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Analgesic Efficacy of Prophylactic Gabapentin and Lornoxicam in Preventing Postendodontic Pain¶

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All authors accept ethical and legal responsibilities.

Abstract

Objective. In dental applications, as in all other medical applications, pain needs to be prevented or at least controlled. The use of the tooth as a model for studying pain mechanisms is well established. In the current study, we aimed to evaluate and compare the analgesic effects of gabapentin and lornoxicam, respectively, vs a placebo for postendodontic treatment pain.

Design and Methods. Clinical research was planned as prospective, randomized, and placebo controlled. Each subject was given 600 mg gabapentin (group G: N = 30), 8 mg lornoxicam (group L: N = 30), or a placebo (group C: N = 30) 30 min prior to endodontic treatment.

Outcome Measures. At 4 (T_3), 8 (T_4), 12 (T_5), and 24 (T_6) h after preoperative (T_0) time points, the analgesic efficacies of the agents were evaluated by using the visual analog scale (VAS).

Results. In group G, VAS values were significantly greater at T_0 time point than at T_5 or T_6. T_0 time point VAS value in group L was lower than at T_4 time point and greater than at T_6. In group C, T_0 time point VAS values were significantly lower at T_3 and T_5 time points and greater than at T_6 time point. VAS values in group G at T_5 time point were significantly lower than in group C or group L ($P < 0.05$).

Conclusions. Based on the obtained data, prophylactic lornoxicam controlled postendodontic treatment pain more effectively than did the placebo drugs, and gabapentin was more effective in controlling the pain than either lornoxicam or the placebo.

Key Words. Prophylactic; Analgesia; Lornoxicam; Gabapentin

Introduction

Pain is the most important factor influencing patient satisfaction and fear. Postoperative pain following endodontic treatment is a significant problem for both patients and endodontists [1]. Although one of the aims of pulpectomy is to alleviate the cause of endodontic pain, it has been reported that about 25% to 80% of patients still experience significant posttreatment pain [1–5].

The use of teeth as models for studying pain mechanisms is well established; its advantages include a profuse representation of pain fibers and the fact that stimulation of a pulpal nerve produces significant pain sensation. The tooth can be considered a specialized receptor for nociception [6–8]. However, the endodontic pain model differs from the surgical incision-induced pain model in that inflammation and pain are usually present before treatment. Postoperative endodontic pain is often linked to inflammatory mediators (prostaglandins, leukotriens, bradykinin, and serotonin) that activate sensitive nociceptors leading to both central

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and peripheral mechanisms of hyperalgesia [1–8]. Some structural features of the dental pulp make pulpal pain unique: The dental pulp is considered a model system to illustrate peripheral pain mechanisms associated with the trigeminal system [7,8]. In a healthy pulp, painful stimuli trigger depolarization of the nociceptors via the Na channel. However, in the event of infection, periradicular nociceptors are depolarized even by nonpainful stimuli [6–8].

Preventive analgesia is defined as giving analgesics to patients before a painful stimulus. This technique is designed to decrease the establishment of central sensitization, a mechanism whereby spinal neurons increase their responsiveness to peripheral nociceptive input. Although there is a large number of studies reporting the use of an analgesic agent after endodontic treatment, studies involving analgesics before pulpectomy and evaluating the efficacy of the agents are lacking in the literature [9–13].

Opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), antidepressants, and anticonvulsants have been used as pharmacological agents to treat pain [9,14–19]. For dental pain, NSAIDs are some of the most frequently preferred analgesic medications [19]. Lornoxicam, which is an NSAID, creates its analgesic effect by cyclooxygenase (COX) I-II inhibition; it has been reported to be effective in alleviating pain after dental procedures [20,21]. However, studies are lacking regarding the preventive use of lornoxicam in dentistry.

Gabapentin is used for neuropathic and postoperative pain [22–26]. Although early studies indicated that gabapentin had a central antiallodynic effect, it has also been shown to inhibit ectopic discharge activity from injured peripheral nerves [27]. Gabapentin is the first pharmacological agent described that interacts with an α-2δ subunit of a voltage-dependent Ca^{2+} channel [28]. Recent studies support that perioperative administration of gabapentin and pregabalin are effective in reducing the incidence of acute and chronic postsurgical pain [29–31].

The main aim of this study was to evaluate the clinical effectiveness of pretreatment with either 8 mg lornoxicam or 600 mg gabapentin in reducing postendodontic pain compared with a placebo.

Materials and Method

This randomized, double-blinded, placebo-controlled study was performed after written approval of the ethics committee. Ninety subjects were admitted to the Gazi University Faculty of Dentistry clinics for endodontic procedures and notified about the purposes of the study, then their written consents were obtained. Patients were included if they had American Society of Anesthesiologists status I or II and aged between 18 and 45 years. Patients were excluded if they were on antibiotics or analgesics 1 week prior to their treatment or were pregnant.

During the patients' clinical evaluation, palpation, percussion, vitality, and cold tests, as well as periodontal and mobility controls, were conducted. Patients were radiographically evaluated. Diagnosis was made after clinical and radiographic evaluation. According to these results, 90 (n) consecutive subjects were included in the study.

The patients were randomly divided into three groups of 30 patients each. The age, gender, tooth vitality, and pain level of each subject was recorded, and the subjects were given oral gabapentin (Neurontin; Pfizer, New York, NY, USA) 600 mg (group G: N = 30) or oral lornoxicam (Xefo; Abdi İbrahim, Turkey) 8 mg (group L: N = 30) 30 min before endodontic treatment (T_1). The control group was given an oral placebo (group C: N = 30). The study time line is shown in Figure 1.

The 100-mm visual analog scale (VAS) was used to evaluate the pain level. The subjects were instructed to indicate their pain level as 0 for no pain, 100 for unbearable pain, and appropriate points in between. The VAS value measured before treatment was recorded as the preoperative value (T_0). All endodontic treatments were conducted by the same endodontist, who was blinded as to group allocation. Articain hydrochloride 40 mg/mL (Ultracain D-S; Sanofi Aventis, Turkey), which included 0.006 mg epinephrine, was used as the local anesthetic, and the doses were recorded (T_2). After isolation with the rubber dam, pulp extirpation and preparation were conducted. Working length was determined, and the canals were enlarged with a 25K file. After preparation, the canals were irrigated with 5.25% NaOCL and dried with a paper point. Cotton pellets were placed at the cavity entrance and a temporary filling was applied.

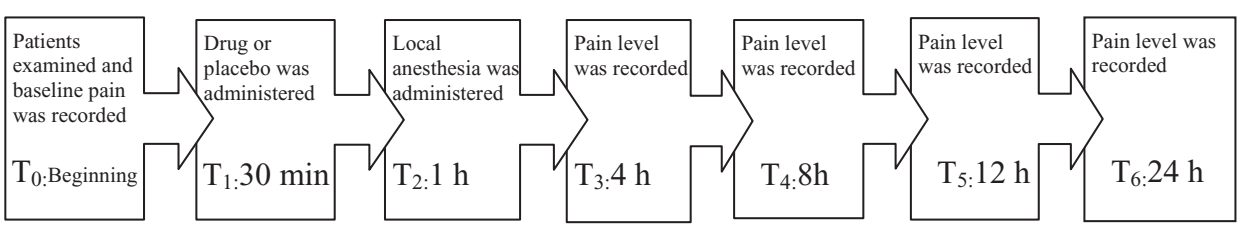


Figure 1 Study time line.

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Table 1 Demographic properties, subjects using additional analgesics, and total amount of local anesthetics used in groups (mean ± SD; N, %)

Variables	Group G (N = 30)	Group L (N = 30)	Group C (N = 30)	*P***
Age (mean ± SD)	33.5 ± 8.2	35.4 ± 6.6	35.2 ± 6.7	0.529
Gender (male/female)	7/23	11/19	9/21	0.530
Body weight (kg [mean ± SD])	67.7 ± 12.05	67.9 ± 11.76	69.2 ± 13.5	0.872
Total amount of local anesthetics used (mg [mean ± SD])	75.7 ± 16.9	74.3 ± 16.9	76 ± 16.3	0.911
Subjects who used additional analgesics (no/yes)	29/1	27/3	25/5	0.201
Number of the patients whose VAS value was more than 4 (N, %)	19 (63.3)	24 (80)	27 (90)*	0.041

*$P < 0.05$, compared with group G.
**P: Significance with ANOVA $P < 0.05$.

The patients were requested to record VAS values at 4 (T_3), 8 (T_4), 12 (T_5), and 24 h (T_6) after the T_0 time point (Figure 1). The patients were advised to take maximum 500 mg acetaminophen as a rescue medication every 6–8 h if needed. They were also urged to notify the endodontist whenever they needed extra analgesics or in the case of an unexpected event.

Statistical Analysis

Before data collection, power analysis and sample size estimation were performed. Power analysis showed that with a power of 0.95 and significance level of 0.05, 26 patients per study group were required. Research was planned to take into account a 10% dropout probability for 30 patients per group. Sample size estimation was performed using a program study size of 3.00.

Statistical analysis was performed using SPSS 17.0 for Windows (SPSS Institute, Chicago, IL, USA). P values <0.05 were considered significant. The Kolmogorov–Smirnov test was used to compare the distribution of all variable groups. Data are presented as mean values and standard deviation, median (25–75%), or N (%). Demographic data between the groups were analyzed using analysis of variance, followed by the Bonferroni test when significance was obtained. VAS parameters were analyzed with the Kruskal–Wallis test, followed by the Mann–Whitney *U*-test when significance was obtained. The Wilcoxon X test was used to compare postoperative VAS values with the T_0 VAS values. Gender (male/female) and subjects who used additional analgesics or had VAS pain levels more than 4 were analyzed with Fisher's test and the χ^2 test.

Results

Age, gender, and body weight characteristics were similar among groups. Total doses of local anesthetics and number of subjects using acetaminophen as an additional analgesic are shown in Table 1. Total doses of the local anesthetics were similar among groups. Number of patients who used additional analgesics (acetaminophen) was nine (group G: N = 1; group L: N = 3; group C: N = 5). The difference was not statistically significant ($P \geq 0.05$).

VAS values were significantly greater at the T_0 time point than at T_5 or T_6 in group G ($P = 0.013$ and

Table 2 Preoperative and postoperative VAS pain levels in groups (mean ± SD; median [25–75%])

Time point	Group G (N = 30)	Group L (N = 30)	Group C (N = 30)	*P**
T_0	20 (0–62.5)	20 (0–60)	20 (0–60)	0.975
T_3	34.7 ± 8.9	37 ± 7.5	39.3 ± 7.9§	0.091
T_4	37.7 ± 6.2	39.7 ± 7.6§	40.3 ± 7.6§	0.334
T_5	14,00 ± 8.55§	20.3 ± 8.1†	30.7 ± 6.9†‡	<0.0001
T_6	0 (0–10)§	10 (0–10)§	10 (0–20)§	0.003

* P: Significance with ANOVA or Kruskal–Wallis $P < 0.05$.
† $P < 0.05$ when compared with group G.
‡ $P < 0.05$ when compared with group L.
§ $P < 0.05$ when compared with T_0.

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$P = 0.001$, respectively). On the other hand, the T_0 time point VAS values in group L were lower than at T_4 and greater than at T_6 ($P = 0.027$ and 0.001, respectively). The T_0 VAS values were significantly lower at the T_3 and T_5 time points and greater than at T_6 in group C ($P = 0.035$, 0.028, and 0.004, respectively; Table 2).

The number of patients whose postendodontic treatment pain level (at any time measurement) was more than VAS 4 was 27 (90%) in group C, 24 (80%) in group L, and 19 (63.3%) in group G. Furthermore, patients with a pain level of more than VAS 4 in group C numbered significantly more than those of group G ($P = 0.015$). The pain level was similar in all groups at the T_0, T_3, and T_4 time points. However, the VAS values in group G at the T_5 time point were significantly lower than in groups C or L ($P < 0.0001$ and $P = 0.008$). Furthermore, VAS values in group C were greater than in group L ($P < 0.0001$). Similarly at T_5, the VAS values in group C at T_5 and T_6 were greater than in group G ($P = 0.001$; Table 2).

When the side effects were evaluated, only two subjects of group L had a short episode of gastrointestinal pain. No other side effects were reported.

Discussion

The endodontic pain model differs significantly from that of postoperative pain because of existing pain and postprocedural inflammation. Pulpectomy, which is performed to alleviate the pain, can itself cause pain. In our study, patients presented similar preoperative pain levels, so we determined that the local anesthetic doses be similar among groups. Although the number of patients requiring analgesia was similar across groups, the pain level was higher in the placebo group. A possible explanation of patients having similar pain levels at T_3–T_4 time points is the remnant effects of the local anesthesia. However, at T_5–T_6, the pain level was lower in the gabapentin group than in the placebo group, and at T_5, the pain level was lower in the lornoxicam group than in the placebo group too.

The major cause of pain is the release of inflammatory mediators that activate sensitive nociceptors surrounding the teeth. The resultant stimulation of both central and peripheral mechanisms is described as hyperalgesia and is defined as an increase in the perceived magnitude of a painful stimulus [1–9]. Peripheral pain should be controlled by anti-inflammatory agents. Lornoxicam affects the synthesis of prostaglandins by inhibiting the COX enzymes [20]. Results have been controversial; some researchers concluded that pretreatment administration of NSAIDs provides better pain control for postendodontic pain [10–13]. However, Attar et al. [32] declared that preoperative administration of NSAIDs does not significantly reduce postoperative endodontic pain. We found a single dose of lornoxicam to be superior to a placebo in alleviating pain [10–13].

Gabapentin has proven effective in relieving chronic pain and that it is indicated for managing neuropathic pain [25,33]. Moreover, gabapentin analogs appear to have significant analgesic properties for managing acute pain following third molar extraction [34,35]. Lopez et al. [36] reported that combining prednisone and gabapentin analogs (pregabalin) is a good option in the management of inferior alveolar nerve damage subsequent to endodontic sealer extrusion. In our research, we observed that pain control was better in the gabapentin group than in the lornoxicam or placebo groups. Thus, we conclude that pretreatment with gabapentin controls postendodontic pain more effectively than either a placebo or lornoxicam.

The average duration of analgesic effect is an important factor in evaluating analgesic efficacy. The time for oral lornoxicam is 3–5 h and for oral gabapentin is 4.8–8.7 h for adolescents [20,23]. The use of local anesthetics was believed to be effective in reducing the pain. In this study, the VAS scores at T_3 could have reflected the effects of the local anesthesia.

Both drugs have specific side effects. However, in the current study, only two subjects in group L experienced brief gastrointestinal pain. No other side effects were reported.

There are a number of limitations to the current study. First, the patient's level of anxiety, origin of the pain (pulpal or periradicular), whether there is a periodontal component, and whether the pain is due primarily to an inflammatory or infectious process were not clarified. Second, there was no dose response evaluation: We used only single doses of the current drugs; however, we selected the most common dosages used in the literature.

Postendodontic treatment pain is defined as a condition of tissue injury. Considering that every traumatic intervention might result in nerve injury, it is not surprising to find neuropathic pain features within posttreatment pain itself. Therefore, the issue of whether postendodontic treatment pain is purely a nociceptive pain remains a topic of debate. In light of these findings, it would be more precise to define posttreatment pain as a combination of nociceptive and neuropathic components instead of pure pain. Thus, the appropriate pain treatment should be based on consideration of both these components.

Conclusions

Within the limits of this study, it was revealed that, in the control of pain, a single prophylactic dose of lornoxicam performed better than did the placebo drugs; gabapentin performed best. Further studies, along with long-term follow-up to evaluate phantom tooth pain, are warranted.

References

1 Maalof EM, Ounsi HF. Pain control after endodontic therapy. Dent News (Lond) 1998;5(2):45–7.

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2 O'Keefe EM. Pain in endodontic therapy: Preliminary study. J Endod 1976;2:315–9.

3 Clem WH. Post treatment endodontic pain. JADA 1970;81(5):1166–70.

4 Seltzer S, Bender IB, Ehrenreich J. Incidence and duration of pain following endodontic therapy: Relationship to treatment with sulfonamides and to other factors. Oral Surg Oral Med Oral Pathol 1961;14: 74–82.

5 Georgopoulou M, Anastassiadis P, Sykaras S. Pain after chemo mechanical preparation. Int Endod J 1986;19(6):309–14.

6 Marbach JJ, Hulbrock J, Hohn C, Segal AG. Incidence of phantom tooth pain: An atypical facial neuralgia. Oral Surg Oral Med Oral Pathol 1982;53(2): 190–3.

7 Diogenes A, Henry MA. Pain pathways and mechanisms of the pulpodentin complex (Chapter 8). In: Hargreaves KM, Goodis HE, Tay FR, eds. Seltzer and Bender's Dental Pulp, 2nd edition. Chicago: Quintessence; 2012:159–84.

8 Henry MA, Hargreaves KM. Peripheral mechanisms of odontogenic pain. Dent Clin North Am 2007; 51(1):19–44.

9 Huynh MP, Yagiela JA. Current concepts in acute pain management. J Calif Dent Assoc 2003;31(5): 419–27.

10 Flath RK, Hicks ML, Dionne RA, Pelleu GB Jr. Pain suppression after pulpectomy with preoperative flurbiprofen. J Endod 1987;13(7):339–47.

11 Menke ER, Jackson CR, Bagby MD, Tracy TS. The effectiveness of prophylactic etodolac on postendodontic pain. J Endod 2000;26(12):712–5.

12 Moore PA, Hersh EV. Celecoxib and rofecoxib. The role of COX-2 inhibitors in dental practice. JADA. 2001;132(4):451–6.

13 Gopikrishna V, Paramewaran A. Effectiveness of prophylactic use of rofecoxib in comparison with ibuprofen on postendodontic pain. J Endod 2003; 29(1):62–4.

14 White PF. Multimodal analgesia: Its role in preventing postoperative pain. Curr Opin Investig Drugs 2008;9(1):76–82.

15 Pogatzki-Zahn EM, Zahn PK. From preemptive to preventive analgesia. Curr Opin Anaesthesiol 2006; 19(5):551–5.

16 Martin WJ, Perez RS, Tuinzing DB, Forouzanfar T. Efficacy of antidepressants on orofacial pain: A systematic review. Int J Oral Maxillofac Surg 2012;41(12):1532–9.

17 Martin WJ, Forouzanfar T. The efficacy of anticonvulsants on orofacial pain: A systematic review. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011; 111(5):627–33.

18 Marshall JG. Consideration of steroids for endodontic pain. Endod Topics 2002;3:41–51.

19 Hargreaves K, Abbott PV. Drugs for pain management in dentistry. Aust Dent J 2005;50(4 suppl 2):S14–22.

20 Radhofer-Welte S, Rabasseda X. Lornoxicam, a new potent NSAID with an improved tolerability profile. Drugs Today 2000;36(1):55–76.

21 Møller PL, Nørholt SE. Analgesic efficacy of quick-release vs standard lornoxicam for pain after third molar surgery: A randomized, double-blind, placebo-controlled, single-dose trial. Clin Drug Investig 2008;28(12):757–66.

22 Turan A, White PF, Karamanlioglu B, et al. Gabapentin: An alternative to the cyclooxygenase-2 inhibitors for perioperative pain management. Anesth Analg 2006;102(1):175–81.

23 Rose MA, Kam PC. Gabapentin: Pharmacology and its use in pain management. Anaesthesia 2002;57(5): 451–62.

24 Dahl JB, Mathiesen O, Møiniche S. "Protective premedication": An option with gabapentin and related drugs? A review of gabapentin and pregabalin in in the treatment of post-operative pain. Acta Anaesthesiol Scand 2004;48(9):1130–6.

25 Kong VK, Irwin MG. Gabapentin: A multimodal perioperative drug? Br J Anaesth 2007;99(6):775–86.

26 Seib RK, Paul JE. Preoperativegabapentin for postoperative analgesia: A meta-analysis. Can J Anaesth 2006;53(5):461–9.

27 Pan HL, Eisenach JC, Chen SR. Gabapentin suppresses ectopic nerve discharges and reverses allodynia in neuropathic rats. J Pharmacol Exp Ther 1999;288(3):1026–30.

28 Gee NS, Brown JP, Dissanayake VU, et al. The novel anticonvulsant drug, gabapentin (Neurontin), binds to the alpha 2 delta subunit of a calcium channel. J Biol Chem 1996;271(10):5768–76.

29 Ucak A, Onan B, Sen H, et al. The effects of gabapentin on acute and chronic postoperative pain after

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coronary artery bypass graft surgery. J Cardiothorac Vasc Anesth 2011;25(5):824–9.

30 Clarke H, Bonin RP, Orser BA, et al. The prevention of chronic postsurgical pain using gabapentin and pregabalin: A combined systematic review and meta-analysis. Anesth Analg 2012;115(2):428–42.

31 Tiippana EM, Hamunen K, Kontinen VK, Kalso E. Do surgical patients benefit from perioperative gabapentin/pregabalin? A systematic review of efficacy and safety. AnesthAnalg 2007;104(6):1545–56.

32 Attar S, Bowles WR, Baisden MK, Hodges JS, McClanahan SB. Evaluation of pretreatment analgesia and endodontic treatment for postoperative endodontic pain. J Endod 2008;34(6):652–5.

33 McCormick Z, Chang-Chien G, Marshall B, Huang M, Harden RN. Phantom limb pain: A systematic neuroanatomical-based review of pharmacologic treatment. Pain Med 2014;15(2):292–305.

34 Hill CM, Balkenohl M, Thomas DW, et al. Pregabalin in patients with postoperative dental pain. Eur J Pain 2001;5(2):119–24.

35 Narita N, Kumar N, Cherkas PS, et al. Systemic pregabalin attenuates sensorimotor responses and medullary glutamate release in inflammatory tooth pain model. Neuroscience 2012;30(218):359–66.

36 López-López J, Estrugo-Devesa A, Jané-Salas E, Segura-Egea JJ. Inferior alveolar nerve injury resulting from overextension of an endodontic sealer: Non-surgical management using the GABA analogue pregabalin. Int Endod J 2012;45(1):98–104.

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