RESEARCH ARTICLE

The Efficacy of Melatonin, Clonidine and Gabapentin in Reducing Preoperative Anxiety and Postoperative Pain in Patients Undergoing Laparoscopic Cholecystectomy: A Randomized Clinical Trial

Vahide Sadat Hoseini[1], Reza Atef Yekta[2], Shaqayeq Marashi[1], Seyed Mojtaba Marashi[2]*

Background: We performed this study to evaluate the efficacy of melatonin, clonidine and gabapentin in reducing preoperative anxiety and postoperative pain in patients undergoing laparoscopic cholecystectomy.

Methods: This study was a randomized clinical trial on patients scheduled for laparoscopic cholecystectomy. A total number of 88 patients were categorized into four groups to receive melatonin, clonidine, gabapentin and placebo (22 patients per group). The anxiety level was evaluated by State-Train Anxiety Inventory (STAI) just before the entrance of patients into the operating room. The intensity of pain was determined according to standard VAS (Visual Analog Scale) criteria for pain assessment at 1, 2, 6, 12 and 24 hours after surgery. The times of receiving the first dose of morphine and also total amount of administered morphine during first 24 hours after surgery were documented. The frequency of vomiting episodes and the intensity of post-operative nausea and vomiting (PONV) during first 24 hours after surgery were recorded according to the VAS criteria.

Results: Regarding age, gender, weight, height, systolic blood pressure, diastolic blood pressure and heart rate, no significant differences were noted between the treatment groups. Also regarding the state-trait anxiety score, there were no significant differences between treatment groups (P=0.27). The pain intensity was different between groups (p<0.01); as the placebo group had the highest score; however paired comparison between intervention groups did not show significant differences. The intensity of pain was significantly decreased by the time (P<0.01) and depending on the assigned group, the pain reduction trend was different among treatment groups (P<0.01). In general, the clonidine group had the least pain score in different time periods.

Conclusion: Use of melatonin as a premedication had the efficacy similar to the efficacy of clonidine and gabapentin in reducing preoperative anxiety, postoperative pain and also reducing narcotic consumption.

Keywords: Melatonin; gabapentin; preoperative anxiety; cholecystectomy; postoperative pain

Among the most common and most predictable perioperative problems are post-operative pain and pre-operative anxiety. Since the anxiety can promote aggressive reactions by patients, so the management and control of postoperative pain would be difficult in such situations [1]. In addition, higher levels of postoperative pain may increase the risk of surgical complications [2]. Therefore, considering the pain as a sensory and emotional experience, it is justified to provide a preoperative treatment for controlling the postoperative pain [3]. The analgesic, anti-inflammatory, anti-anxiety and anti-agitation effects of melatonin have been shown in several studies [4]. Although some studies indicate that preoperative administration of melatonin can reduce postoperative pain and decrease narcotic consumption, but its effect on pain and anxiety has not yet been elucidated to be recommended widely. Also, some other studies have found controversial results in this regard [5-7].

On the other hand, acute pain after laparoscopic cholecystectomy has a complex nature and is not similar to pain in other laparoscopic procedures; so analgesic therapy in this surgery may be different or multi-dimensional [8]. Gabapentin has selective effect on nociceptive process and premedication and has showed promising efficacy in reducing postoperative pain and anxiety [9-11]. Also, treatment with clonidine has several advantages before, during and after surgery; it reduces bleeding, provides hemodynamic stability, reduces pain and need for intraoperative analgesia, reduces effects of intubation on blood pressure and heart rate, reduces nightmare and finally

From the [1]Research Development Center, Shariati General Hospital, Tehran University of Medical Sciences, Tehran, Iran.
[2]Department of Anesthesiology and Critical Care, Shariati General Hospital,Tehran, Iran.
Received: 5 September 2015, Revised: 29 September 2015, Accepted: 14 October 2015
The authors declare no conflicts of interest.
*Corresponding author: Seyed Mojtaba Marashi, MD. Department of Anesthesiology and Critical Care, Shariati General Hospital, Tehran University of Medical. Email: marashi@tums.ac.ir

reduces salivary secretion caused by ketamine [12-16].

Regarding the multiple effects of melatonin, this hormone can play a role in control of pain in these patients. However, it is not sufficient to show clinical efficacy of a new therapeutic option just by comparing it with placebo. In addition to approval of positive effects of a drug in a randomized placebo controlled trial, it is also essential to compare these effects with similar drugs and other pharmaceutical interventions that are extensively used in routine practice as premedication of surgery which have known analgesic and anti-anxiety effects.

In the present study, the primary outcomes for evaluating efficacy of these drugs were reducing postoperative pain and preoperative anxiety. The hemodynamic stability and reduction in PONV were considered as secondary outcomes.

Methods

Eighty eight patients referred to our center in October 2013 to August 2014 for laparoscopic cholecystectomy were randomly divided into four groups of melatonin (M), clonidine (C), gabapentin (G) and placebo (P). All patients had American Society of Anesthesiologists (ASA) class of I or II. Patients with history of congestive heart failure, valvular heart disease, renal or hepatic failure, psychiatric disorders (physical symptoms, depression, loss of energy), drug abuse, uncontrolled hypertension and also patients with language and communication problems were not enrolled in the study. This study was approved by the Ethics Committee of Tehran University of Medical Sciences on August 2013 with reference number of 92/130/912/D and was registered at www.irct.ir website with registration number of IRCT2014041217231N1. All patients signed written informed consent before entering into the study.

The allocation of treatment was done according to table of random numbers with random block sampling for any of the four treatment groups. Based on the allocated treatment, patients received 6mg melatonin or 0.2 mg clonidine or 600 mg gabapentin or placebo orally, 120 minutes before surgery. The investigational drugs or placebo related to each patient had been prepared by pharmacy according to random allocation table in shape of uniform capsules and were provided to a ward nurse within plates specified with patients' numbers. Two hours before surgery, the ward nurse who was not involved in data collection, gave the medication to the patients. No other medication was given to the patients before surgery. During the whole time of the study, blinding and randomization were done by a physician who was not involved in patient evaluation. The anesthesiology resident and anesthesiologist were unaware about the assigned treatment to any group of patients. Also, patients were not aware of medication name. So both researchers and patients were blinded to the pre-treatment.

The patient characteristics were collected by a structured questionnaire. The anxiety level was evaluated by State-Train Anxiety Inventory (STAI) just before the entrance of patients into the operating room.

The hemodynamic status of patients including heart rate, systolic, diastolic and mean arterial blood pressure were determined at the time of entrance into the operating room and also after induction of anesthesia. The intensity of pain was determined according to standard VAS (Visual Analog Scale) criteria for pain assessment at 1, 2, 6, 12 and 24 hours after surgery. The time of receiving the first dose of morphine and also total amount of administered morphine during first 24hours after surgery were documented. The frequency of vomiting episodes and the intensity of post-operative nausea and vomiting (PONV) during first 24 hours after surgery were recorded according to the VAS criteria. The intensity of post-operative pain was evaluated and documented by 10 cm VAS at 1, 2, 6, 12 and 24 hours after surgery [17]. So, the VAS score was ranging from zero (no pain) to 10 (highest possible pain). Also, preoperative anxiety was measured using standard questionnaire of SATI just before the entrance of patients into the operating room. The secondary outcomes including the amount of required narcotics during surgery, heart rate, blood pressure, nausea, vomiting, hypotension before and after induction of anesthesia and finally, chills after operation were also recorded.

Frequency of vomiting and severity of nausea were evaluated by 10 cm VAS within first 24 hours after surgery. The scores ranged from zero (no symptoms) to 10 (maximal symptoms). The amount of required morphine was determined by patient controlled analgesia (PCA) pump during first 24 hours after surgery.

Upon entering into the anesthesia room, all patients underwent standard monitoring. First, non-invasive monitoring devices such as blood pressure cuff, EKG and pulse oximetry were connected to the patients. Then, intravenous infusion of sodium chloride 0.9%, 5 ml/kg was established and then, premedication with sufentanil 0.4µg/kg and lidocaine 1.5 mg/kg was administered and induction of anesthesia was performed using sodium thiopental 4mg/kg and atracurium 0.5 mg/kg. Then, patients were intubated under guide of laryngoscopy. Maintenance of anesthesia was done by isoflurane 1-2 minimum alveolar concentration (MAC) in response to hemodynamic variations. Atracurium 0.3 mg/kg and sufentanil 5 µg were administered every 0.5 hours to the patients.

After transferring the patient to the recovery room, PCA pump containing morphine at a concentration of 0.5 mg/ml was connected to the patients. Device setting was adjusted as "basic infusion of 2 ml/h, demand dose of 1 ml and lockout Interval of 15 minutes". PCA pump was connected to the patients during the first 24 hours after surgery. According to preoperative educations that the patients had received, they were able to control their pain using PCA pump. The consumption of analgesics was measured by recording the amount of morphine they received via PCA.

Statistical analysis

Qualitative variables were reported as frequency and percentage and quantitative variables were reported as mean ± SD. In cases that treatment groups were compared, the analysis technique for quantitative variables was ANOVA, the significance level was defined less than 0.05and also post hoc test and Bonferroni test were used to compare 2×2 groups. For qualitative variables, chi-square test was used. If a variable such as pain was compared at different times between the groups, then repeated measures ANOVA were applied and if the significance level was less than 0.05, the post hoc and Bonferroni were used to compare 2×2 groups. To illustrate the difference between anxiety score, pain and morphine consumption within the first 24 hours after surgery between the intervention groups and the control group, the sample size was calculated separately. If the amount of administered morphine over 24 hours in each of the 3 groups

to be half of the placebo group, with regard to the standard deviation of 0.2mg/kg, α = 0.05 and power of 90%, then 22 patients in each group were required.

In order to show 4 units difference in anxiety score, with standard deviation of 4, α = 0.05 and power of 90%, then 22 patients in each group were required again. With this sample size, it is possible to demonstrate 1 unit difference in pain score with standard deviation of 1 unit. If the above differences to be observed in paired comparisons for 3 groups of melatonin, clonidine, and gabapentin, it stands for the difference between those groups; otherwise the groups would be considered as equal.

Results

Eighty eight patients were randomly divided into four groups of melatonin (M), clonidine (C), gabapentin (G) and placebo (P). The baseline characteristics of patients in a descriptive-analytic way are shown (Table 1). The study results did not show significant differences between intervention groups in terms of age and sex and BMI. Although patients with ASA class I accounted a greater percentage among all treatment groups but there was no statistically significant difference between groups.

One hour after surgery, the mean ±SD of the pain intensity in melatonin, gabapentin, clonidine and placebo groups were 6.14 ± 0.46, 6.36± 0.79, 6.32 ± 0.56 and 6.59 ± 0.74 respectively. The pain intensity at 2, 6, 12 and 24 hours after surgery were presented in (Table 2). The pain intensity was different between groups ($p < 0.01$); as the placebo group had the highest score.

Also, the results indicated that pain reduction by time was significant ($p < 0.01$) and depending on the treatment group of patient, the trend of pain reduction was different ($p < 0.01$); as the lowest reduction of pain was noted in placebo group.

(Table 3) shows that when state and trait anxiety scores were compared in groups, significant differences were not found. Also, the mean of required amount of opioids during operation in melatonin group was lower than other groups, yet this difference was not statistically significant (p= 0.752). Significant differences between the frequency and severity of nausea in the first 24 hours following surgery were not observed between the groups. Regarding the need for morphine in the first 24 hours after surgery, the rate of morphine consumption in the placebo group was higher than other groups ($P < 0.001$), but there was no significant difference between intervention groups.

The trend of systolic and diastolic blood pressure before and after induction of anesthesia are shown (Figure 1-2). According to the findings, the reduction in systolic and diastolic blood pressure was not significantly different between treatment groups. Also, the systolic and diastolic blood pressure was significantly reduced over time ($P <0.001$), yet the trend of decline was not significantly different between groups. The blood pressure level in the clonidine group was lower before and after the induction of anesthesia (clonidine= 119.99 vs. melatonin=131.22, gabapntin= 135.78 and placebo= 133.09) and its decline after induction of anesthesia was lower than other groups; but this difference was not statistically significant (p= 0.273).

According to (Figure 3), the reduction of heart rate did not show significant difference between treatment groups. Also, the heart rate was significantly reduced within 24 hours ($P < 0.01$).

Discussion

This study was a randomized clinical trial on patients who were candidate for laparoscopic cholecystectomy. The participants were categorized into four treatment groups of melatonin (M), clonidine (C), gabapentin (G) and placebo (P). The results showed a significant difference in pain scores between groups; as the highest score was noted in the placebo group while the intervention groups had less pain. The paradigm of pain reduction in the intervention groups was similar. The amount of opioid consumption increased parallel to the increase in the intensity of pain.

According to the results of other studies, after taking gabapentin and melatonin, the intensity of postoperative pain has significantly decreased compared to control group that is consistent with the results of this study [18-20]. However, another study on 44 females who were candidate for laparoscopic cholecystectomy had shown that intravenous administration of melatonin during laparoscopic cholecystectomy had no significant effect on post-operative pain which is inconsistent with the results of the present study [6]. This inconsistency may be due to different route of administration of melatonin, or insufficient sample size. Also, Bhartiet al study on 60 patients who were candidate for cholecystectomy showed that administration of 3µg clonidine could effectively reduce postoperative pain compared with placebo group, which is consistent with the results of the present study [21]. It has been shown in some studies that the degree of preoperative anxiety in melatonin receivers had no significant difference with control group which was consistent with the results of present study [22]. But in another study, the amount of preoperative anxiety was significantly higher in placebo group compared with melatonin group [19]. It is suggested that analgesic effect of melatonin may be due to its anti-anxiety activity [23]. It is also showed that different mechanisms such as activation of melatonin MT1 and MT2 receptors, indirect activation of opioid receptors and inhibition of pro-inflammatory cytokines are responsible for analgesic effects of melatonin [24-25]. According to the results of our study, we did not detect a significant anti-anxiety activity but a significant analgesic effect of melatonin was shown. So, one can conclude that the observed analgesic effect cannot be attributed to melatonin's anxiolytic activity.

According to the results of other studies, administration of clonidine modifies systolic and diastolic blood pressure and reduces the need to adjuvant drugs for controlling hemodynamic symptoms during surgery; so this drug can be used for modification of hemodynamic symptoms during laparoscopic surgeries [13-14]. Similar reduction in systolic and diastolic blood pressure was observed in this study, but that was not statistically significant, which might be due to insufficient sample size.

According to the best of our knowledge, this study was the first study that compared clonidine, melatonin, gabapentin and placebo simultaneously. The results showed that the drugs used in this study had no significant difference in reducing preoperative anxiety compared to placebo; but postoperative pain was significantly decreased in the treatment groups compared with placebo. Regarding the systolic and diastolic blood pressure and heart rate, no

significant differences and no apparent pattern of pain reduction were noted in postoperative pain.

Table 1- Baseline characteristics of the study population

Variable	Studied groups				F statistics	P value
	Placebo	Melatonin	Gabapentin	Clonidine		
Age (Years)	38.14 ± 10.80	39.45 ± 11.40	40.50 ± 8.38	44.14 ± 8.41	1.50	0.22
Weight (Kg)	75.09 ± 8.23	81.82 ± 6.07	76.68 ± 8.92	75.14 ± 21.93	1.38	0.25
Body Mass Index (BMI)	28.14 ± 3.64	29.8 ± 2.21	29.11 ± 4.36	27.71 ± 4.36		0.316
ASA Class I	59.1%	54.5%	59.1%	50%		0.917
ASA Class II	40.9%	45.5%	40.9%	50%		0.917

Table 2- Comparison of post-operative pain in the intervention groups

Intensity of pain	Studied groups				Treatment effect (P value)	Time effect (P value)	Treatment * time effect (P value)
	Placebo	Melatonin	Gabapentin	Clonidine			
1 hour after surgery	6.59 ± 0.74	6.14 ± 0.46	6.36 ± 0.79	6.32 ± 0.56	< 0.01	< 0.01	< 0.01
2 hours after surgery	4.95 ± 1.13	3.36 ± 0.65	3.05 ± 0.65	3.59 ± 0.85			
6 hours after surgery	3.09 ± 1.01	1.50 ± 0.67	1.64 ± 1.02	1.68 ± 0.94			
12 hours after surgery	1.36 ± 1.04	0.95 ± 0.78	0.77 ± 0.57	0.86 ± 1.08			

Table 3- Comparison of clinical characteristics and anxiety

Variable	Studied groups				P value
	Placebo	Melatonin	Gabapentin	Clonidine	
State anxiety	39.73 ± 6.35	41.18 ± 10.15	41.09 ± 4.78	38.65 ± 8.04	0.67
Trait anxiety	38.26 ± 4.48	37.28 ± 9.30	38.47 ± 2.55	40.95 ± 5.19	0.27
Narcotic during surgery	20.91 ± 5.42	19.86 ± 4.36	20.91 ± 5.99	20.59 ± 4.63	0.752
Frequency of vomiting	1.48 ± 0.37	1.27 ± 0.91	1.41 ± 0.58	1.94 ± 0.68	0.226
Severity of nausea	3.37 ± 1.68	3.21 ± 1.64	2.96 ± 1.19	3.18 ± 1.30	0.366
Need to morphine	78.41 ± 13.30	64.77 ± 12.95	65.91 ± 11.81	60.68 ± 10.83	0.001

Figure 1- Trend of systolic blood pressure changes at different times in different treatment groups

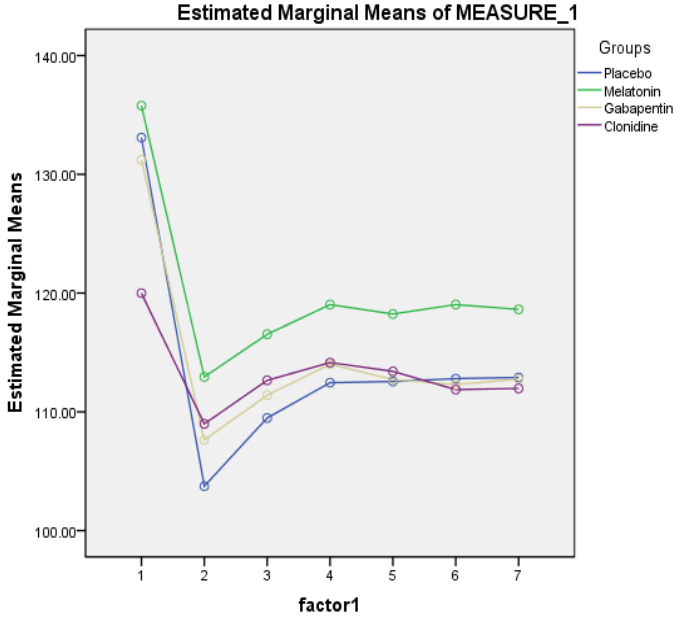


Figure 2- The trend of diastolic blood pressure at different times in different treatment groups

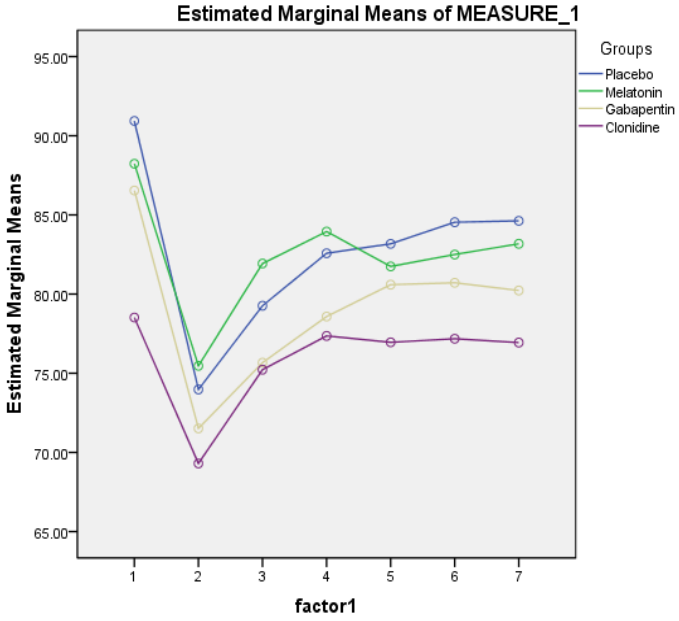
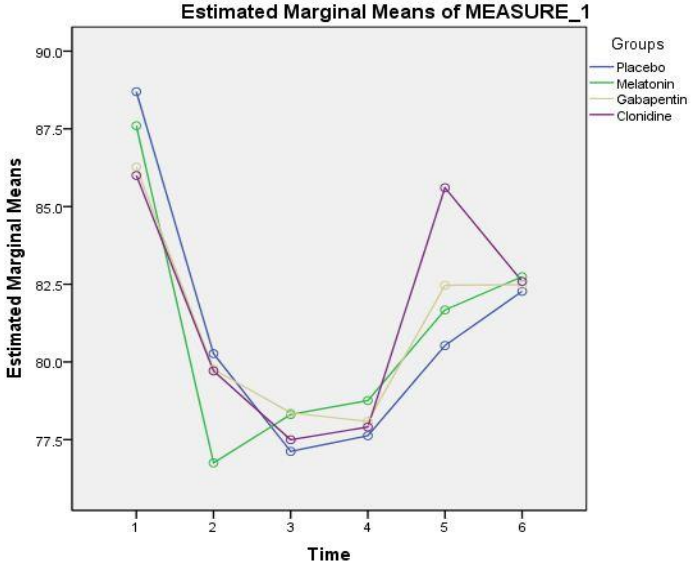


Figure 3- The trend of heart rate at different times in different treatment groups



Conclusion

In general, the results of this study showed that the use of melatonin as a premedication had the efficacy similar to the efficacy of clonidine and gabapentin for reducing postoperative pain and also reducing narcotic consumption.

References

1. Thomas V, Heath M, Rose D, Flory P. Psychological characteristics and the effectiveness of patient-controlled analgesia. Br J Anaesth. 1995; 74(3):271-6.
2. Beattie WS, Buckley DN, Forrest JB. Epidural morphine reduces the riskof postoperative myocardial ischaemia in patients with cardiac risk factors. Can J Anaesth. 1993; 40(6):532-41.
3. Loeser JD, Melzack R. Pain: an overview. Lancet. 1999; 353(9164):1607-9.
4. Kurdi MS, Patel T. The role of melatonin in anaesthesia and critical care. Indian J Anaesth. 2013; 57(2):137-44.
5. Capuzzo M, Zanardi B, Schiffino E, Buccoliero C, Gragnaniello D, Bianchi S, et al. Melatonin does not reduceanxiety more than placebo in the elderly undergoing surgery. Anesth Analg. 2006; 103(1):121-3.
6. Andersen LP, Kucukakin B, Werner MU, Rosenberg J, Gogenur I. Absence of analgesic effect of intravenous melatonin administration during daytime after laparoscopic cholecystectomy: a randomized trial. J Clin Anesth. 2014; 26(7):545-50.
7. Yousaf F, Seet E, Venkatraghavan L, Abrishami A, Chung F. Efficacy and safety of melatonin as an anxiolytic and analgesic in the perioperative period: a qualitative systematic review of randomized trials. Anesthesiology. 2010; 113(4):968-76.
8. Bisgaard T. Analgesic treatmentafter laparoscopic cholecystectomy: a critical assessment of the evidence. Anesthesiology. 2006; 104(4):835-46.
9. Seib RK, Paul JE. Preoperative gabapentin for postoperative analgesia: a meta-analysis. Can J Anaesth. 2006; 53(5):461-9.
10. Ménigaux C, Adam F, Guignard B, Sessler DI, Chauvin M. Preoperative gabapentin decreases anxiety and improves early functional recovery from knee surgery. Anesth Analg. 2005; 100(5):1394-9.
11. Turan A, Karamanlioglu B, Memis D, Usar P, Pamukçu Z, Türe M. The analgesic effects of gabapentin after total abdominal hysterectomy. Anesth Analg. 2004; 98(5):1370-3.

12. Ebneshahidi A, Mohseni M. Premedication with oral clonidine decreases intraoperative bleeding and provides hemodynamic stability in cesarean section. Anesth Pain Med. 2011; 1(1):30-3.
13. Chandrashekaraiah M, Upadya DM, Jayachandran S, Wali M. Effects of clonidinepremedication on hemodynamic changes during laparoscopic cholecystectomy-A randomized control study. Applied Cardiopulmonary Pathophysiology. 2011; 15:91-8.
14. Rafiei M, Hjjat M, Ariana M, Kianersi K. Evaluation of oral clonidine premedication on hemodynamic parameters during laparoscopic cholecystectomy. Ann Mil Health Sci Res. 2012; 10(1):67-71.
15. Kehlet H, Gray A, Bonnet F, Camu F, Fischer H, McCloy R, et al. A procedure-specific systematic review and consensus recommendations for postoperative analgesia following laparoscopic cholecystectomy. Surg Endosc. 2005; 19(10):1396-415.
16. Hackmann T, Friesen M, Allen S, Precious DS. Clonidine facilitates controlled hypotension in adolescent children. Anesth Analg. 2003; 96(4):976-81.
17. Scott J, Huskisson E. Graphic representation of pain. Pain. 1976; 2(2):175-84.
18. Clivatti J, Sakata RK, Issy AM. Revisão sobre o Uso de Gabapentina para Controle da Dor Pós-Operatória. Revista Brasileira de Anestesiologia. 2009; 59(1):87-98.
19. Ionescu D, Badescu C, Ilie A, Miclutia I, Iancu C, Ion D, et al. Melatonin as premedication for laparoscopic cholecystectomy: a double-blind, placebo-controlled study. Southern African J Anaesth Analg. 2008; 14(4):8-11.
20. Srivastava U, Kumar A, Saxena S, Mishra AR, Saraswat N, Mishra S. Effect of preoperative gabapentin on postoperative pain and tramadol consumption after minilap open cholecystectomy: a randomized double-blind, placebo-controlled trial. Eur J Anaesthesiol. 2010; 27(4):331-5.
21. Bharti N, Dontukurthy S, Bala I, Singh G. Postoperative analgesic effect of intravenous (i.v.) clonidine compared with clonidine administration in wound infiltration for open cholecystectomy. Br J Anaesth. 2013; 111(4):656-61.
22. Kücükakin B, Klein M, Lykkesfeldt J, Reiter R, Rosenberg J, Gögenur I. No effect of melatonin on oxidative stress after laparoscopic cholecystectomy: a randomized placebo-controlled trial. Acta Anaesthesiol Scand. 2010; 54(9):1121-7.
23. Caumo W, Levandovski R, Hidalgo MP. Preoperative anxiolytic effect of melatonin and clonidine on postoperative pain and morphine consumption in patients undergoing abdominal hysterectomy: a double-blind, randomized, placebo-controlled study. J Pain. 2009; 10(1):100-8.
24. Ambriz-Tututi M, Rocha-Gonzalez HI, Cruz SL, Granados-Soto V. Melatonin: a hormone that modulates pain. Life Sci. 2009; 84(15-16):489-98.
25. Srinivasan V, Zakaria R, Jeet Singh H, Acuna-Castroviejo D. Melatonin and its agonists in pain modulation and its clinical application. Arch Ital Biol. 2012; 150(4):274-89.