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Efficacy of Different Ibuprofen Formulations with Two Prescription Methods on Post Endodontic Pain of Teeth with Irreversible Pulpitis: A Randomized Clinical Trial

Saeede Zadsirjan[a], Ali Haeri[b], Elham Mohammadi[c*], Sanaz Beiraghdar[d], Mohammadreza Hosseini[b], Soolmaz Heidari[e]

a Department of Endodontics, Dental School, Shahid Beheshti University of Medical Sciences. Tehran, Iran; b Endodontist, Private Practice, Tehran, Iran; c Department of Endodontics, Dental School, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran; d Dentist, Private Practice, Shiraz, Iran; e Department of Operative Dentistry, Dental Caries Prevention Research Center, Qazvin University of Medical Sciences, Qazvin, Iran

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**Corresponding author*: Elham Mohammadi, Dental School, Tehran Medical Sciences, Islamic Azad University, No. 9, 9th Neyestan, Pasdaran Avenue, Tehran 19585175, Iran.

***Tel*:** +98-910 6791032
***E-mail*:** Mohamadi9624@gmail.com

Introduction: Pain management during root canal therapy and after that is of great importance in endodontics. This study aimed to compare the effect of two non-steroidal anti-inflammatory drugs (NSAIDs); ibuprofen and ibuprofen lysine with two methods of prescription on pain after single-visit root canal treatment of first and second mandibular molar teeth with irreversible pulpitis. **Materials and Methods:** This randomized study recruited subjects experiencing moderate to severe pain from a tooth diagnosed with symptomatic irreversible pulpitis (n=120). Subjects were randomized to receive 400 mg ibuprofen acid or 400 mg ibuprofen lysine regularly or on demand. The primary objective was to measure changes in pain scores at post-operative time frames of 6, 12, 18, 24, 48 and 72 hours after the root canal treatment on a 0-10 numerical rating scale (NRS). Independent T-test, Non-parametric Kruskal-Wallis Test and Friedman Test were used to analyze the data. **Results:** Kruskal-Wallis analysis showed a significant difference in NRS score between on-demand ibuprofen group and regular ibuprofen group and also between regular ibuprofen lysine group and regular ibuprofen group at 6 hours after the treatment (P<0.05). But no remarkable difference was observed in the recorded mean pain intensity of four study groups in the other time frames (P>0.05). **Conclusions:** Based on this randomized clinical trial, there was no significant difference in the pain intensity of patients using ibuprofen and ibuprofen lysine. Additionally, there was no significant difference in the degree of pain between the on-demand and regular groups, despite the fact that patients in the on-demand group used less medications. Due to the multiple negative effects of NSAIDs, it would be wise to prescribe ibuprofen on demand.

Keywords: Analgesics; Drug Prescriptions**;** Ibuprofen; Ibuprofen Lysinate; Post Endodontic Pain

Introduction

Postoperative pain following root canal treatment can be distressing for both patients and clinicians [1]. Prevalence of pain after root canal treatment is relatively high and is reported about 3-58% [2]. Endodontic pain control should begin with endodontic therapy and be continued by analgesics and/ or anti-inflammatory drugs [3, 4].

In the inflammatory condition of pulpal or periapical tissues, inflammatory mediators especially prostaglandins are released from blood vessels to pulpal or periapical tissues of an irritated tooth and stimulate peripheral nociceptors which result in pain [5]. The most popular analgesics for postoperative endodontic pain are nonsteroidal anti-inflammatory medications (NSAIDs) [6]. For instance, the most researched NSAID for endodontic pain in clinical trials is ibuprofen acid, which is the medication of preference for the majority of patients [6, 7]. NSAIDs function through blocking cyclooxygenase, which reduces the generation of prostaglandins [8].

To our knowledge, modifying ibuprofen formulation with rapidly dissolving salts such as sodium, lysine, arginine or additional agents such as surfactants (polymeric surface active agent poloxamer) leads to higher ibuprofen concentration in blood and earlier onset of pain relief [9, 10]. Ibuprofen sodium dehydrate and ibuprofen poloxamer are proved to be fast-acting analgesics [10, 11], but there is no recent investigation evaluating ibuprofen lysine efficacy.

Besides, faster acting painkillers cause longer lasting analgesia and also less frequent need for remedication [10, 12]. As a result, it might be a good idea not to administrate analgesics with regular intervals. Few studies have evaluated the effects of NSAIDs used on-demand versus regularly in postoperative pain management after root canal treatment. Yet there is no consensus which one is the best [13-15]. Thus, this study aimed to compare the effect of regular and on-demand prescription of ibuprofen acid and ibuprofen lysine on post-operative pain after root canal treatment in teeth with irreversible pulpitis.

Materials and Methods

This randomized, parallel-group clinical trial was approved by Ethics Committee of Dental School of Shahid Beheshti University of Medical Sciences' (IR.SBMU.RIDS.REC.1395.398) and registered in the Iranian Registry for Clinical Trials (http://www.irct.ir, identifier: IRCT2017051934030N1).

The primary outcome was to measure changes in pain scores at post-operative time frames of 6, 12, 18, 24, 48 and 72 hours after the root canal treatment. The main goal was to measure these score changes. Secondary outcome included the number of analgesic tablets needed to treat.

We recruited healthy men and women (aged 18–60 years old) with a first or second mandibular molar experiencing moderate to severe pain (defined as 4-10 on 0-10 NRS) that had symptomatic irreversible pulpitis diagnosis (defined as positive response to an electrical pulp test (The Elements Diagnosis Units, SybronEndo, Glendora, CA) as well as a prolonged response with moderate to severe pain to a cold pulp test (Roeko Endo-Frost; Roeko Langenau, Germany), normal periapical radiographic appearance and normal response to percussion test. Selected subjects did not show clinical swelling or draining sinus tract at the injection site. No patients with a known hypersensitivity to any analgesic drug or a history of gastric or duodenal ulcers or gastrointestinal bleeding were included in this trial. Participants who had taken any sort of analgesics on the treatment day, had a non-restorable tooth, were allergic to local anesthetics or sulfite, or were allergic to sulfite, pregnant and lactating women, those with systemic diseases and patients who were unable to give informed consent were not included.

We obtained a written informed consent from all patients explaining them the purpose of the study and possible adverse effects of drugs being investigated. All patients were treated in the postgraduate clinic of Endodontic Department of Shahid Beheshti Dental School, Tehran, Iran from September 2017 to January 2018.

First author (Z.S) gauged the patient's pain using the Numerical Rating Scale (NRS) and enrolled participants .The clinician was blinded in the process of the study completely. Although patients were not blinding during the study.

First, patients received the standard inferior alveolar nerve block injection by using 2% lidocaine with 1:80,000 epinephrine (Persocaine; Darupakhsh, Tehran, Iran) before starting the treatment. If patients were experiencing pain during the procedure, they were given supplementary intraligament and intrapulp injections to overcome the pain via the procedure. The working length was measured by an electronic apex locator (Root ZX, J Morita, Kyoto, Japan) .This was confirmed with a periapical radiograph. The working length of each root canal was set at 1 mm less than the radiographic apex. If any over instrumentation or over obturation happened during the treatment, patient was excluded from the study. Root canals were irrigated during canal preparation by 2.5% sodium hypochlorite between each instrument.

The access cavity was prepared with a glide path before the usage of rotary instruments. Next, Gates Glidden drills size Nos. 2 and 3 were used to prepare the coronal portion of the canals. Protaper rotary instruments (DENTSPLY, Ballaigues, Switzerland) were then used to complete the root canal preparation up to a F2 file. The canals were then dried and filled with gutta-percha and AH26 root canal sealer (Dentsply De Tery, Konstanz, Germany) using lateral condensation technique. Finally, the crown of the treated tooth was shortened to protect it from possible damage. The access cavity was temporary filled with Coltosol (Aria Dent, Asia Chemi Teb Co., Tehran, Iran); this process was similar for each patient.

The biggest potential confounder for this randomized trial was sex since some studies have reported greater analgesia in post endodontic pain in females compared with males [16, 17], so we used it as a stratification factor for randomization of the participants. The stratified randomization scheme used a random number generator to create variable size permuted blocks of two and four participants to ensure that the number of participants in each group was balanced within each stratum. We randomized patients into either the *ibuprofen acid* group (Arya Pharmaceutical Company, Tehran, Iran), or *ibuprofen lysin* group (Doctor Abidi Pharmaceutical Company, Tehran, Iran), using 1:1 allocation.

Randomization was performed using stratified permuted

block design. One of the investigators (B.S) allocated the patients randomly into one of the two arms via the drawing of a sealed, opaque envelope. As the randomization was stratified by sex, the envelopes were color-coded where one colored envelope was used to identify male patients and another colored envelope identified female patients. Each patient was randomly given a sealed envelope containing a card displaying *ibuprofen regular*, *ibuprofen on-demand*, *ibuprofen lysin regular* or a card displaying *ibuprofen lysin on-demand* and a paper describing needed information for drug administration. While patients in the regular groups received an analgesic immediately after their endodontic treatment and were instructed to use it regularly every 6 hours for at least 24 hours, those in the on-demand groups did not receive any medication right away and were told to use analgesic tablets only when they experienced pain. Maximum recommended dose was also described in administration paper. Before leaving the clinic, patients in all groups administered the medications in front of the researcher just after the initial phase of root canal treatment.

Participants were also given a *rescue medication* that included 10 tablets of Novafen (200 mg ibuprofen+325 mg acetaminophen+40 mg caffeine, Alhavi Pharmaceutical Company, Tehran, Iran), and they were instructed to use it if the study drug was unable to relief their pain. In this case the patients were required to inform the investigator and were excluded from the study. Moreover, patients experiencing any swelling after treatment were required to refer for examination and prescription of antibiotic if needed. These ones were excluded from the study, too.

Since patient self-reporting is the most accurate indicator of pain, the post-operative pain was measured by Numerical Rating Scale (NRS) system, a numerical pain rating scale ranging from 0-10 implemented with adults. Having no pain is rated as zero (0), and the worst pain that the patient can tolerate is rated as a 10. We instructed patients to complete an NRS form and asked them to record their pain intensity at 6, 12, 18, 24, 48 and 72 hours after the root canal treatment. Furthermore, they were required to record the number of analgesic tablets they had taken on their NRS forms. We reminded participants to complete their NRS form daily during that period of time and asked them to provide us with mentioned forms via WhatsApp application.

Senior author (M.E) also explained that zero meant no pain, 1 to 3 meant mild pain, 4 to 6 meant moderate pain, and 7 to 10 meant severe pain and assigned participants to intervention. Both the diagnostic tests and data collection were performed by a single investigator (H.M) who remained masked about the type of ibuprofen formulation given to the subjects.

The minimum sample size with the type I error of 0.05, the power of 0.9 and the effect size of 0.4, was calculated 20 per group [3]. We anticipated at least a 30% subject dropout and therefore recruited a total of 120 patient. The sample size calculation was computed by G*Power (Version3.1.9.2) [18] using one way analysis of variances technique.

Statistical analyzes

Per-protocol paradigm was used for the statistical analyses. Comparison of pain scores within each group was individually performed by Friedman Test. Nonparametric Kruskal-Wallis Test was used to compare the outcomes between groups. The Independent T-test was used to assess the mean pain severity between males and females and the quantity of analgesics taken. The analyses were computed by using IBM SPSS Statistics (Version 24.0. Armonk, NY: IBM Corp).

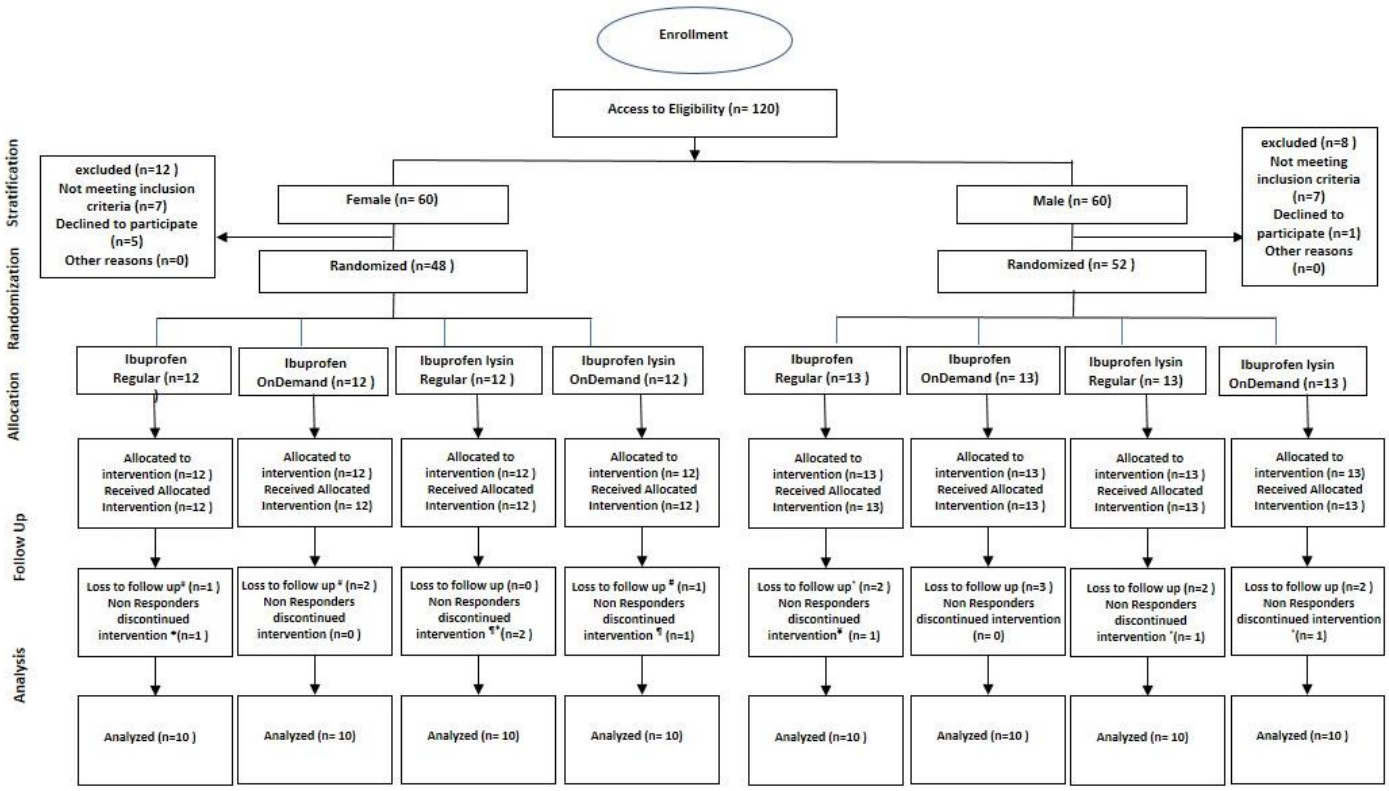
Results

We recruited 120 patients for this study and 80 patients were analyzed eventually. Homogeneity of variances and normal distribution of data were established. Patients' characteristics and clinical features are listed in Table 1. There were no age or sex differences between the participants in the ibuprofen groups and those in the ibuprofen lysine groups. The flow diagram indicates the number of participants in each group who were randomly allocated, received intended treatment, and were analyzed for the outcomes or either excluded after randomization (Figure 1).

Table 1. Demographic and clinical features of participants

		Age (year) Mean (SD)	Mean (SD) NRS						Number of analgesics
			6 h	12 h	18 h	24 h	48 h	72 h	
Ibuprofen	Regular	30.1 (6.4.)	3.60 (1.39)	2.65 (1.26)	2.45 (1.39)	1.8 (1.26)	1.15 (1.04)	0.60 (0.68)	5.3 (0.57)
	On-demand	36.9 (11.2)	2.80 (1.196)	2.45 (1.234)	1.95 (1.395)	1.35 (1.461)	0.85 (0.988)	0.30 (0.571)	1.85 (1.14)
Ibuprofen lysine	Regular	37.2 (8.7)	2.75 (0.967)	2.65 (1.387)	1.90 (1.119)	1.15 (0.671)	0.75 (0.786)	0.25 (0.444)	5.15 (0.37)
	On-demand	36.1 (10.6)	3.00 (1.076)	2.90 (1.021)	1.85 (1.137)	1.25 (1.118)	0.50 (0.688)	0.20 (0.523)	2 (0.65)
P-value		0.067	0.029	0.979	0.387	0.643	0.462	0.092	<0.001

NRS: Numeric Rating Scale



** Patients have taken rescue drug; ¥ They did not complete the NRS form; the drug was not taken at regular time; # the participant did not send the form at the end of study*

Figure 1. Flow diagram of the participants

The results of Friedman Test revealed a general decrease in pain intensity within each group during the 72 hours after treatment ($P<0.05$) (Figure 2). Kruskal-Wallis analysis showed a significant difference in NRS score between on-demand ibuprofen group and regular ibuprofen group and between regular ibuprofen lysine group and regular ibuprofen group at 6 hours after the treatment ($P<0.05$). But no remarkable difference was observed in the recorded mean pain intensity of four study groups in the other time frames ($P>0.05$).

Number of used analgesics in groups with regular administration was significantly higher than groups with on-demand administration. However, there was no meaningful difference between on-demand administration of ibuprofen and ibuprofen lysine ($P>0.05$).

As it is shown in Table 2, mean NRS score in females at 12, 18, 24 and 48 hours after the treatment was significantly greater than males ($P<0.05$).

Discussion

According to the study's findings, all four medication regimens (regular or on-demand prescription of ibuprofen or ibuprofen lysine) significantly reduced pain at the 6h, 12h, 18h, 24h, 48h, and 72h intervals following root canal treatment in pulpitis patients who were experiencing moderate to severe pain.

Pain control following root canal treatment is a big challenge for all of the clinicians. It was important to limit the inclusion criteria to patients with pre-operative moderate to severe pain because pre-operative pain is the greatest predictor of post-endodontic pain [19].

The instruments used for pain assessment, comparison, and correlation remain an issue of past and future discussion. Researchers and clinicians may prefer the NRS rather than the Visual Analogue Scale (VAS) in many settings. First, although the NRS has not been consistently shown to have ratio properties [20], its scores can provide data for parametric analysis [21]. Second, whether a 0-10 NRS or a 0-100 NRS is employed, it has been shown that the NRS is at least as sensitive as the VAS [22]. Third, patients and clinicians preferred NRS to VAS for its relative simplicity and ease of administration and scoring even when administered verbally [21-23]. Fourth, it seems that the VAS has greater failure rates than the NRS, maybe as a result of the NRS's simplicity for patients to comprehend and complete [21-23]. Therefore, the researcher decided to provide assessment form including a 0-10 NRS to evaluate the patient's response to analgesics.

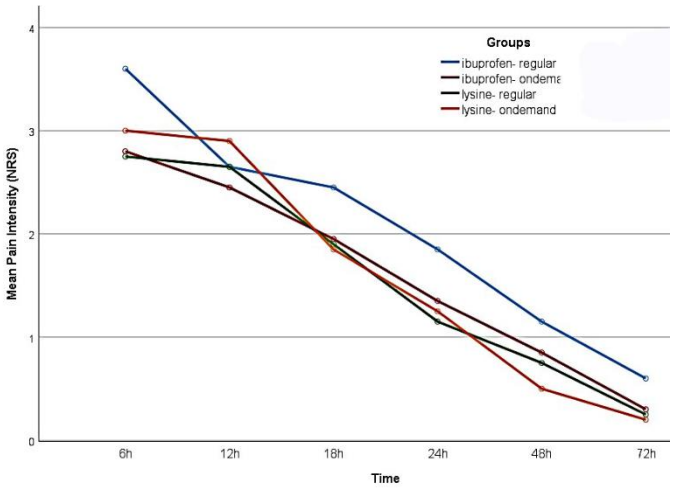


Figure 2. Comparison of mean pain intensity between 4 prescription groups over the 72-hour postoperative following root canal treatment. (NRS: Numeric Rating scale, h: hour

A recently published systematic review and meta-analysis indicated that improved standards include measuring pain relief at regular intervals for at least 3 days [6]; Some studies found that severe postoperative pain was typically reduced to a tolerable level within 3 days [24, 25]. Therefore, we asked the patients to report their pain up to 72 hours after treatment.

NSAIDs are amongst the most recommended medications used for post endodontic pain relief and ibuprofen is of the most used drugs in this group[14]. Although the recommended dose of ibuprofen that considerably reduces pain is reported to be 400 mg or 600 mg, the ceiling effect of ibuprofen is thought to be 400 mg and higher doses will not increase the analgesic potential meaningfully and only result in adverse effects [26]. Thus, for each dosage in the current trial, 400 mg of ibuprofen and ibuprofen lysin were administered.

Table 2. Average NRS scores of 6 time periods in post endodontic pain divided by gender *(N=40)*

Time	Gender	Mean (SD) NRS	*P*-value
6 h	Male	2.90(1.29)	0.311
	Female	3.18 (1.08)	
12 h	Male	2.38 (1.21)	0.031
	Female	2.95 (1.17)	
18 h	Male	1.75 (1.31)	0.040
	Female	2.33 (1.16	
24 h	Male	1.15 (1.16)	0.034
	Female	1.65 (1.14)	
48 h	Male	0.65 (0.94)	0.044
	Female	0.98 (0.83)	
72 h	Male	0.35 (0.58)	0.817
	Female	0.33 (0.57)	

NRS: Numeric Raing Scale

To increase the solubility, Lysinate formulations have been successfully developed. They demonstrated an improved rate of absorption compared to traditional ibuprofen (*i.e.*, ibuprofen acid) [27] .Pharmaco-dynamically, ibuprofen lysinate was shown to provide quicker pain relief than has conventional ibuprofen formulation [28]. It is reasonable to assume that faster analgesic effectiveness would result from faster ibuprofen availability in plasma, as seen with ibuprofen lysinate [28]. Maximum ibuprofen concentrations were reached with fast-acting formulations (arginine, lysine, and sodium salts) approximately after 20 to 40 minutes, but normal formulations took about 90 to 120 minutes. Strong data supports the claim that fast-acting formulations produce bloodstream peak concentrations substantially sooner than conventional formulations [12].

The result of this study showed that at 6 hours after the treatment, the pain intensity in patients who used regular ibuprofen lysine was lower than other groups. This was the first time that efficacy of ibuprofen was compared to ibuprofen lysine in post-endodontic pain. Immediate use of fast-acting drug (regular ibuprofen lysine) seems to have a positive effect on reducing pain 6 hours after treatment. Mehlisch *et al.* found that ibuprofen lysine 400 mg was more effective than acetaminophen 1000 mg in relieving pain of patients who had postoperative dental after surgically removing a third molar [29]. Nelson *et al.* discovered that individuals with moderate to severe post endodontic dental pain responded better to ibuprofen lysine 200 mg than acetylsalicylic acid 500 mg [30].Oral NSAIDs carry risk of systemic adverse effects mostly in gastrointestinal, cardiovascular and renal tissues [31] so it is prudent to prescribe them as little as possible and the researcher decided to assess on-demand concept of drug administration in this study. The concept of regular use of analgesics instead of on-demand prescription of drugs was based on the results of pain relief efficacy studies after surgery in the medical literature [13, 32]. However, the results of the present study showed that there was no remarkable difference on postoperative pain after 12 hours reported by patients using either on-demand or regular 400 mg ibuprofen and ibuprofen lysine, while the number of used analgesics was fewer in patients who administrated on-demand medications. These results are in line with those reported by Parirokh *et al.* who found that there was no significant difference between the groups in terms of how well they responded to the two distinct regimens (regular and on demand) of 400 mg ibuprofen for pain relief [14]. Therefore, it may be inferred that it is not required to recommend regular use of medication after single-visit root canal treatment in patients with irreversible pulpitis.

Faster onset of pain relief is reported to be associated with longer duration, as indicated by no need for remedication [33]. Based on two studies conducted by Moore *et al.* adding a salt to ibuprofen formulation would result in long-standing analgesia which lessens the frequency of using analgesics. [10, 12] But in the present study, there was no significant difference in the number of used analgesics between patients who received ibuprofen lysine versus those who received ibuprofen on demand or regularly. The reason for this difference is the quality of pain between analgesic research studies using an oral surgery model and studies using an endodontic model. Third molar extraction patients are more likely to be young, healthy, and experiencing little or minimal preoperative discomfort. However, a patient requiring root canal treatment could have experienced persistent pain that had centralized and proceeded from an acute to chronic state [34, 35].

Evaluating the effect of patients' sex on their pain level after root canal treatment can be mentioned as one of the strengths of present study. The results indicated that there was a significant difference between males and females' pain intensity at 12, 18, 24 and 48 hours after the treatment, accordingly females experienced noticeably higher pain levels which is consistent with the result of Nusstein *et al.* study [36].

In general, it was reported that female patients have lower pain thresholds and are less tolerant of pain[37]. Additionally, women report using analgesics more often than men [38, 39]. But a study using self-reported pain metrics including the frequency of pain episodes and the average pain intensity failed to find any gender differences [40]. Since there are variations and similarities in women and men's pain experiences, further researches should be conducted on the psychological factors and coping strategies of men and women in pain [36].

This study had several limitations. It was conducted at an academic institution thus it may not reflect the behavior of private practice or community clinic dentists who treat similar patients. Moreover, we were unable to accurately abstract certain factors, such as the clinical difficulty or the length of time needed for a procedure. These factors could influence the kind of discomfort a patient felt [41]. Another drawback was that patients were not blind, since this influences the perception of pain, as the patient knows which group he/she was allocated to.

The measurement of pain is difficult because pain perception is subjective and variable which is regulated by multiple physical and psychological factor [42]. Therefore, evaluating pain level in patients is a difficult procedure since there is no unique scale for measuring this quantity.

Conclusions

The pain level in subjects who administrated on-demand medication versus those who used it regularly was not significantly different, however, the number of used analgesics was fewer in on-demand groups. According to the adverse effects of NSAIDs, on-demand prescription of them might be a good alternative to the regular one. Additionally, patients who used on-demand ibuprofen lysine reported higher analgesia 12 to 72 hours after root canal treatment. Therefore, ibuprofen can be replaced by ibuprofen lysine for pain relief after root canal treatment.

Conflict of Interest: 'None declared'.

References

1. Wong AW, Zhang S, Li SK, Zhu X, Zhang C, Chu CH. Incidence of post-obturation pain after single-visit versus multiple-visit non-surgical endodontic treatments. BMC oral health. 2015;15:96.
2. Sathorn C, Parashos P, Messer H. The prevalence of postoperative pain and flare-up in single- and multiple-visit endodontic treatment: a systematic review. Int Endod J. 2008;41(2):91-9.
3. Mehrvarzfar P, Abbott P, Saghiri M, Delvarani A, Asgar K, Lotfi M, Karamifar K, Kharazifard M, Khabazi H. Effects of three oral analgesics on postoperative pain following root canal preparation: a controlled clinical trial. Int Endod J. 2012;45(1):76-82.
4. Shafie L, Esmaili S, Parirokh M, Pardakhti A, Nakhaee N, Abbott PV, Barghi H. Efficacy of pre-medication with ibuprofen on post-operative pain after pulpotomy in primary molars. Iran Endod J. 2018;13(2):216.
5. Goodis H, Poon A, Hargreaves K. Tissue pH and temperature regulate pulpal nociceptors. J Dent Res. 2006;85(11):1046-9.
6. Smith EA, Marshall JG, Selph SS, Barker DR, Sedgley CM. Nonsteroidal Anti-inflammatory Drugs for Managing Postoperative Endodontic Pain in Patients Who Present with Preoperative Pain: A Systematic Review and Meta-analysis. J Endod. 2017;43(1):7-15.
7. Mokhtari F, Yazdi K, Mahabadi AM, Modaresi SJ, Hamzeheil Z. Effect of premedication with indomethacin and ibuprofen on postoperative endodontic pain: a clinical trial. Iran Endod J. 2016;11(1):57.
8. Shirvani A, Shamszadeh S, Eghbal MJ, Marvasti LA, Asgary S. Effect of preoperative oral analgesics on pulpal anesthesia in patients with irreversible pulpitis—a systematic review and meta-analysis. Clin Oral Investig. 2017;21(1):43-52.
9. Cattaneo D, Clementi E. Clinical pharmacokinetics of ibuprofen arginine. Curr Clin Pharmacol. 2010;5(4):239-45.
10. Moore R, Derry S, Straube S, Ireson-Paine J, Wiffen P. Validating speed of onset as a key component of good analgesic response in acute pain. Eur J Pain. 2015;19(2):187-92.
11. Taggar T, Wu D, Khan AA. A randomized clinical trial comparing 2 ibuprofen formulations in patients with acute odontogenic pain. J Endod. 2017;43(5):674-8.
12. Moore RA, Derry S, Straube S, Ireson-Paine J, Wiffen PJ. Faster,

higher, stronger? Evidence for formulation and efficacy for ibuprofen in acute pain. PAIN®. 2014;155(1):14-21.
13. Owen H, Glavin R, Shaw N. Ibuprofen in the management of postoperative pain. Br J Anaesth. 1986;58(12):1371-5.
14. Parirokh M, Sadr S, Nakhaee N, Abbott PV, Manochehrifar H. Comparison between prescription of regular or on-demand ibuprofen on postoperative pain after single-visit root canal treatment of teeth with irreversible pulpitis. J Endod. 2014;40(2):151-4.
15. Yefet E, Taha H, Salim R, Hasanein J, Carmeli Y, Schwartz N, Nachum Z. Fixed time interval compared with on-demand oral analgesia protocols for post-caesarean pain: a randomised controlled trial. Bjog. 2017;124(7):1063-70.
16. Baradaran M, Hamidi MR, Firoozabad MRM, Kazemi S, Ashrafpour M, Moghadamnia AA. Alprazolam role in the analgesic effect of ibuprofen on postendodontic pain. Caspian J Intern Med. 2014;5(4):196.
17. Ryan JL, Jureidini B, Hodges JS, Baisden M, Swift JQ, Bowles WR. Gender differences in analgesia for endodontic pain. J Endod. 2008;34(5):552-6.
18. Faul F, Erdfelder E, Lang A-G, Buchner A. G* Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods. 2007;39(2):175-91.
19. Menke ER, Jackson CR, Bagby MD, Tracy TS. The effectiveness of prophylactic etodolac on postendodontic pain. J Endod. 2000;26(12):712-5.
20. Price DD, Patel R, Robinson ME, Staud R. Characteristics of electronic visual analogue and numerical scales for ratings of experimental pain in healthy subjects and fibromyalgia patients. Pain. 2008;140(1):158-66.
21. Dijkers M. Comparing quantification of pain severity by verbal rating and numeric rating scales. J Spinal Cord Med. 2010;33(3):232-42.
22. Chanques G, Viel E, Constantin J-M, Jung B, de Lattre S, Carr J, Cissé M, Lefrant J-Y, Jaber S. The measurement of pain in intensive care unit: comparison of 5 self-report intensity scales. PAIN®. 2010;151(3):711-21.
23. Ferreira-Valente MA, Pais-Ribeiro JL, Jensen MP. Validity of four pain intensity rating scales. PAIN®. 2011;152(10):2399-404.
24. Praveen R, Thakur S, Kirthiga M. Comparative evaluation of premedication with ketorolac and prednisolone on postendodontic pain: a double-blind randomized controlled trial. J Endod. 2017;43(5):667-73.
25. Nunes EC, Herkrath FJ, Suzuki EH, Júnior ECG, Marques AAF, Júnior ECS. Comparison of the effect of photobiomodulation therapy and Ibuprofen on postoperative pain after endodontic treatment: randomized, controlled, clinical study. Lasers Med Sci. 2020;35(4):971-8.
26. Hargreaves KM, Berman LH. Cohen's pathways of the pulp expert consult: Elsevier Health Sciences; 2015.
27. Geisslinger G, Dietzel K, Bezler H, Nuernberg B, Brune K. Therapeutically relevant differences in the pharmacokinetical and pharmaceutical behavior of ibuprofen lysinate as compared to ibuprofen acid. Int J Clin Pharmacol Ther Toxicol. 1989;27(7):324-8.
28. Seibel K, Schaffler K, Reeh P, Reitmeir P. Comparison of two different preparations of ibuprofen with regard to the time course of their analgesic effect. A randomised, placebo-controlled, double-blind cross-over study using laser somatosensory evoked potentials obtained from UW-irritated skin in healthy volunteers. Arzneimittelforschung. 2004;54(8):444-51.
29. Mehlisch DR, Jasper RD, Brown P, Korn SH, McCarroll K, Murakami AA. Comparative study of ibuprofen lysine and acetaminophen in patients with postoperative dental pain. Clin Ther. 1995;17(5):852-60.
30. Nelson SL, Brahim JS, Korn SH, Greene SS, Suchower LJ. Comparison of single-dose ibuprofen lysine, acetylsalicylic acid, and placebo for moderate-to-severe postoperative dental pain. Clin Ther. 1994;16(3):458-65.
31. Moore N, Pollack C, Butkerait P. Adverse drug reactions and drug-drug interactions with over-the-counter NSAIDs. Ther Clin Risk Manag. 2015;11:1061-75.
32. De FC, Ripamonti C, Gamba A, Prada A, Ventafridda V. Treatment of postoperative pain: comparison between administration at fixed hours and'on demand'with intramuscular analgesics. Eur J Surg Oncol. 1989;15(3):242-6.
33. Li H, Mandema J, Wada R, Jayawardena S, Desjardins P, Doyle G, Kellstein D. Modeling the onset and offset of dental pain relief by ibuprofen. J Clin Pharmacol. 2012;52(1):89-101.
34. Mehlisch D, Sykes J. Ibuprofen blood plasma levels and onset of analgesia. Int J Clin Pract Suppl. 2013;67:3-8.
35. Mehlisch DR, Ardia A, Pallotta T. A controlled comparative study of ibuprofen arginate versus conventional ibuprofen in the treatment of postoperative dental pain. J Clin Pharmacol. 2002;42(8):904-11.
36. Nusstein JM, Beck M. Comparison of preoperative pain and medication use in emergency patients presenting with irreversible pulpitis or teeth with necrotic pulps. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2003;96(2):207-14.
37. Sadaf D, Ahmad MZ. Factors associated with postoperative pain in endodontic therapy. Int J Biomed Sci. 2014;10(4):243.
38. Fillingim RB, Edwards RR, Powell T. The relationship of sex and clinical pain to experimental pain responses. PAIN®. 1999;83(3):419-25.
39. Eggen AE. The Tromsø Study: frequency and predicting factors of analgesic drug use in a free-living population (12–56 years). J Clin Epidemiol. 1993;46(11):1297-304.
40. Lester N, Lefebvre JC, Keefe FJ. Pain in young adults: I. Relationship to gender and family pain history. Clin J Pain. 1994.
41. Barasch A, Safford MM, McNeal SF, Robinson M, Grant VS, Gilbert GH. Patterns of postoperative pain medication prescribing after invasive dental procedures. Spec Care Dentist. 2011;31(2):53-7.
42. Talebzadeh B, Nezafati S, Rahimi S, Shahi S, Lotfi M, Ghasemi N. Comparison of manual and rotary instrumentation on postoperative pain in teeth with asymptomatic irreversible pulpitis: A randomized clinical trial. Iran Endod J. 2016;11(4):273.

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