J Anesth (2010) 24:155–160
DOI 10.1007/s00540-010-0891-8

ORIGINAL ARTICLE

Effects of preoperative oral melatonin medication on postoperative analgesia, sleep quality, and sedation in patients undergoing elective prostatectomy: a randomized clinical trial

Hale Borazan · Sema Tuncer · Naime Yalcin · Atilla Erol · Seref Otelcioglu

Received: 14 April 2009 / Accepted: 16 December 2009 / Published online: 26 February 2010

Abstract
Purpose Our intention was to assess the effectiveness of preoperative oral melatonin medication on sedation, sleep quality, and postoperative analgesia in patients undergoing elective prostatectomy.
Methods Fifty-two ASA I–II patients undergoing elective prostatectomy were included in this study, randomly divided into two groups. Patients received an oral placebo ($n = 26$) or 6 mg melatonin ($n = 26$) the night before and 1 h before surgery. All patients received a standard anesthetic protocol. At the end of surgery, all patients received tramadol i.v. via a PCA device. Extubation time, intraoperative fentanyl consumption, and recovery time were assessed at the end of the operation. Pain scores, tramadol consumption, and sedation scores were assessed at 1, 2, 4, 6, 12, 18, and 24 h postoperatively, and sleep quality and subjective analgesic efficacy were assessed at 24 h after surgery.
Results There were no significant differences in demographic data between the groups. Extubation time and recovery time from anesthesia were significantly longer in the melatonin group ($P < 0.05$). Intraoperative fentanyl usage, pain scores, and tramadol consumption were significantly lower in the melatonin group ($P < 0.05$). The postoperative sleep quality of patients was significantly better in the melatonin group than in the control group ($P < 0.05$). Postoperative VAS of pain was significantly lower in the melatonin group compared with the control group at 1, 2, 4, 6, 12, 18, and 24 h postoperatively ($P < 0.05$). Subjective analgesic efficacy of patients was significantly different between groups ($P < 0.05$). The sedation scores were significantly higher in the melatonin group than in the control group at 1 h and 2 h after surgery ($P < 0.05$).
Conclusions Preoperative oral melatonin administration decreased pain scores and tramadol consumption and enhanced sleep quality, sedation scores, and subjective analgesic efficacy during the postoperative period.

Keywords Melatonin · Postoperative analgesia · Sedation · Tramadol · General anesthesia

H. Borazan · S. Tuncer · N. Yalcin · A. Erol · S. Otelcioglu
Department of Anesthesiology and Reanimation,
School of Medicine, Selcuk University, Konya, Turkey

H. Borazan (✉)
Selcuk Universitesi Meram Tip Fakultesi Anesteziyoloji ve Reanimasyon A.D., Akyokus, Meram, Konya, Turkey
e-mail: hborazan@hotmail.com

Introduction

Postoperative pain affects recovery from surgery and anesthesia. For effective postoperative pain relief, many different analgesic agents or techniques are commonly used, depending on the choice of doctors [1].

Melatonin, a close derivative of serotonin (5-hydroxytryptamine, 5-HT), is known as a neuro-hormone that is synthesized and secreted by the pineal gland. Its secretion regulates and modifies circadian rhythms and sleep [2]. Environmental changes such as hospital stay, medication, pain, stress, and general anesthesia can affect the sleep–wake cycle. Plasma melatonin levels, which play an important role in the regulation of sleep–wake cycles, are decreased after surgery and in hospitalized patients [3]. Exogenous melatonin, which is often administered orally, has a number of beneficial effects such as facilitating the onset and the quality of sleep [4]; alleviating preoperative anxiety and producing sedation [5]; regulating circadian

rhythms [6]; and producing anticonvulsant and antiinflammatory effects [7]. It has also been suggested that melatonin promotes the release of β-endorphin in the brain, which may be one of the mechanisms of melatonin's action to induce analgesia [8].

Considering the potential wide-spectrum and pharmacological benefits of melatonin as a therapeutic or dietary agent, this randomized, double-blind study was designed and conducted to assess the effects of oral melatonin premedication on postoperative analgesia, sleep quality, subjective analgesic efficacy, and sedation of patients undergoing elective prostatectomy.

Methods

The study was conducted in September 2007–February 2008. The study group comprised 52 ASA physical status I–II patients 50–65 years old who were scheduled for elective open prostatectomy under general anesthesia and who could operate a patient-controlled analgesia (PCA) device. The study was approved by the Institutional and Central Ethics Committee. Prior approval and written informed consent were also obtained from participants.

Exclusion criteria included a history of congestive heart failure, valvular heart disease, hepatic or renal failure, psychiatric disorders, sleep disorders, chronic pain syndromes, mental impairment, and drug or alcohol abuse. Patients receiving drugs with known analgesic properties within 24 h before surgery were also excluded from the study.

The patients were randomly divided into two groups (26 patients in each) by using a computer-generated randomization list. Patients received either a placebo tablet (control group) or a 6-mg oral melatonin tablet (melatonin group: Melatonina tablet; Przedsiebiorstwo Farmaceutyczne, Ostrzykowizna, Zacrozym, Poland) the night before surgery (11 p.m.) and again 1 h before surgery. Tablets were given to the patients in an isolated quiet room in the operating suite by a nurse who was not involved in the study. The staff involved in data collection and patient management were unaware of the group assignments. No other preoperative medication was given.

In the operating room, after monitoring of heart rate (HR), noninvasive blood pressure (NIBP), and oxygen saturation (SpO_2), an 18 G i.v. cannula was inserted. All patients were administered 7 ml/kg saline solution before the induction of anesthesia. After preoxygenation, anesthesia was induced with i.v. 1 mg/kg lidocaine, 2 mg/kg propofol, 1.5 μg/kg fentanyl, and 0.5 mg/kg atracurium. After tracheal intubation, the lungs were ventilated with an initial tidal volume of 6–8 ml/kg, and respiratory frequency of 12 breaths per minute was adjusted to maintain the end-tidal CO_2 between 35 and 40 mmHg. Anesthesia was maintained with 1.0–1.5% isoflurane and 60% nitrous oxide in oxygen. Patients were observed for inadequate anesthesia [9], defined as increases in mean arterial pressure (MAP) >30% from baseline lasting ≥1 min, HR >90 bpm lasting ≥1 min, patient movement, eye opening, swallowing, grimacing, lacrimation, or sweating. When evidence of inadequate anesthesia was observed, an intermittent 50 μg i.v. bolus of fentanyl was given. Tramadol 100 mg was administered i.v. immediately before discontinuing isoflurane and nitrous oxide. At the beginning of skin closure, residual neuromuscular blockade was antagonized with i.v. neostigmine 1.5 mg and atropine 0.5 mg. After the skin closure at the end of surgery, anesthetic agents were discontinued and patients were extubated. After total recovery from anesthesia (as evaluated by the ability to open the eyes, grip a finger, and breathe deeply on request), all patients received PCA with i.v. tramadol and were monitored for 24 h by the study nurses, who were blind to the study protocol. The PCA technique and visual analog scale (VAS) were explained to the patients during the preoperative visit. The PCA solution contained tramadol 10 mg/ml. Tramadol was chosen as a rescue medication because of its less sedative effect. The administration variables were as follows: initial dose of 1 mg/kg, demand dose of 20 mg, lockout interval of 10 min, and no continuous infusion with PCA device (Abbot Pain Management Provider, North Chicago, IL, USA).

The primary endpoint with respect to the efficacy of the study drug was postoperative tramadol consumption. Secondary endpoints were VAS determination, subjective assessment of analgesic efficacy, and sleep quality. Postoperative pain was assessed using a VAS, where 0 cm equaled no pain and 10 cm equaled the worst imaginable pain. Degree of sedation was determined according to a sedation score [10] ranging from 0 to 4 (0, alert; 1, mildly drowsy/easy to rouse; 2, frequently drowsy/easy to rouse; 3, somnolent/difficult to rouse; 4, asleep). The efficacy of analgesia was assessed using a subjective analgesic efficacy score [10] ranging from 1 to 5, in which patients were asked: "How effective was your medication in relieving your pain over the last 24 h?", with responses being 1 = excellent, 2 = good, 3 = satisfactory, 4 = poor, and 5 = very poor. Sleep quality [10] was determined by asking "How was your sleep quality during the last 24 h?," with responses being 1 = much better than usual, 2 = better than usual, 3 = same as usual, 4 = worse than usual, and 5 = much worse than usual. The assessment procedure was explained to the patients during the preoperative anesthesia consultation.

Patients were evaluated according to pain scores, HR, NIBP, SpO_2, tramadol consumption, and sedation scores at 1, 2, 4, 6, 12, 18, and 24 h. Subjective analgesic efficacy

and sleep quality were assessed at 24 h postoperatively. Ondansetron 8 mg was given i.v. when requested by patients or when nausea and vomiting were recorded.

Statistical analyses

Statistical analyses were made using SPSS software (Statistical Package for the Social Sciences, version 13.0; SPSS, Chicago, IL, USA). A sample size of 25 patients was analyzed, and a statistically significant difference of 15% or more was detected in tramadol consumption with a power of 85% and a significance level of 5%. Descriptive statistics are expressed as mean ± SD unless otherwise stated. All normally distributed variables were analyzed using the Kolmogrov–Smirnov test. A Student's *t* test was used for comparison of the mean in normal distribution. A chi-square test was used for categorical data. Analysis of variance (ANOVA with post hoc Tukey's test) was used for repeated measures. A *P* value less than 0.05 was considered to be statistically significant.

Results

There were no significant differences between groups with respect to age, weight, duration of surgery, and anesthesia (Table 1). Extubation time and recovery time from anesthesia (including eye opening, responding to verbal commands, and ability to grip a finger) were longer in the melatonin group ($P < 0.05$). Fentanyl consumption during the operation was significantly lower in the melatonin group ($P < 0.05$) (Table 1).

Postoperative VAS of pain was significantly lower in the melatonin group compared with the control group at 1, 2, 4, 6, 12, 18, and 24 h postoperatively ($P < 0.05$) (Fig. 1).

Table 1 Patient characteristics and intraoperative variables

Variables	Control group ($n = 26$)	Melatonin group ($n = 26$)
Age (year)	58 ± 6	57 ± 7
Weight (kg)	71 ± 7	69 ± 9
ASA-PS I/II (*n*)	8/18	9/17
Duration of anesthesia (min)	109 ± 8	112 ± 9
Duration of surgery (min)	104 ± 16	108 ± 10
Intraoperative fentanyl dosage (μg)	152 ± 25	120 ± 18*
Extubation time (min)	3 ± 2	9 ± 2*
Recovery time (min)	7 ± 2	13 ± 3*

Values are shown as number of patients or mean ± SD

ASA-PS American Society of Anesthesiologists physical status

* $P < 0.05$ versus control group

Tramadol consumption was significantly lower in the melatonin group than in the control group at 1, 2, 4, 6, 12, 18, and 24 h postoperatively ($P < 0.05$) (Fig. 2).

The sleep quality of the patients in the melatonin group was significantly better than that in the control group ($P < 0.05$) (Table 2).

There was a significant difference in subjective analgesic efficacy between groups ($P < 0.05$) (Table 3). The sedation scores were significantly higher in the melatonin group than in the control group at 1 h and 2 h after surgery ($P < 0.05$) (Table 4).

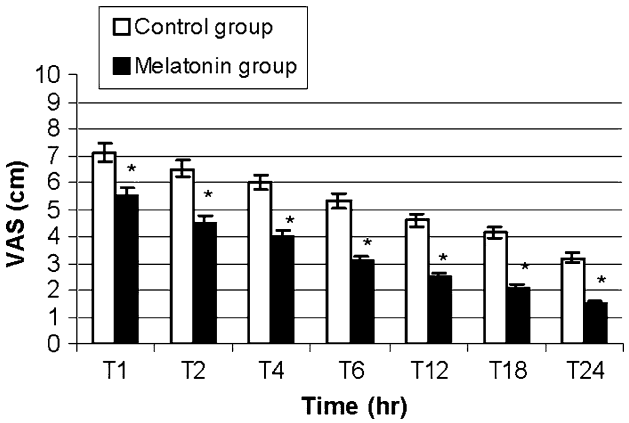

Fig. 1 Visual Analog Scale (VAS) pain scores in the melatonin and control groups. VAS pain scores at T1, T2, T4, T6, T12, T18, and T24 h postoperatively were significantly less in the melatonin group (*black bars*) compared with the control group (*white bars*) ($P < 0.05$). *$P < 0.05$ between melatonin and control groups. Values are presented as mean ± SD

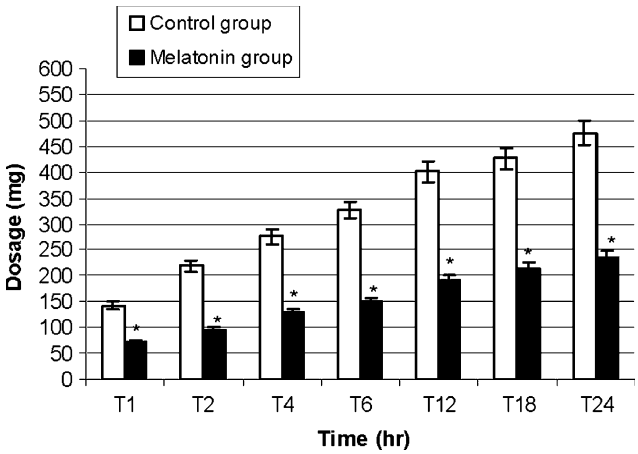

Fig. 2 Patient-controlled analgesia (PCA)-tramadol consumption dosages in the melatonin and control groups. Tramadol consumption at T1, T2, T4, T6, T12, T18, and T24 h postoperatively was significantly lower in the melatonin group (*black bars*) than in the control group (*white bars*) ($P < 0.05$). *$P < 0.05$ between melatonin and control groups. Values are presented as mean ± SD

Discussion

Melatonin has been associated with pain relief in patients with tissue injuries [11] and possesses antiinflammatory effects [12]. Although several findings have fueled speculation that melatonin affects pain sensitivity via an opiatergic mechanism [13], it is conceivable that melatonin may modulate variations in pain perception by affecting the activity of β-endorphin [14]. However, the exact analgesic mechanism of melatonin has been poorly understood to date. The melatonin analgesic effect in the current study was clinically evident by lower pain scores and reduction in PCA-tramadol consumption during the first 24 h after the surgery. With respect to subjective analgesia, the patients who received oral melatonin had better analgesic efficacy, and all patients in this group were satisfied with their postoperative analgesia and stated that they would prefer the same analgesic medication in the future, if needed.

Anesthesia and surgery alter the normal circadian pattern of melatonin production [15]. Isoflurane and propofol anesthesia have been reported to elevate plasma melatonin levels until the recovery period [15]. Patients anesthetized with isoflurane emerged from general anesthesia more slowly than those anesthetized with sevoflurane [16]. However, a mechanism may exist whereby these anesthetics change the levels of circulating melatonin. These anesthetics may have changed GABAergic transmission differently, thereby influencing the melatonin levels [15]. These findings indicate that isoflurane may have a higher potential to increase circulating melatonin levels than sevoflurane. In the present study, longer extubation time and recovery time in the melatonin group were primarily related to exogenous melatonin, which was given before the operation. Secondarily, it also may be related to isoflurane, the inhalation agent used for maintaining anesthesia. The patients in the melatonin group tended to be more sedated during the recovery period. Altered circulatory melatonin levels during and after isoflurane anesthesia may be responsible for the different degrees of postoperative sedation observed between the melatonin and control groups.

It was shown that exogenous melatonin had other benefits, such as prevention of delirium [17] and sleep disturbances following operation [18]. Sleep disturbances are frequently reported by hospitalized patients, and pain appears to be an important factor in these patients [19]. It was shown that poor sleep led to reports of higher pain intensity; also, greater pain affected sleep quality [20]. Providing sufficient analgesia is considered to be one of the

Table 2 Sleep quality of patients

Score	Control group ($n = 26$)	Melatonin group ($n = 26$)
1	0 (0)	4 (15.4)*
2	0 (0)	19 (73.1)*
3	21 (80.8)	3 (11.5)*
4	4 (15.4)	0 (0)*
5	1 (3.8)	0 (0)

Sleep quality of patients at 24 h postoperatively

Values are number (percentage in parentheses)

* $P < 0.05$ versus control group

Table 3 Subjective analgesic efficacy of patients

Score	Control group ($n = 26$)	Melatonin group ($n = 26$)
1	1 (3.8)	14 (53.9)*
2	2 (7.7)	10 (38.4)*
3	18 (69.3)	2 (7.7)*
4	5 (19.2)	0 (0)*
5	0 (0)	0 (0)

Subjective analgesic efficacy of patients at 24 h postoperatively

Values are number (percentage in parentheses)

* $P < 0.05$ versus control group

Table 4 Sedation scores of patients during the first 24 h postoperative periods

Sedation scores (h)	Control group ($n = 26$)					Melatonin group ($n = 26$)				
	0	1	2	3	4	0	1	2	3	4
1	14 (53.9)	10 (38.4)	2 (7.7)	0 (0)	0 (0)	0 (0)*	1 (3.8)*	23 (88.5)*	2 (7.7)	0 (0)
2	7 (26.9)	17 (65.4)	2 (7.7)	0 (0)	0 (0)	0 (0)*	12 (46.1)*	14 (53.9)*	0 (0)	0 (0)
4	5 (19.2)	19 (73.1)	2 (7.7)	0 (0)	0 (0)	3 (11.5)	18 (69.3)	5 (19.2)	0 (0)	0 (0)
6	2 (7.7)	21 (80.8)	1 (3.8)	2 (7.7)	0 (0)	2 (7.7)	18 (69.3)	5 (19.2)	1 (3.8)	0 (0)
12	3 (11.5)	19 (73.1)	2 (7.7)	2 (7.7)	0 (0)	2 (7.7)	18 (69.3)	3 (11.5)	3 (11.5)	0 (0)
18	5 (19.2)	17 (65.4)	4 (15.4)	0 (0)	0 (0)	4 (15.4)	17 (65.4)	5 (19.2)	0 (0)	0 (0)
24	8 (30.8)	16 (61.5)	2 (7.7)	0 (0)	0 (0)	6 (23.0)	18 (69.3)	2 (7.7)	0 (0)	0 (0)

Values are number (percentage in parentheses)

* $P < 0.05$ versus control group

most helpful interventions to reduce sleep disturbances [20]. Anxiety has been suggested as playing another important role in the sleep–wake cycle, and alleviating anxiety may improve the quality of sleep [21]. It is known that melatonin has anxiolytic properties and that it may be mediated via GABAergic system activation [22]. It was demonstrated that 5 mg oral melatonin given preoperatively had a clinical effect on anxiolysis [5, 23]. In another study, Caumo et al. [24] showed the effect of 5 mg oral melatonin in attenuating anxiety and improving postoperative pain response among patients undergoing abdominal hysterectomy with epidural anesthesia. The present study also indicated that reduction of pain during the postoperative period promotes better sleep. Therefore, it is suggested that the sedative-like effects of melatonin decrease preoperative anxiety when given before surgery, and that this effect may be associated with decreased postoperative pain and sleeping problems because poor sleep can influence pain thresholds and, consequently, higher doses of analgesics are required.

In the present study, the mean VAS pain score in the control group was 7 cm at T1. This finding may be the result of an intraoperative small dose of fentanyl, low initial dose of tramadol in PCA, and the method that was used to measure the perceived pain. There is no single well-accepted and widely applicable method of measuring intraoperative pain. In the present study, intraoperative pain was assessed by hemodynamic changes associated with pain, such as increases in HR and BP. In this condition, additional fentanyl was given to patients. It must be stated that the initial dose of 1 mg/kg tramadol from PCA may have been insufficient. Therefore, it may be appropriate to administer an initial dose of 2 mg/kg tramadol for acute, severe postoperative pain for this type of surgery. We assessed postoperative pain with a VAS, which is a valid tool for measurement of pain but that has certain limitations. A VAS measures pain as an nondimensional experience; it quantifies only the intensity of pain and not the quality of pain. Perceptions of pain, and how pain is rated on the VAS scale, may vary considerably between patients. All these factors may account for the high VAS score recorded at the T1 period in the control group.

According to the sedation scores, the patients who received oral melatonin had a significantly higher level of sedation during the first 2-h period after surgery, compared with the control group. Although the sedation level increased in the melatonin group, all patients in both groups were not difficult to arouse. This finding may be related to the use of isoflurane and the cumulative doses of tramadol medication. The reduced pain in the melatonin group (evidenced by lower pain scores) may be related to better sedation levels, which therefore promoted better quality of sleep. Also, previous studies have demonstrated that melatonin both induced sleep and improved sleep quality [3, 25]. Naguib and Samarkandi [5] compared 5 mg oral melatonin and 15 mg midazolam for effects on sedation and found that midazolam produced higher sedation levels. The patients included in their study were young women. A limitation of the current study was that the study investigated only men. Further studies are required to compare the results of both genders within the same study, based on a different type of surgery.

In conclusion, oral administration of melatonin the night before and 1 h before surgery was effective in decreasing both postoperative pain and PCA-tramadol consumption and in increasing sleep quality, sedation, and subjective analgesic efficacy in patients undergoing prostatectomy.

Acknowledgments There are no research grants or sources of financial support related to the topic or topics of the manuscript.

Conflict of interest statement We have no personal or financial relationships that have any potential to inappropriately influence (bias) our actions or the manuscript, and no financial or other potential conflicts of interest exist (including involvement with any organization with a direct financial, intellectual, or other interest in the subject of the manuscript) regarding the manuscript.

References

1. Rawal N, Berggen L. Organization of acute pain services: a low cost model. Pain. 1994;57:117–23.
2. Pacchierotti C, Lapichino S, Bossini L, Pieraccini F, Castrogiovanni P. Melatonin in psychiatry disorders: a review on the melatonin involvement in psychiatry. Front Neuroendocrinol. 2001;22:18–32.
3. Basket JJ, Cockrem JF, Todd MA. Melatonin levels in hospitalized elderly patients: a comparison with community based volunteers. Age Ageing. 1991;20:430–4.
4. Tzischinsky O, Laive P. Melatonin possesses time-dependent hypnotic effects. Sleep. 1994;17:638–45.
5. Naguib M, Samarkandi AH. Premedication with melatonin: a double blind, placebo controlled comparison with midazolam. Br J Anaesth. 1999;82:875–80.
6. Weaver DR, Stehle JH, Stopa EG, Reppert SM. Melatonin receptors in human hypothalamus and pituitary: implications for circadian and reproductive responses to melatonin. J Clin Endocrinol Metab. 1993;76:295–301.
7. Tan DX, Reiter RJ, Manchester LC, Yan MT, El-Sawi M, Sainz RM, Mayo JC, Kohen R, Allegra M, Hardeland R. Chemical and physical properties and potential mechanisms: melatonin as a broad spectrum antioxidant and free radical scavenger. Curr Top Med Chem. 2002;2:181–97.
8. Yu CX, Zhu CB, Xu SF, Cao XD, Wu GC. The analgesic effects of peripheral and central administration of melatonin in rats. Eur J Pharmacol. 2000;403:49–53.
9. Soppit AJ, Glass PS, El-Moalem H, Ginsberg B, Weatherwax K, Gan TJ. Duration and recovery profile of cisatracurium after succinylcholine during propofol or isoflurane anesthesia. J Clin Anesth. 1999;11:652–6.
10. Webb AR, Leong S, Myles PS, Burn SJ. The addition of a tramadol infusion to morphine patient-controlled analgesia after

abdominal surgery: a double-blinded, placebo-controlled randomized trial. Anesth Analg. 2002;95:1713–8.
11. Ebadi M, Govitrapong P, Phansuwan-Pujito P, Nelson F, Reiter RJ. Pineal opioid receptors and analgesic action of melatonin. J Pineal Res 1998;24:193–200.
12. Reiter RJ, Calvo JR, Karbownik M, Qi W, Tan DX. Melatonin and its relation to the immune system and inflammation. Ann NY Acad Sci. 2000;917:376–86.
13. Golombek DA, Escolar E, Burin LJ, De Brito Sánchez MG, Cardinali DP. Time-dependent melatonin analgesia in mice: inhibition by opiate or benzodiazepine antagonism. Eur J Pharmacol. 1991;194:25–30.
14. Shavali S, Ho B, Govitrapong P, Sawlom S, Ajjimaporn A, Klongpanichapak S, Ebadi M. Melatonin exerts its analgesic actions not by binding to opioid receptor subtypes but by increasing the release of beta-endorphin, an endogenous opioid. Brain Res Bull. 2005;64:471–9.
15. Karkela J, Vakkuri O, Kaukinen S, Huang WQ, Pasanen M. The influence of anaesthesia and surgery on the circadian rhythm of melatonin. Acta Anaesthesiol Scand. 2002;46:30–6.
16. Frink EJ Jr, Malan TP, Atlas M, Dominguez LM, DiNardo JA, Brown BR Jr. Clinical comparison of sevoflurane and isoflurane in healthy patients. Anesth Analg. 1992;74:241–5.
17. Hanania M, Kitain E. Melatonin for treatment and prevention of postoperative delirium. Anesth Analg. 2000;94:338–9.
18. Gogenur I, Rosenberg J. Sleep disturbances after non-cardiac surgery. In: Lee-Chiong T, editor. Sleep: a comprehensive handbook. Hoboken: Wiley; 2006. p. 913–25.
19. Closs SJ. Patient's night-time pain, analgesic provision and sleep after surgery. Int J Nurs Stud. 1992;29:381–92.
20. Chassard D, Duflo F, Bouvet L, Boselli E. Chronobiology of postoperative pain: it's time to wake up!. Can J Anesth. 2007;54:685–8.
21. Phillips GD, Cousins MJ. Neurological mechanisms of pain and the relationship of pain, anxiety and sleep. Acute pain management. New York: Churchill Livingstone; 1986. p. 21–48.
22. Wan Q, Man HY, Liu F, Braunton J, Niznik HB, Pang SF, Brown GM, Wang YT. Differential modulation of GABAA receptor function by Mel 1a and Mel 1b receptors. Nat Neurosci. 1999;2:401–3.
23. Naguib M, Samarkandi AH. The comparative dose-response effect of melatonin and midazolam for premedication of adult patients: a double-blinded placebo-controlled study. Anesth Analg. 2000;91:473–9.
24. Caumo W, Torres F, Moreira NL, Auzani JA, Monteiro CA, Londero G, Ribeiro DF, Hidalgo MP. The clinical impact of preoperative melatonin on postoperative outcomes in patients undergoing abdominal hysterectomy. Anesth Analg. 2007;105:1263–71.
25. Wurtman RJ, Zhdanova IV. Improvement of sleep quality by melatonin. Lancet. 1995;346:1491–2.