RESEARCH ARTICLE

F.U. Med.J.Health.Sci.
2021; 35 (1): 62 - 67
http://www.fusabil.org

The Effect of Preemptive Intravenous Ibuprofen on Postoperative Opioid Consumption in Patients for Double Jaw Surgery: A Randomized Double-blind Placebo Controlled Study

İrem ATES [1, a]
Ümit ERTAŞ [2, b]
Muhammed Enes AYDIN [1, c]
Ahmet Murat YAYIK [1, d]
Zehra BEDİR [3, e]
Sara SALCAN [4, f]

[1] Atatürk University, Faculty of Medicine, Anesthesiology and Reanimation Department, Erzurum, TURKIYE

[2] Atatürk University, Faculty of Dentistry, Department of Oral and Maxillofacial Surgery, Erzurum, TURKIYE

[3] Erzurum City Hospital, Department of Anesthesiology and Reanimation, Erzurum, TURKIYE

[4] Binali Yıldırım University, Faculty of Medicine, Public Health Care Department, Erzincan, TURKIYE

[a] ORCİD: 0000-0001-9867-5011
[b] ORCİD: 0000-0003-4043-0868
[c] ORCİD: 0000-0001-8491-6566
[d] ORCİD: 0000-0002-2783-7041
[e] ORCİD: 0000-0001-7347-6649
[f] ORCİD: 0000-0001-5049-1838

Received : 19.01.2021
Accepted : 12.03.2021

Correspondence
Yazışma Adresi

İrem ATES
Atatürk University, Faculty of Medicine, Anesthesiology and Reanimation Department, Erzurum, TURKIYE

driremates@hotmail.com

Objective: The effect of intravenous ibuprofen preemptively administered in pain management after double jaw surgery are limited.The purpose of the present study was to investigate the effects of preemptive intravenous ibuprofen on postoperative analgesia and opioid consumption in patients who undergo double jaw surgery (DJS).

Materials and Methods: After ethical committee approval, 48 patients, American Society of Anesthesiologist (ASA) I-II, scheduled for DJS were randomly assigned into_two groups. The ibuprofen group (n=24) received 800 mg IV ibuprofen in 100 mL saline, while the control group (n=24) received 100 mL saline, thirty minutes before the surgery. All patients were administered 1.000 mg iv paracetamol 30 minutes before the surgery ended and was repeated every 6 hours. Postoperative analgesia was performed with patient controlled analgesia (PCA). The pain of the groups was evaluated with Visual Analog Scale (VAS), and the total opioid consumption was recorded at the end of 24 hours.

Results: VAS scores of the patients were compared with the Control Group, the VAS scores were significantly lower in the ibuprofen group at 1st, 2nd, 4th, 8th, 12th and 24th hours (P<0.05). The total opioid consumption was found to be statistically higher in the control group than in the ibuprofen group (326.04 µcg and 163.95 µcg, P<0.05). The need for additional analgesics was more in the control group than in the Ibuprofen Group (14/24, 6/24). Nausea and vomiting were statistically more in the control group (P<0.05). No significant differences were detected between the groups in terms of hemorrhage (P>0.05).

Conclusion: Preemptive IV Ibuprofen may be one of the alternative analgesic drugs which might be used in DJS.

Key Words: *Double Jaw Surgery, Ibuprofen, preemptive analgesia, postoperative analgesia*

Çift Çene Cerrahisi Yapılan Hastalarda Preemptif Intravenöz İbuprofenin Postoperatif Opioid Tüketimine Etkisi: Randomize Çift Kör Plasebo Kontrollü Çalışma

Amaç: Preemptif uygulanan intravenöz ibuprofenin çift çene cerrahisi sonrası ağrı yönetimindeki rolü ile ilgili bilgi kısıtlıdır. Bu çalışmanın amacı çift çene cerrahisi (ÇÇC) geçiren hastalarda preemptif intravenöz ibuprofenin postoperatif analjezi ve opioid tüketimine etkisini araştırmaktır.

Gereç ve Yöntem: Etik kurul onayı alındıktan sonra, ÇÇC planlanan, Amerikan Anesteziyoloji Derneği (ASA) I-II, 48 hasta, rastgele iki gruba ayrıldı. Ameliyattan otuz dakika önce ibuprofen grubu (n=24) 100 mL salin içinde 800 mg IV ibuprofen alırken, kontrol grubu (n=24) 100 mL salin aldı. Tüm hastalar operasyon bitiminden yarım saat önce 1.000 mg parasetamol aldı ve her 6 saatte bir tekrarlandı. Postoperatif analjezi hasta kontrollü analjezi (HKA) ile sağlandı. Her iki grubun ağrısı Vizüel Analog Skala (VAS) ile değerlendirildi ve 24 saat sonunda toplam opioid tüketimleri kaydedildi.

Bulgular: VAS skorları kontrol grubuyla karşılaştırıldığında ibuprofen grubunda 1., 2., 4., 8., 12. ve 24. saatlerde istatistiksel olarak düşüktür (P<0.05). 24 saat sonundaki toplam opioid tüketimi kontrol grubunda ibuprofen grubuna göre (326.04±209.7 µcg ve 163.95±122.7 µcg, P=0.002) istatistiksel olarak daha fazla bulunmuştur. Ek analjezik ihtiyacı kontrol grubunda ibuprofen grubuna göre daha fazladır (14/24, 6/24). Bulantı kusma kontrol grubunda istatistiksel olarak daha çoktur (P<0.05). Hemoraji açısından gruplar arasında anlamlı bir fark bulunmamaktadır (P>0.05).

Sonuç: Preemptif IV İbuprofen ÇÇC'de kullanılabilecek alternatif analjezik ilaçlardan biri olabilir.

Anahtar Kelimeler: *Çift çene cerrahisi, ibuprofen, preemptif analjezi, postoperatif analjezi*

Introduction

Double jaw surgery is an orthognatic surgery performed to correct the problems involving the maxilla and the mandibula surgically. The target of this surgery is to correct the tooth sequence, in other words, the occlusion, to attract the jaw bones and other soft-hard tissues to their ideal anatomical places, and to provide facial aesthetics. This comprehensive, prolonged, and difficult orthognatic surgery might cause postoperative severe pain. Postoperative inadequate pain control might both physically and physiologically lead to complications, such as hypoxemia, atelectasis, pneumonia, deep vein thrombosis, pulmonary embolism, psychological traumas, prolonged intestinal

distension, urinary retention, myocardial ischemia and infarction both in the early and in late periods (1).

The analgesic effects of the opioids preferred frequently for postoperative pain are strong; however, their side effects, such as respiratory depression, nausea, vomiting, hyperalgesia, constipation, addiction, and tolerance limit their use. Tight elastic bandages are used to reduce the edema and to prevent bleeding after DJS. For this reason, it is especially important for these patients to minimize the side effects of opioids, such as respiratory depression, nausea and vomiting. New and more effective methods have been sought as alternatives to opioids for the prevention of postoperative pain; and as a result of this, new concepts, such as multimodal pain control methods and preemptive analgesia have emerged.

Preemptive analgesia is the administration of analgesics before painful stimuli start to prevent or minimize the pain in postoperative period. The effects of these analgesic drugs continue throughout the surgery, and decrease the afferent nociceptive neurotransmission, which is caused by the surgical stimulus, and therefore, reduce the postoperative pain (2).

Many studies were conducted in the literature showing that preemptive analgesia, which is a component of multimodal analgesia, decreases postoperative opioid consumption and pain scores (3-6).

Ibuprofen, which was used by the researchers in the present study for preemptive analgesia, is an NSAID with a propionic acid-derivative structure. Like other NSAIDs, it has anti-inflammatory, antipyretic, and analgesic effects. Its anti-inflammatory effects are especially important in eliminating the edema developing after DJS. Ibuprofen in oral form has long been acknowledged as one of the most common and safe NSAIDs. The intravenous (iv) form of Ibuprofen has been used in combination with opioids to treat mild, moderate, and severe pain in USA since 2009 (7-9). It has fewer side effects in the gastrointestinal and cardiovascular systems when compared to other NSAIDs (10). As far as we are concerned, there are no studies examining the effects of preemptive 800 mg Ibuprofen on analgesia and opioid consumption in DJS.

The purpose of the present study was to evaluate the effects of iv Ibuprofen administered 800 mg preemptively in patients undergoing double jaw surgery on postoperative pain and opioid consumption.

Materials and Methods

Research and Publication Ethics: Local ethics committee approval was obtained for the study (Ethical Committee of Ataturk University Hospitals, Erzurum, Turkey (B.30.2.ATA.0.01.00/497).

After the patients signed informed consent forms, 48 patients aged between 18-65 years of age with American Society of Anesthesiologist (ASA) Group I-II, and scheduled for DJS were included in this prospective, randomized and double-blind study.

Patients with known cardiac, pulmonary, renal, hepatic and cardiovascular diseases, history of gastrointestinal bleeding, peptic ulcer or inflammatory intestinal disease, any known NSAID or paracetamol allergy, history of anticoagulant medication use, patients with low platelet counts, those who were pregnant or were planning to become pregnant, and those who could not use the PCA device were excluded from the study.

A total of 48 patients who underwent DJS were included in the study. The patients were divided randomly into two groups at a rate of 1:1 by using a computer program (Microsoft Office 365 Excel with the "RAND" function-Microsoft, Redmond, WA, USA, http://www.microsoft.com) before the intervention. Postoperative pain assessors, patients and practitioners were blinded by the study groups and the drug content. Saline preparations used for control group were prepared with the same volumes of intraoperative infusion solutions as those prepared for the group ibuprofen for double-blindization.

Group 1 (Control Group, n=24) and Group 2 (Group ibuprofen, n=24) were created in this respect. The patients were taken to the surgery room; and iv cannulation was applied. Standard ECG, peripheral oxygen saturation (SpO_2), and noninvasive blood pressure monitoring were done. All the measurements were recorded with 5-minute intervals during the surgery.

Group 1 (Control Group, n=24); 100 cc isotonic iv was administered 30 minutes before the surgery.

Group 2 (Ibuprofen Group, n=24); 800mg iv ibuprofen was administered in 100 cc isotonic 30 minutes before the surgery.

General anesthesia was applied to all patients. Before the anesthesia induction, 0.9% NaCl infusion was started, and preoxygenation was done with 100% O_2; and 2-3 mg/kg propofol (Propofol, Fresenius Kabi, Germany), fentanyl (2 µcg /kg), and 0.6 mg/kg rocuronium (Esmeron, Glaxo Smith Kline, England) were administered for the anesthesia induction. All patients underwent nasal intubation. Anesthesia was maintained with 1-2% sevoflurane (Sevorane, AbbVie, England), 50% O_2 and 50% air mixture. Crystalloid infusion (8ml/kg/h) was continued during the procedure. The anesthesia depth was monitored with Bispectral Index (BIS), and the BIS value was kept between 40 and 60. At the end of the surgeries, to antagonize the effect of muscle relaxant, 1.5 mg neostigmine (Neostigmine Ampoule 0.5 mg/mL, Adeka, Samsun, Turkey), and 0.5 mg atropine (Atropine Sulfate Ampoule 0.5 mg/mL, Galen, Istanbul) were administered. When the extubation criteria were fully met in the surgery room, nasal extubation was done; and the patient was taken to PACU.

Surgical Technique: The same surgical team performed all surgeries with the same technique.

Local anesthesia was administered to the related right and left areas that would undergo surgery. For each patient, the inferior alveolar, buccal, and lingual nerves were infiltrated with 2% articaine 80 mg in addition to 1:200,000 epinephrine (Ultracain 2%, ampule; Sanofi Aventis, Istanbul, Turkey) before surgery. A vestibular incision was made between the double-sided zygomatic protrusions in the maxilla, and the flap was elevated. Le fort I osteotomy, and then, down fracture were performed. Fixing was done with the plaques and screws that were placed on the right and left. Then, firstly the right side, and then the left side were intervened in the mandibula. Soft tissue incision was performed from the outside of the retrobulbar area on both sides to the 2nd molar tooth. After bone incisions, sagittal split ramus osteotomy was completed. Mandibula and maxilla were connected with splint and wires. Fixation was performed with one mini-plaque and screws on the left and right in the new position. Two drains were placed in the lower jaw, and the surgery was terminated with sutures.

Postoperative Analgesia Management: The same protocol was applied to the groups for postoperative analgesia management. All the patients were administered 1000 mg iv paracetamol (Perfalgan 10 mg/mL, Bristol-Myers Squibb, France) 30 minutes before the surgery ended, and was repeated every 6 hours following the surgery. The PCA device was programmed at 10 µcq concentration with loading dose 50µcq, 15-minute lock time, 25 µcq bolus without basal infusion, and this was continued for 24 hours in the postoperative recovery room. An anesthetist who was blinded to the grouping performed the evaluation of the patients after the DJ S. The postoperative analgesia was evaluated by using VAS (VAS 0=no pain, VAS 10=The most severe pain which can be felt). The VAS scores were recorded at the 1st, 2nd, 4th, 8th, 12th and 24th hours; and 25 mg Meperidine was administered and recorded for the patients with VAS score 4 and above in the recovery room. The side effects related to PCA, such as nausea, vomiting, antiemetic requirement, constipation, itching, urinary retention, and other side effects, such as NSAID related hemorrhage and dyspepsia were questioned during the two-hour postoperative follow up.

The patients with Aldrete Score 9 and above were sent to the ward. The VAS scores after the surgery, and the total opioid consumption were evaluated at the end of the 24th hour.

Statistical Analysis: The IBM SPSS 20.0 (SPSS Inc., Chicago, IL) Program was used for statistical analysis. The distribution of the variables was analyzed in terms of normality with the Kolmogorov-Smirnov and the Histogram Test. Descriptive statistics were given as Mean±Standard Deviation (SD). The categorical variables were analyzed with the Chi-Square Test. Normally distributed data with continuous variables were analyzed with the Independent Sample t-test. Mann-Whitney U-test was used for non-normally distributed data. P<0.05 was considered to be statistically significant.

Results

The demographic data of patients are shown in Table 1. No differences were detected between the groups in terms of age, height, weight, ASA classification, surgery and anesthesia durations (P>0.05). The VAS values of the patients were lower in the Ibuprofen Group in PACU and at postoperative 1st, 2nd, 4th, 8th, 12th and 24th hours than in the Control Group (P<0.05; Table 2).

The most important complications; nausea and vomiting were lower in the ibuprofen group than in the control group (P<0.05). No significant differences were detected between the two groups in terms of hemorrhage (P>0.05).

As shown in Figure 1 and Table 4, the total Fentanyl consumption was significantly less in ibuprofen Group at the end of 24 hours than in the control group (163.95±122.7 vs. 326.04±209.7 respectively P=0.002). 14 patients needed additional analgesics in the control group, only 6 patients needed them in the ibuprofen group (P=0.039).

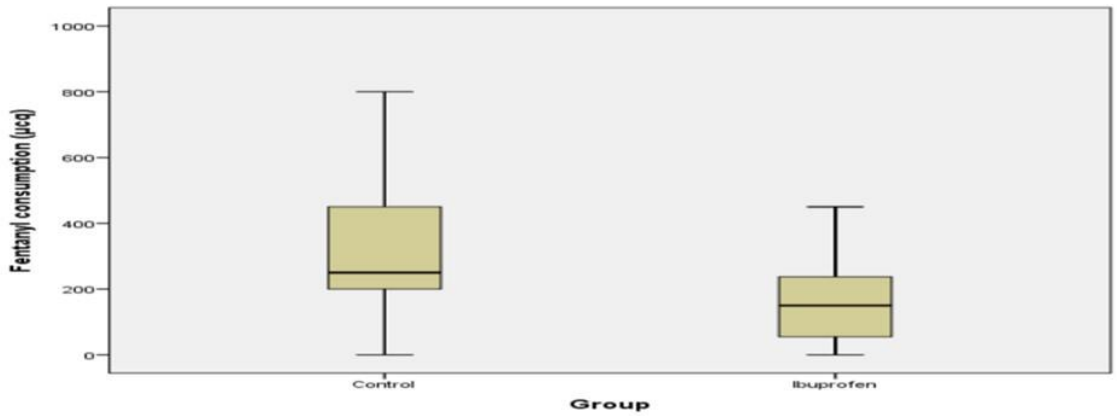

Figure 1. Total fentanyl use of both groups at the end of 24 hours.
P: 0.002 (Independent Sample t-test)

Table 1. Demographic characteristics of the participants

	Control Group	Ibuprofen Group	P
Age	23.7±3.07	24.2±5.6	0.59[1]
Weight	68.6±11.2	66.6±11.9	0.56[2]
BMI	24.1±2.5	23.1±3.5	0.29[2]
Gender (F/M)	15/9	12/12	0.38[3]
ASA (I/II)	17/7	16/8	0.75[3]
Surgery duration	163.7±37.1	171.2±37.3	0.48[2]
Anesthesia duration	184.1±36.3	189.3±36.5	0.62[2]

[1]Mann Whitney U-Test, [2] Independent Sample t-test, [3] Chi-Square Test

Table 2. Comparison of VAS scores at postoperative time points

	Control Group	Ibuprofen Group	P
PACU	4.12±1.56	2.58±1.52	0.003
VAS 1hr	4.00±1.31	2.91±2.41	0.004
VAS 2hr	3.50±1.31	2.20±1.44	0.003
VAS 4hr	3.16±1.52	1.83±1.16	0.001
VAS 8hr	2.83±1.34	1.62±1.01	0.002
VAS 12hr	2.45±1.10	1.33±0.86	0.001
VAS 24hr	2.08±1.05	1.08±0.97	0.001

VAS: Visual Analogue Scale, P<0.05 statistically significant

Table 3. Frequent side effects

	Control Group	Ibuprofen Group	P
Nausea (Y/N)	17/7	10/14	0.42
Vomiting (Y/N)	17/7	10/14	0.42
Hemorrhage (Y/N)	2/22	0/24	0.48

Chi-Square Test, Y: Yes, N: No

Discussion

In the present study, it was shown that 800 mg iv Ibuprofen administered 30 minutes before the elective DJS reduces postoperative opioid consumption and pain scores in the first 24 hours. Some side effects and the need for additional analgesics also decreased.

DJS is a highly comprehensive plastic surgery aimed to provide functional and aesthetic improvements in patients with dento facial deformities (11). Serious distress and pain may be experienced by patients in the postoperative period due to the damage to the soft tissue during surgery, as a result of the osteotomies in the maxilla and mandibula, down fractures, fixing done with plaques and screws, tight bandages, splints, and developing edema following the surgery.

Despite being predictable and preventable, and despite the developments in the knowledge on physiopathology of pain, and new drugs and methods of application, postoperative pain is still an important problem in our present day. It was reported previously that approximately 30-40% of patients suffer from moderate or severe pain in postoperative period (12). Prevention of postoperative pain is very important in terms of preventing metabolic and endocrine stress response, thromboembolic complications; reducing mobilization and rehabilitation durations, hospital stays and costs, protecting cognitive functions, and preventing the development of chronic pain (13).

Studies conducted on postoperative analgesia in DJS are limited. A study conducted on DJS reported that decreases were seen in opioid consumption and VAS scores after Pregabalin that was used for preemptive analgesia (12). Again, preemptive pregabalin and celecoxib were used in maxillomandibular surgery previously, and an effective postoperative analgesia was achieved (13). In another study; however, preoperative diclofenac or tramadol was administered (14). PCA and intraoperative low dose ketamine infusion were other techniques administered for postoperative analgesia in orthognatic surgery (15, 16).

Preemptive analgesia, which was administered in the present study, is used in postoperative pain management, and involves the administration of the analgesic before the pain starts. Many studies have been conducted so far showing the effectiveness of preemptive analgesia; and many systemic and local agents, such as bupivacaine, lidocaine, klonidine, ketorolac, oral ibuprofen, gabapentin and pregabalin were used in these studies; however, studies on the use of iv ibuprofen as a preemptive analgesic are still limited (17-22).

Ibuprofen is an NSAID that has anti-inflammatory, analgesic, and anti-pyretic characteristics. Although its oral form has been used for 40 years, the iv form has been used for the last 12 years. Ibuprofen inhibits cyclooxygenase enzymes (COX) 1 and 2; however, its

main antipyretic, analgesic, and antiinflammatory effects occur with COX_2 (23).

Two iv forms of ibuprofen, 400 mg and 800 mg were used in the studies. For laparoscopic cholecystectomy, 400 mg iv form of ibuprofen was used for preemptive analgesia, and it was observed that opioid consumption and VAS scores decreased in the postoperative period (24, 25). Studies aiming to evaluate 800 mg iv ibuprofen's effectiveness on postoperative pain in abdominal hysterectomy and laparoscopic cholecystectomy surgeries have also shown positive effects on postoperative opioid consumption and VAS scores compared to the placebo group (8, 26). In some studies, 800 mg ibuprofen initiated preoperatively was repeated every 6 hours postoperatively, and opioid consumption decreased significantly after 24 hours (8, 9). Gürkan et al. showed that opioid consumption decreased by 32% with ibuprofen repeated every 6 hours in total hip replacement surgery (27). Southword et al. found that while 800mg ibuprofen significantly reduced postoperative pain and morphine consumption in abdominal and orthopedic surgery, 400mg ibuprofen's effects were less pronounced (28). In this study, we preferred to administer a single preoperative dose of 800 mg ibuprofen. This single dose of adequate analgesia was provided, and opioid consumption was significantly reduced compared to the control group.

As a result of our study, no side effects were detected regarding NSAIDs in any patients. In orthognathic surgery patients, both postnasal bleeding and bleeding from oral tissues leaking and accumulating in the stomach increases the likelihood of nausea and vomiting as well as the effect of general anesthesia. It was reported in previous studies that 7-40% of orthognatic surgery patients had nausea and vomiting complaints (29). In the present study, nausea and vomiting complaints were found to be lower in the ibuprofen group, possibly as a result of the reduced opioid consumption.

This study had several limitations. Firstly, only one single dose (800 mg) of the drug, which has two forms, was used independently from patient weight. The second limitation was the preoperative use of 800 mg only, and the lack of postoperative use. Our purpose was to evaluate the effectiveness of one single dose. Thirdly, the cost-effectiveness of the study, and the duration of hospital stays were not evaluated. Finally, the sampling size was determined by the need for opioids, which was the primary purpose. The side effects regarding iv Ibuprofen may not appear fully with a small sampling. More studies are needed with larger samplings.

As a conclusion, the pain, postoperative opioid consumption, and the need for additional analgesics were reduced in the first 24 hours after DJS by one single dose of 800mg ibuprofen. We believe that multi modal analgesia techniques, which involve preemptive analgesia, can be successfully employed in preventing postoperative pain caused by orthognathic surgery.

References

1. Practice guidelines for acute pain management in the perioperative setting: An updated report by the American Society of Anesthesiologists Task Force on acute pain management. Anesthesiology 2012; 116: 248-273.
2. Soper NJ, Stockmann PT, Dunnegan DL, Ashley SW. Laparoscopic cholecystectomy. The new 'gold standard'? Arch Surg 1992; 127: 917-921.
3. Moucha CS, Weiser MC, Levin EJ. Current strategies in anesthesia and analgesia for total knee arthroplasty. J Am Acad Orthop Surg 2016; 24: 60-73.
4. Liu L, Yi J, Wasson MN. Techniques for Preemptive Analgesia in Gynecologic Surgery. J Minim Invasive Gynecol 2019; 26:197.
5. Kien NT, Geiger P, Van Chuong H, et al. Preemptive analgesia after lumbar spine surgery by pregabalin and celecoxib: A prospective study. Drug Des Devel Ther. 2019; 13: 2145-2152.
6. Kim MP, Godoy C, Nguyen DT, et al. Preemptive pain-management program is associated with reduction of opioid prescriptions after benign minimally invasive foregut surgery. J Thorac Cardiovasc Surg 2020; 159:734-744.e4.
7. Gago Martínez A, Escontrela Rodriguez B, Planas Roca A, Martínez Ruiz A. Intravenous ibuprofen for treatment of post-operative pain: A multicenter, double blind, placebo-controlled, randomized clinical trial. PLoS One 2016; 11: e0154004.
8. Kroll PB, Meadows L, Rock A, Pavliv L. A multicenter, randomized, double-blind, placebo-controlled trial of intravenous ibuprofen (i.v.-ibuprofen) in the management of postoperative pain following abdominal hysterectomy. Pain Pract 2011; 11: 23-32.
9. Moss JR, Watcha MF, Bendel LP, et al. A multicenter, randomized, double-blind placebo-controlled, single dose trial of the safety and efficacy of intravenous ibuprofen for treatment of pain in pediatric patients undergoing tonsillectomy. Paediatr Anaesth 2014; 24: 483-4999.
10. Southworth SR, Woodward EJ, Peng A, Rock AD. An integrated safety analysis of intravenous ibuprofen (Caldolor(®)) in adults. J Pain Res 2015; 8:753-765.
11. Cunningham SJ, Garratt AM, Hunt NP. Development of a condition-specific quality of life measure for patients with dentofacial deformity: I. Reliability of the instrument. Community Dent Oral Epidemiol 2000; 28:195-201.
12. Ahiskalioglu A, İnce İ, Aksoy M, et al. Effects of a single-dose of pre-emptive pregabalin on postoperative pain and opioid consumption after double-jaw surgery: A Randomized Controlled Trial. J Oral Maxillofac Surg 2016; 74: 53.e1-7.
13. Cillo JE, Jr., Dattilo DJ. Pre-emptive analgesia with pregabalin and celecoxib decreases postsurgical pain following maxillomandibular advancement surgery: A randomized controlled clinical trial. J Oral Maxillofac Surg 2014; 72:1909-1914.
14. Tuzuner AM, Ucok C, Kucukyavuz Z, Alkis N, Alanoglu Z. Preoperative diclofenac sodium and tramadol for pain

relief after bimaxillary osteotomy. J Oral Maxillofac Surg 2007; 65: 2453-2458.

15. Kido K, Toda S, Shindo Y, Miyashita H, Sugino S, Masaki E. Effects of low-dose ketamine infusion on remifentanil-induced acute opioid tolerance and the inflammatory response in patients undergoing orthognathic surgery. J Pain Res 2019; 12: 377-385.
16. Chang FS, Burrows SA, Gebauer DP. Patient-controlled analgesia and length of hospital stay in orthognathic surgery: A Randomized Controlled Trial. J Oral Maxillofac Surg 2019; 77: 818-827.
17. Shlaifer A, Sharfman ZT, Martin HD, et al. Preemptive analgesia in hip arthroscopy: A randomized controlled trial of preemptive periacetabular or intra-articular bupivacaine in addition to postoperative intra-articular bupivacaine. Arthroscopy 2017; 33: 118-124.
18. Batista LM, Batista IM, Almeida JP, et al. Preemptive analgesic effect of lidocaine in a chronic neuropathic pain model. Arq Neuropsiquiatr 2009; 67: 1088-1092.
19. Bala R, Kaur J, Sharma J, Singh R. Comparative evaluation of pregabalin and clonidine as preemptive analgesics for the attenuation of postoperative pain following thoracolumbar spine surgery. Asian Spine J 2019; 13: 967-975.
20. Mixter CG, 3rd, Meeker LD, Gavin TJ. Preemptive pain control in patients having laparoscopic hernia repair: A comparison of ketorolac and ibuprofen. Arch Surg 1998; 133: 432-437.
21. 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: 51-55.
22. Fassoulaki A, Patris K, Sarantopoulos C, Hogan Q. The analgesic effect of gabapentin and mexiletine after breast surgery for cancer. Anesthesia and Analgesia 2002; 95: 985-991.
23. Smith HS, Voss B. Pharmacokinetics of intravenous ibuprofen: Implications of time of infusion in the treatment of pain and fever. Drugs 2012; 72: 327-337.
24. Ahiskalioglu EO, Ahiskalioglu A, Aydin P, Yayik AM, Temiz A. Effects of single-dose preemptive intravenous ibuprofen on postoperative opioid consumption and acute pain after laparoscopic cholecystectomy. Medicine (Baltimore) 2017; 96: e6200.
25. Karaca O, Pınar HU, Turk E, et al. Effects of single-dose preemptive pregabalin and intravenous ibuprofen on postoperative opioid consumption and acute pain after laparoscopic cholecystectomy. J Invest Surg 2019; 32:189-195.
26. Ekinci M, Ciftci B, Celik EC, et al. A Randomized, placebo-controlled, double-blind study that evaluates efficacy of intravenous ibuprofen and acetaminophen for postoperative pain treatment following laparoscopic cholecystectomy surgery. J Gastrointest Surg 2020; 24: 780-785.
27. Gürkan Y, Yörükoğlu HU, Işık E, Kuş A. The effect of ibuprofen on postoperative opioid consumption following total hip replacement surgery. Turk J Anaesthesiol Reanim 2019; 47: 31-34.
28. Southworth S, Peters J, Rock A, Pavliv L. A multicenter, randomized, double-blind, placebo-controlled trial of intravenous ibuprofen 400 and 800 mg every 6 hours in the management of postoperative pain. Clin Ther 2009; 31: 1922-1935.
29. Carli F, Kehlet H, Baldini G, et al. Evidence basis for regional anesthesia in multidisciplinary fast-track surgical care pathways. Reg Anesth Pain Med 2011; 36: 63-72.