A Randomized Clinical Trial Comparing 2 Ibuprofen Formulations in Patients with Acute Odontogenic Pain

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Abstract

Introduction: Ibuprofen sodium dihydrate, a new formulation of ibuprofen, was introduced with the claim of faster onset of analgesia. Most of the data on this new ibuprofen formulation are drawn from studies using the oral surgery model. Because this model differs significantly from the endodontic pain model, we conducted a study comparing ibuprofen sodium dihydrate with conventional ibuprofen acid in endodontic pain patients. **Methods:** This randomized, double-masked study recruited subjects experiencing moderate to severe pain from a tooth diagnosed with symptomatic irreversible pulpitis and symptomatic apical periodontitis (n = 41). Subjects were randomized to receive 400 mg ibuprofen acid (Advil; Pfizer, Madison, NJ) or an equivalent dose of 512 mg ibuprofen sodium dihydrate (Advil Sodium, Pfizer). The outcome measures were time to onset of 50% pain relief recorded using a stopwatch, reduction in spontaneous pain experienced on a 100-mm visual analog scale, and change in mechanical allodynia measured using a bite force transducer. The last 2 measures were obtained before and 60 minutes after administration of the drug. **Results:** The median time to onset of 50% pain relief after administration of ibuprofen sodium dihydrate was significantly faster compared with ibuprofen acid (26.5 vs 44 minutes, P = .08). Ibuprofen sodium dihydrate provided a greater reduction in spontaneous pain (50.8% vs 33.3%, P < .05) and mechanical allodynia (15% vs 9%, P > .05). **Conclusions:** In endodontic pain patients, a single dose of ibuprofen sodium dihydrate provides faster onset of pain relief and a greater reduction in spontaneous and evoked pain compared with ibuprofen acid. *(J Endod 2017;■:1–5)*

Key Words

Ibuprofen, nonsteroidal anti-inflammatory drugs, mechanical allodynia, pain, pulpitis

Significance

The results of this randomized, double-masked, controlled study showed that a single dose of ibuprofen sodium dihydrate provides faster and greater pain relief than a comparable dose of conventional ibuprofen acid in endodontic pain patients.

Odontogenic pain associated with irreversible pulpitis usually has an acute onset and is often moderate to severe in intensity (1, 2). A study on the management of odontogenic pain reported that only half of the pain patients initially attempt to contact a dental professional and use over-the-counter (OTC) analgesics instead (3). Another study reported that between 81% and 83% of odontogenic pain patients used OTC analgesics for pain relief (4). These analgesics include aspirin, acetaminophen, and nonsteroidal anti-inflammatory drugs (NSAIDs).

The speed of onset of an analgesic is critical in acute pain conditions, not only because of the relief experienced but also because rapid onset of pain relief reduces the risk of excessive dosing. Patients are likely to use more than the recommended dose of an analgesic or to supplement it with a different type of analgesic when rapid pain relief is not achieved. This can be detrimental because many adverse effects are dose dependent.

Ibuprofen acid has been used for decades to alleviate odontogenic pain and is considered the gold standard NSAID in clinical trials on acute odontogenic pain (5, 6). A limitation of ibuprofen acid is that it is not readily soluble, which, in turn, affects its onset of action (7, 8). Enhancements in ibuprofen acid's pharmacokinetics have led to the development of ibuprofen salts with a faster dissolution rate and onset of action. These ibuprofen salts include ibuprofen lysine, ibuprofen arginine, and ibuprofen sodium dihydrate; only the latter is currently approved by the United States Food and Drug Administration in a tablet formulation. An *in vitro* study showed a faster dissolution of ibuprofen sodium dihydrate at a pH of 1.2, 3.5, and 7.2 in comparison with ibuprofen acid (7). This greater solubility allows greater absorption and subsequently a faster onset of analgesic effect. *In vivo* pharmacokinetic studies using the oral surgery model show that ibuprofen sodium dihydrate has a higher drug plasma concentration (41.47 μg/mL vs 31.88 μg/mL) and a lower time to reach the maximum concentration of the drug (75 minutes vs 90 minutes) than ibuprofen acid, thereby producing faster and more profound analgesia (72) (7, 9, 10).

The previously mentioned data from the oral surgery model, although useful, cannot always be readily translated to endodontic pain patients. In the oral surgery model, the study subjects often presented with either no pain or mild pain before the removal of their third molars. Thus, the acute inflammatory pain evaluated in

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such clinical trials results mostly from the surgical trauma. In contrast, endodontic patients often present in pain that may be moderate to severe in intensity. The objective of this study was to compare the analgesic effect of a single dose of ibuprofen sodium dihydrate with that of a comparable dose of ibuprofen acid in endodontic pain patients presenting with moderate to severe pain.

Materials and Methods

This randomized, double-masked, controlled, parallel-group trial was approved by the Office of Human Research Ethics at our institution. Healthy men and women (aged 18–60 years old) experiencing moderate to severe pain (defined as >30 mm on a 100-mm visual analog scale [VAS]) and diagnosed with symptomatic irreversible pulpitis (defined as spontaneous pain and lingering response to thermal stimuli) and symptomatic apical periodontitis (defined as sensitivity to percussion) were recruited to the study. Subjects who had recently used any type of analgesics were questioned about the dose and type of analgesic used. If it was determined that the potential study subjects could be experiencing the therapeutic effect of the drug at the time of the study, they were excluded. Subjects with a known hypersensitivity to NSAIDs, a history of gastric or duodenal ulcers, or gastrointestinal bleeding were not recruited to the study. We also excluded pregnant and lactating women and subjects classified as American Society of Anesthesiologists class III through V. Written informed consent was obtained from all subjects.

This study lasted 60 minutes and had 3 outcome measures: onset of 50% pain relief, reduction in spontaneous pain, and attenuation of mechanical allodynia after administration of the 2 ibuprofen formulations. Subjects were first asked to report the intensity of the pain they were experiencing on a 100-mm VAS with anchors of 0 mm representing no pain and 100 mm representing the worst pain imaginable (11). We then measured mechanical pain thresholds on the painful and contralateral asymptomatic (control) teeth using a digital bite force transducer as described in previous studies (12–14). Mechanical allodynia was calculated as the difference in mechanical pain thresholds between the controls and the affected teeth (13).

Subjects were randomly assigned to receive a single dose of 400 mg ibuprofen acid (Advil; Pfizer, Madison, NJ) or an equivalent dose of 512 mg (2 tablets × 256 mg) ibuprofen sodium dihydrate (Advil). We used a block randomization plan. The senior author (A.K.) assigned participants, whereas the first author (T.T.) enrolled all participants. After administration of the drug, they were given a stopwatch and instructed to stop it when they felt a 50% decrease in pain intensity. At 60 minutes after administration of the drug, subjects were asked to rate their pain on the VAS, and the mechanical pain thresholds of the painful and control teeth were determined. All the diagnostic tests and data collection were performed by a single examiner (T.T.) who remained masked about the type of ibuprofen formulation given to the subjects.

Statistical Analysis

Sample size analysis was based on our prior studies examining mechanical allodynia in odontogenic pain patients (13, 14). There were 3 outcome variables for this study. The decrease of pain intensity and change in mechanical allodynia were analyzed by fitting a linear mixed-effects model to data via the restricted maximum likelihood. Statistical analysis was performed in R statistical software (version 3.2.3, www.cran.r-project.org). The R function lmer in package lme4 was used for this mixed-effects model in which the subject identification numbers are considered as the random variable to affect the intercept of the regression. The effects of the 3 outcomes are considered as fixed effects. The onset of 50% pain relief was analyzed using the Kaplan-Meier estimator as in survival analysis.

Comparisons were made of control and affected teeth between preadministration and postadministration of the drug within the 60-minute study period. The effects caused by the usage of the different drugs are inferred based on these comparisons. Because of the usage of the mixed-effect model, all analysis considered the data as paired data by the subject identification numbers. After checking the box plot, histogram, and QQ plots of the mechanical pain thresholds, the scores were log2 transformed for a more symmetric distribution so that the assumptions of the models were valid. The restricted maximum likelihood was used for analysis of change in mechanical pain thresholds.

Possible confounders include age and sex. We checked the association between age and each of the 2 outcomes as well as the association between sex and each of the 2 outcomes. Significance was set at $P < .05$. Marginal significance was set at $P = .05–.1$.

TABLE 1. Age and Sex Distribution of Study Subjects

Group	Age	Sex
Ibuprofen acid	37.3 ± 9.7 years	13 women and 8 men
Ibuprofen sodium dihydrate	33.4 ± 11.7 years	10 women and 10 men

Results

Forty-one subjects were enrolled and completed the study between March 2015 and March 2016. The age and sex distributions are listed in Table 1. When comparing subjects in the ibuprofen sodium dihydrate group with those in the ibuprofen acid, there were no differences in age and sex.

The median time to onset of 50% pain relief in the ibuprofen sodium dihydrate group was 26.5 minutes compared with 44.0 minutes in the ibuprofen acid group ($P = .08$) (Figure 1). Twelve patients did not

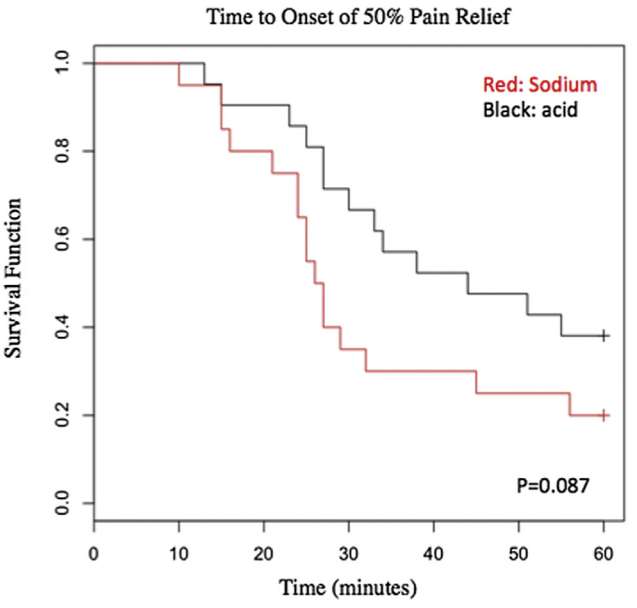

Figure 1. Time to onset of 50% pain relief using the Kaplan-Meier estimator. The administration of ibuprofen sodium dihydrate 512 mg resulted in faster onset of pain relief than ibuprofen acid 400 mg in odontogenic pain patients experiencing moderate to severe pain ($P = .08$).