Journal of Cranio-Maxillo-Facial Surgery 47 (2019) 228–232

Contents lists available at ScienceDirect

Journal of Cranio-Maxillo-Facial Surgery

journal homepage: www.jcmfs.com

The efficiency of extended postoperative antibiotic prophylaxis in orthognathic surgery: A prospective, randomized, double-blind, placebo-controlled clinical trial

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ARTICLE INFO

Article history:
Paper received 31 January 2018
Accepted 20 November 2018
Available online 28 November 2018

Keywords:
Postoperative infection
Perioperative antibiotics
Erythema
Postoperative fever
CRP

ABSTRACT

Postoperative antibiotics are commonly administered in orthognathic surgery, despite the fact that there is no consensus regarding their efficacy. The objective of this study was to investigate the effectiveness of postoperative antibiotics in orthognathic surgery by conducting a prospective, randomized, double-blind, placebo-controlled trial.

Patients were randomly allocated into one of two study groups: the intervention group (treated with 1 g of intravenous (IV) amoxicillin-clavulanate TID) or the placebo group (treated with 50 mL of IV 0.9% NaCl TID). The infection rate was assessed using clinical and laboratory parameters.

The intervention group included 38 patients, with 40 patients in the placebo group. Baseline and surgical characteristics were comparable between both groups. Mean postoperative C-reactive protein (CRP) and temperature were similar for both groups. Serous discharge was observed in two patients (both in the placebo group), and one of them required surgical intervention. Overall, infection rate was similar in both groups (p-value > 0.1).

To conclude, administration of postoperative antibiotics in healthy, young patients undergoing orthognathic surgery did not show a significant advantage in reducing surgical infection rate.

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1. Introduction

The current trend in orthognathic surgery is maxillofacial surgery used to correct and normalize facial abnormalities, whilst creating harmony between the different tissues that make up the face (Charrier, 2014). The most common complication, occuring in 2.0–33.4% of surgeries, is postoperative infection (Davis and Gregoire, 2012; Oomens et al., 2014). Since postoperative infections both increase the morbidity rate of orthognathic procedures and create an extra burden on the medical system, reducing their prevalence is critical in increasing the success of this unique branch of surgery (Oomens et al., 2014).

Although preoperative prophylaxis is known to decrease the rate of postoperative infections in orthognathic surgery, there is still no consensus regarding the efficacy of postoperative antibiotics in preventing postoperative infection (Tan et al., 2011b; Peterson and Booth, 1976). Furthermore, there is a wide variation in indication for postoperative antibiotics. Danda recommended the extended use of a postoperative antibiotic, based on a meta-analysis study that he published in 2011, which demonstrated the role of postoperative antibiotics in decreasing the risk of wound infection after orthognathic surgery. However, he recommended more clinical trials to standardize the regimen (Danda and Ravi, 2011). Tan found that administration of a more cost-effective oral antibiotic prophylaxis, which caused less comorbidity compared with intravenous antibiotics, can be considered a safe option following bimaxillary orthognathic surgery with segmentalizations (Tan et al., 2011a).

The risk factors of excessive antibiotic use, including anaphylactic shock, diarrhea, vomiting, and the development of antibiotic-resistant infections (Thornhill et al., 2015), necessitate a rational, wise, and cost-effective approach in administrating antibiotics. The

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https://doi.org/10.1016/j.jcms.2018.11.017
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aim of this clinical trial was to investigate the efficacy of postoperative antibiotics in orthognathic surgery, with the null hypothesis being that postoperative antibiotic administration (either orally or intravenously) does not significantly decrease the infection rate following orthognathic surgery.

2. Materials and methods

This prospective, double-blind, placebo-controlled, stratified (>18 years old, with balanced randomization [1:1]), clinical trial was conducted according to the principles expressed in the Declaration of Helsinki. Patient consent was obtained, and the study was registered at ClinicalTrials.gov (No. NCT02740647). The study was conducted in the Oral and Maxillofacial Surgery Department of the Baruch Padeh Medical Center, Poriya, Israel. Patients scheduled for maxillary, mandibular, or bimaxillary orthognathic surgery, and who met the inclusion criteria described below, were included in the study. A comprehensive explanation was given to the patients by the principal investigator, and a signed consent form was obtained from each participant.

Inclusion criteria were as follows: 1) good general health; 2) over 18 years of age; 3) neither pregnant nor lactating; 4) hemoglobin >10.5 mg/dl, WBC >4000/mm^3, platelets >140.00/mm^3; 5) no consumption of immunosuppressive drugs (e.g. corticosteroids, cyclosporine, methotrexate) or anti-cancer agents during the past year (patient using topical corticosteroids to treat dermatological conditions covering not more than 5% of the body surface area were included).

Patients suffering from any acute or chronic viral, bacterial, immune, or other abnormal cellular immunity-related disease (such as HIV, hepatitis, lung disease, diabetes mellitus), and patients with a known allergy to penicillin (amoxicillin clavulanate) were excluded from the study.

The study subjects were allocated into two groups (intervention group and placebo group), with an allocation ratio of 1:1, through the use of *randomization* and *blinding*.

The intervention group received, intravenously, 1 g of amoxicillin clavulanate (Smithkline Beecham plc, UK), three times a day for 5 days postoperatively. The placebo group recieved, intravenously, 0.9% NaCl 50 ml (placebo) three times a day, for 5 days postoperatively. All of the patients received, as a single dose intravenously, 1 g of amoxicillin clavulanate during anesthetic induction, and 20 mg dexamethasone (Teva, Israel) during the operation, followed by 8 mg every 8 h postoperatively for 1 day, then every 12 h in the second perioperative day, and finally one last single dose on the third day. All the patients were prescribed Corsodyl mouthwash (UK, Nottingham, Ltd B) immediately after the operation and for a period of 1 month.

Allocation of the patients to either the intervention or placebo group was conducted using random allocation software, and neither the patients nor the principal investigator were aware of their assigned group during the trial. Block randomization, with a block size of four, was used to ensure approximately equal numbers of subjects in each study group. The trial was double-blinded — the patients and both the principal investigator and the clinical expert responsible for identifying specific clinical infection symptoms were blinded to the intervention regimen (placebo/amoxicillin clavulanate). The antibiotic and the placebo were identical in size, shape, and color, and were handed to the nurses in sequentially numbered, opaque, sealed envelopes.

Both groups were monitored for the development of postoperative infections once a week for 6 weeks in the outpatient clinic. The following quantitative, previously reported parameters were documented and scored for each patient at each follow-up visit:

1. Hospitalization for more than 14 days: 5 points
2. Erythema: if present 5 points, otherwise 0
3. Serous discharge: if present 5 points, otherwise 0
4. Wound exudates from the surgical site: if present 10 points, otherwise 0
5. Isolation of pathogens: positive 10 points, otherwise 0
6. Dehiscence: if present 10 points, otherwise 0
7. The need for additional treatment: antibiotic administration 10 points; debridement of the wound under general anesthesia 10 points; drainage of pus under local anesthesia 5 points

A total score of >21 points was defined as mild wound infection, >30 as moderate infection, and >40 as severe infection (Classen et al., 1992; Kang et al., 2009).

Average daily pyrexia (measured three times a day) was monitored for both groups during the first 5–7 postoperative days and highly sensitive C-reactive protein (CRP) was measured at four time points: on admission (CRP0), 1 day post-surgery (CRP1), 2 days post-surgery (CRP2), and 5 days post-surgery (CRP3). The overall average was calculated for each group, and then statistically analyzed for significant differences.

All the osteotomies were performed in the operation room, under general anesthesia and induced hypotension. The operations were conducted by both senior and resident staff. All bone osteotomies were performed using burs and saws by Stryker (Michigan, USA), and fixated with titanium osteosynthesis plates and screws. Surgical wounds were irrigated and sutured with Ethicon coated vicryl 3-0 and 4-0 (Johnson & Johnson International) sutures.

2.1. Statistical analysis

Sample calculations determined that in order to detect a difference of 0.3 °C in temperature and in CRP between both groups, with an alpha error of 5% and power of 75%, 78 patients were required. Parameters for the two groups were compared using two-sided Fisher's exact tests and two-sample Mann-Whitney U tests for non-parametric variables (CRP and systemic fever). Fisher's exact tests were also used to determine significant differences between the infection rates in the two study groups, based on the infection indicator parameters monitored (pyrexia, CRP, swelling, erythema, and the formation of purulent exudates, age, sex, and mean operative time). All statistical analyses were performed using SPSS version 23.

3. Results

78 patients were included in this clinical trial — 46 females and 32 males — with a mean age of 22.69 years (range 18–35) (Fig. 1). 65 patients underwent maxillary surgery, of which three underwent segmentalized maxillary surgery; 58 patients underwent mandibular surgery (43 advancement procedures and 15 setback procedures), of which only one patient underwent vertical ramus osteotomy (for advancement). The mean CRP0, CRP1, CRP2, and CRP3, values were 4.74, 86.96, 36.06, and 20.48 respectively. Average pyrexia on days 0 (admission day), 2, 4, and 6, were 36.50 °C, 36.42 °C, 36.60 °C and 36.50 °C respectively.

The patients were allocated randomly into two groups: intervention and placebo. The intervention group comprised 38 patients, and the placebo group 40 patients. Both groups were statistically comparable with regards to male/female ratio, mean age, mean operation time, and surgical procedure (Table 1). The mean CRP values on the operation day (CRP1) were 86 and 87 for the intervention and placebo group respectively (p-value = 0.4), and an exponential decrease was observed in both groups

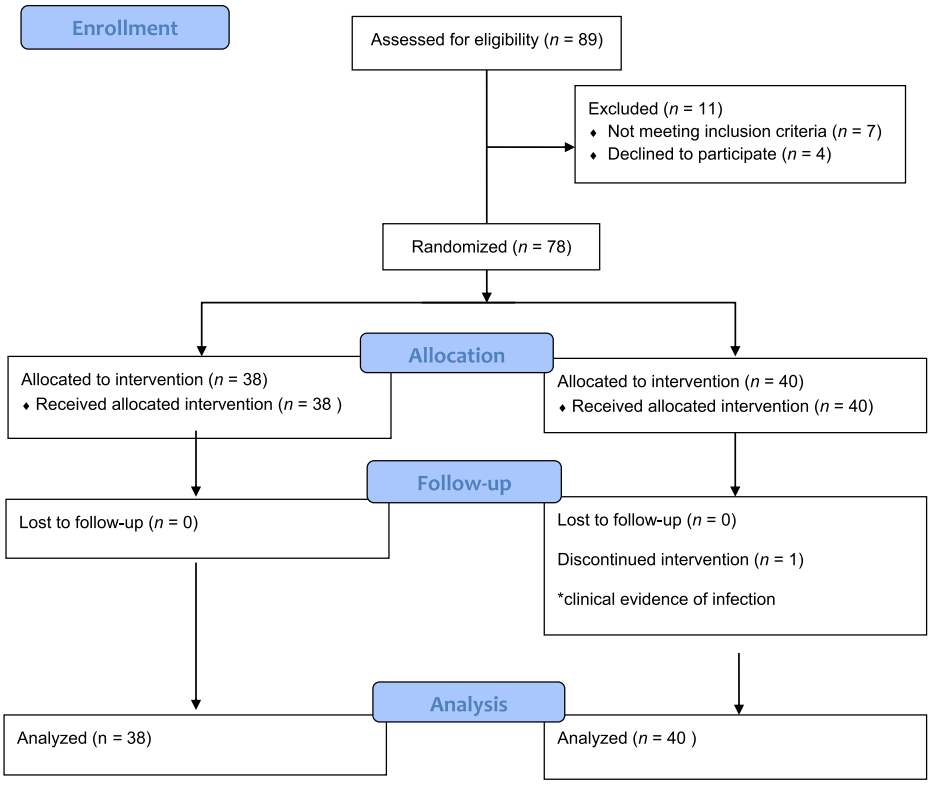

Fig. 1. Participants flow diagram.

Table 1
Demographic and clinical data for the study sub-groups.

Characteristic	Intervention group	Placebo group	*p*-value
n	38	40	
Mean age ± SD	22 ± 6.1 years	23 ± 7 years	0.17
Range	18–28 years	18–35 years	
Gender			0.4
Female	22	24	
Male	16	16	
Mean Operation time	342 min	350 min	0.5
Surgical procedure			0.4
Maxillary surgery (without segmentalization)	32	30	
Maxillary surgery with segmentalization	1	2	
Mandibular surgery	27	31	
Bilateral sagittal osteotomy	25	30	
Advancement	20	23	
Set-back	5	7	
Vertical ramus osteotomy (advancement)	2	1	
Genioplasty	4	5	
Bimaxillary surgery	26	27	
CRP values			
CRP0 mean ± SD	5 ± 10	4 ± 2	0.4
CRP1 mean ± SD	86 ± 23	87.1 ± 13	0.4
CRP2 mean ± SD	34 ± 23	38 ± 20	0.6
CRP3 mean ± SD	21 ± 20	20 ± 10	0.7
Systemic temperature			
Day 0 mean ± SD	36.5 ± 0.2	36.43 ± 0.3	0.1
Day 2 mean ± SD	36.43 ± 0.2	36.41 ± 0.3	0.7
Day 4 mean ± SD	36.6 ± 0.2	36.5 ± 0.3	0.7
Day 6 mean ± SD	36.48 ± 0.3	36.51 ± 0.3	0.6
Infection	0	1	0.10

(CRP3 = 21 and 20 for the intervention and placebo group respectively, *p*-value = 0.7). A similar pattern was seen for mean pyrexia during the hospitalization period in both groups, with no significant difference observed. Maximum swelling occured 1 day postoperatively, followed by a steady and exponential decrease during the first 2–3 weeks of follow-up in both groups.

Three patients in the intervention group had moderate erythema in the 1–3 days post surgery (the erythema lasted for 2 days in two patients, and 3 days in the third). Two patients in the placebo group developed mild erythema, both for 2 days (*p*-value > 0.1). Serous discharge was observed in two patients from the placebo group, which began 4 and 9 days post surgery. In one patient, a 25-

year-old female who underwent bi-maxillary surgery, a serous discharge originating at the right mandible began 4 days post surgery. The discharge required no additional intervention and sealed 6 days postoperatively. The second patient, a 29-year-old male who underwent bimaxillary surgery (maxillary Le Fort I osteotomy for impaction, and mandibular BSSO set-back), suffered serous discharge from 9 days post surgery. In this case additional intervention was needed, and it sealed 13 days postoperatively. According to the records, the patient was discharged post-operatively with no clinical evidence of infection (CRP3 11, systemic fever 36.5 °C, and no redness), and 2 days later (9 postoperative days), he complained about excessive pain in his lower jaw. Upon examination, the serous discharge was observed, along with wound dehiscence in the left mandible. Culture and sensitivity tests on the serous discharge showed oral commensals only, so the patient was treated with intravenous amoxicillin clavulanate 1 g × 3/day and local irrigation using normal saline and Corsodyl mouthwash.

Overall, only one patient reached the cutoff score for infection. This patient, part of the placebo group, had wound dehiscence, serous discharge for 4 days, and needed additional antibiotic therapy (total score of 35 points, moderate infection — see Table 3). Nevertheless, no significant difference was found between the placebo and intervention groups (p-value = 0.09). Moreover, no patients from either group developed mild or severe infection (Table 3).

Post-hoc calculation gave a power value of 78.8%, based on objective parameters only (wound discharge, isolation of pathogen, and dehiscence) (see Table 2).

4. Discussion

Orthognathic surgery is a commonly performed oral and maxillofacial surgical procedure. This surgery aims to achieve correct occlusal function and esthetic facial harmony in patients with severe dentofacial deformities that require surgical repositioning of the maxilla or mandible. While this surgery is classified as 'clean-contaminated', the rate of postoperative infection (2.0–33.4%) poses a primary concern and manifests as one of the most commonly reported complications (Kang et al., 2009). To reduce the incidence of infection, perioperative antibiotics are commonly used.

In this trial, all the patients received a single dose of 1 g intravenous amoxicillin clavulanate during anesthetic induction. Amoxicillin clavulanate belongs to the β-lactam antibiotics family, known for its antimicrobial activity against oral and nasal flora, the predominant contaminants in orthognathic surgery. The administration of amoxicillin clavulanate was carried out 1 h before the operation, to enable the drug to reach an adequate concentration level in the tissues during the surgery (Burke, 1961; Classen et al., 1992). The underlying rationale for using perioperative antibiotics is that, during the operation, direct communication between the exposed bones and the flora of the nasal and oral cavity may provide a predisposing niche for infection (Conover et al., 1985; Wilson et al., 1986; Koole and Egyedi, 1987; Peterson, 1990; Peel and Taylor, 1991; Zijderveld et al., 1999; Danda and Ravi, 2011).

None of the patients in the intervention group developed an infection, and only one patient developed a moderate infection in the placebo group. This patient was a healthy 29-year-old male, who underwent bi-maxillary surgery. He was re-hospitalized due to serous discharge, along with dehiscence of the surgical wound in

Table 3
Outcome categorization.

	Intervention group	Placebo group
Mild infection (%)	0	0
Moderate infection (%)	0	1 (2.5)
Severe infection (%)	0	0
Total (%)	0	1

Table 2
Comparison of scored parameters for the study groups.

Parameter	Intervention group	Placebo group	p-value
Hospitalization >14 days			–
Number of patients (%)	0	0	
Overall score			
Erythema (5 points/day)			0.4
Number of patients (%)	3 (7)	2 (5)	
Patient-level summary: No. of days			
Patient 1	2	2	
Patient 2	2	2	
Patient 3	3	–	
Overall score	35	20	
Serous discharge (5 points/day)			0.3
Number of patients (%)	0	2 (5)	
Patient-level summary: No. of days			
Patient 1		2	
Patient 2		4	
Overall score		30	
Wound exudate (10 points/day)	0	0	–
Number of patients (%)			
Overall score			
Isolation of pathogen (10 points)	0	0	–
Number of patients (%)			
Overall score			
Wound dehiscence (5 points)	0		0.15
Number of patients (%)		1 (2)	
Overall score		5	
Need for further intervention	0		0.15
Antibiotic therapy (10 points)			
Number of patients (%)		1 (2)	
Overall score		10	
Overall (mean ± SD)	35 (0.9 ± 3.2)	65 (1.6 ± 6)	0.09

the mandible, without any erythema, swelling, or pyrexia. The limitation of adequate healing in the mandible could be explained by the poorer blood supply to the mandible compared with the maxilla, the pooling of the saliva around the surgical site, and its susceptibility to infection (Danda and Ravi, 2011). In our case, the infection could also be attributed to the lack of adequate closure of the surgical site (dehiscence and plate exposure), since both senior and resident staff conducted the osteotomies. Nevertheless, no pathogen was isolated, and the culture and sensitivity tests revealed oral commensals only. The patient was then treated with amoxicillin calvunate, and the serous discharge ceased several days later. The fact that no pathogen was isolated made the presence of infection uncertain, and the serous discharge would most likely have ceased spontaneously after adequate closure and irrigation of the wound.

CRP and pyrexia are significant indicators for oral infection (Wilson et al., 1986; Koole and Egyedi, 1987). Thus, these parameters were monitored and documented during the clinical trial. For comparison, a two-sample Mann-Whitney *U* analysis test was used. On the admission day, the mean CRP values were 4 and 5 in the placebo and intervention groups respectively, Generally, CRP is present in small amounts in a normal healthy person (less than 10 mg/L), and is involved in the innate immune system, where its functions are activation of complement, clearance of antigens, and mediation of phagocytosis by the activation of neutrophils (Jundt and Gutta, 2012). In infections or inflammatory reactions CRP concentrations in serum rise, up to 1000-fold within just a few hours of the development of clinical symptoms. The CRP concentration continues to rise until the infection is treated and falls rapidly after the inflammation has resolved. Its rapid rise and fall with the inflammatory process makes it a much more sensitive indicator of an inflammatory process than erythrocyte sedimentation rate (ESR) or white cell count (WCC) (Sharma et al., 2014).

sOne day post surgery, the recorded mean CRP values were as high as 86 and 87 in the intervention and placebo groups respectively. These high values were caused by the acute plasma reaction initiated by the surgical wound, because the primary signal for CRP synthesis is the production of interleukin-1 by macrophages at the site of tissue injury (Jundt and Gutta, 2012). Thereafter, a similar exponential decrease in the CRP values was observed in both groups, which indicated the absence of infection in both groups.

Although the infection rate in the placebo group was higher than the intervention group (2.5% versus 0), this difference was all attributable to a single patient, which we believe represents an exceptional event of poor healing due to an inadequate surgical wound closure. Overall, no significant difference was found for any of the investigated infection parameters, and the administration of postoperative antibiotics did not show superiority in preventing infections in orthognathic surgery. It is important to note, that, our trial included only healthy, young patients. Moreover, the surgical procedures did not include multiple segmentalizations. Thus, the results and conclusions presented here may not necessarily apply to older patients, or when multiple segmental osteotomies are planned.

Postoperative antibiotics should be administered wisely, considering the costs, as well as the risks of bacterial resistance, gastrointestinal side effects, skin rash, and severe anaphylactic shock, and weighing these against the advantages of prescribing antibiotics. Thus, this study does not support automatic administration of antibiotics post orthognathic surgery in young, healthy patients.

5. Conclusions

Administration of postoperative antibiotics should be considered carefully in orthognathic surgery, especially in healthy patients. In this study, antibiotic prophylaxis post orthognathic surgery did not show a significant advantage in reducing surgical infection rate. On the other hand, perioperative antibiotics appear to be effective in preventing surgery-related infection, and is thus indicated in all patients.

Acknowledgements

All authors have reviewed and agreed to the submission.

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