



Preemptive Analgesia with a Second Dose of Pregabalin, Acetaminophen, Naproxen, and Dextromethorphan: A Comparative Clinical Trial in Major Surgeries

Hamid Reza Amiri¹, Solmaz Ohadian Moghadam¹, Seyed Ali Momeni¹ and Majid Amini^{2,*}

¹Uro-Oncology Research Center, Tehran University of Medical Sciences, Tehran, Iran

²Department of Anesthesiology and Critical Care, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran

*Corresponding author: Department of Anesthesiology and Critical Care, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran. Email: aminimajid1990@gmail.com

Received 2020 January 16; Revised 2020 August 03; Accepted 2020 August 08.

Abstract

Background: Postoperative pain management can improve patients' quality of life and decrease hospitalization rates. Preemptive analgesia may provide an effective approach for both pain control and opioid consumption decrease. A common approach for pain management after surgery is to relieve the pain that has already occurred.

Objectives: The aim of this clinical trial was to compare the preemptive analgesic effect of single-dose versus two-dose administration of pregabalin, acetaminophen, naproxen, and dextromethorphan (PAND) combination.

Methods: This study involved 60 patients who had undergone one surgery (including nephrectomy, cystectomy, prostatectomy, colectomy, Whipple, and RPLND). They were randomly divided into two groups: The first group received a single dose of PAND, while the other group received a second dose within 6 hours after discharge from recovery. Pain intensity was assessed by the Universal Pain Assessment Tool (UPAT) in both groups 2, 4, 6, 8, 12, 24, and 48 hours postoperatively. The postoperative morphine dose in both groups was also recorded. Data were analyzed using SPSS version 25.

Results: Mean pain scores were significantly different between the two groups at 2, 12, 24, and 48 hours after surgery ($P < 0.05$). There was a statistically significant difference between the two groups in terms of opioid consumption ($P < 0.001$). The total opioid consumption in the second group (with the second administration of PAND) was lower than the first group.

Conclusions: Preemptive analgesia with a second dose of PAND is an effective method for reducing pain and morphine consumption after surgery.

Keywords: Preemptive Analgesia, Postoperative Pain, Major Surgeries

1. Background

Pain is one of the most common clinical problems, especially in patients after surgery. Pain reduction can increase patient satisfaction and decrease postoperative hospitalization (1, 2). Pain receptors in the damaged tissues can transfer signals that cause a cascade increasing the central and peripheral nervous response. Sensory processing changes cause a severe response to stimuli and pain. Blocking these signals may inhibit cascade progression and reduce postoperative pain (3). In the preemptive analgesic method, painkillers are used before painful stimulation, whereas in the conventional analgesic method, they are used after pain development. This method was first introduced in animal studies to reduce postoperative pain by Wall in 1988 (4) and Woolf in 1991 (5). Postoperative pain

can increase the hospitalization time and the risk of infection. Acute postoperative pain is observed in 10% - 65% of patients after surgery (6, 7). A common approach for pain management after surgery is to relieve the pain that has already occurred. On the other hand, there is a growing popularity for preoperative prescriptions of painkillers to reduce postoperative pain (8). Tissue damage during the surgical procedure causes the release of inflammatory chemical mediators. Some of these mediators, including histamine, acetylcholine, and bradykinin, cause pain, and some others, such as prostaglandins, cause hyperalgesia, which is characterized by a decrease in pain threshold and an increase in sensitivity to extrinsic stimuli (9). It is hypothesized that preventive analgesia leads to inhibition of central sensitization caused by an inflammatory stimulus of surgery (10). Therefore, this may spare patients from

long-term side effects and chronic pain, which usually lasts months after surgery (11). Chronic pain can lead to physical, mental, and social disabilities (11). Therefore, postoperative pain management is very important. Reducing postoperative pain increases satisfaction in most patients and decreases hospitalization as well as immobility complications. Thus effective preventive analgesia improves quality of life and reduces financial costs (12).

2. Objectives

The aim of the current clinical trial is to use a specific method of a two-stage preemptive analgesic method after 6 major surgeries by administration of pregabalin, acetaminophen, naproxen, and dextromethorphan (PAND) to develop a new method to reduce postoperative pain and reduce drug use in patients.

3. Methods

3.1. Patients

A double-blind study was conducted on 61 subjects that were aged between 18 and 80 years, and had an American Society of Anesthesiology (ASA) physical status between 1 and 3, who were referred to the operating room of Imam Khomeini Hospital affiliated to Tehran University of Medical sciences for one of the elective surgeries including radical prostatectomy, radical nephrectomy, radical cystectomy, Whipple procedure, total colectomy, and retroperitoneal lymph node dissection (RPLND) (Figure 1). This study was approved by the ethics in the research committee of Tehran University of Medical Sciences (code: IR.TUMS.IKHC.REC.1398.017). Signed informed consent was obtained from all participants of the study. Moreover, the current trial was registered in the Iranian registry of clinical trials (IRCT) at 2019-04-19, with IRCT code: IRCT20181219042046N1.

Exclusion criteria included opioids addiction, history of antidepressant and anticonvulsant drug use in the last 6 months, nonelective surgery, ASA physical status more than 3, history of drug sensitivity to preemptive analgesia agents used in this study (PAND), and the patients who did not extubate after surgery.

All patients received a combination of PAND with a small amount of water one hour before entering the operating room. After transferring to the ward, the patients were randomly divided into two groups for receiving the second dose. Simple randomization, based on a random number table, was used to randomize the participant. One (included odd numbers) that was given the second dose of PAND combination and one (included even numbers) that

did not receive any medication. Only the research guide was aware of the prescribed drug and none of the prescribing persons and patients were aware of the prescribed medicine. In the first group, a combination of pregabalin (151 mg), acetaminophen (one gram), naproxen (511 mg), and dextromethorphan (31 mg) was administered one hour before surgery and a second dose of the same combination was given within 6 hours after discharge from recovery. In the second group, the same combination is prescribed only one hour before surgery. All patients were transferred to the operating room and received 2 mg midazolam in addition to 2 mg/kg fentanyl as premedication. Then anesthesia was induced with 2 - 3 mg/kg thiopental sodium in addition to 0.5 mg/kg atracurium.

Anesthesia was followed with 0.8 - 1.2 isoflurane and a 50:50 mixture of nitrous oxide and oxygen. Before surgical incision, 1 μ g/kg fentanyl was injected, and atracurium, as well as fentanyl, were administered as needed for maintenance during anesthesia.

After skin closure, 40 μ g/kg neostigmine and 20 μ g/kg atropine were given to restore the neuromuscular block. The duration of each surgery was recorded in minutes from the moment of the incision until wound closure. Following extubation, the patients were transferred to recovery. After achieving complete consciousness, the pain intensity was assessed by the universal pain assessment tool (UPAT) (time zero). In addition, Pain intensity was assessed at 2, 4, 6, 8, 12, 24, and 48 hours postoperatively. The type of pain (somatic pain vs. acute neuropathic pain) was also recorded. Morphine was prescribed according to the protocol for pain scores greater than 4 (UPAT > 4) to control the patient's pain. Patients' first need for analgesic medication, cumulative doses of morphine used to control pain, and drug induced complications were recorded in the postoperative period.

Diagnosis of somatic pain and acute neuropathic pain was performed based on the standard definition for somatic and neuropathic pain (13) and the nature of the pain that the patient felt and described as well as our findings on physical examination.

3.2. The Randomization and Blinding Method

The randomization method was as follows: Patients were divided into two groups randomly according to the random number table to receive the second dose after being transferred to the ward. Accordingly, a random number was assigned to each patient (individual or paired). The combination of the drug and the placebo were packed in similar white bags by the research guide and were used as the second dose.

The group with odd numbers received a second dose of the drug compound, and the other group (even num-

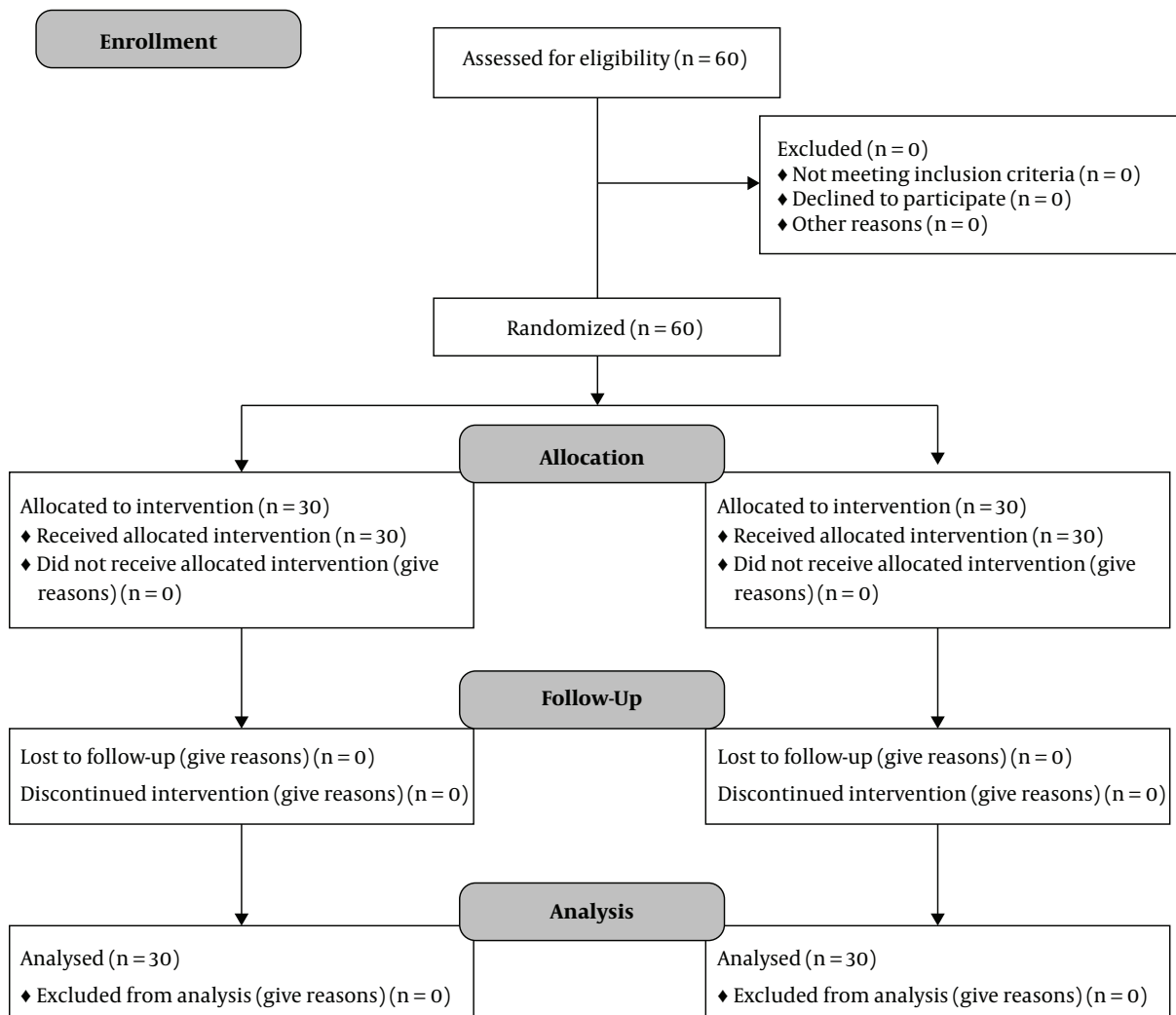


Figure 1. CONSORT 2010 flow diagram for the current study

bers) received the placebo. The only person who knew the contents of the envelope was the research guide, and the patients, the administrators, and outcome evaluators were blinded.

3.3. Statistical Analysis

Statistical analysis was performed with the Statistical Package for Social Sciences (SPSS) version 25.0 statistics software.

Central and dispersion indices were calculated for quantitative data (mean, standard deviation, and amplitude). An independent *t*-test was used to compare the effect of treatment in the two groups, Descriptive statistics and regression analysis was used for data analysis (ASA-ps,

gender, type of surgery, age over 75 years, units of blood consumption, and duration of anesthesia).

4. Results

Demographic data in the two groups (The one dose and two dose groups) are shown in Table 1. There was no statistically significant difference in the demographic data between the two groups.

Table 2 shows the mean pain scores in both groups at times 0, 1, 2, 6, 12, 24, and 48 hours postoperatively. Mean pain scores were significantly different in two groups at 2, 12, 24, and 48 hours after surgery ($P < 0.05$).

The mean pain score changes from 0 to 1, 1 to 2, 2 to 6, 6 to 12, 12 to 24, and 24 to 48 hours after surgery are shown in

Table 1. Demographic Characteristics in the One Dose and Two Dose Groups^{a, b}

Variable	Group I (N = 30)	Group II (N = 30)	P Value
Age, y	55.50 ± 13.73	58.20 ± 12.67	0.431
BMI, kg/m ²	25.16 ± 4.02	25.41 ± 3.72	0.802
Sex, M/F	25/5	22/8	0.347
ASA			0.186
I	17 (56.7)	10 (33.3)	
II	9 (30.0)	13 (43.4)	
III	4 (13.3)	7 (23.3)	
Type surgery			0.054
Prostatectomy	6 (20)	10 (33.3)	
Nephrectomy	1 (3.3)	5 (16.7)	
Cystectomy	9 (30.0)	3 (10.0)	
Whipple	5 (16.7)	2 (6.6)	
Colectomy	8 (26.7)	5 (16.7)	
RPLND	1 (3.3)	5 (16.7)	

Abbreviations: ASA, American Society of Anesthesiology; BMI, body mass index; SD, standard deviation.

^aValues are expressed as mean ± SD or No. (%).

^bStatistically significant difference: $P < 0.05$.

Table 2. Pain Scores in the One Dose and Two Dose Groups at 0, 1, 2, 6, 12, 24, and 48 Hours After Surgery^a

Time h	Group I	Group II	P Value
0	0.43 ± 1.35	0.50 ± 1.52	0.784
1	1.27 ± 2.05	1.0 ± 1.70	0.688
2	3.50 ± 2.67	2.13 ± 2.31	0.043
6	2.57 ± 2.67	1.90 ± 2.17	0.304
12	4.57 ± 2.68	1.37 ± 1.93	< 0.001
24	3.27 ± 2.149	2.07 ± 2.11	0.027
48	2.10 ± 1.78	1.03 ± 1.60	0.016

^aValues are expressed as mean ± SD.

Table 3. Based on the results, there was a significant difference between the two groups at 6 to 12 and 12 to 24 hours after surgery ($P < 0.05$). There was no significant difference in mean pain scores between the two groups at other times ($P > 0.05$).

Figure 2 shows the mean pain scores in both groups at times 0, 1, 2, 6, 12, 24, and 48 hours postoperatively. Mean pain scores were significantly different in two groups at 2, 12, 24, and 48 hours after surgery ($P < 0.05$).

Comparison of pain intensity at 0, 1, 2, 6, 12, 24, and 48 hours after surgery in patients over 65 years, over 90 kg, with BMI less than and greater than 25, with anesthesia duration less than 4 hours and longer than 4 hours among two groups are summarized in **Figure 3**.

Table 3. The Mean Pain Score Changes in the One Dose and Two Dose Groups^a

Postoperative Time, h	Group I	Group II	P Value
0 - 1	0.83 ± 1.46	0.50 ± 1.10	0.324
1 - 2	2.23 ± 3.26	1.13 ± 2.99	0.179
2 - 6	-0.93 ± 4.00	-0.23 ± 3.25	0.461
6 - 12	2.00 ± 3.62	-0.53 ± 3.18	0.006
12 - 24	-1.30 ± 2.94	0.70 ± 3.07	0.013
24 - 48	-0.30 ± .87	-0.53 ± 1.00	0.343

^aValues are expressed as mean ± SD.

4.1. Determination and Comparison of Total Opioid Consumption

According to the results shown in **fig 1**, the mean opioid consumption was 31.50 ± 7.08 and 19.0 ± 8.55 in the first and second groups, respectively. There was a statistically significant difference between the two groups in terms of opioid consumption ($P < 0.001$). The total opioid consumption in the second group (with the second administration of PAND) was lower than the first group.

5. Discussion

In the current study, the effect of single-dose versus two-dose administration of PAND combination was evaluated among patients who had undergone one of the surgeries (including nephrectomy, cystectomy, prostatectomy, colectomy, Whipple, and RPLND). Our findings showed the preemptive analgesia with a second dose of PAND as an effective method for reducing pain after surgery. Preemptive analgesia has certain clinical benefits, including reducing psychological distress, sleep disturbances, and the need for analgesics with the associated complications (14-17), as well as faster recovery and earlier and safer discharge (18).

Gabapentinoids, including pregabalin, have traditionally been used as anti-epileptic drugs and are currently widely used to relieve neuropathic pain. It decreases the number of pain signals that are sent out by injured nerves, indicating its analgesic effect (19). Acetaminophen has an anti-inflammatory effect via inhibition of cyclooxygenase enzymes 1 and 2 (COX1 and 2) and is extensively prescribed for pain management. Naproxen is also inhibiting COX 1 and 2 enzymes and is a nonsteroidal anti-inflammatory drug (NSAID) (20, 21). Moreover, Dextromethorphan inhibits the action of, the N-Methyl-D-spartate receptor (NMDAR) and also plays a role in neuropathic pain reduction. It may have an analgesic effect on postoperative acute pain (22, 23). The preoperative analgesic approach may minimize postoperative pain by a variety of complex mechanisms. The COX2 inhibitors inhibit cyclooxygenase and re-

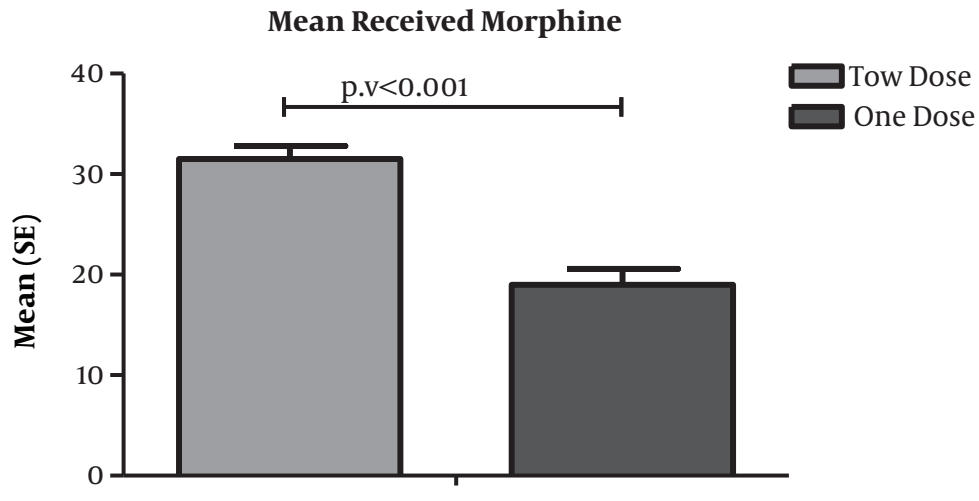


Figure 2. Comparison of total opioid consumption in two groups

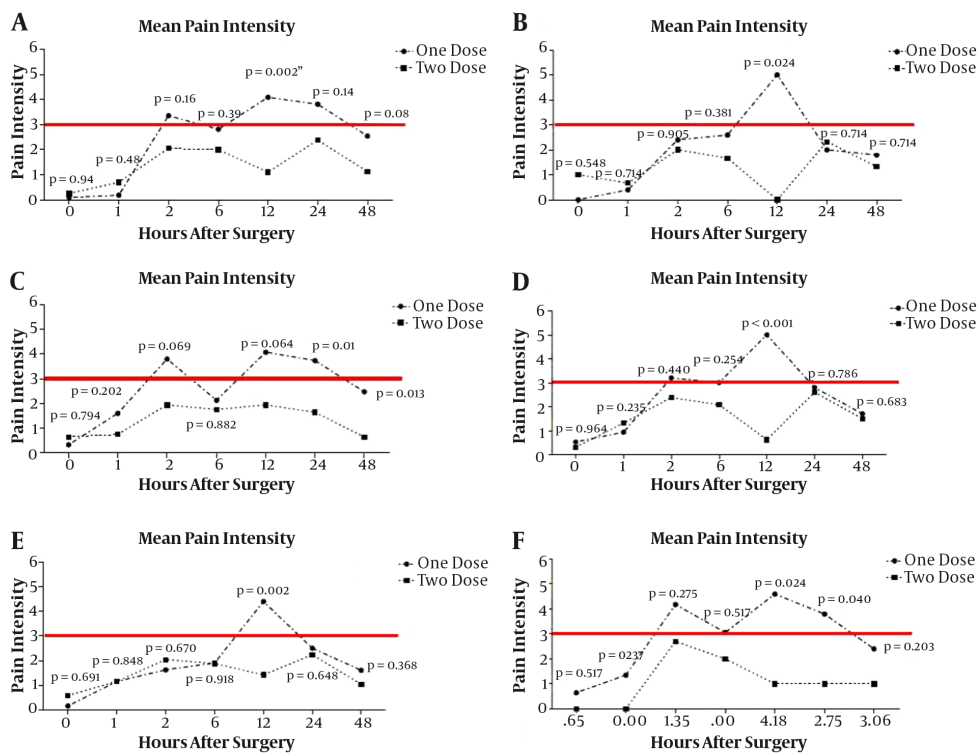


Figure 3. Pain intensity at 0, 1, 2, 6, 12, 24, and 48 hours after surgery in patients over 65 years (A), over 90 kg (B), with a BMI less than (C) and greater than 25 (D), with anesthesia duration less than 4 hours (E) and longer than 4 hours (F) among two groups.

duce prostaglandin production (24), and provide analgesia by reducing the sensitivity of peripheral pain receptors to mechanical stimuli (25).

In this study, postoperative pain was significantly reduced for the group that received the second dose of PAND postoperatively. The mean pain scores were significantly

different in two groups at 2, 12, 24, and 48 hours after surgery ($P < 0.05$) and were significantly lower in the second group than the first group.

In the current medical approach, opiates are commonly used to control postoperative pain. These can cause many side effects, including nausea, vomiting, and itching. In addition, using opiates has shown insufficient efficacy in postoperative pain management (26). However, in the present study, no side effects were observed. There is increasing evidence suggesting the benefits of a variety of pharmacological agents that are used before surgery to reduce postoperative pain. These include opiate analgesics (27-30), nonsteroidal anti-inflammatory drugs (31-33), neuromodulatory agents (34-37), and clonidine (24, 25, 38). In this trial, the total dose of administered opioid was also lower for the two-dose group compared with the one-dose group ($P < 0.001$). This is consistent with a prior study on the effects of preemptive analgesia (39), which has suggested that using a combination of PAND as preventive analgesia can decrease the need for opioid consumption and improve pain control.

In a previous study, preemptive acetaminophen was associated with increased analgesia and decreased postoperative analgesic consumption (40). In addition, it has been shown that multi-modal analgesics (gabapentin with NSAIDs or a combination of acetaminophen with NSAIDs) are superior to either of these two alone (41, 42) in terms of decreasing pain after surgery.

In a study conducted to evaluate the effect of oral pregabalin on the duration and quality of postoperative analgesia in spinal anesthesia, it was shown that oral pregabalin extended the duration of postoperative analgesia and reduced morphine intake. Moreover, it improved sleep quality during the first postoperative night (43). In another study aimed at investigating the effect of prophylactic use of oral pregabalin-acetaminophen-naproxen on pain control and morphine usage in patients who had undertaken laparotomy, patients in the PAN group (pregabalin 150 mg, acetaminophen 1 g, and naproxen 250 mg) experienced lower pain and the morphine use was also significantly lower than the control group (44). A previous study on the effect of prophylactic analgesia in women undergoing abdominal hysterectomy suggested the higher satisfaction scores of patients who received a combination of gabapentin and paracetamol compared to those who received gabapentin alone. The authors also claimed decreased narcotic requirements among patients who received preemptive narcotic and nonnarcotic medications prior to hysterectomy (45). The inability to assess the incidence of chronic pain due to time constraints was one of the limitations of the current study. In summary, several agents are examined for preventive analgesia (44). Signif-

icant opioid sparing and a decreased pain score following preemptive gabapentin was also reported in several other studies (46-48).

5.1. Conclusions

To conclude, in the current study, the PAND combination was used to pain management. Our results show that preemptive analgesia with a second dose of PAND is an effective method for reducing pain and morphine consumption after surgery. The prerequisite for making preemptive analgesia guidelines is more research in various surgeries.

Footnotes

Authors' Contribution: Study concept and design: Hamid Reza Amiri and Majid Amini. Acquisition of data: Seyed Ali Momeni and Solmaz Ohadian Moghadam. Data analysis and interpretation: Solmaz Ohadian Moghadam, Seyed Ali Momeni, and Majid Amini. Drafting of the manuscript: Solmaz Ohadian Moghadam. Critical revision of the manuscript for scientific and factual content: Hamid Reza Amiri, Solmaz Ohadian Moghadam, Seyed Ali Momeni, and Majid Amini. Statistical analysis: Solmaz Ohadian Moghadam, Seyed Ali Momeni, and Majid Amini. Supervision: Hamid Reza Amiri.

Clinical Trial Registration Code: The clinical trial registration code was IRCT20181219042046N1.

Conflict of Interests: All authors certify that they do not have any direct or indirect commercial financial incentive associated with publishing the article, and there was no source of extra-institutional commercial funding. All authors do not have any conflict of interests.

Ethical Approval: This study was approved by the Ethics in Research Committee of Tehran University of Medical Sciences, ethic number: IR.TUMS.IKHC.REC.1398.017.

Funding/Support: This research was supported by Tehran University of Medical Sciences, Tehran, Iran.

Informed Consent: Signed informed consent was obtained from all participants of study.

References

- Entezari SR, Derakhshan P, Darvishi A, Alebouyeh M. Efficacy of Combined Dextromethorphan and Gabapentin as Premedication on Postoperative Pain Management in Knee Arthroscopy: A Clinical Trial. *J Mazandaran Univ Med Sci.* 2019;**29**(179):65-73.
- Faiz SHR, Nikoubakht N, Sayarifard A, Rahimzadeh P. A Comparative Study of the Effect of Oral Dextromethorphan and Placebo on the Pain After Vitrectomy Surgery: A Double-Blind, Placebo-Controlled, Randomized Clinical Trial. *Iran Red Crescent Med J.* 2018;**In Press**(In Press). doi: 10.5812/ircmj.64763.

3. Woolf CJ, Salter MW. Neuronal plasticity: increasing the gain in pain. *Science*. 2000;**288**(5472):1765-9. doi: [10.1126/science.288.5472.1765](https://doi.org/10.1126/science.288.5472.1765). [PubMed: [10846153](https://pubmed.ncbi.nlm.nih.gov/10846153/)].
4. Wall PD. The prevention of postoperative pain. *Pain*. 1988;**33**(3):289-90. doi: [10.1016/0304-3959\(88\)90286-2](https://doi.org/10.1016/0304-3959(88)90286-2). [PubMed: [3419835](https://pubmed.ncbi.nlm.nih.gov/3419835/)].
5. Woolf CJ. Generation of acute pain: central mechanisms. *Br Med Bull*. 1991;**47**(3):523-33. doi: [10.1093/oxfordjournals.bmb.a072490](https://doi.org/10.1093/oxfordjournals.bmb.a072490). [PubMed: [1794070](https://pubmed.ncbi.nlm.nih.gov/1794070/)].
6. Basse L, Hjort Jakobsen D, Billesbolle P, Werner M, Kehlet H. A clinical pathway to accelerate recovery after colonic resection. *Ann Surg*. 2000;**232**(1):51-7. doi: [10.1097/00000658-200007000-00008](https://doi.org/10.1097/00000658-200007000-00008). [PubMed: [10862195](https://pubmed.ncbi.nlm.nih.gov/10862195/)]. [PubMed Central: [PMC1421107](https://pubmed.ncbi.nlm.nih.gov/PMC1421107/)].
7. Ballantyne JC, Kupelnick B, McPeck B, Lau J. Does the evidence support the use of spinal and epidural anesthesia for surgery? *J Clin Anesth*. 2005;**17**(5):382-91. doi: [10.1016/j.jclinane.2004.10.005](https://doi.org/10.1016/j.jclinane.2004.10.005). [PubMed: [16102692](https://pubmed.ncbi.nlm.nih.gov/16102692/)].
8. Woolf CJ, Chong MS. Preemptive analgesia—treating postoperative pain by preventing the establishment of central sensitization. *Anesth Analg*. 1993;**77**(2):362-79. doi: [10.1213/00000539-199377020-00026](https://doi.org/10.1213/00000539-199377020-00026). [PubMed: [8346839](https://pubmed.ncbi.nlm.nih.gov/8346839/)].
9. Trombelli L, Schincaglia GP, Zangari F, Scapoli C, Calura G. Effect of pretreatment with ketorolac tromethamine on post-operative pain following periodontal surgery. *J Clin Periodontol*. 1996;**23**(2):128-32. doi: [10.1111/j.1600-051x.1996.tb00545.x](https://doi.org/10.1111/j.1600-051x.1996.tb00545.x). [PubMed: [8849849](https://pubmed.ncbi.nlm.nih.gov/8849849/)].
10. Kissin I. Preemptive analgesia. *Anesthesiology*. 2000;**93**(4):1138-43. doi: [10.1097/00000542-200010000-00040](https://doi.org/10.1097/00000542-200010000-00040). [PubMed: [11020772](https://pubmed.ncbi.nlm.nih.gov/11020772/)].
11. Macrae WA. Chronic pain after surgery. *Br J Anaesth*. 2001;**87**(1):88-98. doi: [10.1093/bja/87.1.88](https://doi.org/10.1093/bja/87.1.88). [PubMed: [11460816](https://pubmed.ncbi.nlm.nih.gov/11460816/)].
12. Dashputra AV, Badwaik RT. Utilization of analgesics in perioperative cases of teaching hospital. *Inter J Med Pharm Sci*. 2013;**3**(6):14-9.
13. Gilron I, Watson CP, Cahill CM, Moulin DE. Neuropathic pain: a practical guide for the clinician. *CMAJ*. 2006;**175**(3):265-75. doi: [10.1503/cmaj.060146](https://doi.org/10.1503/cmaj.060146). [PubMed: [16880448](https://pubmed.ncbi.nlm.nih.gov/16880448/)]. [PubMed Central: [PMC1513412](https://pubmed.ncbi.nlm.nih.gov/PMC1513412/)].
14. Akca T, Colak T, Kanik A, Yaylak F, Caglikulekci M, Aydin S. The effect of preoperative intravenous use of tenoxicam: a prospective, double-blind, placebo-controlled study. *J Invest Surg*. 2004;**17**(6):333-8. doi: [10.1080/08941930490524390](https://doi.org/10.1080/08941930490524390). [PubMed: [15764501](https://pubmed.ncbi.nlm.nih.gov/15764501/)].
15. Celik JB, Gormus N, Gormus ZI, Okesli S, Solak H. Preoperative analgesia management with rofecoxib in thoracotomy patients. *J Cardiothorac Vasc Anesth*. 2005;**19**(1):67-70. doi: [10.1053/j.jvca.2004.11.012](https://doi.org/10.1053/j.jvca.2004.11.012). [PubMed: [15747272](https://pubmed.ncbi.nlm.nih.gov/15747272/)].
16. Riest G, Peters J, Weiss M, Dreyer S, Klassen PD, Stegen B, et al. Preventive effects of perioperative parecoxib on post-discectomy pain. *Br J Anaesth*. 2008;**100**(2):256-62. doi: [10.1093/bja/aem345](https://doi.org/10.1093/bja/aem345). [PubMed: [18079431](https://pubmed.ncbi.nlm.nih.gov/18079431/)].
17. Srivastava S, Gupta D, Naz A, Rizvi MM, Singh PK. Effects of preoperative single dose Etoricoxib on postoperative pain and sleep after lumbar discectomy: prospective randomized double blind controlled study. *Middle East J Anaesthesiol*. 2012;**21**(5):725-30. [PubMed: [23265037](https://pubmed.ncbi.nlm.nih.gov/23265037/)].
18. Horattas MC, Evans S, Sloan-Stakleff KD, Lee C, Snoke JW. Does preoperative rofecoxib (Vioxx) decrease postoperative pain with laparoscopic cholecystectomy? *Am J Surg*. 2004;**188**(3):271-6. doi: [10.1016/j.amjsurg.2004.06.007](https://doi.org/10.1016/j.amjsurg.2004.06.007). [PubMed: [15450833](https://pubmed.ncbi.nlm.nih.gov/15450833/)].
19. Maneuf YP, Gonzalez MI, Sutton KS, Chung FZ, Pinnock RD, Lee K. Cellular and molecular action of the putative GABA-mimetic, gabapentin. *Cell Mol Life Sci*. 2003;**60**(4):742-50. doi: [10.1007/s00118-003-2108-x](https://doi.org/10.1007/s00118-003-2108-x). [PubMed: [12785720](https://pubmed.ncbi.nlm.nih.gov/12785720/)].
20. Anderson BJ. Paracetamol (Acetaminophen): mechanisms of action. *Paediatr Anaesth*. 2008;**18**(10):915-21. doi: [10.1111/j.1460-9592.2008.02764.x](https://doi.org/10.1111/j.1460-9592.2008.02764.x). [PubMed: [18811827](https://pubmed.ncbi.nlm.nih.gov/18811827/)].
21. Graham GG, Davies MJ, Day RO, Mohamudally A, Scott KF. The modern pharmacology of paracetamol: therapeutic actions, mechanism of action, metabolism, toxicity and recent pharmacological findings. *Inflammopharmacology*. 2013;**21**(3):201-32. doi: [10.1007/s10787-013-0172-x](https://doi.org/10.1007/s10787-013-0172-x). [PubMed: [23719833](https://pubmed.ncbi.nlm.nih.gov/23719833/)].
22. Weinbroum AA, Gorodetzky A, Nirkin A, Kollender Y, Bickels J, Marouani N, et al. Dextromethorphan for the reduction of immediate and late postoperative pain and morphine consumption in orthopedic oncology patients: a randomized, placebo-controlled, double-blind study. *Cancer*. 2002;**95**(5):1164-70. doi: [10.1002/cncr.10784](https://doi.org/10.1002/cncr.10784). [PubMed: [12209704](https://pubmed.ncbi.nlm.nih.gov/12209704/)].
23. Suski M, Bujak-Gizycka B, Madej J, Kacka K, Dobrogowski J, Woron J, et al. Co-administration of dextromethorphan and morphine: reduction of post-operative pain and lack of influence on morphine metabolism. *Basic Clin Pharmacol Toxicol*. 2010;**107**(2):680-4. doi: [10.1111/j.1742-7843.2010.00559.x](https://doi.org/10.1111/j.1742-7843.2010.00559.x). [PubMed: [20346057](https://pubmed.ncbi.nlm.nih.gov/20346057/)].
24. McCormack K. The spinal actions of nonsteroidal anti-inflammatory drugs and the dissociation between their anti-inflammatory and analgesic effects. *Drugs*. 1994;**47** Suppl 5:28-45. discussion 46-7. doi: [10.2165/00003495-199400475-00006](https://doi.org/10.2165/00003495-199400475-00006). [PubMed: [7525183](https://pubmed.ncbi.nlm.nih.gov/7525183/)].
25. Higgins MS, Givogre JL, Marco AP, Blumenthal PD, Furman WR. Recovery from outpatient laparoscopic tubal ligation is not improved by preoperative administration of ketorolac or ibuprofen. *Anesth Analg*. 1994;**79**(2):274-80. doi: [10.1213/00000539-199408000-00012](https://doi.org/10.1213/00000539-199408000-00012). [PubMed: [7639363](https://pubmed.ncbi.nlm.nih.gov/7639363/)].
26. Gan TJ, Habib AS, Miller TE, White W, Apfelbaum JL. Incidence, patient satisfaction, and perceptions of post-surgical pain: results from a US national survey. *Curr Med Res Opin*. 2014;**30**(1):149-60. doi: [10.1185/03007995.2013.860019](https://doi.org/10.1185/03007995.2013.860019). [PubMed: [24237004](https://pubmed.ncbi.nlm.nih.gov/24237004/)].
27. Liukkonen K, Santanen U, Pere P, Erkola O, Rautoma P. Peroral tramadol premedication increases postoperative nausea and delays home-readiness in day-case knee arthroscopy patients. *Scand J Surg*. 2002;**91**(4):365-8. doi: [10.1177/145749690209100411](https://doi.org/10.1177/145749690209100411). [PubMed: [12558088](https://pubmed.ncbi.nlm.nih.gov/12558088/)].
28. Reiter A, Zulus E, Hartmann T, Hoerauf K. Preoperative oral administration of fast-release morphine sulfate reduces postoperative piritramide consumption. *Wien Klin Wochenschr*. 2003;**115**(12):417-20. doi: [10.1007/BF03040434](https://doi.org/10.1007/BF03040434). [PubMed: [12918185](https://pubmed.ncbi.nlm.nih.gov/12918185/)].
29. Wilder-Smith OH, Tassonyi E, Crul BJ, Arendt-Nielsen L. Quantitative sensory testing and human surgery: effects of analgesic management on postoperative neuroplasticity. *Anesthesiology*. 2003;**98**(5):1214-22. doi: [10.1097/00000542-200305000-00025](https://doi.org/10.1097/00000542-200305000-00025). [PubMed: [12717144](https://pubmed.ncbi.nlm.nih.gov/12717144/)].
30. Pozos-Guillen A, Martinez-Rider R, Aguirre-Banuelos P, Perez-Urizar J. Pre-emptive analgesic effect of tramadol after mandibular third molar extraction: a pilot study. *J Oral Maxillofac Surg*. 2007;**65**(7):1315-20. doi: [10.1016/j.joms.2006.10.079](https://doi.org/10.1016/j.joms.2006.10.079). [PubMed: [17577495](https://pubmed.ncbi.nlm.nih.gov/17577495/)].
31. Takada M, Fukusaki M, Terao Y, Yamashita K, Inadomi C, Takada M, et al. Preadministration of flurbiprofen suppresses prostaglandin production and postoperative pain in orthopedic patients undergoing tourniquet inflation. *J Clin Anesth*. 2007;**19**(2):97-100. doi: [10.1016/j.jclinane.2006.05.028](https://doi.org/10.1016/j.jclinane.2006.05.028). [PubMed: [17379119](https://pubmed.ncbi.nlm.nih.gov/17379119/)].
32. Kesimci E, Gumus T, Izdes S, Sen P, Kanbak O. Comparison of efficacy of dexketoprofen versus paracetamol on postoperative pain and morphine consumption in laminectomy patients. *Agri*. 2011;**23**(4):153-9. doi: [10.5505/agri.2011.86548](https://doi.org/10.5505/agri.2011.86548). [PubMed: [22290679](https://pubmed.ncbi.nlm.nih.gov/22290679/)].
33. Mowafi HA, Telmessani L, Ismail SA, Naguib MB. Preoperative lornoxicam for pain prevention after tonsillectomy in adults. *J Clin Anesth*. 2011;**23**(2):97-101. doi: [10.1016/j.jclinane.2010.07.002](https://doi.org/10.1016/j.jclinane.2010.07.002). [PubMed: [21377071](https://pubmed.ncbi.nlm.nih.gov/21377071/)].
34. Al-Mujadi H, A. Refai AR, Katarzov MG, Dehrab NA, Batra YK, Al-Qattan AR. Preemptive gabapentin reduces postoperative pain and opioid demand following thyroid surgery. *Can J Anaesth*. 2006;**53**(3):268-73. doi: [10.1007/BF03022214](https://doi.org/10.1007/BF03022214). [PubMed: [16527792](https://pubmed.ncbi.nlm.nih.gov/16527792/)].
35. Agarwal A, Gautam S, Gupta D, Agarwal S, Singh PK, Singh U. Evaluation of a single preoperative dose of pregabalin for attenuation of postoperative pain after laparoscopic cholecystectomy. *Br J Anaesth*. 2008;**101**(5):700-4. doi: [10.1093/bja/aen244](https://doi.org/10.1093/bja/aen244). [PubMed: [18716003](https://pubmed.ncbi.nlm.nih.gov/18716003/)].
36. Grover VK, Mathew PJ, Yaddanapudi S, Sehgal S. A single dose of preop-

- erative gabapentin for pain reduction and requirement of morphine after total mastectomy and axillary dissection: randomized placebo-controlled double-blind trial. *J Postgrad Med.* 2009;**55**(4):257-60. doi: [10.4103/0022-3859.58928](https://doi.org/10.4103/0022-3859.58928). [PubMed: [20083871](https://pubmed.ncbi.nlm.nih.gov/20083871/)].
37. Kinney MA, Mantilla CB, Carns PE, Passe MA, Brown MJ, Hooten WM, et al. Preoperative gabapentin for acute post-thoracotomy analgesia: a randomized, double-blinded, active placebo-controlled study. *Pain Pract.* 2012;**12**(3):175-83. doi: [10.1111/j.1533-2500.2011.00480.x](https://doi.org/10.1111/j.1533-2500.2011.00480.x). [PubMed: [21676165](https://pubmed.ncbi.nlm.nih.gov/21676165/)]. [PubMed Central: [PMC3200555](https://pubmed.ncbi.nlm.nih.gov/PMC3200555/)].
 38. Mayson KV, Gofton EA, Chambers KG. Premedication with low dose oral clonidine does not enhance postoperative analgesia of intrathecal morphine. *Can J Anaesth.* 2000;**47**(8):752-7. doi: [10.1007/BF03019477](https://doi.org/10.1007/BF03019477). [PubMed: [10958091](https://pubmed.ncbi.nlm.nih.gov/10958091/)].
 39. Amiri HR, Mirzaei M, Beig Mohammadi MT, Tavakoli F. Multi-Modal Preemptive Analgesia With Pregabalin, Acetaminophen, Naproxen, and Dextromethorphan in Radical Neck Dissection Surgery: A Randomized Clinical Trial. *Anesth Pain Med.* 2016;**6**(4). e33526. doi: [10.5812/aapm.33526](https://doi.org/10.5812/aapm.33526). [PubMed: [27843771](https://pubmed.ncbi.nlm.nih.gov/27843771/)]. [PubMed Central: [PMC5099949](https://pubmed.ncbi.nlm.nih.gov/PMC5099949/)].
 40. Khalili G, Janghorbani M, Saryazdi H, Emaminejad A. Effect of preemptive and preventive acetaminophen on postoperative pain score: a randomized, double-blind trial of patients undergoing lower extremity surgery. *J Clin Anesth.* 2013;**25**(3):188-92. doi: [10.1016/j.jclinane.2012.09.004](https://doi.org/10.1016/j.jclinane.2012.09.004). [PubMed: [23567482](https://pubmed.ncbi.nlm.nih.gov/23567482/)].
 41. Gilron I, Orr E, Tu D, O'Neill JP, Zamora JE, Bell AC. A placebo-controlled randomized clinical trial of perioperative administration of gabapentin, rofecoxib and their combination for spontaneous and movement-evoked pain after abdominal hysterectomy. *Pain.* 2005;**113**(1-2):191-200. doi: [10.1016/j.pain.2004.10.008](https://doi.org/10.1016/j.pain.2004.10.008). [PubMed: [15621380](https://pubmed.ncbi.nlm.nih.gov/15621380/)].
 42. Ong CK, Seymour RA, Lirk P, Merry AF. Combining paracetamol (acetaminophen) with nonsteroidal antiinflammatory drugs: a qualitative systematic review of analgesic efficacy for acute postoperative pain. *Anesth Analg.* 2010;**110**(4):1170-9. doi: [10.1213/ANE.0b013e3181cf9281](https://doi.org/10.1213/ANE.0b013e3181cf9281). [PubMed: [20142348](https://pubmed.ncbi.nlm.nih.gov/20142348/)].
 43. Omara AF, Ahmed SA, Abusabaa MM. The Effect Of The Use Of Pre-Emptive Oral Pregabalin On The Postoperative Spinal Analgesia In Patients Presented For Orthopedic Surgeries: Randomized Controlled Trial. *J Pain Res.* 2019;**12**:2807-14. doi: [10.2147/JPR.S216184](https://doi.org/10.2147/JPR.S216184). [PubMed: [31686901](https://pubmed.ncbi.nlm.nih.gov/31686901/)]. [PubMed Central: [PMC6777433](https://pubmed.ncbi.nlm.nih.gov/PMC6777433/)].
 44. Amiri H, Mirzaei M, Pournaghi M, Fathi F. Three -Agent Preemptive Analgesia, Pregabalin-Acetaminophen-Naproxen, in Laparotomy for Cancer: A Randomized Clinical Trial. *Anesth Pain Med.* 2017;**7**(2). e33269. doi: [10.5812/aapm.33269](https://doi.org/10.5812/aapm.33269). [PubMed: [28824854](https://pubmed.ncbi.nlm.nih.gov/28824854/)]. [PubMed Central: [PMC5556332](https://pubmed.ncbi.nlm.nih.gov/PMC5556332/)].
 45. Steinberg AC, Schimpf MO, White AB, Mathews C, Ellington DR, Jeppson P, et al. Preemptive analgesia for postoperative hysterectomy pain control: systematic review and clinical practice guidelines. *Am J Obstet Gynecol.* 2017;**217**(3):303-313 e6. doi: [10.1016/j.ajog.2017.03.013](https://doi.org/10.1016/j.ajog.2017.03.013). [PubMed: [28351670](https://pubmed.ncbi.nlm.nih.gov/28351670/)].
 46. Alimian M, Imani F, Hassani V, Rahimzadeh P, Sharifian M, Safari S. Effects of single-dose pregabalin on postoperative pain in dacryocystorhinostomy surgery. *Anesth Pain Med.* 2012;**2**(2):72-6. doi: [10.5812/aapm.4301](https://doi.org/10.5812/aapm.4301). [PubMed: [24223341](https://pubmed.ncbi.nlm.nih.gov/24223341/)]. [PubMed Central: [PMC3821116](https://pubmed.ncbi.nlm.nih.gov/PMC3821116/)].
 47. Pandey CK, Navkar DV, Giri PJ, Raza M, Behari S, Singh RB, et al. Evaluation of the optimal preemptive dose of gabapentin for postoperative pain relief after lumbar discectomy: a randomized, double-blind, placebo-controlled study. *J Neurosurg Anesthesiol.* 2005;**17**(2):65-8. doi: [10.1097/O1.ana.0000151407.62650.51](https://doi.org/10.1097/O1.ana.0000151407.62650.51). [PubMed: [15840990](https://pubmed.ncbi.nlm.nih.gov/15840990/)].
 48. Pandey CK, Priye S, Singh S, Singh U, Singh RB, Singh PK. Preemptive use of gabapentin significantly decreases postoperative pain and rescue analgesic requirements in laparoscopic cholecystectomy. *Can J Anaesth.* 2004;**51**(4):358-63. doi: [10.1007/BF03018240](https://doi.org/10.1007/BF03018240). [PubMed: [15064265](https://pubmed.ncbi.nlm.nih.gov/15064265/)].