Evaluation of Pretreatment Analgesia and Endodontic Treatment for Postoperative Endodontic Pain

Sayeed Attar, DDS, MS, Walter R. Bowles, DDS, MS, BPharm,† Michael K. Baisden, DDS,†*
James S. Hodges, PhD,‡ and Scott B. McClanahan, DDS, MS†

Abstract

This study compares single-dose ibuprofen pretreatment for postoperative endodontic pain. Thirty-nine emergent patients were randomly assigned to 3 groups: placebo, ibuprofen tablets, or ibuprofen liquigels. Patients recorded their pain levels before and at the end of treatment, then every 6 hours for 24 hours after administration of the medications and standard endodontic treatment. Pain evaluations by using 3 pain scales (visual analog scale [VAS], category, and Heft-Parker) were highly correlated, suggesting the rationale for only using one pain scale in pain studies. No significant differences in postoperative pain levels were found between either single-dose ibuprofen formulation or the placebo control group ($P = .84$). Patients treated with calcium hydroxide versus obturation did not differ in postoperative pain levels ($P = .44$). This study suggests that single-dose pretreatment analgesia alone in endodontic pain patients will not significantly reduce postoperative pain below the reduction in pain from endodontic treatment. *(J Endod 2008;34: 652–655)*

Key Words

Analgesia, endodontic pain, preemptive

*From Private practice, Plymouth, Minnesota, †Division of Endodontics, University of Minnesota School of Dentistry, Minneapolis, Minnesota, ‡Division of Biostatistics, University of Minnesota, Minneapolis, Minnesota.

Address requests for reprints to Walter Bowles, DDS, MS, 8-166 Moos Tower, 515 Delaware St SE, Minneapolis, MN 55455. E-mail address: bowle001@umn.edu.

Preemptive analgesia has historically been defined as an antinociceptive treatment that prevents altered processing of afferent input amplifying postoperative pain (1). Because in many cases endodontic patients come to the office already in pain, a more clinically relevant term to use in endodontics would be pretreatment analgesia, providing analgesia to patients before endodontic treatment is started. This technique may decrease the establishment of central sensitization, a mechanism whereby spinal neurons increase their responsiveness to peripheral nociceptive input.

For dental pain, nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most frequently taken analgesic medications. Their popularity is attributed to their abundant over-the-counter availability, efficacy in relieving pain and fever, and low side effect profile at therapeutic doses. Numerous studies have shown ibuprofen to be very effective in controlling or reducing dental pain at various dosages, especially at doses of 600–800 mg (2–4). After the oral administration of ibuprofen, the plasma concentration generally reaches, in principle, a single, well-defined peak (C_{max}) at the time of maximum concentration (t_{max}). In 1995, a liquigel formulation of ibuprofen 200 mg (Advil liquigels; Wyeth Pharmaceutical, Madison, NJ) was developed that has a pharmacokinetic profile similar to ibuprofen suspension, with both an earlier t_{max} and a higher C_{max} than tablet formulations. The rate and extent of absorption are correlated with analgesic onset and overall efficacy (5–7). Several randomized, double-blinded, placebo-controlled clinical trials have shown that liquigels (400 mg ibuprofen) provide faster time to relief and greater analgesic efficacy than 1000 mg acetaminophen in oral surgical model (8, 9). Because onset, peak effect, and total effect are very important characteristics of analgesics in acute pain situations, it is believed that the liquigel formulation has some advantages when compared with its traditional tablet counterpart.

In many oral pain studies, absorption and distribution of the medication are allowed to occur before the initiation of surgical tissue damage and resultant production of inflammatory mediators. The endodontic pain model is considerably different from the oral surgery model, in that inflammation and pain are usually present before treatment. When using pretreatment analgesia for pulpectomies, Flath et al. (10) found no difference in pain scores at 7 and 24 hours after administering an NSAID (flurbiprofen) before a tooth pulpectomy as compared with 3 hours after pulpectomy.

Pain is a very subjective experience personally influenced by many factors, including, but not limited to, behavioral and cultural learning and expectations, attention response from surrounding people, physical (genetic) factors, and psychological factors. Quantifying and standardizing pain objectively across a group of individuals can be challenging. Numeric and verbal self-rating scales or behavioral observation scales have traditionally been used in clinical studies. Coll et al. (11, 12) critically reviewed nursing and health care publications for some of the available objective and subjective measures of pain and established the suitability of a visual analog scale (VAS) (a 100-mm line with 0 mm marking no pain and 100 mm marking maximum pain) for measuring the intensity of pain after day surgery. On the basis of their established criteria, the VAS was found to be methodologically sound, conceptually simple, easy to administer, and unobtrusive to the respondent. It has a continuous frequency distribution allowing for rigorous statistical tests on average pain levels. On these grounds, the VAS seems to be most suitable for measuring intensity of pain after day surgery (11, 12). The VAS has also been shown to be highly reproducible and unaffected by gender (13). A second type of pain scale is the categorical scale, a 4-point scale composed of no pain, mild pain, moderate pain, and severe pain. In spite of its simplicity, the categorical scale has

TABLE 1. Demographics and Treatment Group Diagnostic Categories

	N	Average age (y ± SEM)	Sex (M:F)	Pulp diagnosis, IRP	Pulp diagnosis, necrosis	Periradicular APP	Periradicular APA	Periradicular normal
Placebo	12	45.8 ± 5.1	9:3	7	5	2	9	1
Ibuprofen tablet	14	44.9 ± 4.0	7:7	9	5	3	10	1
Ibuprofen liquigel	13	41.6 ± 4.3	7:6	8	5	1	11	1

IRP, irreversible pulpitis; APA, acute periradicular pulpitis, APA, acute periradicular abscess.

been shown to be a reliable and reproducible measuring tool for clinical pain trials. For each categorical score, however, there are a wide range of VAS responses, with overlaps between categories. A combined metric scale (Heft-Parker) for pain measurement that provides the subject with multiple cues might improve communication and concordance between scales for individual pain determination (14). The Heft-Parker scale integrates irregular spacing of 6 categorical scale descriptive words onto a 170-mm horizontal line. The inventors stressed that patients make categorical judgments on the basis of their understanding of the words, and that the categorical ratings are not an ordinal index (15).

The purpose of this study was to evaluate postoperative pain in endodontic pain patients receiving endodontic treatment after pretreatment analgesia with a single pretreatment dose of 600 mg of ibuprofen (liquigel or tablets), compared with placebo.

Materials and Methods

This study was a randomized, double-blinded, placebo-controlled clinical trial focused on pretreatment administration of the NSAID ibuprofen for evaluation of postoperative endodontic pain after endodontic treatment. The study protocol was approved by the appropriate human subjects review board, and each patient provided informed consent to participate in the study. Each study participant completed a baseline 100-mm VAS to establish that their preoperative pain level met the inclusion criterion of ≥30 mm. Before the initiation of treatment, demographic data were recorded, and the test medications were administered to the patient in a double-blind manner. The medications were paired so that every patient received 3 tablets and 3 liquigels. The 3 treatment groups were group 1 (placebo tablets + placebo liquigels), group 2 (ibuprofen tablets + placebo liquigels), and group 3 (placebo tablets + ibuprofen liquigels). For patient groups receiving pretreatment ibuprofen (groups 2 and 3), the 600-mg dose of ibuprofen was administered to study the initial difference between dosage forms (liquigel vs tablet), with the onset of the liquigel to occur before access and instrumentation (approximately 15 minutes), whereas the tablet would not have onset until after access and instrumentation (approximately 30 minutes). Only a single dose of analgesic was administered before treatment for the reason that if subsequent doses had been allowed, the plasma levels of ibuprofen in both the liquigel and tablet groups would be similar, thereby negating any differences. After local anesthetic administration (long-acting local anesthetic was not used for any patients), an endodontic resident or an undergraduate dental student under the supervision of an endodontic faculty member provided appropriate endodontic treatment, which included endodontic access and instrumentation of all canals. The minimum instrumentation considered acceptable for study inclusion was to at least a #25 file (Flexofile; Dentsply Maillefer, Tulsa, OK) to within 0.5–1.0 mm of the radiographic apex of the root. The coronal portions of the canals were enlarged with size 2 through 4 Gates-Glidden burs (Dentsply Maillefer) and/or GT nickel-titanium rotary files (Dentsply Maillefer). Corrected working length was determined, and sodium hypochlorite (3% or 6%) was used for intracanal irrigation. All partial treatments were temporized with the use of calcium hydroxide (Ultracal; Ultradent Products Inc, South Jor-

dan, UT; or Calasept; Nordiska Dental AB, Angelholm, Sweden), a cotton pellet, and Cavit (3M; St Paul, MN). All completed treatments were obturated with gutta-percha and either Roth's 801 ZOE sealer or AH Plus resin sealer by using System B (SybronEndo Corp, Orange, CA) and Obtura (Obtura Spartan, Fenton, MO) backfill followed by a cotton pellet and Cavit temporary, or a permanent restoration with amalgam or resin build-up.

On completion of the emergent endodontic treatment, the patient completed the first of 5 postoperative questionnaires to measure immediate post-treatment pain and to ensure patient understanding of the questionnaires. Study participants were asked to record their discomfort levels on the provided questionnaires every 6 hours after treatment through 24 hours after treatment. Included in the patients' packets were escape medication (Tylenol ES; McNeil, Fort Washington, PA) for inadequate pain control from the trial medication.

Statistical Methods

Baseline comparisons of the study groups used either one-way analysis of variance (ANOVA) or Pearson χ^2 test. The primary analysis was a repeated-measures ANOVA, with the VAS score as its dependent variable, subject as the random effect, and fixed effects study group (ibuprofen liquigel, ibuprofen tablet, or placebo), measurement time (0, 6, 12, 18, 24 hours), and their interaction. The method of analysis was restricted likelihood (REML), and the analyses were computed by using JMP (v 6; SAS Institute, Inc, Cary, NC). Secondary analyses considered one patient characteristic (sex, age, treatment rendered) in addition to study group. These were also repeated-measures ANOVA, with one extra (between-subject) fixed effect, along with all of its interactions with the other 2 fixed effects.

Results

A total of 45 patients were enrolled into this clinical trial. Six patients were lost to follow-up by not returning the questionnaires, leaving a total of 39 patients to be included for analysis, with 12 patients in the placebo group, 14 patients included in the ibuprofen tablet group, and 13 patients in the ibuprofen liquigel group. No patients took any of the escape medication, which was provided in case of inadequate pain control. Within the 3 treatment groups, there were no significant differences with respect to sex ($P = .29$), age ($P = .78$), pulpal diagnosis ($P = .68$), or periradicular diagnosis ($P = .84$). Patient characteristics are shown in Table 1.

First evaluated was the correlation between the VAS, Heft-Parker, and categorical pain scales at all time points combined and separately (0, 6, 12, 18, 24 hours). All 3 pairs of pain scales were highly correlated, justifying the decision to subsequently analyze the data by using

TABLE 2. Pain Scale Correlations, All Times Included

	Correlation
VAS-HP	0.9465
VAS-categorical	0.9104
HP-categorical	0.9535

HP, Heft-Parker; VAS, visual analog scale.

only VAS responses (Table 2). The correlations between pairs of scales were very similar at each individual time point.

Pretreatment pain levels between treatment groups were virtually identical and the complete VAS scores of the 3 groups are shown in Figure 1. For the main study comparison, treatment groups were compared according to VAS without considering other patient characteristics such as sex, age, etc. First, the ANOVA evaluated the main effect for the study groups, which addresses the question "If, for each study group, you average its pain scores over the follow-up times, and then you compare the groups according to these averages, do the study groups differ?" The study groups did not differ significantly according to these averages ($P = .60$).

The main effect for follow-up time was analyzed, which addresses the question "If at each time you average all the patients' VAS scores, irrespective of treatment group, do the times differ?" The main effect for follow-up time was significant ($P < .0001$), showing a decrease in pain after treatment compared with pretreatment pain. However, the time paths between 3 groups did not differ significantly from each other (study-group-by-time interaction, $P = .84$).

When comparing differences between treatment groups and the treatment provided ($Ca(OH)_2$ vs obturation), no significant differences ($P = .44$) were noted in postoperative pain (Fig. 2).

Discussion

Traditionally, impacted third molar extractions have served as an excellent pain model for testing analgesic efficacy. This model predictably, consistently, and reproducibly induces pain that is of adequate severity to discriminate between different strengths of analgesics (16). In designing clinical trials for the treatment of acute pain, the U.S. Food and Drug Administration recommends enrollment of patients with moderate to severe pain, even when the desired indication is treatment of mild pain. They conclude that including patients with a higher degree of baseline pain in the postoperative dental pain model has the potential to increase discrimination of analgesic properties of new drugs (17). Oral surgical studies tend to have a patient population biased toward a younger, healthier, and preoperatively asymptomatic group participating in elective surgery. In addition, many surgical clinical trials studying preemptive analgesic regimens also use oral, intravenous, or inhalation sedation, which limits their relevance to general practice.

The endodontic model differs from the surgical model in several ways. First, emergent endodontic patients often can vary considerably in
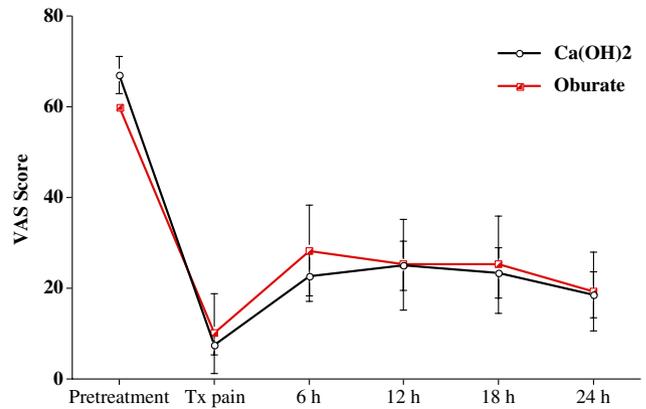
Figure 2. Treatment rendered comparison. Patients treated with calcium hydroxide versus obturation did not differ in postoperative pain levels ($P = .44$). Error bars = standard error of the mean.

health status and age. Second, they have preexisting pulpal and/or periradicular pathosis attributing to their preoperative pain. Preoperative pain has the potential to significantly confound the results of preemptive analgesic clinical trials. Preexisting pulpal and/or periradicular pain, resulting from acute inflammation of the associated anatomic structures, can cause neuroplastic changes in the dorsal horn (18). In animal models, the peripheral nociceptive barrage from inflamed pulps has been shown to be sufficient enough to cause a 5-fold increase in dorsal horn neuron discharge rate (19) and up to a 3-fold increase in the size of the receptive field of A-delta fibers (20).

Because the groups demonstrated no significant preoperative differences and all were provided with similar endodontic treatment as part of the study, it can be concluded that there were no differences between the treatment groups before giving the test medications. Differences between groups might have been seen at earlier time points (before the 6-hour measurement), but these measurements could have been confounded by local anesthetic residual effects. This study demonstrated no significant difference between the liquigel or tablet formulations of ibuprofen 600 mg and the placebo group, suggesting that single-dose preoperative NSAID treatment will not significantly reduce postoperative pain over the reduction in pain from endodontic treatment. Statistical analysis also showed no difference in postoperative pain levels between patients treated with instrumentation and either calcium hydroxide or obturation.

Figure 1. VAS averages per group at each time. Single-dose pretreatment with ibuprofen did not significantly reduce postoperative pain over reduction in pain from endodontic treatment ($P = .84$). N = 39. Error bars = standard error of the mean.

References

1. Kissin I. Preemptive analgesia. Anesthesiology 2000;93:1138–43.
2. Dionne RA, Campbell RA, Cooper SA, Hall DL, Buckingham B. Suppression of postoperative pain by preoperative administration of ibuprofen in comparison to placebo, acetaminophen, and acetaminophen plus codeine. J Clin Pharmacol 1983;23:37–43.
3. Cooper SA. Five studies on ibuprofen for postsurgical dental pain. Am J Med 1984;77:70–7.
4. Dionne RA, Cooper SA. Evaluation of preoperative ibuprofen for postoperative pain after removal of third molars. Oral Surg Oral Med Oral Pathol 1978;45:851–6.
5. Seymour RA, Ward-Booth P, Kelly PJ. Evaluation of different doses of soluble ibuprofen and ibuprofen tablets in postoperative dental pain. Br J Oral Maxillofac Surg 1996;34:110–4.
6. Monti NC, Gazzaniga A, Giansello V, et al. Activity and pharmacokinetics of a new oral dosage form of soluble ibuprofen. Arzneim-Forsch Drug Res 1992;42:556–9.
7. Laska EM, Sunshine A, Marrero I, Olson N, Siegel C, McCormick N. The correlation between blood levels of ibuprofen and clinical analgesic response. Clin Pharmacol Ther 1986;40:1–7.
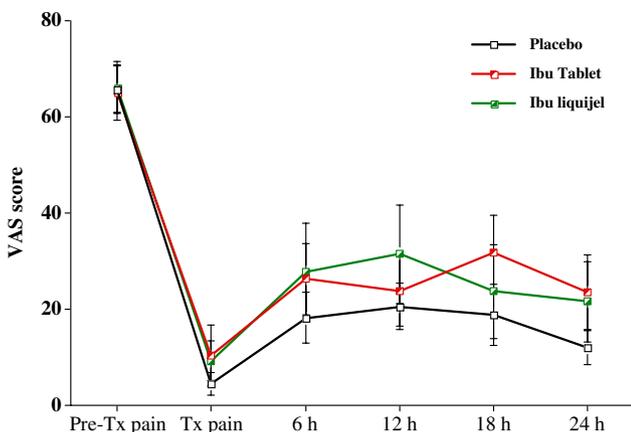
8. Hersh EV, Levin LM, Cooper SA, et al. Ibuprofen liquigel for oral surgery pain. Clin Ther 2000;22:1306–18.

9. Olson NZ, Otero AM, Marrero I, et al. Onset of analgesia for liquigel ibuprofen 400 mg, acetaminophen 1000 mg, ketoprofen 25 mg, and placebo in the treatment of postoperative dental pain. J Clin Pharmacol 2001;41:1238.

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

11. Coll AM, Ameen JR, Moseley LG. Reported pain after day surgery: a critical literature review. J Adv Nurs 2004;46:53–65.

12. Coll AM, Ameen JR, Mead D. Postoperative pain assessment tools in day surgery: literature review. J Adv Nurs 2004;46:124–33.

13. Goddard G, Karibe H, McNeill C. Reproducibility of visual analog scale (VAS) pain scores to mechanical pressure. Cranio 2004;22:250–6.

14. Averbuch M, Katzper M. Assessment of visual analog versus categorical scale for measurement of osteoarthritis pain. J Clin Pharmacol 2004;44:368–72.

15. Heft MW, Parker SR. An experimental basis for revising the graphic rating scale for pain. Pain 1984;19:153–61.

16. Urquhart E. Analgesic agents and strategies in the dental pain model. J Dent 1994;22:336–41.

17. Averbuch M, Katzper M. Severity of baseline pain and degree of analgesia in the third molar post-extraction dental pain model. Anesth Analg 2003;97:163–7.

18. Torneck CD, Kwan CL, Hu JW. Inflammatory lesions of the tooth pulp induce changes in brainstem neurons of the rat trigeminal subnucleus oralis. J Dent Res 1996;75:553–61.

19. Chiang CY, Park SJ, Kwan CL, Hu JW, Sessle BJ. NMDA receptor mechanisms contribute to neuroplasticity induced in caudalis nociceptive neurons by tooth pulp stimulation. J Neurophysiol 1998;80:2621–31.

20. Närhi M, Ngassapa D. Function of intradental nociceptors in normal and inflamed teeth. In: Shimono MMT, Suda H, Takahashi K, eds. Dentin/pulp complex. Tokyo: Quintessence, 1996:136–40.