Melatonin versus Gabapentin. A comparative study as preemptive medications

K Radwan, M Youssef, A El-Tawdy, M Zeidan, N Kamal

Citation

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Abstract

Objective:

Comparing impact of premedication of melatonin and gabapentin on postoperative pain and analgesic requirements.

Subjects and Methods:

Seventy-five patients scheduled for elective abdominal surgery under general anesthesia were randomly assigned for oral premedication with 600 mg gabapentin (G group), 6 mg melatonin (M group), or placebo (C group) in double-blind manner. Pain and sedation scores, first and total pethidine requirements in 24 hr were recorded.

Results:

A preemptive gabapentin or melatonin reduces the pain scores evidenced by VAS evaluation. Median time to first analgesic demand was 16 h, 4 h and, 0 h in G, M and C groups respectively ($p < 0.001$).

The total 24h postoperative pethidine requirements in G group (72.4 ±15.8) was significantly lower than C (126.4 ±14.5) and M (97.4 ±10.9) groups ($p < 0.001$).

Conclusion

: Oral Gabapentin produced significantly more analgesia, while oral Melatonin was significantly more sedative when given 1 hr preoperatively

INTRODUCTION

The concept of preemptive analgesia, which is an analgesic treatment initiated before, as opposed to after the surgical procedure, was introduced to protect the central nervous system from deleterious effects of noxious stimuli, and the patient from the resulting allodynia, and increased pain[1].

Postoperative pain is typically regarded as a type of nociceptive pain involving peripheral mechano-receptor stimulation. It is clear that inflammatory, neurogenic, and visceral mechanisms also contribute to acute pain symptoms. It has been suggested that central neuronal sensitization contributes to postoperative hypersensitivity to pain[2]. As such, post-operative pain may be considered as a transient, reversible type of “neuropathic” pain and, consequently there is a rationale for the exploitation of anti-hyperalgesic drugs for post-operative analgesia[3].

Gabapentin, a 3-alkylated analog of □-aminobutyric acid and anticonvulsant drug, was initially reported to be effective in treating neuropathic pain[4], diabetic neuropathy[5], post-herpetic neuralgia[6] and reflex sympathetic dystrophy[7]. It has a selective effect on the nociceptive process involving

central sensitization[8]. Pretreatment with gabapentin can block the development of hyperalgesia[9]. Early clinical studies of surgical patients suggested that preoperative administration of gabapentin decreased postoperative pain scores and opioid analgesic requirements after mastectomy[10,11], spinal surgery[12], and otolaryngologic surgery[13].

Melatonin (N-acetyl-5-methoxytryptamine), is a hormone synthesized principally in the pineal gland that has been classically associated with endocrine actions. Melatonin is present in almost all tissues, with or without the melatonin receptors, because it acts both as a hormone and an antioxidant[14]. However, several lines of evidence suggest that melatonin plays a role in pain modulation. The antinociceptive effect of melatonin has been evaluated in diverse pain models, and several findings show that melatonin receptors modulate pain mechanisms as activation induces an antinociceptive effect at spinal and supraspinal levels under conditions of acute and inflammatory pain . More recently, melatonin induced-antinociception has been extended to neuropathic pain states[15]. Oral melatonin has been used to alleviate jet lag[16] and as a preoperative sedative[17-19]. Also, it has been associated with the relief of pain in patients with extensive tissue injuries[20].

Considering the hypothesis behind preemptive analgesia where antinociceptive treatment started before surgery is more effective in reducing postoperative pain than treatment started in the early postoperative period[21], and the potential pharmacological benefits of both melatonin and gabapentin, this study was designed to compare the impact of oral premedication of either melatonin or gabapentin on postoperative pain, and analgesic requirements regarding their efficacy, potency and safety in a randomized, placebo-controlled double-blind way.

MATERIALS AND METHODS

After institutional ethical committee approval and written informed consent, 75 patients, ASA classification I–II, aged 30–55 yr scheduled for elective abdominal surgery under general anesthesia were enrolled into the randomized, double-blind, placebo controlled study. Patients with previous treatment with either melatonin or gabapentin, mental impairment, chronic pain, pregnancy, or a history of congestive heart failure, valvular heart disease, renal or hepatic disease, or who had used psychotropic drugs in the present or in the past, or had language or communication difficulties were excluded. Also, patients with a body mass index higher than 25 kg m^{-2}, those with sleep disorders, a history of psychiatric disorder or known allergy to any drug used, or a history of a peptic ulcer or bleeding diathesis were excluded.

The patients were randomly divided into 3 groups with 25 patients each and allocated in a double-blind manner, using computer generated random numbers, to receive orally one hour before surgery either 6 mg melatonin (Melatonin 3 mg tablet; Sigma Chemical, St. Louis, MO); M group, 600 mg gabapentin (Gaptine 300 mg capsule; Pfizer, Goedecke GmbH, Germany); G group or two placebo tablets as control; C group. No other preoperative medication was given.

Blinding and randomization were performed by two investigators not involved in the patients' evaluations. Other individuals involved in the patient's care were unaware of patient group assignment. All patients were instructed preoperatively on the use of a visual analogue scale (VAS, range 0-10 cm) using a ruler.

In the operating room, a crystalloid infusion was started through an IV cannula inserted in an antecubital vein, and put on continuous electrocardiography. The mean arterial blood pressure (MAP), heart rate (HR), peripheral oxygen saturation (SpO_2) and end tidal carbon dioxide were monitored (Dragger Infinity Kappa, Monitor version VF-5W, Germany) and recorded at five-minute intervals.

Anesthesia was induced with propofol 2 mg kg^{-1} and fentanyl 2 μg kg^{-1}. Atracurium 0.5 mg kg^{-1} IV was used to facilitate orotracheal intubation. Neuromuscular block was maintained with intermittent atracurium when indicated. Mechanical ventilation was adjusted to maintain end-expiratory CO_2 between 34-36 mm Hg. General anesthesia was maintained with isoflurane and a fresh gas flow of 2 L min^{-1} (30% air in oxygen). The con¬centration of agent was adjusted to maintain adequate depth of anesthesia (stable heart rate and blood pres¬sure) as in routine practice. Thirty minutes before end of surgery, ketorolac 30 mg IM was given for immediate post-operative pain to the three groups. After completion of surgery, neuromuscular blockade was reversed with neostigmine 0.04 mg kg^{-1}, and atropine 0.02 mg kg^{-1} and patients were extubated when adequate spontaneous ventilation was established. After tracheal extubation, patients were transferred to the postanesthesia care unit (PACU).

Assessment of postoperative pain was made by a physician, who was not the part of the anesthesia team, on the basis of the visual analogue score (VAS), where VAS; 0 cm = no pain to 10 cm = the worst possible pain. Patients received pethidine 0.5 mg kg^{-1} IV on demand (VAS ≥ 4). The time from the end of the surgery until the first bolus of pethidine administered on demand and the total rescue analgesic requirements in the first 24 hours were recorded. Postoperative sedation was assessed by using a four-point scale (1 = awake, 2 = drowsy but responsive to verbal command, 3 = drowsy but responsive to physical stimulus, 4=unresponsive to verbal or physical stimulus)[22].

During the first hour in the PACU, then at 2, 4, 6, 8, 12, 16, 20, and 24 h, patients were evaluated for pain scores, HR, SpO_2, MAP, respiratory rate, sedation, pethidine use, and its total dose. The occurrence of any side effects, such as nausea, vomiting, constipation, respiratory depression, dizziness, nystagmus, tremor, diplopia, somnolence, peripheral edema, diarrhea, headache, and pruritis was recorded. Postoperative nausea and vomiting were treated with 4 mg IV ondansetron.

STATISTICAL ANALYSIS

The data were analyzed with SPSS version 15.0 (SPSS Inc, Chicago, IL, USA). On the assumption that a 20% difference in pethidine consumption between the groups would be of clinical interest, a sample size of 25 patients in each group is required to have a power ß = 80% and = 0.05. Continuous variables were described as mean±SD or SE of means as appropriate. Comparison between the three groups was done using ANOVA test. ANOVA for repeated measures was used to evaluate the effect of each drug. Categorical data were compared using Chi-square test. The data were considered significant if p values were equal to or less than 0.05.

RESULTS

There were no differences between groups regarding demographic characteristics or duration of surgery as shown in table 1. Postoperative hemodynamic values (heart rate, MAP) and SpO_2 were comparable in the three groups. Median time to first analgesic demand was 16 hours (range 10-20 h) in G group in comparison to 4 h (range 2-4) in M group ($p < 0.001$). The total postoperative pethidine requirement in 24 hr in the G group (72.4±15.8 mg) was significantly lower than in both M and C groups (97.4±10.9 mg and 126.4 ±14.5mg respectively) ($p < 0.001$) (Table 2). Gabapentin reduced pethidine consumption by 42.7%, while melatonin produced 22.9% reduction compared to control group.

Figure 1

Table 1: Demographic and intra-operative variables in the three studied groups

Variables	Control (n= 25)	Gabapentin (n= 25)	Melatonin (n= 25)
Age (yrs)	35.62 ± 7.5	40.62 ± 8.2	40.32 ± 7.84
Gender (male/ female)	11/14	12/13	13/12
Weight (Kg)	74.28 ± 6.97	72.92 ± 8.02	75.08 ± 7.08
BMI	24.31 ± 3.65	22.92 ± 4.29	23.74 ± 3.54
Duration of surgery (min)	106.60 ± 13.05	110.0 ± 22.17	117.60 ± 24.37
Duration of Anesth. (min)	117.0 ± 15.74	122.40 ± 22.23	127.60 ± 23.46

Data are expressed as mean ± SD

Figure 2

Table 2: Postoperative analgesic requirements of the three studied groups

Variables	Control (n= 25)	Gabapentin (n= 25)	Melatonin (n= 25)
Total analgesic dose (mg, mean±SD)	126.4 ±14.5	72.4 ±15.8*	97.4 ±10.9**
Median time to first analgesic demand (h)	0 (0-2)	16 (10-20) *	4 (2-4) **

Data are expressed as mean ± SD or median (range).
*p< 0.05 relative to the control group
*p< 0.05 relative to gabapentin group

The VAS scores were significantly lower in G and M groups compared with the control group starting immediately and at (2h, 6h and 8 hours) postoperatively. VAS scores were significantly lower in G group compared to M group (Table 3). Four cases of G group did not need any analgesia during the first 24 hours postoperatively. On the other hand, 20 controls and a single patient of M group needed an analgesic immediately postoperative. Sedation scores were significantly higher in M group compared to both G and control groups up to 20 hours postoperatively (Figure1).

Figure 3

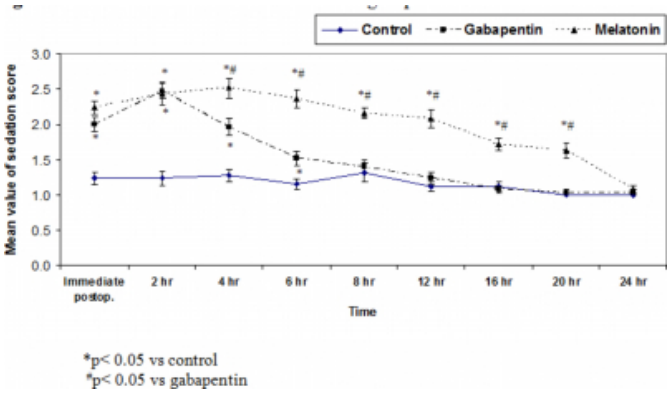
Table 3: Visual analogue score (VAS) in different studied groups

Variables	Control (n= 25)	Gabapentin (n= 25)	Melatonin (n= 25)
VAS immediate PO	4.44 ± 0.19	1.00 ± 0.15*	2.96 ± 0.32* ¤
VAS 2 hr	2.72 ± 0.27	1.24 ± 0.17*	3.52 ± 0.28* ¤
VAS 4 hr	2.12 ± 0.13	1.64 ± 0.15	3.16 ± 0.43 * ¤
VAS 6 hr	3.68 ± 0.2	1.76 ± 0.13*	1.04 ± 0.2*¤
VAS 8 hr	2.96 ± 0.24	2.00 ± 0.12*	2.12 ± 0.22*
VAS 12 hr	3.28 ± 0.23	2.44 ± 0.22*	3.68 ± 0.28 ¤
VAS 16 hr	2.92 ± 0.24	2.84 ± 0.26	2.88 ± 0.41
VAS 20 hr	3.12 ± 0.22	2.44 ± 0.38	1.88 ± 0.24*
VAS 24 hr	3.72 ± 0.17	1.32 ± 0.14*	2.00 ± 0.14**

Data are expressed as mean ± SE of means.
*p< 0.05 vs control
¤p< 0.05 vs gabapentin.
PO= Postoperattive.

Figure 4

Figure 1 : Sedation score in different studied groups



The most frequent side effect in G group was somnolence (36%) followed by headache (28%). Dizziness, drowsiness, somnolence as well as headache were rather common side effects of melatonin. No cases of pruritis or urinary retention were recorded in G and M groups (Table 4)

Figure 5

Table 4 : Side effects in different studied groups

Variables	Control (n= 25)	Gabapentin (n= 25)	Melatonin (n= 25)
Drowsiness	5 (20%)	1 (4%)	21 (84%)**
Dizziness	4 (16%)	4 (16%)	22 (88%)**
Somnolence	3 (12%)	9 (36%)*	19 (76%)**
Fatigue	14 (56%)	3 (12%)*	6 (24%)*
Nystagmus	0 (0%)	0 (0%)	1 (4%)
Headache	14 (56%)	7 (28%)*	13 (52%)
Blurred vision	0 (0%)	0 (0%)	2 (8%)
Nausea	10 (40%)	4 (16%)	1 (4%)*
Vomiting	10 (40%)	5 (20%)	1 (4%)*
Urinary retention	6 (24%)	0 (0%)*	0 (0%)*
Constipation	5 (20%)	4 (16%)	8 (32%)
Pruritis	6 (24%)	0 (0%)*	0 (0%)*

Data are expressed as n (%).
*p< 0.05 relative to control group
*p< 0.05 relative to gabapentin group.

DISCUSSION

This study demonstrated that, in patients undergoing abdominal surgery, gabapentin (600 mg, orally) one hour before surgery resulted in a significant reduction of the postoperative pethidine con¬sumption during the first 24 hours as well as lowering of pain score and increasing sedation score compared to placebo. Melatonin (6 mg, orally) produced similar effects. However, gabapentin showed significantly lower analgesic requirements and pain score while melatonin had significantly higher sedative effect.

In this study, gabapentin was used preoperatively as previous animal experiments showed that pretreatment with gabapentin was more effective and longer lasting than post-treatment. Pretreatment with a single dose of gabapentin blocked the develop¬ment of hyperalgesia (which is N-methyl-D-aspartate mediated NMDA) and tactile allodynia [which is -amino-3-hydroxy-5-methyl-4-isoxazolaproprionate (AMPA) and metabotropic receptor-mediated] for up to two days in a rat model of postoperative pain, while gabapentin one hour after intervention reduced symp¬toms for only three hours[23].

The chosen dose (600 mg) is within the limits of a recommended single dose in the treatment of neuropathic pain (300 to 1200 mg three times daily) [6]. Pandey et al.[24] randomized patients undergoing lumbar discectomy to receive a one-time dose of either placebo or gabapentin 300, 600, 900 or 1200 mg pre-operatively. The optimal dose was 600 mg; at higher doses (900 and 1200 mg), patients exhibited more side effects with no additional reduction in pain.

The test drugs were administered one hour before surgery as the peak plasma level of gabap¬entin is achieved 3 hours after ingestion of a single 300 mg capsule.[25] The time required to reach peak values of melatonin ranged from 0.25h to 13h.[26]

Promising results were reported in previous clinical studies using gabapentin for postoperative analgesia, in doses ranging from 300 to 1200 mg. A single dose of oral gabap¬entin 1200 mg administered preoperatively resulted in 50% reduction in movement related pain two and four hours after radical mastectomy.[27] The same dose resulted in a similar effect in spinal surgery patients.[28] In an another study, gabapentin 300 mg administered before and during the first 24 hr after abdominal hysterectomy reduced morphine consump¬tion by 32%, without significant effects on pain scores at rest or during mobilization.[29]

Smith et al.[30] dem¬onstrated that a single dose of 1200 mg gabapentin given 2 to 2.5 hr before induction of anesthesia reduced the need for additional postoperative pain treatment by 40% during the first 20 postoperative hours in patients undergoing vaginal hysterectomy. Also, preoperative gabapentin decreased pain scores and postoperative morphine consumption in patients following thyroid surgery.[1]

A meta-analysis of perioperative administration of gabapentinoids for postoperative pain relief reported that opioid-sparing effect was not related to the gabapentin dose[31]. In one trial, increasing the dose from 300 mg to 600-1200 mg improved the analgesic and opioid-sparing

effect of gabapentin, but there were no significant differences between the effects of the higher doses [24].

In the current study, pain VAS scores were significantly reduced in gabapentin-treated group. Similar results were reported in previous studies regardless the dif¬ference in surgical procedures. Meta-analyses have demonstrated that this anticonvulsant drug leads to a reduction in post-operative pain scores in addition to reduction of post-operative opioid use[25,32-34]. Hurley et al.[31] showed that perioperative administration of gabapentin decreased both pain intensity scores and opioid consumption for up to 24 h. Preemptive use of gabapentin significantly decreases postoperative pain and rescue analgesic requirement in laparoscopic cholecystectomy[35].

With a small dose of 300 mg of gabapentin orally, Montazeri et al.[21], reported significant decreases postoperative pain and rescue analgesic requirements in patients undergoing lower extremity orthopaedic surgery.

This study compared the antinociceptive effects of both melatonin and gabapentin that demonstrated analgesic effects as a preemptive analgesic and in acute postoperative pain management.

Recent evidence has demonstrated analgesic, anti-inflammatory, and anxiolytic properties of melatonin. Anxiety can produce aggressive reactions, which result in an increase in the distress experienced by the patient, and make the management and control of postoperative pain more difficult[36]. Anxiolytic and analgesic effects of melatonin may improve the control of postoperative pain through controlling the higher anxiety that accompanies surgical interventions.

A recent randomized clinical trial demonstrated that preoperative melatonin, 5 mg on the night before the surgery and 1 hour before the start of surgery, produced clinically relevant anxiolytic and analgesic effects in the first 24 postoperative hours[37].

A more recent study found that patients treated with melatonin preoperatively presented a greater reduction in pain and required lower morphine consumption in the postoperative period. The benefits of these interventions were statistically and clinically significant to produce postoperative anxiolysis, which led to lower postoperative pain, as well as lower morphine consumption throughout the first 24 hours after surgery[38].

In the present study, gabapentin was found to have higher effects than melatonin with respect to intensity of pain, and opioid consumption during the postoperative period. Melatonin, on the other hand, was more superior in its sedative effect. This difference can be attributed to the more direct analgesic effects of gabapentin, in addition to its anxiolytic properties[39-41], while melatonin was mainly anxiolytic drug dealing with the emotional component of pain rather than its sensory component.

The mechanism of action of gabapentin is likely mediated by binding to the 21 subunits of the presynaptic voltage-gated calcium channels, which are upregulated in the dorsal root ganglia and spinal cord after surgical trauma. It may produce antinociception by inhibiting calcium influx via these channels[25].

Gabapentin has antiallodynic and antihyperalgesic properties with only a minor effect on normal nociception[42]. It reduces the hyperexcitability of dorsal horn neurons induced by tissue injury[27,43]. Central sensitization of these neurons is important in chronic neuropathic pain, but also occurs after trauma and surgery. Reduction in central sensitization may reduce acute postoperative pain. Gabapentin may also prevent opioid tolerance[44].

In conclusion, a pre-emptive oral dose of 600 mg of gabapentin or 6 mg of melatonin reduces the pain scores and pethidine requirements in the first postoperative 24 hours in patients undergoing abdominal 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 postoperative period, otherwise gabapentin is preferable.

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Author Information

Khalda Radwan, MD
Associate Professor of Anesthesiology, Department of Anesthesia, Theodor Bilharz Research Institute, Giza, Egypt

Maha Youssef, MD
Associate Professor of Anesthesiology, Department of Anesthesia, Theodor Bilharz Research Institute, Giza, Egypt

Amr El-Tawdy, MD
Lecturer of Anesthesiology, Department of Anesthesia, Theodor Bilharz Research Institute, Giza, Egypt

Mohamed Zeidan, MD
Lecturer of Anesthesiology, Department of Anesthesia, Theodor Bilharz Research Institute, Giza, Egypt

Nabaweya Kamal, MD
Associate Professor of Anesthesiology, Department of Anesthesia, Theodor Bilharz Research Institute, Giza, Egypt