Comparison of paracetamol, ibuprofen, and diclofenac potassium for pain relief following dental extractions and deep cavity preparations

Giath Gazal, PhD, Khalid H. Al-Samadani, PhD.

ABSTRACT

الهدف : مقارنة تأثير أنواع مختلفة من المسكنات تعُطى قبل خلع وتحضير الحفر السنية العميقة لتخفيف مستوى الألم والإنزعاج الذي يتلو المعالجة السنية .

الدراسة : هذه دراسة سريرية تم تنفيذها في الفترة ما بين May 2016 لغاية November 2015 and. مئة وعشرون مريضاً تم اشراكهم في هذه الدراسة . أربعون تم اعطاؤهم 1g paracetamol و أربعون أعطوا 400mg ibuprofen وأربعون أخرى أعطوا 50mg diclofenac potassium. تقييم مستويات الألم بعد معالجة السنية تمت بعد مضى ساعتين ، أربع ساعات ، ستة ساعات بإستخدام مقياس المحاكاة البصرية وتقييم مستوى الإزعاج تم قبل المعالجة السنية وبعد المعالجة مباشرة .

النتائج :كان هناك نقص ملحوظ في مستويات الألم عند المرضى الذين أعطوا diclofenac potassium مقارنة بالمرضى الذين أعطوا paracetamol أو ibuprofen وذلك بعد أربع ساعات وستة ساعات التي تلمت المعالجة السنية p=0.001 ، p=0.0001 (p=0.04، p=0.005) .

الخلاصة : هذه الدراسة أظهرت أن diclofenac potassium كان أكثر فعالية من paracetamol أو ibuprofen في تخفيف الألم المرافقة لخلع الأسنان وتحضير الحفر السنية العميقة . مستوى الإنزعاج عند المرضى بشكل عام تحسن فور انتهاء المعالجة السنية .

Objectives: To compare the effectiveness of different oral analgesics for relieving pain and distress in adults following the extraction of teeth and deep cavity preparations under local anesthesia.

Methods: This randomized controlled study was conducted between November 2015 and May 2016. One hundred and twenty patients were randomly allocated to 3 groups. Forty patients were in the paracetamol (1 gram) group, 40 in the ibuprofen (400 mg) group and 40 in the diclofenac potassium (50 mg) group. Evaluation of the post extraction and deep cavity preparations pain was made by patients immediately postoperatively, 2, 4 and 6 hours postoperatively on standard 100 mm visual analogue scales (VAS). Furthermore, each patient was observed preoperatively and immediately postoperatively for signs of distress by using a 5 point face scale.

Results: There were significant decreases in mean pain VAS scores for diclofenac potassium group compared to paracetamol and ibuprofen groups at 4 hours postoperatively (one-way Analysis of Variance: p=0.0001, p=0.001) and 6 hours postoperatively (p=0.04, p=0.005). Changes in distress scores from the preoperative score to the postoperative score were made using the paired sample t-test. There were significant decreases in distress scores between the preoperative and postoperative scores (p=0.0001).

Conclusions: Diclofenac potassium was more effective than paracetamol or ibuprofen for reducing postoperative pain associated with tooth extraction and deep cavity preparation. Patients' distress levels can be alleviated by using preemptive analgesics.

Saudi Med J 2017; Vol. 38 (3): 284-291
doi: 10.15537/smj.2017.3.16023

From the Department of Oral and Maxillofacial Surgery (Gazal), and the Department of Restorative Dentistry (Al-Samadani), Taibah University, Al Madinah Al Munawwarah, Kingdom of Saudi Arabia.

Received 3rd August 2016. Accepted 7th December 2016.

Address correspondence and reprint request to: Dr. Giath Gazal, Department of Oral and Maxillofacial Surgery, College of Dentistry, Taibah University, Al Madinah Al Munawwarah, Kingdom of Saudi Arabia. E-mail: gazal73@yahoo.co.uk
ORCID ID: orcid.org/0000-0003-1434-0703

It was well documented that the postoperative pain associated with surgical tooth extractions can range in intensity from moderate to severe during the first 24 hours.[1-4] Pain intensity reaches its maximum peak between 6 and 8 hours when a conventional local anesthetic is used.[5] Surgical dental extraction and deep

cavity preparation are usually associated with a trauma to both the soft and hard tissues. This trauma is often accompanied with pain and swelling.[6,7] Nonsteroidal anti-inflammatory drugs are one of the treatment options to be used as pain relief for surgical teeth extraction and cavities preprations.[4,8] By administering the pre-operative analgesics, the postoperative pain intensity can be subsided and delayed as a result of the reduction in the amount of pain triggers (prostaglandins) discharged into the site of the injuries.[9-11] Accumulation of prostaglandins released from the injured tissues increased by the time leading to the amplification of the pain intensity.[5,9-11]

Diclofenac works by blocking the chemical substances called cyclo-oxygenase (COX) enzymes. These enzymes trigger the information of prostaglandins in the body. Sites of injury or harm are considered the normal place for production of the prostaglandins, which cause pain and inflammation. By obstructing the influence of COX enzymes, a smaller amount of prostaglandins are formed and as a consequence less pain and inflammation are felt.[12]

There are 2 formulas of diclofenac in the market; diclofenac sodium and diclofenac potassium. The absorption of diclofenac potassium to patient's blood stream is faster than diclofenac sodium.[7] As a rule, the earlier the analgesic absorbed the quicker the onset of action will be. So, diclofenac potassium is a fast acting analgesic and useful for the patients who are required immediate relief from inflammatory pain.[12]

A study by Ferraiolo and Veitz-Keenan[13] was conducted to compare the effectiveness of different types of analgesics following third molar extractions. Data regarding the level of pain relief and the need for additional analgesics were collected at 6 hours following the surgery. The outcome of this study revealed that the ibuprofen was more effective than paracetamol at doses of 200 mg to 512 mg and 600 mg to 1000 mg, respectively. Krishnan et al[14] carried out a study on 40 healthy patients aged from 18-50 years with deeply carious, lower molars teeth indicated for extraction under local anesthesia (LA). Subjects were divided into 2 groups. First group received transdermal diclofenac patches whilst second group received oral diclofenac for control of post-extraction pain. The pilot study outcome revealed that the effectiveness of transdermal diclofenac was similar to oral diclofenac in reducing post-extraction pain. Bauer et al[15] study concluded that the preemptive analgesia with only ibuprofen is insufficient to prevent pain in third molar surgery. However, the combination of ibuprofen with dexamethasone was more effective in inhibiting central sensitization.

The aim of this study was to investigate the effectiveness of 50 mg diclofenac potassium compared with 400 mg ibuprofen, and 1 g paracetamol, on post extraction and deep cavity preparation pain in a double-blind randomized controlled trial. The null hypothesis was oral administrations of diclofenac potassium, ibuprofen and paracetamol are equally effective in reducing post-surgical teeth extraction and deep cavity preparation pain.

Methods. This randomized controlled study was conducted between November 2015 and May 2016. The design and performance of this clinical study was carried out in accordance with the principles of Helsinki Declaration. Taibah Dental School Research Ethics Committee had approved the study. Written consent had been obtained from 125 patients who attended the Oral and Maxillofacial Department. Inclusion criteria for enrolling patients in this study were American Society of Anesthesiologists (ASA) class I or II patients who were healthy, or with mild systemic disease and had no risk from administration of LA with adrenaline; aged 16-70 years; presenting for elective one simple tooth extraction or one deep cavity restoration with the maximum of 2 cartridges of LA. Exclusion criteria involved patients who were sensitive to ibuprofen, declofenac potassium, or paracetamol; having surgical or multiple teeth extractions; having teeth with reversible pulpitis; having history of active peptic ulcer, attack of asthma, angioedema, aurticaria or acute rhinitis and acute porphyria. Slips of paper were labeled with 1g paracetamol (control group), 400 mg ibuprofen, or 50 mg emifenac using computer generated random number and placed in sequentially numbered envelops. The secretary of the clinic who was not associated with the study did this work. When all the screening procedures had completed and the eligibility of the patient had confirmed; the patient was allocated the next numbered envelope. This was opened The dental assistant not associated with the study opened the envelope and named it analgesic on the slip of the paper and handed it over to the patient. The slip was placed back into the envelope, and put back into the patient's records. To ensure that both the patients and investigator were blinded to the study group assignment.

Disclosure. Authors have no conflict of interests, and the work was not supported or funded by any drug company.

Patients were pre-medicated with paracetamol (1 g), ibuprofen (400 mg) or diclofenac potassium (50 mg) at least 15 minutes before administering the local anaesthetic for extractions or deep cavity preparations (**Figure 1**). The paracetamol, diclofenac potassium and ibuprofen doses used for this study were chosen according to manufacturer's recommendation and set at such a level as to keep the minimum side effects.[16-19] Local anesthesia (1.8 ml mepivacaine 2% with epinephrine 1:100,000) was administered to the patient after sitting on dental chair. For upper teeth, patients were given buccal infiltrations and for lower teeth, either buccal infiltrations or inferior alveolar nerve block (IANB). Standard deep cavity preparation diamond bur is used and for extraction elevators and dental forceps were employed. The researcher was just an observer. Each patient was observed for signs of distress and these were recorded using Faces Distress Scale. This scale was developed by the first author (Giath Gazal) who evolved the Modified Smiley Faces Scale.[20] **Figure 2** shows the evaluation of distress, which was measured immediately after pre-operative, and postoperative extraction or deep cavity preparation. The distress scores were rated as; score 0 representing "no distress" to score 4 representing "very severe distress" whilst the scores in between representing mild, moderate, and severe distress. Pain assessment was carried out postoperatively, 2 hours postoperatively, 4 hours postoperatively and 6 hours postoperatively by independent assessor. Pain scores were recorded by asking the patients directly after each treatment on standard 100 mm visual analogue scales (VAS), tagged at the endpoints with "no pain" (0 mm) and "unbearable pain" (100 mm). However, pain assessment after 2, 4, and 6 hours postoperatively, were carried out through the phone call. Any extra analgesic was reported during the first 6 hours following the extraction. The pain and distress observation was measured by a trained and completely independent of the whole process.

Statistical analysis. Sample size calculation of this study was based on the study by Gazal et al.[21] Forty patients in each group would have 90% power to detect a difference in means of 0.90 for both pain and distress scores. A total of 130 patients were recruited for this study. Statistical analysis was performed using a software package (SPSS; version 20, SPSS Inc., Chicago, IL). These statistical tests were independent sample t-test, one-way Analysis of Variance (ANOVA), and paired sample t-test.

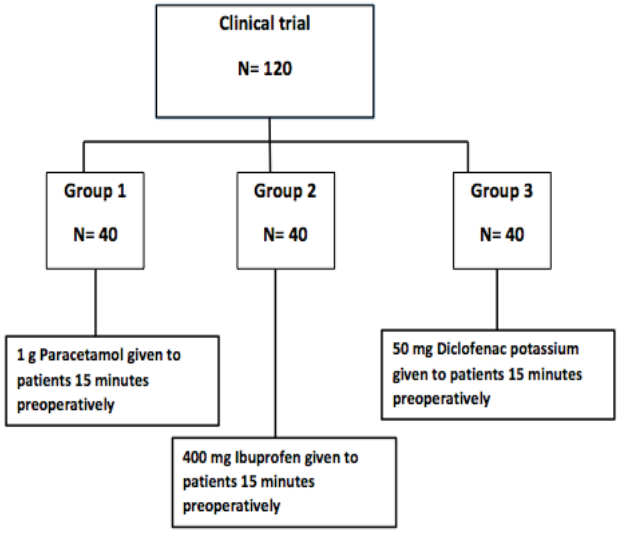

Figure 1 - Description of 120 patients with 40 in the normal dose of 1 gram of paracetamol (control group), 40 in the normal dose of 400 mg of ibuprofen, and 40 in the normal dose of 50 mg of diclofenac potassium.

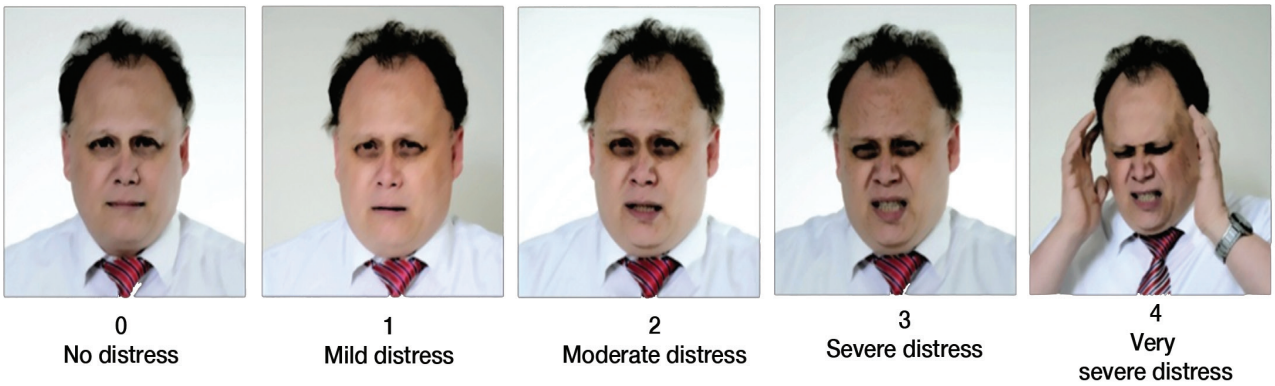

Figure 2 - Evaluation of distress measured immediately after pre-operative, and postoperative extraction or deep cavity preparation using the Giath distress scale.

Results. Of the 130 recruited, 10 patients were excluded by the dental surgeon as they were considered unsuitable for including in this study (5 had LA overdoses, 2 fainted after local anesthetic injection, 2 of their teeth extraction was carried out surgically and one refused extraction after local anesthetic injection). The final sample size therefore comprised 120 patients with 40 in the normal dose of 1 gram of paracetamol (control group), 40 in the normal dose of 400 mg of ibuprofen, and 40 in the normal dose of 50 mg of diclofenac potassium (**Figure 1**). It was considered appropriate to use parametric tests to analyze the data due to the distribution of the data and the large numbers in each group. The mean number of teeth extracted per patient was 1 and the mean age was 40.7 years. Immediately postoperatively, patients were still under local anesthetic effects for that reason their pain intensity was very mild or absent. There were no statistically significant differences between the mean pain scores for the paracetamol, ibuprofen, and diclofenac potassium groups post-operatively (p-values from one-way ANOVA: 1.00, 1.00, and 1.00). For both paracetamol and diclofenac potassium groups at 2 hours postoperatively, there were no significant decreases in mean pain scores compared with the ibuprofen group (p-values from one-way ANOVA: 1.000, 0.06, **Table 1**). However, for diclofenac potassium group there were statistically significant decreases in the mean pain scores at 2 hours postoperative comparing with the paracetamol (control group) (p-values from one-way ANOVA: 0.008, **Table 1**). At 4 and 6 hours postoperatively, it was found that patients in the diclofenac potassium group recorded lower pain scores than patients in the paracetamol and ibuprofen groups. These differences were statistically significant (**Table 1**). However, there were no significant differences between the mean pain scores for the paracetamol and ibuprofen groups 4 and 6 hours post-operatively (p-values from one-way ANOVA: 1.00, and 1.00, **Table 1**). Clinically, all groups showed reduction in maximum and medium pain intensity scores and pain frequency. However, the extent of reduction was greater in the diclofenac potassium group.

The number of patients who requested rescue analgesia was 32 (n=14 [35%] in the paracetamol group, n=14 [35%]) in the ibuprofen group, and 4 [10%] in the diclofenac potassium group, **Table 2**).

Table 1 - Comparison between mean pain scores for the paracetamol, ibuprofen, and diclofenac potassium groups 2, 4 and 6 hours post operatively.

Study treatments	Number of patients (n=120)	Mean ± SD	f-value (df =118)	P-value
2 hours postoperative			5.12	
Paracetamol	40	15.3 ± 18.3		1.00
Ibuprofen	40	12.8 ± 19.0		
Paracetamol	40	15.3 ± 18.3		0.008
Diclofenac potassium	40	4.3 ± 9.3		
Ibuprofen	40	12.8 ± 19.0		0.06
Diclofenac potassium	40	4.3 ± 9.3		
4 hours postoperative			10.80	
Paracetamol	40	26.3 ± 22.2		1.00
Ibuprofen	40	24.5 ± 22.3		
Paracetamol	40	26.3 ± 22.2		0.0001
Diclofenac potassium	40	7.8 ± 13.1		
Ibuprofen	40	24.5 ± 22.3		0.001
Diclofenac potassium	40	7.8 ± 13.1		
6 hours postoperative			5.43	
Paracetamol	40	24.1 ± 24.83		1.00
Ibuprofen	40	27.6 ± 26.51		
Paracetamol	40	24.1 ± 24.83		0.04
Diclofenac potassium	40	11.5 ± 14.06		
Ibuprofen	40	27.6 ± 26.51		0.005
Diclofenac potassium	40	11.5 ± 14.06		

df - degrees of freedom

Table 2 - A summary of the number of patients who requested rescue analgesics in paracetamol, ibuprofen, and diclofenac potassium groups postoperatively.

Treatment group	Number of patients with rescue analgesic				Total number of patients (%)
	0 hour postoperatively	2 hour postoperatively	4 hour postoperatively	6 hour postoperatively	
Diclofenac potassium	0	0	1 (2.5)	3 (7.5)	4 (10)
Ibuprofen	0	2 (5.0)	4 (10.0)	8 (20)	14 (35)
Paracetamol	0	1 (2.5)	5 (12.5)	8 (20)	14 (35)
Total					**32 (100)**

Table 3 - Comparisons between mean distress scores for the patients in the preoperative and postoperative groups.

Groups	Number of patients	Mean±SD	Paired t- value (df=199)	*P*-value
Preoperative distress scores	120	0.96 ± 0.97	5.301	0.0001
Postoperative distress scores	120	0.41 ± 0.77		

For all the groups, ibuprofen, diclofenac potassium and control [paracetamol] changes in distress scores from the preoperative score to the post-operative score were made using the paired sample t-test. There were significant decreases in distress scores between the pre-operative and post-operative scores (p=0.0001, **Table 3**). Patients' distress levels eased off automatically once the dental treatment has completely finished.

Discussion. Clinically, the findings of this study revealed that all the 3 preemptive analgesics (paracetamol at dosage of 1 g, ibuprofen at dosage of 400 mg and diclofenac potassium at dosage of 50 mg) reduced the post extraction and deep cavity preparation pain intensity and the need for rescue analgesic. The mean pain scores recorded by patients in all the groups on standard 100 mm visual analogue scales (VAS) were respectively (10.8) at 2 hours postoperatively, (19.5) at 4 hours postoperatively and (21.2) at 6 hours postoperatively. However, the result of this study also showed that the diclofenac potassium was statistically stronger than paracetamol and ibuprofen in terms of reduction of pain intensity and frequency. Taking a single dose of 50 mg diclofenac potassium preoperatively is sufficient to achieve reliable pain control following exodontia and deep cavities preparations. In the present study, there were only 4 (10%) patients in diclofenac potassium group who requested additional analgesics postoperatively. In contrast, there were 14 (35%) patients with paracetamol and 14 (35%) patients with ibuprofen groups who required supplementary rescue analgesia.

Interestingly, preemptive analgesics resulted in increased time to first rescue analgesic request. Out of 4 patients who request rescue analgesics in the diclofenac potassium group, 3 were at 6 hours postoperatively. However, there were 16 patients in both paracetamol and ibuprofen groups who asked for additional analgesics at 6 hours postoperatively.

There are 2 possible explanations for recommending the use of diclofenac potassium over both the paracetamol and ibuprofen regimes. First, the diclofenac potassium (dissolvable tablets of Emifenac 50 mg) used in this study has rapid onset of action due to its rate of absorption into the body was fast.[2,3,12] Early pain relief and function after teeth extraction and deep cavity preparations were achieved. Derry et al's[22] study compare the effectiveness of 2 different formulations of a single dose of oral diclofenac used for acute postoperative pain management in adults. The findings of this study revealed that oral diclofenac potassium was significantly more effective than diclofenac sodium for relief moderate to severe postoperative pain. The number of patients who experienced 50% pain relief over 4-6 hours postoperatively in the diclofenac potassium group was more than those having the diclofenac sodium. A double blind placebo controlled trial conducted by Yue et al[23] to investigate the efficacy and speed of action of different strengths of normal and fast-dissolving paracetamol on postsurgical dental pain. The outcome of this study demonstrated that the fast dissolving paracetamol was significantly more effective than placebo. Patients in the fast dissolving paracetamol 1000 mg group reported less postoperative pain and increased time to first rescue analgesics than patients in either the normal dose of paracetamol 500 mg or fast dissolving paracetamol 500 mg tablets groups. The

current study result is similar to the findings from the study by Derry et al,[24] who reported that the clinical advantages for using fast-dissolving and absorbed diclofenac potassium is including better pain relief than those that are absorbed slowly. They concluded that diclofenac potassium at 50 mg single dose is considered as a good pain relief for moderate postoperative pain in adults. A Cochrane overview was conducted by Moore et al[25] to summarize the efficacy of a single dose of oral analgesics for postoperative acute pain relief in adults. Thirty-nine Cochrane reviews of randomized trials have examined the analgesic efficacy of individual drug interventions in acute postoperative pain. The results of this Cochrane study confirmed that the use of single dose of analgesics is sufficient to achieve good and long lasting pain relief at relatively low doses. This can be achieved by using fast acting formulations and fixed dose combinations of analgesics.

The second possible account for the superiority of diclofenac potassium over ibuprofen and paracetamol could be as a result of the slight differences in their mechanism of actions. Both diclofenac potassium and ibuprofen have similarity in the mode of action because they exert their efficacy by blocking the effect of COX enzymes. Less prostaglandins are produced.[12,26] Diclofenac potassium is derivative from acetic acid and ibuprofen is derivative from propionic acid. Peripherally, both diclofenac potassium and ibuprofen Inhibit the construction of the prostaglandin particularly PGE2 at peripheral pain receptor.[27,28] The PGE2 enhances the pain receptor's sensitivity to algesic substances such as bradykinin and substance P.[29] Centrally, prostaglandins act in the spinal cord and higher centers to promote the transmission of pain signals to the brain.[30] A study by Silva et al,[31] was carried out to investigate the effectiveness of ibuprofen and etodolac for controlling pain, swelling, and trismus following surgical removal of the lower third molars. The result of this study reported that the patients in the etodolac group recorded lower intensity of postoperative pain, swelling, and trismus than those having oral dose of ibuprofen. The great ability of Etodolac bound to plasma proteins (99%) justifies its potency over the ibuprofen.[32] This study demonstrated the effectiveness of diclofenac potassium over ibuprofen which could be as a result of the differences in the chemical properties rather than the mode of action. Diclofenac potassium 50 mg tablets used in this study was faster in dissolving and absorbing than ibuprofen 400 mg tablets. So, a rapid onset and longer duration of action was achieved by using diclofenac potassium.

Patients in diclofenac potassium group had less pain at 4 hours and 6 hours postoperatively, and required less rescue analgesic than patients in the paracetamol group. Differences between diclofenac potassium and paracetamol in reducing postoperative pain intensity due to their mode of actions. There is considerable evidence that the antipyretic effect of paracetamol is centrally by inhibiting of prostaglandin E synthesis within the hypothalamus.[33] However, the analgesic effect of paracetamol is peripherally by blocking impulse generation within the bradykinin sensitive chemoreceptors.[34,35] The findings of this study are consistent with the results of another 2 studies. El Batawi[36] administered one hour preoperatively a paracetamol and diclofenac sodium for children with traumatic dental treatments under general anesthesia. El Batawi's[36] reported that the diclofenac sodium was more effective than paracetamol for pain relief postoperatively. Another study carried out by Eslampour et al,[37] who compared the effectiveness of 3 analgesic drugs, which were administrated preoperatively for reducing postoperative pain associated with photorefractive keratectomy. Their findings revealed that the patients in diclofenac group reported less pain than patients in paracetamol and ibuprofen groups.

These results also exposed that patients who showed greater levels of distress preoperatively, showed significantly lower levels of distress after the dental extraction and deep cavity preparations. There was a very interesting point to show in this study, that distress scores were influenced by the lower levels of pain intensity which the patients recorded at the postoperative stage of the assessment. Literatures have provided evidences that the level of patient's distress is determined as a combination of 2 factors: pain and anxiety.[38-41] In this study by using a single dose of pre-emptive analgesics, postoperative pain intensity was eased off and as a consequence a reduction in patient's level of distress was achieved.

This study has highlighted a new area for further research. These include investigating if there are analgesics effects of paracetamol, ibuprofen, and diclofenac on the level of cortisone and adrenaline in the patients who showed high and lower scores of pain and distress. Do analgesics exert effect on the level of cortisone and adrenaline in the blood?

In conclusion, this study has shown that diclofenac potassium was more effective than paracetamol or ibuprofen for postoperative analgesia in adults who are having teeth extracted and deep cavities prepared under local anesthesia. Patients' distress levels can be alleviated by using preemptive analgesics.

Preemptive analgesics play an important role in reducing postoperative pain and distress associated

with painful dental procedures under LA. Using diclofenac potassium could be of great help to patients who are in moderate to severe pain. So it is strongly recommended for all dental surgeons and practitioners in the Saudi Arabia to administer diclofenac potassium preoperatively for their patients with traumatic dental treatments. In this study, there were no female patients participation because in Taibah University College of Dentistry, only male patients are treated. Therefore, the sample size with male and female patients might have more valid conclusion.

Acknowledgment. *We would like to thank the dentists, dental assistants, receptionists, and the Oral and Maxillofacial and Restorative Units staff involved in the local anesthetic extraction and cavities preparation services in Taibah College of Dentistry, Al Madinah Al Munawwarah, Kingdom of Saudi Arabia. for their help and assistance.*

References

1. Rana M, Gellrich N, Ghassemi A, Gerressen M, Riediger D, Modabber A. Three-dimensional evaluation of postoperative swelling after third molar surgery using 2 different cooling therapy methods: a randomized observer-blind prospective study. ***J Oral Maxillofac Surg*** 2011; 69: 2092-2098.
2. Majid OW, Al-Mashhadani BA. Perioperative bromelain reduces pain and swelling and improves quality of life measures after mandibular third molar surgery: a randomized, double-blind, placebo-controlled clinical trial. ***J Oral Maxillofac Surg*** 2014; 72: 1043-1048.
3. Norholt SE, Hallmer F, Hartlev J, Pallesen L, Blomlof J, Hansen EJ, et al. Analgesic efficacy with rapidly absorbed ibuprofen sodium dihydrate in postsurgical dental pain: results from the randomized QUIKK trial. ***Int J Clin Pharmacol Ther*** 2011; 49: 722-729.
4. Al-Sukhun J, Al-Sukhun S, Penttila H, Ashammakhi N, Al-Sukhun R. Preemptive analgesic effect of low doses of celecoxib is superior to low doses of traditional nonsteroidal anti-inflammatory drugs. ***J Craniofac Surg*** 2012; 23: 526-529.
5. Orozco-Solis M, Garcia-Avalos Y, Pichardo-Ramirez C, Tobias-Azua F, Zapata-Morales JR, Aragon-Martinez OH, et al. Single dose of diclofenac or meloxicam for control of pain, facial swelling, and trismus in oral surgery. ***Med Oral Patol Oral Cir Bucal*** 2016; 21: e127-e134.
6. Gazal G, Fareed WM, Zafar MS, Al-Samadani KH. Pain and anxiety management for pediatric dental procedures using various combinations of sedative drugs: A review. ***Saudi Pharml J*** 2016; 24: 379-385.
7. Velasquez G, Santa Cruz L, Espinoza M. Ketoprofen is more effective than diclofenac after oral surgery when used as a preemptive analgesic: a pilot study. ***J Oral Facial Pain Headache*** 2014; 28: 153-158.
8. De Menezes S, Cury P. Efficacy of nimesulide versus meloxicam in the control of pain, swelling and trismus following extraction of impacted lower third molar. ***Int J Oral Maxillofac Surg*** 2010; 39: 580-584.
9. Grösch S, Niederberger E, Geisslinger G. Investigational drugs targeting the prostaglandin E2 signaling pathway for the treatment of inflammatory pain. ***Expert Opin Investig Drugs*** 2016; 20: 1-11.
10. Huang J, Wu J, Yang HZ, Hong Y. [Inhibition of prostaglandins synthesis in the inflamed site results in opioid-mediated hypoalgesia in rats]. ***Sheng Li Xue Bao*** 2016; 68: 241-248.
11. Grga D, Dzeletović B, Damjanov M, Hajduković-Dragojlović L. Prostaglandin E2 in apical tissue fluid and postoperative pain in intact and teeth with large restorations in two endodontic treatment visits. ***Srp Arh Celok Lek*** 2013; 141: 17-21.
12. Gupta R. Spinal Cord Stimulation. In: Pain Management: Essential Topics for Examinations. Berlin (Heidelberg): Springer Berlin Heidelberg; 2014. p. 121-122.
13. Ferraiolo DM, Veitz-Keenan A. Ibuprofen is superior to paracetamol for pain relief following third molar removal. ***Evidence-Based Dentistry*** 2014; 15: 106-107.
14. Krishnan S, Sharma P, Sharma R, Kumar S, Verma M, Chaudhary Z. Transdermal diclofenac patches for control of post-extraction pain. Pilot randomized controlled double-blind study. ***Oral Maxillofac Surg*** 2015; 19: 5-12.
15. Bauer HC, Duarte FL, Horliana AC, Tortamano IP, Perez FE, Simone JL, et al. Assessment of preemptive analgesia with ibuprofen coadministered or not with dexamethasone in third molar surgery: a randomized double-blind controlled clinical trial. ***Oral Maxillofac Surg*** 2013; 17: 165-171.
16. Drwal-Klein LA, Phelps SJ. Antipyretic therapy in the febrile child. ***Clin Pharm*** 1992; 11: 1005-1021.
17. Murphy KA. Acetaminophen and ibuprofen: fever control and overdose. ***Pediatr Nurs*** 1992; 18: 428-31, 433.
18. Anker AL, Smilkstein MJ. Acetaminophen. Concepts and controversies. ***Emerg Med Clin North Am*** 1994; 12: 335-349.
19. Food and Drug Administration. Medication guide for non-steroidal anti-inflammatory drugs (NSAIDs). [cited: 2011). Available from URL: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020938s020,021530s008MedGuide.pdf
20. Gazal G, Mackie IC. Distress related to dental extraction for children under general anaesthesia and their parents. ***Eur J Paediatr Dent*** 2007; 8: 7-12.
21. Gazal G, Mackie IC. A comparison of paracetamol, ibuprofen or their combination for pain relief following extractions in children under general anaesthesia: a randomized controlled trial. ***Int J Paediatric Dent*** 2007; 17: 169-177.
22. Derry P, Derry S, Moore RA, McQuay HJ. Single dose oral diclofenac for acute postoperative pain in adults. ***Cochrane Database of Systematic Reviews*** 2009; Issue 2: CD004768.
23. Yue Y, Collaku A, Brown J, Buchanan WL, Reed K, Cooper SA, et al. Efficacy and speed of onset of pain relief of fast-dissolving paracetamol on postsurgical dental pain: two randomized, single-dose, double-blind, placebo-controlled clinical studies. ***Clin Ther*** 2013; 35: 1306-1320.
24. Derry S, Wiffen PJ, Moore RA. Single dose oral diclofenac for acute postoperative pain in adults. Cochrane Database Syst Rev 2015; 7: CD004768.
25. Moore RA, Derry S, Aldington D, Wiffen PJ. Single dose oral analgesics for acute postoperative pain in adults - an overview of Cochrane reviews. ***Cochrane Database Syst Rev*** 2015; (9): CD008659.
26. Landry KA, Sun P, Huang C, Boyer TH. Ion-exchange selectivity of diclofenac, ibuprofen, ketoprofen, and naproxen in ureolyzed human urine. ***Water Res*** 2015; 68: 510-521.

27. Alaa A, Abou-Zeid LA, ElTahir KEH, Ayyad RR, Magda A, El-Azab AS. Synthesis, anti-inflammatory, analgesic, COX-1/2 inhibitory activities and molecular docking studies of substituted 2-mercapto-4 (3H)-quinazolinones. ***Eur J Med Chem*** 2016; 121: 410-421.
28. Kitaya K, Tada Y, Hayashi T, Taguchi S, Funabiki M, Iwaki Y, et al. Diclofenac suppository pretreatment in prevention of vasovagal reflex-associated complications for infertile women undergoing local endometrial injury. ***Clin Exp Obstet Gynecol*** 2015; 42: 723-724.
29. Orak MM, Ak D, Midi A, Lacin B, Purisa S, Bulut G. Comparison of the effects of chronic intra-articular administration of tenoxicam, diclofenac, and methylprednisolone in healthy rats. ***Acta Orthop Traumatol Turc*** 2015; 49: 438-446.
30. Haroon N, Ather MH, Khan S, Kumar P, Salam B. Diclofenac Suppository as a Preemptive Analgesia in Ultrasound-guided Biopsy of Prostate: Randomized Controlled Trial. ***Urology*** 2015; 86: 682-685.
31. Silva de Oliveira JC, Grossi de Oliveira GA, Bassi AP. Comparative assessment of the effect of ibuprofen and etodolac on edema, trismus, and pain in lower third molar surgery: A randomized clinical trial. ***J Oral Maxillofac Surg*** 2016; 74: 1524-1530.
32. Miwa Y, Hamamoto H, Ishida T. Lidocaine self-sacrificially improves the skin permeation of the acidic and poorly water-soluble drug etodolac via its transformation into an ionic liquid. ***European Journal of Pharmaceutics and Biopharmaceutics*** 2016; 102: 92-100.
33. Raffaeli G, Orenti A, Gambino M, Peves Rios W, Bosis S, Bianchini S, et al. Fever and pain management in childhood: Healthcare providers' and parents' adherence to current recommendations. ***Int J Environ Res Public Health*** 2016; 13: 499.
34. Schwartz JI, Musser BJ, Tanaka WK, Taggart WV, Mehta A, Gottesdiener KM, et al. Inhibition of prostacyclin and thromboxane biosynthesis in healthy volunteers by single and multiple doses of acetaminophen and indomethacin. ***Clin Pharm Drug Develop*** 2015; 4: 337-345.
35. McNicol ED, Ferguson MC, Haroutounian S, Carr DB, Schumann R. Single dose intravenous paracetamol or intravenous propacetamol for postoperative pain. ***Cochrane Database Syst Rev*** 2016; (5): CD007126.
36. El Batawi H. Effect of intraoperative analgesia on children's pain perception during recovery after painful dental procedures performed under general anaesthesia. ***European Archives of Paediatric Dentistry*** 2015; 16: 35-41.
37. Eslampour A, Malaekeh-Nikouei B, Abrishami M, Bayani R. Efficacy of extended-release oral diclofenac in postoperative pain management after photorefractive keratectomy. ***J Ocular Pharm Therapeut*** 2013; 29: 670-673.
38. Al-Samadani KH, Gazal G. Effectiveness of benzocaine in reducing deep cavity restoration and post-extraction stress in dental patients. ***Saudi Med J*** 2015; 36: 1342-1347.
39. Gazal G, Tola AW, Fareed WM, Alnazzawi AA, Zafar MS. A randomized control trial comparing the visual and verbal communication methods for reducing fear and anxiety during tooth extraction. ***Saudi Dent J*** 2016; 28: 80-85.
40. Gazal G, Fareed W, Zafar M. Effectiveness of gaseous and intravenous inductions on children's anxiety and distress during extraction of teeth under general anesthesia. ***Saudi J Anaesth*** 2015; 9: 33-36.
41. Giath G, Anas A, Wamiq F, Albraa A, Esam O, Mohammad N. Clinical anxiety among junior dental students: Trainers and students. ***Saudi J Oral Dent Res*** 2016; 1: 108-112.

Illustrations, Figures, Photographs

All figures or photographs should be submitted in a high resolution (minimum 300 DPI) electronic version saved in jpeg or tiff format. Original hard copies of all figures may be requested when necessary. Photographs will be accepted at the discretion of the Editorial Board. All lettering, arrows, or other artwork must be done by an artist or draftsman. If arrows are used please ensure they appear in a different color to the background color, preferably black with a white border, or white with a black border. If arrows distinguish different items on the figure then different arrow styles should be used ie. long, short, wide, narrow. Written informed consent for publication must accompany any photograph in which the subject can be identified. Written copyright permission, from the publishers, must accompany any illustration that has been previously published.