Aus der Klinik und Poliklinik für Mund-, Kiefer- und Gesichtschirurgie - Plastische Operationen

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Systemic antibiotic prophylaxis for preventing infectious complications in maxillofacial trauma surgery: A Cochrane systematic review and meta-analyses

Systemische antibiotische Prophylaxe zur Vorbeugung infektiöser Komplikationen nach maxillofazialer Traumachirurgie: Eine Cochrane systematische Übersichtsarbeit und Metaanalyse

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To my family

for nourishing my soul with immeasurable love

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1G	first generation
3G	third generation
d	day
ENT	Otorhinolaryngology (Ear, nose, and throat surgery)
GDT	Guideline development tool
GRADE	Grading of Recommendations Assessment, Development and Evaluation
h	Hour
i.v.	intravenous drug administration
i.m	intramuscular drug administration
Intra-Op	intraoperatively
mIU	Million international Units
mU	Million Units
OMFS	Oral and maxillofacial surgery
OR	Odds ratio
pre-Op	preoperatively
p.o.	peroral, i.e. oral administration of a medication
post-Op	postoperatively
Q4H	every 4 hours
QID	Four times a day (Quattuor in dies: Latin)
RR	Risk ratio
SSI	Surgical site infection
TID	Three times a day (Tribus in dies: Latin)
ZMC	Zygomatic maxillary complex

Related publications

Alsharif U, Al-Moraissi E, Alabed S. Systemic antibiotic prophylaxis for preventing infectious complications in maxillofacial trauma surgery (Protocol). Cochrane Database of Systematic Reviews 2017, Issue 3. Art. No.: CD012603. DOI: 10.1002/14651858.CD012603.

Abstract

Background: Antibiotics are commonly administrated perioperatively to prevent postoperative surgical site infection (SSI) of facial fractures treated with open reduction and internal fixation (ORIF). However, there is no consensus on the optimal duration and class of prophylactic antibiotics. We investigated the effect of different antibiotic regimens and examined the efficacy and safety antibiotics for preventing complications following the surgical reduction of facial fractures.

Methods: In October 2019, we searched the Cochrane Central Register of Controlled Trials; Ovid MEDLINE; and Ovid EMBASE. We included randomized controlled trials (RCTs) involving people undergoing ORIF for maxillofacial trauma surgery and comparing one regimen of antibiotic prophylaxis with any other regimen, placebo or no antibiotics. The primary outcomes were SSI and systemic infections. Secondary outcomes were rate of retreatment surgery, adverse events, total treatment costs, duration of stay in hospital and health-related quality of life. Two assessors examined the title and abstracts of references identified in the literature search, extracted data and assessed the risk of bias in included studies.

Main results: We included 14 RCTs in this review that reported the rate of SSI. We pooled the studies into subgroups based on the prophylaxis regimen. Comparing intraoperative prophylaxis and postoperative prophylaxis in terms of SSI showed no to little difference between groups (RR 1.23, 95% CI 0.74 to 2.04; participants = 408; studies = 5; I^2 = 0%; moderate-quality evidence). Also, comparing short-term and long-term postoperative antibiotic prophylaxis showed no to little reduction in the risk of SSI (RR 0.76, 95% CI 0.39 to 1.47; participants = 570; studies = 7; I^2 = 0%; moderate-quality evidence) and the risk of adverse events (RR 0.61, 95% CI 0.27 to 1.38; participants = 295; studies = 4; I^2 = 0%, high-quality evidence). There was no difference in terms of retreatment surgery and systemic infections in both comparisons. Most studies had an unclear risk of bias prompting us to downgrade the quality of evidence for outcomes.

Conclusions: There is little or no difference between single-shot intraoperative prophylaxis or short-term (<48 hours) or long-term (>48 hours) postoperative prophylaxis in the rate of SSI and adverse events. The studies comparing antibiotic prophylaxis for facial fractures other than mandibular fractures were scarce. Further evidence for these fracture sites is needed.

Zusammenfassung

Hintergrund: Antibiotika werden üblicherweise perioperativ verabreicht, um eine postoperative Infektion der Operationsgebiet von Gesichtsfrakturen zu verhindern, welche mit einer Reposition und Osteosynthese (ORIF) behandelt wurden. Ein Konsens über die optimale Dauer und Klasse der prophylaktischen Antibiotika besteht jedoch nicht. Wir untersuchten die Wirksamkeit und die Sicherheit der perioperativen antibiotischen Prophylaxe nach der ORIF von Gesichtsfrakturen.

Methoden: Im Oktober 2019 führten wir eine Suche in den folgenden elektronischen Datenbanken durch: Cochrane Central Register of Controlled Trials, Ovid MEDLINE, Ovid EMBASE und EBSCO CINAHL. Nur randomisierte kontrollierte Studien (RCTs), die Patienten mit durch ORIF behandelten maxillofazialen Frakturen rekrutierten, wurden eingeschlossen. Wir verglichen daraufhin unterschiedlichen Regimen der Antibiotikaprophylaxe miteinander, mit Placebo oder mit keiner Prophylaxe. Der primäre Outcome ist die postoperative Infektion. Sekundäre Outcomes waren systemische Infektionen, Rate der Nachbehandlungsoperationen, unerwünschte Ereignisse, Gesamtbehandlungskosten, Dauer des Krankenhausaufenthalts und gesundheitsbezogene Lebensqualität. Zwei Gutachter untersuchten den Titel und die Abstracts der in der Literaturrecherche identifizierten Referenzen, extrahierten Daten und bewerteten das Risiko einer Verzerrung in eingeschlossenen Studien.

Hauptergebnisse: Wir haben 14 RCTs eingeschlossen und basierend auf dem Prophylaxeschema in Untergruppen zusammengefasst.

Der Vergleich der intraoperativen Prophylaxe und der postoperativen Prophylaxe hinsichtlich der postoperativen Infektion zeigte keinen bis geringen Unterschied zwischen den Gruppen (RR: 1,23; 95% CI 0,74 bis 2,04; Teilnehmer = 408; Studien = 5; I^2 = 0%; mäßiger Evidenzqualität). Der Vergleich der kurz- und langfristigen postoperativen Antibiotikaprophylaxe zeigte ebenso keine bis geringe Verringerung des Infektionsrisikos (RR: 0,76; 95% CI 0,39 bis 1,47; Teilnehmer = 570; Studien = 7; I^2 = 0%; mäßige Evidenzqualität) und das Risiko unerwünschter Ereignisse (RR: 0,61; 95% CI 0,27 bis 1,38; Teilnehmer = 295; Studien = 4; I^2 = 0%, hochwertige Evidenzqualität). In beiden Vergleichen gab es keinen Unterschied in Bezug auf Nachbehandlungsoperationen und systemische Infektionen. Die meisten Studien hatten ein unklares Verzerrungspotenzial, was uns dazu veranlasste, die Qualität der Evidenz für die Ergebnisse herabzustufen.

Schlussfolgerungen: Es gibt kaum oder keinen Unterschied zwischen einer

intraoperativen Einzelschussprophylaxe oder einer kurzzeitigen (<48 Stunden) oder langfristigen (> 48 Stunden) postoperativen Prophylaxe in Bezug auf die Rate der postoperativen Infektionen und unerwünschte Ereignisse. Die Studien zum Vergleich der Antibiotikaprophylaxe bei anderen Gesichtsfrakturen als Unterkieferfrakturen waren rar. Weitere Studien für diese Frakturstellen sind erforderlich.

1. Introduction

Facial trauma is commonly encountered in the emergency departments globally, with most injuries being caused by blunt trauma (Sethi 2014). Facial trauma is often accompanied by fractures of the facial bones, so called maxillofacial fractures. Many maxillofacial fractures require reduction and fixation, which is achieved through surgery. The method of fracture reduction and fixation depend largely on fracture site and complexity. Personal factors such as the preference of the surgeon and the condition of the patient play a determinant role of the treatment method (Cienfuegos 2008; Cornelius 2017). Most surgeons prefer surgery through the oral cavity, to avoid causing scares in aesthetic areas and to protect important vessels and nerves in the face (Ehrenfeld 2012). However, surgery through the oral cavity is associated with higher risk of postoperative infection in comparison with surgery through the skin. To reduce postoperative infections and facilitate optimal healing, antibiotics are often administrated prophylactically before, during and after facial trauma surgery.

Two randomized clinical trials (Chole 1987; Zallen 1975) published over 40 years ago compared antibiotic prophylaxis to no prophylaxis in the conservative and surgical treatment of maxillofacial trauma. These studies reported that up to 50% of participants who did not receive antibiotics developed postoperative infections compared to 13% in those who did. As a result, antibiotic prophylaxis became very common in the perioperative management of facial fractures.

However, knowledge gaps remain unanswered in the clinical practice. It is unclear whether extending the antibiotic prophylaxes prior to or after the perioperative window reduces the postoperative infection. Additionally, the proper prophylaxis of fractures in children and elderly, the most suitable antibiotic class and the necessity of antibiotics for each fracture location is very controversial. In daily practice, surgeons' decision of the extent and intensity of antibiotic prophylaxis is driven by clinical factors such as the patient's general status and compliance, the fracture location, wound contamination and method of reduction.

To address these uncertainties, we conducted a Cochrane systematic review with meta-analyses of the randomized clinical trials on the benefit of antibiotic prophylaxis in preventing infectious complications after the open reduction and internal fixation of maxillofacial factures.

2. Background

2.1. Maxillofacial fractures

2.1.1. Definition

Maxillofacial fractures are fractures of the bony structures of the forehead, the midface and mandible; those include fractures of the frontal sinus, orbit, nose, zygoma, maxilla and mandible. Road traffic accidents, assaults and falls are the most common causes of maxillofacial fractures. Clinically, they might present with pain, bruising, swelling and numbness of surrounding tissues, nosebleeds, and facial deformities. Fractures of the mandible are often accompanied by limited and painful mouth opening and numbness of the lower lip and chin (Cienfuegos 2008; Cornelius 2017).

2.1.2. Epidemiology

The face is the fourth most common body region to suffer injuries, after the lower extremities, the head and the upper extremities (Chang 2016). Due to the anatomical prominence of the nose, it is the third most common fracture in the human skeleton and the most common fractured facial bone followed by the mandible (Al-Moraissi 2015a; Hwang 2010). The Global Burden of Disease Study 2017 estimated more than 7,5 million new facial fracture cases for the year 2017, accounting for about 117 thousand years lost to disability, which reflects an increase of almost 28.2% from 1990. The global age-standardized incidence rates of facial fractures per 100,000 person-years in 2017 were 131 (95% CI: 107 – 159) for men and 99 (95% CI: 80 – 124) for women, respectively (Lalloo 2020). The known gap between sexes did not widen over this duration. The incidence curve peaks in the age group 20 to 30 years especially in males. Falls are the main cause of facial fractures globally. However, in low-income and middle-income countries, road traffic accidents and interpersonal violence are the main cause of maxillofacial fractures (Lalloo 2020; Boffano 2015; Owusu 2016; Simsek 2007). In high-income countries on the other hand, there is an increasing number of facial fractures caused by falls in elderly people, while the number of fractures caused by assault and road traffic accidents is dropping (Atisha 2016; Boffano 2014; Martinez 2014).

2.1.3. Diagnosis and management

Radiological assessment (i.e. X-rays and CT scans) confirms the diagnosis of a

fracture along with patient's history and clinical examination (Ceallaigh 2006; Ceallaigh 2007). Anatomical location, degree of fracture displacement, and soft-tissue involvement - among other factors- are important considerations when choosing the treatment method (Cornelius 2017). There are three main methods to treat a maxillofacial fracture: observation, closed reduction, and open reduction with or without internal fixation (Cienfuegos 2008; Cornelius 2017; Ellis 2006). Open reduction with internal fixation (ORIF) is the preferred method of treatment for most facial fractures especially displaced and comminuted fractures, as it provides superior outcomes such as higher stability and earlier mobilization of the temporomandibular joint (Al-Moraissi 2015b; Cienfuegos 2008; Cornelius 2017). Open reduction means realigning a displaced fracture through surgery, while internal fixation refers to stabilizing a fracture by using mechanical devices - usually lag screws, titanium plates or a reconstruction plate - that bridge and stabilize the fracture zone and allow healing (Cienfuegos 2008; Cornelius 2017; Ellis 2006). Nonetheless, ORIF is associated with a higher rate of postoperative complications (Villarreal 2004). Most facial fractures can be approached intraorally (from inside the oral cavity) but certain fractures demand an extraoral (from outside the oral cavity) approach (Ellis 1999; Toma 2003).

2.1.4. Treatment complications

In general, surgical wounds are classified according to their potential risk of infectious complications into clean, clean-contaminated, contaminated and dirty wounds (Cruse 1992; Mangram 1999). Wounds from the surgical reduction of facial fractures can be classified as either clean-contaminated, contaminated or dirty depending on the nature of the injury (closed or open fracture), penetration of the aerodigestive tract in the surgery, and the duration between injury and the surgical treatment (Horan 1992; Mangram 1999). Following wound dehiscence, surgical site infection (SSI) is the most common complication after the open reduction of facial fractures (Lamphier 2003; Schaefer 2013). The US Centers for Disease Control and Prevention (CDC) set a number of clinical findings which indicate an SSI including: purulent exudate draining from the surgical site, positive microbiological culture obtained from the surgical site, at least one clinical sign of infection (pain, swelling, erythema, warmth) in a surgical site reopened by the surgeon or a diagnosis of an infection by the surgeon (Mangram 1999). Postoperative SSI rate after ORIF of a maxillofacial fracture ranges between 0% and 30% with an average of 12% (Schaefer 2013; Wladis 2013). Risk factors for postoperative SSI include open fracture, fracture site, preoperative infection,

involvement of teeth in the fracture line, >72 hours delay of surgery, patient's age and comorbidities (Czerwinski 2008; Hindawi 2011; Li 2016; Seemann 2010; Soriano 2005).

2.2. Antibiotic prophylaxis

Surgical antibiotic prophylaxis is defined as the administration of antibiotics to prevent SSI (Mangram 1999). There are three main regimens of administrating antibiotic prophylaxis: preoperatively, perioperatively and postoperatively. Preoperative antibiotic prophylaxis is given from time of injury up to 2 hours before surgical intervention; perioperative antibiotic prophylaxis is given immediately prior to surgical intervention and lasts during surgery, but not more than 24 hours after surgery; and postoperative antibiotic prophylaxis which lasts past the perioperative period (World Health Organization 2016). In maxillofacial trauma surgery, prophylactic broad-spectrum antibiotics such as penicillin, cephalosporins and erythromycin are preferred unless the patient is sensitive to penicillin or if microbiological culture and sensitivity tests indicate otherwise (Zallen 1976). This practice is based on the two landmark studies by Zallen and Chole (Chole 1987; Zallen 1976). However, there is a lack of agreement on the most appropriate type, dose, and schedule that should be used (Zallen 1976; Kyzas 2011). The use of antibiotics is associated with allergic or toxic reactions, adverse effects and drug interactions. Long courses of antibiotics do not only put the patient at risk of adverse events, they also increase the risk of developing multidrug-resistant bacterial infections (Li 2016).

2.3. How antibiotics work

Bacterial flora of the oral and nasal cavity contaminate surgical wounds following facial fractures surgery which leads to high SSI rate (Zallen 1976). Additionally, the placement of titanium plates and screws in ORIF provides a suitable environment for bacteria to grow and produce their toxins. Therefore, local and regional infectious complications can be the end result (Jhass 2014; Greenberg 2002; Schmidt 2000). Different antibiotics inhibit bacterial growth and multiplication through interfering with the synthesis of bacterial DNA, metabolism and cell wall structure. This prevents the adherence of bacteria to implant surface and allows the healthy immune system to overcome the infection (Hollinger 2007; Karow 2014). Thus, making antibiotics the mainstay treatment of SSI. Antimicrobial prophylaxis prevents SSI by reducing the amount and virulence of microorganisms at the surgical site before, during and after

an operative procedure (Mangram 1999).

2.4. The Aim and importance of the review

The benefit and the most appropriate regimen of antibiotic prophylaxis in maxillofacial trauma surgery is a matter of debate. Some studies report reduced postoperative infection rate in patients who received postoperative prophylactic antibiotics (Chole 1987; Miles 2006; Zallen 1975) while others found no evidence of protective effect (Gaal 2016; Hindawi 2011; Lovato 2009; Wladis 2013). The average length of stay in hospital after a maxillofacial fracture ranges from 2 to 10.6 days (Boffano 2015; Pena 2014). An SSI can lead to an extended hospital stay, failure of surgery and in certain cases a need for a second operation, which means further increasing morbidity and costs (Kirkland 1999). Although a few systematic reviews attempted to determine the effects of antibiotic prophylaxis in patients suffering maxillofacial fractures (Andreasen 2006; Kyzas 2011; Habib 2019), all of these reviews included retrospective studies and have not included several recent randomized clinical trials (RCTs). Therefore, there is a need for a systematic review including only RCTs assessing the benefits and harmful effects of antibiotic prophylaxis in maxillofacial trauma surgery, in order to provide the best evidence to clinicians.

We aimed to assess the effects of systemic antibiotic prophylaxis for preventing surgical site infections in people undergoing open reduction with or without internal fixation of trauma-induced maxillofacial fractures, and if possible, to determine the most effective antibiotic type, dosage and duration.

3. Methods

3.1. Outline of research methods and results

Following the Cochrane Collaboration methodology (Deeks 2011), we conducted a systematic search of studies reporting treatment outcomes of antibiotic prophylaxis in patients with maxillofacial fractures. In a protocol stage (Alsharif 2017), we defined eligibility criteria of the studies and participants that were to be included. Terms and resources for literature search were defined. We identified treatment outcomes of interest and specified the statistical analyses that were to be conducted. Finally, we identified the method of presenting the results. After conducting the search, we systematically checked for predefined eligibility criteria and extracted data from the included publication using prepared forms. We then reported the results and conducted the meta-analyses and sensitivity analyses where suitable. We discussed the results in the manner usually recommended by the Cochrane collaboration (Deeks 2011).

3.2. Criteria for including studies in this review

3.2.1. Types of studies included in this review

We included only randomized controlled trials (RCTs) reporting at least one of the outcomes of interest. The target population was people of any age and gender with maxillofacial fractures (orbits, nose, zygoma, maxilla and mandible) undergoing surgical reduction of the maxillofacial fracture with or without internal fixation. We excluded studies of non-traumatic fractures (i.e. pathological fractures). We also excluded studies that included patients treated conservatively (e.g. Watch and Wait, or closed reduction).

3.2.2. Types of interventions

As an intervention, we included any type of systemic antibiotic given preoperatively, intraoperatively, or postoperatively and administrated in any route (i.e: oral, intramuscular, or intravenous) or dose, regardless of co-interventions given. We accepted all possible comparisons such as placebo, another antibiotic, another regimen of the same antibiotic or no antibiotic prophylaxis at all.

To pool the studies in a meaningful way and allow a meta-analysis, we categorized possible prophylaxis regimens into one of five possible application protocols:

- No antibiotics at all neither pre- nor postoperatively, or only placebo.
- Pre-operative prophylaxis from the time of presentation to the time of the surgical intervention.
- Intraoperative prophylaxis or intraoperative prophylaxis only, with or without postoperative placebo.
- Short-term postoperative prophylaxis spanning for 48 hours postoperatively, regardless of the pre- or intraoperative prophylaxis.
- Long-term postoperative prophylaxis, which extends over 48 hours postoperatively, here also regardless of the pre- or intra- operative prophylaxis.

3.2.3. Types of outcome measures

Studies reporting any of the following outcomes were eligible for inclusion if participants have had at least one week of postoperative follow-up.

3.2.3.1. Primary Analyses

1. Surgical site infection (SSI) rate: this outcome was defined as any superficial or deep infection as defined by the US Centers for Disease Control and Prevention (CDC) criteria (Mangram 1999) in or adjacent to the anatomical structures involved in the surgery will be included. Where possible, we aimed to differentiate between superficial infection and deep infection that required drainage and deep infection that did not require drainage. We also accepted the authors' definition of surgical site infection.
2. Systemic infections: defined as a systemic inflammatory response syndrome (SIRS) resulting from the postoperative surgical site infection (SSI) up to three months after surgery.

3.1.3.2. Secondary Analyses

1. Adverse events due to the antibiotic administration.
2. Rate of retreatment surgery due to infection.
3. Length of hospital stay defined as the number of days of hospital stay from admission to discharge.
4. Total direct and indirect costs for antibiotic treatment and postoperative

infection treatment per patient.

5. Participant health-related quality of life (HRQoL): as measured using a standardized questionnaire such as EQ-5D (EuroQol Group 1990), Short Form SF-6 (Brazier 2002), SF-12 (Muller-Nordhorn 2004) or SF-36 (McHorney 1994; McHorney 1993; Ware 1992), or wound-specific questionnaires such as the Cardiff wound impact schedule (Price 2004).

3.3. Search methods for identification of studies

With the assistance of a Cochrane Oral Health's Information Specialist, we conducted systematic searches for randomized controlled trials and controlled clinical trials in several databases. The search covered the period from the beginning of the database to 17th of October 2019. No other restrictions were placed on the language or date of publication when searching the electronic databases. The electronic search covered the following databases for relevant trials:

- Cochrane Oral Health's Trials Register
- the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library
- MEDLINE Ovid
- Embase Ovid

The subject strategies for databases was modeled on the search strategy designed for MEDLINE Ovid (See Appendix:Appendix

MEDLINE OVID Search strategy). Where appropriate, the search strategy was combined with subject strategy adaptations of the highly sensitive search strategy designed by Cochrane for identifying randomized controlled trials and controlled clinical trials (as described in the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0, box 6.4.c (*Lefebvre 2011*).

Searching other resources

The following trials registries were searched at the Cochrane Oral Health editorial base:

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (http://clinicaltrials.gov/)
- World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch)

Additionally, we checked the bibliographies of included studies and any relevant systematic reviews identified for further references to relevant trials.

We did not perform a separate search for adverse effects of interventions. We only considered adverse effects described in included studies.

3.4. Data collection and analysis

3.4.1. Selection of eligible studies

Two assessors (Ubai Alsharif (UA) and Prof. Dr. Essam Al-Moraissi (EAM)) independently screened the titles and abstracts of references identified in the search. All potentially relevant articles were selected for full-text screening. Studies must have included over 10 participants in each arm to be eligible for inclusion. No studies were excluded based on their language. Two studies in German were extracted by UA and Samer Alabed, MD MPH (SA). One study in Spanish was translated by Gemma Villanueva and Dr. Anna Lourdes Robles Villela, MD. We utilized the Covidence platform (Babineau 2014; Veritas Health Innovation 2016) throughout the whole process of data collection, data extraction and while assessing the risk of bias in the included studies. We added a study flow diagram to summarize the results of searching and selecting the studies for inclusion as recommended by the PRISMA Statement (Moher 2009).

3.4.2. Data extraction and management

Two assessors (UA and EAM) independently extracted the data from the selected studies using a standardized form in Covidence. Discrepancies were discussed with one of the two arbiters ((SA) and Prof. Dr. Dr. Bilal Al-Nawas (BA)). We contacted study authors for clarification or missing data where necessary and feasible.

We recorded the following data for each included study in the 'Characteristics of included studies' table.

- Trial design, location, number of centers, recruitment period.
- Inclusion/exclusion criteria, age and gender of participants, number randomized/analyzed, location of fracture.
- Detailed description of the intervention and comparator, including type, dosage and duration.
- Details of the outcomes reported, including method of assessment and time(s)

assessed, length of follow-up.

- Details of adverse effects, funding sources, declarations/conflicts of interest.

3.4.3. Assessment of risk of bias in included studies

Based on the full text of the included studies, two assessors (UA and EAM) independently evaluated the risk of bias using the Cochrane risk of bias tool (as described in Chapter 8 of the (*Higgins* 2011) while utilizing all the domains of the tool (random sequence generation, allocation concealment, blinding of participants, personnel and outcomes, incomplete outcome data, selective outcome reporting, and other sources of bias). Disagreements were first discussed between the two review authors until a consensus was reached. In the few cases where no consensus was achieved another assessor (SA or BA) acted as an arbiter. The included studies were classified as having a low, high, or unclear risk of bias. We attempted to contact the study authors to obtain missing data if insufficient information of randomization and other aspects of the trials were provided.

3.4.4. Measures of treatment effect

We calculated Risk ratios (RR) and its 95% confidence interval (CI) for dichotomous outcomes (i.e. mortality, SSI rate, adverse events, systemic infections).

3.4.6. Dealing with missing data

Whenever possible, we contacted the original investigators to request missing data. We tried to make assumptions about the cause of the missing data and if the data were missing at random or because of a specific outcome.

3.4.7. Assessment of heterogeneity

Statistical heterogeneity

The presence of heterogeneity was assessed using the Chi^2 test using a significance level of 0.1. The I^2 statistic was used to quantify inconsistency across the studies. We interpreted an I^2 greater than 50% to demonstrate high heterogeneity.

Clinical heterogeneity

We assessed clinical heterogeneity by considering patients, intervention characteristics and trial settings, and evaluated methodological heterogeneity using

the different domains of the risk of bias tool (Higgins 2011).

3.4.8. Assessment of reporting biases

We aimed to explore publication bias if there was a sufficient number of trials and reasons for any asymmetry. For this, we planned to use a funnel plot asymmetry only when there are at least 10 studies included in the meta-analysis, because a funnel test with fewer studies would have had too low a power to distinguish chance from real asymmetry (Section 10.4.3.1 in Higgins 2011). However, this was not feasible due to insufficient number of studies in each comparison.

3.4.9. Data synthesis

We pooled data in meta-analyses where data were available, and where it was clinically acceptable to do so. Otherwise we presented a narrative overview of the studies. We used Review Manager (RevMan) 5.3 software (Cochrane Collaboration 2014) to conduct meta-analyses. For the statistical analyses, our general approach was to use a random-effects model. With this approach, the CIs for the average intervention effect would be wider than those that would be obtained using a fixed-effect approach, leading to a more conservative interpretation.

3.4.10. Subgroup analysis and investigation of heterogeneity

We considered subgroup meta-analyses where possible and appropriate. We aimed to conduct subgroup analyses by:

- Antibiotic types, doses, and modes of administration.
- Studies controlled with placebo or no intervention to assess the efficacy of antibiotic prophylaxis.
- Fracture location: mandibular fractures, orbital fractures, all other fractures (nasal, maxillary, zygoma) together. This is because the proximity to the oral cavity is an important risk factor for infection.
- Isolated fractures and multiple concurrent maxillofacial fractures.
- Age: with distinctive analyses for children (less than 18 years), and the elderly (over 65 years).

3.4.11. Sensitivity analysis

Where possible and appropriate, we conducted sensitivity analyses on the primary

outcomes to analyze the effect of including only studies at low risk of bias. If meta-analyses include several small studies and a single very large study, we planned to undertake a sensitivity analysis comparing the effect estimates from both random-effects and fixed-effect models. If these were different, we would have reported on both analyses as part of the results section and considered possible interpretation.

3.4.12. Presentation of main results

We used the GRADE approach, adopted by Cochrane, to interpret findings (Schunemann 2011), and we used the GRADEprofiler GDT software (GRADEpro GDT 2015) to import data from RevMan 5.3, to create the 'Summary of findings' tables. In GRADEpro, evidence relative to each specific outcome is rated as high, moderate, low and very low quality. We started the rate of the outcomes of all randomized trials as high and downgraded them depending on the following factors: limitations in study design or execution, indirectness of evidence, unexplained heterogeneity, imprecision of results and high probability of publication bias. The grades of evidence are as following:

- High certainty: Meaning that we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate certainty: Moderately confidence in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
- Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
- Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

4. Results

4.1. Description of the studies

We screened 1237 references by title and abstract and reviewed 25 full texts and included 14 studies (Abubaker 2001; Aderhold 1983; Baliga 2014; Campos 2015; Gerlach 1988; Heit 1997; Mamthashri 2018; Momeni 2018; Perepa 2018; Raichoor 2017; Schaller 2013; Soong 2014; Vazquez-Barro 1994; Zix 2013). Two studies were published in German (Aderhold 1983; Gerlach 1988) and one study was published in Spanish (Vazquez-Barro 1994). All other trials were published in English. One trial was available only as an abstract despite contacting the main investigator (Raichoor 2017).

We found no trials from reference checking and no ongoing trials upon searching ClinicalTrials.gov and the International Clinical Trials Registry Platform.

4.1.1. Included studies

See (Appendix Characteristics of included studies) for further details.

Setting

All included trials were single-center trials conducted in departments of oral and maxillofacial surgery. Six studies were conducted in Europe (Aderhold 1983; Gerlach 1988; Schaller 2013; Soong 2014; Vazquez-Barro 1994; Zix 2013), four in India (Baliga 2014; Mamthashri 2018; Raichoor 2017; Perepa 2018), two in the USA (Abubaker 2001; Heit 1997), one in Brazil (Campos 2015) and one in Iran (Momeni 2018). Most trials were published in the last decade.

According to the principle investigator, one study conducted in Bern, Switzerland was planned as one large trial. However, the trial plan was changed during the study. The study was re-planed, analyzed and reported as three separated trials (Schaller 2013; Soong 2014; Zix 2013) stratified by fracture site.

Table 1 shows the characteristics of the included studies and the participating patients.

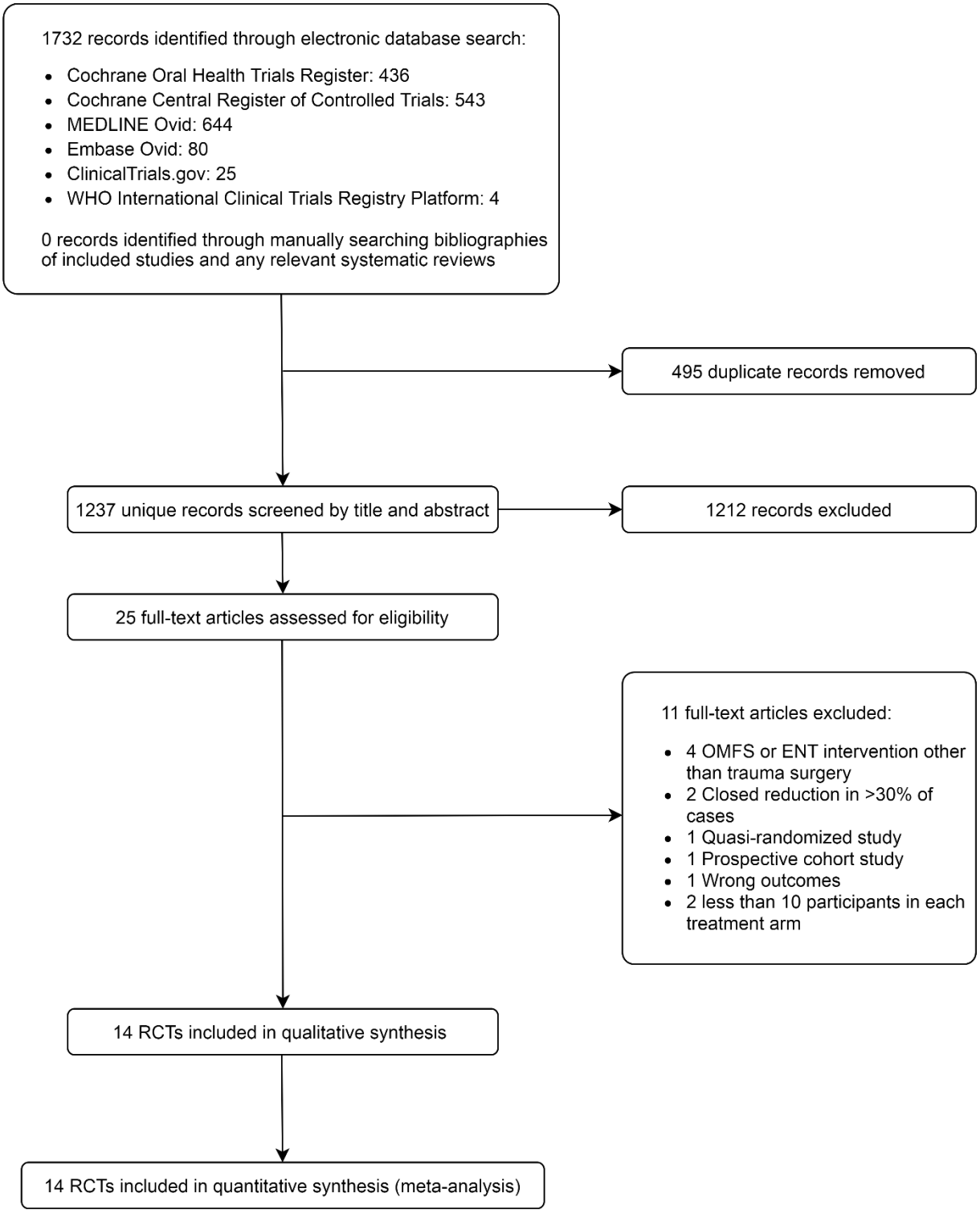

Figure 1 Flowchart of the search results and study selection

Participants

Three trials (Schaller 2013; Soong 2014; Zix 2013) reported a sample size calculation and did not reach the planned sample size. The other studies did not report sample size calculations. The included trials recruited between 30 (Abubaker 2001) and 200 (Gerlach 1988) participants. One RCT (Heit 1997) did not report the number of participants in each treatment arm in the original paper. We contacted the study authors who stated both treatment arms were equally sized (45 participants in each arm). The average age of participants was between 20 and 35 in all included studies. Two studies (Campos 2015; Vazquez-Barro 1994) did not report the average age of participants. All studies reported the sex distribution of participants. No studies reported outcomes in children or elderly population separately.

Open reduction and internal fixation was the method of surgical treatment in all included studies. One study included 3 out of 30 participants treated with closed reduction (Abubaker 2001).

Five studies compiled fractures from multiple locations (Baliga 2014; Campos 2015; Mamthashri 2018; Raichoor 2017; Vazquez-Barro 1994). Seven studies restricted the fracture site to the mandible only (Abubaker 2001; Aderhold 1983; Gerlach 1988; Heit 1997; Raichoor 2017; Momeni 2018; Perepa 2018; Schaller 2013). However, only one of these studies restricted mandibular fractures to those involving the alveolar ridge (Schaller 2013). One study (Perepa 2018) used an intraoral approach exclusively and three studies used both intra and extraoral approaches (Baliga 2014; Campos 2015; Heit 1997). The other studies did not mention the surgical approach used. Four studies on mandibular fractures reported their management of teeth involved in the fracture site (Campos 2015; Mamthashri 2018; Momeni 2018; Schaller 2013). One study only examined orbital fractures (Zix 2013).

Studies	Publish year	Country	Language	Recruitment Period	Fracture site	Follow-up (weeks)	Nr. of participants	Mean age	% Female	Infection Criteria	SSI cases	Overall SSI Rate (%)
Abubaker	2001	USA	English	01/97 - 12/97	Mandible	6	30	32	10%	clinical	4	13.3
Aderhold	1983	Germany	German	n.a.	Mandible	unclear	120	39	28%	clinical	14	11.7
Baliga	2014	India	English	2008 - 2010	ZMC / Mandible	3	60	30	7%	clinical	2	3.3
Campos	2015	Brazil	English	12/11 - 12/12	All facial fractures	6	74	n.a.	16%	clinical	7	9.5
Gerlach	1988	Germany	German	n.a.	Mandible	3	200	29	24%	clinical	19	9.5
Heit	1997	USA	English	n.a.	Mandible	8	90	30	16%	clinical	4	4.4
Mamthashri	2018	India	English	11/04 - 06/06	All facial fractures	5	50	30	10%	clinical	2	4.0
Momeni	2018	Iran	English	09/15 - 09/16	Mandible	3	65	27	23%	CDC	24	36.9
Perepa	2018	India	English	01/11 - 06/15	Mandible	12	144	29	13%	CDC	4	2.8
Raichoor	2017	India	English	n.a.	All facial fractures	unclear	70	unclear	unclear	unclear	3	4.3
Schaller	2013	Switzerland	English	01/07 - 01/11	Mandible	24	59	31	17%	CDC	12	20.3
Soong	2014	Switzerland	English	01/08 - 07/11	ZMC / Le-Fort	24	94	45	21%	CDC	2	2.1
Vazquez-Barro	1994	Spain	Spanish	01/91 - 01/92	All facial fractures	24	57	20 - 65	18%	CDC	7	12.3
Zix	2013	Switzerland	English	01/06 - 04/10	Orbit	24	60	42	37%	CDC	3	5.0

Table 1 Main characteristics of the included studies

Interventions

All studies except two compared different treatment regimens of the same antibiotic. Two studies (Heit 1997, Raichoor 2017) compared two different antibiotics to each other. Intravenous administration was the most common administration route used for intraoperative and short postoperative prophylaxis, while oral administration was used for long postoperative prophylaxis. All studies were parallel two-arm studies except for two studies (Aderhold 1983; Gerlach 1988). Aderhold 1983 compared no prophylaxis to short-term prophylaxis and long-term prophylaxis. Gerlach 1988 compared no prophylaxis to intraoperative prophylaxis (single-shot) to short postoperative prophylaxis (24 hours) and long-term prophylaxis. Five studies were placebo-controlled studies (Abubaker 2001; Momeni 2018 ; Schaller 2013; Soong 2014; Zix 2013). Seven studies compared short-term to long-term prophylaxis while four studies compared long-term prophylaxis to preoperative prophylaxis. Table 1 shows the type of antibiotic and regimen applied in the included studies.

Study	Compared regimes				Used antibiotics groups	Preoperative and intraoperative prophylaxis	Postoperative prophylaxis
	Arm	Pre	Intra	Post (days)			
Abubaker	1	✓	✓	short (0.5)	Penicillin	Penicillin G 2mU i.v. Q4H starting admission until 12h post-Op	After 12h post-Op Penicillin V p.o. 500mg QID or Placebo p.o. QID for 5 days
	2	✓	✓	long (5)			
Aderhold	1		✓	short (2)	Cephalosporine 3G / Penicillin	not mentioned	Several AB (mostly Cefotaxime and Mezlocillin/Oxacillin) for either 2 or 4 days
	2	✓	✓	long (4-7)			
	3	No AB					
Baliga	1	✓	✓		Cephalosporine 3G/Metronidazole	Cefotaxime 1g i.v. BID and Metronidazole 500mg i.v. TID	Cefotaxime 1g i.v. BID and Metronidazole 500mg i.v. TID for 5 days
	2	✓	✓	long (5)			
Campos	1		✓		Cephalosporine 1G	Single-shot Cefazolin 2g i.v. perioperatively	Cefazolin 1g QID for 1 day
	2		✓	short (1)			
Gerlach	1		✓		Penicillin	single-shot Mezolocillin/Oxacillin-combination (2:1) 6g i.v. 30 mins preoperatively for AB Arms	Mezolocillin/Oxacillin-combination (2:1) 6g i.v. TID for 1 or 3 days
	2		✓	short (1)			
	3		✓	long (3)			
	4	No AB					
Heit	1	✓	✓	short (1)	Cephalosporine 3G	Ceftriaxone i.v. 1gm once daily	Same regime for 1 postoperative day
	2	✓	✓	short (1)	Penicillin	Penicillin G 2mU i.v. 6 dailyQ4H	
Mamthashri	1	✓		long (5)	Amoxicillin, Cloxacillin, Metronidazole	Amoxicillin 500mg i.v., Cloxacillin 500mg i.v., Metronidazole 400mg i.v. TID at the day of admission	Amoxicillin 250mg, Cloxacillin 250mg, Metronidazole 400mg p.o. TID from the 2nd to the 5th post-Op day
	2		✓	long (5)		Same AB on the operative day before surgery and the time of induction of general anesthesia	

Study	Compared regimes				Used antibiotics groups	Preoperative und intraoperative prophylaxis	Postoperative prophylaxis
	Arm	Pre	Intra	Post (days)			
Momeni	1	✓	✓		Lincosamide	pre and intraoperative prophylaxis was administered but not reported in detail	Clindamycin 600 mg i.v. or Placebo i.v. every 8 hours for a period of 5-7 days
	2	✓	✓	long (5-7)			
Perepa	1	✓	✓	short (1)	Penicillin/Beta-lactamase inhibitor/ Metronidazole	Amoxicillin with Clavulanic acid and Metronidazole i.v. or p.o.	Amoxicillin/Clavulanic acid 1.2mg i.v. and Metronidazol 500mg i.v. for 1 day
	2	✓	✓	long (5)			Amoxicillin/Clavulanic acid 1.2mg and Metronidazol 500mg i.v. for 1 day then 4 days AB Amoxicillin/Clavulanic acid 625mg p.o. and Metronidazol 400mg p.o.
Raichoor	1	unclear		short (1)	Cephalosporine 3G	unclear	Certriaxone 1g BID for 1 day postoperatively
	2			short (1)	Penicillin		Amoxicillin 1 g TID for 1 day postoperatively
Vazquez Barro	1		✓		Cephalosporine 1G	Cefazolin 2g i.m. once 1h before surgery	
	2		✓	short (1)		Cefazolin 1g i.v. QID for one day starting before surgery	Same regime for 1 postoperative day
Schaller	1	✓	✓	short (1)	Penicillin/Beta-lactamase inhibitor	Starting admission: Amoxicillin/Clavulanic acid 1,2g i.v. until 24h post-Op	Amoxicillin/Clavulanic acid 625mg p.o. TID or placebo p.o. for 4 days
	2	✓	✓	long (4)			
Soong	1	✓	✓	short (1)			
	2	✓	✓	long (4)			
Zix	1	✓	✓	short (1)			
	2	✓	✓	long (4)			

Table 2 Antibiotics and regimens compared in the included studies [1]

[1] AB: Antibiotics, mU: million Units, mIU: million International Units, i.v.: intravenously, p.o.: orally, i.m: intramuscular, 1G: first generation, 3G: third generation

pre-Op: preoperatively, Intra-Op: intraoperatively, post-Op: postoperatively, TID: 3 times a day, QID: 4 times a day, Q4H: every 4 hours, d: day, h: hours

Outcomes and follow-up

All included studies reported SSI as an outcome and nine studies reported the rate of systemic infections (Abubaker 2001; Baliga 2014; Heit 1997; Mamthashri 2018; Momeni 2018; Perepa 2018; Schaller 2013; Soong 2014; Vazquez-Barro 1994; Zix 2013). Six studies (Momeni 2018 ; Perepa 2018; Schaller 2013; Soong 2014; Vazquez-Barro 1994; Zix 2013) stated identified postoperative infection according to the criteria for surgical site infections published by the Centers of Disease Control and Prevention (Mangram 1999), while the other studies used different clinical and laboratory parameters to determine an infection. Six trials reported adverse events due to antibiotic administration (Aderhold 1983; Heit 1997; Mamthashri 2018; Schaller 2013; Soong 2014; Vazquez-Barro 1994; Zix 2013). All studies except for three (Aderhold 1983; Raichoor 2017; Perepa 2018) reported the rate of retreatment surgery due to infection. None of the included studies reported treatment costs, length of hospital stay or HRQoL. Table 3 shows the outcomes reported by each included study.

The follow-up duration varied between studies. One study did not report follow-up (Raichoor 2017). The shortest follow-up duration was 3 weeks (Baliga 2014; Gerlach 1988), however, most studies followed-up participants for up to 6 months (Schaller 2013; Soong 2014; Vazquez-Barro 1994; Zix 2013).

Conflicts of interest and funding

Three studies (Schaller 2013; Soong 2014; Zix 2013) stated that they received public funding (Swiss Accident Insurance Body, University Hospital of Bern) and private funding from pharmaceutical companies (Mepha Pharma AG and GlaxoSmithKline AG). The latter two provided antibiotics for these studies. One study (Campos 2015) received support from the Brazilian Company of Hospital Services (EBSERH: Empresa Brasileira de Serviços Hospitalares). Four studies (Baliga 2014; Mamthashri 2018; Momeni 2018; Perepa 2018) received no support or stated no conflicts of interest. The source of funding was not reported in the other five studies.

Studies / Outcomes	SSI	Systemic infection	Adverse events	Rate of retreatment surgery	Length of Hospital Stay	Total costs	HRQoL
Abubaker	✓	✓	n.r.	✓	n.r.	n.r.	n.r.
Aderhold	✓	n.r.	✓	n.r.	n.r.	n.r.	n.r.
Baliga	✓	✓	n.r.	✓	n.r.	n.r.	n.r.
Campos	✓	n.r.	n.r.	✓	n.r.	n.r.	n.r.
Gerlach	✓	n.r.	n.r.	✓	n.r.	n.r.	n.r.
Heit	✓	✓	✓	✓	n.r.	n.r.	n.r.
Mamthashri	✓	✓	✓	✓	n.r.	n.r.	n.r.
Momeni	✓	✓	n.r.	✓	n.r.	n.r.	n.r.
Perepa	✓	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Raichoor	✓	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Schaller	✓	✓	✓	✓	n.r.	n.r.	n.r.
Soong	✓	✓	✓	✓	n.r.	n.r.	n.r.
Vazquez-Barro	✓	n.r.	✓	✓	n.r.	n.r.	n.r.
Zix	✓	✓	✓	✓	n.r.	n.r.	n.r.

Table 3 Outcomes reported by included studies [2]

4.1.2. Excluded studies

Twenty-three studies underwent full-text screening and ten were excluded from this review (See Characteristics of excluded studies). Four studies were excluded because participants had surgical interventions for indications other than a maxillofacial fracture (Conover 1985; Henkel 1994; Marcucci 1990; Sixou 2012). Two studies were excluded as more than one-third of all participants underwent closed reduction (Chole 1987; Zallen 1975). We excluded two studies (Eschelman 1971; Hotz 1994), which addressed the need for antibiotic prophylaxis in all ENT or OMFS surgical interventions. There were less than 10 participants with maxillofacial fractures in each arm in both studies.

One study was excluded because it was a non-randomized trial (Meier 1984). We excluded one study conducted in people with fractures of the maxillary sinus but only reported acute sinusitis as an outcome and none of our target outcomes (Schmidt 2015).

[2] n.r. : not reported.

Finally, we excluded one large and known study (Miles 2006) due to its design and conduct. This study used every-other method to allocate participants to treatment groups, which is not considered as an adequate randomization or allocation concealment method (Higgins 2011). Crossovers occurred between the two trial arms which results in imbalances between the number of participants in each arm. Additionally, the baseline characteristics of participants were not presented by intervention but by the outcome, which made assessing baseline balance between groups even more difficult. And finally, this study had a drop-out rate of 37% and the results were reported for participants who adhered to the short follow-up duration of 5 weeks.

4.2. Risk of bias in included studies

See Risk of bias tables for details on the risk of bias in included studies individually (Characteristics of included studies). Figure 2 shows the risk of bias assessment per study and domain, and Figure 3 shows the risk of bias assessment per domain across all studies. Two studies had a low risk of bias in all domains (Schaller 2013; Soong 2014), while one study had a high risk of bias in most domains (Campos 2015).

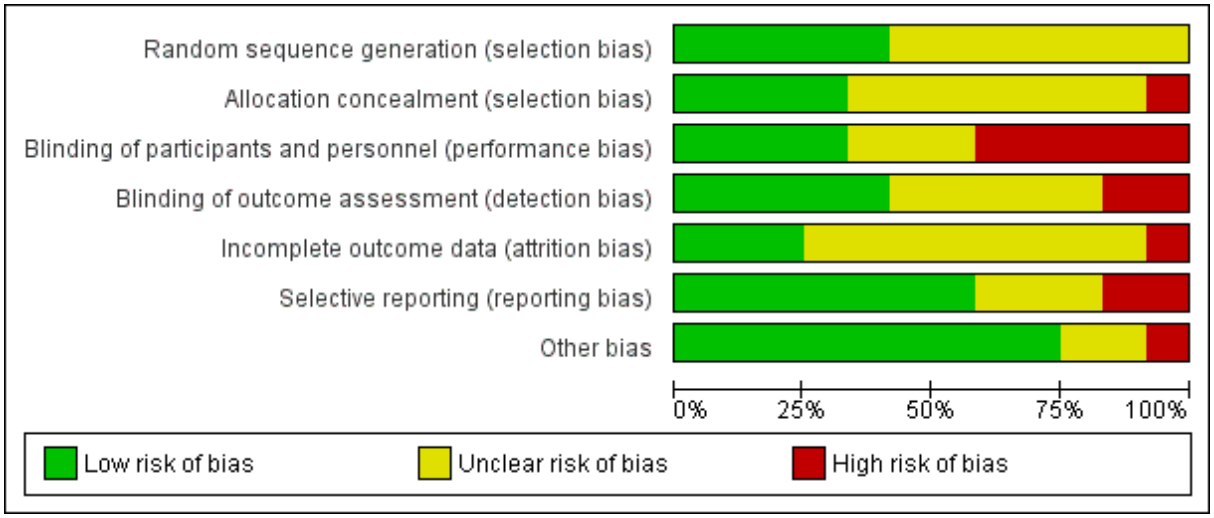

Figure 2 Risk of bias graph

4.2.1. Allocation (selection bias)

Random sequence generation

The method of sequence generation was described in five studies. Schaller 2013, Soong 2014 and Zix 2013 used a computer-generated randomization number was and Abubaker 2001 used randomization codes. The other studies merely described the allocation of participants to the intervention and comparison groups as being random and did not provide any details regarding the method of sequence generation. Hence, they were judged as having an unclear risk of bias in this domain.

Allocation concealment

All included studies reported a random sequence allocation, however, only four trials described the method used in enough detail. Schaller 2013; Soong 2014; Zix 2013 used central randomization through a third party, while Mamthashri 2018 used sealed envelopes. One study showed a significant difference in the baseline characteristics of studied groups and thus was judged to have a high risk of bias in sequence generation (Campos 2015).

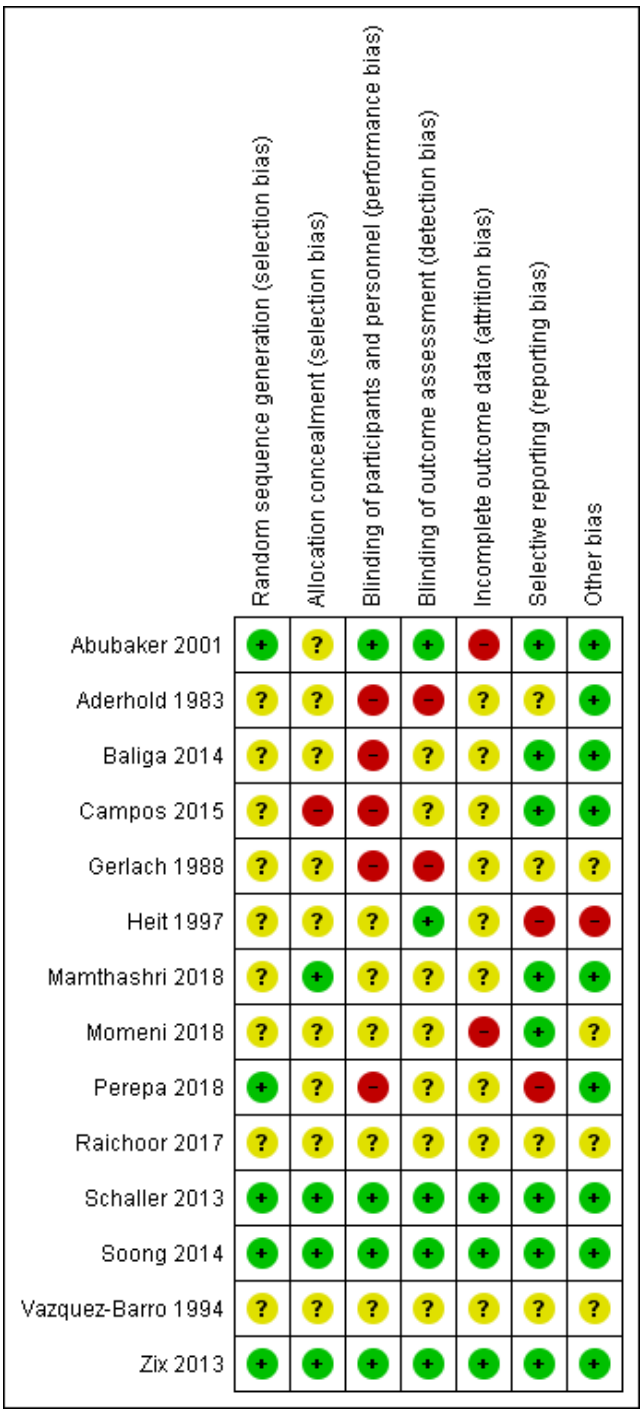

Figure 3 Risk of bias summary

4.2.2. Blinding (performance bias and detection bias)

Four studies were judged as having a low risk of bias in the blinding domain (Abubaker 2001; Schaller 2013; Soong 2014; Zix 2013). The remainder of the included studies were open-label and have a high risk of performance bias. Outcomes assessors were

not blinded in two studies (Aderhold 1983; Gerlach 1988) and therefore had a high risk of detection bias. Blinding of outcome assessors was not mentioned in the rest of the studies and therefore they were judged to have an unknown risk of bias.

4.2.3. Incomplete outcome data (attrition bias)

All reported outcomes were clinically relevant. All studies reported SSI along with some other relevant outcomes. However, only three trials (Schaller 2013; Soong 2014; Zix 2013) reported the number of participants lost to follow-up and provided an intention to treat analysis. One study (Abubaker 2001) lost almost one-third of the participants due to incomplete follow-up which we judged as a high risk of bias. Four studies (Baliga 2014; Mamthashri 2018; Momeni 2018; Perepa 2018) stated that patients not adhering to follow-up were to be excluded. However, these studies did not the number of participants lost to follow-up. The other trials did not report lost to follow-up and were judged as having an unclear risk of bias in this domain.

4.2.4. Selective reporting (reporting bias)

Four trials are registered on clinicaltrials.gov and have a publicly available protocol (Campos 2015; Schaller 2013; Soong 2014; Zix 2013). Study protocols were not available for the other trials. Two studies were assessed as having a high risk; Perepa 2018 mentioned adverse events in the methods section as an outcome but did not report this outcome later. Heit 1997 and Raichoor 2017 did not report the distribution of the fracture site and the site of infection.

4.2.5. Other potential sources of bias

We judged one study (Heit 1997) that compared the efficacy of two different antibiotics as having a high risk of bias because it favored one of the two in terms of average cost but had an unclear funding source. Two studies (Gerlach 1988; Vazquez-Barro 1994) were judged as having an unclear risk of bias due to very brief reporting of the results.

Publication bias

A funnel plot was not appropriate for assessment of publication bias, as none of the analyses in this review included more than 10 studies (Sterne 2011).

4.3. Effects of interventions

The included studies showed considerable clinical heterogeneity in the compared antibiotic regimens. To address this heterogeneity, we categorized the comparison arms in the included studies based on the prophylaxis regimens into one of five possible application protocols:

- No antibiotics at all neither pre- nor postoperatively
- Preoperative prophylaxis: administrated starting admission until before surgery.
- Intraoperative prophylaxis: administrated at the beginning and during surgery.
- Short-term postoperative prophylaxis: spanning for 48 hours postoperatively
- Long-term postoperative prophylaxis: which extends over 48 hours postoperatively.

Seven trials were conducted in patients with mandibular fractures only and 5 other trials included patients with mandibular fractures. We were able to stratify analyses by fracture site (mandibular fractures, fractures in sites other than the mandible). Only two studies compared different classes of antibiotics to each other.

4.3.1. Comparison I. Any prophylaxis compared with no prophylaxis

Studies comparing any antibiotic prophylaxis to no antibiotic prophylaxis were included in this comparison. Two studies (Aderhold 1983; Gerlach 1988) provided data. All participants had mandibular fractures only. The results of the two trials were pooled for the outcome postoperative SSI using a random-effects model. Participants who received any antibiotic prophylaxis were less likely to develop an SSI than those who did not receive any prophylaxis (RR 3.48, 95% CI 1.82 to 6.63; participants = 320; studies = 2; I^2 = 0%, Analysis 1.1).

Gerlach 1988 reported the rate of retreatment surgery. There is little or no difference in the need for retreatment surgery in people who received antibiotic prophylaxis compared to people who did not receive prophylaxis (RR 6.16, 95% CI 0.57 to 66.51; participants = 200; studies = 1; I^2 = 0%, Analysis 1.1). Aderhold 1983 reported adverse events. Prophylaxis probably slightly increases the risk of adverse events (RR 0.06, 95% CI 0.00 to 0.92; participants = 120; studies = 1; I^2 = 0%, Analysis 1.1). No trial reported other outcomes comparing prophylaxis with no prophylaxis. Figure 4 shows the results of the meta-analysis of the two included trials.

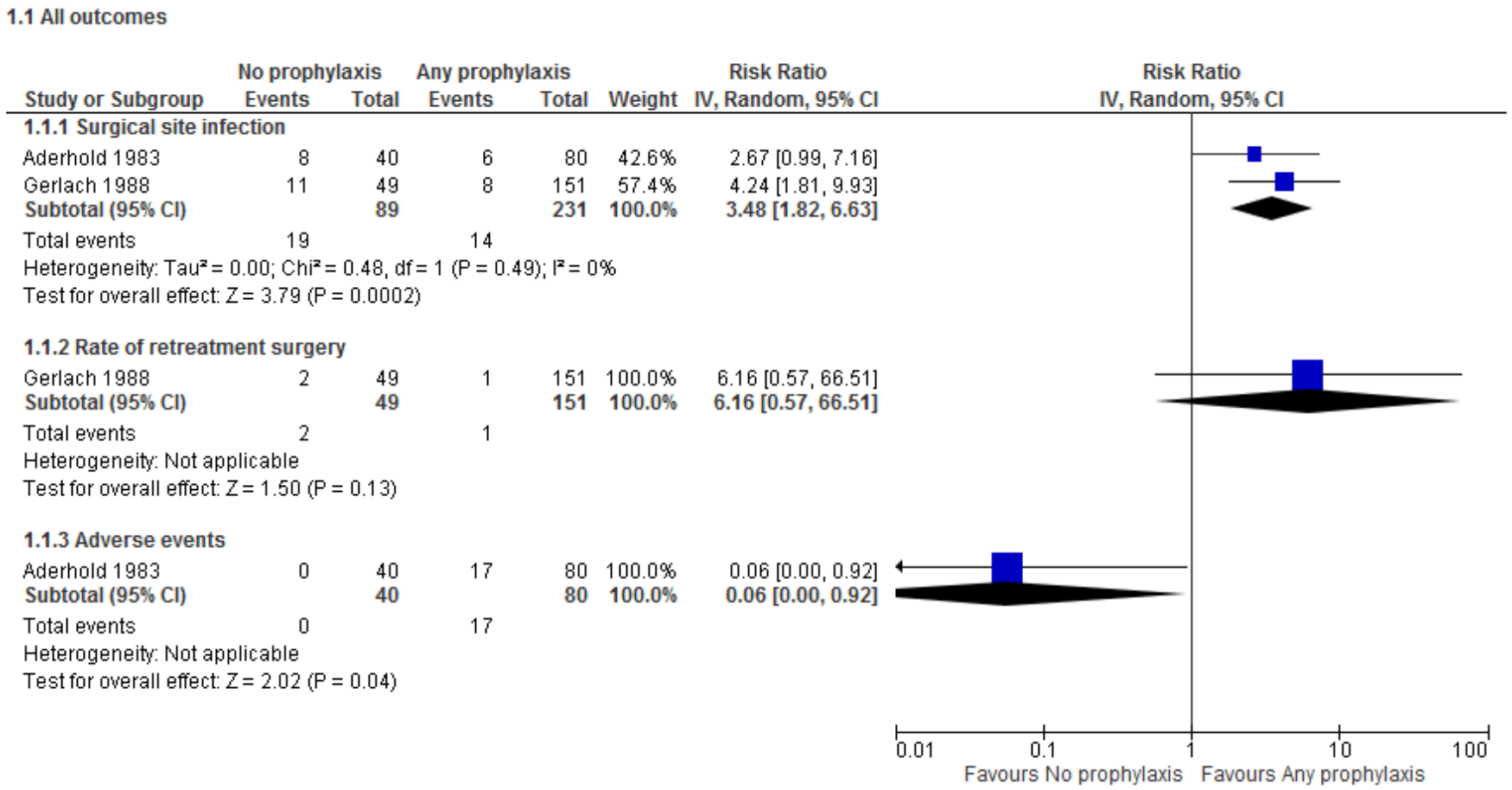

Figure 4 Comparison 1: Any prophylaxis compared with no prophylaxis

4.3.2. Comparison II. Intraoperative compared with postoperative prophylaxis

Studies comparing intraoperative prophylaxis only with intraoperative and postoperative prophylaxis were included in this analysis. Five trials (Baliga 2014; Campos 2015; Gerlach 1988; Momeni 2018; Vazquez-Barro 1994) provided data for this comparison and reported SSI and rate of retreatment surgery. There is little or no difference between intraoperative and postoperative prophylaxis (RR 1.23, 95% CI 0.74 to 2.04; participants = 408; studies = 5; I^2 = 0%, Analysis 2.1).

Two trials (Baliga 2014, Momeni 2018) reported systemic infections. However, no systemic infections occurred in both arms in both studies. A meta-analysis was not possible. Retreatment surgery was only needed in two trials despite all five trials reporting this outcome. Expanding the antibiotic prophylaxis postoperatively did not improve this outcome (RR 0.37, 95% CI 0.04 to 3.29; participants = 408; studies = 5; I^2 = 0%, Analysis 2.1). One small study (Vazquez-Barro 1994) reported adverse events. However, no adverse events occurred in the comparison arms. No trials reported length of hospital stay, treatment cost or treatment-related quality of life for this comparison.

Figure 5 shows the results of the meta-analyses for this comparison for each outcome.

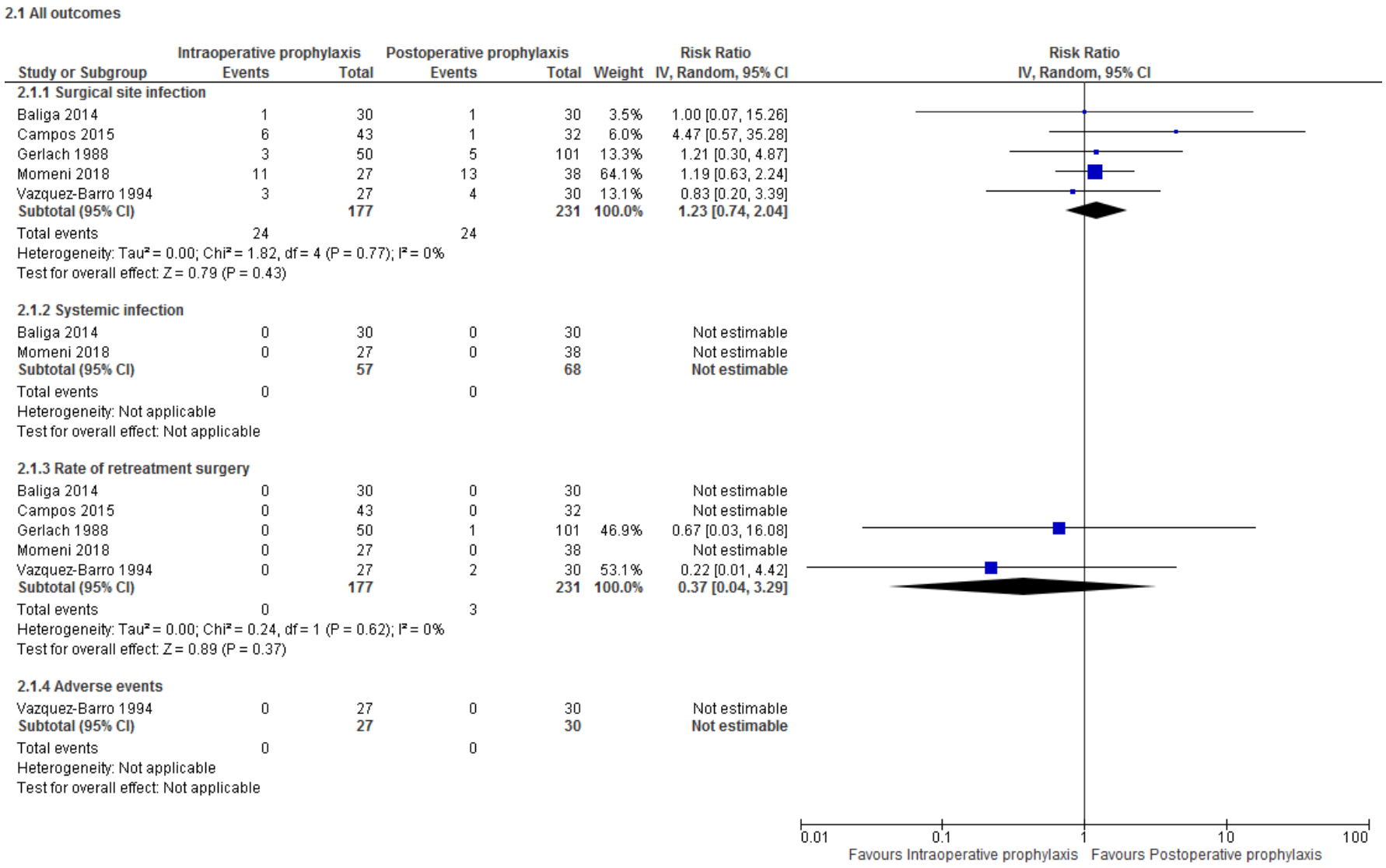

Figure 5 Comparison II: Intraoperative compared with postoperative prophylaxis

4.3.3. Comparison III. Short compared with long postoperative prophylaxis

Seven trials (Abubaker 2001; Aderhold 1983; Gerlach 1988; Perepa 2018; Schaller 2013; Soong 2014; Zix 2013) reported outcomes for this comparison and all reported SSI. There is little or no difference in SSI between participants who received short or long postoperative prophylaxis (RR 0.76, 95% CI 0.39 to 1.47; participants = 570; studies = 7; I^2 = 0%, Analysis 3.1). When we stratified the analysis by fracture site (mandibular fractures vs. all other facial fractures), we had an effect estimate that slightly favored short postoperative prophylaxis for mandibular fractures (RR 0.64, 95% CI 0.31 to 1.30; participants = 414; studies = 5; I^2 = 0%, Analysis 3.1). However, a single study (Schaller 2013) with low risk of bias in all domains showed no difference between both regimens (RR 0.97, 95% CI 0.35 to 2.65). The effect estimated for facial fractures other than mandibular fractures was imprecise (RR 2.44, 95% CI 0.37 to 16.09; participants = 156; studies = 2; I^2 = 0%, Analysis 3.1).

Figure 6 shows the results of meta-analysis of SSI stratified by fracture site.

Systemic infection was reported by four trials (Abubaker 2001; Schaller 2013; Soong 2014; Zix 2013). No systemic infections occurred in the comparison arms. In a sensitivity analysis, we included three studies (Schaller 2013; Soong 2014; Zix 2013) with low risk of bias in all domains. There is little or no difference between both prophylaxis regimes (RR 1.19, 95% CI 0.49 to 2.89; participants = 215; studies = 3; I^2 = 0%, Analysis 3.3). Five studies reported the rate of retreatment surgery (Abubaker 2001; Gerlach 1988; Schaller 2013; Soong 2014; Zix 2013). Only one fracture in one study in the long postoperative prophylaxis group required hardware removal due to postoperative infection (RR 0.34, 95% CI 0.01 to 8.15; participants = 346; studies = 5; I^2 = 0%, Analysis 3.2).

Adverse events were reported by four studies (Aderhold 1983; Schaller 2013; Soong 2014; Zix 2013). There is little or no difference in the rate of adverse events between participants who received short or long postoperative prophylaxis (RR 0.7=0.61, 95% CI 0.27 to 1.38; participants = 295; studies = 4; I^2 = 0%, Analysis 3.2). After restricting the meta-analyses to the three studies with low risk of bias in all domains (Schaller 2013; Soong 2014; Zix 2013), the effect estimate favored long postoperative prophylaxis in terms of adverse events. However, this estimate is imprecise due to the low rate of adverse events in each arm (RR 1.76, 95% CI 0.37 to 8.32; participants = 215; studies = 3; I^2 = 0%, Analysis 3.3).

Figure 6 Comparison III: Short vs. long postoperative prophylaxis: Outcome SSI

No trial reported length stay in hospital, treatment cost or treatment-related quality of life. Figure 7Figure 6 Comparison III: Short vs. long postoperative prophylaxis: Outcome SSI shows the meta-analyses for outcomes other than SSI for this comparison.

4.3.4. Comparison IV. Preoperative compared with intraoperative prophylaxis

One study (Mamthashri 2018) reported outcomes for this comparison. In this study, participants received either preoperative prophylaxis starting admission but no intraoperative prophylaxis or no preoperative prophylaxis but intraoperative prophylaxis. Both arms received long postoperative prophylaxis. In other terms, this study compares skipping intraoperative prophylaxis with skipping preoperative prophylaxis. This study reported SSI, rates systemic infection and retreatment surgery as well as adverse events. There is little or no difference between the two groups in terms of SSI (RR 1.00, 95% CI 0.07 to 15.12; participants = 50; studies = 1; I^2 = 0%, Analysis 4.1). One participant in the intraoperative prophylaxis group required extraoral incision and drainage due to SSI (RR 0.33, 95% CI 0.01 to 7.81; participants = 50; studies = 1; I^2 = 0%, Analysis 4.1). There was no need for hardware removal in both groups. Neither systemic infections nor adverse events occurred in the comparison groups.

Figure 7 Comparison III: Short vs. long postoperative prophylaxis: Other outcomes

4.3.5. Comparison V. Ceftriaxone compared with Penicillin derivates

Two trials (Heit 1997, Raichoor 2017) reported outcomes for this comparison. Heit 1997 compared Ceftriaxone 1gm i.v. once daily to Penicillin G 2mu i.v. every four hours. Raichoor 2017 compared Ceftriaxone Certriaxone 1g twice daily to Amoxicillin 1 g three times daily. In both studies, antibiotics were administrated for 1 day only postoperatively. There is little to no difference between both antibiotic groups (RR 1.32, 95% CI 0.30 to 5.83; participants = 160; studies = 2; I^2 = 0%, Analysis 5.1). Only Heit 1997 reported other outcomes. There were no systemic infections, no need for retreatment and no adverse events in the treatment arms in this study.

4.3.6. Subgroup analysis

Most studies were conducted in participants with mandibular fractures. We conducted a subgroup analysis on the fracture site where sufficient studies were available (Analysis 3.1). We did not find enough data to carry out other subgroup analyses.

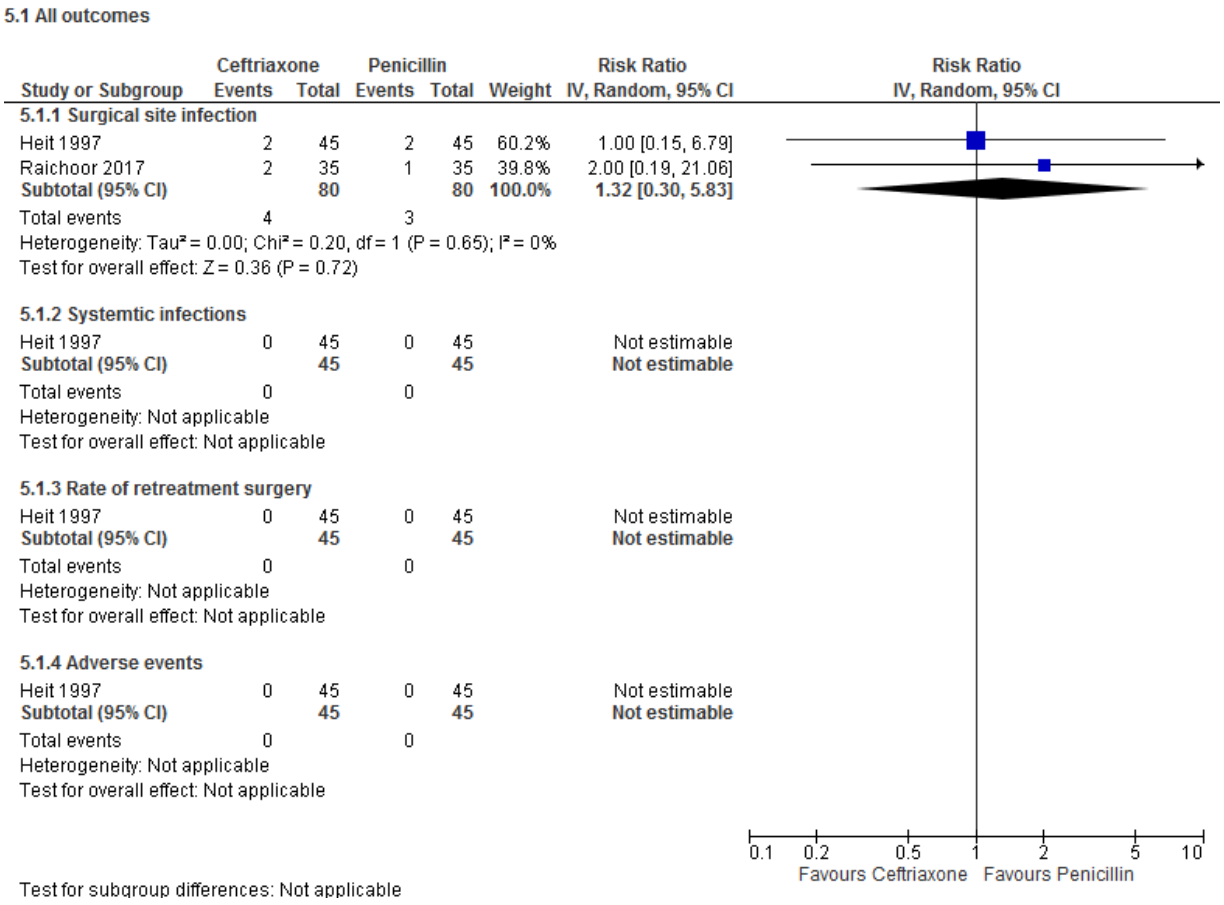

Figure 8 Comparison V: Ceftriaxone compared with Penicillin derivates

4.4. Summary of Findings and certainty of evidence

We summarized the results using the GRADEpro Tool assessed the certainty of the evidence. For Comparison I: No antibiotics compared with any prophylaxis, we downgraded the level of evidence for all outcomes due to the risk of bias in the included studies. We downgraded the quality of evidence further due to imprecision for the outcomes rate of retreatment surgery and adverse events. However, the large effect observed for SSI and rate of retreatment surgery strengthened the level of evidence for SSI and rate of retreatment surgery. Table 4 shows the summary of findings for Comparison I.

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Any prophylaxis	Risk with No prophylaxis				
Surgical site infection	61 per 1,000	**211 per 1,000** (110 to 402)	**RR 3.48** (1.82 to 6.63)	320 (2 RCTs)	⊕⊕⊕⊕ HIGH [a]	We accepted the authors' definitions of SSI.
Rate of retreatment surgery	7 per 1,000	**41 per 1,000** (4 to 440)	**RR 6.16** (0.57 to 66.51)	200 (1 RCT)	⊕⊕⊕◯ MODERATE	Retreatment surgery was defined as the need to remove the osteosynthesis material or the need for an extraoral incision and drainage of a postoperative infection.
Adverse events	213 per 1,000	**15 per 1,000** (0 to 255)	**RR 0.07** (0.00 to 1.20)	120 (1 RCT)	⊕⊕⊕◯ MODERATE [a,b]	We accepted the authors' definitions of adverse events.

a. High risk of bias in several domains in the included study or studies.
b. Strong measure of effect with very wide confidence interval.

Table 4 Summary of Findings Table: No antibiotics compared to any antibiotics

For Comparison II. Intraoperative prophylaxis only versus intra and postoperative prophylaxis, we downgraded the certainty of evidence of all outcomes due to serious risk of bias and in the included studies and the imprecision in the estimates. Table 5 shows the summary of the evidence for this comparison.

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Postoperative prophylaxis	**Risk with Intraoperative prophylaxis**				
Surgical site infection	66 per 1,000	**100 per 1,000** (56 to 178)	**RR 1.50** (0.84 to 2.68)	524 (5 RCTs)	⊕⊕◯◯ LOW [a]	We accepted the authors' definition of SSI.
Systemic infection	not pooled	not pooled	not pooled	241 (2 RCTs)	⊕⊕◯◯ LOW [a]	No events occurred in the included studies.
Rate of retreatment surgery	26 per 1,000	**20 per 1,000** (7 to 60)	**RR 0.78** (0.26 to 2.36)	524 (5 RCTs)	⊕⊕◯◯ LOW [a,b]	Retreatment surgery was defined as the need to remove the osteosynthesis material or the need for an extraoral incision and drainage of a postoperative infection.
Adverse events	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	57 (1 RCT)	- [a]	We accepted the authors' definition of adverse events. No events occurred in both arms in the included study.

a. Most studies had unknown or high risk of bias in all RoB domains.
b. Weak measure of effect with wide confidence intervals.

Table 5 Summary of Findings Table: Intraoperative prophylaxis compared to postoperative prophylaxis

We downloaded the certainty of evidence for the third comparison, Comparison III short postoperative compared to long postoperative prophylaxis due to imprecision of the effect measure estimates of the included studies. We considered the imprecision very serious for the rate of retreatment surgery. Additionally, the certainty of the evidence was further reduced for the outcome adverse events due to the inconsistency between the studies' estimates. See Table 6 for further details.

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Long postoperative prophylaxis	**Risk with Short postoperative**				
Surgical site infection	74 per 1,000	**56 per 1,000** (29 to 109)	**RR 0.76** (0.39 to 1.47)	570 (7 RCTs)	⊕⊕⊕◯ MODERATE [a,b]	We accepted the authors' definition of SSI.
Systemic infection	not pooled	not pooled	not pooled	245 (4 RCTs)	⊕⊕⊕⊕ HIGH	No systemic infections were reported in both treatment arms in all 4 studies.
Rate of retreatment surgery	6 per 1,000	**2 per 1,000** (0 to 47)	**RR 0.34** (0.01 to 8.15)	346 (5 RCTs)	⊕⊕◯◯ LOW [b]	Retreatment surgery was defined as the need to remove the osteosynthesis material or the need for an extraoral incision and drainage of a postoperative infection.
Adverse events	88 per 1,000	**54 per 1,000** (24 to 162)	**RR 0.61** (0.27 to 1.83)	295 (4 RCTs)	⊕◯◯◯ VERY LOW [a,c]	We accepted the authors' definition of adverse events.

a. The direction of the measure of effects from included studies differed by fracture site.
b. Very wide confidence intervals due to very low event rate.
c. Wide confidence intervals. The magnitude and strength of effect differed between studies.

Table 6 Summary of Findings Table: Short postoperative compared to Long postoperative prophylaxis

5. Discussion

This review includes 1173 participants from 14 trials and examines the efficacy and safety of antibiotic prophylaxis in patients treated with surgery for maxillofacial trauma. We compared four different antibiotic regimens, as well as two antibiotic classes.

Several factors of clinical heterogeneity complicated the synthesis of the evidence and the interpretation of the results. In particular, the duration of the antibiotic prophylaxis is of major importance. Different studies compared different durations of antibiotic prophylaxis and we had to categorized these to make meaningful interpretations.

This comparison was only doable after extracting data from the included studies and was defined as a subgroup analysis in the protocol stage.

5.1. Summary of main results

Systemic antibiotics significantly reduce the risk of SSI in people undergoing surgery for maxillofacial trauma when compared with no treatment. Low rates of SSI were seen in patients receiving postoperative prophylaxis. Patients receiving short term postoperative prophylaxis (<48 hours) had a similar or lower risk of SSI compared with those who received antibiotics for longer durations.

The rate of adverse events was low in all compared regimen. There was not enough evidence to compare intraoperative with postoperative prophylaxis in terms of adverse events. Short term postoperative prophylaxis is associated with a lower rate of adverse events compared to long postoperative prophylaxis.

Systemic infections did not occur any of the trials that reported this outcome. The rate of retreatment surgery was very low and there were no differences between the compared regimens.

5.2. Overall completeness and applicability of evidence

All included studies reported SSI, eight reported systemic infections, eleven reported rates of retreatment surgery and seven reported the rate of adverse events. None of the studies reported length of stay in hospital, total treatment costs or HRQoL.

Most studies were conducted in academic departments of oral and maxillofacial surgery. The results of the studies were consistent over time and country which

supports the generalizability of the results and the applicability of the evidence to different populations. None of the studies reported outcomes for elderly or children, or in patients with risk factors such as smokers. Additionally, several studies excluded patients with general medical conditions compromising the function of the immune system.

Participants had all possible sites of facial fractures with mandibular fractures forming the majority. The evidence for fractures of the orbit, zygoma, maxilla and Le-fort fractures is scarce. However, the rate of infection in the aforementioned sites is known from the literature to be lower than that of the mandible and was indeed lower in the included studies. Therefore, the generalizability of the conclusions to fractures other than the mandible is not a concern.

We made a considerable effort to obtain data and contact authors from published and unpublished literature. All included studies have been published, therefore there is potential for publication bias. We did not test for publication bias due to the small numbers of studies per comparison.

5.3. Quality of the evidence

All included studies stated they were randomized trials; however, the method of randomization was incompletely reported in most studies. Five studies specified how randomization was undertaken (Abubaker 2001; Perepa 2018; Schaller 2013; Soong 2014; Zix 2013), and four (Mamthashri 2018; Schaller 2013; Soong 2014; Zix 2013) described the method of allocation concealment in sufficient detail.

The quality of evidence varied depending on the comparison and the outcome of interest. The quality of evidence for the outcome SSI was high when comparing any prophylaxis to no prophylaxis and low for other comparisons. The quality of evidence was downgraded due to either high risk of bias or inconsistency. The quality of evidence for the outcome adverse events was rated as either very low or moderate due to the presence of high risk of bias in the included studies, inconsistency and imprecision. See Summary of findings table 1; Summary of findings table 2; Summary of findings table 3.

5.4. Potential biases in the review process

We conducted the review according to the previously published protocol. Two authors independently performed the literature search, study selection, data extraction and risk

of bias assessment. We contacted authors for additional information when needed. We also compared the included studies with other systematic reviews on this question. We believe that it is unlikely that we overlooked any randomized trials with the potential for inclusion.

5.5. Agreements and disagreements with other studies or reviews biases

Habib 2018 published the most recent systematic review and meta-analysis of randomized clinical trials and retrospective cohort studies comparing intraoperative and postoperative prophylaxis for maxillofacial trauma surgery. The authors included 13 studies in total and concluded that there was no difference between the two regimens in terms of SSI, adverse events, systemic infection or retreatment surgery. Blatt 2019 conducted a systematic review of latest evidence for antibiotic prophylaxis and therapy in oral and maxillofacial surgery and had similar conclusions for maxillofacial trauma.

6. Conclusion

6.1. Implications for practice

This systematic review shows that there is probably no added benefit from administrating prolonged regimes of antibiotic prophylaxis after the open reduction and internal fixation of facial fractures. The available evidence suggests that there is a small or no difference between short-term postoperative, long-term postoperative or intraoperative prophylaxis. The evidence does not allow a reliable comparison of different antibiotics to each other.

6.2. Implications for research

There is a need of randomized clinical trials for certain fractures site such as the orbit, maxilla and Le-Fort fractures. Future RCTs need to report other outcomes important for clinical decision making such as adverse events, duration of stay in hospital, type of re-treatment surgery and HRQoL.

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8. Appendix

8.1. MEDLINE OVID Search strategy

1. exp Maxillofacial injuries/
2. ((maxillofacial or nasal or facial or jaw$ or face$ or maxilla$ or mandib$ or orbital or zygoma$ or nose$ or cheek$) adj5 (fractur$ or injur$ or break$ or broken or trauma$ or surgery or surgical$)).ti,ab.
3. 1 or 2
4. anti-bacterial agents/
5. (antibacterial$ or anti-bacterial$ or antibiotic$ or anti-biotic$ or antimycobacterial$ or anti -mycobacterial$ or bacteriocid$).ti,ab.
6. exp Amoxicillin/
7. (actimoxi or amoclen or amolin or amopen or amopenixin or amox or amoxibiotic or amoxicilina or amoxicillin or amoxicilline or amoxicillinum or amoxil or amoxycillin or ampc or "apo amoxi" or augmentinxr or ax or clamoxyl or dispermox or efpenix or flemoxin or hiconcil or hydroxyampicillin or ibiamox or imacillin or larotid or moxacin or moxal or moxatag or ospamox or pamoxicillin or penamox or polymox or trimox or wymox or penicillin$).ti,ab.
8. Metronidazole/
9. (acromona or anabact or arilin or clont or danizol or deflamon or efloran or elyzol or entizol or flagyl or fossyol or ginefalvir or klion or klont or metrolyl or metronidazol or metronidazole or metronidazolum or metrotop or nalox or nidagel or noritate or novonidazol or protostat or rosadan or satric or takimetol or trichazol$ or trichex or trichopol or "tricowas b" or trikacide or trikozol or trivazol or vandazole or vertisal or zadstat).ti,ab.
10. exp Cephalosporins/
11. (ancef or cefamezin or cefazolin or cefazolina or cefazoline or cefazolinum or cephamezine or cephazolidin or cephazolin or cephazoline or cez or elzogram or kefzol or zolicef).ti,ab.
12. (ceftin or cefurax or cefuroxim or cefuroxime or cefuroximo or cefuroximum or cephuroxime or elobact or kefurox or oraxim or sharox or supacef or zinacef or "zinacef danmark" or zinnat).ti,ab.
13. Levofloxacin/
14. (cravit or elequine or floxel or iquix or "l ofloxacin" or leroxacin or levaquin or levofloxacin or levofloxacine or levofloxacino or levofloxacinum or levokacin or levox or levoxacin or mosardal or nofaxin or "ofloxacin s form" or quixin or reskuin or tavanic).ti,ab.
15. Antibiotic prophylaxis/
16. (antibiotic adj2 (prophylaxis or premedication or pre-medication)).ti,ab.
17. or/4-16
18. 3 and 17
19. randomized controlled trial.pt.
20. controlled clinical trial.pt.
21. randomized.ab.
22. placebo.ab.
23. drug therapy.fs.
24. randomly.ab.
25. trial.ab.
26. groups.ab.
27. or/1-8exp
28. animals/ not humans.sh.
29. 27 not 28

8.2. Characteristics of included studies

Abubaker 2001

Sponsorship source: Not reported
Country: USA
Setting: Single center secondary care
Authors name: A. Omar Abubaker
Institution: Department of Oral and Maxillofacial Surgery, School of Dentistry, Medical College of Virginia Hospital of Virginia Commonwealth University, Richmond, VA
Email: abubaker@vcu.edu
Address: Dr Abubaker, VCU School of Dentistry,521 North 11th St. Richmond, VA, USA
Recruitment period: 1/1/1997 - 31/12/1997

Study design: Randomized controlled trial
Study grouping: Parallel group
Surgical approach: Closed reduction and ORIF.
Peri- und postoperative Management: 2 million units Aqueouspenicillin G i.v. every 4 hours from admission through the preoperative and intraoperative periods and for 12 hours postoperatively (3 postoperative doses).
Follow-up: 1,2,4 and 6 weeks postoperatively
Infection Criteria: The patient's axillary temperature was recorded, and the surgical site was evaluated for infection at each postoperative visit. Criteria for infection included:1. Purulent drainage from the surgical or fracturesite.2. Increased facial swelling beyond postoperative day 7.3. Fistula formation at the surgical or fracture site, with evidence of drainage.4. Fever associated with local evidence of infection (swelling, erythema, or tenderness).
Treatment of SSI: The infected surgical sites were successfully treated with local incision and drainage and proper antibiotic therapy.
Included fracture sites: Mandibular fractures of all sites
Inclusion criteria: Healthy males and females with uncomplicated mandibular fractures
Exclusion criteria: comminuted fractures; infection of the fracture site on initial presentation; fractures resulting from gunshot wounds; associated systemic or midface injuries; a documented immunocompromised medical status; allergy to penicillin; and non-compliance in taking postoperative medications.
Pretreatment: -

Baseline Characteristics

	Postoperative prophylaxis (long)	Postoperative prophylaxis (short)	Overall
Nr of Participants	14	16	30
Gender (female/male)	2/12	1/15	3/27
Average age	33.2	31	32
Multiple fracture sites	10	8	18

Intervention Characteristics

Postoperative prophylaxis (long)

- *postoperative AB Type, Dose (g), and administration method, frequency (times per day) and duration (days)*: Penicillin VK p.o. 500mg QID for 5 days
- *Antibiotic regimen protocol*: pre + peri + post (5 days)

Perioperative prophylaxis

- *postoperative AB Type, Dose (g), and administration method, frequency (times per day) and duration (days)*: Placebo p.o. QID for 5 days
- *Antibiotic regimen protocol*: pre + peri (12 hours)

Bias	Risk of bias	Comment to support judgement
Random sequence generation	Low	Judgement Comment: Randomization codes were used.
Allocation concealment	Unclear	Judgement Comment: No method of allocation concealment was mentioned.
Blinding of participants and personnel	Low	Quote: "None of these surgeons were aware of the regimen assigned."
Blinding of outcome assessment	Low	Quote: "the investigators were not aware of the randomization codes until the study was completed."
Incomplete outcome data	High	Judgement Comment: The study reports PP analysis. It's unclear why 8 patients were excluded.
Selective reporting	Low	Judgement Comment: All outcomes were reported.
Other bias	Low	Judgement Comment: There is no evidence for other sources of bias.

Aderhold 1983

Sponsorship source: not mentioned
Country: Germany
Setting: Secondary Care Single Center
Authors name: Lutz Aderhold
Institution: Abteilung für Mund-, Kiefer- und Gesichtschirurgie Universität Frankfurt am Main (Department of Oral and Maxillofacial Surgery in Frankfurt, Germany)
Address: Klinik für Mund-, Kiefer- und Gesichtschirurgie, Universität Frankfurt am Main, Theodor-Stern-Kai 7, Frankfurt, Germany
Clinical Trial Identifier: not available
Recruitment Period: not mentioned
Study design: Randomized controlled trial
Study grouping: Parallel group
Follow-up: not mentioned
Included fracture sites: Mandibular fractures only
Infection Criteria: purulent discharge with positive culture
Pre, peri- und postoperative management: not mentioned
Surgical approach: Surgical reduction within 48 hours using plate osteosynthesis
Treatment of SSI: not mentioned
Inclusion criteria: open mandible fractures surgically treated with 48 hours
Exclusion criteria: Primary infection at time of surgery
Pretreatment:

Baseline Characteristics

	No prophylaxis	Postoperative prophylaxis (short)	Postoperative prophylaxis (long)	Overall
Nr of patients after excluding drop-outs	40	40	40	120
Gender (female/male)	9/31	13/27	12/28	34/86
Age in years: mean (Range)	37	39	42	39.3
Time between trauma and operation (h): Mean (SD)				max of 48 hours

Intervention Characteristics

No prophylaxis

- *postoperative AB Type, Dose, administration method, frequency and duration (days)*: no AB
- *Antibiotic regimen protocol*: None

Postoperative prophylaxis (short)

- *postoperative AB Type, Dose, administration method, frequency and duration (days)*: Ab for 48 hours postoperatively, several AB were used
- *Antibiotic regimen protocol*: peri + post (short-term)

Postoperative prophylaxis (long)

- *postoperative AB Type, Dose, administration method, frequency and duration (days)*: Ab for 4 to 7 days (avg= 5.8 days), several AB were used
- *Antibiotic regimen protocol*: pre + peri + post (long-term)

Bias	**Risk of bias**	**Comment to support judgement**
Random sequence generation	Unclear	Method of randomization wasn't mentioned.
Allocation concealment	Unclear	wasn't mentioned.
Blinding of participants and personnel	High	different treatment protocols, since participants didn't receive a placebo, they were not blinded.
Blinding of outcome assessment	High	No blinding.
Incomplete outcome data	Unclear	it's unclear whether it's a PP or ITT analysis. Dropouts were not reported.
Selective reporting	Unclear	No pre-study protocol available.
Other bias	Low	No evidence for other sources of bias

Baliga 2014

Sponsorship source: not clear
Country: India
Setting: Single center secondary care
Comments: No conflicts of interest
Authors name: S. D. Baliga
Institution: Department of Oral and Maxillofacial Surgery
Email: baliga1974@rediffmail.co.in
Address: Department of Oral and Maxillofacial Surgery, K.L.E.S. V.K.Institute of Dental Sciences Nehru Nagar, Belgaum 590010, India
Recruitment Period: 2008 – 2010

Study design: Randomized controlled trial
Study grouping: Parallel group
Infection Criteria: 1. Purulent drainage from surgical or fracture site2. Increased facial swelling beyond post-op day 73. Fistula formation at surgical or fracture site with evidence of drainage/pus accumulation4. Fever/malaise associated with local evidence of infection viz. swelling, erythema, tenderness or foul smell, etc.
Follow-up: at least 3 weeks post-operatively.
Peri- und postoperative management: Both groups received pre and intraoperative antibiotics as well as:

1. Injection diclofenac sodium 3 cc/IM/BD 3 days
2. Injection dexamethasone 8 mg/IV stat dose intra-op followed by 4 mg/IV/TID on 1st post-operative day and tapered thereafter
3. Injection ranitidine 2 cc/IV/BD
4. Injection ondansetron 2 cc/IV/SOS
5. Chlorhexidine mouthwash QID for 15 days

Surgical approach: Open reduction and internal fixation with titanium miniplate, using intraoral/extra oral approach or through existing lacerations or combination of the above.
Treatment of SSI: For all these cases resuturing was per-formed after thorough irrigation and the wounds subsequently healed uneventfully. they were treated symptomatically with paracetamol. No antibiotics were given to both of them and they were recalled for observation. It subsided after 1 day.
Included fracture sites: ZMC and mandibular fractures

Baseline Characteristics

	Postoperative prophylaxis (long)	Intraoperative prophylaxis	Overall
Nr of Patients	30	30	60
Nr of Female/Male	1/29	3/27	4/56
Mean age in years (Range)	30 (19-47)	29 (18-42)	30 (18-47)
Dropouts	0	0	0
Nr of smoking patients	5	3	60
ZMC fractures	15	15	30
Mandibular fractures	17	16	41
Multiple fracture sites	8	8	16
only intraoral approach / only extra oral / intra+extraoral approach	19/2/9	19/2/9	38/4/18
Duration between trauma and operation (days): Mean	4.86	30.6	4.2
OP duration in hours	<3 hours	<3 hours	<3 hours

Inclusion criteria:

1. Patients above 15 years and below 65 years of age.

2. Open reduction and internal fixation of either mandibular(at least 1 fracture) or ZMC fracture with or with out minimally displaced other facial bone fracture which requires intervention
3. Patients reporting for follow-up till at least 3 weeks post-operatively
4. Patients with controlled hypertension/diabetes mellitus

Exclusion criteria:

1. Fractures infected at the time of treatment.
2. Severely displaced/or comminuted zygomatic fracture
3. Severely comminuted mandibular fracture
4. Patients failing to report for follow-up till 3 weeks post-operatively
5. Patients with immuno-compromising status
6. Fracture purely pathologic (pathologic fracture)

Pretreatment: Some of them have different Interval between injury and operation. Also, some of them have some habits as alcohol and smoking.

Intervention Characteristics

Postoperative prophylaxis (long)

- *AB Type, Dose (g), and administration method, frequency (times per day) and duration (days)*: Cefotaxime 1g i.v. BID and Metronidazole 500mg i.v. TID for 5 days
- *Antibiotic regime protocol*: Pre + Peri + Post

Intraoperative prophylaxis

- *AB Type, Dose (g), and administration method, frequency (times per day) and duration (days)*: n.A.
- *Antibiotic regime protocol*: Pre + Peri

Bias	**Risk of bias**	**Comment to support judgement**
Random sequence generation	Unclear	Randomization method was not mentioned
Allocation concealment	Unclear	Method of allocation was not mentioned.
Blinding of participants and personnel	High	Since participants did not receive placebo it is very likely that there were not blinded
Blinding of outcome assessment	Unclear	Not clear whether assessors were blinded to the treatment allocation.
Incomplete outcome data	Unclear	no reported about drop out
Selective reporting	Low	Adverse events were not reported.
Other bias	Low	

Campos 2015

Sponsorship source: None
Country: Brazil
Setting: Single center secondary care
Comments: -
Authors name: Giordano BP Campos
Institution: Department of Oral and Maxillofacial Surgery of the Onofre Lopes University Hospital
Email: adrianogermanoufrn@yahoo.com.br
Address: Adriano Rocha Germano, Department of Oral and Maxillofacial Surgery Hospital Universitário Onofre Lopes Universidade Federal do Rio Grande do Norte-UFRNAv. Nilo Peçanha620-Petrópolis, Brasil
Clinical Trial Identifier: NCT01993134
Study duration: December 2011 to December 2012

Study design: Randomized controlled trial
Study grouping: Parallel group
Follow-up: after 1st, 2nd, 4th and 6th weeks postoperatively.
Included fracture sites: All facial fractures
Infection Criteria:

a. pus drainage at the fracture site or in the vicinity of the surgical intervention site.
b. increased swelling 7 days after the operation.
c. presence of a fistula in the area of the surgical intervention or at the site of the fracture, with active drainage.
d. other clinical features observed by the evaluator including typical signs of infection such as fever, edema, and localized redness.

Pre, peri- und postoperative management: The interval between the trauma event and the surgical intervention varied from 1 to 8 weeks but in 68% of cases, surgery took place within 21 days.
Surgical approach: surgery under general anesthetic for the reduction and/or fixation from intra- and extraoral approaches.
Treatment of SSI: Oral administration of antibiotics was used to treat the infections, generally in doses of 500 mg of Amoxicillin every 8 hours for 10 days duration and chlorhexidine irrigation, surgical incision and drainage.

Baseline Characteristics

	Postoperative prophylaxis (short)	Intraoperative prophylaxis	Overall
Nr of patients after excluding drop-outs	32	42	74
Gender (female/male)	not reported	not reported	12/62

Inclusion criteria:

1. no gender restriction
2. at the age of 15-70
3. surgical anesthetic risk categories should be I or II or III-
4. the facial fractures should show no signs of infection prior to surgery
5. not be allergic to the antibiotics used in the research.

Exclusion criteria:

1. patients pan-facial fractures
2. patients requiring surgery longer than six hours

Pretreatment: Groups differ in size. Group I had 38% mandibular fractures while Group II had only 5.6%!!! Demographics for groups are not available.

Pretreatment: -

Intervention Characteristics

Postoperative prophylaxis (short)

- *postoperative AB Type, Dose, administration method, frequency and duration (days)*: Perioperatively single-shot Cefazolin 2g i.v., postoperatively 1g QID for 1 day
- *Antibiotic regimen protocol*: 24h postoperatively

Intraoperative prophylaxis

- *postoperative AB Type, Dose, administration method, frequency and duration (days)*: Perioperatively single-shot Cefazolin 2g i.v., and no postoperative AB
- *Antibiotic regimen protocol*: single-shot.

Bias	**Risk of bias**	**Comment to support judgement**
Random sequence generation	Unclear	Sequence generation method was not stated.
Allocation concealment	High	Although the method of allocation concealment was not mentioned, the baseline differences between both groups are large, so we strongly suspect that the allocation of patients was not concealed.
Blinding of participants and personnel	High	Control group received no postoperative treatment and no placebo.
Blinding of outcome assessment	Unclear	This was not mentioned in the study article.
Incomplete outcome data	Unclear	Dropouts were not reported. It is unclear whether patients were reassigned from the control arm to the other. The significant difference in the sizes of both arms suggest so. The method of analysis (PP or ITT) is not clear.
Selective reporting	Low	All outcomes were reported according to the study protocol.
Other bias	Low	No evidence for other sources of bias.

Gerlach 1988

Sponsorship source: Not mentioned
Country: Germany
Setting: Secondary Care - Single center
Comments: -
Authors name: Klaus Louis Gerlach
Institution: Abteilung für Mund- und Kieferchirurgie der Universitäts Zahn- und Kieferklinik Köln (Department of Oral and Maxillofacial Surgery, University Köln, Germany)
Email: n.A.
Address: Abteilung für Mund- und Kieferchirurgie der Universitäts Zahn- und Kieferklinik, Köln, Joseph-Stelymann-Str. 50924 Köln

Study design: Randomized controlled trial
Study grouping: Parallel group
Follow-up: 2,6,10 and 21 days postoperatively through two different examiners.
Included fracture sites: Only mandibular fractures
Infection Criteria: Pus discharge from the wound
Peri- und postoperative management: No
Surgical approach: ORIF
Treatment of SSI: Antibiotic therapy, incision, drainage, hardware removal, MMF.

Baseline Characteristics

	No prophylaxis	Intraoperative prophylaxis	Postoperative prophylaxis (short)	Postoperative prophylaxis (long)	Overall
Nr of patients after excluding drop-outs	49	50	50	51	200
Gender (female/male)	not reported	not reported	not reported	not reported	48/152
Age in years: mean (Range)	not reported	not reported	not reported	not reported	28.8 (13-89)

Inclusion criteria: unclear
Exclusion criteria:

1. Patients under 13 years of age
2. pregnant patients
3. Patients with nephropathies
4. Patients with known penicillin or cephalosporin allergy- primarily infected fractures
5.

Pretreatment: none

Intervention Characteristics
Postoperative prophylaxis (short)

- *postoperative AB Type, Dose (g), and administration method, frequency (times per day) and duration (days)*: Mezolocillin/Oxacillin-combination (2:1) 6g i.v. preoperatively and twice only afterwards every 8 hours.
- *Antibiotic regimen protocol*: Peri + Post (1 day)

Intraoperative prophylaxis

- *postoperative AB Type, Dose (g), and administration method, frequency (times per day) and duration (days)*: Mezolocillin/Oxacillin-combination (2:1) 6g i.v. preoperatively once postoperatively.
- *Antibiotic regimen protocol*: Peri only

Postoperative prophylaxis (long)

- *postoperative AB Type, Dose (g), and administration method, frequency (times per day) and duration (days)*: Mezolocillin/Oxacillin-combination (2:1) 6g i.v. preoperatively and TID for 3 days postoperatively.
- *Antibiotic regimen protocol*: Peri + Post (3 days)

No prophylaxis

- *postoperative AB Type, Dose (g), and administration method, frequency (times per day) and duration (days)*: No antibiotics and no placebo
- *Antibiotic regimen protocol*: No antibiotics
-

Bias	Risk of bias	Comment to support judgement
Random sequence generation	Unclear	Randomization method not mentioned
Allocation concealment	Unclear	method wasn't mentioned.
Blinding of participants and personnel	High	Study not blinded. Different treatment regimens would require active blinding methods.
Blinding of outcome assessment	High	Study not blinded. Different treatment regimens would require active blinding methods.
Incomplete outcome data	Unclear	Lost to follow-up was not reported. Unclear whether PP or ITT analysis.
Selective reporting	Unclear	Study protocol not available. All outcomes identified in the methods were reported.
Other bias	Unclear	It's unclear whether other sources of bias exist.

Heit 1997

Sponsorship source: not stated
Country: USA
Setting: Single center department based
Comments:
Authors name: James M. Heit
Institution: University of Miami Medical School
Email: n.a.
Address: Mark R. Stevens, Doctor' s Hospital 5000 University Dr. Coral Gables, F1 331
Clinical Trial Identifier: n.a.
Recruitment Period: n.a.

Study design: Randomized controlled trial
Study grouping: Parallel group
Follow-up: 2,4,6 and 8 weeks.
Included fracture sites: only mandibular fractures.
Infection Criteria: Clinical assessment: presence of fever, edema, erythema, increasing pain, and purulent discharge
Pre, peri- und postoperative management: Solumedrol 125 mg i.v. once at the start of the operation.
Surgical approach: ORIF with plates or wires using intraoral or extraoral approach and 6 weeks of MMF postoperatively.
Treatment of SSI: local debridement, removal of fixation devices, and oral antibiotics

Baseline Characteristics

	Ceftriaxone	Penicillin	Overall
Nr of Patients	45	45	90
Drop-out	not reported	not reported	not reported
Nr of patients after excluding drop-outs	45	45	90
Gender (female/male)	not reported	not reported	14/76
Age in years: mean (Range)	not reported	not reported	29.6 (10 - 63)

Inclusion criteria: - exposed compound mandibular fracture
Exclusion criteria: not stated
Pretreatment: by fractures site

Intervention Characteristics

Ceftriaxone

- *AB Type, Dose, administration method, frequency and duration (days)*: Preoperative: Ceftriaxon i.v. 1gm once daily, Postoperative: same regeim for one postoperative day.
- *Antibiotic regimen protocol*: pre + peri + post (short)

Penicillin

- *AB Type, Dose, administration method, frequency and duration (days)*: Preoperative: Penicillin G 2mU i.v. daily, Postoperative: further every 4 hours for 1 day.
- *Antibiotic regimen protocol*: pre + peri + post (short)

Bias	**Risk of bias**	**Comment to support judgement**
Random sequence generation	Unclear	Method of randomization was not mentioned.

Allocation concealment	Unclear	The method of allocation concealment was not mentioned.
Blinding of participants and personnel	Unclear	not stated.
Blinding of outcome assessment	Low	"Patients were monitored at 2-week intervals for 8 weeks by examiners who were blinded to which treatment protocol the patient had received."
Incomplete outcome data	Unclear	drop out were not mentioned. Unclear whether it's a PP or ITT analysis.
Selective reporting	High	The distribution of fracture sites in each arm was not reported, also the site of infected fractures was also not reported.
Other bias	High	unclear funding source in a study that compares efficacy of medication.

Mamthashri 2018

Sponsorship source: None
Country: India
Setting: Academic OMFS department
Comments:
Authors name: Veeranjaneyalu Mamthashri
Institution: Department of Oral and Maxillofacial Surgery, Government Dental College and Research Institute
Email: mamthashri15@gmail.com
Address: Department of Oral and Maxillofacial Surgery, Government DentalCollege and Research Institute, Bengaluru, Karnataka, India
Clinical Trial Identifier: -
Recruitment Period: Nov 2004 - June 2006

Study design: Randomized controlled trial
Study grouping: Parallel group
Follow-up: 1st, 2nd, 3rd, and 5th week postoperatively.
Included fracture sites: All facial fractures
Infection Criteria: Clinical assessment: evaluating for the presence of erythema,a rise in temperature, purulent discharge, and swelling around the wound; and wound status.
Pre, peri- und postoperative management:
Surgical approach: Open reduction and internal fixation with titanium miniplate, using intraoral/extra oral approach or through existing lacerations or combination of the above.

Baseline Characteristics

	Preoperative prophylaxis	Intraoperative prophylaxis	Overall
Nr of Patients	25	25	50
Drop-out	0	0	0
Nr of patients after excluding drop-outs	25	25	50
Gender (female/male)	1/24	4/21	5/45
Age in years: mean (SD)	27.9 (5.7)	31.2 (11)	29.6
Duration between trauma and operation (days): Mean (SD)	2.8 (0.8)	2.4 (0.9)	2.6

Inclusion criteria:
1. Patients willing to consent to be a participant in the study.

2. Patients with compound facial fractures requiring surgical intervention by open reduction and rigid internal fxation.
3. Routine blood and urine examination values being within normal parameters.
4. Patient being available for the entire period of assessment.

Exclusion criteria:

1. Patients who refused to consent to the procedure.
2. Patients who failed to return for postoperative visits.
3. Immunocompromised patients and patients with systemic conditions, such as pregnancy, diabetes mellitus, cardiovascular disease, and bleeding disorders.
4. Complex and comminuted fractures.
5. Patients who were already on antibiotics or those who were allergic to penicillin.
6. Patients with abscess or infected fractures preoperatively
7. those who had received prophylactic antibiotics 1 week before the admission
8. fractures older than 36 hours

Intervention Characteristics

Pre/postoperative prophylaxis Arm

- *pre/perioperative AB Type, Dose, administration method, frequency and duration (days)*: Amoxicillin 500mg, Cloxacillin 500mg, Metronidazole 400mg i.v. TID at the day of admission
- *Postoperative AB Type, Dose, administration method, frequency and duration (days)*: Amoxicillin 250mg, Cloxacillin 250mg, Metronidazole 400mg p.o. TID from the 2nd til 5th postoperative day
- *Antibiotic regimen protocol*: pre + post (5 days)

Peri/postoperative prophylaxis Arm

- *pre/perioperative AB Type, Dose, administration method, frequency and duration (days)*: Amoxicillin 500mg, Cloxacillin 500mg, Metronidazole 400mg i.v. on the operative day before surgery and the time of induction of general anaesthesia.
- *Postoperative AB Type, Dose, administration method, frequency and duration (days)*: Amoxicillin 250mg, Cloxacillin 250mg, Metronidazole 400mg p.o. TID from the 2nd til 5th postoperative day
- *Antibiotic regimen protocol*: peri + post (5days)

Bias	Risk of bias	Comment to support judgement
Random sequence generation	Unclear	The method of sequence generation was not mentioned.
Allocation concealment	Low	"each patient was randomly assigned into one of the two treatment groups (Groups I and II), using prepared randomization in sealed envelopes."
Blinding of participants and personnel	Unclear	Blinding was not reported.
Blinding of outcome assessment	Unclear	Blinding was not reported.
Incomplete outcome data	Unclear	The number of participants lost to follow-up is not clear.
Selective reporting	Low	All outcomes were reported.
Other bias	Low	There is no evidence for other sources of bias.

Momeni 2018

Sponsorship source: not clear
Country: Iran
Setting: Single center secondary care
Comments: No conflicts of interest
Authors name: ehrnoush Momeni
Institution: Department of Oral and Maxillofacial Surgery
Email: Drmo_mortazavi@Yahoo.com

Address: Department of Oral and Maxillofacial Surgery
Tehran University of Medical Sciences, Tehran, Iran
Recruitment Period: September 2015- September 2016

Study design: Randomized controlled trial
Study grouping: Parallel group
Infection Criteria: CDC infection criteria:
1. Purulent drainage from the surgical or fracture site.
2. Increased facial swelling beyond postoperative day 7.
3. Fistula formation at the surgical or fracture site, with evidence of drainage.
4. Fever associated with local evidence of infection (swelling, erythema, or tenderness).
Follow-up: 2 and 3 weeks postoperatively. at least 3 weeks postoperatively.
Peri- und postoperative management:
Surgical approach: ORIF after placement of the arch bars. Teeth in the fracture line were extracted if they prevented proper reduction or were mobile and grossly carious.
Treatment of SSI: administrating oral clindamycin 600 mg IV every 8 hours for a period of 5-7 days and irrigation with mouth wash (Chlor-hexidine).
Included fracture sites: mandibular fractures only

Baseline Characteristics

Characteristic	Postoperative prophylaxis (long)	Intraoperative prophylaxis	Overall
Nr of Patients			73
Drop-out			8
Nr of patients after excluding drop-outs	38	27	65
Gender (female/male)	6/32	9/18	15/50
Age in years: mean (SD)	26.3 (7.4)	28.3 (9.3)	
Nr of smoking patients	15	9	24
Duration between trauma and operation (days): Mean (SD)	6.6 (6.4)	6.1 (3.6)	
Tooth in the fracture line	29	17	46

Inclusion criteria:

1. At least 1 fracture of the mandible.
2. Open reduction and internal fixation treatment.
3. Follow-up for at least 3 weeks.

Exclusion criteria:

1. Comminuted fractures.
2. Infection of the fracture site initial presentation.
3. Associated systemic disease.
4. Pathological fractures
5. Skull base fractures.
6. A documented immunocompromised medical status.

Intervention Characteristics

Postoperative prophylaxis (long)

- *AB Type, Dose (g), and administration method, frequency (times per day) and duration (days)*: Clindamycin 600mg i.v. TID for 5-7 days
- *Antibiotic regime protocol*: Pre + Intra + Post (long-term)

Intraoperative prophylaxis

- *AB Type, Dose (g), and administration method, frequency (times per day) and duration (days)*: Placebo i.v. TID for 5-7 days

- *Antibiotic regime protocol*: Pre + Intra

Bias	Risk of bias	Comment to support judgement
Random sequence generation	Unclear	wasn't mentioned.
Allocation concealment	Unclear	wasn't mentioned.
Blinding of participants and personnel	Unclear	wasn't mentioned.
Blinding of outcome assessment	Unclear	wasn't mentioned.
Incomplete outcome data	High	Eight patients were excluded with unclear reasons of exclusion. This is a PP-analysis.
Selective reporting	Low	all outcomes were reported.
Other bias	Unclear	no evidence for other sources of bias.

Perepa 2018

Sponsorship source: not reported
Country: India
Setting: Single center department based
Authors name: Anisha Perepa
Institution: Department of Oral and Maxillofacial Surgery, Sri SaiCollege of Dental Surgery, Vikarabad, India
Email: kperepa@gmail.com
Address: Department of Oral and Maxillofacial Surgery, Sri Sai College of Dental Surgery, Vikarabad, India
Recruitment Period: 01/01/2011 to 01/06/2015

Study design: Randomized controlled trial
Study grouping: Parallel group
Follow-up: 1st day, 3rd day, 1 week, 1st month and 3 months postoperatively.
Included fracture sites: Only isolated mandibular fractures
Infection Criteria: CDC (Centre for Disease Control) Criteria.
Pre, peri- und postoperative management: Either i.v. or p.o. Antibiotics (Amoxicillin with Clavulanic acid and Metronidazole) and Dexamethasone 8mg i.v. perioperatively.
Surgical approach: ORIF via an intraoral approach only.

Baseline Characteristics

	Postoperative prophylaxis (long)	Postoperative prophylaxis (short)	Overall
Nr of Patients	72	72	144
Drop-out	0	0	0
Nr of patients after excluding drop-outs	72	72	144
Gender (female/male)			18/126
Age in years: mean (Range)	29.82	27.9	28.86
Duration of surgery (min)	146	156	151
Duration between trauma and operation: (under 1 week, more than 1 week)	18/54	16/56	34/110
VAS Score (pre-op / post-op)	1.40/1.53	1.35/1.49	1.37/1.51
Tooth in the line of fracture (%)	17.5	19	18.25

Inclusion criteria:

1. linear isolated fracture
2. follow-up of at least 6 weeks

Exclusion criteria:

1. infected fracture at the time of treatment
2. pathological fracture
3. skull base fractures
4. history of malignancy or radiation to the head and neck area
5. known hypersensitivity or allergy to penicillin or other betalactam antibiotic
6. reduced body weight (<40 kg or BMI<17)
7. insufficient patient compliance
8. insufficient follow-up

Intervention Characteristics

Postoperative prophylaxis (long)

- *postoperative AB Type, Dose, administration method, frequency and duration (days)*: 1st day i.v. AB post-op: Amoxicillin/Clavulanic acid 1.2mg and Metronidazol 500mg. Then 4 days p.o. AB Amoxicillin/Clavulanic acid 625mg and Metronidazol 400mg.
- *Antibiotic regimen protocol*: pre + peri + post (4 days)

Postoperative prophylaxis (short)

- *postoperative AB Type, Dose, administration method, frequency and duration (days)*: Only 1 day i.v. AB post-op: Amoxicillin/Clavulanic acid 1.2mg and Metronidazol 500mg.
- *Antibiotic regimen protocol*: pre + peri (24 hours)

Bias	Risk of bias	Comment to support judgement
Random sequence generation	Low	"One hundred and forty-four subjects (2011–2015) who belonged to the above entities were randomly categorized into 2 groups of 72 each, on lottery method." Judgement Comment: Lottery method was used.
Allocation concealment	Unclear	wasn't mentioned.
Blinding of participants and personnel	High	Patients didn't receive a placebo, so they were not blinded.
Blinding of outcome assessment	Unclear	Although the study is "single blinded" it's not unclear who exactly was blinded the surgeon or the investigator who assessed the presence of an infection.
Incomplete outcome data	Unclear	Dropouts were not reported. It's unclear whether it's a ITT or PP analysis.
Selective reporting	High	Quote: "Both the groups were followed up on the 1st day, 3rd day, 1st week, 1st month, 3rd month post operatively and were evaluated for pain, swelling, infection, fever, spontaneous wound dehiscence, purulent discharge and any other adverse effects." Judgement Comment: Adverse events were not reported although they were assessed as mentioned here.
Other bias	Low	no evidence of other sources of bias.

Raichoor 2017

Sponsorship source: unclear
Country: India
Comments: All facial fractures
Authors name: Anil Kumar Raichoor
Institution: Late Baliram Kashyap Memorial Government Medical College
Email: drrakumar@yahoo.com
Address: Dimrapal, Jagdalpur, Chhattisgarh 494001, India
Study duration: unclear
Study design: Randomized controlled trial
Study grouping: Parallel group
Follow-up: 7, 14, 21 days postoperatively.
Included fracture sites: all facial fractures
Peri- und postoperative management: antibiotics were administrated for 24 hours postoperatively.
Surgical Approach: ORIF
Infection Criteria: unclear
Treatment of SSI: unclear
Inclusion criteria: unclear
Exclusion criteria: unclear
Pretreatment: unclear

Baseline Characteristics

	Ceftriaxone	Penicillin	Total
Nr. Of participants	35	35	70

Intervention Characteristics

Certriaxone

- *postoperative AB Type, Dose (g), and administration method, frequency (times per day) and duration (days)*: Certriaxone 1g BID for 1 day postoperatively. Administration route is unclear.
- *Antibiotic regimen protocol*: unclear

Penicillin

- *postoperative AB Type, Dose (g), and administration method, frequency (times per day) and duration (days)*: Amoxicillin 1 g TID for 1 day postoperatively. Administration route is unclear.
- *Antibiotic regimen protocol*: unclear

Bias	Risk of bias	Comment to support judgement
Random sequence generation	Unclear	wasn't mentioned.
Allocation concealment	Unclear	wasn't mentioned.
Blinding of participants and personnel	Unclear	wasn't mentioned.
Blinding of outcome assessment	Unclear	wasn't mentioned.
Incomplete outcome data	Unclear	wasn't mentioned.
Selective reporting	Unclear	wasn't mentioned.
Other bias	Unclear	wasn't mentioned.

Schaller 2013

Sponsorship source: – SUVA (Swiss Accident Insurance Body; 6002 Luzern, Switzerland). University Hospital of Bern, 3010 Bern, Switzerland. MephaParma AG, 4147 Aesch,Switzerland.– GlaxoSmithKline AG, 3053 Münchenbuchsee, Switzerland.
Country: Switzerland
Setting: Single center secondary care
Comments: Only patients with mandibular fractures.
Authors name: Benoit Schaller
Institution: Department of Cranio-Maxillofacial Surgery, University Hospital Bern, Bern, Switzerland
Email: olieger@hotmail.com (Olivier Lieger)
Address: Department of Oral and Maxillofacial Surgery, Hospital LuzernCH-6000 Luzern Switzerland
CLINICAL TRIAL IDENTIFIER: NCT01583062
Study duration: January 2007 to January 2011

Study design: Randomized controlled trial
Study grouping: Parallel group
Follow-up: 1,2,4,6, and 12 weeks, and 6 months
Included fracture sites: Mandibular fractures
Peri- und postoperative management: From admission until 24 h postoperatively, all patients were given prophylactic amoxicillin/clavulanic acid 1.2g (GlaxoSmithKline AG, Münchenbuchsee, Switzerland) intravenously every 8 h.
Surgical Approach: Maxillomandibular fixation was applied using arch bars (Medartis®, Basel, Switzerland) before open reduction to obtain an optimal occlusion. Internal fixation was then added using plates and screws (Medartis®, Basel, Switzerland or Synthes®, Oberdorf, Switzerland). Teeth in the fracture line were extracted if they impeded proper reduction or were grossly carious or mobile. Patients were not placed into postoperative maxillomandibular fixation. Panoramic tomography was done postoperatively as a routine.
Infection Criteria: Center of Disease Control and Prevention (CDC) Criteria. Those include: - purulent discharge (with or without microbiological confirmation)- spontaneous wound dehiscence- abscess- deliberate opening of the wound by a surgeon for the presence of signs or symptoms of infection such as localised pain or tenderness- fever (>38 ◦C).
Treatment of SSI: All infections were successfully treated within a week using daily wound irrigation (povidone iodine). In cases of deeper infection, the treatment protocol included the immediate use of a broad-spectrum antibiotic with subsequent modification if needed, depending on the results of culture and sensitivity tests.

Baseline Characteristics

	Postoperative prophylaxis (long)	Postoperative prophylaxis (short)	Overall
Nr of Patients	31	31	62
Drop-out	1	2	3
Gender (female/male)	6/24	4/25	10/49
Age in years: mean (SD)	32 (15)	30 (15)	31 (15)
Nr of smoking patients	11	13	24
Time between trauma and antibiotic treatment (h): Mean(SD)	44 (70)	47 (69)	45 (69)
Time between trauma and operation (h): Mean (SD)	57 (71)	63 (66)	60 (68)
OP duration in minutes: Mean (SD)	142 (58)	142 (61)	142 (59)
Multiple fracture sites	7	4	11
Nr of patients after excluding drop-outs	30	29	59

Inclusion criteria: mandibular fractures that extended to the alveolar regions and who were treated with ORIF
Exclusion criteria: need for intensive care, presence of an acute bacterial infection, gunshot wounds, pathological fracture (for example, cysts or metastases), fracture of the skull base with rhinoliquorrhoea or intracranial emphysema, history of malignancy or radiation to the head and neck area, hypersensitivity or allergy to penicillin or other betalactam antibiotics, compromised host defence (immunosuppression, malabsorption, maldigestion, cachexia, reduced body weight (<40 kg or BMI < 17), severe renal insufficiency (stage≥4 according to the Kidney Disease Outcomes Quality Initiative), poor compliance, Patients with isolated fractures of the ramus and condyle, or who needed postoperative maxillomandibular fixation
Pretreatment: none

Intervention Characteristics
Postoperative prophylaxis (long)

- *postoperative AB Type, Dose (g), and administration method, frequency (times per day) and duration (days)*: Amoxicillin/clavulanicacid 625mg i.v. TID for 4 days post-op
- *Antibiotic regimen protocol*: pre + peri + post (4days)

Postoperative prophylaxis (short)

- *postoperative AB Type, Dose (g), and administration method, frequency (times per day) and duration (days)*: Placebo TID for 4 days post-op
- *Antibiotic regimen protocol*: pre + peri (1day post-op)

Bias	Risk of bias	Comment to support judgement
Random sequence generation	Low	"Patients were then randomly assigned into 2 groups according to a computer-generated protocol (RandList ®, Version 1.0, DatInf GmbH, Tübingen, Germany)."
Allocation concealment	Low	"The list with the computer- generated numbers was kept by the pharmacist responsible. Details of the list were unknown to any of the attending surgeons or nurses."
Blinding of participants and personnel	Low	"The antibiotics and placebo were prepared by the pharmacy using identical gelatine capsules. The surgeons, nurses and patients were unaware of which postoperative prophylaxis was being given. The code was revealed to the main investigator only at the end of the trial."
Blinding of outcome assessment	Low	See annotation from the previous item.
Incomplete outcome data	Low	ITT analysis. Low and comparable dropout rates in the two groups.
Selective reporting	Low	All outcomes were reported.
Other bias	Low	This study seems to be free from other sources of bias.

Soong 2014

Sponsorship source: – SUVA (Swiss Accident Insurance Body; 6002 Luzern, Switzerland).– University Hospital of Bern, 3010 Bern, Switzerland.– MephaParma AG, 4147 Aesch,Switzerland.– GlaxoSmithKline AG, 3053 Münchenbuchsee, Switzerland.
Country: Switzerland
Setting: Single center secondary care
Comments: Only patients with Le Fort and zygomatic fractures.
Authors name: Poh Luon Soong
Institution: Department of Cranio-Maxillofacial Surgery, University Hospital Bern, Bern, Switzerland
Email: olieger@hotmail.com (Olivier Lieger)
Address: Department of Oral and Maxillofacial SurgeryHospital LuzernCH-6000 Luzern Switzerland
CLINICAL TRIAL IDENTIFIER: NCT01583062
Study duration: January 2008 to July 2011

Study design: Randomized controlled trial
Study grouping: Parallel group
Follow-up: 1,2,4,6, and 12 weeks, and 6 months
Included fracture sites: Zygomatic complex/Le Fort fractures
Infection Criteria: Centers of Disease Control and Prevention (CDC) Criteria. Those include: -purulent discharge (with or without microbiological confirmation)- spontaneous wound dehiscence-abscess- deliberate opening of the wound by a surgeon for the presence of signs or symptoms of infection such as localised pain or tenderness- fever (>38 ◦C).
Peri- und postoperative management: From admission until 24 h postoperatively, all patients were given prophylactic amoxicillin/clavulanic acid 1.2g (GlaxoSmithKline AG, Münchenbuchsee, Switzerland) intravenously every 8 h.

Surgical Approach: The frontozygomatic fracture was routinely exposed through a lateral eyebrow incision, and it was then reduced using a malar hook. In cases of comminution of the bone, difficult reduction, or insufficient stability, we obtained additional surgical access (intraoral or transconjunctival). After verification of the correct position of the zygoma, the fracture was fixed using standard titanium miniplates and screws (Synthes, Oberdorf, Switzerland or Medartis, Basel, Switzerland) where necessary.Le Fort I and II fractures After arch bars had been placed, we made an intraoral vestibular incision and dissected subperiosteally. In Le Fort II fractures we made additional transconjunctival incisions. The fracture was exposed then reduced, teeth were wired into the intermaxillary fixation, and the fracture was fixed using standard titanium miniplates and screws (Synthes or Medartis). In cases in which the nasal bone and septum were involved, they were repositioned by closed reduction, and stabilised using septal splints and a nasal cast.

Treatment of SSI: All infections were successfully treated within a week using daily wound irrigation (povidone iodine). In cases of deeper infection, the treatment included the immediate use of a broad-spectrum antibiotic with subsequent modification if needed, depending on the results of culture and sensitivity tests.

Baseline Characteristics

	Postoperative prophylaxis (long)	Postoperative prophylaxis (short)	Overall
Nr of Patients	46	52	98
Drop-out	1	3	4
Gender (female/male)	13/32	7/42	20/74
Age in years: mean	44	46	45
Nr of smoking patients	18	22	40
Multiple fracture sites	6	4	10

Time between trauma and antibiotic treatment (h): Mean	21	19	20
Time between trauma and operation (h): Mean	42	43	42.5
OP duration in minutes: Mean	106	110	108
only intraoral approach / only extra oral / intra+extraoral approach	1/22/2	1/24/2	2/46/4

Inclusion criteria: Patients with zygomatic or Le Fort fractures that needed treatment with open reduction and internal fixation

Exclusion criteria: need for intensive care, presence of an acute bacterial infection, gunshot wounds, pathological fracture (for example, cysts or metastases), fracture of the skull base with rhinoliquorrhoea or intracranial emphysema, history of malignancy or radiation to the head and neck area, hypersensitivity or allergy to penicillin or other betalactam antibiotics, compromised host defence (immunosuppression, malabsorption, maldigestion, cachexia, reduced body weight (<40 kg or BMI < 17), severe renal insufficiency (stage≥4 according to the Kidney Disease Outcomes Quality Initiative), poor compliance, Patients with isolated fractures of the ramus and condyle, or who needed postoperative maxillomandibular fixation

Pretreatment: none

Intervention Characteristics

Postoperative prophylaxis (long)

- *postoperative AB Type, Dose (g), and administration method, frequency (times per day) and duration (days)*: Amoxicillin/clavulanicacid 1.2g i.v. TID for 4 days
- *Antibiotic regimen protocol*: pre + peri + post (4days)

Postoperative prophylaxis (short)

- *postoperative AB Type, Dose (g), and administration method, frequency (times per day) and duration (days)*: Placebo 4 days post-op TID
- *Antibiotic regimen protocol*: pre + peri (1day post-op)

Bias	Risk of bias	Comment to support judgement
Random sequence generation	Low	"Patients were then randomly assigned into 2 groups according to a computer-generated protocol (RandList ®, Ver- sion 1.0, DatInf GmbH, Tübingen, Germany)."
Allocation concealment	Low	"The list with the computer- generated numbers was kept by the pharmacist responsible. Details of the list were not known by any of the attending surgeons or nurses."
Blinding of participants and personnel	Low	"The antibiotics and placebo were pre- pared by the pharmacy using identical gelatine capsules. The surgeons, nurses, and patients were unaware of which post- operative prophylaxis was being given. The main investigator found out the code only at the end of the trial."
Blinding of outcome assessment	Low	See annotation from the previous item.
Incomplete outcome data	Low	ITT analysis. Low and comparable dropout rates in the two groups.
Selective reporting	Low	All outcomes were reported.
Other bias	Low	This study seems to be free from other sources of bias.

Vazquez-Barro 1994

Sponsorship source: Not reported
Country: Spain
Setting: Single centre, secondary care
Comments: Hospital General del Complejo Canalejo de La Coruna
Authors name: Vazquez-Barro
Institution: Not reported (most likely Hospital General del Complejo Canalejo de La Coruna, as this is where the study was conducted)
Email: Not reported
Address: Not reported
Clinical Trial Identifier: Not reported
Recruitment Period: 01-01-1991 to 31-01-1992

Study design: Randomized controlled trial
Study grouping: Parallel group
Follow-up: At least 6 months
Included fracture sites: Facial trauma requiring osteosynthesis
Infection Criteria: CDC criteria
Pre, peri- und postoperative management: Post-operative prophylaxis (short): 1 gram of intravenous Cefazolin one hour before the start of the intervention + 1 gram of Cefazolin every 6 hours, for a total of 4 doses. Intraoperative prophylaxis: A single dose of 2 grams of intramuscular Cefazolin 1 hour before the intervention. Daily assessment of presence of infection in the the fracture and surgical wound (including pain erythema, edema, heat and suppuration) and hospital infection (such as urinary and nocosomial pneumonia).
Surgical approach: Open reduction and internal fixation with osteosynthesis
Treatment of SSI: Not reported

Baseline Characteristics

	Postoperative prophylaxis (short)	Intraoperative prophylaxis	Overall
Nr of Patients	30	27	57
Drop-out	NR	NR	NR
Nr of patients after excluding drop-outs	30	27	57
Gender (female/male)	NR	NR	10/47
Age in years: mean (Range)	NR	NR	range: 20 to 65 years

Inclusion criteria: Patients with acute facial trauma or sequelae in which the use of osteosynthesis material was expected.
Exclusion criteria: Patients who received antibiotic treatment 5 days prior to the intervention. Patients with suspected allergy to penicillin or cephalosporin. Patients in which the surgical indication was modified, so that ostosynthesis was not performed. Patients in which the administration schedule was incorrect. Patients in which a focus of suppuration was found during surgery (after randomization). Patients in which follow-up was not complete (after randomization).
Pretreatment: Not reported
Fracture details: ZMC fracture - IV cefazolin n = 5; IM cefazolin n = 6, Mandibular fracture - IV cefazolin n = 12; IM cefazolin n = 13 Complex fractures - IV cefazolin n = 11; IM cefazolin n = 6 Sequels of facial fractures - IV cefazolin n = 2; IM cefazolin n = 2

Intervention Characteristics

Postoperative prophylaxis (short)

- *postoperative AB Type, Dose, administration method, frequency and duration (days)*: Cefazolin 1g i.v. QID for one day starting before surgery
- *Antibiotic regimen protocol*: Pre-, intra- and postoperative (1 day)

Intraoperative prophylaxis

- *postoperative AB Type, Dose, administration method, frequency and duration (days)*: Cefazolin 2g i.m. once one hour before surgery
- *Antibiotic regimen protocol*: Pre- and intraoperative

Bias	Risk of bias	Comment to support judgement
Random sequence generation	Unclear	"This is a randomized study..." no further details reported
Allocation concealment	Unclear	No details reported
Blinding of participants and personnel	Unclear	No details reported
Blinding of outcome assessment	Unclear	No details reported
Incomplete outcome data	Unclear	The authors excluded participants with incomplete follow-up data, number not reported
Selective reporting	Unclear	Protocol not available, and limited details provided in the methods section.
Other bias	Unclear	Source of funding not reported. Conflict of interest not reported.

Zix 2013

Sponsorship source: – SUVA (Swiss Accident Insurance Body; 6002 Luzern, Switzerland).– University Hospital of Bern, 3010 Bern, Switzerland.– MephaParma AG, 4147 Aesch,Switzerland.– GlaxoSmithKline AG, 3053 Münchenbuchsee, Switzerland.
Country: Switzerland
Setting: Single center secondary care
Comments: Only patients with orbital fractures.
Authors name: Jürgen Zix
Institution: Department of Cranio-Maxillofacial Surgery, University Hospital Bern, Bern, Switzerland
Email: olieger@hotmail.com (Olivier Lieger)
Address: Department of Oral and Maxillofacial SurgeryHospital LuzernCH-6000 Luzern Switzerland
Recruitment Period: January 2006 to April 2010
Clinical Trial Identifier: NCT01583062

Study design: Randomized controlled trial
Study grouping: Parallel group
Follow-up: 1,2,4,6, and 12 weeks, and 6 months
Infection Criteria: Centers of Disease Control and Prevention (CDC) Criteria. Those include: - purulent discharge (with or without microbiological confirmation)- spontaneous wound dehiscence- abscess- deliberate opening of the wound by a surgeon for the presence of signs or symptoms of infection such as localised pain or tenderness- fever (>38 ◦C).
Pre, peri- und postoperative management: From admission until 24 h postoperatively, all patients were given prophylactic amoxicillin/clavulanic acid 1.2g (GlaxoSmithKline AG, Münchenbuchsee, Switzerland) intravenously every 8 h.
Surgical approach: - transconjunctival incision- combined transconjunctival-transcaruncular - modified medial eyebrow
Treatment of SSI: All infections were successfully treated within a week using daily wound irrigation (povidone iodine), without additional antibiotic treatment.
Included fracture sites: Orbital fractures

Baseline Characteristics

	Postoperative prophylaxis (long)	Postoperative prophylaxis (short)	Overall
Nr of Patients	29	33	62
Drop-out	0	2	2
Nr of patients after excluding drop-outs	29	31	60
Gender (female/male)	11/18	11/20	22/38
Age in years: mean (Range)	not reported	not reported	42 (13-92)
Nr of smoking patients	8	16	24
Time between trauma and antibiotic treatment (h): Mean(SD)	21.6 (45.3)	60.3 (109.8)	41.6 (86.5)
Time between trauma and operation (h): Mean (SD)	44.6 (47)	81.4 (106.8)	63.9 (84)
Duration between trauma and operation (h): Mean (SD)	45.5 (43.4)	41.5 (22.7)	43 (34.2)

Inclusion criteria: All patients presenting with orbital blow-out fractures
Exclusion criteria: - need for intensive care- presence of an acute bacterial infection, gunshot wounds- pathological fracture (for example, cysts or metastases)- fracture of the skull base with rhinoliquorrhoea or intracranial emphysema- history of malignancy or radiation to thehead and neck area- hypersensitivity or allergy to penicillin or other betalactam antibiotics- compromised host defence (immunosuppression, malabsorption, maldigestion, cachexia, reduced body weight (<40 kg or BMI <

17), severe renal insufficiency (stage≥4 according to the Kidney Disease Outcomes Quality Initiative)- poor compliance
Pretreatment: There are notable differences between the two groups in two aspects: - time between trauma and perioperative antibiotic treatment: 21.6 hours in AB group vs 60.3 hours in placebo group)- time between trauma and operation: 44.6 hours in AB group vs 81.4 hours in placebo group)

Intervention Characteristics

Postoperative prophylaxis (long)

- *postoperative AB Type, Dose, administration method, frequency and duration (days)*: Amoxicillin/clavulanicacid 1.2g i.v. TID for 4 days
- *Antibiotic regimen protocol*: pre + peri + post (4days)

Postoperative prophylaxis (short)

- *postoperative AB Type, Dose, administration method, frequency and duration (days)*: Placebo 4 days post-op TID
- *Antibiotic regimen protocol*: pre + peri + post (1 day)

Bias	Risk of bias	Comment to support judgement
Random sequence generation	Low	"Patients were then randomly assigned into 2 groups according to a computer-generated protocol (RandList ®, Ver- sion 1.0, DatInf GmbH, Tübingen, Germany)."
Allocation concealment	Low	"The list with the computer- generated numbers was kept by the pharmacist responsible. Details of the lists were unknown to any of the surgeons or nurses."
Blinding of participants and personnel	Low	"The antibiotic and placebo were prepared by the phar- macy using identical gelatine capsules. Neither surgeons, nor nurses, nor patients were aware of which postoperative pro- phylaxis was being given. The code was broken by the main investigator only at the end of the trial."
Blinding of outcome assessment	Low	see annotation from previous item.
Incomplete outcome data	Low	PP analysis, but very low drop-out rates, which are comparable between both groups.
Selective reporting	Low	All outcomes were reported.
Other bias	Low	There is no evidence for other sources of bias.

8.3. Characteristics of excluded studies

Study	Reason
Chole 1987	Closed reduction in >30% of cases
Conover 1985	OMFS or ENT intervention other than trauma surgery
Eschelman 1971	less than 10 participants in each treatment arm
Henkel 1994	OMFS or ENT intervention other than trauma surgery
Hotz 1994	less than 10 participants in each treatment arm
Marcucci 1990	OMFS or ENT intervention other than trauma surgery
Meier 1984	Not RCT
Miles 2006	Quasi-randomized study
Schmidt 2015	Wrong outcomes
Sixou 2012	OMFS or ENT intervention other than trauma surgery
Zallen 1975	Closed reduction in >30% of cases

Anteilserklärung

I prepared the review proposal that was accepted by Cochrane in 2016. I drafted the protocol's background and methods sections and edited the final version of the protocol. I screened all studies, assessed the risk of bias and extracted data from studies in English and German, conducted the meta-analyses, conducted the evidence quality assessment and drafted the final manuscript of the review. I am the main correspondence for Cochrane Oral Health Group.

I drafted this doctoral thesis unassisted.

U. Alsharif

09.06.2020