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Efficacy and safety comparison of two amoxicillin administration schedules after third molar removal. A randomized, double-blind and controlled clinical trial

Ramón Luaces-Rey [1], Jorge Arenaz-Búa [1], José-Luis López-Cedrún-Cembranos [1], Cristina Martínez-Roca [2], Sonia Pértega-Díaz [3], Sheyla Sironvalle-Soliva [1]

[1] Department of Oral and Maxillofacial Surgery, A Coruña University Hospital
[2] Department of Clinical Pharmacology
[3] Department of Epidemiology and Biostatistic

Correspondence:-Búa
Servicio de Cirugia Maxilofacial
Complexo Hospitalari A Coruña
As Xubias 84
15006, A Coruña, Spain
ramon.luaces.rey@sergas.es

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Abstract

Objective: The aim of this comparative double-blind, prospective, randomized, clinical trial was to evaluate two amoxicillin administration patterns. The first was a short prophylactic therapy and the second a long postoperative regimen.

Study Design: The study population consisted of 160 patients who underwent mandibular third molar extraction. Patients were randomized into two equal groups. In group 1, 2 grams of amoxicillin were administered 1 hour before the procedure and 1 gram 6 hours after surgery. In group 2, patients received 1 gram of amoxicillin 6 hours after surgery followed by 1 gram every 8 hour for 4 days. All patients received the same number of tablets thanks to the use of placebo pills. A total of 25 variables were evaluated, such as alveolitis, surgical infection, number of analgesic needed, subjective pain scale, post-surgical inflammation, consistency of the diet, axillary temperature and millimetres of mouth opening loss after the surgery.

Results: No statistically significant post-operative differences were found within the recorded parameters between the groups.

Conclusions: Postoperative 4-days amoxicillin therapy is not justified.

Key words: *Antibiotic prophylaxis, third molar surgery, oral surgery.*

Introduction

Surgical third molar removal is one of the most usual procedures in oral and maxillofacial surgery (1,2). It is considered a clean-contaminated procedure due to oral colonization by more than 400 aerobic and anaerobic species (3-5). Usual postoperative sequelae are pain, trismus and facial swelling. The procedure can also lead to complications such as alveolitis (0.5-60%), and surgical infection (1-25%) (6) which is more frequent than in any other teeth extraction (2).

More than 40 years ago Kay obtained a spectacular inflammatory and infectious events reduction with the

only administration of one dose of penicillin prior to wisdom teeth removal. Since then, antibiotic administration is a standard practice for this purpose (1,7,8). However there is not a widely accepted antibiotic protocol yet. Nowadays the most usual guideline is the postoperative administration of oral amoxicillin for 4-8 days, for inflammatory sequelae prevention mainly (9,10). However, despite 60 years of experience with the use of antibiotics, its systematic use for this procedure remains controversial (4,6). Some authors state that the percentage of post- surgical infections does not increase without the use of antibiotics (2,11), and the opposite opinion has been supported by others (1).

Resistant bacterial stocks selection, secondary effects of the drugs (headache, allergic and digestive events mainly) and also the added economical cost are the disadvantages of antibiotic use. Amoxicillin has extended spectrum coverage with low toxicity and unfrequent and well-known secondary effects (5,10,12). Although specific antibiotic against anaerobic bacteria such as metronidazole are useful for the prevention dry-socket, amoxicillin is more useful avoiding of wound infection. Some authors showed that an only dose of antibiotic is useful for prevention of dry-socket but not for prevention of wound infection (1). Many authors defend the need to obtain therapeutic levels at the beginning of the procedure, recommending the oral administration at least 1 hour before the surgery (2,9,13). The objective of this clinical trial was to compare two amoxicillin administration patterns. The first one is a short prophylactic therapy (2 doses in 1 day) and the second is a long postoperative regimen (4 days).

Materials and Methods

This is a randomized, double-blinded, controlled clinical trial. Two oral amoxicillin administration patterns for third molar surgery are compared. The initial study population consisted of 160 patients in whom the extraction of 1 total or partial impacted mandibular third molar was performed in the Department of Oral and Maxillofacial Surgery of A Coruña University Hospital. The basic criterion for including the patient in the study was a need for surgical extraction of retained or partially erupted lower third molar due to malposition or any previous infectious or pain episode.

Exclusion criteria were: age under 18 or over 60, erupted third molar or with cavity, pericoronitis or abscess in the previous month, systemic infectious disease, immunodepression, patients on corticosteroids or citostatic treatment, antibiotic administration in previous 48 hours, history of allergy or intolerance regarding any of the drugs prescribed in the study, intolerance to lactose, antecedents of recent and/or symptomatic peptic ulcer, pregnancy or breast-feeding, acute oral diseases and difficult follow-up or carry-out the treatment.

All patients were informed about the study, and written, dated, informed consent was obtained from all patients prior to study entry. The decision could be revoked at any time. Patients were randomly enrolled to one of the two treatments. Patients in group 1 (prophylaxis regimen group) received 2 grams of amoxicillin 1 hour before surgery in a single dose, and a second dose of 1 gram of amoxicillin 6 hours after surgery. Afterwards patients took one tablet of placebo every 8 hours for 4 days.

Patients in group 2 (Postoperatively regimen group) received two tablets of placebo in a single dose 1 hour before surgery, followed by a second dose of 1 gram of amoxicillin 6 hours after and one tablet of 1 gram amoxicillin every 8 hours for 4 days. All patients had the same number of tablets due to placebo pills.

The study was designed as a double blind trial in which the patients were randomly assigned through a blocking randomization scheme to two test groups according to the type of antibiotic treatment (short prophylactic antibiotic regimen or long postoperatively regimen). One of the pharmacists of the hospital was responsible for the blindness of the trial. To ensure so, a random assignment code was enclosed to the pharmacist, who was responsible for providing the surgeon with a pack containing 14 tablets for every patient. The first two pills would be administrated 1 hour before the surgery, and these would contain 1 gram of amoxicillin or placebo (depending of the assigned group). The size, color and shape of the tablets were exactly the same across the two groups so as to preserve the blindness of the study for both the patient and the surgeon. Furthermore, he designed his own internal secret drug code which was labeled to the outer side of the tablet`s pack. The pharmacist kept a log matching each individual treatment`s composition to the drug code (a random alpha-numerical code) and to the randomization code. That way he was the only person able to unmask the treatment assignation for any patient in case a severe and/or unexpected side-effect would take place. The same anti-inflammatory and analgesic drugs completed the treatment in every patient deflazacort 30 mg (Zamene®, Laboratorio Menarini, Spain) was used as anti-inflamatory drug (one pill every 12 hours for 5 days) and dexketoprofen in 25 mg capsules (Enantyum®, Laboratorio Menarini, Spain) was used for pain rescue, every 8 h depending on the presence of pain for the necessary time (the number of analgesic pills during the week was recorded). Mouthwash with 0.12% chlorhexidine (Laboratorio Lacer, Spain) every 8 hours the first week was used as well.

At the time of surgery, the surgeon was provided with a set of opaque, sealed envelopes, containing each the drug code for one patient. Every time a patient fulfilled the inclusion criteria and gave informed consent, an envelope was opened and the patient was provided the

tablets pack which matched the drug number. This drug number was registered in the patient's diary.

The extractions were performed under local anesthesia following the standard technique: 4% artricaine with epinefrine 1:200.000 (Ultracain®, Hoechst AG, Germany). A full-thickness mucoperiosteal flap was raised. Bone removal and odontosection were performed as needed, and recorded. Closure was done with resorbable sutures (3-0) of Polyglactin 910 (Vicryl rapid®, Ethicon, US). Each procedure was timed from first incision to completion of last suture and recorded classifying this variable in 3 groups (less than 5 minutes, between 5 and 10 and more than 10 minutes). Variables were recorded by the surgeon on the day of the procedure, daily by the patient the first week and by an observer the seventh postoperative day. The three of them (patient, surgeon and observer) were blind for the treatment group assigned during all the study (Table 1).

Table 1. Recorded variables the day of surgery and 1 week post-operatively.

	GROUP 1 (2doses)	GROUP 2 (4 days therapy)
SEX		
Female	50 (71.4%)	47 (62.7%)
Male	20 (28.6%)	28 (37.3%)
AGE (mean)	27,9	26,5
CAUSE OF EXTRACTION		
Malposition	21	21
Malposition+Infection	23	25
Infection	11	20
Malposition+Pain	10	6
Malposition+Infection+Pain	5	3
MANDIBULAR SIDE		
Left	37 (52.9%)	36 (48%)
Right	33 (47.1%)	39 (52%)
IMPACTION		
Included	26 (37.1%)	31 (41.3%)
Semi-erupted	44 (62.9%)	44 (58.7%)
ANGULATION TYPE		
Mesioangular	26 (37.1%)	36 (48%)
Distoangular	9 (12.9%)	5 (6.7%)
Vertical	19 (27.1%)	12 (16%)
Horizontal	16 (22.9%)	22 (29.3%)
DURATION		
<5 min	19 (27.1%)	21 (28%)
5-10 min	32 (45.7%)	37 (49.3%)
>10 min	19 (27%)	17 (22.7%)
OSTECTOMY	58 (79.5%)	67 (87%)
TOOTH SECTION	38 (52.1%)	43 (55.8%)
INFECTION	3 (4.3%)	4 (5.3%)
ALVEOLITIS	2 (2.9%)	0
HAEMATOMA	0	2 (2.6%)
WOUND DEHISCENCE	23 (32.9%)	23 (30.3%)
INTRAORAL INFLAMMATION	35 (50%)	30 (40%)
POST-SURGICAL MOUTH OPENING LOSS (MEAN IN MM)	8.5	8.4
HYPOESTHESIA	0	3 (4%)
DIARRHOEA	1 (1.4%)	1 (1.3%)
NAUSEA OR VOMIT	0	2 (2.6%)
EPIGASTRALGIA	1 (1.4%)	0
CUTANEOUS RASH	0	0

Age, sex, cause of extraction (pain, orthodontics, malposition or infection), the tooth to be extracted (left, right) and the degree of impaction (total or parcial), position (vertical. mesioangular, distoangular, horizontal), maximum preoperative oral opening between incisors (using Therabite® scale) were noted at the preoperative radiographic and clinical examination. The technical characteristics were recorded after the surgery: time duration (less than 5 minutes, 5-10 minutes, more than 10), bone removal and sectioning of the tooth.

After surgery, every patient was provided the antibiotic tablets pack, a diary form and given homogeneous instructions for postoperative care and on how to fill in each item. So the patient's answers and judgments are free of knowledge about the treatment received. A daily registration form includes the daily registration of pain with a subjective pain scale ranging horizontally from 0 to 10 (visual analogue scale –VAS-), type of diet (liquid, soft or normal), corporal temperature and the number of analgesic pills taken every day (Table 2).

All patients were then given an appointment to be seen 7 days post-operatively and written instructions to consult the hospital at any time on any day in case of complications. Care was also taken to ensure that complaints noted on a day other than that of the regular check-up were recorded in the file. On the seventh day, a blind observer who did not participate in the surgical procedure was in charge of clinical follow-up of all the patients. Inflammatory and infectious symptoms were registered: alveolar osteitis, wound infection, haematoma, wound dehiscence, intraoral inflammation hypoesthesia of lingual or alveolar nerve and maximum postoperative mouth opening measured using the same ruler used before (Therabite®) in order to estimate the millimetres of mouth opening loss. Side effects such as nausea, vomiting, epigastralgia, abdominal discomfort, skin rash or headache were inquired about for the examination. Besides it was noted the possible causes if the patient did not complete the treatment correctly.

Clinical criteria of infection were any of the following 1) presence of purulent discharge in the extraction socket and/or excessive swelling with fluctuation, 2) presence of a local abscess, 3) onset of facial or cervical cellulitis plus other signs suggesting infection such as pain, increased heat, erythema and/or fever; 4) excessive swelling with or without pain not related to the surgical trauma. For alveolar osteitis diagnosis: absence of the haematic clot of the orifice and presence of a putrid smell and intense neuralgic type pain. In the last case, a second look at the wound and surgical cleaning were necessary.

Numeric variables were trismus (mouth opening loss, calculated from preoperative and postoperative measurement, considering a 5 millimetres difference as clinically significant), subjective pain scale, number of analgesic tablets needed and axillary temperature. All the others were categorical variables. The statistical software application SPSS release 16.0 for Windows was used to carry out the statistical analyses. For categorical variables, testing for statistical differences was made with the x2 test or Fisher's exact test when necessary. Relative risk and 95% confidence intervals were calculated. For continuous variables t Student test for independent samples was performed. All tests were done from a bilateral approach. P-value of less than 0.05 was considered statistically significant

Table 2. Evaluated variables by the patient during the first week.

GROUP 1	**DAY 1**	**DAY 2**	**DAY 3**	**DAY 4**	**DAY 5**	**DAY 6**	**DAY 7**
Number of analgesic needed (mean)	2.19	1.96	1.77	1.44	1.21	0.99	0.71
Diet							
Liquid	56 (80%)	20 (28.6%)	13 (18.6%)	3 (4.3%)	3 (4.3%)	2 (2.9%)	2 (2.9%)
Soft	13 (18.6%)	45 (64.3%)	42 (60%)	44 (62.9%)	35 (50%)	27 (38.6%)	21 (30%)
Normal	1 (1.4%)	5 (7.1%)	15 (21.4%)	23 (32.9%)	32 (45.7%)	41 (58.6%)	47 (67.1%)
Axillary Temperature (Cº)	36.6	36.6	36.5	36.5	36.4	36.4	36.3
Subjective Pain Scale (0-10)	6.7	5.0	4.2	3.6	3.2	2.8	2.4
GROUP 2	**DAY 1**	**DAY 2**	**DAY 3**	**DAY 4**	**DAY 5**	**DAY 6**	**DAY 7**
Number of analgesic needed (mean)	2.16	2.13	1.76	1.35	1.00	0.85	0.69
Diet							
Liquid	65 (86.6%)	26 (34.6%)	10(13.3%)	2 (2.7%)	1 (1.3%)	1 (1.3%)	0
Soft	10 (13.4%)	46 (61.4%)	49 (65.3%)	39 (52%)	35 (46.7%)	23 (30.7%)	16 (21.3%)
Normal	0	3 (4%)	16 (21.3%)	34 (45.3%)	39 (52%)	51 (68%)	59 (78.7%)
Axillary Temperature (Cº)	36.6	36.5	36.6	36.5	36.4	36.5	36
Subjective Pain Scale (0-10)	6.8	4.8	3.8	3.0	2.5	2.2	1.8

Results

One hundred and sixty patients were included initially in this study. Fifteen patients were excluded (9.4%), 9 in group 1 and 6 in group 2. The exclusion cause was absence from the follow-up examination in 11 patients, failure to follow the recommended treatment in 3 and 1 did not correctly fill the registration form. Phone interviews showed that all patients who did not came to the appointment argued personal reasons and no medical impediment.

A total of 145 patients were included finally in the study. 70 were assigned to group 1 (48.3%) and 75 patients in group 2 (51.7%), 97 women and 48 men. Both groups were homogeneous in every evaluated parameters, such as sex distribution (71.4% women in group 1and 62.7% in group 2) , age (mean 27.9 +- 6.7 years in group 1 and 26.5 +- 6.3 in group 2), inclusion criterion, preoperative mouth opening, side and degree of impaction of the third molar (26 included and 44 semi-erupted in group 1 , while 31 included and 44 semi-erupted in group 2), position (group 1:37.1% mesioangular, 12.9% distoangular, 27.1% vertical, 22,9% horizontal. Grop 2: mesioangular 48%, distoangular 6.7%, vertical 16%, horizontal 29.3%), duration of surgery, ostectomy or section of the tooth.

Postoperative infection was present in 5 patients (3.4%), 2 in group1 (2.9%) and 3 in group 2(4%). These were diagnosed by purulent discharge in surgical wound in 2 patients and excessive painfull swelling not related to the surgical trauma (1 of whom needed hospital admission for intravenous antibiotic treatment). Just 2 cases of alveolitis were recorded, both of them in group 1 (2.9%). No statistical relation was found either with the treatment group assigned or with surgical difficulty. There were 2 patients with surgical infection in the less than 5 minutes procedure group, another 2 in the group between 5-10 minutes and 1 in a surgical extraction longer than 10 minutes.

No statistically significant correlation between the treatment group and inflammatory symptoms was found. The mean of analgesic intake was 10.27 +-6.52 in group 1 and 9.88+-7.23 in group 2. There were no differences in the consistency of the diet neither the subjective pain scale. With regard to other variables such as haematoma appearance, wound dehiscence, intraoral inflammation (present in 50.7% in group 1 and in 40% in group 2), trismus (mouth opening loss mean of 8.5 mm +- 9.7 in group 1 and 8.4 mm +- 10,8 in group 2) or lingual or alveolar nerve hypoesthesia no significant differences were found. Side effects as diarrhoea (1 patient in each group) nausea or vomit (2 cases in group 2) epigastralgia (1 case in group1), cutaneous rash (none patient) were very rare and without relation with the assigned treatment. Persistent bad postoperative was present in 3 patients in each group (4.3% in group 1 and 4% in group 2).

Discussion

In spite of the high number of wisdom teeth renoval procedures, there is no antibiotic therapy protocol widely accepted. Some studies connect surgical complications with cases with ostectomy (3,4,6) and with duration of surgical procedure (3). In this study these connections are not found. Despite total amoxicillin dose difference between both groups, there are no statistical difference in infectious and inflammatory events. Wound infection and alveolitis rates are similar to other published works (6). Some authors support the use o an only presurgical dose of amoxicillin in cases with no ostectomy required, extended to postoperative period in cases with bone removal (3). Other authors recommend a single presurgical prophylactic dose in cases with no previous coronitis if ostectomy is needed, leaving without antibiotic coverage cases when is not necessary (2). Anyway we consider unnecessary the long postoperative antibiotic patterns, because the results in the 25 study variables are comparable to the ones obtained with short presurgical prophylactic patterns. The implementation of presurgical prophylactic doses could lead added difficulty, because cooperation of the patient is necessary. We agree with other authors about the advantages of presurgical antibiotic administration as more effective than postoperative patterns (1,2). In this study the results are similar despite patients in presurgical administration group receive 4 times less antibiotic dose.

Conclusions

Postoperative infection rate was 3,5%, with no statistically differences between groups. Inflammatory symptoms were similar in both antibiotic administration patterns groups. This study demonstrated that postoperative amoxicillin therapy is not justified because it does not obtain better results than the short prophylactic pattern, although in group 1 each patient receives 3 grams of amoxicillin in comparison with 12 grams of group 2. Side effects of antibiotic overdoses such as selection of resistant bacterial straits, allergic events and economic overcost would be avoided.

It is not clear yet in which patients the antibiotic therapy is more beneficial to prevent inflammatory and infectious events after third molar surgery. More multicenter randomized clinical trials with high external validity comparing alternative antibacterial therapies are needed. The objective should be identifying patients most likely to benefit from antibiotic administration.

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The protocol was approved by the Galician Regional Ethics Committee (Xunta de Galicia) in 2006 and written, dated, informed consent was obtained from all patients prior to study entry.