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Comparative Efficacy of Analgesics for Pain Relief in Patients with Symptomatic Irreversible Pulpitis Prior to Emergency Endodontic Treatment: A Randomized Controlled Trial

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Introduction This study aimed to compare the efficacy of ibuprofen, Novafen, mefenamic acid (MA), and celecoxib for pain relief in patients with symptomatic irreversible pulpitis prior to emergency endodontic treatment. **Materials and Methods:** This clinical trial was conducted on 120 patients with moderate to severe pain due to symptomatic irreversible pulpitis seeking emergency endodontic treatment. The patients were randomly divided into 4 groups to receive Novafen, MA, Celecoxib, and ibuprofen. The pain score of patients was measured before and 1 hour after analgesic intake using a visual analog scale (VAS). The success of analgesic treatment was analyzed by the binary logistic regression model. **Results:** A total of 117 patients including 76 females and 41 males with a mean age of 30.29 years completed the study and were statistically analyzed. Ibuprofen had the highest analgesic efficacy followed by Novafen, and caused a significantly greater reduction in pain score compared with MA and celecoxib [OR (Ibuprofen vs MA)=1.28, OR (Ibuprofen vs Celecoxib)=3.74, OR (Novafen vs MA)=2.94, OR (Novafen vs Celecoxib)=2.94, $P<0.05$]. Ibuprofen and Novafen had no significant difference in analgesic efficacy ($P>0.05$). Baseline pain score was a predictive factor for the success of analgesics ($P<0.05$). The success of analgesic treatment decreased by 0.68 times with each unit increase in pain score ($P<0.05$). Gender and age of patients had no significant effect on success of analgesics ($P>0.05$). **Conclusion:** Both ibuprofen and Novafen can serve as the analgesics of choice for pain relief in patients with symptomatic irreversible pulpitis with moderate to severe pain when emergency endodontic treatment cannot be immediately performed.

Keywords: Acute Pain; Celecoxib; Ibuprofen; Mefenamic Acid; Novafen, Root Canal Therapy

Introduction

Pulpitis is among the most common causes of orofacial pain. Irreversible pulpitis is characterized by a painful pulpal response to thermal stimuli which is not immediately eliminated after discontinuation of stimulation. Pain is an unpleasant experience due to actual or potential tissue injury. It is a subjective concept, and the pain threshold varies among different individuals. The cold and heat tests are commonly used clinically for diagnosis of symptomatic irreversible pulpitis. Irreversible pulpitis mainly occurs due to an infection as the result of caries or loss of restoration seal and microleakage. Dental trauma, pulpal exposure, and cracks can also cause severe pulpitis[1]. Pain due to irreversible pulpitis is the reason for over 45% of emergency dental visits [2]. However, some patients may have to tolerate pain for some time before visiting a dentist due to inaccessibility of dental care services, high cost of treatment, not having insurance, *etc.*

Analgesics are commonly used for pain control [3-9], and can be categorized into two groups of opioids and non-opioids.

Morphine, codeine, caffeine, meperidine, oxycodone, and tramadol are among the opioid analgesics. Although opioid analgesics are effective for moderate to severe pain, they have limited applications due to their side effects such as nausea, vomiting, dizziness, drowsiness, constipation, respiratory depression, and drug dependence [10]. The majority of non-opioid analgesics have anti-inflammatory effects, and can be divided into two main groups of steroidal anti-inflammatory (corticosteroids) and non-steroidal anti-inflammatory drugs (NSAIDs). Corticosteroids such as dexamethasone and prednisolone inhibit the formation of arachidonic acid from the phospholipids released from the inflammatory cell membrane, prevent the cyclooxygenase and lipoxygenase pathways, and subsequently impede prostaglandin and leukotriene synthesis [11]. Prostaglandins sensitize the nerve ending receptors to bradykinins and histamines and increase vascular permeability and sensitivity of pain receptors to other inflammatory mediators and cause chemotaxis and fever [12]. NSAIDs including ibuprofen, mefenamic acid (MA), naproxen, indomethacin, diclofenac sodium, and celecoxib decrease the inflammatory response by inhibiting the cyclooxygenase pathway and subsequent production of prostaglandins [13]. Thus, the clinicians benefit from this property for endodontic pain control by NSAIDs [14]. However, NSAIDs also have side effects such as gastrointestinal irritation and gastric ulcer [15].

Ibuprofen is quickly absorbed after oral intake and reaches its maximum serum concentration within 1-2 h. Approximately 99% of the medication is attached to plasma proteins, and is metabolized in the liver. It has a half-life of 8 h and is excreted through the urine. MA has a similar mechanism of action to ibuprofen. It is slowly absorbed after oral intake and its maximum serum concentration is reached 1 to 2 h after intake. It is deactivated in the liver, has a half-life of 2 h, and is finally excreted through the urine and feces. Celecoxib is another NSAID which inhibits the cyclooxygenase 2 enzyme. It has a fast gastrointestinal absorption and a half-life of 11 h. Its metabolism is mainly through the liver and is excreted through feces and urine [16].

Novafen is a combination of 325 mg acetaminophen, 200 mg ibuprofen, and 30 to 40 mg caffeine. Caffeine is a mild stimulator of the central nervous system and causes vasoconstriction, which can lead to pain relief. The analgesic and anti-inflammatory effects of Novafen are related to acetaminophen and ibuprofen in its composition. Caffeine is well absorbed through the gastrointestinal system and has a half-life of 3-4 h. It has low adhesion to plasma proteins, and has a mainly hepatic metabolism. Acetaminophen and ibuprofen are also well absorbed through the gastrointestinal system and have a hepatic metabolism. Acetaminophen has insignificant binding to plasma proteins [17].

Comparative efficacy of different analgesics for endodontic pain relief has been the topic of many previous investigations. Baghaie *et al.* [18] evaluated the attitude of Iranian dentists towards prescription of analgesics, and reported that a high percentage of Iranian dentists would prescribe ibuprofen and acetaminophen codeine for pulpal pain relief. A relatively high percentage would recommend MA and indomethacin, and 20% would prescribe naproxen. Approximately 13.5% would suggest Novafen. Also, 10% would prescribe tramadol and 5% celecoxib. Only a small percentage would prescribe dexamethasone.

The suggested emergency treatment for patients with symptomatic irreversible pulpitis is partial endodontic treatment under local anesthesia [19]. Compared with complete pulpectomy, pulpotomy would result in lower level of postoperative pain [12, 20].

Several studies have assessed the efficacy of different analgesics for resolution of post-endodontic pain [14, 21-25]. However, to the best of the authors' knowledge, the efficacy of different analgesics for pain relief in patients with symptomatic irreversible pulpitis prior to endodontic treatment has only been previously evaluated in one study by Tggar *et al.* [26].

Thus, this study aimed to compare the efficacy of ibuprofen, Novafen, MA, and celecoxib for pain relief in patients with symptomatic irreversible pulpitis prior to emergency endodontic treatment. The null hypothesis was that no significant difference would be found in analgesic efficacy of the abovementioned medications for pain relief in patients with symptomatic irreversible pulpitis prior to endodontic treatment.

Materials and Methods

This study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the university on February 6, 2017, with the ethical code IR.KMU.REC.1395.1002. Additionally, the study was registered in the Iranian Registry of Clinical Trials with the registration number IRCT20171109037332N1.

Trial design

A clinical trial was conducted in which, patients with moderate to severe pain due to symptomatic irreversible pulpitis seeking emergency endodontic treatment were randomly divided into 4 groups to receive Novafen, MA, celecoxib, and ibuprofen for pain relief. The results were reported according to the guidelines of the Consolidated Standards of Reporting Trials.

Participants, eligibility criteria, and settings

The inclusion criteria were (I) patients with confirmed diagnosis of symptomatic irreversible pulpitis and normal periapical radiographic appearance without sensitivity to percussion, (II) A positive response to an electric pulp test in addition to a prolonged response with moderate to severe pain to a cold pulp test(III) non-feasibility of immediate emergency endodontic treatment for any reason, (IV) age over 18 years, and (V) patients signing informed consent forms for participation in the study.

The exclusion criteria were (I) patients who had taken analgesics within the past 4 h, (II) patients with contraindications for the intake of respective analgesics, (III) presence of underlying medical conditions such as myocardial infarction, stroke, heart failure, hypertension, asthma, nasal polyp, liver or kidney disease, gastric ulcer, systemic lupus erythematosus, and coagulopathy, among others [27], (IV) pregnancy or nursing, (V) patients with oral diseases, and (VI) history of allergy to corticosteroids or NSAIDs.

The sample consisted of 120 patients with confirmed symptomatic irreversible pulpitis and moderate to severe pain with a visual analog scale (VAS) score > 3.

Interventions

All patients signed informed consent forms prior to study enrolment. Sensibility tests to diagnose irreversible pulpitis & all interventions were performed by the same operator. They were then randomly divided into 4 groups (n=30). The analgesics were obtained from the manufacturers in the form of powder and encapsulated in capsules with equal shape and size in a double blind manner such that both the research manager and patients were blinded to the type of analgesics. Patients in group 1 received Novafen comprising of 325 mg acetaminophen, 200 mg ibuprofen, and 40 mg caffeine (Alhavi pharmaceutical company, Tehran, Iran). Patients in group 2 received 250 mg MA (Raha pharmaceutical company, Isfahan, Iran). Patients in group 3 received 200 mg celecoxib (Amin pharmaceutical company, Tehran, Iran), and those in group 4 received 600 mg ibuprofen (Prepared by a pharmaceutics specialist). The patients received VAS forms and were instructed on how to express their level of pain using this scale. The VAS consisted of a 10 cm horizontal line, with 0 indicating no pain, 1-3 indicating mild pain, 4-6 indicating moderate pain, and 7-10 indicating severe pain; 10 indicated the most severe pain imaginable. The patients were asked to record their pain score immediately after receiving the form and 1 h after taking the analgesic. Since the definitive treatment is not possible to be scheduled for the next 6 months in endodontic department of Kerman dental school, after 1 h, all patients underwent emergency endodontic treatment (pulpotomy or pulpectomy). Pain score< 4 (no pain or mild pain) was considered as an indicator of a successful analgesic treatment [25].

Outcomes

The main objective of this study was to assess the efficacy of the aforementioned medications for pain relief in patients with symptomatic irreversible pulpitis with moderate to severe pain prior to emergency endodontic treatment.

Sample size calculation

According to Solete *et al.* [28] study, the effect size was estimated at 0.35 and the sample size was calculated to be 30 in each group assuming alpha=5%, and study power of 80% and 25% dropout rate.

Interim analyses and stopping guidelines

No interim analyses were performed, and no stopping guidelines were established.

Randomization

After encapsulation of analgesics, 30 of capsules of each analgesics was placed in a coded box. The boxes were placed in a black bag, and one box was randomly selected and allocated to each group of patients.

The method used for randomization was simple randomization. After encapsulation of analgesics, 30 capsules of each analgesics was placed in a coded box. The boxes were placed in a black bag, and one box was randomly selected and allocated to each of patients by an independent person who was not otherwise involved in the study. He had no access to patient information or the study protocol to maintain the integrity of the randomization. The allocation of participants to their respective treatment groups was carried out by a designated study coordinator who had access to the random allocation. The coordinator ensured that the allocation was concealed and that each patient was assigned to a group in a manner consistent with the randomization. This assignment was performed after patients had been enrolled and baseline assessments had been completed, guaranteeing that neither patients nor investigators were aware of their group assignments during the enrolment process.

Blinding

Both the research manager and patients were blinded to the type of analgesics and group allocation of patients. Also, the statistician who analyzed the data was blinded to the group allocation of patients.

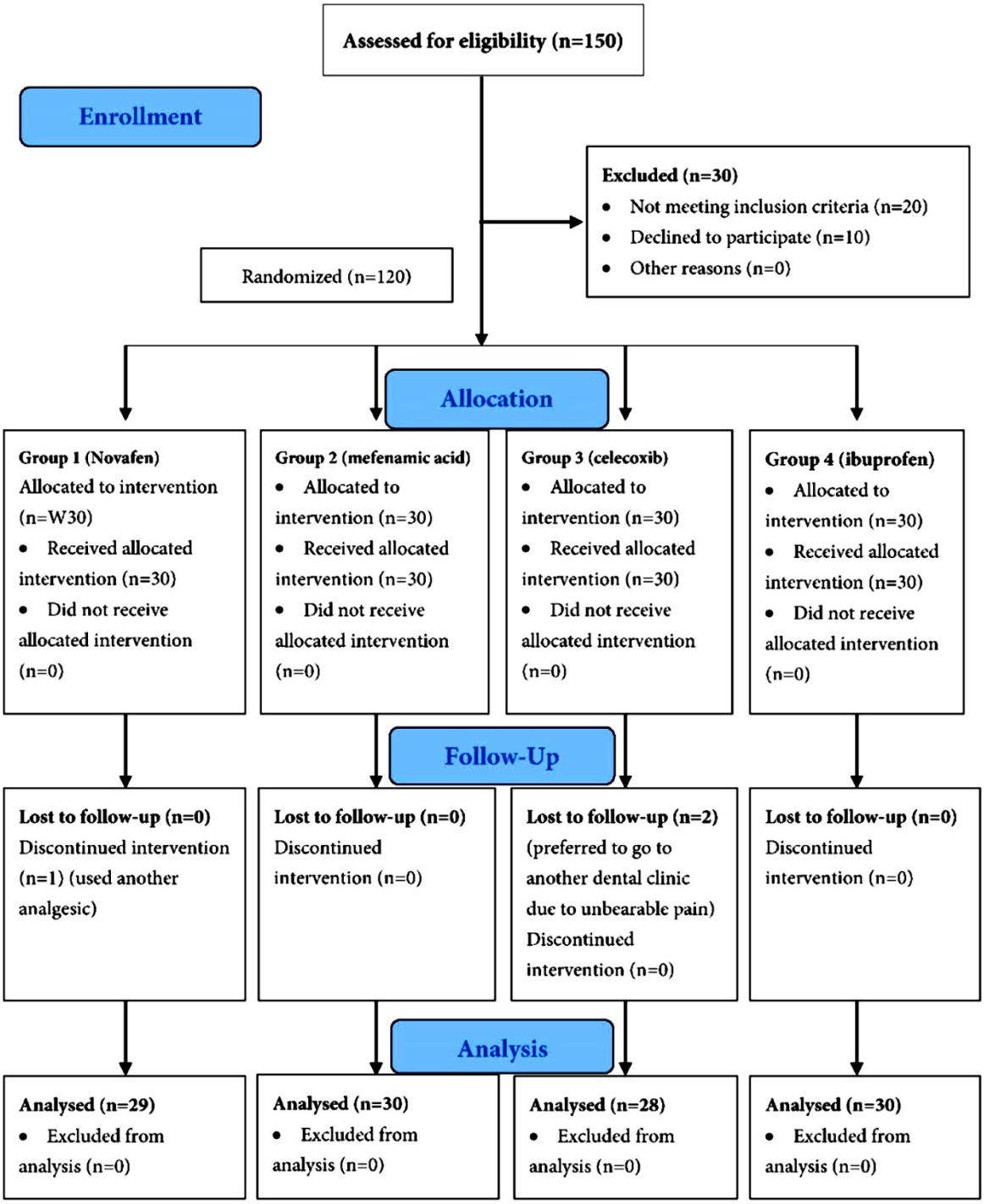

Figure 1. CONSORT flow diagram of patient selection and allocation

Statistical analysis

Data were analyzed using SPSS software (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0., IBM Corp., Armonk, NY, USA) by binary logistic regression model to compare the success rate of the four types of analgesics by adjusting the effect of age, gender, and baseline pain score of patients. The model goodness of fit was assessed by Hosmer-Lemeshow test and area under curve (AUC). The Hosmer-Lemeshow test was insignificant (P>0.05), indicating that the model was a good fit to the data. The area under curve of the fitted model was 0.73, which is a good predictive power.

Results

Participant flow

The sample consisted of 120 patients in four groups (n=30). Two patients in group 1 (Novafen) and 1 patient in group 3 (celecoxib) either used another analgesic or preferred to go to another dental clinic due to unbearable pain. Figure 1 shows the CONSORT flow diagram of patient selection and allocation. Finally, 117 patients including 76 females and 41 males completed the study. The mean age of patients was 30.2 (3.1) years. The porportion of female in the Ibuprofen, Novafen, M and celecoxib group was 26.3%, 26.3%, 28.9% and 18.4% respectively, which was not statistically significant (P=0.096). The mean age of participants in the Ibuprofen, Novafen, MA and celecoxib group was 30.6±7.9, 29.5±6.5, 30±8.2 and 30.9±6.7, respectively. There was no significant difference in the mean age of the participants among the study groups (P=0.875).

Harms

No patients were harmed during the study.

Subgroup analyses

Table 1 presents the effect of different variables on the efficacy of analgesics. Ibuprofen had the highest analgesic efficacy and caused a significantly greater reduction in pain score compared with MA and celecoxib (Table 2, P<0.05). Novafen ranked second in terms of efficacy and caused a significantly greater reduction in pain score compared with MA and celecoxib (Table 2, P<0.05). Ibuprofen and Novafen had no significant difference in analgesic efficacy (Table 2, P>0.05). Baseline pain was a predictive factor for the success of analgesics (Table 1, P=0.001). The success of analgesic treatment decreased by 0.68 times with each unit increase in pain score. Gender and age of patients had no significant effect on success of analgesics (Table 1, P>0.05).

Discussion

This study compared the efficacy of ibuprofen, Novafen, MA, and celecoxib for pain relief in patients with symptomatic irreversible pulpitis prior to emergency endodontic treatment. The null hypothesis was that no significant difference would be found in analgesic efficacy of the abovementioned medications for pain relief in patients with symptomatic irreversible pulpitis. The results showed that ibuprofen was the most effective analgesic for pain control in patients with symptomatic irreversible pulpitis prior to emergency endodontic treatment followed by Novafen, and these two analgesics had significantly higher analgesic efficacy than other medications tested. Thus, the null hypothesis of the study was rejected. The optimal efficacy of ibuprofen is due to inhibition of cyclooxygenase enzyme [19, 29], and optimal efficacy of Novafen is due to the fact that it is composed of acetaminophen, ibuprofen, and caffeine [30]. Selection of the abovementioned medications for the present study was due to their common use by the Iranian dentists for pain control [18].

Table 1. Odds ratios of analgesics, gender, age, and baseline pain score on success rate of pain relief

Variable	Category	Adjusted OR	95% CI for the adjusted OR		Sig.
			Lower	Upper	
Analgesics	Novafen	0.78	0.24	2.49	0.678
	Mefenamic acid	0.26	0.08	0.83	0.023*
	Celecoxib	0.26	0.08	0.87	0.029*
	Ibuprofen	Reference			
Gender	Female	0.91	0.38	2.16	0.845
	Male	Reference			
Age		0.99	0.94	1.05	0.960
Baseline pain score		0.68	0.54	0.85	0.001*

OR: Odds ratio; CI: Confidence intervals; Sig: Significance

Table 2. Multiple comparisons of mefenamic acid, Celecoxib, ibuprofen, and Novafen pain relief success rate

Analgesics		Adjusted OR	95% CI for Adjusted OR	*P*-value
Mefenamic acid	Novafen	0.34	(0.11, 1.05)	0.531
Celecoxib	Novafen	0.34	(0.11, 1.08)	0.507
Ibuprofen	Novafen	1.28	(0.40, 4.08)	0.059
Celecoxib	Mefenamic acid	1.01	(0.33, 3.08)	0.072
Ibuprofen	Mefenamic acid	3.76	(1.20, 11.77)	0.039
Ibuprofen	Celecoxib	3.74	(1.15, 12.17)	0.039

OR: Odds ratio; CI: Confidence intervals

There is no strong evidence in the literature regarding the most effective analgesics for pain control prior to seeking emergency dental treatment. Relevant studies have mainly focused on post-endodontic pain control. Search of the literature by the authors yielded only one similar study that compared the analgesic efficacy of oral prednisolone and pulpotomy for pain control in patients, and concluded that prednisolone is a suitable alternative to pulpotomy for pain relief. They performed endodontic treatment for patients after 72 h. Bane *et al.* [27] compared the efficacy of intraosseous injection of methyl prednisolone for pain reduction in patients with acute pulpal pain, compared with pulpotomy, and reported that intraosseous prednisolone injection may be a less invasive and more effective modality for pain reduction compared with pulpotomy. They performed endodontic treatment for patients after 7 days.

Several studies have assessed the effect of pharmaceutical therapy on success of inferior alveolar nerve block for treatment of mandibular molars with symptomatic irreversible pulpitis [31-34]. A systematic review by Nagendrababu *et al.* [35] showed that premedication with NSAIDs increased the success of inferior alveolar nerve block for mandibular molars with symptomatic irreversible pulpitis. However, ibuprofen doses < 400 mg were not effective. However, Elnaghy *et al.* [36] demonstrated that 100 mg tramadol was a better choice than ibuprofen and a combination of ibuprofen and acetaminophen for success of inferior alveolar nerve block. A systematic review by Pulikkotil *et al.* [37] showed that dexamethasone was the most effective medication for success of inferior alveolar nerve block injection followed by ibuprofen, which also significantly increased the success of block injection. In total, most studies have confirmed the efficacy of ibuprofen alone or in combination with acetaminophen for increasing the success of nerve block. Thus, ibuprofen and Novafen may not only decrease the patients' pain preoperatively, but may also increase the success of local anesthesia and enhance the emergency procedure for dental clinicians.

Some studies have emphasized on the significance of premedication for post-endodontic pain control [14, 16, 21, 23, 31, 38]. Some others showed the superior efficacy of ibuprofen for premedication for reduction of post-endodontic pain compared with other analgesics [31, 39]. In a systematic review, Nagendrababu *et al.* [9] concluded that prednisolone is the most effective premedication for reduction of post-endodontic pain, and NSAIDs were reported to be the least effective. However, they added that the reviewed studies all had a low quality, and recommended high quality studies to cast a final judgment in this regard. Suresh *et al.* [40] in their double-blind randomized clinical trial showed that 4 mg dexamethasone was more effective than 20 mg piroxicam taken orally as premedication for reduction of post-endodontic pain in patients with symptomatic irreversible pulpitis and symptomatic acute apical periodontitis. All the above mentioned studies emphasized on the significance of premedication for reduction of post-endodontic pain.

The severity of baseline preoperative endodontic pain has been confirmed to be a predictive factor for post-endodontic pain [41, 42]. In the present study, the severity of pain was also found to be an influential factor in success of analgesics for pain control, such that by each one unit increase in VAS pain score, the odds of success of analgesic treatment decreased by 68%; however, this finding does not indicate low chance of success of analgesic treatment in patients with severe pain since pain reduction also occurred in patients with maximum pain score of 10 in the present study.

In the current study, age and gender of patients had no significant effect on success of analgesic treatment. However, many studies have shown that females often experience greater level of pain after endodontic treatment than males [32-34, 43]. In contrast, Al-Rawhani *et al.* (38) reported that males had higher post-endodontic pain than females. Also, aging was reported as a predator of post-endodontic pain in some studies [33, 34].

In the present study, the analgesic efficacy of celecoxib was inferior to that of ibuprofen despite having the same mechanism of action, which may be due to the dosage of celecoxib (200 mg) compared with ibuprofen (600 mg). Evidence shows that 600 mg ibuprofen can effectively decrease post-endodontic pain [3, 39]. Thus, this dosage was administered for patients in the present study. Further studies on different doses of analgesics for maximum pain relief are required.

In the present study, the efficacy of analgesics was evaluated 1 h after administration in patients who, for some reason, could not immediately undergo emergency endodontic treatment. However, assessment of the efficacy of analgesics for longer periods of time was not possible due to ethical reasons. Future studies are required on the efficacy of other analgesics such as tramadol and dexamethasone for pain relief prior to endodontic treatment. Also, the effect of other factors such as patient expectation from treatment on pain should be investigated. The efficacy of analgesics for pain relief in patients with necrotic pulp or acute apical periodontitis should be investigated as well.

Our study had some limitations. First, the relatively small sample size of 120 patients, with 30 individuals in each treatment group, may limit the precision of our findings and their

generalizability to a broader population of patients with varying degrees of pain due to symptomatic irreversible pulpitis. Second, the exclusion of patients who had taken analgesics within the past 4 h or had contraindications for specific analgesics, such as those with underlying medical conditions, restricts the study's applicability to a subset of potential patients seeking emergency endodontic care. Third, the short-term follow-up of pain relief outcomes immediately after medication intake and 1 h later may not fully capture the longer-term efficacy of the analgesics.

Conclusion

Both ibuprofen and Novafen can serve as the analgesics of choice for pain relief in patients with symptomatic irreversible pulpitis with moderate to severe pain when emergency endodontic treatment cannot be immediately performed.

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Conflict of Interest: 'None declared'.

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