Assessment of Preemptive Analgesia with Etodolac in Conventional and Flapless Dental Implant Surgeries

Klasik ve Flepsiz İmplant Cerrahileri Sonrası Ağrı Kontrolünde Etodolakın Preemptif Kullanımı

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ABSTRACT Objective: This study aimed to investigate the effects of preemptive single-dose etodolac administration on pain prevention and patient comfort following conventional flapped and flapless dental implant surgeries. **Material and Methods:** Thirty-two patients who had bilateral partial or total edentulism in the upper jaw were divided into two groups. Half of the patients were selected for conventional surgery and half for flapless surgery. Each patient received etodolac, 600 mg, or a placebo randomly one hour before surgery. Pain intensity and discomfort scores were recorded by participants based on a visual analog scale and four-point verbal rating scale at the postoperative first, second, fourth, sixth, 12th, 24th, and 48th hours. Furthermore, it was suggested that the patients use a rescue analgesic only if the pain was intolerable and to record it. **Results:** Etodolac was superior to placebo in both the traditional and flapless surgery groups, and the results were better in the flapless surgery-etodolac premedication group, especially at the second, fourth, and sixth hours. Pain and discomfort scores and rescue medication use were similar in the conventional surgery-etodolac premedication group and the flapless surgery-placebo premedication group. **Conclusion:** The findings of this study suggest that the preemptive single-dose etodolac (600 mg) medication was considerably effective in the management of postoperative pain and discomfort following both surgeries.

Key Words: Toothache; etodolac; analgesics; dental implants; pain measurement

ÖZET Amaç: Bu çalışma, preemptif tek doz etodolak kullanımının klasik veya flepsiz teknikle gerçekleştirilen implant operasyonlarını takiben oluşan ağrının önlenmesi ve hasta konforu üzerine etkilerini araştırmayı amaçlamaktadır. **Gereç ve Yöntemler:** Üst çenelerinde çift taraflı kısmi veya tam diş eksiklikleri olan otuz iki hasta iki gruba ayrıldı. Hastaların yarısı klasik cerrahi diğer yarısı ise flepsiz cerrahi grubuna dahil edildi. Her bir hastaya ameliyat başlangıcından bir saat önce rastgele olarak etodolak, 600 mg, veya plasebo verildi. Ağrı yoğunluğu ve konfor durumu değerlendirmeleri operasyonu takiben birinci, ikinci, dördüncü, altıncı, on ikinci, yirmi dördüncü ve kırk sekizinci saatlerde görsel analog skala ve dört noktalı sözel kategori ölçeğini kullanarak hastalarca kaydedildi. Bunun yanı sıra, ağrıları dayanılmaz olduğunda kendilerine reçete edilen ağrı kesiciyi kullanmaları ve bunu her seferinde forma kaydetmeleri bildirildi. **Bulgular:** Hem klasik hem de flepsiz cerrahi gruplarında, etodolak plaseboya kıyasla daha üstün olup en iyi sonuçlar, özellikle de ikinci, dördüncü ve altıncı saatlerde, flepsiz cerrahi-etodolak profilaksi grubunda gözlendi. Ağrı ve konfor durumunu gösteren değerler ile ek ağrı kesici kullanımı açısından klasik cerrahi-etodolak profilaksi ve flepsiz cerrahi-plasebo profilaksi gruplarında sonuçlar benzerdi. **Sonuç:** Çalışma sonuçları, preemptif tek doz etodolak (600 mg) kullanımının her iki cerrahi tekniği takiben ağrı kontrolünde ve hasta konforunun artırılmasında son derece etkili olduğunu göstermektedir.

Anahtar Kelimeler: Diş ağrısı; etodolak; analjezikler; diş implantları; ağrı ölçümü

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The insertion of dental implants has become a routine method for the prosthetic rehabilitation of partially and completely edentulous jaws, and major emphasis is now being placed on predictable treatment

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planning with maximum patient comfort and minimal patient morbidity.[1] Dental implants can be placed with either the conventional flapped implant placement technique or the flapless technique. In recent years, the flapless technique has become more popular because it has some advantages, such as decreased operation time, less traumatic surgery, fewer postsurgical complications, rapid postsurgical healing, and increased patient comfort.[2,3] Komiyama et al. concluded that postoperative discomfort such as swelling and pain is almost negligible with the flapless technique.[3]

Non-steroidal anti-inflammatory drugs (NSAIDs) have become an accepted part of pain control in non-surgical and surgical dental treatments.[4-6] NSAIDs reduce the synthesis of prostaglandins from arachidonic acid by inhibiting two separate isoforms of cyclooxygenase (COX-1 and COX-2) enzyme, thus blocking the nociceptive response to inflammation mediators. COX-1 synthesizes protective prostaglandins, which preserve the integrity of the stomach and intestinal lining. It is also responsible for maintaining normal renal function in a compromised kidney and maintaining platelet function. COX-2 mediates inflammatory processes, including pain, inflammation, and fever, and controls cell growth.[7,8] COX-2 is induced by proinflammatory cytokines and growth factors. COX-2 inhibitors make it possible for physicians to reduce inflammation and pain without removing COX-1 activity. COX-2 inhibitors minimize adverse gastrointestinal and renal effects more effectively than conventional NSAIDs do, and they should be administered to patients with upper gastrointestinal bleeding risk or peptic ulcer history[8]. In addition, these drugs do not inhibit platelet aggregation as conventional NSAIDs do, and thus, they do not increase the risk of perioperative and postoperative bleeding.[9] Etodolac is a selective COX-2 inhibitor NSAID that has been proven to be an effective analgesic for pain management after oral surgery and in the management of rheumatoid arthritis.[10-13]

Preemptive analgesia is a protocol that aims to reduce postoperative pain and discomfort; in addition, it reduces the need for rescue analgesic use.[14-16] It can be provided via several methods: prevention of input to the noniceptors by local anesthesia; prevention of central sensitization by narcotic analgesics; and inhibition of inflammation and peripheral sensitization by NSAIDs.[17,18] It has been noted that the administration of NSAIDs previous to surgery may be more efficient as compared with the peri or postoperative intake by early inhibiting the production of prostaglandins and activation of peripheral and central sensitization.[19,20]

Although the use of etodolac as a preemptive analgesic in endodontic, periodontal, and oral surgical procedures have recently been investigated, to our knowledge, there is a lack of data in the literature regarding the analgesic efficiency of using a preemptive single dose of etodolac on postoperative patient comfort after dental implant surgery.[12,21-23] Therefore, the objective of this study was to evaluate the effect of preemptive single-dose etodolac (600 mg) administration for pain prevention after conventional and flapless dental implant surgeries in patients with partial or total edentulous upper jaws, and to compare these surgical techniques in terms of pain intensity and discomfort.

MATERIAL AND METHODS

STUDY POPULATION

In this double-masked, placebo-controlled, randomized clinical trial, the effects of preemptive single-dose etodolac (600 mg) administration for pain prevention after traditional and flapless dental implant surgeries were evaluated by analyzing self-rated visual analog scale (VAS) and four-point verbal rating scale (VRS-4) discomfort scores. The need for rescue analgesic use following surgery was also evaluated. Thirty-two patients who had partial or total bilateral edentulism in the upper jaw were selected at the department of periodontology, Ataturk University, Erzurum, Turkey, between February 2012 and November 2012. Exclusion criteria were 1) history of uncontrolled diabetes mellitus, hypertension, bleeding disorder, liver disorder, kidney disorder, hepatitis, epilepsy, or gastric ulcer; 2) pregnant or lactating; 3) allergic to

any of the formulations used in this study; 4) routine use of analgesics and/or anti-inflammatory drugs; 5) at risk for infective endocarditis; and 6) obesity. This study was approved by the Ethical Committee of Ataturk University Faculty of Dentistry in accordance with the Helsinki Declaration of 1975, as revised in 2000 and 2008. The participants were informed about the objective and design of the study prior to undergoing their surgical procedures.

STUDY DESIGN

Thirty-two patients who had bilateral partial or total edentulism in the upper jaw were divided into two equal groups. Half of the patients were selected for conventional surgery and the other half for flapless surgery. In both the conventional and flapless surgery groups, second surgeries were performed on the other side of the upper jaw three weeks after the first surgeries. A placebo or etodolac (600 mg) (Dolarit; Drogsan, Ankara, Turkey) was administered one hour prior to each surgery. The study groups were as follows: Group 1 (G1), conventional surgery-placebo premedication; Group 2 (G2), conventional surgery-etodolac premedication; Group 3 (G3), flapless surgery-placebo premedication; and Group 4 (G4), flapless surgery–etodolac premedication. Both group creation and choice of the administered drug were achieved randomly. The study was carried out in double-blinded fashion.

All of the surgeries were performed under local anesthesia (4% articaine with 1/100.000 epinephrine). In the traditional surgery groups, the surgical procedures were initiated with crestal and intrasulcular incisions, and the mucoperiosteal flaps were elevated, exposing the bone sufficiently. Following, the sockets were prepared and the implants were placed according to the manufacturer's instructions. Finally, elevated flaps were repositioned and sutured with silk 4-0 sutures. In the flapless surgery groups, no flap elevation was performed. At the implant recipient side, the soft tissue was prepared using a punch method and removed with curettes before the socket preparation and the implantation. The punch edges were not sutured after placing the cover screws. All patients in both groups received antibiotics (amoxicillin-clavulanic acid 625 mg, twice a day for a week) and chlorhexidine digluconate (Kloroben; Drogsan, Ankara, Turkey) (twice a day for a week) after the surgeries. The patients were also advised to choose a soft diet during the first postoperative week.

The location, implant number, volume of local anesthesia (ml), and time required to perform the surgical procedure (minutes) were recorded for each surgery. The patients were asked to record their level of pain according to a VAS consisting of a 10-cm line anchored by two end points ("No pain" and "Pain as bad as it could be") at the postoperative first, second, fourth sixth, 12th, 24th, and 48th hours. The patients were also asked to choose, at the same time periods, one of four selections on the VRS-4: "no discomfort," "some transitory discomfort," "persistent discomfort," and "pain".[24] For ethical reasons, all participants received rescue medication-naproxen sodium (550 mg) (Apranax Fort; Abdi Ibrahim, Istanbul, Turkey)-and were instructed to use it if necessary and to wait at least six hours between doses and record each use on a form.

STATISTICAL ANALYSIS

The similarities between the groups in number of placed implants, duration of surgery, used anesthetic volume, and number of rescue pills taken was analyzed using a one-way analysis of variance (ANOVA). A Kruskal-Wallis non-parametric test was used to determine differences among the groups on the VAS scale at each hour. The Dunn multiple comparison test was used to perform pairwise multiple comparisons. The frequency of patients reporting "no discomfort," "some transitory discomfort," "persistent discomfort," and "pain" on the VRS-4 was compared among the groups using the Cochran Q test. The Spearman rank correlation test was used to assess correlation between VAS and VRS-4 values. Statistical analysis of the study data was conducted using a software program (SPSS 17.0 for Windows; IBM, Chicago, IL), and $p<0.05$ was defined as statically significant for all tests.

RESULTS

Thirty-two patients (17 males, 15 females; 27-66 years old; mean age: 43±5 years) completed the study. The similarities between the treatment groups were evaluated by comparing number of placed implants, surgery duration, anesthetic volume, and number of rescue pills taken. The number of placed implants and the volume of used local anesthetics were similar among the four groups (p=0.73, p=0.59, respectively). In contrast, surgery duration was significantly longer in the traditional surgery groups (Groups 1 and 2) than in the flapless surgery groups (Groups 3 and 4). Similarly, the number of rescue pills taken was significantly higher in Group 1 than in the other groups (p=0.00, p=0.00, respectively) (Table 1).

Evaluation of the VAS pain scores revealed that lower pain scores were obtained in the etodolac groups than in the placebo groups at the second hour (p=0.002). Significantly lower pain scores were obtained in Group 4 than in Groups 1 and 2 at the fourth and sixth hours (p=0.006, p=0.010, respectively). Similar VAS pain scores were observed in Group 2 and Group 3 at the second, fourth, and sixth hours. In the etodolac groups; lower VAS pain scores were obtained with flapless surgery than with traditional surgery, particularly at the second, fourth, and sixth hours (p=0.006, p=0.001, p=0.030, respectively). In the placebo groups, flapless surgery resulted in lower pain scores at the same time periods (p=0.003, p=0.000, p=0.009, respectively) There were no significant differences among the four groups at the first, 12th, 24th, and 48th hours. The mean, standard deviation (SD), and median of pain intensity based on the VAS scores for all of the four groups at each time period are shown in Table 2.

The distribution (percentage) of patients with "no discomfort," "some transitory discomfort," "persistent discomfort," and "pain" for all of the four groups in each time period were shown in Figure 1.

TABLE 1: Variables (Mean ± SD) for the groups*.

	Conventional		Flapless		
	Placebo	Etodolac	Placebo	Etodolac	P value
Variables	(Group 1)	(Group 2)	(Group 3)	(Group 4)	(ANOVA)
Number of placed implant (n)	2.3±0.9^{A}	2.6±0.9^{A}	2.3±0.7^{A}	2.3±1.0^{A}	0.73^{NS}
Duration of surgery (minutes)	29.0±10.4^{B}	31.8±9.6^{B}	18.6±5.7^{A}	19.8±7.9^{A}	0.00
Anesthetic volume (ml)	4.2±1.5^{A}	3.7±3.0^{A}	3.7±1.2^{A}	3.5±1.3^{A}	0.59^{NS}
Number of rescue pills taken (n)	1.75±1.2^{B}	0.50±0.6^{A}	0.75±0.9^{A}	0.19±0.4^{A}	0.00

* Within the same time, values with the same letter are not statistically different. Letters (A or B) in the same line indicate significant differences between groups.
NS: Not statistically significant.

TABLE 2: Mean (SD)/median for pain values using VAS for the groups at each time period*.

	Conventional		Flapless		
	Placebo	Etodolac	Placebo	Etodolac	P value
Variables	(Group 1)	(Group 2)	(Group 3)	(Group 4)	(Kruskal-Wallis)
1 hour	1.40(0.7)/1.5^{A}	0.96(0.7)/1.0^{A}	1.46(1.1)/1.5^{A}	1.15(0.7)/1.0^{A}	0.293^{NS}
2 hours	4.09(1.1)/2.0^{C}	3.12(0.9)/3.0^{B}	2.93(0.9)/2.0^{B}	1.96(0.6)/2.0^{A}	0.002
4 hours	5.62(0.9)/5.5^{C}	4.59(1.0)/4.0^{B}	3.90(0.9)/3.8^{AB}	3.15(0.9)/3.0^{A}	0.006
6 hours	5.37(1.5)/5.5^{C}	4.56(1.3)/4.0^{BC}	3.96(1.1)/3.0^{AB}	3.34(0.9)/3.5^{A}	0.010
12 hours	3.37(1.3)/3.5^{A}	2.56(1.1)/2.5^{A}	2.78(0.9)/2.5^{A}	2.37(1.0)/2.5^{A}	0.071^{NS}
24 hours	1.75(1.0)/2.0^{A}	1.09(1.0)/1.0^{A}	1.31(0.8)/1.5^{A}	1.09(0.8)/1.0^{A}	0.154^{NS}
48 hours	0.96(0.5)/1.0^{A}	0.75(0.5)/0.5^{A}	1.12(1.1)/1.0^{A}	0.56(0.3)/0.5^{A}	0.101^{NS}

* Within the same time, values with the same letter are not statistically different. Letters (A, B or C) in the same line indicate significant differences between groups.
VAS: Visual analog scale; NS: Not statistically significant.

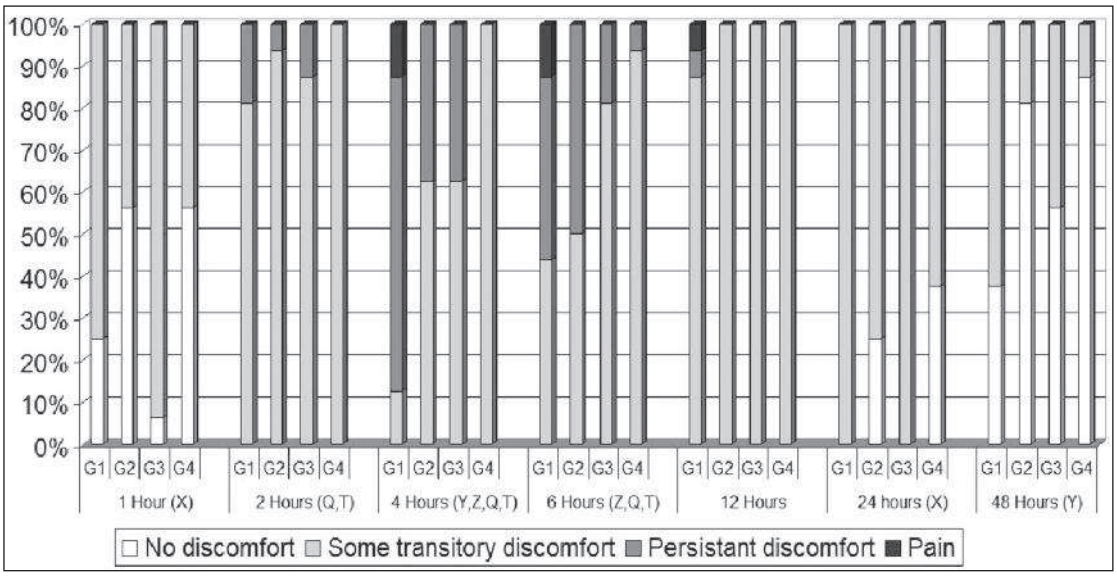

FIGURE 1: Distribution (%) of patients with "no discomfort," "some transitory discomfort," "persistent discomfort," and "pain" for all of the four groups at each time period. G1: conventional surgery-placebo premedication; G2: conventional surgery-etodolac premedication; G3: flapless surgery-placebo premedication; G4: flapless surgery-etodolac premedication.

X: Statistically significant differences between G1 and G2 ($p<0.05$); Y: Statistically significant differences between G3 and G4 ($p<0.05$); Z: Statistically significant differences between G2 and G4 ($p<0.05$); Q: Statistically significant differences between G1 and G3 ($p<0.05$); T: Statistically significant differences among G1, G2, G3, and G4 ($p<0.05$).

Significant differences in discomfort were observed among the groups at the first, fourth, sixth, and 48th hours ($p=0.004$, $p=0.002$, $p=0.003$, $p=0.008$, respectively). When the traditional and flapless surgery groups or the etodolac and placebo groups were compared, it was observed that the flapless surgery and etodolac groups were superior to the traditional surgery and placebo groups in terms of discomfort (Figure 1). A statistically significant correlation was observed between the VAS and VSR-4 values ($r=0.448$; $p=0.001$).

No adverse effects, such as gastrointestinal side effects, were reported for any of the medication. In addition, no postoperative surgical problems such as infection, severe pain, or paresthesia were reported in any of the groups.

DISCUSSION

Reduction of dental anxiety and effective postoperative pain management are very important issues in our day-to-day practice. Compared with conservative dental treatment procedures, oral surgical procedures such as dental implant surgery cause intense dental anxiety and postoperative complications.[25-27] Pain is a common postoperative complication of dental implant surgery.[28] Recent studies have shown that the surgical placement of dental implants caused mild to moderate levels of pain that generally decrease with time.[29,30] Al Khabbaz et al. concluded that operator experience, female gender, surgical difficulty, and previous pain were significantly related to patient's reports about pain experienced after surgical placement of dental implants.[30]

Recent studies have demonstrated an important role for prostaglandins within the central and peripheral nervous systems.[7,8,31] Therefore, pain following oral surgical procedures can be effectively controlled by NSAIDs, and it has been reported that these analgesic agents may be more effective when administrated prior to surgery.[4,5,9,12,32-35] This approach is called preemptive analgesia and is defined as an antinociceptive treatment that is begun preoperatively and is active during surgery and postoperatively. Although the extraction of impacted third molars and periodontal surgeries have become the most widely accepted model to evaluate or compare the efficacy of the preemptive use of

such analgesic agents, only one study has compared the preemptive use of analgesic agents in dental implant surgery.[4,5,14-16,32] Karabuda et al. aimed to compare the analgesic and anti-inflammatory efficacies of the conventional NSAID tenoxicam (20 mg) and the selective COX-2 inhibitor meloxicam (15 mg) after dental implant surgery.[35] In their study, analgesics were received for four days: the day before surgery, one hour preoperatively, and two days thereafter. The researchers reported that both agents exhibited similar analgesic and anti-inflammatory efficacy.

In the current study, in order to yield parallel results in terms of predictive validity and number of subjects who correctly respond to them, pain intensity and discomfort scores were recorded by the participants on both the VAS and VRS-4 scales at the postoperative first, second, fourth, sixth, 12th, 24th, and 48th hours. A statistically significant correlation was found when the VAS and VSR-4 scales were compared. Taking these values together, it was observed that etodolac was significantly more effective than the placebo, especially at the second, fourth, and sixth hours. It was also found that the flapless surgery-etodolac premedication group had the best results in terms of pain intensity and discomfort, while the conventional surgery-placebo premedication group had the worst results, particularly at the second, fourth, and sixth hours. Etodolac is primarily used for the treatment of arthritis and musculoskeletal diseases, and it provides analgesic efficacy with a low rate of adverse effects.[13] Furthermore, etodolac has been proven to be an effective analgesic agent in the management of postoperative pain in oral surgery models.[10,11,36,37] Tirunagari et al. reported that etodolac (200 mg) may be a useful analgesic in postoperative acute pain management, with efficacy similar to that of paracetamol (1000 mg) and celecoxib (200 mg).[23] Higher doses of 400 mg may provide analgesia equivalent to more commonly prescribed NSAIDs, such as ibuprofen (400 mg), naproxen (500 mg), and diclofenac (50 mg). The authors also noted that single-dose etodolac was well tolerated and had a low rate of adverse events, similar to the placebo.

Studies have reported the efficiency of prophylactic etodolac use on post-endodontic pain and the pain following surgical endodontic treatment.[12,21] Giglio and Campbell noted that a single 200 or 400 mg dose of etodolac provided similar analgesic efficacy as that achieved with zomepirac (100 mg) and superior efficacy to a placebo following third molar extractions.[37] In another study, it was reported that the analgesic effect achieved with a single 50 or 200 mg dose of etodolac was comparable to that of 650 mg of aspirin after oral surgery.[10] Recently, Vardar and Baylas designed a single-blind, placebo-controlled study to evaluate the effects of preemptive administration of a single dose of etodolac (600 mg) on patient comfort after periodontal surgery.[22] They reported that VAS scores were significantly lower in the etodolac group compared to the placebo group, particularly at the postoperative second, third, fourth, and fifth hours. They also noted that the number of rescue pills taken by the placebo group was nearly twice that of the study group. The results of these previous studies were compatible with ours.

As an interesting finding, our results also demonstrated that pain and discomfort scores and rescue medication use were similar in the conventional surgery-etodolac premedication group and the flapless surgery-placebo premedication group. In other words, with the preferance of flapless surgery, preoperative and postoperative NSAID needs may be reduced or eliminated. We thought that, in postoperative pain control, this finding is of an importance in terms of supporting the studies, which suggested the superiority of the flapless implant surgery compared to the conventional implant surgery, with objective findings.[2,3,38]

CONCLUSION

The results of the present study show that preemptive single-dose etodolac (600 mg) administration is significantly more effective than placebo in the prevention of postoperative pain and discomfort and in the reduction of the consumption of rescue analgesics. Based on the results obtained

in this study, flapless implant placement surgery with preemptive single-dose etodolac (600 mg) administration may be recommended for decreased pain and discomfort perception. However, this study has some limitations, such as number of patients and complexity of selected cases. Additional studies with a larger number of patients and advanced implant surgical procedures such as guided bone regeneration or sinus lifting procedures, which result in more pain and discomfort, are necessary. The lack of comparisons of the effectiveness of etodolac and those of other COX-2 inhibitors and conventional NSAIDs are another limitation of this study.

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