

Comparison of the analgesic effects of single-dose 75 mg oral pregabalin versus single-dose 400 mg oral ibuprofen after impacted third mandibular molar surgery: A randomized, double-blind, split-mouth clinical trial

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Abstract

Background. Pain is the most prevalent complication after dentoalveolar surgery. Failure in effective pain control could potentially lead to systemic sequels, such as tachycardia, hypertension, improper nutrition, and central sensitization. Pregabalin is a gamma-aminobutyric acid (GABA) analog with inhibitory and analgesic effects on the central nervous system (CNS). Prescribing gabapentinoids as complementary analgesics reduces the consumption of opioid and non-opioid analgesics, and consequently their side effects.

Objectives. The main purpose of the present study was to compare the analgesic effects of pregabalin (single-dose 75 mg) vs. ibuprofen (single-dose 400 mg) on patients' pain levels after impacted third mandibular molar surgery.

Material and methods. In this randomized, double-blind, split-mouth clinical trial, 24 patients aged 19–34 years volunteered for 2 consecutive (1 month apart) third mandibular molar surgeries (the contralateral teeth). The patients were randomly placed into 2 groups: group G1 ($n = 12$) was prescribed pregabalin (single-dose 75 mg) after the 1st surgery and ibuprofen (single-dose 400 mg) after the 2nd surgery; and group G2 ($n = 12$) was prescribed the exact opposite of the G1 arrangement. During the first 24 h post-surgery, the patients recorded the number of complementary analgesics they took (single-dose 400 mg ibuprofen) and their level of pain on a visual analog scale (VAS) every 2 h.

Results. The average level of pain at 2 h post-surgery (T1) was significantly lower when pregabalin was prescribed ($p < 0.05$). Most patients needed complementary analgesics at 4 h post-surgery (T2). However, during the first 24 h post-surgery, the patients required significantly more complementary analgesics when ibuprofen was prescribed.

Conclusions. In comparison with oral ibuprofen (single-dose 400 mg), oral pregabalin (single-dose 75 mg) had a stronger analgesic effect at 2 h after impacted third mandibular molar surgery ($p < 0.05$). Pregabalin resulted in a significantly lower consumption of complementary analgesics in the first 24 h post-surgery as compared to ibuprofen.

Keywords: pain, ibuprofen, pregabalin, third mandibular molar surgery

Introduction

Pain is the most prevalent complication after dentoalveolar surgery (~80%),¹ and the practitioner is normally expected to ensure pain control so that it could be acceptable. Failure in effective pain control not only results in patient dissatisfaction and reduced quality of life, but it may also lead to systemic sequels, such as tachycardia, hypertension, improper nutrition, and central sensitization, which develops resistance to the effects of most common analgesic drugs.² The injection of long-acting local anesthetics, prescribing nitrous oxide (N₂O),³ as well as opioid and non-opioid oral analgesics, are some methods to control post-operation pain.⁴ However, N₂O can cause nausea, vomiting, headache, drowsiness, and excessive sweating or shivering.⁵ Opioids, such as naldemedine, can cause diarrhea,⁶ while tramadol can potentially cause seizures.⁷ Non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, are the most recommended drugs for acute dentoalveolar pain, but they can cause nausea, diarrhea and excessive bleeding.⁸

Gabapentinoids (e.g., gabapentin and pregabalin) are gamma-aminobutyric acid (GABA) analogs with significant anticonvulsant and pain relief effects. Prescribing gabapentinoids as complementary pain relievers reduces the consumption of opioid and non-opioid analgesics, and consequently their side effects.⁹

Pregabalin was initially used to treat muscle spasms, but due to its effects on convulsions, allodynia and hyperalgesia, it has gradually received more attention.¹⁰ Optimal effects on diabetic neuropathic pain, post-herpetic neuralgia and fibromyalgia make this drug more noticeable,¹¹ and due to its anti-anxiety effects, along with the prevention of sensitization and resistance to analgesics, pregabalin has become a considerable complementary drug after surgical procedures.^{12,13} The post-operation usage of pregabalin is more efficient than pre-surgical prescription,¹⁴ with its analgesic effects (300 mg) after third mandibular molar extraction verified. However, side effects, including dizziness, blurred vision, restlessness, headache, xerostomia, and drowsiness have been reported.^{15–17} The pre-operative prescription of single-dose pregabalin (75 mg) significantly decreases pain after septorhinoplasty.¹⁸

Fibromyalgia causes various musculoskeletal and soft tissue pain, as does third mandibular molar surgery. Pregabalin has shown remarkable results when used as a single drug in the treatment of fibromyalgia,¹⁹ and also plays a noticeable role in controlling chronic pain after spinal surgery.²⁰ Furthermore, pregabalin brings positive effects in relieving post-mastectomy chronic pain (PMCP) and consequent anxiety.¹⁰ However, studies have shown contradictory results with regard to analgesic effects and complications after the consumption of low-dose pregabalin.^{14,16}

The main purpose of this randomized, double-blind, split-mouth clinical trial was to compare the efficiency and analgesic effects of oral pregabalin capsules

(single-dose 75 mg) vs. oral ibuprofen capsules (single-dose 400 mg) after third mandibular molar surgery. Pregabalin and ibuprofen were both tested on each patient for their effects in reducing pain levels and the need to take supplementary analgesics.

Material and methods

Study design, participants and ethical practices

This randomized, double-blind, split-mouth clinical trial was designed and conducted according to the randomized, double-blind clinical trial protocol and the split-mouth design, and followed the Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines.²¹ The Iranian Ministry of Health and Medical Education and the Research Ethics Committee of Dental Research Center at the Shahid Beheshti University of Medical Sciences, Tehran, Iran, approved the trial on February 18, 2017 (IR.SBMU.RIDS.REC.1395.392). The trial was also registered with the Iranian Registry of Clinical Trials (<https://www.irct.ir>) (IRCT2016122131501N1).

Between December 31, 2017, and December 30, 2020, 95 patients who were candidates for the extraction of their bilateral impacted third mandibular molars visited the Department of Oral and Maxillofacial Surgery of the School of Dentistry at the Shahid Beheshti University of Medical Sciences. All clinical evaluations and third mandibular molar surgical procedures were executed in the above-mentioned department by an oral and maxillofacial surgeon (OMFS). A complete and comprehensive medical history was collected from each patient and documented. Out of the 95 patients, 57 were eligible to take part in our clinical trial, and 24 (13 men and 11 women) volunteered. Figure 1 displays a complete and comprehensive CONSORT flow diagram of the patients' enrollment and allocation. All participants read and signed a patient consent form. The patients were fully informed that their personal information (e.g., first name, last name, phone number, home address, work address, and photographs) would not be reported and/or published anywhere and that they were allowed to leave the study whenever they wanted.

Inclusion criteria

The inclusion criteria were as follows:

- healthy participants classified according to the American Society of Anesthesiologists as class I or II (ASA I/II), candidates for bilateral impacted third mandibular molar extraction; and
- healthy bilateral impacted third mandibular molars with the same level of difficulty regarding the tooth angle, the impaction level and the relation to the anterior ramus border.

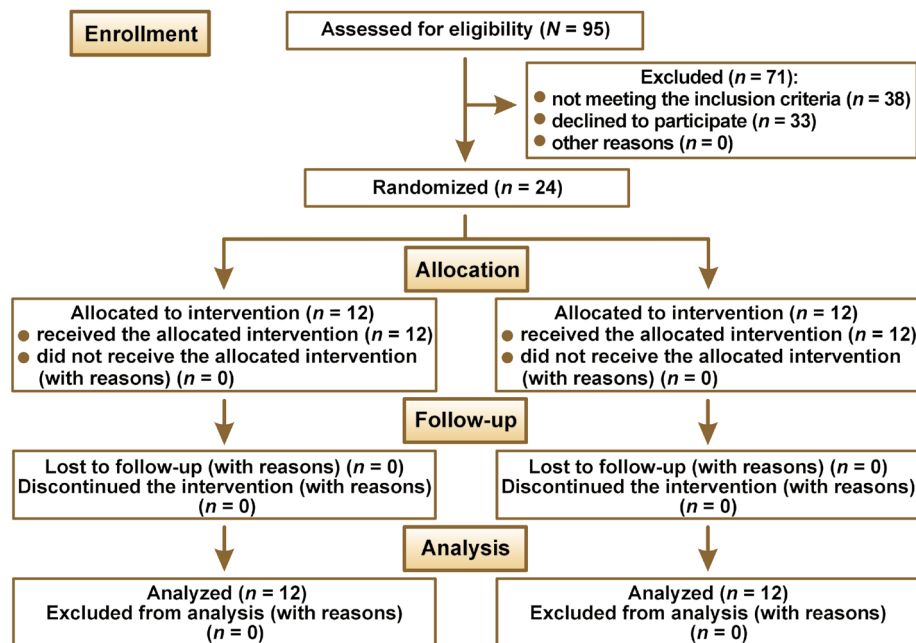


Fig. 1. CONSORT (Consolidated Standards of Reporting Trials) 2010 flow diagram

Exclusion criteria

The exclusion criteria were as follows:

- a current lesion surrounding bilateral impacted third mandibular molars;
- a history of chronic use of NSAIDs, pregabalin, sedative drugs, and/or corticosteroids;
- present or past addiction to analgesics;
- the usage of any analgesics 1 week before both surgeries;
- psychological disorders;
- menstruation (to prevent the distortion of the data on the female patients' pain levels in the 2nd half of the menstrual cycle (the luteal phase), the female patients were asked about the regularity and duration of their cycle; by doing so, we were able to schedule both of their surgeries in the 1st half of their cycle);
- a current bone disease;
- current orofacial pain;
- patients with epilepsy; and
- a history of allergies to local anesthesia.

Randomization, allocation concealment and blinding

A person not involved in this study in any way (neither a patient nor a clinician/researcher) was kindly asked to randomize all the 24 participants into 2 groups – group 1 (G1) and group 2 (G2), each with the same number of participants ($n = 12$) – using a computer-generated system (<http://www.jerrydallal.com/random/randomize.htm>; seed code: 25592). Group 1 was prescribed oral pregabalin (single-dose 75 mg) (Lyrica™; Pfizer Inc., New York, USA) after the 1st surgery and oral ibuprofen (single-dose 400 mg) (Advil Liqui-Gel™;

Wyeth, Madison, USA) after the 2nd surgery. Group 2 was prescribed the exact opposite of the G1 arrangement, receiving oral ibuprofen (single-dose 400 mg) after the 1st surgery and oral pregabalin (single-dose 75 mg) after the 2nd surgery. All surgeons, clinicians and researchers responsible for the design and execution of this clinical trial, as well as all participants, were blinded to the name and type of the drug prescribed.

Interventions

All participants had a digital orthopantomogram (OPG) panoramic view of their teeth and jaw taken 1 month before surgery (or more recently). All patients underwent the surgical extraction of impacted third mandibular molars, conducted by an OMFS under local anesthesia. The patients were asked to refrain from taking analgesics 1 week before both surgeries. All 48 surgeries were carried out according to the protocol of the clinical trial executed by Demirbas et al.,²² with the inferior alveolar nerve block (IANB) (the Halsted technique) and the long buccal nerve block performed using 2 carpules (1.8 mL) of lidocaine (2%) and epinephrine (1:100,000) (Loghman Pharmaceutical and Hygienic Co., Tehran, Iran) for optimum local anesthesia. If the patients were still feeling pain during surgery, a third carpule (1.8 mL) of lidocaine (2%) with epinephrine (1:100,000) was used for another round of IANB. The bone surface was exposed through a sulcular incision with distal extension, using a #15 scalpel blade. The buccal and lingual flaps were displaced and retracted by using a #9 molt periosteal elevator, with the lingual flap retracted to protect the lingual nerve. Third mandibular molars were exposed after proper osteotomy and odontotomy with

the use of fissure and round-shaped burs on high-speed handpieces. Sterile saline was used as a coolant/irrigant throughout the whole surgery. Third mandibular molars were then sectioned using the fissure and round-shaped burs, and extracted using #79 (for lower wisdom teeth) or #222 forceps. The flaps were replaced and sutured in an interrupted style, using braided, non-absorbable 3-0 USP (the United States Pharmacopeia system) silk sutures (Hur Teb, Takestan, Iran) and a reverse cutting needle (19 mm, 3/8 circle).

After the completion of the surgery (T0), either oral pregabalin capsules (single-dose 75 mg) or oral ibuprofen capsules (single-dose 400 mg) (control) were prescribed based on the blinding principle and the randomization performed earlier (G1 and G2). One month after the 1st surgery, the 2nd surgery was performed on the contralateral teeth by the same operator using the same techniques and materials in exactly the same operation room as the 1st surgery. If the patients were prescribed ibuprofen after the 1st procedure, pregabalin was prescribed after the 2nd procedure, and vice versa.

Outcomes

A visual analog scale (VAS) questionnaire was designed to document the patients' post-operative pain severity (from 0 = no pain to 10 = unbearable pain). Identical questionnaires were used after both procedures. Time point T0 demonstrated the time of surgery completion, while T12 was the end point of the first 24 h post-surgery. During the first 24 h post-surgery, the patients recorded the number of complementary analgesics they took (single-dose 400 mg ibuprofen) and their level of pain on VAS every 2 h (T0, T1, T2, T3, T4, T5, T6, and T12). All surgeries were scheduled to be performed somewhere between 8 a.m. and 10 a.m. Therefore, at T6 (12 h post-surgery), most patients would have been asleep, and we asked them to go to bed between 10 p.m. and 11 p.m. so that the results could be comparable. Hence, we did not include the sleeping period (i.e., T7, T8, T9, T10, and T11) in our questionnaires. However, if the patients had any sleeping difficulties and/or unbearable pain that was preventing them from going to sleep, T7–T11 were also completed in their questionnaires. The patients were allowed to use complementary analgesics (single-dose 400 mg ibuprofen) if they experienced moderate to severe pain, which was grade 5 or higher on VAS. The time and amount of the analgesic intake were also recorded.

Statistical analysis

A repeated-measures analysis of variance (ANOVA) model was used to compare the pain distribution between the 2 surgeries for each patient. The level of significance set for the study was 0.05.

Results

Interventions

A single OMFS performed all 48 impacted third mandibular molar surgeries (24 patients, each with bilateral impacted third mandibular molar surgeries, 2 consecutive surgeries, 1 month apart) under local anesthesia. The 2 consecutive surgeries for each patient were performed exactly at a 1-month interval, as planned. None of the surgeries was delayed or performed before the completion of the 1-month gap. None of the patients needed any extra local anesthetics, and the initial 2 carpules (1.8 mL) of lidocaine (2%) with epinephrine (1:100,000) were efficient for all participants. There were no complications during and/or after any of the surgeries.

Participants

All 24 participants had both surgeries completed and were asked to visit the Department of Oral and Maxillofacial Surgery 1 week after each surgery for follow-up. The VAS questionnaires completed by the patients were also collected 1 week after each surgery. None of the patients had any sleeping difficulties, and all reported that they were asleep by 10–11 p.m. None of the patients experienced unbearable pain before, during or after their sleep.

Outcomes

Patients' pain severity

The average levels of the patients' post-operative pain (from 0 to 10 on VAS) at the specified time points (T0–T12) are shown in Table 1 (both surgeries included, G1 and G2 combined). According to the VAS questionnaire, the pain levels differed between the 2 groups at T1 post-surgery. The pregabalin group experienced significantly less pain at T1 ($p < 0.05$). At T1, the average pain levels were 0.52 ± 0.87 and 0.80 ± 1.12 when pregabalin and ibuprofen were prescribed, respectively. However, at all other time points (i.e., T0, T2, T3, T4, T5, T6, and T12), there were no significant differences between the 2 groups.

Supplementary analgesics

Table 2 shows the total number of supplemental analgesics (single-dose 400 mg ibuprofen) taken by all patients at each time point (both surgeries included, G1 and G2 combined). At 4 h post-surgery (T2), most of the patients experienced moderate to severe pain and took supplementary analgesics (single-dose 400 mg ibuprofen). At T2, 43 supplementary analgesics were taken – 20 when pregabalin (single-dose 75 mg) was prescribed and 23 when ibuprofen (single-dose 400 mg) was prescribed. At 6 h post-surgery (T3), 19 supplementary analgesics were

Table 1. Average levels of post-operative pain severity on a visual analog scale (VAS) in the participants after the completion of both surgeries

Time point	Pregabalin (single-dose 75 mg) (G1 and G2 combined)	Ibuprofen (single-dose 400 mg) (control) (G1 and G2 combined)	<i>p</i> -value
T0	0.24 ±0.66	0.28 ±0.74	0.714
T1	0.52 ±0.87	0.80 ±1.12	0.016*
T2	5.96 ±1.31	5.88 ±1.42	0.692
T3	4.12 ±1.51	3.92 ±1.15	0.446
T4	1.84 ±1.43	1.96 ±1.67	0.694
T5	0.64 ±0.76	0.64 ±0.76	1.000
T6	0.56 ±0.77	0.44 ±0.77	0.574
T12	0.36 ±0.49	0.32 ±0.63	0.802

Data presented as mean ± standard deviation ($M \pm SD$). G1 – group 1 (the patients who were prescribed pregabalin after the 1st surgery and ibuprofen after the 2nd surgery); G2 – group 2 (the patients who were prescribed ibuprofen after the 1st surgery and pregabalin after the 2nd surgery); T0–T12 – immediately and every 2 h post-surgery; VAS scoring – from 0 = no pain to 10 = unbearable pain; * statistically significant.

Table 2. Total number of supplemental analgesics (single-dose 400 mg ibuprofen) taken by the participants after the completion of both surgeries

Time point	Pregabalin (G1 and G2 combined)	Ibuprofen (G1 and G2 combined)	<i>p</i> -value
T0	0	0	1.000
T1	0	0	1.000
T2	20	23	0.018*
T3	7	12	0.050*
T4	2	2	1.000
T5	0	0	1.000
T6	0	0	1.000
T12	0	0	1.000
Total	29	37	0.043*

* statistically significant.

taken, including 7 when pregabalin was prescribed and 12 when ibuprofen was prescribed. At 8 h post-surgery (T4), 4 supplementary analgesics were taken, with 2 taken when pregabalin was prescribed and 2 when ibuprofen was prescribed. None of the patients required supplemental analgesics at any other time point (i.e., T0, T1, T5, T6, and T12).

The patients who were prescribed ibuprofen (single-dose 400 mg) needed more complementary analgesics during the first 24 h post-operation as compared to those with the prescribed pregabalin (single-dose 75 mg) ($p < 0.05$). The number of supplemental analgesics taken at T2 and T3 was significantly lower for the pregabalin group than for the ibuprofen group. In total, the patients needed 29 supplemental analgesics after pregabalin and 37 after ibuprofen during the first 24 h post-surgery.

The data extracted from the patients' VAS questionnaires and the recorded documents showed that one of the patients did not need any supplemental analgesics at any time

point after both surgeries. All patients declared that even if they needed to, they would take only one supplemental analgesic (single-dose 400 mg ibuprofen). Therefore, at all time points, the number of supplemental analgesics shows the exact number of patients that used them (Table 2).

Discussion

Post-surgical pain and discomfort affect patients' quality of life and satisfaction with treatment. Tissue trauma during surgery and tooth extraction causes cellular damage and inflammation.²³ Phospholipase A2 (PLA2) enzymes catalyze the hydrolysis of cell membrane phospholipids, resulting in cyclooxygenase-derived leukotrienes and lipoxygenase-generated prostaglandins.²⁴ Non-steroidal anti-inflammatory drugs have strong peripheral and anti-inflammatory effects, and can manage chronic pain perfectly. Ibuprofen, a member of the NSAID family, suppresses the synthesis of powerful inflammatory mediators, but also inhibits platelet attachment and extends the bleeding time.²⁵

Gamma-aminobutyric acid analogs is a family of inhibitory neurotransmitters (e.g., gabapentin and pregabalin). Their exact mechanism of action is not clear, though pregabalin is known to diminish CNS irritability by affecting voltage-dependent calcium (Ca) channels and reducing the release of glutamate, noradrenaline and substance P. The drug is completely absorbed after oral administration, distributed to most tissues, and it crosses the blood–brain barrier (BBB). Pregabalin has a 6-hour half-life and minimum metabolism in the liver, resulting in a very low rate of drug interactions. More than 90% of pregabalin is excreted by the kidneys without any change.²⁶ Pregabalin exerts its analgesic effect by manipulating voltage-dependent Ca and potassium (K) channels, which guide inflammatory amino acids.²⁶

This double-blind, randomized clinical trial was designed to examine differences between the analgesic effects of oral pregabalin capsules (single-dose 75 mg) and oral ibuprofen capsules (single-dose 400 mg) after third mandibular molar surgical extraction. When pregabalin was prescribed, the patients experienced significantly less pain only 2 h post-surgery (T1) as compared to ibuprofen ($p < 0.05$). However, during the remaining 22 h, no significant differences were observed between the 2 groups. Tiippana et al. reviewed the effects of gabapentin, pregabalin and narcotic drugs on post-surgical pain; their results corroborate our findings, though the optimum dosage was not reported.¹⁷

Generalized anxiety disorder (GAD) and CNS sensitivity exacerbate post-surgical pain. Clinical studies show that prescribing GABA analogs before surgery decreases the release of glutamate – an excitatory neurotransmitter – and reduces patients' anxiety. According to this, pregabalin declines pain intensity, opioid consumption and drug adverse effects after surgery.^{12,13}

In many clinical cases, pregabalin has shown a better analgesic effect than NSAIDs.²⁶ In this clinical trial, we found that pregabalin produced better results during the first 2 h. Pereira-Santos et al. claimed that diminishing the anxiety of patients undergoing dentoalveolar surgery significantly decreased pain.²⁷ Meanwhile, Hill et al. discovered that 300 mg pregabalin resulted in remarkably less pain than 50 mg pregabalin in molar extraction; however, the side effects of high-dose pregabalin were not considered.²⁸

Paech et al. declared that single-dose pregabalin (50 mg) had no significant analgesic effect on acute pain after minor obstetrics and gynecology (OB-GYN) surgeries.²⁹ Women undergoing OB-GYN surgeries can express various pain levels depending on their pathological backgrounds, allergies, sensitivity, and mental health. Additionally, the prescribed dosage of pregabalin in the abovementioned study²⁹ (50 mg) was lower than the conventional dose used in similar studies. Furthermore, pregabalin mainly has an analgesic effect on acute bone-derived pain and does not show a significant effect on visceral pain.²⁹ Controlled-release pregabalin can significantly reduce musculoskeletal pain in fibromyalgia patients.³⁰ Indeed, Pauer et al. demonstrated that 450 mg of pregabalin per day significantly reduced pain in fibromyalgia patients and improved their sleep quality.³¹ In addition, Cheung et al. evaluated pain after third mandibular molar surgery in 40 patients and discovered that prescribing pregabalin (75 mg) post-surgery had a significantly better analgesic effect than pre-operative administration.¹⁴

Olmedo-Gaya et al. discovered that patients who received 2 doses of pregabalin (75 mg) before and after third molar surgery had a significantly lower demand for supplementary analgesics than the group that did not take pregabalin.¹⁶ Both groups were prescribed acetaminophen (650 mg) every 8 h for the first 48 h.¹⁶

In this randomized clinical trial, we discovered that patients in both groups started consuming supplementary analgesics (single-dose 400 mg ibuprofen) 4 h after the operation. This time coordinates with the half-life of the local anesthetic drug administered and a significant decrease in blood lidocaine concentration.¹⁶ There was a significant difference in supplementary analgesic demand, with the control group requiring more supplementary analgesics (single-dose 400 mg ibuprofen) in the first 24 h post-surgery.

Limitations

The study limitations are as follows:

- determining the pain level was a challenging process for some patients;
- the anxiety rates had a direct effect on the patients' perception of pain, and sometimes led to exaggeration and inaccuracy in the VAS records; and
- finding patients who had the same level of impaction in their third mandibular molars was time-consuming.

Recommendations

More randomized clinical trials should be designed to investigate these findings further.

We suggest designing supplementary studies with more participants in all study groups and an additional focus on patients' mental health. The patients' stress and anxiety levels caused by the fear of surgery significantly affected their perception of pain. A section of the questionnaire could be dedicated to patients' stress and anxiety levels.

Patients could be studied for an extended period of time, with pregabalin being prescribed for days after surgery.

The effect of pregabalin and its superiority/inferiority with regard to NSAIDs could be examined in other oral surgeries (e.g., dental implants, pathologies and soft tissue surgeries).

Pregabalin could be compared with other analgesics, including combinational drugs.

Conclusions

Oral pregabalin (single-dose 75 mg) had a better analgesic effect in the first 2 h after impacted third mandibular molar surgery than oral ibuprofen (single-dose 400 mg) ($p < 0.05$). Furthermore, pregabalin (single-dose 75 mg) significantly decreased the need for supplemental analgesics during the first 24 h post-surgery as compared to ibuprofen (single-dose 400 mg).

Trial registration

The trial was registered with the Iranian Registry of Clinical Trials (<https://www.irct.ir>) (IRCT2016122131501N1).

Ethics approval and consent to participate

The study was approved by the Iranian Ministry of Health and Medical Education and the Research Ethics Committee of Dental Research Center at the Shahid Beheshti University of Medical Sciences, Tehran, Iran (IR.SBMU.RIDS.REC.1395.392). All participants provided written informed consent.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

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