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Prevalence and risk factors of early and delayed postoperative infections after lower third molar surgery: a meta-analysis.

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INDEX

Prevalence and risk factors of early and delayed postoperative infections after lower third molar surgery: a meta-analysis.

1.1 ABSTRACT

Aim: To determine the prevalence and possible risk factors associated with early and delayed postoperative infections after lower third molar surgery, a meta-analysis of clinical studies was performed.

Materials and Methods: A systematic electronic and hand search was performed and 14 articles were finally included. Sample size, number of lower third molars extracted, infection criteria, number of infections and follow-up period were evaluated from each study reviewed. Meta-analysis was performed by the pooled prevalence of early and delayed postoperative infections and by the pooled odds ratio (OR) of risk factors. Eight randomized controlled trials, 2 case control studies, 3 cohort studies and 1 non-randomised controlled trial were included for data extraction.

Results: The pooled estimated prevalence of early infection was 2.05 % with a standard error of 397,2. *Pell & Gregory* category C was not significantly associated to infection, having an OR=1.66 (95 % CI: 0.81 to 3.41). Vertical third molar's position was not significantly associated with infection with an OR= 0.910 (95% CI: 0.411 to 2.01). The use of antibiotics either as a prophylaxis before or immediately after extraction, did not significantly reduce the infection risk with an OR= 0.91 (95% IC: 0.41 to 2.01). However, having a pooled OR=2.52 (95% CI: 1.22 to 5.21) class III in the classification of *Pell & Gregory* seemed to be the only risk factor statistically significant for developing early infections. Delayed infections' data could not be statistically analyzed in present meta-analysis.

Conclusion: Prevalence of early infection is estimated at 2.05%, so it is low compared with other postoperative complications. The only risk factor that seems to be statistically associated with postoperative infections is class III of *Pell & Gregory* classification.

KEY WORDS: "Wisdom tooth removal AND infection", "lower third molar surgery AND postoperative infection", "Postoperative complications AND third molar surgery".

1.2 RESUM

Objectiu: Per a determinar la prevalença i els possibles factors de risc associats amb les infeccions postoperatòries immediates i tardanes, en extraccions de cordals inferiors, s'ha realitzat un meta-anàlisi amb estudis clínics.

Materials i mètodes: Una recerca sistemàtica electrònica i manual s'ha dut a terme i finalment s'han inclòs 14 articles. La mida mostral, el nombre de tercers molars inferiors extrets, el criteri d'infecció, el nombre d'infeccions i el període de seguiment han estat els ítems avaluats en cada estudi revisat. En el meta-anàlisi s'ha calculat la prevalença combinada de les infeccions postoperatòries i la odds ratio combinada(OR) dels possibles factors de risc. Vuit assajos clínics aleatoritzats, 2 estudis cas control, 3 estudis de cohorts i 1 assaig clínic no aleatoritzat han estat inclosos per a extreure'n les dades.

Resultats: La prevalença combinada estimada de les infeccions immediates ha estat de 2.05% amb un error estàndard de 397,2. La categoria "C" de la classificació *Pell & Gregory* no és estadísticament significativa com a factor de risc, tenint una OR=1.66 (95% CI: 0.81 to 3.41). La posició vertical del molar no és estadísticament significativa com a factor de risc, tenint una OR= 0.910 (95% CI: 0.411 to 2.01). L'ús d'antibiòtics tan abans com després de l'extracció tampoc és estadísticament significatiu com a factor de risc amb una OR= 0.91 (95% IC 0.41 to 2.01). No obstant, amb una OR= 2.52 (95% CI: 1.22 to 5.21), la classe III de la classificació *Pell & Gregory* sí que és significativa estadísticament com a factor de risc. Les dades de les infeccions tardanes no han pogut ésser estadísticament analitzades.

Conclusió: La prevalença de les infeccions immediates és estimada en un 2.05%; així doncs és baixa comparada amb altres complicacions postoperatòries. L'únic factor de risc que sembla ser estadísticament cert és la classe III de la classificació de *Pell & Gregory* en el cas de les infeccions immediates.

PARAULES CLAU: "Wisdom tooth removal AND infection", "lower third molar surgery AND postoperative infection", "Postoperative complications AND third molar surgery".

2. INTRODUCTION

Surgical removal of mandibular third molars is one of the most common procedures in oral and maxillofacial surgery.[1,2,3,4,5,6] The main reasons for the extraction of these teeth are pericoronitis, cysts, tumours, periodontal problems, presence of a carious lesion on the second or third mandibular molar and neurogenic and myofascial pains.[3,7]

Difficulty of lower third molar extraction is due to their late formation and due to the phylogenetic evolution of the mandible, which results in a lack of space for lower third molars and, consequently, they have not a normal eruption bringing problems because of its position.[8] However, there are some of them, which are normally erupted without complications even being a possible abutment for a prosthetic rehabilitation; particularly if the second lower third molar is absent and cannot perform this function.[8]

This procedure is usually related to several complications which can have a biological and social impact.[9] Numerous studies have reported the most frequent postoperative complications of this intervention such as alveolar osteitis, pain, swelling, trismus, nerve dysfunction, bleeding and postoperative infection.[10,11,12,13] Focusing on postoperative infections, it is known that there are early and delayed infections;[1,2] the early ones, are usually developed during the first week after the extraction while delayed infections appear from the first month after the surgery to the third month after.[1,2] On one hand, delayed infections are not well known and because of this, there are not many studies dealing with them, whereas on the other hand, early infections are the most reported in the current studies.[2]

The extraction of mandibular third molars is considered as a clean-contaminated operation and so these surgeries easily cause bacteremia and can develop infections.[14] That is the reason why, although using aseptic techniques, meticulous tissue management, hemostasis and lavage of extraction sites, infection may occur.[15] Moreover, if the first acute infection spreads to deep facial spaces, it can cause significant airway problems for the patient.[14,16] It is important to take into account that a simple infection can spread to the mandibular vestibule, buccal space, submasseteric space, pterygomandibular space, parapharyngeal space, or

submandibular space. It can also reach the retropharyngeal tissues up to the mediastinum; then, the infection is life-threatening.[16]

During the years, risk factors for developing a postoperative infection after lower third molar removal are being evaluated to be able to prevent this complication. Some of the preoperative conditions considered as potential risk factors are: female gender, having more than 25 years of age, the impaction of the teeth and its anatomic position, the experience of the surgeon and the operation time, the prescription or non- prescription of antibiotics, the medical history of the patient, the previous condition of third molars and the use or non- use of a suture. However, there is a controversy between studies in regard to some of these possible risk factors being impossible to get a definite conclusion.[3,4,7,9,16,17,18]

The present meta-analysis is undertaken to gather and evaluate data of different published studies to know the prevalence and the main risk factors of early and delayed postoperative infections after lower third molar removal. Relevant questions are which is the prevalence of infections after mandibular third molar removal and whether patients with or without a positive medical history, have risk factors that increase the risk to develop this complication.

3. MATERIALS AND METHODS

Search and Selection

A search of English literature published from 1965 to 2014, was conducted. The selected database was MEDLINE, though the platform Pubmed. The search strategy consisted of the following keywords:

- "Wisdom tooth removal AND infection [MeSH term]"
- "Lower third molar surgery AND postoperative infection"
- "Postoperative complications [MeSH term] AND third molar surgery [MeSH term]"

A supplementary hand search was performed through 2 relevant peer-reviewed dental journals published in 2007 and 2011 respectively: *Journal of Oral and Maxillofacial Surgery* and *Head & Face Medicine.*

Search was carried out between February 2014 and April 2014. The majority of the studies searched were on line and could be accessed through CRAI UB, the library of the Dental School of the University of Barcelona. For articles that could not be recovered, we tried to obtain information directly from the authors, but without results, due to the time elapsed from the publication date. PRISMA statement for reporting systematic reviews and meta-analysis was followed[19] and a methodology to calculate pooled prevalence was used.[20]

Studies were included into the study if they met the following inclusion criteria: (1) Patients subjected to lower third molar extraction. (2) Prospective or retrospective clinical investigations in humans. (3) Criteria for surgical wound infection clearly defined. (4) Detailed data on demographic characteristics, surgical technique and follow-up period. (5) Mean follow-up: minimum 1 control visit the week after the surgery. (6) Peer-reviewed journals. (7) Articles written in English language.

Articles which report dry socket and abscesses as the sole infection criteria have been excluded from the study.

Data abstraction and collection

Out of 67 full-text articles screened, 14 articles were finally included in the meta-analysis. The study quality has not been assessed. For each study following information was recorded: year of publication, country where the investigation took place, number of subjects included in the study, number of lower third molars extracted, mean age of subjects, its inclusion and exclusion criteria, the infection criteria of the study, the number of infections, the follow-up period, the follow-up variables, outcomes and authors' comments. From all 67 full-text articles included at first, 14 articles[21,22,23,24,25,26,27,28,29,30,31,32,33,34] were excluded from our meta-analysis because of the impossibility to access them and 1 more article[35] was excluded because of the impossibility to get relevant data (we tried to contact to the author of this article but without results).

Twenty-nine articles[7,8,9,10,11,12,14,17,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56] were excluded because of the lack of infection criteria defined or because of errors in their infection criteria (errors such as including dry sockets, abscesses or other signs not mentioned in our infection criteria defined), 4 articles[18,57,58,59] were refused for having their third molar data mixed with maxillary and mandibular molars and 5 articles[13,60,61,62,63] were not about infection complication.

Outcome measures

Outcome measures were secondary infections after mandibular third molar extraction, defined as a chronic inflammation with suppuration at the extraction site, painfulness of the mucosa in the region around the sutures and high temperature in the zone of the extraction. Another definition well accepted by this study is the one measured by acute-phase protein levels as indicators of infective sockets, more specifically, serum levels of C-reactive protein and alpha-1 antitrypsin. All other infection criteria including any other different conditions (such as dry socket or abscesses) were excluded from present study. Also, patients without a minimum of 1 control visit after the extraction were not taken into account.

To difference from early to delayed infections, these definitions have been followed: early infections develop during the first week after extraction to 8 days after the

surgery and, delayed infections are defined as the ones that develop at least 1 week after surgery.

Quantitative data synthesis

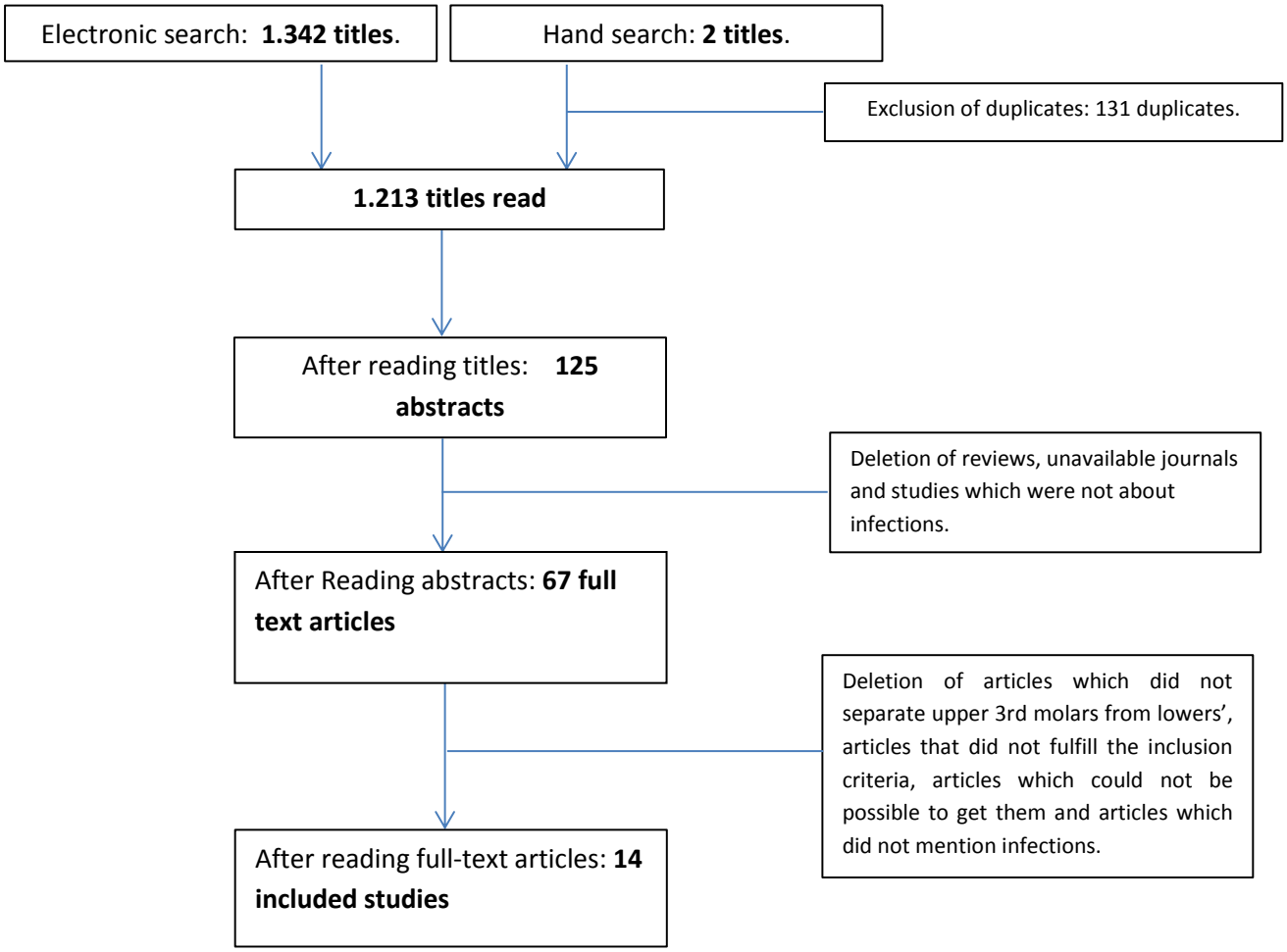
Data were processed using Microsoft Excel for Mac and Epidat 3.1 software (http://www.sergas.es/EPIWB/SolicitudeEpidat.aspx?IdPaxina=62715&idv=1&lng=es), consulted in June 1st 2014. The prevalence of infection was estimated with the formula $p = \frac{\sum_i pi/Var(pi)}{\sum_i 1/Var(pi)}$. The SE of the prevalence was calculated with the formula SE(p)= $\sqrt{\sum_i 1/Var(pi)}$.

To analyze risk factors of infection, the pooled OR was calculated when there was at least one event in all the cells. Heterogeneity was calculated with the Dersimonian and Laird's test. When heterogeneity was significant, the random effects model was selected. Otherwise, the fixed effects models were chosen. Publication bias was assessed with the Begg test and funnel plots. A sensitivity analysis was performed when there were more than 2 selected articles.

4. RESULTS

MEDLINE search yielded 1.342 titles and from hand search we took 2 more references. Of these 1.344 articles screened by their title, we deleted 131 duplicates and so 1.213 titles were read. From these 1.213 titles, 125 abstracts were read. After an accurate reading of the abstracts, 67 articles were selected as preliminary candidates. All this preliminary references had been read carefully and 14 articles constituted the final selection (Fig.1). Search had been done without any year limit. If there was any data not clearly specified, it had been tried to get the needed information independently through the same article.

Figure 1: Flow chart



From the included studies in present meta-analysis, 8 were randomised controlled trials, 1 was non-randomised controlled trial, 2 were case control studies, and 3 were cohort studies; the oldest article included was from 1985 and the most up to date article was from 2014.

Table 1 has the detailed data information of every included article and Table 2 specifies all different designs of selected articles.

Table 1: Descriptive information of all 14 included studies.

ARTICLES INCLUDED	Sample (n)	Infection criteria	Infection (n)	Mean follow-up
1. Sweet et al. (1985)[64]	400	Purulent drainage from surgical site or increase swelling and pain noted after 3 to 4 days with or without accompanying generalized signs of infection.	13	4th to 6th postoperative day.
2. Bulut et al. (2001)[65]	30	Diagnosed by acute-phase protein levels; specifically, serum levels of C-reactive protein and alpha-1 antitrypsin measured pre and postoperatively.	4	Postoperative 24-32 hours, postoperative 72-80 hours and a week after the operation.
3. Yoshii et al. (2002)[66]	178	The presence of cellulitis; the presence of fluctuance; the presence of purulent or nonpurulent drainage from the socket more than 72h after surgery; pain and swelling that either worsened or failed to improve 48h after surgery; and hyperpyrexia (body temperature higher than 37.8°C) 48 or longer after surgery without local signs or symptoms, if no other source of the fever could be found.	1	1 week after and more.
4. Poeschl et al. (2004)[6]	288	Local swelling, hyperemia, purulent drainage, painfulness of the mucosa in the region around the sutures.	25	2 days, 10 days and 4 weeks after the surgery.
5. Figueiredo et al. (2005)[1]	772	Infectious swelling with onset after purulent discharge, generally 1 week after extraction.	14	1 week after extraction and more.
6. Chiu et al. (2006)[67]	275	When there was redness, swelling, pus discharging or systemic fever.	4	1 week after surgery.
7. Figueiredo et al. (2007) (Case control study)[2]	Infected group: 35 Control group: 143	Infectious swelling with onset after purulent discharge, generally 1 week after extraction.	-	1 week after extraction and more.
8. Blondeau et al. (2007)[3]	327	Purulent discharge at the extraction site and/or painful induration.	12	2 days and 4 weeks after surgery.
9. Al-Asfour et al. (2009)[5]	90	Simultaneous presence of all of the following signs: pain at the extraction site, localized swelling and purulent discharge.	6	1 week after and 6 months (by phone).
10. Siddiqi et al. (2010)[68]	95	Clinical signs of pus collection and fever.	4	3 days, 7 days and 2 weeks after surgery.
11. López-Cedrún et al. (2011)[69]	123	Purulent discharge in the socket and/or excessive swelling, with or without pain. Palpable cervical lymph nodes and facial or cervical cellulitis were also included.	5	1 week after surgery.
12. Bello et al. (2011)[70]	82	History of pus discharge with or without pain, bleeding about 1 week or more after surgery, and suppurative socket with or without fever.	2	2, 5 and 7 days after surgery and 1 month after.
13. Freudlsperger et al. (2012)[4]	443	Inflammatory infiltrate.	10	2, 3, 4, and 10 days after surgery.
14. Lee et al. (2014)[71]	890	Gingival swelling, persistent pain and discharge of pus from the extraction socket.	14	1 week after surgery.

Table 2: Studies' design and year from the articles included

ARTICLES INCLUDED	YEAR	DESIGN OF STUDY
1. Sweet et al.	1985	Randomised Controlled Trial.
2. Bulut et al.	2001	Randomised Controlled Trial.
3. Yoshii et al.	2002	Randomised Controlled Trial.
4. Poeschl et al.	2004	Randomised Controlled Trial.
5. Figueiredo et al.	2005	Case Control Study.
6. Chiu et al.	2006	Randomised Controlled Trial.
7. Figueiredo et al.	2007	Case Control Study.
8. Blondeau et al.	2007	Prospective Cohort Study.
9. Al-Asfour et al.	2009	Retrospective Cohort Study.
10. Siddiqi et al.	2010	Randomised Controlled Trial.
11. López-Cedrún et al.	2011	Randomised Controlled Trial.
12. Bello et al.	2011	Randomised Controlled Trial.
13. Freudlsperger et al.	2012	Retrospective Cohort Study.
14. Lee et al.	2014	Non-Randomised controlled Trial

Table 3: Prevalence of early infections of included studies.

ARTICLE	YEAR	PREVALENCE	SAMPLE (n)
A. Al-Asfour	2009	0,066	90
Blondeau	2007	0,04	327
Chiu	2006	0,015	275
Freudlsperger	2012	0,022	443
Poeschl	2004	0,086	288
Lee	2014	0,016	890
L.Cedrún	2011	0,04	123
Siddiqi	2010	0,042	95
Yoshii	2002	0.006	178
Sweet	1985	0,0325	400
Bulut	2001	0,13	30

The prevalence and the number of participants of the selected studies can be seen in table 3. The pooled estimated prevalence of early infection was 2.05 %. However, the standard error of the prevalence (SE(p)) was 397.2, due to the low proportion and the overall small size of the studies.

Lack of space of the lower third molar (*Pell & Gregory* classification)

Class III of Pell & Gregory lack of space classification was significantly associated to secondary infection. Compared to other categories, there was no heterogeneity (Q=0.7257; df=1; p=0,3943). The forest plot is in Figure 2. The pooled OR was 2.52 (95% CI: 1.22 to 5.21). There was no evidence of publication bias (Z<0.0001; p=1.0000).

Depth of the lower third molar (*Pell & Gregory* classification).

Pell & Gregory category C was not significantly associated to infection. Compared to other categories, there was no heterogeneity (Q=0.1747; df=1; p=0.6760). The forest plot is in Figure 3. The pooled OR was 1.66 (95 % CI: 0.81 to 3.41). There was no evidence of publication bias (Z<0.0001; p=1.0000).

Figure 2: Forest plot of class III third molars in Pell & Gregory's classification.

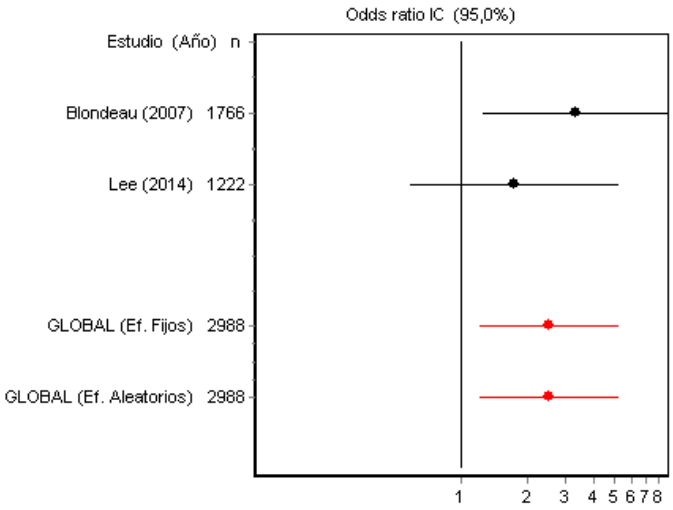
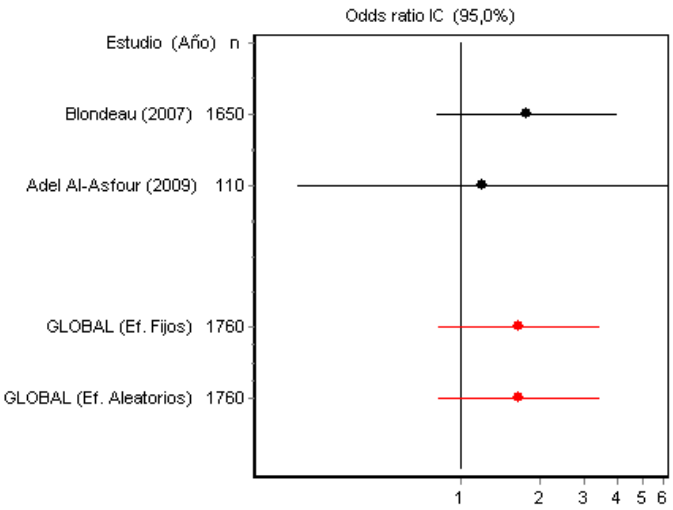


Figure 3: Forest plot of Pell & Gregory's C category of lower third molars.



Position of the lower third molar (*Winter's* classification)

The position was not related to the infection prevalence. Vertical third molars were not significantly associated with infection. There was no heterogeneity (Q=0.0044; df=1; p=0.9470). The forest plot is shown in Figure 4. The pooled OR was 0.910 (95% CI: 0.411 to 2.01). There was no evidence of publication bias (Z<0.0001; p=1.0000). The effect of other positions could not be calculated because of lack of data.

Antibiotic use

The use of antibiotics either as a prophylaxis before the extraction or immediately after, did not significantly reduce the infection risk. There was no heterogeneity (Q=0.3265; df=3; p=0.9550). The forest plot is in Figure 5. The OR of antibiotic use was 0.91 (95% IC: 0.41 to 2.01). There was no evidence of publication bias (Z=0.3397; p=0.7341), although there were no studies with high standard error without association. Figure 6 shows the funnel plot.

Figure 4: Forest plot of third molar position.

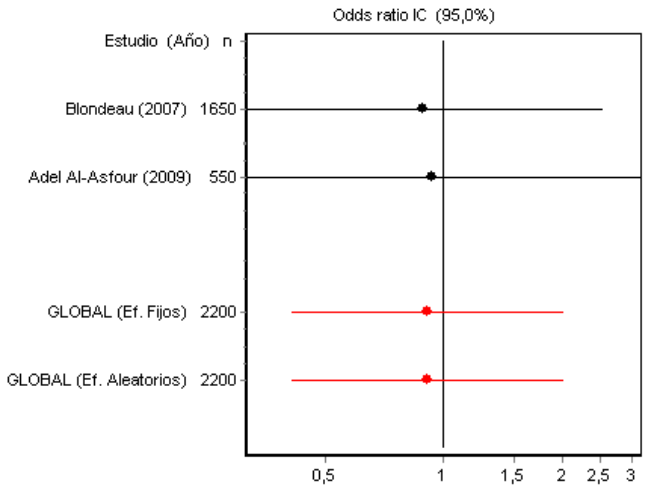


Figure 5: Forest plot of antibiotic use.

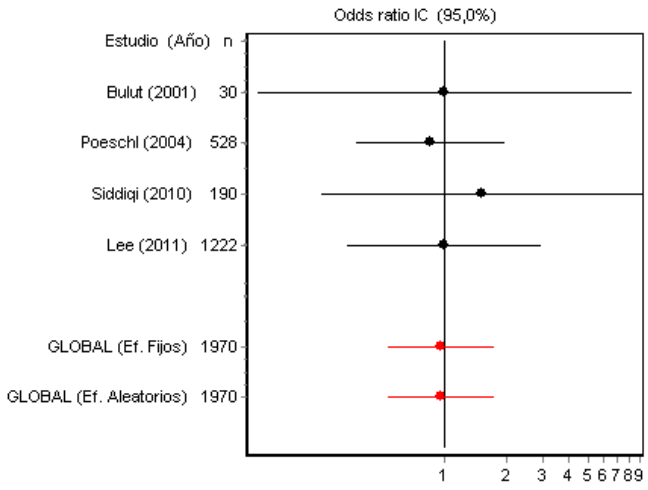
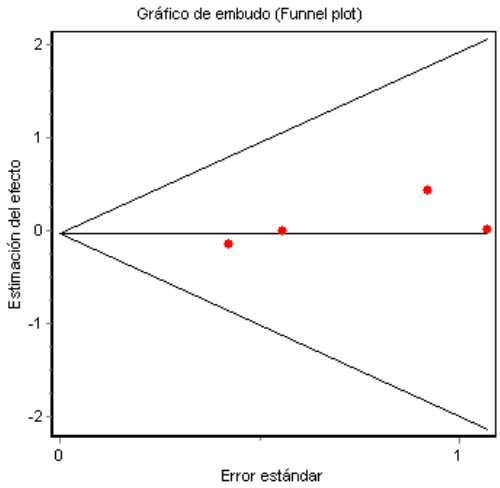


Figure 6: Funnel plot of antibiotic use.



The other possible risk factors were not assessed in present meta-analysis because of the low number of included studies which analyzed them. And, if there were two articles which reported a specific risk factor, there was at least a category with less than 1 event and so it was impossible to calculate odds ratios. However, Table 4 summarizes the information of these articles calculating the odds ratio of the possible risk factors for developing an early-onset infection and their confidence intervals. Furthermore, it was not possible to do the statistical part of this meta-analysis with delayed infections' data for the same reason but, in Table 5, odds ratio (OR) of the different possible risk factors for developing delayed onset infections with their confidence intervals (CI) are summarized. Moreover, sensitivity analysis was not displayed due to the small number of included studies.

Table 4: Other possible risk factors for developing an early postoperative infection.

ARTICLE	RISK FACTOR	OR [CI 95%]
Chiu 2006	Gloves (clean VS steryle)	3,02 [0,31-29,42]
Blondeau 2007	Gender (female VS male)	8,25 [1,05-64,68]
Sweet 1985	mouth rinse (saline/others)	1,08 [0,29-3,97]
	mouth rinse (Chloramine-T/others)	0,91 [0,25-3,36]
	mouth rinse (povidone iodine/others)	1,33 [0,40-4,36]
	mouth rinse (sodium bicarbonate/others)	0,89 [0,24-3,26]

Other possible risk factors for developing an early secondary infection (Table 4):

- Type of gloves (clean VS sterile): No significantly associated with secondary infections.
- Gender (female VS male): Female gender seems to be significantly more prone to develop early secondary infections.
- Mouth rinses: No significantly associated with secondary infections.

Table 5: Other possible risk factors for developing a delayed-onset infection

ARTICLE	RISK FACTOR	OR [CI 95%]
Figueiredo 2007	Female gender	0,77 [0,35-1,69]
	Left operated site	1,62 [0,76-3,47]
	Oral contraceptives	0,81 [0,27-2,41]
	Previous infection	0,56 [0,26-1,18]
	Adjacent second molar	0,99 [0,98-1,01]
	Radiotransparent lesion	1,12 [0,52-2,42]
	Ostectomy	2,42 [0,80-7,34]
	Tooth sectioning	2,81 [1,20-6,61]

Possible risk factors for developing a delayed-onset infection (Table 5): The only significant risk factor is tooth sectioning that increases the OR for delayed-onset infections.

5. DISCUSSION

Prevalence of early and delayed – onset infections

The prevalence of early postoperative infection has been reported to be relatively low compared with other postoperative complications after lower third molar surgery procedure; in the literature, the prevalence of them varies from 1% to 10% for the majority of studies.[3,5,65] However, there are fewer, such as Freudlsperger et al,[4] that reported a prevalence up to 30%.

The low pooled prevalence of this meta-analysis, estimated at 2.05%, has corroborated these first articles mentioned. However, because of the low proportion and the overall small size of the studies, standard error of this pooled prevalence is very high, which means that there is a lot of variability between different selected studies.

Moreover, we tried to estimate a pooled prevalence for delayed-onset infections after lower third molar surgeries but, unfortunately, there were only 3 included studies [1,2,70] on this subject and it was misleading to make the pooled prevalence with them. However, it is interesting to know their reported data; for Bello et al, [70] delayed-onset infections' prevalence is 2.4% (sample of 82 subjects) and for Figueiredo et al, [1] it is 1.8% (sample of 772 subjects).

Possible risk factors for early and delayed – onset infections

Although the prevalence of secondary infections is low, there are some risk factors to take into account:

Depth of the lower third molar (*Pell & Gregory* classification)

One of the risk factors that seems to be important for developing a secondary infection after third molar surgery is the grade of its impaction; the more impacted the tooth is, the more easer it is to develop this postoperative complication.[17,18,40,43] However, present study has refused this first theory: present data shows that third molar depth is not associated with increased infection risk.

Although this meta-analysis has not corroborated the first theory exposed, some articles which reported a certain relation between depth of third molar and early

infections, explain some reasons for this: on one hand, there is an association between the level of impact and the development of pathological entities such as pericoronitis, periodontal disease and caries when there is a communication between the impacted dental follicle and the oral cavity.[72] On the other hand, a deep impaction of the third molar means an increase of surgical trauma.[15]

Finally, Benediktsdóttir et al, in their article published in 2004, reported that visible inferior alveolar nerve was 7 times higher risk for general infection than if the nerve was not visible. This is directly proportional with operation time and, also, with the depth of lower third molar.[43]

Lack of space of the third molar (*Pell & Gregory* classification)

Present meta-analysis has shown a relation between class III of *Pell & Gregory* classification and the development of early infections. Other categories of this classification have not been possible to analyze. However, for some clinical trials[3,72] class II of *Pell & Gregory* classification is the main type of tooth implicated in preoperative and postoperative pathologies; One of these studies[72] analyzed the relationship between position of the molar and preoperative complications and it concluded that, third molars partially or totally covered with bone, present a twofold to fourfold lesser risk for infectious preoperative complications and, position IIA and IIB, are teeth more prone to develop preoperative infections.

Position of the third molar (*Winter's* classification)

Another possible risk factor is the position of the lower third molar in the mandible. According to *Winter's* classification, there are four possible positions; mesioangular position (MA), distoangular position (DA), vertical position (V) and horitzontal position (H). The present meta-analysis has shown that there is no statistical evidence for this fact.

Blondeau et al,[3] reported that mesioangular and distoangular positions were the ones with more complications rate. However, for another clinical trial,[5] there was no significant difference of infection development with regards to *Winter's* position.

The use of antibiotics

"Antibiotic therapy, if indiscriminately used, may turn out to be a medicinal flood that temporarily cleans and heals, but ultimately destroys life itself" as Fèlix Martí-Ibáñez stated in 1995.

In this meta-analysis, the use of antibiotics either as a prophylaxis before the extraction or immediately after, did not significantly reduce the infection risk. Halpern and Dodson,[73] in their randomised control trial, confirmed that the intravenous administration of penicillin or clindamycin 1 hour before surgery prevented the apparition of secondary infections. Also, Artegoita et al, [53] in their clinical trial concluded that the administration of amoxicillin/clavulanic acid after surgery was efficacious in reducing the incidence of inflammatory complications but should not be prescribed in all patients. Conversely, Bezerra et al, [35] reported that the administration of amoxicillin before surgery did not prevent postoperative infections. Another clinical trial in agreement with Bezerra et al is Calvo et al, [10] who concluded that the administration of antibiotics preoperatively or after surgery, was not beneficial for preventing infections. Moreover, a meta-analysis of randomized controlled clinical trials published in 2007, [74] dealing with antibiotic prophylaxis after third molar surgeries, reported a frequency of postoperative infection of 4% among antibiotic prophylaxis' patients and 6.1% for the control group. This meta-analysis concluded that giving antibiotics before surgery was efficacious for preventing surgical wound infections.[74]

However, the use of antibiotics may play a role in preventing dry sockets; as a systematic review of randomized controlled trials reports, local treatment with tetracycline seem to have a preventive effect on dry sockets' ocurrence.[75] Furthermore, Ren et al,[74] in their meta-analysis mentioned before, reported a frequency of alveolitis of 6.2% among patients receiving antibiotic prophylaxis and it reported a 14.4% among those who did not take them. So, it concluded that giving antibiotics before the extraction is beneficial for preventing dry sockets.[74]

Even so, it is important to consider that the extraction of lower third molar is a clean-contaminated operation which means that the surgery is performed in an environment contaminated with a large number of bacteria.[14,50,52] Thus, the oral cavity is recovered

with a complex ecosystem and its changes are constantly; there is an endogenous flora that may cause disease if provided with the optimal conditions to become pathogenic.[76] In front of this, it is important to work with aseptic conditions.[67]

Another important thing to take into account is that systematically prescription of antibiotics can decrease their effectiveness, allergic reactions can appear, and it can induce antibiotic resistances.[14,35,52,76,77] However, the controversies between specialists are still a current problem.

As history shows, from 1928, the discovery of the first antibiotic, Penicillin, by Alexander Fleming, to nowadays, many resistant bacteria have appeared, such as the case of *Staphylococcus aureus*, the first resistance observed, in 1940.[78] Since then, more resistant bacteria have appeared and the total effectiveness of penicillin is decreasing more and more.[78] In front of this, controlling antibacterial resistance is an international priority in terms of public health.[78]

All these undesirable effects that decrease the effectiveness of antibiotic treatment, are partially due to the high prescription rate of broad spectrum antibiotics, the empirical prescription based on clinical and bacteriological epidemiological factors, and also the prescription of a very narrow range of antibiotics[77] (the majority of the antibiotics prescribed by dentists are amoxicillin, penicillin and metronidazole).[76]

Smoking habit

This risk factor was not possible to estimate in present study because of scarcity of data. As a case-control study published in 2006 reported, tobacco has been shown to decrease the fibrinolytic activity in comparison with non-smokers so this could explain why smokers have a delay in wound healing.[39] Furthermore, tobacco affects negatively different cell types; Pabst et al. stated that tobacco smoke has deleterious effects upon host immune system, affecting the phagocytic activity of neutrophils and macrophages, increasing the risk of bacterial colonization and thus the infection of the socket.[39]

Age of the subject

Despite the impossibility to make the statistical analysis for this risk factor in present meta-analysis, some reports indicate that the age play a role in developing a postoperative infection. Several reviewed articles [17,18,36,40,43,58] reported that the best moment of patient's life to have their lower third molars extracted is under 25 years of age and, patients older than 25, have a higher risk for postoperative complications, including secondary infections. A review of 2012,[79] exposed some reasons for this finding related to older age; on one hand, extractions are more difficult because of the increasing bone sclerosis, the continued root development, the fact that the periodontal ligament becomes thinner with the possibility to lead to ankylosis of the tooth and hypercementosis. On the other hand, the older the patient is, the more comorbidities they have. Benediktsdóttir et al[43] also reported that younger people have a lower risk of an extended operation time than older patients, having a 2 to 2.5 times higher risk for an operation time above 10 minutes compared to young patients. Because of this augmented operation time, there could be a relation between time and secondary infections. [43]

The experience of the surgeon

It has not been possible to make the statistical analysis because there were not enough data in the included articles. However, some articles reported the association between the experience of the surgeon and postoperative infections. Jerjes et al [57] in their clinical trial of 2006 concluded that oral and maxillofacial Senior House Officers (OMFS residents) were twice as likely to develop infection compared with specialists in surgical dentistry. They said that this result could be related to the fact that OMFS residents treated more women who were said to develop easily infections and complications in general. [57] Another more recent study of Jerjes et al,[12] reported that patients operated by OMFS residents were nearly 50 times more likely to develop postoperative infections compared with patients operated by senior specialists. These results were also attributed to the fact that OMFS residents had more females than senior surgeons. [12] Another study which treated this risk factor is Sisk et al: [11] twenty-one patients developed secondary infections of the 708 subjects of the study; 8 of these patients were treated by faculty group and 13 by resident group. Thus, its

conclusion was that postoperative infections were four times more frequent in the resident group than in faculty group. [11]

Type of gloves used: clean or sterile

The use of clean gloves during the surgery procedure is said to be a risk factor for developing infections compared with the use of sterile gloves. Although it has been not possible to analyze it in this meta-analysis, Chiu et al[67] proved that clean gloves do not increase the incidence of postoperative clinical complications; there were more bacterial colonies on clean glove surfaces than on sterile gloves (only 1 of the 20 sterile glove yielded a positive culture result). However, the species found on the sterile glove surface were all Gram-positive spore-forming bacilli, maybe of saprophytic clostridial species with non-pathogenic potency. And, most bacteria of clean gloves were gram-positive cocci and spore-forming bacilli, so, they were also non-pathogenic because pathogenic species are commonly gram-negative microbes. [67]

As already mentioned in results, it was no possible to make a statistical analysis of risk factors for developing delayed-onset infections. However, there is some remarkable information to comment from two included studies which reported delayed infections.

From one hand, Bello et al[70] in their clinical trial which compared partial with total closure techniques after third molar surgery, concluded that there was no difference between both techniques regarding with postoperative infections. Even so, they concluded that partial technique reduced facial swelling compared with total technique but, at the same time, partial closure seemed to be related with more bleeding.[70]

On the other hand, Figueiredo et al[2] in their case control study of 2007, concluded that lower third molars with total soft tissue retention, a lack of distal space and with a vertical or mesioangular tilt, were more likely to develop delayed infections of the socket. Other possible risk factors reported were tooth sectioning, bone retention and depth of inclusion. Finally, this retrospective study concluded that heavy smokers (more than 20 cigarettes per day) in infected group were 6-fold greater than in control group; however, the difference was not significant (maybe due to the low sample of heavy smokers: n=5).

5.1 Limitations of the meta-analysis

In present meta-analysis, we had some limitations. First of all, there were few articles from which could be possible to extract enough data: on one hand, several articles did not specify any infection criteria and so they were automatically excluded. On the other hand, there were some articles which were unavailable and finally, there were some studies which in some cases we tried to get in contact with the authors but without answer. Moreover, few articles could be included in the selection but lower third molars' data were mixed with upper third molars' data.

Another limitation was the different designs of the 14 articles included. Furthermore, some data of these 14 articles were insufficiently described. Also, *Winter's* classification was a problem too, because categories are not ordered. Moreover, there was an error of measuring the angulation of teeth (combination bias).

Furthermore, statistical analysis of the risk factor antibiotic use, had been done mixing all different types, doses and moments (before and after surgery) of antibiotic treatment.

Moreover, because of the lack of studies, some possible risk factors mentioned in the introduction, such as age over 25 years or partial or total closer of the wound, had not been analyzed.

6.1 CONCLUSIONS

1. Prevalence of early secondary infections after lower third molar surgery is according with the reviewed literature, [3,5,6,65] 2.05% (Standard error of 397.2, due to the low proportion and the overall small size of the studies included). This result means that early-onset infections are not frequent in this procedure.

2. Prevalence of delayed-onset infections was not estimated, but could be around 0.7 to 2.2 %.[1]

3. The only risk factor which seems to be related to early postoperative infections is the lack of space for the eruption of lower third molar in the classification of *Pell & Gregory* (class III).

4. The other risk factors were not statistically significant in present meta-analysis.

5. It has not been possible to analyze risk factors of delayed postoperative infections.

Future research would require a meta-analysis to ascertain whether antibiotic treatment is a risk factor for secondary infections and which type, doses and timing (preoperatively or postoperatively) are the best to avoid this complication.

Finally, other interesting future researches could be randomized controlled trials on this subject, with an infection criteria clearly defined and with higher sample sizes.

6.2 CONCLUSIONS

1. La prevalença de les infeccions postoperatòries immediates després de l'extracció de cordals inferiors coincideix amb la literatura revisada[3,5,6,65] estimada en un 2.05% (amb un error estàndard de 397.2, per la baixa proporció i la baixa mida mostral dels estudis inclosos). Aquest resultat significa que les infeccions immediates no són gaire freqüents en aquests procediments.

2. La prevalença de les infeccions postoperatòries tardanes no ha estat estimada però sembla situar-se entre el 0.7 i el 2.2%. [1]

3. L'únic factor de risc que sembla tenir una influència sobre l'aparició de les infeccions postoperatòries immediates és la classe III de la classificació de *Pell & Gregory* de l'espai d'erupció que tenen els cordals.

4. Els altres possibles factors de risc pel desenvolupament d'infeccions immediates no han resultat estadísticament significatius en aquest meta-anàlisi.

5. Els factors de risc pel desenvolupament d'infeccions postoperatòries tardanes no han pogut ésser estadísticament analitzats.

De cara al futur, seria interessant la realització d'un meta-anàlisi per a esbrinar si l'ús d'antibiòtics és realment un factor de risc per les infeccions postoperatòries i quin tipus, dosis i en quin moment (preoperatori o postoperatori) és el millor per a la seva administració.

Finalment, també seria positiva l'elaboració de més assajos clínics aleatoritzats sobre les infeccions postoperatòries, tot definint clarament el criteri d'infecció utilitzat i també amb mides mostrals majors.

6.3 CONCLUSIONES

1. La prevalencia de infecciones postoperatorias tempranas después de la extracción de cordales inferiores coincide con la literatura revisada[3,5,6,65] estimada en un 2.05% (con un error estándar de 397.2, por la baja proporción y el bajo número de muestra de los estudios incluidos). Este resultado significa que las infecciones tempranas no son muy frecuentes después de este tipo de procedimientos.

2. La prevalencia de las infecciones tardanas no ha sido calculada estadísticamente, pero parece ser entre 0.7 y 2.2%.[1]

3. El único factor de riesgo que parece tener una influencia sobre la aparición de las infecciones postoperatorias tempranas es la clase III de la clasificación de *Pell & Gregoy* del espacio de erupción de los cordales.

4. Los otros factores de riesgo posibles para la aparición de infecciones tempranas no han resultado ser estadísticamente significativos en el presente meta-análisis.

5. Los factores de riesgo de las infecciones postoperatorias tardanas no han sido analizados estadísticamente.

En un futuro, sería interesante la realización de un meta-análisis para saber si el uso de antibióticos es realmente un factor de riesgo para las infecciones postoperatorias y qué tipo, dosis y qué momento (preoperatorio o postoperatorio) es el mejor para su administración.

Finalmente, también sería positiva la elaboración de más ensayos clínicos aleatorizados sobre las infecciones postoperatorias, definiendo claramente el criterio de infección utilizado y también con un mayor número de muestra.

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9. ANNEX I: PRISMA statement

Section/topic	#	Checklist item	Reported on page #
TITLE			1
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			1
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			3
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			5
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	-
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	-
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	-
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			8
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	-
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	11
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	12
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	13
DISCUSSION			15
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22
FUNDING			-
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	-