Combined Application of Amoxicillin and Clavulanic Acid After Oral Surgical Interventions

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Abstract

Antibiotics represent a powerful weapon against infections. As dentists we are faced almost on a daily basis with the need to proscribe antibiotics. At the same time, we can often see that the antibiotics use tends to get out of control or that they are used indiscriminately with no real need. The aim of this case study is to investigate the effectiveness of amoxicillin and clavulanic acid combination in various dental ailments but also to demonstrate possible difference in the severity of symptoms after the use of amoxicillin and antibiotic combination of amoxicillin and clavulanic acid after surgical and oral interventions.The investigation involved 102 patients who were divided into two groups (the first group consisting of 59 and the second one of 43 patients). Following surgical treatment the first group of patients was proscribed antibiotic combination of amoxicillin and clavulanic acid in the dosage of 625 mg, 3 times per day. The second group of 43 patients was proscribed amoxicillin in the dosage of 500 mg, 4 times per day. The recommended therapy for antibiotic combination of amoxicillin and clavulanic acid was 5 to 10 days after the operation and 8 to 10 days for amoxicillin. In other words, both groups of patients started to use antibiotics after the surgical or oral intervention such as operative removal of impacted wisdom teeth, apicotomy or complicated extractions, and also after the treatment of odontogenic abscesses etc. The same parameters were measured prior to the surgical intervention in cases when patients demonstrated the symptoms before the operational treatment while in all other cases the parameters were measured 48 hours and seven days following the operation. The measured parameters were: pain, swelling, body temperature, dysfunction such as dysphagus trismus, chewing disorder and possible allergic or gastrointestinal reactions. All parameters observed were precisely set in order to harmonize the investigation criteria and facilitate statistical data processing. With respect to pain before the operation there was no substantial statistical difference, $p>0.05$ ($t=0.56$; $t=0.69$). With respect to the onset of pain and the use of antibiotics after 48 hours there is a significant difference in favor of antibiotic combination of amoxicillin and clavulanic acid ($\chi= 14.83$, $p= 0.002$; $p <0.01$). Thus, pain is less acute if antibiotic combination of amoxicillin and clavulanic acid is administered. With respect to swelling and administration of antibiotics 48 hours after the operation there is no significant difference between the use of the two antibiotic therapies ($\chi= 4.89$; $p=0.18$; $p>0.05$). The investigation conducted seven days after the operation with regard to pain and the use of either antibiotic therapies demonstrated significant statistical difference ($\chi=9.35$, $p<0.01$) in favor of antibiotic combination of amoxicillin and clavulanic acid. In other words, patients who used amoxicillin and clavulanic acid felt significantly less intense pain. With respect to swelling, significant statistical difference between the two groups of patients was estalished in favor of antibiotic combination of amoxicillin and clavulanic acid, i.e. $p<0.05$ ($\chi=6.45$, $p=0.03$). The combination of amoxicillin and clavulanic has proven to be significantly more effective in comparison with the use of amoxicillin after oral - surgical interventions, and therefore antibiotic combination of amoxicillin and clavulanic acid is recommended for use in further practice.
KEY WORDS: antibiotics, oral-surgical interventions

Introduction

Antibiotics are still considered to be powerful agents against infections. As dentists we find ourselves almost on a daily basis in situations when we have to proscribe antibiotics. At the same time, we are aware of the uncontrolled and indiscriminate use of antibiotics in dental practice. The questions being asked at this point are: "What are the indications for antibiotics application in dental practice? What kind of antibiotics should we opt for?" Hooley and Whitecare (1) deal with the question of indications for the use of antibiotics in dental practice. Together with their associates they addressed this issue as early as 1984. According to these authors antibiotics can serve as a useful tool in the treatment of infection. On the other hand, random and inappropriate use of antibiotics can prove detrimental for a patient suffering from dental infection but also for the treatment of other infections. The antibiotics abuse in the treatment of infections is of minor therapeutic value and only incurs unnecessary costs. In addition, it can complicate clinical picture and compromise further treatment. Broad abuse of antibiotics, according to the same authors, has led to an increase of resistance in bacteria, widespread allergies in patients so that the long-term effectiveness of antibiotics is reduced. Based on the above the same authors refer to indications and counter indications in the use of antibiotics in dental practice:

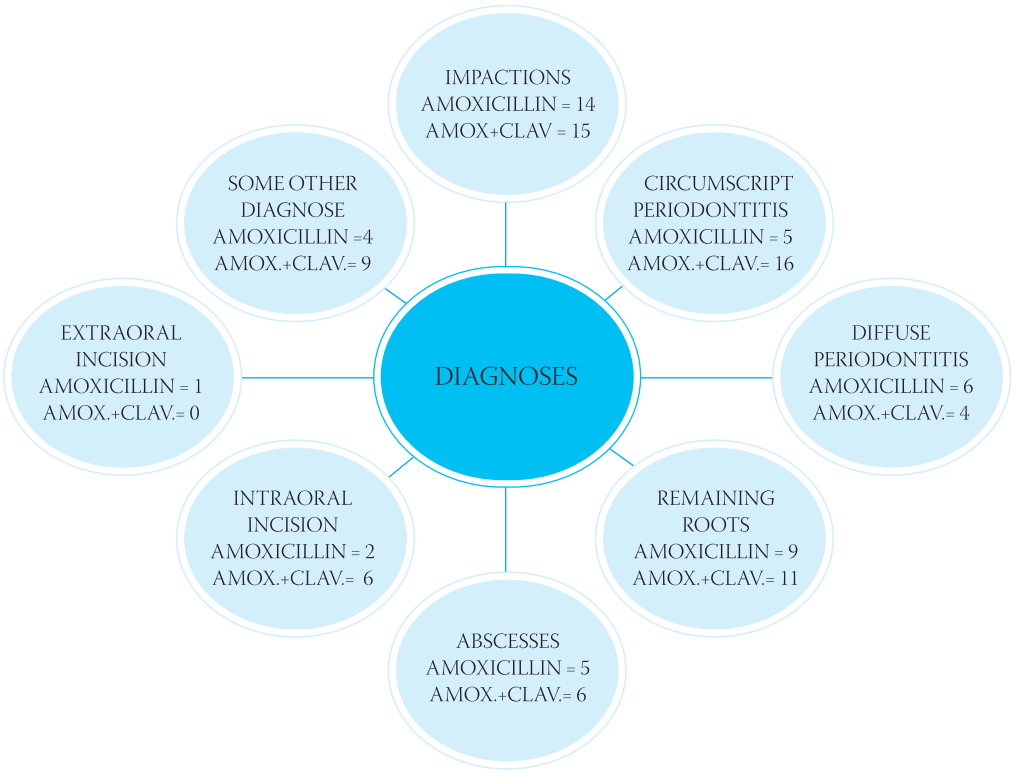
INDICATIONS
For treatment of acute infection
If the immune system of the host is seriously threatened because of primary disease or use of drugs.
As a prophylaxis from infection in patients with artificial valves, hip transplant etc.
When infection is the cause of systemic limphadenopathy.
With facial and cervical cellulitis
With acute pericoronitis
With osteomyelitis
With fungal infection
With acute periapical and periodontal abscess
When appropriate therapy cannot be applied and/or surgical intervention (extraction, incision)

COUNTER INDICATIONS
With minor chronic, well localized infections (chronic periodontal abscess).
For improved wound healing
As a prophylaxis in minor surgical and dental interventions
For sterilization of the root canal
For treatment of chronic pericoronitis and chronic gingivitis
For treatment of localized osteitis, acute osteitis and acute alveolar osteitis
As a prophylaxis in oroantral communications smaller than 2 mm
After minor surgical interventions such as: tooth extraction, small excisions on the palate, cheek, alveolar mucosa etc.
As a component of periodontal packaging
As packaging is applied in surgical wound

In dental medicine the most commonly proscribed antibiotics are broad-specter penicillin drugs which are used either orally or parenterally. Pain and swelling in the area of oral cavity or face, the impaired function and increased body temperature are the most common symptoms that bring patient to the dentist. The combat against these symptoms implies the use of antibiotics. The same symptoms appear after oral and surgical interventions such as:

- Surgical removal of wisdom teeth
- Apicotomy
- Surgical removal of the remaining roots
- Abscess incisions
- Surgical closing of the maxillary sinus
- Treatment of osteomyelitis etc.

In order to reduce the symptoms and to make the postoperative period of recovery more comfortable for the patient we have opted to proscribe the penicillin antibiotic Amoxicillin*. Amoxicillin is polysynthetic penicillin of a broad specter similar to ampicillin. Its range of action is based on inhibiting transpeptidisis, the enzyme which prevents the synthesis of mucopeptides in the bacterial membrane and the former prevents its building. Amoxicillin belongs to ß group of lactam antimicrobes and is sensitive to ß lactamasis. It acts against gram-positive and gram-negative microorganisms (bacteria). The dosage for the adult patients is 500 mg or 4 times per day. At this, one capsule contains 500 mg of amoxicillin in the form of amoxicillin trihydrate. Its good property lies in a wide range between its therapeutic and toxic dosage. Similar to this antibiotic is amoxicillin+clavulanic acid antibiotic, which is in fact the combination between amoxicillin and clavulanic acid Clavulanic acid is irreversible inhibitor of ß lactamasis which forms stable and inactive compounds together with enzymes, and in this way, prevent further resorption of amoxicillin increasing at the same time its ef-



GRAPH 1. Treated diagnoses (amox.+clav.=amoxicillin+clavulanic acid)

fect on poorly sensitive and penicillin-resistant bacteria. Anti-bacterial range of effect of this compound involves:
Aerobe gram-positive bacteria
Aerobe gram-negative bacteria
Anaerobe bacteria

Unlike Amoxicillin which is manufactured in capsules and forte suspensions, antibiotic combination of amoxicillin and clavulanic acid is manufactured in film tablets, suspension, forte suspension and injections. The aim of this case study is to investigate the effectiveness of antibiotic combination of amoxicillin and clavulanic acid in various dental ailments and to find evidence that supports the existence of differences in the symptom intensity after the application of amoxicillin in comparison with antibiotic combination of amoxicillin and clavulanic acid after the oral - surgical interventions.

SUBJECTS AND METHODS USED IN THE INVESTIGATION

This investigation was done respecting ethical standards stipulated in Helsinki Declaration. The total of 102 patients were included in the investigation. They were divided into two groups: (one group consisted of 59 patients and the other of 43 patients). The first group (59 patients) were proscribed antibiotic combination of amoxicillin and clavulanic acid after the operation in the dosage of 625 mg, 3 times per day. The second group (43 patients) was proscribed amoxicillin after the operation in the dosage of 500 mg, 4 times per day. The recommended therapy duration for antibiotic combination of amoxicillin and clavulanic acid was 5 to 10 days and 8 to 10 days for amoxicillin. Thus, in both groups the patients started using antibiotic after an oral-surgical intervention such as

- Operative removal of wisdom tooth
- Apicotomy in diffuse and circumscript periodontitis
- Operative removal of the remaining roots
- Treatment of dental abscesses etc. (Graph. 1.)

The same parameters were measured before the surgical intervention in cases when the patients had the symptoms before the operation and in all cases after 48 hours and 7 days following the operation. The parameters measured were pain, swelling, body temperature, dysfunction such as dysphagia trismus, chew-

ing dysfunction. All the parameters were strictly defined in order to harmonize the investigation criteria and facilitate statistical data processing. The parameters follow: Pain 0- the patient does not feel any pain
Pain 1- insignificant pain that does not impair function
Pain 3- a considerable pain with the impaired function
Pain 4- an intense pain which prevents peaceful sleeping

Swelling 0 - it is not shown visually
Swelling 1 - insignificant swelling detected by palpation
Swelling 2 - swelling is visually noticed, ex. the erased nasolabial furrow.
Swelling 3 - significant swelling which affected one area
Swelling 4 - exceptionally visible swelling which has spread to other areas

Results

	PAIN 0	PAIN 1	PAIN 2	PAIN 3
AMOXICILLIN	1	7	10	8
AMOXICILLIN+CLAV.ACID	4	16	9	6

TABLE 1. Pre-operative symptoms: Pain

	SWELLING 0	SWELLING 1	SWELLING 2	SWELLING 3	SWELLING 4
AMOXICILLIN	7	7	4	6	2
AMOXICILLIN+CLAV.ACID	13	16	4	2	0

TABLE 2. Pre-operative symptoms: Swelling

With respect to the pain symptom before the operation there was no significant statistical difference, $p>0.05$ ($t=0.56$; $t=0.69$). With respect to the swelling symptom before the operation there was no significant statistical difference, $p>0.05$: $t=0.1$; $p=0.48$). The results of the above tables indicate that the sample was exceptionally homogenous and therefore, valid for the above-indicated calculations.

	PAIN 0	PAIN 1	PAIN 2	PAIN 3
AMOXICILLIN	19	16	5	2
AMOXICILLIN AND CLAV.ACID	27	22	8	0

TABLE 3. The first check-up after 48 hours: Pain symptom

Between the onset of pain and the use of two antibiotics there is significant statistical difference in favor of antibiotic combination of amoxicillin and clavulanic acid ($\chi=14.83$, $p=0.002$; $p<0.01$).

	SWELLING 0	SWELLING 1	SWELLING 2	SWELLING 3	SWELLING 3
AMOXICILLIN	12	13	13	4	0
AMOXICILLIN AND CLAV.ACID	10	30	12	5	0

TABLE 4. The first check up after 48 hours: Swelling symptom

Between the onset of swelling and the use of two antibiotics there is not a significant statistical difference ($\chi=4.89$; P=0>18; P-0.05).

	PAIN 0	PAIN 1	PAIN 2	PAIN 3
AMOXICILLIN	32	7	1	0
AMOXICILLIN AND CLAV.ACID	56	1	0	0

TABLE 5. The second check-up after 7 days: 'Pain' symptom

After 7 days there is a significant statistical difference in relation to 'pain' symptom and the use of two antibiotics: $H2= 9.35$, $p<0.01$, and it tilts significantly in favor of antibiotic combination of amoxicillin and clavulanic acid use. In other words, the pain is significantly smaller after the administration of antibiotic combination of amoxicillin and clavulanic acid.

	SWELLING 0	SWELLING 1	SWELLING 2	SWELLING 3	SWELLING 4
AMOXICILLIN	32	6	2	0	0
AMOXICILLIN AND CLAV.ACID	55	21	0	0	0

TABLE 6. The second check-up after 7 days: 'Swelling' symptom

After 7 days, with respect to swelling there is a significant statistical difference between the patients regarding the treatment with the two antibiotics, $p<0.05$ ($H2= 6.45$, $p = 0.03$) in favor of antibiotic combination of amoxicillin and clavulanic acid.

	EXCELLENT THERAPY	GOOD THERAPY	UNSATISFACTORY THERAPY
AMOXICILLIN	31	10	2
AMOXICILLIN AND CLAV.ACID	50	7	2

TABLE 7. Effectiveness of therapy

With regard to the therapy outcome between the users of the two antibiotics there is a significant statistical difference in favor of antibiotic combination of amoxicillin and clavulanic acid ($\chi=15.00$; $p= 0.001$; $p<0.001$).
We have also monitored the emergence of potential allergic reactions and gastrointestinal disorders in course of the antibiotic administration:

GRADE*	NUMBER OF PATIENTS
ALLERGIC REACTIONS 0	42
ALLERGIC REACTIONS 1	0
ALLERGIC REACTIONS 2	0
ALLERGIC REACTIONS 3	3
GASTROINTESTINAL REACTIONS 0	41
GASTROINTESTINAL REACTIONS 1	0
GASTROINTESTINAL REACTIONS 2	1
GASTROINTESTINAL REACTIONS 3	1
OTHER UNDESIRABLE REACTIONS	0

*Grade: 0 = no reaction; 1 = mild reaction; 2 = moderate reaction; 3 = severe reaction

TABLE 8. Undesirable reactions to amoxicillin

GRADE*	NUMBER OF PATIENTS
ALLERGIC REACTIONS 0	57
ALLERGIC REACTIONS 1	0
ALLERGIC REACTIONS 2	2
ALLERGIC REACTIONS 3	0
GASTROINTESTINAL REACTIONS 0	48
GASTROINTESTINAL REACTIONS 1	6
GASTROINTESTINAL REACTIONS 2	3
GASTROINTESTINAL REACTIONS 3	2
OTHER UNDESIRABLE REACTIONS	3

*Grade: 0 = no reaction; 1 = mild reaction; 2 = moderate reaction; 3 = severe reaction

TABLE 9. Undesirable reactions to antibiotic combination of amoxicillin and clavulanic acid

Discussion

As it was stressed at the beginning of this case study report antibiotics play an exceptionally important role in medicine in general, and also in dental medicine. General dental practitioner and especially oral surgeon are often brought into a situation when he/she faces a dilemma regarding antibiotic prescribing. Uncritical and careless antibiotic proscribing brings more harm than benefit. This problem is still tackled by many authors. Thus, Haas and his associates (2) deal with the problem of resistance to antimicrobes in their study conducted in 1998. They emphasize that the resistance of bacteria, fungi and viruses to antimicrobes is steadily increasing with detrimental effects. The role of dentistry in this respect is still unclear. Nevertheless, the dentists need to know how to proscribe antibiotics properly, treat infections effectively and minimize likely development of bacterial resistance to antimicrobes. The aim of the above authors study was to raise the awareness of dentists of the dangers involved in treating antimicrobial resistance and to the ways of avoiding the same (2). Furthermore, Epstein and his associates (3) assert that antibiotics play an important role in the treatment and prophylaxis of infections. Because of the resistance to antibiotics the authors have conducted their research with the aim of benefiting assessment of particular antibiotics in the dental practice. The data were gathered on the basis of the sample filled in by trained dentists in British Columbia in Canada. The total of 2.542 sample forms were sent to them, out of which 19.9 ? were returned either by fax or mail. The collected data were analyzed by applying chi test. It was proven that penicillin and its derivatives were the most commonly proscribed antibiotics following a dental treatment. An average duration of antibiotic therapy was 6.9 days. On average, dentists proscribed antibiotics 1.15 times per week as prophylaxis against bacterial endocarditis, 17.5 % of physicians proscribed antibiotics as prophylactic protection postoperatively in the duration of one to seven days. Antibiotics were proscribed preoperatively to patients who suffered from rheumatic fever, heart murmur or those with an artificial hip. Antibiotics were commonly proscribed in surgical interventions to patients who suffere from the immune-deficiency syndrome. In their conclusion, the above authors have stressed that the appropriate and timely antibiotic administration is a way to ensure an effective treatment and avoid bacterial resistance to antibiotics. In order to raise the standards, dentists are advised to get to know pharmacology and be committed to lifelong learning (3). Beckford – Ball (4) states that since the discovery of penicillin antibiotics have had a significant impact on health maintenance. However, practitioners are faced with the common proscribing dilemma. How can we continue with the practice of appropriate antibiotic proscribing with the minimum risks of bacterial resistance to antibiotics (4)? Our view is that an appropriate antibiotic proscribing is a very topical issue. In our environment beset with very low standards regarding oral hygiene and health, the dentists are often placed into a situation to proscribe antibiotics. In order to ensure full effectiveness of the proscribed drug it is important to know the appropriate dosage and duration of its administration. In our study report in view of the severity of the clinical picture we proscribed antibiotic combination of amoxicillin and clavulanic acid for 5 to 10 days in the dosage of 625 mg 3 times per day, and amoxicillin for 8 to 10 days in the dosage of 500 mg 4 times per day. We had to stop administering antibiotic combination of amoxicillin and clavulanic acid in two patients after the expiration of two days because of side effects. In other cases when we proscribed antibiotic combination of amoxicillin and clavulanic acid the patients used it arbitrarily for 2, 3, 6 or 7 days in accordance with their personal feelings. In cases of amoxicillin proscription some patients have also arbitrarily reduced the duration of the therapy to 3 or 5 days depending on their individual state. Some patients took the medication only for 2 days because of allergic reaction. Therefore, the patients themselves are often responsible for the bacterial resistance to antibiotics because of their failure to follow the proscription instructions. Pallasch (5) stresses that due to the antibiotic abuse people have brought about the situation wherein all microorganisms acquired resistance to some antibiotics while other microorganisms became resistant to all antibiotics. The greatest benefit of the antibiotic use is assistance to the host in controlling and defending against infection. On the other hand, antibiotics may cause toxic and allergic reactions, super-infections followed by resistant bacteria, chromosome mutations that lead to microbe resistance and also they can instigate eruption of dormant, resistant genes (5). Palmer with his associates (6) deal with the same problem. In their work (published in 2001) they point to the problem of unselective and inappropriate antibiotic proscribing in the form of solutions that are given to children. This can contribute to the development of bacterial resistance. The way to prevent such a situation is to follow clear instructions about the kind of antibiotic that is to be proscribed, its

dosage and the duration (6). The aim of the study conducted by Anderson and his associates (7) in 2000 was to compare the level of proscribing and the kind of antibiotic proscribed by general practitioners (GPs) and dentists for various dental ailments. In their conclusion they state that GPs tend to proscribe antibiotics for dental problems more often than dentists. There are also differences in proscribing broad-specter antibiotics. According to these authors GPs and dentists as well should rationalize the administration of antibiotics (7). In our investigation we came across problems when GPs did not obey the dentist's proscription of antibiotic combination of amoxicillin and clavulanic acid but instead proscribed some other antibiotic, mostly cephalosporins. Unfortunately, this is the case of lack of cooperation between the GP and the dentist. Oral cephalosporins are not effective against many anaerobic gram-positive cocci such as peptococcus and peptostreptococcus as well as against many anaerobic gram-negative bacteria such as *Bacteroides species*, i.e. *Bacteroides fragilis* which is often the cause of odontogenic infection. Thus, the use of oral cephalosporin for the treatment of odontogenic infection can result in super-infection (1). The issue of rational antibiotic administration is also topical. In this respect, the aim of the study conducted by Palmer and his associates (6) was to investigate whether the clinical revision may improve antibiotic proscribing by general dentists. The investigation was conducted in general dental surgeries in the north-west of England involving 175 general dentists. The records were kept about the kind of antibiotic proscribed, its dosage and the duration of therapy, clinical indicators and the health state of patients, but also about other reasons which led to the antibiotic proscription. The comparison was made between the antibiotic proscribing before and after the clinical revision. The study results have shown that antibiotics proscribing has decreased by 42.5% after the revision (or following the instructions). In all situations the most commonly proscribed antibiotics were amoxicillin (57.6 %), metronidazol (23.8 %), penicillin (9.3 %) erythromycin (4.8%) and the combination of amoxicillin and metronidazol (1.7 %). In the aftermath of issuing the instructions with regard to the antibiotic proscription a significant decrease in proscriptions followed ($p< 0.05$). The results of this study lead to the conclusion that the clinical revision in view of antibiotic proscribing and the publication of written instructions and the educational training may rationalize the use of antibiotics in general dental surgeries (8). In this way, in order to avoid indiscriminate and scientifically unfounded use of antibiotics, it is an imperative to follow rigorously strict indications for the use of antibiotics. It is also a way to decrease costs and increase good results of the treatment. We believe that it is by and large the responsibility of oral surgeons to proscribe antibiotics for specific dental ailments. This was confirmed by the author Preus and his associates (9) in their work conducted in 1992. They investigated the practice of antibiotic proscribing by Norwegian dentists. The results showed that antibiotics were most commonly proscribed by oral surgeons and paradontologists in comparison with general dentists (9). A particular segment of antibiotic use consists of antibiotic prophylaxis. Nevertheless, not all cardiological states demand antibiotic prophylaxis. Indiscriminate use of antibiotics for these purposes can also bring more harm than benefit. Tong and his associates dealt with this problem in 2000. According to their review article the latest recommendations of AHA association were that only in few situations was the antibiotic prophylaxis necessary prior to the dental intervention. The same authors believe that, at the present moment, the risks of inappropriate use of antibiotics and the development of bacterial resistance outweigh the possible benefits. In their conclusion they recommend antibiotics use only in strictly defined situations that are scientifically grounded (10). Antibiotic combination of amoxicillin and clavulanic acid is not suitable for a single-day antibiotic prophylaxis because the dosage of 2 grams of this antibiotic would amount to the overdose with clavulanic acid, and that, in turn, could bring about the undesirable reaction such as diarrhea. One of the reasons for the use of antibiotics is the protection against the infection after the surgical intervention. Thomas and his associates (11) indicate to the fact that antibiotic use as a prophylactic measure against the infection after the removal of impacted third molars is widespread. It seems that the benefits of resorting to this kind of prophylaxis are marginal. Also, according to the same authors there is little evidence to support the use of the second and third generation of antibiotics in routine prophylaxis. In their study the above authors indicated the need to rationalize the use of antibiotics which would also be cost-effective (11).Classen and his associates tackled the same problem (12). They point to the fact that randomized control studies have shown the efficacy of antibiotic prophylaxis in the prevention of infection of surgical wounds (12). In our study we have attempted to investigate the intensity of postoperative symptoms, especially of pain and swelling after the use of antibiotic combination of amoxicillin and clavulanic acid and amoxicillin antibiotics. The idea to undertake this investigation was born after we noticed that the

administration of antibiotic combination of amoxicillin and clavulanic acid contributed to faster recovery of patients in the postoperative period. Our aim was to find evidence to support that this was not a mere accident and we have conducted our investigation on the sample that is sufficiently large for statistical analysis.

Conclusion

The combination of amoxicillin and clavulanic acid has proven to be significantly more effective after the oral-surgical interventions in relation to the effect of amoxicillin antibiotic. Therefore, we recommend the proscription of antibiotic combination of amoxicillin and clavulanic acid in the future dental practice.

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