conclusion:* Both melatonin and gabapentin reduced post operative pain and analgesic consumption. Gabapentin had higher analgesic effect while melatonin was more sedative. Administration of melatonin before surgery may accelerate the resynchronization of circadian rhythm in the post operative period suggesting better recovery quality.

Keywords: Gabapentin; Melatonin; Female Patients; Post Operative Pain; Modified Radical Mastectomy.

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Introduction

The most expected and frequent problems in post operative context and event are pain and anxiety. High levels of post operative pain and anxiety increase patients discomfort, analgesic consumption, delay discharge and increases overall post operative morbidity [1,2].

The concept of pre-emptive analgesia is an analgesic treatment started before the surgical procedure, to protect the central nervous system

(CNS) from deleterious effect of noxious stimuli and the patient from the resulting allodynia and increase pain [3]. Moreover, pre operative anxiety is shown to have increased post operative analgesic requirement.

Benzodiazepines and opioids are the most commonly used drugs at present for reducing anxiety and pain. They however impair psychomotor function, cause excessive sedation, increases incidence of post operative nausea and vomiting (PONV), urinary retention etc. This increases overall post operative morbidity [4].

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Pre-emptive melatonin accelerate the resynchronization of circadian rhythm in the post operative period and this may be the cause of melatonin effect on pain and anxiety which augment pattern of disruption in stressful conditions [5]. In addition inhibition of pro-inflammatory cytokines and activation of opioid and melatonin MT_1 and MT_2 receptors are responsible for analgesic action of melatonin [6,7]. Even large doses of melatonin do not cause impairment of fine motor skill, memory or visual sensitivity [8].

Gabapentin was introduced in 1993 as an adjuvant anticonvulsant drug and subsequently, it was used in treating various chronic pain conditions [9,10,11,12]. Recently its use is extended into the management of acute conditions in the peri operative periods. Many clinical trials have shown the efficacy of gabapentin for post operative analgesia and pre operative anxiolysis [13,14,15].

This study was designed to compare the efficacy of melatonin and gabapentin with that of placebo in reducing postoperative pain and analgesic requirement, prolongation of analgesia as well as their side effects.

Materials and Methods

After taking approval from the ethical committee and informed consent from the patients and relatives, 90 adult women of ASA 1 and 2, in the age group of 18-60 years, who were posted for modified radical mastectomy (MRM) were selected with 30 patients in each group.

Exclusion criteria included ASA grade 3 and above, analgesics given within 24 hours prior to surgery, history of allergy or contraindication to the study drug, drug addiction, BMI > 40, h/o chronic pain, regular medication with analgesics, patients with significant medical or psychiatric problems.

No premedication was given on the day of operation. The patients were randomly allocated into three groups.

Group G (N = 30): Tab. Gabapentin (600 mg) 300 mg two tab.

Group M (N = 30): Tab. Melatonin (6 mg) 3 mg two tab.

Group C (N=30): Tab. Placebo 2 placebo tablets as control.

The study drugs were given 90 minutes prior to surgery.

The anesthetic technique was identical in all the patients. Induction of anaesthesia was done with IV Glycopyrrolate (0.01mg/kg), Thiopentone sodium (5-7 mg/kg), Fentanyl 1-2 µg/kg and Vecuronium bromide 0.1 – 0.2 mg/kg. Airway was secured with proper sized endotracheal tube. Maintenance with O_2 + N_2O + Sevoflurane + Vecuronium. After completion of surgery, reversal of anaesthesia was done with Glycopyrrolate 0.02 mg/kg IV and Neostigmine 0.05 mg/kg IV and after full muscle tone and power trachea was extubated.

Postoperatively the following parameters were recorded every 30 minutes for the first 2 hours and then at 4, 6, 8, 12 and 24 hours.

1. *Pain assessed by visual analogue scale (VAS)*
where 0 = "no pain" while score of 10 = "worst imaginable pain".
2. *Sedation score:*
0- alert on conversant
1-awake but drowsy
2-asleep but arousable
3-asleep and not arousable
3. *Time to first analgesic requirement.*
4. *Total analgesic consumption in 24 hours when VAS score was ≥ 4 , injection diclofenac (75mg) intravenous diluted was given slowly as a Rescue analgesic.*
5. *Side effects* like nausea, vomiting, headache, dizziness, skin rash, urinary retention and visual disturbances.

Observation

All data were recorded and expressed in terms of mean \pm standard deviation. P value < 0.05 was considered significant. Statistical software from www. Graphpad/instat3 site was used.

Table 1 The groups were comparable with respect to age, weight, and duration of surgery. Mean age (year), wt (kg) and surgical duration in all the three groups were comparable and statistically not significant (P > 0.05).

Table 2 shows the VAS score was significantly lower in group M and group G as compared with group C starting immediately and in the post operative period (p < 0.05). Also VAS score was significantly lower in group G as compared to group M. (p < 0.05)

Three cases of group G and two cases of group M did not require any analgesic in the 24 hour postoperative period.

Twenty five cases of group C and one case of group M required analgesic dose in the immediate post operative period.

Table 3 shows Sedation score was significantly more with melatonin group as compared to group G and C.

Table 4 shows that the Time to first analgesic requirement was 16.58±4.47 hrs in Group G, 6.09±5.12 hrs in Group M and 2.80±0.83 hr in Group

C. The p- value of group G vs group M <0.05 while that of group G and M vs group C < 0.001 Total 24 hr post operative diclofenac requirement in Group G (96.77±34.60) was significantly lower than Group C (166.93±31.87) and M (142.74±44.81) (p<0.0001).

Table 5 shows that the most common side effect in group G was somnolence and headache, while in group M it was drowsiness, dizziness and while in group C it was nausea and vomiting.

Table 1: Demographic data

Variables	Group G (n=30)	Group M (n=30)	Group C (n=30)	P value
Age (years)	53.16±9.53	52.93±10.12	52.86±8.77	0.99
Weight (kgs)	54.93±11.66	56.83±14.34	60.06±15.26	0.353
Duration Of Surgery (mins)	112.36±10.80	110.63±11.41	110.7±11.21	0.793

Data expressed as mean±sd. Mean age (yr) and wt (kg) in all the groups are comparable and statistically not significant (p>0.05). Mean surgical duration in all the groups is statistically not significant (p>0.05).

Table 2: Vas score at different time intervals

Vas Score	Group G	Group M	Group C
0 min	1.67±0.65 ^b	2.54±0.88 ^{ba}	3.61±0.76
30 mins	1.38±0.84 ^b	2.29±0.64 ^{ba}	3.29±0.90
1 hr	1.38±0.55 ^b	2.74±0.81 ^{ba}	2.67±0.79
2 hr	1.41±0.92 ^b	2.87±0.92 ^{ba}	2.61±0.95
4 hr	1±1 ^b	3.45±1.09 ^{ba}	3.54±0.72
6 hr	1.87±0.61 ^b	2.70±1.2 ^{ba}	3.09±1.07
12 hr	1.03±0.91 ^b	2.03±0.91 ^{ba}	2.67±0.70
24 hr	1.64±0.66 ^b	2.45±0.80 ^{ba}	2.46±0.84

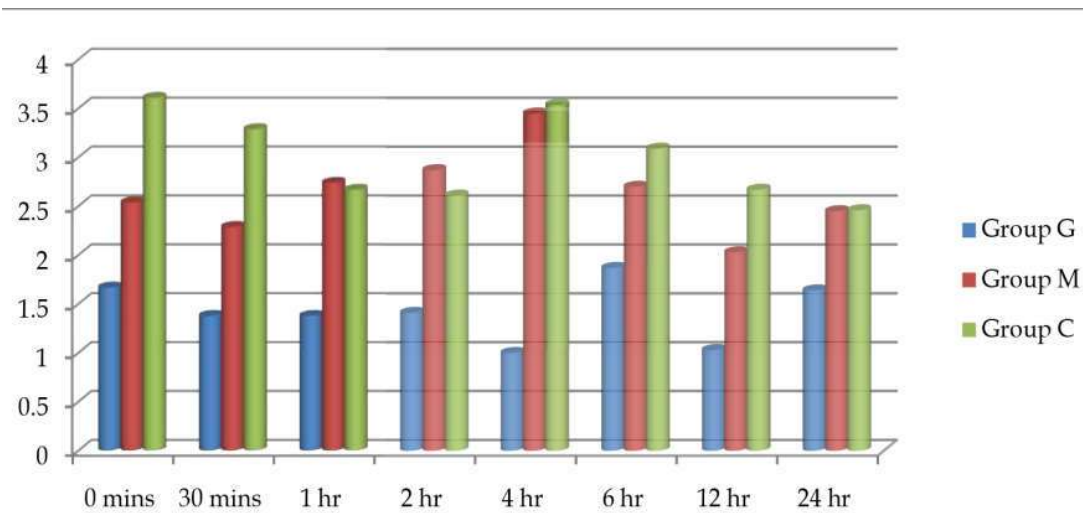
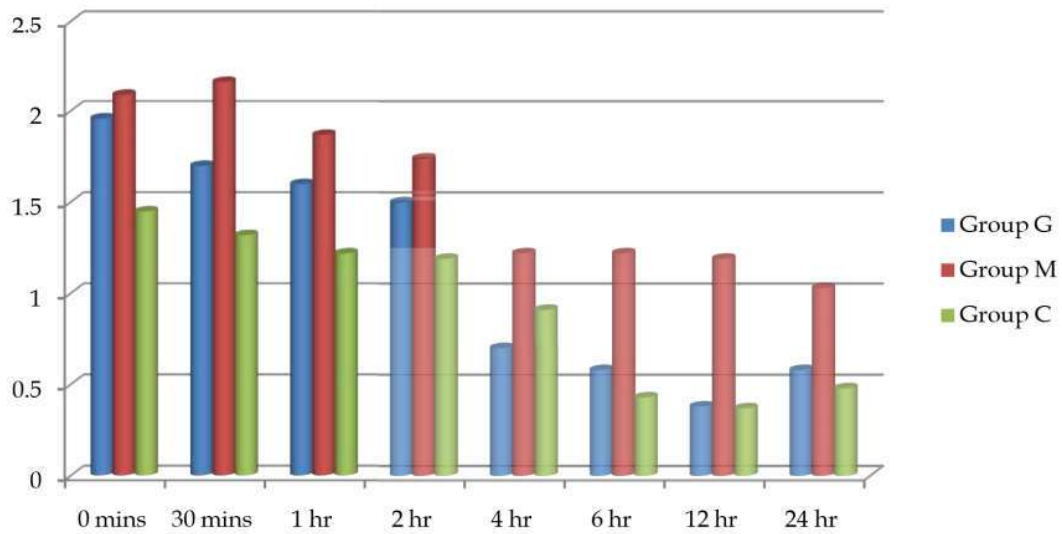


Table 1: Vas score at different time intervals

Data expressed as mean±SD.

^aP value < 0.05 in Group G & Group M versus Group C.

^bP value < 0.05 in Group G versus Group M.



Graph 3: Sedation score at different time intervals

Data expressed as mean ± SD.

^aP value < 0.05 in Group G & Group M versus Group C.

^bP value < 0.05 in Group G versus Group M.

Table 3: Sedation score at different time intervals

Sedation score	Group G	Group M	Group C
0 mins	1.96±0.31 ^a	2.09±0.64 ^{ba}	1.45±0.50
30 mins	1.7±0.47 ^a	2.16±0.37 ^{ba}	1.32±0.47
1 hr	1.6±0.42 ^a	1.87±0.34 ^{ba}	1.22±0.42
2 hr	1.5±0.34 ^a	1.74±0.44 ^{ba}	1.19±0.40
4 hr	0.70±0.46 ^a	1.22±0.56 ^{ba}	0.91±0.37
6 hr	0.58±0.50 ^a	1.22±0.56 ^{ba}	0.43±0.51
12 hr	0.38±0.49 ^a	1.19±0.41 ^{ba}	0.37±0.54
24 hr	0.58±0.50 ^a	1.03±0.48 ^{ba}	0.48±0.50

Table 4: Time to first analgesic and rescue analgesic requirement

Variables	Group G (mean ± SD)	Group M (mean ± SD)	Group C (mean ± SD)
Time to first analgesic requirement(hrs)	16.58±4.47 ^b	6.09±5.12 ^{ab}	2.80±0.83
Total diclofenac requirement(mg)	96.77±34.60 ^a	142.74±44.81 ^{ab}	166.93±31.87

^aP value < 0.001 Group G & Group M versus Group C

^bP value < 0.05 Group G versus Group M

Table 5: Side effect

Variables	Group G	Group M	Group C
Drowsiness	2	6	0
Nausea	4	1	9
Vomiting	5	1	8
Headache	5	2	2
Blurred Vision	1	0	0
Fatigue	0	0	1
Pruritus	0	0	2

Discussion

This study demonstrates that both melatonin and gabapentin given 90 minutes before induction reduced post operative pain and analgesic requirement compared to placebo. Gabapentin 600 mg had higher analgesic effect while Melatonin 6 mg had more sedative effect.

Preemptive analgesia is more efficacious in reducing post operative pain, preoperative anxiety, attenuation of the haemodynamic response to laryngoscopy and intubation and preventing chronic post surgical pain [16].

Wilhemsen M et al. in his review found that melatonin has analgesic action in all experimental studies regardless of mode of pain induction [17]. They also found that route of administration of melatonin is irrelevant in analgesic action and analgesia is dose dependent.

Gabapentin was used preoperatively as previous animal experiments showed pretreatment with gabapentin was more effective and longer lasting than post operative treatment [18].

We administered the study drugs 90 minutes prior to surgery as after oral administration a peak melatonin concentration is reached approximately in 60 minutes and thereafter its concentration declines over a four hour period [19]. While after oral administration a peak gabapentin concentration is reached approximately in two to three hours and its concentration declines over six to eight hours [16].

The chosen dose of gabapentin (600mg) is the most commonly used single dose in the treatment of acute and chronic pain trials and could be given 1-2 hour before surgery [20]. Pandey et al studied different doses of gabapentin premedication (300 mg, 600mg, 900 mg, 1200mg) in patients undergoing lumbar discectomy [21]. The optimal dose they found was 600 mg as with higher dose side effects are more with no further reduction in pain. V. K. Grover et al in their randomized placebo controlled trial with single dose of 600 mg gabapentin concluded that 600 mg gabapentin produces effective and significant post operative analgesia after total mastectomy without significant side effects [22].

Exogenous melatonin dose range from 3 to 15mg and was administered 90-100 min before induction via oral [5,23,24,25,26] and sublingual route. [27,28,29]. We chose 6 mg melatonin as it is commonly used dose in the treatment of acute and chronic pain trials and also the optimal effective analgesic dose of melatonin is still unclear. Ionescu

et al. used 3 mg melatonin as a premedication for laproscopic cholecystectomy and found that is associated with anxiety, analgesic property and better recovery profile without impairment of psychomotor function post operatively [23,27]. Caumo et al. compared 5 mg melatonin and 100 microgm clonidine with placebo given night before surgery and one hour before surgery and found both the drugs comparable in terms of anxiety and post operative analgesic consumption [24]. Study with 10 mg oral melatonin premedication 90 minutes before cataract surgery found that melatonin has anxiolytic, increased analgesic, and IOP reducing effects [25] and same dose before IVRA reduced tourniquet related pain and improved perioperative analgesia [26]. Contradictory result were found with 10 mg oral melatonin study by Capuzzo et al. where there was no significant reduction in anxiety and pain in elderly patients undergoing elective surgery [30].

Four studies with melatonin showed improvement in pain scores compared to placebo and that was statistically significant ($p < 0.05$) [5,24,25,26] and three studies results for pain scores were contradictory [27,28,29]. Naguib et al and Acil et al found no significant difference in pain scores in melatonin group as compared to placebo group post operatively where they used only a single dose of melatonin and placebo [27,28]. However Caumo et al found statistically significant reduction in pain scores post operatively using dual dose of melatonin and clonidine [24]. Ajori et al. in his study of 600 mg preemptive gabapentin orally in patients undergoing abdominal hysterectomy found that gabapentin group had significantly lower VAS scores at every time interval compared to placebo group [31].

In our study VAS scores were significantly lower in group G as compared to group M. Similar results were found in previous study with 6 mg melatonin and 600 mg gabapentin in patients undergoing elective abdominal surgery [18]. VAS scores were significantly lower in both the study groups as compared to placebo at all the levels. Three cases of group G and two cases of group M did not require any analgesic drug during first 24 hours postoperative.

Caumo et al in his study of melatonin and clonidine found that the anxiolytic effect of both drugs reduced postoperative morphine consumption by more than 30% in patients undergoing abdominal hysterectomy. The incidence of post operative moderate to intense pain was 33.2% and 40% in melatonin and clonidine group respectively compared with 92.3% in placebo group [24]. K. Radwan et al. found that time to first

analgesic demand was 16 hr, 4 hr, 0 hr in group G(600 mg), group M (6 mg) and group C respectively ($p < 0.001$). The total postoperative analgesic requirement in 24 hr is significantly lower in group G(72.4 ± 15.8) than group M (97.4 ± 10.9) and C (126.4 ± 14.5) [18]. MB Khezri et al. in their study found that time to first analgesic request prolonged in group M3(208.19 ± 122.66 min) compared to group M6(196.82 ± 127.25 min) and placebo group P(152.13 ± 79.4 min) [32]. Increasing the dose of melatonin to 6 mg failed to enhance analgesia and increased the incidence of headache. V.S Hoseini et al in his study of 6 mg melatonin, 600 mg gabapentin and 0.2mg clonidine premedication concluded that melatonin premedication has similar efficacy as clonidine and gabapentin for reducing postoperative pain and also reducing narcotic consumption [33]. Dalia AN et al. in his study of Melatonin 6 mg vs pregabalin 150 mg given one hour before induction in gynecological surgery found that the time for first analgesic demand in group M (114.3 ± 4.8) minute and group P (118.1 ± 6.2) minute and the number of patients requiring Diclofenac at six hours [group M (50%) vs group P (40%)] and 12 hours [group M (60%) vs group P (40%)] postoperatively were similar in both groups [34]. PWH Peng in his metaanalysis on gabapentin for postoperative pain control concluded that gabapentin decreases analgesic consumption and opioid related adverse effect however it is associated with increased incidence of sedation and dizziness [35].

In our study time to first analgesic requirement was prolonged in group G as compared to group M and C.

Borazaa H. et al. in his study of pre-emptive oral melatonin 6 mg in dual dose, the night before and one hour before surgery found reduced pain scores and tramadol consumption and improved sleep quality with increased sedation score post-operatively in patients undergoing elective prostatectomy [36]. Acil M et al. found increased level of sedation only at 90 minute after premedication with melatonin versus placebo ($p < 0.05$) [27]. Naguib and Samarkandi in his study on 75 women who received premedication with 5 mg melatonin 100 minutes preoperatively found significant decrease in anxiety level and increase in sedation level before operation [28].

In our study patients who received melatonin had more sedation score than group G and C at all the readings post-operatively. ($p < 0.001$).

Melatonin has excellent safety profile and is well tolerated even with very high doses [37,38,39]. A

metaanalysis conducted by Buscemi N et al found headache, nausea, drowsiness and dizziness to be the most common side effects of melatonin and concluded that melatonin is safe for short term use [40]. Large dose of melatonin (20mg) administered to children without any adverse effect apart from sedation [41].

The most frequent side effects in group G of our study were headache, dizziness and somnolence. Headache and drowsiness were more common in group M while in group C the most common complaint was pain, nausea, vomiting and urinary retention. These results were similar to those of K Randwan et al. [18] and Ismail & Movafi [25].

There was no significant difference in vital signs during operation and post-operative period among three groups.

Conclusion

Pre-emptive oral dose of 600 mg of gabapentin and 6 mg of melatonin reduces the pain score and analgesic requirements in the first 24 hours in patients undergoing MRM surgery. Gabapentin had higher analgesic effect, while melatonin was more sedative. Owing to its anxiolytic effects, melatonin can be administered whenever anxiety seems to be more marked during the perioperative period, otherwise gabapentin is preferable.

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