THE EFFECTS OF AMOXICILLIN WITH OR WITHOUT CLAVULANIC ACID ON THE POSTOPERATIVE COMPLAINTS AFTER THIRD MOLAR SURGERY: A RETROSPECTIVE CHART ANALYSIS

Üçüncü Büyük Ağı Diş Cerrahisi Sonrasında Kullanılan Klavulanik Asit İçeren ve İçermeyen Amoksilinin Preparatlarının Postoperatif Yakınmalar Üzerine Etkisi: Retrospektif Çalışma

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ABSTRACT

Purpose: The aim of this chart-based retrospective study was to evaluate the effects of orally administered amoxicillin alone or amoxicillin combined with clavulanic acid on the frequency of post-operative complications and patients’ comfort after mandibular third molar surgery.

Materials and Methods: The records of patients who had undergone lower third molar surgery between October 2014 and December 2015 were examined. A total of 62 patients who had fully impacted teeth in mesioangular position and who had been prescribed same type and dose of anti-inflammatory drug were included in this study. Among them, 32 subjects were found to have been prescribed 500 mg amoxicillin trihydrate orally every 8 h for 5 days (Group A) and 30 patients 500 mg amoxicillin trihydrate plus 125 mg potassium clavulanate orally every 8 h for 5 days postoperatively (Group AC). Post-operative pain levels, swelling, presence of trismus, frequency of alveolar osteitis and quality of life (QoL) scores were gathered from patients’ charts and were statistically compared.

Results: Analysis of the variables showed that there were no significant differences between the Groups A and AC regarding pain levels, swelling, trismus and QoL scores. The frequency of alveolar osteitis was found to be 1.6% in the Group A, however, no significant difference was observed among study groups.

Conclusion: Within the limitations of this retrospective chart review, it can be stated that amoxicillin and amoxicillin with clavulanic acid might provide similar outcome in terms of patient comfort following third molar surgery.

Keywords: Third molar surgery; amoxicillin-clavulanic acid; wound infection; alveolar osteitis; quality of life

ÖZ

Amaç: Hasta kayıtlarının incelenmesine dayanan bu geriye dönük çalışmanın amacı; ağı yoluyla sadece amoksilinin ve amoksilinin-klavulanik asit içeren antibiyotiklerin verilmesinin girişim sonrasında meydana gelen komplikasyonların sıkılığı ve hasta konforu üzerindeki etkilerini değerlendirme.

Gereç ve Yöntem: 2014 yılı Ekim ayı ile 2015 yılı Aralık ayı arasında cerrahi olarak alt üçüncü büyük ağı dişleri çekilen 453 hastanın kayıtları incelendi. Bu çalışmaya kriterlere uygun, dişleri mesioangular pozisyonda konumlanmış ve aynı antiinflamatuar ilacı kullanmış olan toplam 62 hasta dâhil edildi. Bu hastaların arasından 32 kişinin girişim sonrası 5 gün boyunca, her sekiz saatte bir oral yoldan 500 mg amoksilinin trihidrat (A grubu), 30 hastanın ise her sekiz saatte bir oral yoldan 500 mg amoksilinin trihidrat + 125 mg potasyum clavulanat (AC grubu) kullandığı belirlendi. Girişim sonrasında hissedilen ağrı seviyeleri, şişlik, trismus varlığı, alveolar osteitis sıkılığı ve yaşam kalitesi (YKÖ) skorları ile ilgili veriler hasta dosyalarından edilecek istatistiksel olarak karşılaştırıldı.

Bulgular: Çalışmanın değişkenleri incelendiğinde; gruplar arasında ağrı, şişlik, trismus ve YKÖ skorları bakımından istatistiksel olarak anlamlı bir farklık olmadıkça saptanmadı. A grubunda alveolar osteitis sıkılığının %6.0 olduğu bulunmasına karşılık çalışma grupları arasında anlamlı bir farklılık izlenmedi.

Sonuç: Hasta kayıtları temel alınarak yapılan bu geriye dönük çalışmanın sonuçlarını dahilinde, alt üçüncü büyük ağı dişinin cerrahi çekimi sonrasında sadece amoksilinin ya da amoksilinin-klavulanik asit içeren antibiyotiklerin kullanımının hasta konforu üzerinde benzer etkileri olduğu söylenebilir.

Anahtar kelimeler: Alt üçüncü büyük ağı dişi cerrahisi; amoksilinin-klavulanik asit; yara enfeksiyonu; alveolar osteitis; yaşam kalitesi

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**Introduction**

Removal of the impacted third molars is one of the most frequently performed procedures in oral surgery (1). Common postoperative complications are pain, localized swelling and trismus. Alveolar osteitis (AO) and surgical wound infection associated with bacterial contamination can also be observed. The incidences of AO and postoperative infection have been reported ranging from 1% to 6.3% and 2% to 12%, respectively (1, 2). In order to prevent such occurrences, preoperative or postoperative antibiotics can be prescribed but there is still no consensus on this subject (3). Considering the type of the antibiotics, amoxicillin is one of the mostly used penicillin derivatives in previous clinical studies, followed by amoxicillin/clavulanic acid, clindamycin and metronidazole (1, 4, 5).

Recently, the development of resistance to beta-lactam antibiotics has become a serious concern. One of the most important reasons which may lead to the resistance is the beta-lactamase enzymes produced by gram positive and gram negative bacteria (6). Oral flora contains more than 400 species of aerobic and anaerobic bacteria. Dental infections usually consist of a mixture of gram-positive aerobic and gram-negative anaerobic bacteria. More than half of these bacteria are capable of producing beta-lactamase, which may lead to inadequate treatment of dental infections (7). Clavulanic acid is a beta lactamase inhibitor that has a strong bactericidal effect when used in combination with amoxicillin. Systemic circulation of the amoxicillin/clavulanic acid exhibits a good permeation and it reaches the antibacterial concentrations in bone, middle ear, peritoneum and synovial fluid (8). The aim of this retrospective study is therefore to assess the effects of orally administered amoxicillin alone or amoxicillin combined with clavulonic acid antibiotics on the frequency of postoperative complications and patients’ discomfort after mandibular third molar surgery.

**Materials and Methods**

**Chart selection**

This retrospective study was approved by Necmettin Erbakan University, Ethics Committee of the Faculty of Dentistry (Project no: 2016003). The records of 453 patients who had undergone lower third molar surgery between October 2014 and December 2015 in the Department of Oral and Maxillofacial Surgery of the same institution were examined. The inclusion criterion were; to be operated for at least one mandibular fully impacted third molar tooth in mesioangular position, to be between 18 and 40 years of age, to be prescribed amoxicillin trihydrate or amoxicillin trihydrate combined with potassium clavulanate, to use same type and dose of anti-inflammatory drug post-operatively. To be younger than 18 and older than 40 years of age, pregnancy, allergy to penicillin, presence of acute pericoronitis or abscesses, previous antibiotic administration in last two weeks before surgery, history of smoking and/or alcohol abuse, and presence of previously diagnosed systemic diseases that could affect the healing mechanisms were the exclusion criterion. Only fully completed charts in which demographic information and duration of surgery are clearly written, were considered to be eligible for evaluation. As a result of this chart review, only 62 patients complying with aforementioned criteria were included in this study (N=62).

Among them, Thirty-two patients (n=32) were found to have used 500 mg amoxicillin trihydrate orally every 8 h for 5 days (Group A) and 30 were observed to have taken 500 mg amoxicillin trihydrate plus 125 mg potassium clavulanate orally every 8 h for 5 days (Group AC, n=30). Patients in both groups had been prescribed the same anti-inflammatory drug (Flurbipron 100 mg, every 12 h for 5 days).

**Surgical standards**

According to their charts, standard surgical techniques had been used in each patient. A triangular mucoperiosteal flap had raised and bone had removed using a rounded bur cooled with sterile saline solution. After the tooth is separated, it had been removed and the socket had been rinsed with physiologic saline solution. The wounds had been closed with 3.0 silk sutures (Dogsan, Trabzon, Turkey) which is the standard suture material used in our clinic.

**Assessment instruments**

Two forms are given to all patients routinely in our clinic. The first form contains two verbal rating scales ranging from 0 (no pain and no swelling) to 5 (unbearable pain and extremely severe swelling), showing the daily degree of pain and swelling records. The second form contains numbers from 0 to 100...
indicating the Quality of Life (QoL). Scores range from the extremely poor to the excellent quality of life (9). Forms are handed back by the patients to the clinicians before removal of the sutures at 7th day after surgery. Postoperative infection and AO were diagnosed according to previously published clinical criteria (1, 3, 7). Infection was diagnosed via fluctuation pus drainage, the presence of excessive pain and hyperemia. AO was determined as absence of clot with necrotic remains present in the alveolus accompanied by halitosis and severe pain.

**Statistical analysis**

Data was evaluated by using SigmaPlot v12.5 software (Systat Software Inc., Richmond, CA, USA). Firstly, all data was analyzed using Shapiro-Wilk normality test. If a particular data set was normally distributed, parametric tests were used. Otherwise, a non-parametric equivalent was employed. According to this, comparison of age range was done with Student’s t test. Operation time, QOL and pain-swelling scores were compared using Mann-Whitney U test. Complication rates were compared using Chi-Square test. Statistical significance level was set at \( p < 0.05 \).

**Results**

There were 52 females and 10 male patients in the study groups. The mean age of the study population was 24 years. Demographic data is summarized in Table 1. No significant difference was observed with regard to the age, gender distribution, and operation time between the two groups.

Statistical analysis of the postoperative results showed that there were no significant differences between the two groups regarding pain and swelling (Table 2 and Table 3). AO had been noted in 1 patient in group A with a frequency of 1.6%. Postoperative infection was found in 1 patient from the group A, again with a frequency of 1.6%. Trismus was present in 1 patient in group AC. No statistically significant difference was found between the two groups regarding AO, infection, trismus and QoL scores (Table 4).
Amoxicillin and amoxicillin combined with clavulanic acid were the use of 0.2% chlorhexidine gluconate mouth rinse third molar surgery. Delibasi reducing risk both of AO and infection after mandibular systemic antibiotic therapy was statistically significant in treatment group in the same study. Authors reported that reported 4% in the antibiotic group and 6.1% in the no received a placebo or no treatment. Wound infection was determined, if there was purulent discharge from the surgical site or there were other signs of infection, such as fever, lymphadenopathy, persistent swelling and pain that cannot be explained by surgical trauma. A diagnosis of AO was made when there was purulent discharge from the surgical site and there were other signs of infection, such as fever, lymphadenopathy, persistent swelling and pain that cannot be explained by surgical trauma. Regarding the postoperative AO and infection, the reported incidence of AO varies between 1% and 6.3% and that of infection from 1% and 12.6% (2). In a meta-analysis of randomized controlled clinical trials by Ren and Malmstrom (1), AO has been reported to occur in 84 of 1350 patients (6.2%) who had received systemic antibiotics and in 228 of 1582 patients (14.4%) who had received a placebo or no treatment. Wound infection was reported 4% in the antibiotic group and 6.1% in the no treatment group in the same study. Authors reported that systemic antibiotic therapy was statistically significant in reducing risk both of AO and infection after mandibular third molar surgery. Delibasi et al. (17) also reported that the use of a 0.2% chlorhexidine gluconate mouth rinse and amoxicillin combined with clavulanic acid were effective for the prevention of AO. However, the other clinical studies suggested that the use of antibiotics is unnecessary as they do not affect the frequency of AO or infection in the postoperative period (3, 4, 15). In the present study, postoperative AO rate was 1.6% and infection rate also was 1.6%. AO and infection were not diagnosed in group AC, however no significant difference was found between the two groups. However, these findings should be approached with caution since our sample size is limited.

There are some important clinical studies related with amoxicillin or amoxicillin combined with clavulanic acid in the literature. Arteagoitia et al. (10) designed a double-blind placebo-controlled randomized clinical study including 490 patients who had been treated with postoperative placebo or amoxicillin/clavulanic acid (500/125 mg, 3 times a day, 4 days). They reported that amoxicillin/clavulanic acid is useful in reducing the incidence of AO and infection following third molar extraction but should not be prescribed in all cases. On the other hand, some researchers published another placebo-controlled clinical study including amoxicillin combined with clavulanic acid 10 years later and they concluded that antibiotic therapy was more effective for pain relief, reduction of edema and enabling mouth opening than placebo, but not for the prevention of postoperative infections (18). Another prospective study reported by Poeschl et al. (19) revealed different results. The study involved three groups of patients requiring the removal of third molars. The patients received antibiotic treatment with amoxicillin clavulanic acid combination for five days postoperatively in the first group. In the second group, clindamycin was used and in the third group no antibiotic was given. They concluded that the postoperative antibiotic treatment did not contribute to a better wound healing, less pain or increased mouth opening. It could not prevent the inflammatory problems after surgery, and therefore was not recommended for routine use. Adde et al. (12) demonstrated that in postoperative prophylaxis there was no difference regarding the indication of amoxicillin, clindamycin or no antibiotic for prevention of postoperative complications in third molar surgery. Siddiqi et al. (3), Ataoglu et al. (20) and Rey et al. (21) also concluded that antibiotic prophylaxis was not useful for the prevention of postoperative complications. Bezerra et al. (22) reported that osteotomy or tooth sectioning was not associated with an increased incidence of inflammatory events and they suggested that the use of amoxicillin before third molar surgery did not significantly reduce the complications whether
they are related with infection or not. Recently, Xue et al. (16) investigated the effect of antibiotic prophylaxis on postoperative inflammatory complications after impacted lower third molar surgery. They concluded that amoxicillin is not effective for prevention or reduction of postoperative inflammatory complications in Chinese patients. Postoperative sequels after third molar surgery can significantly affect the patient’s QoL (1). Therefore, the reduction of postoperative complications is very important to ensure the comfort of patients after surgery. Although different methods have been used to assess QoL, it can be difficult to reach meaningful conclusions (9, 23). Some factors such as systemic disease, gender, analgesic use and duration of surgery can affect QoL after third molar surgery (24). Especially pain during the postoperative period after third molar surgery is the most important factor affecting the patients’ QoL (25). In this retrospective study, the type of antibiotic did not differ in terms of patient-reported QoL. Postoperative wound infections also can also affect patients’ QoL. The potential consequences of the wound infection for patients range from having increased pain to going into sepsis. Therefore, for the surgeons, surgical wound classification is important in predicting postoperative surgical site infections and associated risks. Surgical wound classification according to degree of contamination is evaluated into four groups as clean, clean-contaminated, contaminated and dirty wounds (26). Oral surgical procedures are included in the clean-contaminated group. The use of antimicrobial prophylaxis for the majority of clean-contaminated procedures is recommended because of the normal flora of the mouth is responsible for most infections that follow clean-contaminated surgical procedures (27). However, it should be kept in mind that the routine use of antibiotics may increase the risk of adverse effects and lead to the emergence of resistant organisms.

Conclusion

In this retrospective study, a strict inclusion criterion was used to determine the outcome of two different antibiotics. Within the limitations of the chart review design, it can be stated that amoxicillin and amoxicillin with clavulanic acid might provide similar outcome in terms of patient comfort following third molar surgery.

References

1. Ren YF, Malmstrom HS. Effectiveness of antibiotic prophylaxis in third molar surgery: A meta-analysis of randomized controlled clinical trials. J Oral Maxillofac Surg 2007;65(10):1909-1921.
2. Martin MV, Kanatas AN, Hardy P. Antibiotic prophylaxis and third molar surgery. Br Dent J 2005;198(6):327-330.
3. Siddiqi A, Morkel JA, Zafar S. Antibiotic prophylaxis in third molar surgery: A randomized double-blind placebo-controlled clinical trial using split-mouth technique. Int J Oral Maxillofac Surg 2010;39(2):107-114.
4. Kaczmarzyk T, Wichinski J, Stypulkowska J, Zaleska M, Panas M, Woron J. Single-dose and multi-dose clindamycin therapy fails to demonstrate efficacy in preventing infectious and inflammatory complications in third molar surgery. Int J Oral Maxillofac Surg 2007;36(5):417-422.
5. Limeres J, Sanroman JF, Tomas I, Diz P. Patients’ perception of recovery after third molar surgery following postoperative treatment with moxifloxacin versus amoxicillin and clavulanic acid: A randomized, double-blind, controlled study. J Oral Maxillofac Surg 2009;67(2):286-291.
6. Williams JD. Beta-lactamases and beta-lactamase inhibitors. Int J Antimicrob Agents 1999;12 Suppl 1:S3-7; discussion S26-27.
7. Lacasa JM, Jimenez JA, Ferras V, Bossom M, Sola-Morales O, Garcia-Rey C, Aguilar L, Garau J. Prophylaxis versus pre-emptive treatment for infective and inflammatory complications of surgical third molar removal: A randomized, double-blind, placebo-controlled, clinical trial with sustained release amoxicillin/clavulanic acid (1000/62.5 mg). Int J Oral Maxillofac Surg 2007;36(4):321-327.
8. Bush LM, Johnson CC. Ureidopenicillins and beta-lactam/beta-lactamase inhibitor combinations. Infect Dis Clin North Am 2000;14(2):409-433.
9. Hyland ME, Sodergren SC. Which global quality of life scale is most reliable and most preferred? Quality of Life Research 1997: 6 (Abstracts: 4th Annual Conference of ISOQOL, 167); 662-663.
10. Arteagoitia I, Diez A, Barbier L, Santamaria G, Santamaria J. Efficacy of amoxicillin/clavulanic acid in preventing infectious and inflammatory complications following impacted mandibular third molar extraction. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2005;100(1):e11-18.
11. Monaco G, Tavernese L, Agostini R, Marchetti C.
Evaluation of antibiotic prophylaxis in reducing postoperative infection after mandibular third molar extraction in young patients. J Oral Maxillofac Surg 2009;67(7):1467-1472.

12. Adde CA, Soares MS, Romano MM, Carnaval TG, Sampaio RM, Aldarvis FP, Federico LR. Clinical and surgical evaluation of the indication of postoperative antibiotic prescription in third molar surgery. Oral Surg Oral Med Oral Pathol Oral Radiol 2012;114(5 Suppl):S26-31.

13. Bulut E, Bulut S, Etkan I, Koseoglu O. The value of routine antibiotic prophylaxis in mandibular third molar surgery: Acute-phase protein levels as indicators of infection. J Oral Sci 2001;43(2):117-122.

14. Calvo AM, Brozoski DT, Giglio FP, Goncalves PZ, Sant’ana E, Dionisio TJ, Lauris JR, Santos CF. Are antibiotics necessary after lower third molar removal? Oral Surg Oral Med Oral Pathol Oral Radiol 2012;114(5 Suppl):S199-208.

15. Sekhar CH, Narayanan V, Baig MF. Role of antimicrobials in third molar surgery: Prospective, double blind, randomized, placebo-controlled clinical study. Br J Oral Maxillofac Surg 2001;39(2):134-147.

16. Xue P, Wang J, Wu B, Ma Y, Wu F, Hou R. Efficacy of antibiotic prophylaxis on postoperative inflammatory complications in Chinese patients having impacted mandibular third molars removed: A split-mouth, double-blind, self-controlled, clinical trial. Br J Oral Maxillofac Surg 2015;53(5):416-420.

17. Dellibasi C, Saracoglu U, Keskin A. Effects of 0.2% chlorhexidine gluconate and amoxicillin plus clavulanic acid on the prevention of alveolar osteitis following mandibular third molar extractions. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2002;94(3):301-304.

18. Arteagotia I, Ramos E, Santamaria G, Barbier L, Alvarez J, Santamaria J. Amoxicillin/clavulanic acid 2000 /125 mg to prevent complications due to infection following completely bone-impacted lower third molar removal: A clinical trial. Oral Surg Oral Med Oral Pathol Oral Radiol 2015;119(1):8-16.

19. Poeschl PW, Eckel D, Poeschl E. Postoperative prophylactic antibiotic treatment in third molar surgery—a necessity? J Oral Maxillofac Surg 2004;62(1):3-8, discussion 9.

20. Ataoglu H, Oz GY, Canderli C, Kiziloglu D. Routine antibiotic prophylaxis is not necessary during operations to remove third molars. Br J Oral Maxillofac Surg 2008;46(2):133-135.

21. Luaces-Rey R, Arenaz-Bua J, Lopez-Cedrun-Cembranos JL, Martinez-Roca C, Pertega-Diaz S, Sironvalle-Soliva S. Efficacy and safety comparison of two amoxicillin administration schedules after third molar removal. A randomized, double-blind and controlled clinical trial. Med Oral Patol Oral Cir Bucal 2010;15(4):e633-638.

22. Bezerra TP, Studart-Soares EC, Scaparo HC, Pita-Neto IC, Batista SH, Fontes ES. Prophylaxis versus placebo treatment for infective and inflammatory complications of surgical third molar removal: A split-mouth, double-blind, controlled, clinical trial with amoxicillin (500 mg). J Oral Maxillofac Surg 2011;69(11):e333-339.

23. Colorado-Bonnin M, Valmaseda-Castellon E, Berini-Aytes L, Gay-Escoda C. Quality of life following lower third molar removal. Int J Oral Maxillofac Surg 2006;35(4):343-347.

24. Braimah RO NK, Owoh DR, Aregbesola SB. Impact of oral antibiotics on health-related quality of life after mandibular third molar surgery: An observational study. Nig J Clin Pract Article in Press.

25. Adeyemo WL, Taiwo OA, Oderinu OH, Adeyemi MF, Ladeinde AL, Ogunlewe MO. Oral health-related quality of life following non-surgical (routine) tooth extraction: A pilot study. Contemp Clin Dent 2012;3(4):427-432.

26. Berard F, Gandon J. Postoperative wound infections: The influence of ultraviolet irradiation of the operating room and of various other factors. Ann Surg 1964;160(Suppl 2):1-192.

27. Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaerter PG, Bolon MK, Fish DN, Napolitano LM, Sawyer RG, Slain D, Steinberg JP, Weinstein RA, American Society of Health-System P, Infectious Disease Society of A, Surgical Infection S, Society for Healthcare Epidemiology of A. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Am J Health Syst Pharm 2013;70(3):195-283.

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