EUROPEAN ENDODONTIC JOURNAL

ORIGINAL ARTICLE

Analgesic Efficacy of Ibuprofen and Diclofenac Potassium on Postoperative Endodontic Pain in Maxillary and Mandibular First Molars with Irreversible Pulpitis: A Randomised Controlled Trial

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ABSTRACT

Objective: The management of postoperative endodontic pain (PEP) is essential to contemporary endodontic practice. Diclofenac and ibuprofen (IBU) are two of the most widely-used non-steroidal anti-inflammatory analgesics. However, their comparative data are neither sufficient nor conclusive. This prospective randomised clinical trial aimed to compare the analgesic efficacy of diclofenac potassium (DFK) with IBU on PEP in maxillary and mandibular first molars diagnosed with irreversible pulpitis after single-visit non-surgical root canal treatment.

Methods: Sixty-four patients were randomised into two groups of DFK (n=32) and IBU (n=32), using the stratified permuted randomisation method, and 61 participants completed the trial. After root canal treatment, patients randomly received IBU 400 mg every 6 hours (n=31) or DFK 50 mg every 8 hours (n=30) for 24 hours. Patients recorded their pain level on 0-100 mm visual analogue scales (VAS) at 2, 4, 6, 12, and 24 hours after the treatment. Recorded VAS scores and the number of pain-free patients (VAS<5) were compared between the two groups. A generalised linear estimation equation model, Chi-Square test, and Mann–Whitney U test were used to analyse the data.

Results: The mean overall PEP score was statistically significantly lower in the DFK group than the IBU group with a p value of 0.030. Pain scores at 2 (p=0.034), 4 (p=0.021), and 24 hours (p=0.042) after the treatment were also significantly lower for DFK than IBU. The number of pain-free patients was also significantly higher in the DFK group at 2-hour (p=0.015) and 4-hour (p=0.048) time points and overall (p=0.013) compared to the IBU group. There was no adverse effect observed in either group.

Conclusion: Based on the results, taking multi-dose DFK 50 mg by the clock had better analgesic outcomes than multi-dose IBU 400 mg for PEP management.

Keywords: Diclofenac, ibuprofen, non-steroidal anti-inflammatory agents, postoperative pain, root canal therapy

HIGHLIGHTS

- For managing PEP in first molars with irreversible pulpitis, diclofenac potassium 50 mg intake rendered significantly more patients pain-free than ibuprofen 400 mg.
- The mean pain scores patients reported in the diclofenac potassium group was significantly lower than the ibuprofen group at several time points.
- Collectively, diclofenac potassium had better analgesic efficacy than ibuprofen and could be a viable option to manage PEP in first molars with established irreversible pulpitis.

Please cite this article as:
Vatankhah M, Zargar N, Naseri M, Salem S, Baghban AA, Etemadi A, Dianat O. Analgesic Efficacy of Ibuprofen and Diclofenac Potassium on Postoperative Endodontic Pain in Maxillary and Mandibular First Molars with Irreversible Pulpitis: A Randomised Controlled Trial. Eur Endod J 2023; 8: 133-9

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Received January 10, 2022,
Revised June 04, 2022,
Accepted June 16, 2022

Published online: March 20, 2023
DOI 10.14744/eej.2022.45238

INTRODUCTION

Despite recent advancements in root canal treatments, post-operative endodontic pain (PEP) continues to be a common unfavourable outcome, with a reported incidence of 3%–58% (1, 2). The periradicular tissues could be irritated by mechanical instrumentation, irrigants, and intracanal medicaments, leading to PEP (2). Although root canal therapy decreases odontogenic pain in many cases, analgesics are often required to mitigate PEP adequately (3). Various medications, including paracetamol, corticosteroids, and non-steroidal anti-inflammatory drugs (NSAIDs), can reduce PEP (3). NSAIDs have both peripheral and central impacts on pain reduction (4). As the most frequently used NSAIDs, ibuprofen (IBU) and diclofenac account for almost 40% of global oral NSAID sales (4). Although the exact sales ratio for IBU and diclofenac varies by country, they are regularly used, well-accepted, and have long been in the market (5).

IBU is very well known to dentists and endodontists and is the most studied NSAID in the endodontic literature (6). Due to its relatively broad spectrum of indications, good tolerance, and safety, IBU is suitable for self-medication; it has been ranked as the safest conventional NSAID by the spontaneous adverse drug reaction reporting system in the United Kingdom (7).

Diclofenac is a non-selective, amphiphilic, phenylacetic acid-derivative cyclooxygenase inhibitor (8). It is available in oral formulations paired with sodium, potassium, or sodium and misoprostol (9). In low, middle, and high-income countries, it is the most commonly used NSAID (10). Diclofenac's mechanisms of action are unique and distinct from other NSAIDs. Its efficacy in inhibiting blood cyclooxygenase levels and the synthesis of pro-inflammatory and nociceptive prostaglandins is 3 to 1000 times more than other NSAIDs (11). Additionally, diclofenac has a 50-fold higher affinity for peroxisome proliferator-activated γ receptors than other NSAIDs. As a result, diclofenac affects spinal nociceptive processing by activating these receptors and decreasing prostaglandin synthesis (9, 11).

The solubility and absorption of different formulations of diclofenac depend on its contained salt form, with diclofenac potassium (DFK) being more rapidly absorbed than diclofenac sodium (9). Therefore, DFK immediate-release sugar-coated tablets (Cataflam®, Novartis Pharmaceuticals Corporation, Basel, Switzerland) were introduced for their rapid uptake (8, 9). Faster-acting analgesics such as DFK can lead to earlier onset, possibly longer-lasting, and higher pain relief and reduce the need for repeat medication; as a result, additional intake will be less frequent (12). Therefore, acute dental pain could benefit from the short onset of action of DFK (13).

Both IBU (6) and diclofenac (14) have been shown to diminish PEP. A trial by Makkar et al. (15) showed that a single-dose combination of diclofenac sodium + paracetamol had more analgesic effects on PEP than a combination of IBU + paracetamol. Nevertheless, another study found that a single-dose combination of IBU + paracetamol had no statistically significant difference from a single-dose combination of DFK + paracetamol on PEP (14). A recent study demonstrated that a single-dose premedication of DFK could significantly reduce PEP (12).

This study aimed to address the above discrepancies and the lack of data about the analgesic efficacy of multiple-dose DFK. To our knowledge, this is the first study to compare the analgesic efficacy of DFK and IBU regarding PEP levels in maxillary and mandibular first molars diagnosed with irreversible pulpitis (IP).

MATERIALS AND METHODS

This prospective, superiority, parallel-designed, two-arm, randomised clinical trial adhered to the recommendations of the CONSORT statement (16). The trial protocol was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.RIDS.REC.1394.137) and adhered to the Declaration of Helsinki 1975. The clinical protocol was registered in the Iranian Registry of Clinical Trials (IRCT20180618040138N1). The samples consisted of patients attending the Department of Endodontics, School of Dentistry, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Informed consent was obtained from all individual participants in the present study.

Sample Size

Based on a pilot study on 10 patients (5 in each group) following results were assessed: $\mu1=33.1$, $\sigma1=12.9$, $\mu2=43.2$, $\sigma2=13.1$ (μ represents mean pain levels and σ represents the standard deviation). Accordingly, the minimum sample size required was 29 in each group, assuming a type I error of 0.05, an 80% power. It was increased to 32 participants per group to account for anticipated refusals and a loss of 10% during the different study stages and to ease the stratification. The pilot research participants were not included in the final samples. The allocation was made on a ratio of 1:1. PASS 15.0 software (NCSS, LLC, Kaysville, Utah, USA) was used for two-sided sample size calculation.

Inclusion and Exclusion Criteria

Inclusion criteria for enrolled participants were as follows: (1) age range of 18–65 years, (2) demonstrating no underlying systemic disease, (3) having one maxillary or mandibular first molar with the diagnosis of irreversible pulpitis requiring one-visit endodontic treatment, (4) no pregnancy or nursing for female participants, (5) ability to read and comprehend the visual analogue scale (VAS) sheets and informed consent, (6) absence of any radiographic evidence of periapical lesions, (7) absence of generalised periodontal disease, (8) no intake of analgesics in the past 6 hours, (9) absence of any known allergies to the materials used in the root canal treatment or NSAIDs, (10) not currently taking opioids, tricyclic antidepressants, carbamazepine, gabapentin, monoamine oxidase inhibitors, diuretics, or anticoagulants, (11) and no history of opioid addiction.

Cases were excluded if (1) no bleeding was evident following the access cavity preparation or initial filing or (2) another visit was required to complete the endodontic treatment.

Diagnosis

The investigator diagnosed irreversible pulpitis (either symptomatic or asymptomatic) based on the clinical and radiographic examination; a moderate to severe (VAS>44; a 100 mm VAS scale (17)) or lingered pain response to the cold test

with Endolce (1,1,1,2 tetrafluoroethane; Hygenic Corp, Akron, OH, USA). In addition, patients recorded their pain response to the cold test on a 100 mm VAS diagram.

Randomisation

The stratified permuted randomisation approach was applied to divide 64 subjects into four strata (n=16), each of which contained participants with the same gender and type of tooth (maxillary or mandibular first molar). From each stratum, eight patients were randomly assigned to each intervention group of IBU (n=32) and DFK (n=32). The statistician generated random digits to determine the random sequence within each stratum via Microsoft Excel 2013 software (Microsoft Corporation, Redmond, WA, USA).

A nurse put four IBU 400 mg (Hakim Pharmacy Co, Tehran, Iran) or three DFK 50 mg immediate-release tablets (Cataflam 50 mg tablets, Novartis Pharma AG, Basel, Switzerland) in envelopes. Next, each patient was given a rescue dosage of two acetaminophen 300 + codeine 20 mg tablets (Codamol, Aryadaru, Tehran, Iran), packed and labelled individually.

Endodontic Treatment

A single board-certified endodontist performed the endodontic treatment after anaesthetising the involved tooth using an inferior alveolar nerve block for mandibular molars and a local infiltration for maxillary molars, both with 1.8 ml of 2% lidocaine with 1:80,000 epinephrine (Lignospan Special; Septodont, Saint-Maur-des-Fossés, France). Supplementary anaesthesia was applied when primary anaesthesia failed to provide profound anaesthesia. All patients underwent the same hybrid technique treatment: coronal and apical preparations were done with the crown-down approach by rotary nickel-titanium (ProTaper Gold; Dentsply Sirona, Ballaigues, Switzerland) (18) and hand instrumentation (K-files; Mani, Utsunomiya, Japan), respectively. The working length was determined with an apex locator (Root ZX; J Morita Corp, Tokyo, Japan) and was confirmed to be 0.5 mm shorter from the radiographic apex using a periapical radiograph. Final apical files were #40 or #45 for palatal and distal canals and #25 or #30 for mandibular mesial and maxillary buccal canals. Canals were irrigated with 1 ml 2.5% sodium hypochlorite between each filing. Apical patency was achieved with a #10 file during the treatment. For the final rinse, 5 ml 2.5% sodium hypochlorite followed by 10 ml distilled water. Paper points of the same size as the final apical files were used to dry canals. Then, canals were obturated using the cold lateral condensation technique (19) with gutta-percha (Meta-Biomed, South Korea) and resin-based sealer (AH 26®; Dentsply, Ballaigues, Switzerland). No occlusal reduction was applied, and the access cavity was restored with a temporary filling material (Coltosol; Coltène, Altstätten, Switzerland).

Intervention

Patients marked their preoperative anxiety level before the treatment using the visual analogue scale for anxiety (VAS-A), consisting of a 100 mm ruler with left and right endpoints labelled 'none' and 'as bad as it could be,' respectively (20). In addition, each patient marked the maximum pain felt in the preceding 24 hours on a 100 mm VAS as the preoperative pain level. The VAS diagram consisted of a 100 mm ruler with two labels of 'no pain' and 'worst pain imaginable.'

The nurse thoroughly gave medication instructions to each patient. Patients took the first dose of either medication at the clinic. After that, they were instructed to take one tablet every 6 hours for the IBU groups and one tablet every 8 hours after the treatment for the DFK group, up to 24 hours.

Outcomes Assessment

The primary outcome was to compare PEP levels in IBU and DFK groups at 2, 4, 6, 12, and 24 hours after the treatment. The overall mean score was defined as the mean value of PEP scores of all five time points. The secondary outcome was to compare the overall mean scores and percentage of pain-free patients (VAS<5 mm (17)) at each time point between the two groups.

A pain diary was given to each patient to record the perceived pain 2, 4, 6, 12, and 24 hours after the treatment. The nurse taught participants how to mark the VAS diagram. In addition, they were instructed to take the rescue dose in the event of unbearable pain and to record any adverse effects of their treatment in their pain diaries. After the treatment, the nurse gave the numbered envelopes to the patients of each stratum and wrote down the allocated number tag in the patients' profiles. To increase the patients' compliance, a text message was sent to each patient as a reminder at each medication intake time. The number of leftover tablets was also included in the diary to assess patients' compliance.

Allocation Concealment and Blinding

For allocation concealment, identical opaque envelopes with sequential numbers were used. The investigator and the practitioner were unaware of which medication was delivered because only the random numbers distinguished the medications. The statistician was also blinded to the aim of the study. However, since the medications were purchased and not made in the laboratory with the same appearance, complete blinding of the participants was not feasible.

Statistical Analysis

The analyses were conducted using SPSS 18 (SPSS Inc. Released 2009. PASW Statistics for Windows, Ver.18.0. Chicago, Il, USA). All statistical tests were interpreted at a significance level of 5%. The normality of preoperative anxiety, pain levels, and demographic factors in the two groups was assessed using the Kolmogorov–Smirnov test. The Chi-Square test was used to compare genders and the number of pain-free patients between the two groups. The Mann–Whitney U test was used to compare the two experimental groups' preoperative anxiety and pain scores. A generalised linear estimation equation (GEE) with an unstructured link function was used to reveal possible correlations between preoperative anxiety level, preoperative pain, sex, or type of tooth with PEP score over time. GEE was further used to compare the PEP scores through time in two groups. Finally, the post-hoc Mann–Whitney U test was used to compare PEP scores between the two groups.

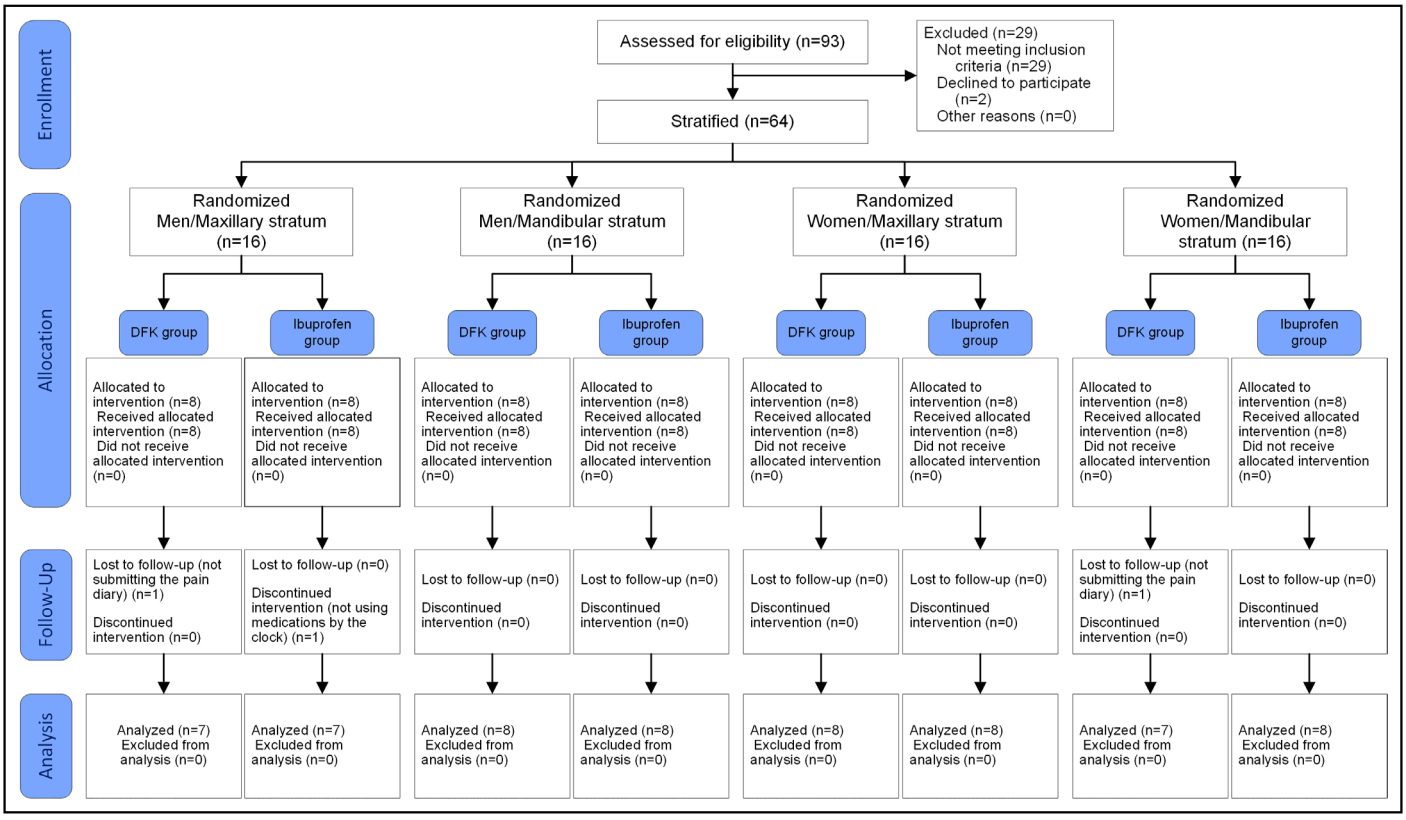

Figure 1. A CONSORT flow diagram of the present study

DFK: diclofenac potassium

RESULTS

After evaluating 110 patients, 64 met the inclusion criteria and were randomised. Two patients were lost to follow-up, and one voluntarily ceased participation in the trial after submitting an incomplete pain diary (Fig. 1). Finally, 61 patients with a mean age of 40.1±2.04 submitted a completed pain diary, and their data were collected and analysed. The CONSORT flow diagram for this experiment is depicted in Figure 1.

Table 1 demonstrates no statistically significant difference between the two main groups regarding mean age, mean preoperative anxiety, and pain scores.

GEE analysis revealed higher preoperative pain ($p<0.001$) and higher pain scores in response to the cold test ($p=0.001$) as significant risk factors for higher PEP scores. However, the effect of gender, type of tooth, age, and anxiety was not significant ($p>0.05$).

GEE showed that PEP scores were significantly different in the two groups ($p<0.001$) and dropped significantly with time ($p=0.023$). Furthermore, this model showed that the interaction between medications and time was not statistically significant ($p=0.078$). According to Table 2 and Figure 2, the post-hoc Mann–Whitney U test showed that the mean PEP score was significantly lower in the DFK group at 2 ($p=0.034$), 4 ($p=0.021$), and 24-hour time points ($p=0.042$), and in the overall mean ($p=0.030$), compared to the IBU group. The mean PEP scores at 6 and 12 hours were lower for DFK, but this difference was not statistically significant ($p>0.05$).

The percentage and number of pain-free patients at different time points are shown in Table 3. Pain-free patients were seen more in the DFK group at all time points. This difference was statistically significant at the 2-hour time point ($p=0.013$), 4-hour time point ($p=0.048$), and in the overall mean ($p=0.030$) and was at the statistical borderline at the 12-hour time point ($p=0.054$). It was, however, not significant at 6 and 24-hour time points ($p>0.05$). Of the 62 patients who completed and submitted pain diaries, 61 (98.38%) took tablets by the clock.

DISCUSSION

This randomised clinical trial aimed to scrutinise the analgesic efficacy of DFK compared with IBU. Regarding the primary and secondary outcomes, DFK resulted in better analgesic effects. This superiority was statistically significant at 2, 4, and 24-hour time points and in the overall mean concerning the primary outcome; and at 2 and 4-hour time points and in the overall mean regarding the secondary outcome.

Several preoperative, intraoperative, and postoperative factors can affect the experience of PEP: Preoperative pain is the most mentioned prognostic factor associated with PEP (13). Other factors such as gender, age, tooth type, preoperative anxiety, single- or double-visit treatment (21, 22), irrigation material (23), occlusal reduction (24), and instrumentation technique (25) have been postulated to affect PEP. Only first molars requiring single-visit treatment (20, 25) with a similar endodontic treatment protocol (23, 24) were included in this study to depreciate possible confounding factors. As most patients experience PEP in the first 24 hours after the treatment (26), PEP scores were assessed at 2, 4, 6, 12, and 24 hours after.

TABLE 1. Demographic factors of participants in each group.

	IBU (n=31)		DFK (n=30)		p
	n	%	n	%	
Gender					
Male (n=30)	15	48.4	15	50	1.00
Female (n=31)	16	51.6	15	50	
Type of the tooth					
Maxillary (n=30)	15	48.4	15	50	1.00
Mandibular (n=31)	16	51.6	15	50	
Mean age (years±SE)	40.53±2.24		40.5±1.84		0.99
Mean preoperative pain† (mm±SE)	54.29±2.58		54.93±2.34		0.88
Mean preoperative anxiety‡ (mm±SE)	16.61±3.02		16.67±3.04		0.89
Mean preoperative cold test pain§ (mm±SE)	59.13±2.68		56.77±3.14		0.20

†, ‡, §: 0–100 mm VAS scale. VAS: Visual analogue scales, IBU: Ibuprofen, DFK: Diclofenac potassium, SE: standard error

TABLE 2. Mean postoperative pain scores on 0-100 mm VAS (mm±SE) at 2, 4, 6, 12, and 24 hours after the treatment, and the overall mean score

	Preoperative pain	2 h	4 h	6 h	12 h	24 h	Overall mean score
IBU	54.29±2.58	23.94±3.73	25.16±3.50	22.97±3.53	16.52±2.98	12.65±2.77	20.24±3.11
95% CI	49.02–59.56	16.32–31.55	18.01–32.31	15.77–30.17	10.44–22.6	6.98–18.31	13.88–26.61
DFK	54.93±2.34	12.20±3.30	14.43±3.11	17.07±3.80	10.20±2.97	6.00±1.98	11.98±2.84
95% CI	50.14–59.72	5.45–18.95	8.07–20.80	9.29–24.84	4.12–16.28	1.95–10.05	6.17–17.79
p	0.879	0.034*	0.021*	0.153	0.078	0.042*	0.030*

*: Statistically significant. VAS: Visual analogue scales, SE: standard error, h: hour, IBU: Ibuprofen, CI: confidence interval, DFK: Diclofenac potassium

Our findings refute previous research by demonstrating that preoperative anxiety did not significantly affect PEP (1, 26). Furthermore, in the current study, neither tooth type (maxillary vs mandibular) nor gender significantly influenced PEP scores. Similarly, another trial showed a significant reduction of PEP scores without a substantial difference between the maxillary and mandibular molars, or females and males, with four different analgesic regimens. These regimens comprised an IBU + paracetamol combination, a DFK + paracetamol combination, and two other combinations (22). Furthermore, our data indicated that the preoperative pain score and pain response to the cold test significantly affected PEP scores, correlating with previous studies (13, 27).

After a notable drop in PEP values at the 2-hour time point, both groups had a rise in PEP scores between 2 and 4 hours in both

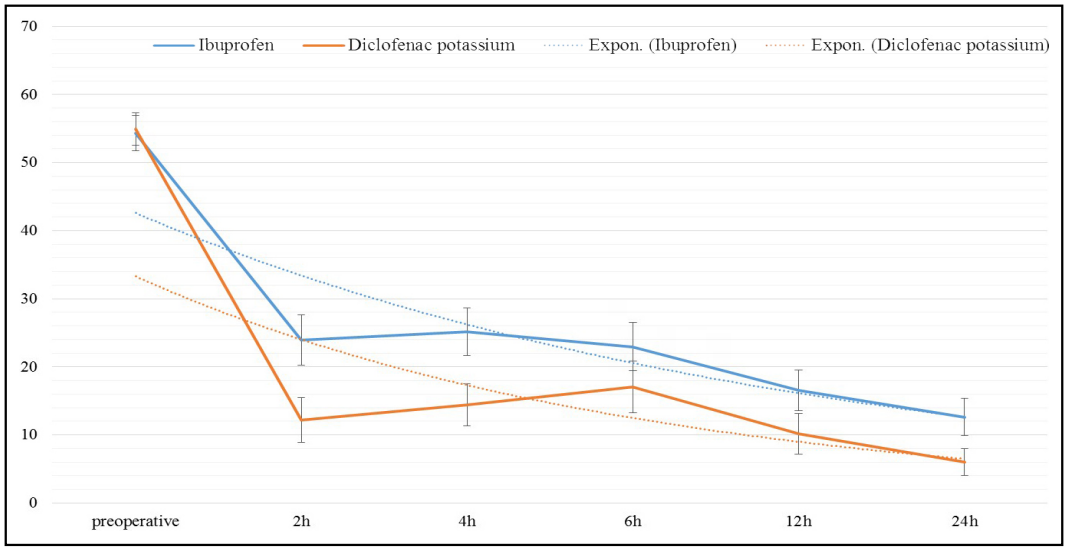

Figure 2. Postoperative endodontic pain scores with standard errors and exponential curves on 0-100 mm VAS at each time point for ibuprofen and diclofenac potassium groups

Expon.: Exponential curve, VAS: Visual analogue scales

TABLE 3. The percentage of pain-free patients (VAS≤5 mm) at different time points for ibuprofen and DFK groups

	2 h		4 h		6 h		12 h		24 h		Overall mean score	
	n	%	n	%	n	%	n	%	n	%	n	%
IBU	10	32	7	23	8	26	12	39	17	55	7	23
RR for no pain	0.52		0.56		0.62		0.61		0.73		0.48	
95% CI	0.30–0.92		0.29–1.07		0.33–1.14		0.36–1.03		0.45–1.19		0.25–0.94	
DFK	19	61	14	47	14	45	19	61	21	68	16	53
RR for no pain	1.91		1.67		1.55		1.67		1.41		1.89	
95% CI	1.10–3.29		1.03–2.71		0.95–2.53		0.97–2.89		0.79–2.53		1.15–3.10	
p	0.015*		0.048*		0.090		0.054**		0.222		0.013*	

*: Statistically significant. **: At the borderline of statistical significance. VAS: Visual analogue scales, DFK: Diclofenac potassium, h: hour, IBU: Ibuprofen, RR: relative risk, CI: confidence interval

groups compared to preoperative pain levels. This might be related to the wear-off of the anaesthesia and half-life of 2-2.5 hours and 1–2 hours for IBU and diclofenac, respectively (28). This rise persisted between 4 and 6-hour time points in the DFK group but not in the IBU group. This discrepancy might be explained by the two medications' different half-lives and mechanisms of action. In all groups, however, PEP ratings fell between the 6 and 12-hour time points and between the 12 and 24-hour time points. This may have been due to patients in both groups taking further doses of the medications during these periods.

No pain status as a dichotomous outcome can alter the subsequent perception of patients toward endodontic treatment (29, 30). Patients with no pain were more frequent, and PEP scores were lower in the DFK group. The lower PEP scores might imply a notable advantage for DFK over IBU in delivering more reliable analgesia in maxillary and mandibular first molars with IP. Different mechanisms of action for DFK and its earlier onset of action could explain these findings (9). To the best of our knowledge, there is only one study investigating the analgesic effect of DFK alone on PEP with a single-dose DFK 50 mg premedication. Its results showed a significant analgesic effect, similar to our findings within the DFK group (13). However, another study illustrated a similar analgesic effect for combinations of IBU+paracetamol and DFK+paracetamol (14). Using a single dose or a combination of medications could describe these differences.

Treatment with oral NSAIDs has been linked to several side effects, including cardiovascular, gastrointestinal, and hepatic complications (9). A recent study on the analgesic efficacy of diclofenac sodium on PEP for three days reported that two patients (4% of the participants) and one patient (2% of the participants) experienced vomiting and earache, respectively (31). None of the patients in this trial in either group recorded any adverse effects during the 24 hours of the study. Similarly, recent placebo-controlled research revealed that the administration of single-dose DFK or diclofenac sodium leads to a similar rate of side effects compared to placebo (32). These controversial results may emerge from the difference in the number of administrated tablets or periods of the studies. However, the possibility of reporting unrelated side effects to the medications should not be ignored. IBU is considered the safest conventional NSAID by spontaneous adverse drug reaction (7). Patients in the IBU group reported no adverse effects in this study like earlier studies (33–35). Although diclofenac has a variety of mechanisms of action, and it could produce an early onset of pain relief (11, 12), it has been shown to potentially impose more cardiovascular and gastrointestinal adverse effects than IBU (36). However, this difference may not be apparent in the three-dose uptake over a single day but could be observed with a 30-day and extended administration of these analgesics (36). Collectively, based on the literature on analgesic use in dentistry and the findings of our study, a single-day use of both DFK and IBU could be considered safe. However, well-designed prospective studies are recommended to reinvestigate the veracity of this assertion.

As a strength of this trial, the stratified permuted randomisation approach eliminated the possible confounding effects of the type of tooth. However, a limitation of this study was that the medications had not the same appearance, compromising patients' blinding. Further studies with different doses and settings are recommended.

CONCLUSION

Multi-dose DFK 50 mg had better pain relief after single-visit non-surgical endodontic treatment of maxillary and mandibular first molars exhibiting irreversible pulpitis than multi-dose IBU 400 mg. Although this significant superiority was not consistently evident at several studied time points, DFK could be a viable choice for reducing PEP levels.

Disclosures

Conflict of interest: The authors deny any conflict of interest.

Ethics Committee Approval: This study was approved by The Shahid Beheshti University of Medical Sciences Ethics Committee (Date: 09/02/2016, Number: IR.SBMU.RIDS.REC.1394.137).

Peer-review: Externally peer-reviewed.

Financial Disclosure: This study did not receive any financial support.

Authorship contributions: Concept – N.Z., M.N., A.A.B.; Design – N.Z., M.N., A.A.B., O.D.; Supervision – M.N., N.Z.; Funding - S.S., A.E.; Materials - A.E., N.Z.; Data collection and/or processing – S.S., M.V., A.E.; Analysis and/or interpretation – A.A.B., M.V.; Literature search – N.Z., M.V., O.D.; Writing – M.V., N.Z.; Critical Review – N.Z., O.D., M.N.

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