

## Postoperative or preoperative medication? Which one is more effective in the management of postoperative extraction dental pain in children?

Fatemeh Jahanimoghadam DDS, MSc<sup>1</sup>, Hoda Shamsaddin DDS, MSc<sup>2</sup>,  
Mahboobeh Shokrizadeh DDS<sup>3</sup>

### Original Article

#### Abstract

**BACKGROUND AND AIM:** Alleviating a painful procedure like tooth extraction by compound analgesics in a single dose using the synergistic effects, particularly before the beginning of extraction pain, is favourable. The aim of the present study was to evaluate the beneficial effect of time (preoperative/postoperative) to prescribe medication in the management of postoperative dental pain following primary tooth extraction.

**METHODS:** The present double-blind clinical trial study included 121 healthy children aged 6-12 years old. The children were classified into four groups, including Group 1: Neurobion forte-vitamin B complex-vitamin B12 as placebo 30 minutes before extraction, Group 2: Neurobion forte-vitamin B complex-vitamin B12 30 minutes after extraction, Group 3: concurrent ibuprofen-acetaminophen combination 30 minutes before extraction, and Group 4: concurrent ibuprofen-acetaminophen combination 30 minutes after extraction. The researcher was blind about which group took placebo or main drug. Patient was blind too. The rate of pain was evaluated with visual analogue scale (VAS) immediately, 30 minutes after extraction, and 6 and 24 hours later. Data were collected and analyzed using SPSS software. T-test was used to compare between groups ( $P < 0.05$ ). Repeated measures test was used to compare between the placebo and main drug groups during measurement times.

**RESULTS:** Population of the study included 58 (47.9%) boys and 63 (52.1%) girls. It was found that mean pain intensity in group 3 was considerably lower than other groups immediately after intervention. Moreover, in group 2, it was significantly more than other groups. However, under 30 minutes, 6 hours, and 24 hours, repeated measures test showed that the mean severity of pain in group 2 was significantly more than other groups.

**CONCLUSION:** According to the results, concurrent preoperative ibuprofen-acetaminophen administration would provide better analgesic efficacy compared to the postoperative ibuprofen-acetaminophen combination in 6-12 years old children. Moreover, the effect of induction in children could be demonstrated.

**KEYWORDS:** Ibuprofen; Acetaminophen; Pain; Tooth Extraction

**Citation:** Jahanimoghadam F, Shamsaddin H, Shokrizadeh M. **Postoperative or preoperative medication? Which one is more effective in the management of postoperative extraction dental pain in children?** J Oral Health Oral Epidemiol 2021; 10(1): 43-50.

It is widely accepted that pain management in pediatric dentistry is a real challenge. In fact, pain is the most common cause of stress in children. Pain is an inherently subjective experience and should be assessed and treated as such. Anxiety can upregulate pain

perception; many of our behavior management methods such as distraction, Tell-Show-Do (TSD), relaxation, and coping can downregulate pain. Moreover, several methods, including medication therapy, acupuncture, nitrous oxide, cryotherapy, and so forth were provided for reducing the pain.

1- Associate Professor, Oral and Dental Diseases Research Center AND Kerman Social Determinants on Oral Health Research Center AND Department of Pediatric Dentistry, School of Dentistry, Kerman University of Medical Sciences, Kerman, Iran

2- Assistant Professor, Oral and Dental Diseases Research Center AND Kerman Social Determinants on Oral Health Research Center AND Department of Pediatric Dentistry, School of Dentistry, Kerman University of Medical Sciences, Kerman, Iran

3- Resident, Department of Pediatric Dentistry, School of Dentistry AND Oral and Dental Diseases Research Center, Kerman University of Medical Sciences, Kerman, Iran

Address for correspondence: Mahboobeh Shokrizadeh DDS; Department of Pediatric Dentistry, School of Dentistry AND Oral and Dental Diseases Research Center, Kerman University of Medical Sciences, Kerman, Iran; Email: shokrizadeh.k96@gmail.com

In fact, dental extraction for children is similar to and possibly easier than those performed for adults. The greatest difference is in patient management. It is necessary that the dentist take time and introduce armamentarium as child language.

In dentistry, procedures on hard tooth structure that will not involve the pulp create mild inflammatory reaction, although soft tissues traumatized, like what happens in extractions, will have a pain response.<sup>1</sup>

Extraction of even a loose tooth causes pain. Thus profound local anesthesia is required to prohibit pain during removal procedures. Local anesthesia must be certainly profound to omit sensation from the pulp, periodontal ligament, and adjacent soft tissues. However, even with profound local anesthesia, patients will still feel discomfort from pressure placed on a tooth and surrounding tissues during more extractions. It is important for practitioner to recognize the anxiety that most often exists in patients about tooth extraction. Most often, inflammatory process of consequent irreversible pulpitis or pulp necrosis is the reason of insufficient anesthesia. Acidophilic pH does not allow the local anesthesia to act adequately and we will not reach to a profound local anesthesia. Moreover, any pain could increase child anxiety.

However, the primary cause of pain seems to be inflammatory mediators, which activate the sensory nociceptors around the teeth.<sup>2</sup> Thus, resultant stimulation of both central nervous system (CNS) and peripheral nervous system (PNS) is referred to as hyperalgesia and marked as an increased reaction in perceiving a painful stimulus.<sup>3</sup>

Analgesic medications in pediatric dentistry are administered for relieving acute or chronic pain and postoperative pain as well as for controlling adjunctive intraoperative pain.<sup>4</sup> Moreover, these medications could be given preoperatively to alleviate both postoperative pain and decrease postoperative pain medication requirement.<sup>5</sup> In addition, oral medications can improve children compliance by reducing their stress and

enhancing the clinical outcomes.<sup>1</sup>

According to the studies, acetaminophen and ibuprofen are the most common prescribed analgesics for management of postoperative extraction pain in children.<sup>6</sup> Ibuprofen is a member of the nonsteroidal anti-inflammatory drugs (NSAIDs), prohibiting the cyclooxygenase (COX) enzymes. The pharmacokinetic profile of ibuprofen in younger children is similar to older ones and this pharmacokinetics is not different between children and adults. Therefore, the pharmacokinetics of ibuprofen in children was evaluated in both forms of single-dose and multiple-dose. Following the single dose of 5-10 mg/kg in 2-11 years old children, peak plasma concentration was observed less than 2 hours. Multiple doses (20-40 mg/kg/day ibuprofen suspension in divided doses) are prescribed to 1.5-16 years old children with juvenile arthritis. Ibuprofen is absorbed from the upper gastrointestinal (GI) tract (less than 0.25 hours in granule form and less than 2 hours in tablet form).<sup>7</sup>

Since 1950s, acetaminophen, which is known as paracetamol in United States (US), has been accessible as an analgesic agent in the US and United Kingdom (UK).<sup>8</sup> In fact, paracetamol is the most common analgesic and antipyretic medication in pediatric medicine and is prescribed for short-term management of mild-to-moderate pain and reducing baby fever. The prescribed dose can range from 10 to 15 mg/kg in 4-6 hours. Maximum dose should not be more than 5 doses in 24 hours. However, tylenol has poor peripheral anti-inflammatory reaction, limited GI side effect, and a minor clinical effect on the platelet function.<sup>8</sup>

However, combination of analgesics enables us to benefit from the synergic effect of two drugs, but probability of overdoses particularly in children is still a concern, so implementation of the minimum dose in recommended dose spectrum can assure us that the safe dose is considered.

Although there are many reports that evaluated the efficacy of

ibuprofen/acetaminophen in the postoperative pain, only few studies compared the effect of combination and time of prescription of acetaminophen-ibuprofen on the postoperative pain.<sup>1</sup> Most of studies proved the effect of one of these analgesics after the procedures; however, it is more important to eliminate pain before beginning pain instead of reducing it. Moreover, combination of the common analgesics such as acetaminophen and ibuprofen in the belief that it improve analgesic efficacy. However, evidence to prove this belief is limited.<sup>7-11</sup>

The present study described the results of the concurrent prescription of ibuprofen-acetaminophen preoperatively and postoperatively on the postoperative pain following primary tooth extraction.

### Methods

This double-blind, randomized, controlled clinical trial was registered at Iranian Registry of Clinical Trials (IRCT20180521039763N3) and approved by the Ethics Committee of Kerman University of Medical Sciences, Kerman, Iran. The ethical code of the present clinical trial was IR.KMU.REC.1397.478. The protocol of this study was in accordance with the Declaration of Helsinki for Human Rights. This research was performed at Department of Pediatric Dentistry of Kerman University of Medical Sciences between December 2018 and January 2019. By using analysis of variance (ANOVA) test, 120 patients in 4 groups were selected as our statistical population. 120 healthy patients referred to Kerman School of Dentistry for dental extraction participated in this study. Then, written informed consent was obtained from each parent before screening for drug prescription and dental extraction. The researcher was blind about which group received placebo or main drug. Also, patients were blind about which compound was given to them.

The inclusion criteria consisted of:

1. 6-12 years of age
2. Being cooperative (Frankel III, IV)
3. The presence of two hopeless primary molars with at least 1/3 root length

4. Being in acceptable psycho-social development  
The exclusion criteria consisted of:

1. Children with acute abscess or dental pain caused by inflammation
2. Anxiety disorders [with Spence Children's Anxiety Scale (SCAS)]
3. History of the prescribed corticosteroids
4. History of the use of analgesics in the last 24 hours
5. Previous unpleasant dental extraction
6. Children with immune system disorders or medical problem
7. Ankylosed teeth
8. Any additional/supplementary injection if necessary
9. Any drug allergy

Randomization sequence was performed before any intervention by the study statistician. The statistician maintained a confidential schedule of participant numbers according to time of drug which should be prescribed. Each eligible participant was assigned to give an envelope with numbers from 1 to 4; the participant read the number and according to the number, was assigned in one of the groups. According to randomization, patients were divided into four groups: Group 1: Neurobion forte-vitamin B complex-vitamin B12 10 mg/kg 30 minutes before extraction as a placebo (30 patients), Group 2: Neurobion forte-vitamin B complex-vitamin B12 10 mg/kg 30 minutes after extraction as a placebo (30 patients), Group 3: ibuprofen suspension 2.5 mg/kg and acetaminophen syrup 7.5 mg/kg 30 minutes before extraction (31 patients), and Group 4: ibuprofen suspension 2.5 mg/kg and acetaminophen syrup 7.5 mg/kg 30 minutes after extraction (30 patients).

To avoid any bias, every medication was poured into a smoked glass and covered with paper. Also, another postgraduate student was asked to give drugs to each child.

The test group, which was the third group, received a dose of acetaminophen-ibuprofen one hour before extraction according to the exact weight calculated with digital scale (Personal Scale Business counting Digital

Scale, KG 180). Therefore, 100 mg/5 ml of ibuprofen suspension (Alborz Darou Co., Iran) in dose of 2.5 mg/kg and 60 mg/5 ml of acetaminophen syrup (Ramo Farmin Co., Iran) in dose of 7.5 mg/kg were calculated. The group 4 received a dose of acetaminophen-ibuprofen combination 1 hour after extraction, similar to the group 3.<sup>6</sup> During this time, patients and their parents were asked to stay in waiting room and child was asked to eat anything. Also, the reason of this instruction about eating was explained to parents. Therefore, they could help us more in managing their child by distraction or by watching TV in waiting room.

The control group received the placebo as 16 oz./473 ml syrup (Neurobion forte-vitamin B Complex-vitamin B12, OTC Pharmaceutical Products, www.otcpharmausa.com) with the same dose of acetaminophen-ibuprofen combination one hour before extraction. However, the dose was prescribed one hour after extraction to the group 2.

An anesthetic gel containing 2% benzocaine (Master-Dent Co., USA) was applied as a surface anesthetic agent. In order to eliminate the confounding factors, injections were administered using Septoject 27-gauge needles with a length of 21 mm (septodont.co.uk). The anesthetic cartridge contained 2% lidocaine with 1:80000 epinephrine (Persocaine, Daroopaksh Company, Tehran, Iran). The injection syringe (Jooya Informatics Group, Iran) was the same for all children and injection was performed in sixty seconds. Educated resident of pediatric dentistry applied

anesthetic gel and then local anesthesia was injected. Extraction procedure was done with the same resident. If the tooth required any section, patient was removed from the study.

Visual analogue scale (VAS) is one of the scales to evaluate the pain intensity in children. In fact, it is the most common and simple method for children to comprehend it. VAS is a self-reported scale. A VAS is a line approximately 100 mm in length or 6 faces (no pain versus severe pain). The child indicates the degree of perceived pain by pointing the faces or by making a mark on the line. The length of the line from left-hand margin to the mark shows the magnitude of pain. Before procedure, faces in VAS were explained to children. Immediately after tooth extraction, VAS was displayed and the child was asked for the rate of his/her pain by assistant. Respectively, 30 minutes after extraction, and 6 and 24 hours later, any eventual pain was followed up. For measuring the amount of pain after 6 and 24 hours, making a video call was scheduled and the faces of VAS again were illustrated to child and he/she was asked about any pain. If the child had any pain during the first 24 hours, the parents could use more doses of analgesic.

Moreover, the rate of pain intensity was classified into four categories:

0: None

1-3: Mild pain that is distinguishable but with no discomfort

4-6: Moderate pain that makes inconvenience but is tolerable

7-9: Severe pain that is hardly endurable (Figure 1)

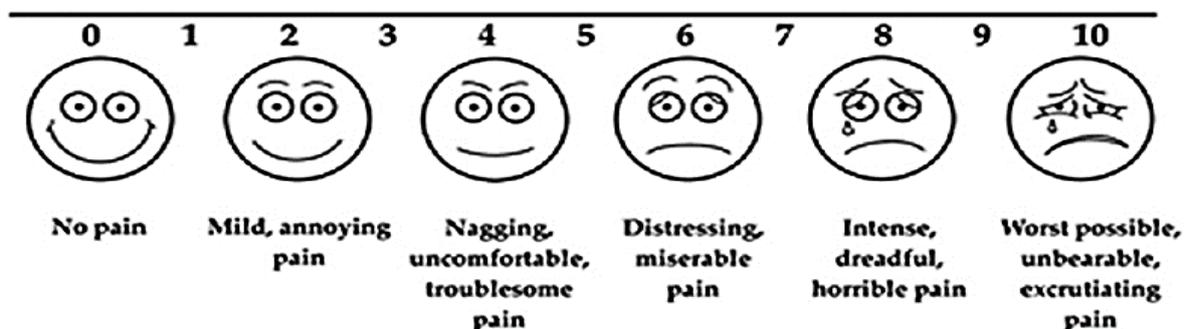


Figure 1. Visual analogue scale (VAS)

Data were collected and analyzed using SPSS software (version 20, IBM Corporation, Armonk, NY, USA). Shapiro-Wilk test was used to evaluate the normality of the data. Kruskal-Wallis test was used to compare severity of pain between four groups in each time. Chi-square test was used to compare the categorical variables between four groups. P-value of  $< 0.05$  was considered statistically significant.

## Results

This study included 121 children (58 boys and 63 girls) with a mean age of  $8.0 \pm 1.7$  years. Moreover, there were no significant differences between the four treatment groups in terms of gender ( $P = 0.970$ ) and age ( $P = 0.056$ ). The mean age group as follows (group 1: 8.15, group 2: 7.98, group 3: 8.35, group 4: 7.21).

According to the comparison of the mean pain scores in the group taking the combination therapy with ibuprofen-acetaminophen, immediately after intervention and during 30 minutes, the level of pain in the group receiving the drug before treatment was considerably lower than that

of the group taking drug after treatment ( $P = 0.030$ ).

However, 6 hours, and 24 hours after treatment, there was no significant difference between the group receiving drug after treatment and the group taking drug before treatment. In addition, pain significantly reduced in both groups.

Moreover, in the placebo group, comparison of the mean pain scores at immediately, 30 minutes, 6 hours, and 24 hours after treatment showed a significant difference in the group receiving drug before treatment in comparison with the group taking drug after treatment. However, the severe pain score was lower in all four times in the group receiving drug before treatment (Table 1).

Based on the comparison between the main drug and placebo at different times, the level of pain immediately after intervention was significantly different between the placebo group and the group receiving the main drug in the children who took drug both before and after treatment ( $P = 0.001$ ). Moreover, the group taking ibuprofen/acetaminophen had less pain.

**Table 1.** Comparison of pain intensity frequency between 4 groups according to time

	Groups	Placebo (before)	Placebo (after)	Analgesic (before)	Analgesic (after)	P
Time	Pain	N	N	N	N	
Immediately	No pain	14	4	15	6	0.0001
	Mild	6	8	14	14	
	Moderate	2	8	1	7	
	Severe	8	10	0	3	
	P	0.0220		0.0100		
After 30 minutes	No pain	22	7	30	25	0.0001
	Mild	7	6	0	4	
	Moderate	1	14	0	1	
	Severe	0	3	0	0	
	P	0.0001		0.0650		
After 6 hours	No pain	28	9	30	29	0.0001
	Mild	2	13	0	1	
	Moderate	0	7	0	0	
	Severe	0	1	0	0	
	P	0.0001		0.3100		
After 24 hours	No pain	30	18	30	29	0.0001
	Mild	0	10	0	1	
	Moderate	0	2	0	0	
	Severe	0	0	0	0	
	P	0.0010		0.3100		

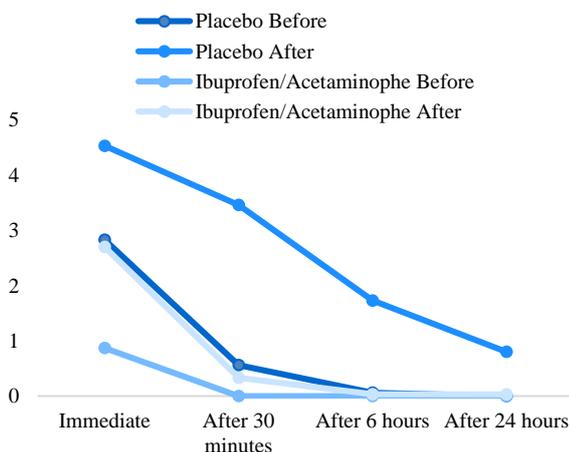
**Table 2.** Comparison of the main drug and placebo in terms of the level of pain according to the measurement time

Pain measurement time	Drug utilization time	Compared groups	Mean difference	SE	P
Immediately	Before treatment	Ibuprofen/acetaminophen Placebo	1.96	0.68	0.0300
	After treatment	Ibuprofen/acetaminophen Placebo	1.83*	0.69	0.0500
After 30 minutes	Before treatment	Ibuprofen/acetaminophen Placebo	0.56	0.37	0.7950
	After treatment	Ibuprofen/acetaminophen Placebo	3.13*	0.37	0.0001
After 6 hours	Before treatment	Ibuprofen/acetaminophen Placebo	0.06	0.23	> 0.9999
	After treatment	Ibuprofen/acetaminophen Placebo	1.70*	0.24	0.0001
After 24 hours	Before treatment	Ibuprofen/acetaminophen Placebo	6.93	0.15	> 0.9999
	After treatment	Ibuprofen/acetaminophen Placebo	0.76	0.15	0.0001

SE: Standard error

\*Statistically significant P-value

In addition, the level of pain during 30 minutes, 6 hours, and 24 hours after treatment was not significantly different between the placebo group and the group taking the main drug; however, in the groups which took drug after treatment, the level of pain was significantly lower in the group receiving the main drug in the mentioned three times (Table 2, Figure 2).

**Figure 2.** Comparison of the level of pain in both ibuprofen and placebo groups according to the prescription time and pain measurement time

## Discussion

This study discussed the relationship between children's pain after tooth extraction by prescribing preoperative/postoperative

acetaminophen and ibuprofen combination and the pain experienced by the child under the four times (immediately, 30 minutes, 6 hours, 24 hours) following extraction.

Since there were no statistically significant differences for the effect of age and gender, these two variables would be minimized between 4 groups. However, there was a statistically significant difference in the severity of pain. According to the findings, when medications were taken before extraction (preoperative medication therapy), the immediate pain was significantly low. Moreover, the effect of induction in children could be demonstrated. In spite of the prescription of placebo before extraction (group 1), lower pain could be seen in comparison with group 2.

Our report results give a new approach in premedication therapy in children. In addition, it was emphasized on the result of other studies that experience of pain could cause irregular dental visit or even dentistry phobia; therefore, if a favorable visit is established without any pain, it will be a great success. Several studies suggested postoperative analgesic administration and more effectiveness of the combination of two analgesics like acetaminophen and ibuprofen in alleviating the pain in comparison to the

prescription of these agents alone.<sup>11,12</sup> Kimiaei Asadi et al. studied 108 patients and found a reduction in the level of pain in intervention group consisting of acetaminophen/ibuprofen and caffeine combination after impacted wisdom tooth surgery.<sup>12</sup>

Moreover, Kharouba et al. compared the analgesic efficacy of acetaminophen, ibuprofen, and placebo by administration of acetaminophen/ibuprofen/placebo alone in order to manage the postoperative pain and reported that two groups for whom ibuprofen/acetaminophen was prescribed prior to extractions were less likely to need an analgesic.<sup>13</sup> In contrast, Abou et al. evaluated the effect of pre-emptive analgesia on efficacy of buccal infiltration during pulpotomy of mandibular primary molars.<sup>14</sup> Their results showed that there was not any significant difference in the success rate between acetaminophen/ibuprofen group and placebo group.

It could be stated that the analgesic effect of ibuprofen is the result of inactivation of COX, an enzyme which turns arachidonic acid (AA) into eicosanoids like prostaglandins (PGs) and leukotrienes.<sup>12</sup> In this regard, Hosseinzadeh Nik et al. compared acetaminophen versus soluble ibuprofen for control of pain and reported that liquefied ibuprofen and acetaminophen showed similar potential in pain alleviating, the form which was prescribed in our study.<sup>12,15,16</sup>

However, the mechanism of acetaminophen is still in question. Although studies demonstrated that CNS would be affected by acetaminophen and the majority of analgesic mechanisms develop in the CNS, acetaminophen showed an inhibitory effect on PGs via COX pathway,<sup>17</sup> which enhances the descending serotonergic inhibitory pain pathways<sup>18</sup> and stimulation of indirect activation of cannabinoid receptor type 1 (CB<sub>1</sub> receptor) and prohibits nitric oxide

pathways by N-methyl-D-aspartate (NMDA) or substance P.<sup>19,20</sup>

However, after oral administration, peak acetaminophen plasma concentration reached by 45-60 minutes. Therefore, the concurrent administration of ibuprofen/acetaminophen could develop an additive or synergic effect on the pain relief.<sup>13,14,21,22</sup> Hence, peak plasma concentration would be useful for managing more comfortable visits with a pleasant experience, in particular, for children.<sup>22</sup>

This study has some limitations such as the flavour of drug that was not pleasant for some children or parents stated that she/he withstood taking drugs every time. Also, some of the parents were out of reach and we called several times for preventing of samples shedding. Moreover, it is recommended that this intervention should be repeated with larger sample sizes with different age. Moreover, systemic status should be evaluated in order to provide pain reduction strategies based on the presented method in the future.

## Conclusion

According to the data obtained from this study, it is found that concurrent prescription of ibuprofen-acetaminophen preoperatively would be more effective on the reduction of pain after tooth extraction. Moreover, postoperative administration of concurrent ibuprofen and acetaminophen was effective in the children. In addition, there are other variables like the induction effect of drugs that can be determined in future studies.

## Conflict of Interests

Authors have no conflict of interest.

## Acknowledgments

This study was supported by Kerman University of Medical Sciences that we thank sincerely.

## References

1. Baygin O, Tuzuner T, Isik B, Kusgoz A, Tanriver M. Comparison of pre-emptive ibuprofen, paracetamol, and placebo administration in reducing post-operative pain in primary tooth extraction. *Int J Paediatr Dent* 2011; 21(4): 306-13.
2. Kashefimehr A, Babaloo A, Ghanizadeh M, Ghasemi SH, Mollazadeh H. Effect of prophylactic administration of Novafen for periodontal surgery on postoperative pain relief. *J Med Life* 2017; 10(2): 127-30.
3. Derry S, Derry CJ, Moore RA. Single dose oral ibuprofen plus oxycodone for acute postoperative pain in adults. *Cochrane Database Syst Rev* 2013; (6): CD010289.
4. Derry S, Wiffen PJ, Moore RA. Single dose oral ibuprofen plus caffeine for acute postoperative pain in adults. *Cochrane Database Syst Rev* 2015; (7): CD011509.
5. Gaskell H, Derry S, Wiffen PJ, Moore RA. Single dose oral ketoprofen or dexketoprofen for acute postoperative pain in adults. *Cochrane Database Syst Rev* 2017; 5: CD007355.
6. Gross EL, Nowak AJ. The dynamics of change. In: Nowak AJ, Christensen JR, Mabry TR, Townsend JA, Wells MH, editors. *Pediatric dentistry*. 6<sup>th</sup> ed. Philadelphia, PA: Elsevier; 2019. p. 181-99.
7. Serna Munoz C, Perez Silva A, Solano F, Castells MaT, Vicente AN, Ortiz Ruiz AJ. Effect of antibiotics and NSAIDs on cyclooxygenase-2 in the enamel mineralization. *Sci Rep* 2018; 8(1): 4132.
8. Hartling L, Ali S, Dryden DM, Chordiya P, Johnson DW, Plint AC, et al. How safe are common analgesics for the treatment of acute pain for children? A Systematic Review. *Pain Res Manag* 2016; 2016: 5346819.
9. Le MS, Ali S, Khadra C, Drendel AL, Trottier ED, Gouin S, et al. Pain management of pediatric musculoskeletal injury in the emergency department: A systematic review. *Pain Res Manag* 2016; 2016: 4809394.
10. Vincent-Viry M, La Du BN, Lepage L, Mikstacki T. Distribution of different phenotypes of paraoxonase in a French population. *Ann Biol Clin (Paris)* 1986; 44(3): 233-8. [In French].
11. Heller GZ, Manuguerra M, Chow R. How to analyze the Visual Analogue Scale: Myths, truths and clinical relevance. *Scand J Pain* 2016; 13: 67-75.
12. Kimiaei Asadi H, Jamalpour MR, Saeedi A. Clinical trial of combination of acetaminophen, ibuprofen and caffeine on pain relief and analgesic use after impacted lower third molar surgery. *Shiraz E-Med J* 2017; 18(7): e13092.
13. Kharouba J, Ratson T, Somri M, Blumer S. Preemptive analgesia by paracetamol, ibuprofen or placebo in pediatric dental care: A randomized controlled study. *J Clin Pediatr Dent* 2019; 43(1): 51-5.
14. Abou El FR, Gowely M, Helmi M, Obeid M. Effects of pre-emptive analgesia on efficacy of buccal infiltration during pulpotomy of mandibular primary molars: a double-blinded randomized controlled trial. *Acta Odontol Scand* 2019; 77(7): 552-8.
15. Demirbas AE, Karakaya M, Bilge S, Canpolat DG, Kutuk N, Alkan A. Does single-dose preemptive intravenous ibuprofen reduce postoperative pain after third molar surgery? A prospective, randomized, double-blind clinical study. *J Oral Maxillofac Surg* 2019; 77(10): 1990-7.
16. Hosseinzadeh Nik T, Shahsavari N, Ghadirian H, Ostad SN. Acetaminophen versus liquefied ibuprofen for control of pain during separation in orthodontic patients: A randomized triple blinded clinical Trial. *Acta Med Iran* 2016; 54(7): 418-21.
17. Bondarsky EE, Domingo AT, Matusa NM, Taylor MB, Thode HC, Singer AJ. Ibuprofen vs acetaminophen vs their combination in the relief of musculoskeletal pain in the ED: A randomized, controlled trial. *Am J Emerg Med* 2013; 31(9): 1357-60.
18. de MM, Chiarugi A, Boner A, Montini G, De' Angelis GL. Working towards an appropriate use of ibuprofen in children: An evidence-based appraisal. *Drugs* 2017; 77(12): 1295-311.
19. Cardile S, Martinelli M, Barabino A, Gandullia P, Oliva S, Di NG, et al. Italian survey on non-steroidal anti-inflammatory drugs and gastrointestinal bleeding in children. *World J Gastroenterol* 2016; 22(5): 1877-83.
20. Berlin H, Vall M, Bergenas E, Ridell K, Brogardh-Roth S, Lager E, et al. Effects and cost-effectiveness of postoperative oral analgesics for additional postoperative pain relief in children and adolescents undergoing dental treatment: Health technology assessment including a systematic review. *PLoS One* 2019; 14(12): e0227027.
21. Gazal G, Al-Samadani KH. Comparison of paracetamol, ibuprofen, and diclofenac potassium for pain relief following dental extractions and deep cavity preparations. *Saudi Med J* 2017; 38(3): 284-91.
22. Nugrahani I, Khalida FN. Green method for act and ibuprofen simultaneous assay in the combination tablet using FTIR. *Int J App Pharm* 2018; 10(3): 77-85.