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A Double-Blind Randomized Crossover Study to Evaluate the Timing of Pregabalin for Third Molar Surgery Under Local Anesthesia

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Purpose: This double-blind randomized crossover study compared the analgesic efficacy of pre- and postoperative administration of oral pregabalin 75 mg using a postsurgical dental pain model.

Materials and Methods: Patients requiring third molar surgery in 2 separate stages under local anesthesia were recruited. They were given pregabalin 75 mg either 1 hour before or after their first surgical extraction. They then received the same dose of pregabalin at their second surgical extraction, but those who received it before surgery received it postsurgery, and vice versa. Postoperative analgesic effects were assessed at postoperative hours 2, 4, 8, 12, 24, 48, and 72. Time to first analgesic, analgesic consumption and adverse events were also evaluated.

Results: Forty patients were recruited, and 34 completed the study. The area under curves for numerical rating scale pain scores 1 to 24 hours were significantly lower at rest but not during mouth opening for patients receiving postoperative pregabalin ($P < .048$). Pain relief was similar for the period of 24 to 72 hours. No significant difference was found in time to first analgesic, total analgesic consumption, and side effects between preoperative and postoperative groups. No difference in the incidence of adverse events was noticed in relation to the timing of pregabalin administration.

Conclusions: Postoperative administration of oral pregabalin 75 mg appears to offer better analgesic efficacy than preoperative administration after third molar surgery under local anesthesia.

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Pregabalin [(S)-(t)-3-(aminomethyl)-5-methylhexanoic acid] is an alkylated gamma-aminobutyric acid (GABA) analog pharmacologically similar to gabapentin, [1-(aminomethyl) cyclohexaneacetic acid]. It is believed to bind to the α_2-δsubunit of N-type voltage-gated calcium channels,[1] which reduces the release of glutamate,[2] thus inhibiting neuronal excitability following tissue injury. It is 3 to 10 times more potent than gabapentin.[3] Its absorption shows a linear pharmacokinetic profile with bioavailability exceeding 90%.[4] Its peak plasma concentration is reached within 1 hour after ingestion, and steady state is achieved within 24

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to 48 hours after repeated dosing.[5,6] It is minimally protein-bound or metabolized and is excreted unchanged by the kidneys with an elimination half-life of approximately 5 hours.[7] Dizziness and somnolence are the most commonly reported side effects, but others include dry mouth, peripheral edema, blurred vision, weight gain, myoclonus, asterixis, and gynecomastia.[8-10] Preclinical and clinical data suggest that pregabalin is more than an analog of gabapentin and is effective in treating nociceptive inflammatory pain resistant to gabapentin.[11]

Pregabalin is well established in chronic pain management, but there is now evidence showing effectiveness in acute pain conditions.[12] However, there is as yet no consensus on timing, dose, and duration of pregabalin for postoperative acute pain control because only a limited amount of clinical trial data are available. Because acute postoperative dental pain is a common analgesic model and can be debilitating,[13,14] we conducted this double-blind randomized crossover study to assess whether timing (before or after third molar surgery) of pregabalin administration would have any effect on postoperative pain relief in third molar surgery under local anesthesia. The analgesic effects were studied up to the 72nd hour postoperatively to evaluate any potential preemptive analgesic effect. We hypothesized that preoperative pregabalin would confer better pain relief than postoperative pregabalin. Secondary outcomes such as postoperative analgesic consumption and adverse events were also assessed.

Materials and Methods

The study protocol was approved by our local institutional review board, and written consent was obtained from all the participants. Eligibility for recruitment included American Society of Anesthesiologists physical status I and II, patient age between 18 and 40 years with bilateral impacted third molar teeth scheduled for surgical removal on 2 separate occasions under local anesthesia. Exclusion criteria included impaired liver or renal function, alcohol consumption in excess of 28 U per week, pregnancy, patient refusal, known psychiatric illness, chronic sedative or analgesic use, and being allergic to or currently taking pregabalin. Patients with preoperative inflammation and pain at the site of surgery were also excluded.

After obtaining written informed consent, all patients were randomly allocated to either group P1 or group P2. Group P1 consisted of patients receiving pregabalin 75 mg 1 hour before operation and placebo 1 hour after operation. Group P2 received placebo 1 hour before operation and pregabalin 75 mg 1 hour after operation. This was a crossover comparison, and thus, at the hospital visit for the second operation, patients transferred to the other study group. A computer-generated random sequence was used for group allocation, and this was prepared by a statistician who was unaware of the clinical nature of the study. Two third molars on each side were extracted at least 4 weeks apart. All placebo capsules were identical in size, color, and taste to pregabalin 75 mg. All investigators, dental surgeons, and patients were blind to the group assignment and treatment received.

Surgical removal of the third molars was performed under local anesthesia using 2% lignocaine with 1:80,000 epinephrine by the same surgeon on each occasion. The volume of local anesthetic used and duration of operation were recorded. Difficulty of surgical removal was assessed using the depth of impaction of the third molar (Winter's line) and also graded by the operating surgeon using a numerical rating scale (NRS; 0 = least difficult, 10 = most difficult). Patients were discharged on the same day at the discretion of the attending dental surgeon, and they were given a diary. NRS pain scores (0 = no pain, 10 = worst pain imaginable) at rest and upon mouth opening were self-graded by each patient at postoperative hours 2, 4, 8, 12, 24, 48, and 72.

Patients were prescribed 2 analgesic tablets, each containing paracetamol 320 mg and dextropropoxyphene 32.5 mg (Dolpocetmol; Synco Limited, Hong Kong, China), on an as-needed basis to a maximum of 4 times daily. The oral analgesic was allowed 1 hour after taking the study medication postoperatively. It was explained that pain medications prescribed could be taken if the postoperative pain score was equal to or more than 3. Time to first rescue analgesic and its consumption were noted. On the subsequent morning and up to the 72nd postoperative hour, patients recorded the daily rescue analgesic consumption, adverse events, and their severity. Log books were sent back to investigators by mail after completion.

During data analysis, patients receiving preoperative pregabalin were allocated to the Pr group, and those receiving postoperative pregabalin to the Po group. From our previous study of third molar surgery under local anesthesia, the average AUC for pain scores from 1 to 24 hours was 92 with a standard deviation of 44 among patients. By considering an average difference of 24 of AUC for pain scores at 1 to 24 hours between the Pr and Po groups to be clinically significant, we calculated that the total sample size required for a two-period crossover trial with 80% power of test was 29 at the 5% level of significance. To account for possible dropouts due to protocol violation or missing data, 40 patients were recruited. Demographic data were analyzed by t test, χ^2 test, and Mann-Whitney U test. The NRS pain scores up to 72nd postoperative hours were expressed as areas under the curve (AUC) and compared between the 2 treatments by Wilcoxon signed-ranks test. Time to first rescue analgesic were analyzed by survival analysis