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Original Article

Effect of Pregabalin on Morphine Consumption, Sleep, Mood and Ability to Change Position After Colorectal Cancer Surgery

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Abstract

Introduction: Pregabalin is a co-analgesic to improve the pain control after colorectal cancer surgeries. There is less knowledge about the effect of Pregabalin on postoperative sleep and the ability to change the position of patients after surgery. This study aimed to assess the impact of Pregabalin on postoperative morphine consumption, pain, sleep, mood, and ability to change position after colorectal cancer surgery.

Methods: This double-blind, randomized, controlled, single-center clinical trial was performed in Tehran, Iran, from June 2017 to June 2018. Seventy patients were included for colorectal cancer surgery randomly divided into two groups (A, B). Group A received two doses Pregabalin (150 mg) pre-operative and post-operative, and group B as a placebo was administered at the same scheme. The two groups had similar analgesia and anesthesia regimens. The pain was scored by a numerical rating scale (NRS); disturbance in sleep,

and mood. The daily activity was numbered based on a scoring system such as BPI questionnaires; and, nausea- vomiting, morphine consumption, and fatigue headache were evaluated 48 hours after surgery.

Results: Morphine consumption was lower in the Pregabalin group 24 h after surgery (P=0.01). The two groups were similar regarding sleep interference scores and side effects (P>0.05). But, mood and actions interference scores in the Pregabalin group showed a significant improvement in 48 h postoperative (P<0.05) (Table 3).

Conclusion: The results showed that Pregabalin could reduce postoperative morphine consumption and improve mood and actions interference scores after colorectal cancer surgery. However, there was no difference between Pregabalin and placebo in postoperative pain management and sleep interference scores after colorectal cancer surgery.

Keywords: Pregabalin, colorectal cancer surgery, pain management, morphine consumption sleep, mood, actions.

Introduction

Colorectal surgery proceeds acute pain, particularly in the early postoperative days [1, 2]. Because of the dependence of the pain nature to multifactorial conditions, various analgesia administration may be recommended after colorectal surgery. However, the effective postoperative pain management regimen for colorectal surgery is debatable [3, 4]. Intense pain following surgery can be together with prolonged wound healing, increased infections, development of chronic pain, and rising costs [5-7]. Opioids are the first option for managing moderate to severe postoperative pain, but opioids application has limitations such as possible adverse effects [6-12].

Pregabalin is used as an anticonvulsant in the first-line medication for neuropathic pain syndromes. Different dosages of pregabalin have been extensively applied as a co-analgesic medication to reduce postoperative pain in various types of operations such as total knee arthroplasty, spinal surgery, cholecystectomy, total hip

arthroplasty, and nasal surgery. Researches assessed the perioperative administration of pregabalin-applied doses varying from 50 to 300 mg and daily doses varying from 50 to 750mg [5-7, 14-28].

Pregabalin and gabapentin are gamma-aminobutyric acids and (because of similar molecular form), both materials outcomes in the same pathway [8-12].

They bind to calcium channels and modulate calcium influx like GABAergic neurotransmission effects [8-10].

Some studies have assessed Pregabalin in different types of surgery and but still for pain management after colorectal surgery is under investigation [29-32]. Studies have shown that preemptive use of Pregabalin in the laparotomy analgesia scheme displayed a reduction in opioid demands and better postoperative pain management [11-14].

There is the advantageous effect of Pregabalin in postoperative pain relief and adverse events in laparoscopic operations [14-16]. The application of Pregabalin for postoperative pain management is off-label, and hence, there is no agreement in dosing guidelines for this implication.

However, the effect of the Pregabalin regimen in colorectal cancer surgery is still questionable. Also, the impact of Pregabalin on the postoperative sleep and ability to change position of patients after surgery is less well known. This study aimed to assess the effect of Pregabalin on sleep, mood, morphine consumption, and ability to change position numeric scores, after colorectal cancer surgery.

Methods

This double -blind, randomized, controlled, single-center clinical trial was performed in Imam Khomeini hospital, Tehran, Iran from June 2017 to June 2018.

Seventy patients with the American Society of Anesthesiologists (ASA) physical status I or II, underwent elective open colorectal cancer surgery under general anesthesia.

Seventy patients were included for colorectal cancer surgery randomly by block randomization divided into two groups.

Exclusion criteria were history of chronic pain, regular usage of analgesics or Pregabalin, intolerance or allergy to Pregabalin renal or hepatic insufficiency, uncontrolled chronic diseases such as hypertension and diabetes, psychiatric diseases, and any drug abuse disability or movement disorders.

Anesthetic and surgery methods were performed by the same groups. Noninvasive monitoring (such as oxygen saturation (SpO2), electrocardiogram (ECG), noninvasive blood pressure (NIBP), and intravenous access) were adjusted for all patients in the operating room After monitoring general anesthesia of patients was established. Anesthesia was performed with fentanyl 3 µg/kg and midazolam 0.03 mg/kg. Induction of anesthesia was done with 5 mg/kg Sodium thiopental and 0.5 mg/kg Atracurium was performed. Then, 10 mg Atracurium, and 50 µg fentanyl per 30 min intraoperative were used.

Group A received two doses of Pregabalin (150 mg) pre-operatively and post-operatively, and group B as placebo was administered at the same scheme. The two groups had identical analgesia regimens otherwise. 30 min before the end of the operation, 0.8 mg of IV (Intravenous) morphine was injected and one gram of IV paracetamol was infused. After extubation, the patients were transferred to the recovery area. According to the hospital protocol, in case of moderate to severe pain, and if the sedation score was 0 or 1, respiratory rate > 7/ min, systolic BP > 90 mmHg, then IV morphine was titrated at a dose of 2 mg every 5 minutes until the pain improved or the patient was comfortable. After morphine titration was accomplished, the IV morphine was administered every 4 hours. If the patient had met discharge criteria, the patient transferred to the intensive care unit. A total opioid dose administered to patient in the preceding 12 hours was recorded and provided upon handover of patient to another clinical area. For the breakthrough pain (additional pain on top of basal pain upon any activity), one tenth of the preceding daily morphine consumption was injected before any planned activity (like respiratory physiotherapy, changing the dresses, etc.). On the first night after the surgery, patents in the case group received 150 mg oral Pregabalin. The patient's pain score was measured every three hours for the first and second 24 hours after the surgery. The IV paracetamol was infused every 6 hours as well.

All variables such as pain score, sleep, mood, ability to change position, morphine consumption, and possible side-effects (nausea- vomiting, fatigue, headache, dizziness drowsiness, blurred vision, fatigue, dry mouth, headache, impaired balance) of Pregabalin were evaluated at 24 and 48 hours postoperative.

NRS was explained for participants as a ruler that is

numbered from 0 to 10. A score of zero indicates no pain, and a score of 10 shows the imaginable worst pain.

The variables such as sleep, mood, and actions interference scores (how pain interfered with sleep, mood and actions) were recorded based on BPI questionnaires during 24 and 48 postoperative periods. The Sleep mood and actions interference scores contain an 11-point Likert scale in assessed patients that how pain has interfered with their sleep and mood during the past 24 and 48 hours' post-operative, that 0 indicates no sleep and mood interference and 10 is the worst imaginable sleep, mood and actions interference.

To preventing of bias, the checklist form was enrolled in the postoperative stage by an assistant who was blinded to the analgesia groups the patients, and were blinded to analgesia group.

Ethical consideration

The research protocol was approved by the Ethics Committee of Tehran University of Medical Sciences under IR.TUMS.IKHC.REC.1397.333 cod. All patients were written informed consent form. The analgesia was provided for all patients.

Data analysis

Data were analyzed by SPSS-21 software. Mean, standard deviation, frequency and percent were presented for description of data. Chi2, Fishers' exact test, and Mann-Whitney test were used for comparing data between two groups. A P-value less than 0.05 was considered statistically significant.

Results

Overall, 70 patients were included in the two groups. There was no difference between the two groups regarding demographic characteristics such as gender, age and BMI (P>0.05) (Table 1).

Pain (NRS min) showed a decreasing trend in both study groups (P<0.001). The trend of decreasing changes in the Pregabalin group was similar to the placebo group (P>0.05). Pain (NRS average) showed a decreasing trend in both study groups (P<0.001). The trend of decreasing changes in the Pregabalin group was similar to the placebo group (P>0.05). Also, pain (NRS max) showed a decreasing trend in both study groups (P<0.001). The trend of decreasing changes in the Pregabalin group was similar to the placebo group (P>0.05) (Table 2).

Table 1: Patients demographics characteristics

	Pregabalin	Placebo	P-value
Male/female (no.)	17/18	16/19	0.94
Age, (years±SD)	42.11±11.21	41.07±9.10	0.54
BMI (kg/m^2±SD)	26.36±2.98	26.80±4.02	0.87

Table 2: Comparison of pain (NRS min., average and max.) in the two groups

Pain, NRS	Pregabalin	Placebo	P-value
NRS min., 24 Hour	2.80±1.62	3.28±2.12	0.27
48 Hour	2.08±1.35	2.57±1.59	0.17
NRS average, 24 Hour	4.82±1.63	5.25±1.69	0.29
48 Hour	3.74±1.55	4.32±1.42	0.11
NRS Max., 24 Hour	6.88±1.96	7.25±1.46	0.37
48 Hour	5.57±1.81	6.14±1.57	0.17

The two groups were similar in terms of sleep interference scores (P>0.05). But, there were differences between the two groups regarding the ability to change the position scores (P<0.05). Mood interference scores in the Pregabalin group showed a significant improvement in 48 h postoperatively (P<0.05) (Table 3).

Morphine consumption was lower in the Pregabalin group at 24 h postoperatively (P=0.01). Morphine consumption in both groups showed a decreasing trend. The trend of decreasing changes in the pregabalin group is more than the placebo group and this difference was statistically significant (table 4).

The two groups were similar in terms of possible side effects of pregabalin (P>0.05). The incidence of dizziness, as well as drowsiness, headache, itching, blurred vision, fatigue, dry mouth, headache, impairment balance did not differ between the two groups (Table 5).

Table 3: Sleep, mood and actions interference scores in the two groups

Sleep interference scores	Pregabalin	Placebo	P-value
First 24 Hours	5.68±2.60	6.11±2.21	0.46
Second 24 hours	3.60±2.46	4.21±1.90	0.26
Mood interference scores			
First 24 Hours	4.20 ±2.27	5.01 ± 3.02	0.22
Second 24 hours	2.25±1.68	3.45±2.55	0.009
Action interference scores (ability to change position)			
First 24 Hours	6.54 (2.36)	7.88 (2.20)	0.02
Second 24 hours	3.51 (2.72)	5.37 (2.26)	0.003

Table 4: Comparison of morphine consumption in the two groups

morphine consumption	Pregabalin	Placebo	P-value
First 24 Hours(mg)	11.26±5.97	14.29±3.93	0.01
Second 24 hours(mg)	9.17±5.54	11.24±6.10	0.15

Table 5: Complications of patients in 48-hour after surgery

Items	Pregabalin	Placebo	P-value
Dizziness	7 (20.0%)	13 (37.1%)	0.33
Drowsiness	3 (8.6%)	1 (2.9%)	0.63
Blurred vision	3 (8.6%)	1 (2.9%)	0.63
Fatigue	4 (11.4%)	1 (2.9%)	0.36
Dry mouth	20 (57.1)	22 (62.9%)	0.63
Headache	2 (5.7%)	2 (5.7%)	0.99
Impaired balance	2 (5.7%)	4 (11.4%)	0.67

Discussion

The results showed that Pregabalin could reduce postoperative morphine consumption and improve mood and actions interference scores after colorectal cancer surgery. However, there were no differences between Pregabalin and placebo group regarding postoperative sleep interference scores and side effects. A multimodal pain management strategy needs to be used to enhance analgesic effectiveness and decrease the amount of opioid consumption [5-7]. There is a difference in analgesic agents in surgeries [6-8]. Though, the standard of administration for postoperative pain control in colorectal cancer surgery has not been recognized still [5]. Different studies have examined several methods to reduce the incidence and severity of postoperative pain [17]. Several interventions such as incisional or intraperitoneal installation of local anesthetics, steroids, cyclooxygenase-2 inhibitors, epidural anesthesia, NSAIDs, opioids have been assessed for postoperative pain control after colorectal surgeries [2, 18-21].

The results of the current study showed that the use of Pregabalin decreases postoperative opioid consumption as well as can improve mood and actions interference scores in colorectal cancer surgery. Also, the previous studies showed no significant effect of Pregabalin on postoperative pain management [23-24, 30]. Zhang et al (2011) showed that Pregabalin doses of <300 and ≥300 mg/day can reduce 24-hour opioid consumption but not affect pain amounts after the operation. Engelman et al. (2011) assessed studies according to the various Pregabalin dose grouped in 50–150, 225 –300, and 600 –750 mg/day. They showed that the lowest efficient Pregabalin dose for decreasing postoperative opioid consumption was 225 –300 mg/day with no decrease in pain amounts [31]. Chang et al. (2009) demonstrated that there was no significant effect of 300 mg Pregabalin on pain management after laparoscopic shoulder surgery [24]. The current study showed that the two groups were similar in terms of postoperative side effects and the incidence of dizziness, as well as drowsiness, headache, itching, blurred vision, fatigue, dry mouth, headache, impairment balance, which did not differ between the two groups. Agarwal et al. (2008) showed that opioid consumption is lower in the group with imposing 150 mg/hour Pregabalin before laparoscopic cholecystectomy than the placebo group. But, there were no differences in side effects in the two groups [22]. Peng et al. (2008) showed the efficacy of two doses of Pregabalin (50 and 75 mg) on the analgesia relief in laparoscopic cholecystectomy at the first 90 min. But, there were no significant differences with the placebo group in over 90 min. They showed 75 mg dose of Pregabalin administered better pain relief than 50 mg, but there was no decrease in opioid consumption. There were no differences in side-effects between groups [23]. Balaban et al. (2012) demonstrated the influence of two different doses (150 mg and 300 mg) of preoperative Pregabalin on pain relief after laparoscopic cholecystectomy. They showed that a dose of 300 mg Pregabalin showed better analgesia than a placebo two hours postoperative, and also, 300 mg showed superior analgesia than 150 mg one hour after surgery. There was a decrease in opioid consumption for the first 30 min. But, the side effects were similar between the groups [25]. Gianesello et al. (2011) showed a reduction of pain after major spinal surgery with a starting dose of 300 mg Pregabalin pre-operative and 150 mg Pregabalin twice a day for 48 hours after surgery. The outcomes extend

previous information in the course of preemptive analgesia and encourage the use of higher doses of Pregabalin as preemptive analgesia [12]. Many studies showed that preemptive Pregabalin reaches significant postoperative analgesia [12, 22, 25]. However, further studies should be done about differences in Pregabalin dose in postoperative pain [29-32]. In the present study, opioid consumption was decreased in the Pregabalin group. Also, it can improve mood and actions interference scores. In the previous studies, Pregabalin was administered as a single preoperative dose one hour or two doses before and after surgery in dosages varying from 50 to 600 mg [11-25]. The results were not similar between studies and outcomes. This difference in outcomes are related to the different methodology, analgesic dose, different patients, and surgical methods [32]. It reported that low Pregabalin doses have a restricted analgesic effect, whereas greater doses are cause an increased incidence of side effects.

To the best of our knowledge, the current study is the initial randomized control trial study that assesses the effect of Pregabalin use in postoperative sleep, mood, and the actions interference scores (how pain interfered with sleep mood and actions) in colorectal cancer surgery. The results showed that there were no differences between Pregabalin and the placebo group in terms of postoperative sleep interference scores. Perhaps sleeping in the two groups was not significantly different due to other sleep-disturbing factors such as light and sound. However, the ICU conditions were the same for both groups. Also, the current study showed that the performance of two doses of 150 mg Pregabalin pre-operatively and post-operatively, compared to placebo, significantly decreased postoperative opioid consumption 24 hours after the surgery. So it can improve mood and actions interference scores after colorectal cancer surgery. Also, the side effects were similar in both groups. On the other hand, due to intestinal preparation, the long duration of patients' NPO and late postoperative PO, there is a possibility of dizziness, weakness, blurred vision, and imbalance in patients, which can cause no significant differences in side effects between the two groups.

Conclusion

The results showed that Pregabalin could reduce postoperative morphine consumption and improve mood and actions interference scores after colorectal cancer surgery. However, there was no relationship between Pregabalin and placebo in postoperative pain management and sleep interference scores after colorectal cancer surgery.

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Conflict of Interest Disclosures

The authors declare that they have no conflicts of interest.

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Authors' Contributions

Concept: Arman Taheri, Fatemeh Arjmandnia, Mojgan Rahimi; Data gathering: Arman Taheri, Fatemeh Arjmandnia, Hossein Majedi, Alireza Kazemeini, Fardin Yousefshahi, Mojgan Rahimi; Draft preparation and data analysis: Arman Taheri, Fatemeh Arjmandnia, Mojgan Rahimi.

Ethical Statement

The research protocol was approved by the Ethics Committee of Tehran University of Medical Sciences under IR.TUMS.IKHC.REC.1397.333 cod. All patients were written informed consent form. The analgesia was provided for all patients.

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