# Efficacy of chlorhexidine in the prevention of alveolar osteitis after permanent tooth extraction. Systematic review and meta-analysis.

## Eficacia de la clorhexidina en la prevención de la osteítis alveolar después de la exodoncia de dientes permanentes. Revisión sistemática y meta análisis

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**Abstract:** Background: Dental extraction is a routine task performed by dental surgeons. This procedure may sometimes cause associated postoperative complications such as: edema, pain, trismus and alveolar osteitis (AO). Objective: To evaluate the efficacy of chlorhexidine (CHX) in the prevention of alveolar osteitis after permanent tooth extraction, through a systematic review and meta-analysis. Materials and Methods: A literature search was carried out until December 2018 in the following biomedical databases: *PubMed, Embase, SciELO, Science Direct, SIGLE, LILACS, Google Scholar* and *The Cochrane Central Register of Controlled Trials* (CENTRAL). The selection criteria for the studies were: randomized clinical trials published in the 5 years prior to the realization of this study, which reported the use of CHX in the prevention of AO. The risk of study bias was analyzed through the Cochrane Manual for systematic reviews of interventions. Results: The search strategy resulted in a selection of 22 articles; 17 of these were used to perform the meta-analysis. All of them reported that CHX is effective in preventing AO. Conclusion: The literature reviewed suggests that the use of CHX is effective in AO prevention; however, more studies comparing the efficacy of chlorhexidine gel with chlorhexidine used as an irrigant or as mouthwash are necessary.

*Keywords: Alveolar osteitis; dry socket; chlorhexidine; review; meta-analysis; clinical trial.*

**Resumen:** Antecedentes: La extracción dental es una tarea rutinaria llevada a cabo por los cirujanos dentales, este procedimiento llega a causar, en algunas ocasiones, complicaciones postoperatorias asociadas como son: edema, dolor, trismo y osteítis alveolar (OA). Objetivo: Evaluar la eficacia de la clorhexidina (CHX) en la prevención de la osteítis alveolar después de la exodoncia de dientes permanentes mediante una revisión sistemática y un metaanálisis. Material y Método: Se realizó una búsqueda de la literatura hasta diciembre del 2017, en las bases de datos biomédicas: *PubMed, Embase, SciELO, Science Direct, SIGLE, LILACS, Google Scholar* y el *Registro Central de Ensayos clínicos Cochrane.* Se definieron los criterios de selección de los estudios los cuales fueron: ensayos clínicos aleatorizados, con una antigüedad máxima de 5 años y que reporten el uso de CHX para la prevención de OA. Se analizó el riesgo de sesgo de los estudios por medio del Manual Cochrane de revisiones sistemáticas de intervenciones. Resultados: La estrategia de búsqueda resultó en 22 artículos de los cuales 17 se usaron para la realización de un metaanálisis. Todos reportaron que la CHX es eficaz en la prevención de la OA. Conclusión: La literatura revisada sugiere el uso de CHX en eficaz en la prevención de la OA, sin embargo, son necesarios más estudios que comparen la eficacia de la clorhexidina en gel con la clorhexidina como irrigante o como enjuague bucal.

***Palabras Clave:*** *Osteítis alveolar, alveolitis seca, clorhexidina, revisión, metaanálisis, ensayo clínico.*

## INTRODUCTION.

Dental extraction is a routine task performed by dental surgeons. This procedure may sometimes cause associated postoperative complications such as: edema, pain, trismus and alveolar osteitis (AO).[1] AO, also known as dry socket, is one of the most common postoperative complications after permanent tooth extraction. It is a lesser known form of postoperative pain located in or around the area of extraction due to the partial or total loss of a blood clot. AO occurs between the first and third postoperative day, with or without halitosis. It was described by Crawford in 1986 and by Blum in 2002, who gave it a universal definition based on clinical diagnosis.[1-7]

It has been reported that the incidence of AO varies from 0.5 to 68.4%. These vastly mixed results may be due to differences in diagnostic criteria, surgical procedures, and factors related to the patient and dental extraction. AO appears most frequently within the mandible, it is more frequent in females than males (5:1), and in the age group between 40 and 45 years old, and when posterior teeth are extracted (10 times more common in third molars).[1-7]

The etiology of AO is not clearly defined, but the following are considered as triggering factors: hypovascularity (due to bone density), anesthetic agents (vaso-constriction), systemic diseases, smoking, age, oral contraceptives use, surgical injuries, drug history, antibiotics use prior to surgery, previous infections in the surgical area, immediate irrigation with saline solution and traumatic extraction.[1,3,5-7] AO occurs due to an increase in local fibrinolysis that leads to clot disintegration and is characterized by severe pain. It is a self-limited condition, but it requires several clinical follow-up visits due to its intense pain, increasing the morbidity and the cost of treatment.[1,3,5-7]

The objective of AO treatment includes reducing pain, preventing bacterial growth and controlling bleeding. Treatment options are limited, but the use of eugenol dressing, chlorhexidine (CHX), antibiotics, analgesics, lidocaine gel, and alveolus irrigation are some of the methods employed to reduce its incidence.[1,3,5-7]

Due to the severe pain associated with AO, preventing it decreases morbidity, the cost of treatment and reduces repeated dental visits. Therefore, various prevention methods have been researched, however, there is still a great deal of controversy regarding which one is the most effective and appropriate. Some publications examined the effect of CHX on the prevention of AO, concluding that this was the only local method for which there was moderate evidence about AO prevention. However, other studies suggested it was ineffective.[1,3,5-7] Due to this controversy, the aim of this paper was to evaluate the efficacy of chlorhexidine in the prevention of OA after the extraction of permanent teeth.

## MATERIALS AND METHODS.

This systematic review was carried out according to a research protocol that was previously developed following the PRISMA guidelines.[8]

### Literature search

A comprehensive search was carried out in the following biomedical databases: *PubMed, Embase, SciELO, Science Direct, SIGLE* (System of Information on Gray Literature in Europe), *LILACS, Google Scholar* and in t*he Cochrane Central Register of Controlled Trials*. Furthermore, a manual search was conducted in important oral and maxillofacial surgery journals such as: *the Journal of Orofacial Pain, Journal of Oral & Facial Pain* and *Headache, Journal of Oral and Maxillofacial Surgery, Journal of Cranio-Maxillofacial Surgery, International Journal of Oral, Maxillofacial Surgery, and the British Journal of Oral & Maxillofacial Surgery*; considering publications from January 02, 2013 to November 01, 2018, and using a combination of thematic titles with the following keywords: *"dry socket"* or *"alveolar osteitis"*; *"chlorhexidine"*, *"CHX gel"* or *"chlorhexidine gel"*; and *"dental surgery"* or *"dental extraction"*.

### Selection criteria

**Inclusion criteria:**

- Articles reporting the use of CHX for OA prevention.
- Articles published in the last 5 years prior to the realization of this study.
- Articles that were clinical trials, without language restriction.

**Exclusion criteria:**

- Articles from non-indexed journals.
- Articles having children as patients.

### Data selection and extraction process

A review of the titles and abstracts of all the studies collected using the inclusion and exclusion criteria was

carried out. The full text of the selected studies was obtained in order to determine their respective risk.

In order to assess the studies, a duplicate checklist was drawn up to extract information of interest and to collate the data obtained. Two reviewers (MS and EI) independently grouped the articles according to title, author, year of publication, type of study, number of patients, patient ages, follow-up period, country where the study was conducted, study groups, number of patients per study group, postoperative medication, number of dry socket cases, treatment success rate and risk of bias. For the resolution of any discrepancies between the reviewers, a meeting and discussion was arranged with a third reviewer (FC) in order to reach an agreement.

### Assessment of the risk of study bias

Each study was analyzed according to the Cochrane Manual for systematic reviews of interventions in order to assess the risk of study bias.[9]

### Analysis of results

The data from each study was entered and analyzed in the RevMan 5.3 program (Cochrane Group, UK).

## RESULTS.

### Study selection

The initial search yielded a total of 639 studies, available from January 2013 to November 2018. From these, 27 had duplicated titles and were excluded, resulting in 612 selected studies. The remaining titles were read, 487 studies were ruled out, and only 125 were selected. Their respective abstracts were analyzed, discarding those that did not meet the inclusion criteria. Twenty-two articles were chosen for a comprehensive review of their content and methodology, while five articles were discarded before the meta-analysis step. (Figure 1)

### Characteristics and results of the studies

The number of patients ranged between 25 and 744, with the follow-up period ranging between 3 to 8 days in the selected studies.[10-31] Nineteen studies,[10-25,27,28,30] reported that the mean age of patients ranged between 21.12 and 43.43 years old. Nineteen[10-20,22-28,30] others reported that the total number of patients, according to gender (male and female), were 1580 and 1458, respectively. Eighteen[10-19,21,23-25,27-30] reported that the patients' age ranged between 16 and 76 years old. The countries where

the studies were conducted were India[10,16,17,20,23], Chile,[11] Iran,[12,24,27,28] Australia,[13] Pakistan,[14,25,30] Nigeria,[15] South Africa,[18] Peru,[19,31] Sweden,[21] Spain,[22] Saudi Arabia[26] and Republic of Kosovo.[29] In all these studies[18-31] patients received a AO prevention regime. (Table 1)

The total number of patients who received treatment were 3260. Eighteen studies,[10-12,14-23,25,27-29,31] included a control group: in one study[13] 0.02% CHX was used as an irrigant and as mouthwash; in another,[24] 0.1% and 0.2% CHX gel was used; in another study,[26] 0.2% CHX gel with 0.12% CHX was employed; and, finally, in another study,[30] 0.2% CHX gel was used with 0.2% CHX solution.

In 11 studies,[10,12,14,20,22-24,27-30] impacted mandibular third molars were extracted, while another eight,[13,15-19,21,31] reported the extraction of mandibular third molars; one study[11] reported that maxillary and mandibular permanent teeth were extracted, and two studies[25,26] reported the extraction of maxillary and mandibular molars. Regarding postoperative medication,[8] studies[10,12,14,15,17,19,20,28] described the use of antibiotics,[19] studies[10,12-24,26,28-31] detailed the use of non-steroidal anti-inflammatory drugs, and one study[22] reported the use of a proton pump inhibitor. (Table 1)

### Analysis of risk of study bias

Thirteen studies[10,14-20,22,23,26,29,31] reported high risk of bias, while nine studies[11-13,21,24,25,27,28,30] indicated low risk of bias. (Figure 2)

### Synthesis of results (Meta-analysis)

### 0.02% Chlorhexidine as an intra-alveolar irrigant

The use of chlorhexidine as an intra-alveolar irrigant was detailed in two studies,[10,13] revealing there was a significant difference ($p$=0.005; mean difference=0.22; 95% confidence interval=0.08, 0.63; fixed-effect model; I2=0%), favoring the use of 0.02% chlorhexidine as an intra-alveolar irrigant for AO prevention. (Figure 3)

### 0.12% Chlorhexidine as mouthwash

The use of 0.12% chlorhexidine as mouthwash was described in four studies,[11,15,17,31] revealing there was a significant difference ($p$=0.0007; mean difference=0.47; 95% confidence interval=0.31, 0.73; fixed-effect model; I2=0%), favoring the use of 0.12% chlorhexidine as mouthwash for AO prevention. (Figure 4)

### Chlorhexidine as intra-alveolar gel

The use of chlorhexidine as a intra-alveolar gel was reported in 11 studies,[12,14,16,19-23,25,27,28] revealing there
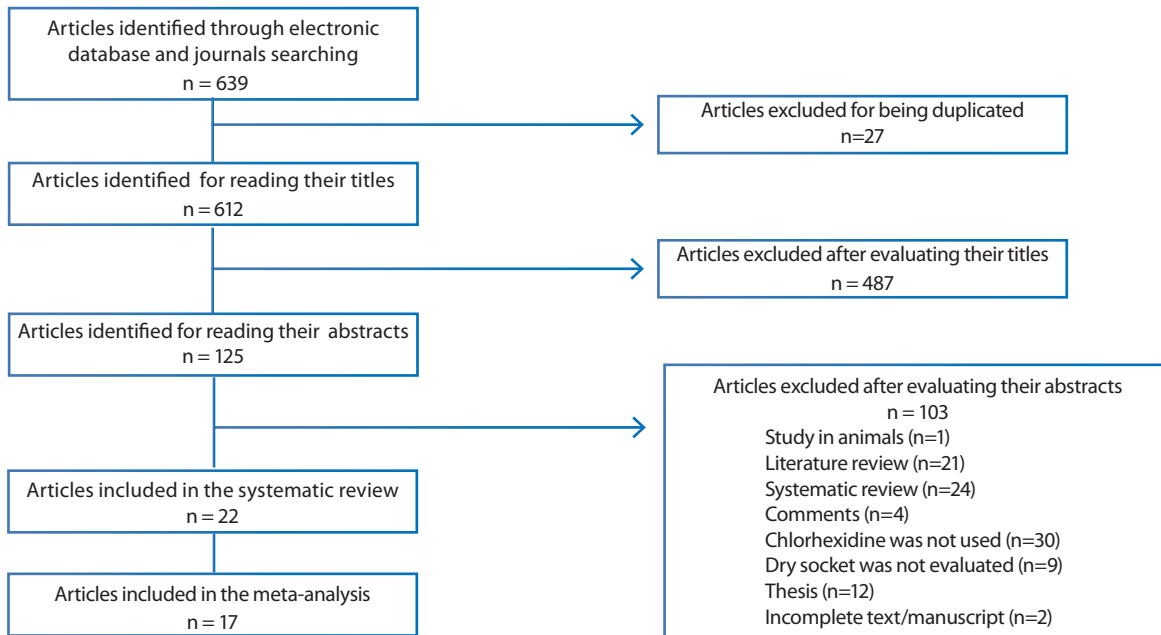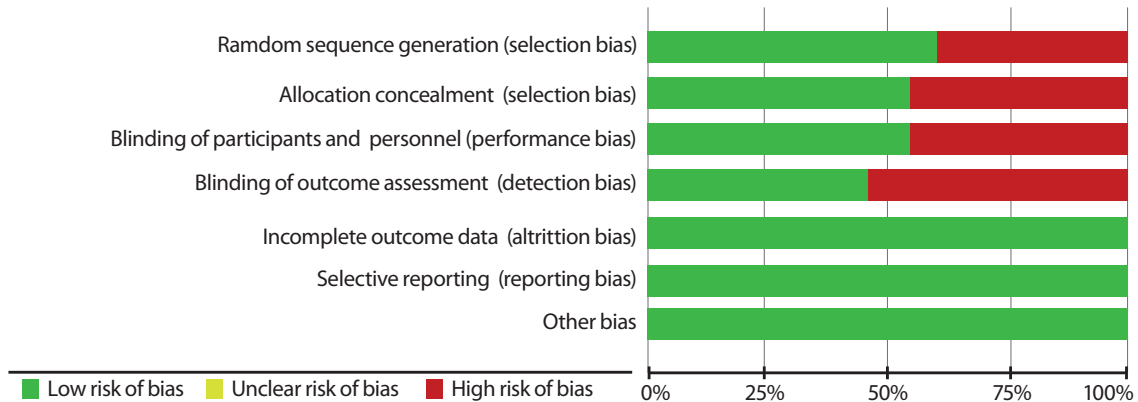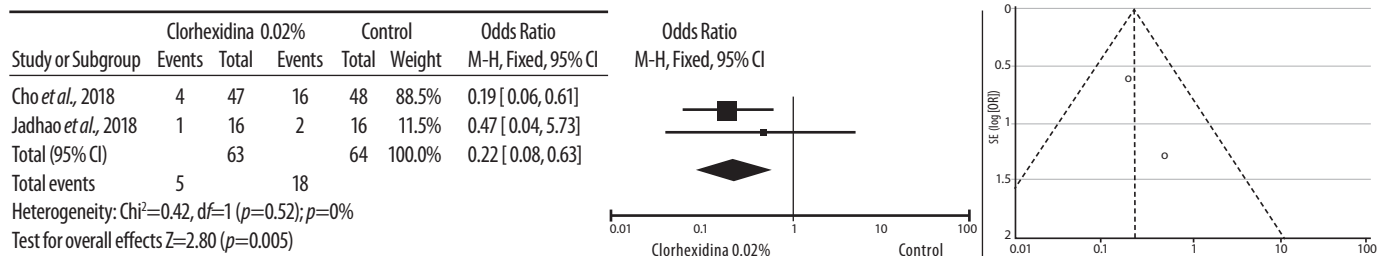
**Figure 1.** Flowchart of articles selection.



Articles identified through electronic database and journals searching
n = 639

Articles excluded for being duplicated
n=27

Articles identified for reading their titles
n = 612

Articles excluded after evaluating their titles
n = 487

Articles identified for reading their abstracts
n = 125

Articles excluded after evaluating their abstracts
n = 103
Study in animals (n=1)
Literature review (n=21)
Systematic review (n=24)
Comments (n=4)
Chlorhexidine was not used (n=30)
Dry socket was not evaluated (n=9)
Thesis (n=12)
Incomplete text/manuscript (n=2)

Articles included in the systematic review
n = 22

Articles included in the meta-analysis
n = 17

**Figure 2.** Risk of study bias.



| | Younus et al. 2014 | Shahakbari et al. 2015 | Shaban et al. 2014 | Sánchez et al. 2014 | Rubio-Palau et al. 2015 | Requena-Calla et al. 2016 | Quresshi et al. 2018 | Jesudasan et al. 2015 | Kaur et al. 2017 | Khan et al. 2015 | Osunde et al. 2017 | Gopee et al. 2017 | Halabi et al. 2018 | Haraji et al. 2014 | Inamdar et al. 2015 | Jadhao et al. 2018 | Abu-Mostafa et al. 2015 | Ahmedi et al. 2014 | Cho et al. 2018 | Choubarga et al. 2017 | Eshgpour et al. 2018 | Freudenthal et al. 2015 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ramdom sequence generation (selection bias) | + | + | + | + | + | − | − | − | + | − | + | − | − | + | + | − | + | + | − | + | − | + |
| Allocation concealment (selection bias) | + | + | + | + | − | − | − | − | + | − | − | − | − | + | + | + | + | + | − | + | − | + |
| Blinding of participants and personnel (performance bias) | + | + | + | + | − | − | − | + | + | − | − | − | − | + | + | − | + | + | − | + | − | + |
| Blinding of outcome assessment (detection bias) | + | + | + | − | − | − | − | + | + | − | − | − | − | + | + | + | − | + | − | + | − | − |
| Incomplete outcome data (altrittion bias) | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Selective reporting (reporting bias) | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Other bias | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |

**Figure 3.** Forest plot and Funnel plot of the event
"Effectiveness of 0.02% chlorhexidine as an intra-alveolar irrigant for AO prevention"
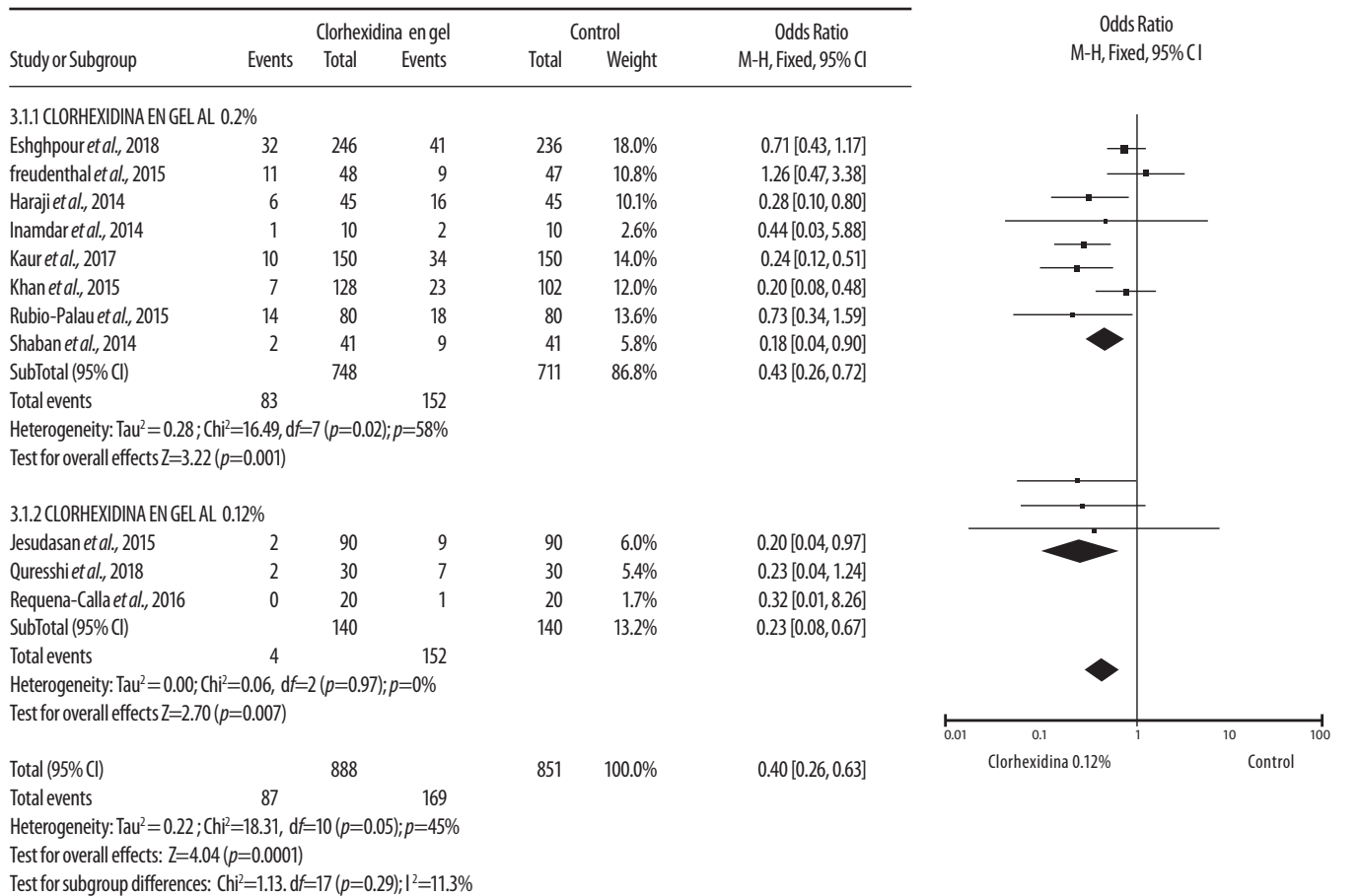


| Study or Subgroup | Clorhexidina 0.02% Events | Total | Control Events | Total | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Cho et al., 2018 | 4 | 47 | 16 | 48 | 88.5% | 0.19 [0.06, 0.61] |
| Jadhao et al., 2018 | 1 | 16 | 2 | 16 | 11.5% | 0.47 [0.04, 5.73] |
| Total (95% CI) | | 63 | | 64 | 100.0% | 0.22 [0.08, 0.63] |
| Total events | 5 | | 18 | | | |

Heterogeneity: Chi$^2$=0.42, df=1 (p=0.52); p=0%
Test for overall effects Z=2.80 (p=0.005)

**Figure 4.** Forest plot and Funnel plot of the event
"Effectiveness of 0.12% chlorhexidine as a mouthwash for AO prevention"



| Study or Subgroup | Clorhexidina 0.12% Events | Total | Control Events | Total | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Choubarga et al., 2017 | 17 | 110 | 26 | 110 | 35.1% | 0.59 [0.30, 1.16] |
| Halabi et al., 2018 | 10 | 372 | 27 | 372 | 42.0% | 0.35 [0.17, 0.74] |
| Osunde et al., 2017 | 1 | 50 | 2 | 50 | 3.1% | 0.49 [0.04, 5.58] |
| Sánchez et al., 2014 | 9 | 51 | 15 | 51 | 19.7% | 0.51 [0.20, 1.31] |
| Total (95% CI) | | 583 | | 583 | 100.0% | 0.47 [0.31, 1.31] |
| Total events | 37 | | 70 | | | |

Heterogeneity: Chi$^2$=1.04, df=3 (p=0.79); p=0%
Test for overall effects Z=3.40 (p=0.0007)

**Figure 5.** Forest plot of the event "Efficacy of chlorhexidine as intraalveolar gel for AO prevention"



| Study or Subgroup | Clorhexidina en gel Events | Total | Control Events | Total | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **3.1.1 CLORHEXIDINA EN GEL AL 0.2%** | | | | | | |
| Eshghpour et al., 2018 | 32 | 246 | 41 | 236 | 18.0% | 0.71 [0.43, 1.17] |
| freudenthal et al., 2015 | 11 | 48 | 9 | 47 | 10.8% | 1.26 [0.47, 3.38] |
| Haraji et al., 2014 | 6 | 45 | 16 | 45 | 10.1% | 0.28 [0.10, 0.80] |
| Inamdar et al., 2014 | 1 | 10 | 2 | 10 | 2.6% | 0.44 [0.03, 5.88] |
| Kaur et al., 2017 | 10 | 150 | 34 | 150 | 14.0% | 0.24 [0.12, 0.51] |
| Khan et al., 2015 | 7 | 128 | 23 | 102 | 12.0% | 0.20 [0.08, 0.48] |
| Rubio-Palau et al., 2015 | 14 | 80 | 18 | 80 | 13.6% | 0.73 [0.34, 1.59] |
| Shaban et al., 2014 | 2 | 41 | 9 | 41 | 5.8% | 0.18 [0.04, 0.90] |
| SubTotal (95% CI) | | 748 | | 711 | 86.8% | 0.43 [0.26, 0.72] |
| Total events | 83 | | 152 | | | |

Heterogeneity: Tau$^2$ = 0.28 ; Chi$^2$=16.49, df=7 (p=0.02); p=58%
Test for overall effects Z=3.22 (p=0.001)

| | Clorhexidina en gel Events | Total | Control Events | Total | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **3.1.2 CLORHEXIDINA EN GEL AL 0.12%** | | | | | | |
| Jesudasan et al., 2015 | 2 | 90 | 9 | 90 | 6.0% | 0.20 [0.04, 0.97] |
| Qureshhi et al., 2018 | 2 | 30 | 7 | 30 | 5.4% | 0.23 [0.04, 1.24] |
| Requena-Calla et al., 2016 | 0 | 20 | 1 | 20 | 1.7% | 0.32 [0.01, 8.26] |
| SubTotal (95% CI) | | 140 | | 140 | 13.2% | 0.23 [0.08, 0.67] |
| Total events | 4 | | 152 | | | |

Heterogeneity: Tau$^2$ = 0.00; Chi$^2$=0.06, df=2 (p=0.97); p=0%
Test for overall effects Z=2.70 (p=0.007)

| | Events | Total | Events | Total | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Total (95% CI) | | 888 | | 851 | 100.0% | 0.40 [0.26, 0.63] |
| Total events | 87 | | 169 | | | |

Heterogeneity: Tau$^2$ = 0.22 ; Chi$^2$=18.31, df=10 (p=0.05); p=45%
Test for overall effects: Z=4.04 (p=0.0001)
Test for subgroup differences: Chi$^2$=1.13. df=17 (p=0.29); I$^2$=11.3%

**Table 1.** Characteristic of included studies.

| Author | Year | Type of study | Number of Patients (male/female) | Mean age in years (range) | Follow-up time | Country | Study groups | Number of Patients per group | Teeth | Postoperative medication | No. of AO / No. of cases | Success rate (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Jadhao et al.[10] | 2018 | RCT | 48 (26-22) | 24.5 (24-31) | 1 week | India | Saline solution | 16 | Impacted | Amoxiclav 625mg every 12 hrs | 2/16 | 87.5 |
| | | | | | | | CHX 0.02% | 16 | mandibular | Paracetamol 500mg every 4 to 6 hrs | 1/16 | 93.75 |
| | | | | | | | Povidone-iodine 0.5% | 16 | third molars | Rantac 150 mg every 12 hrs for 7 days | 3/16 | 81.25 |
| Halabi et al.[11] | 2018 | RCT | 744 (363/381) | 43.43 (> 18) | 1 week | Chile | Sterile water | 372 | Maxillary and mandibular | NR | 27/372 | 92.74 |
| | | | | | | | CHX 0.12% | 372 | | | 10/372 | 97.31 |
| Eshghpour et al.[12] | 2018 | RCT | 241 (99/142) | 24.34 (18-35) | 1 week | Iran | Platelet-rich fibrin | 118 | Impacted mandibular third molars | Amoxicillin 500mg every 8 hrs for 7 days | 41/236 | 82.63 |
| | | | | | | | CHX 0.2% gel + PRF | 123 | | Paracetamol 500 mg every 8 hrs for a max. of 3 days | 32/246 | 86.99 |
| Cho et al.[13] | 2018 | RCT | 95 (53/42) | 35.5 (18-76) | 1 week | Australia | CHX 0.02% (irrigation) | 48 | Impacted mandibular third molars | Paracetamol + codeine (500/15mg) every 4 to 6 hrs | 4/47 | 91.49 |
| | | | | | | | CHX 0.02% (mouthwash) | 30 | | Ibuprofen 200mg every 4 to 6 hrs | 16/48 | 66.67 |
| Quresshi et al.[14] | 2018 | RCT | 60 (39/21) | 22 (>18) | 1 week | Pakistan | CHX 0.12% gel | 30 | Impacted mandibular third molars | Amoxicillin 500mg every 8 hrs | 2/30 | 93.3 |
| | | | | | | | Control | | | Ibuprofen 200mg every 4 to 6 hrs | 7/30 | 76.7 |
| Osunde et al.[15] | 2017 | RCT | 100 (46/54) | 29.8 (18-45) | 1 week | Nigeria | Hot saline solution | 50 | Mandibular third molars | Amoxicillin 500 mg every 8 hrs for 5 days; Metronidazole 200mg every 8 hrs | 2/50 | 97 |
| | | | | | | | CHX 0.12% | 50 | | Naproxen Sodium 550 mg every 12 hours for 5 days | 1/50 | 98 |
| Kaur et al.[16] | 2017 | RCT | 150 (86/64) | 30.5 (20-45) | 1 week | India | Metronidazole + CHX 0.2% gel | 150 | Mandibular third molars | Aceclofenac + serratio-peptidase every 12 hrs for 3 days | 10/150 | 93.33 |
| | | | | | | | Control | 150 | | | 34/150 | 77.33 |
| Choubarga et al.[17] | 2017 | RCT | 220 (98/122) | 31.12 (18-58) | 1 week | India | Warm saline solution | 110 | Impacted mandibular third molars | Amoxicillin 500mg, Metronidazole 400mg | 26/110 | 74 |
| | | | | | | | CHX 0.12% | 110 | | Aceclofenac every 8 hrs for 5 days | 17/110 | 84.54 |
| Gopee et al.[18] | 2017 | RCT | 100 (48/52) | 27.75 (18-50) | 1 week | South Africa | CHX 0.2% | 50 | Mandibular third molars | Paracetamol + 1g codeine | 3/50 | 94 |
| | | | | | | | Control | 50 | | 400mg ibuprofen | 2/50 | 96 |
| Requena-Calla et al.1[19] | 2016 (23/17) | RCT | 40 | 22.98 (16-40) | 5 days | Peru | CHX 0.12% gel | 20 | Mandibular third molars | Celecoxib 200 mg, Paracetamol 500 mg and Amoxicillin 500 m. | 0/20 | 100 |
| | | | | | | | Control | 20 | | Some patients needed parenteral medication (Ketoprofen 100 mg and Dexamethasone 4 mg) | 1/20 | 95 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Jesudasan et al.[20] | 2015 | RCT | 270 (160/110) | 28.33 | 1 week | India | Control | 90 | Impacted mandibular third molars | Metronidazole 400mg every 8 hrs for 3 days | 9/90 | 90 |
| | | | | | | | CHX 0.12% gel | 90 | | Zerodol every | 2/90 | 97.78 |
| | | | | | | | Eugenol | 90 | | 12 hrs for 3 days | 0/90 | 100 |
| Freudenthal et al.[21] | 2015 | RCT | 95 (19–65) | 33.5 | 1 week | Sweden | CHX 0.2% gel | 48 | Mandibular third molars | Alvedon (paracetamol 1g) | 11/48 | 77.08 |
| | | | | | | | Control | 48 | | Citodon (paracetamol + 500mg/codeine 5mg) for 7 days | 9/47 | 80.85 |
| Rubio-Palau et al.[22] | 2015 | RCT | 160 (74/86) | 25.04 | 1 week/ 1 day | Spain | CHX 0.2% gel | 80 | Impacted mandibular third molars | Diclofenac 50 mg every 8 hrs alternating with metamizole 575mg every 8 hrs | 14/80 | 82.5 |
| | | | | | | | Control | 80 | | omeprazole 20 mg every 24 hrs | 18/80 | 77.5 |
| Inamdar et al.[23] | 2015 | RCT | 30 (17/13) | 32.02 (18-60) | 1 week | India | Control | 10 | Impacted mandibular third molars | Diclofenac 50mg every 8hrs | 2/10 | 80 |
| | | | | | | | CHX 0.2% gel | 10 | | | 1/10 | 90 |
| | | | | | | | Ornidazol gel | 10 | | | 0/10 | 100 |
| Shahakbari et al.[24] | 2015 | RCT | 40 (12/28) | 21.12 (18-35) | 1 week | Iran | CHX 0.1% gel | 40 | Impacted mandibular third molars | Acetaminophen, 500mg every 8 hrs in case of pain | 4/40 | 90 |
| | | | | | | | CHX 0.2% gel | 40 | | | 5/40 | 87.5 |
| Khan et al.[25] | 2015 | RCT | 253 (102/151) | 36.65 (18-65) | 3 days | Pakistan | CHX 0.2% gel | 128 | Mandibular and mandibular molars | NR | 7/128 | 94.5 |
| | | | | | | | Control | 125 | | | 23/102 | 77.45 |
| Abu -Mostafa et al.[26] | 2015 | RCT | 301 (236/65) | NR | 1 week | Saudi Arabia | CHX 0.2% gel | 160 | Maxillary and mandibular molars | Ibuprofen 600mg every 8 hrs for 3 days | 23/160 | 85.63 |
| | | | | | | | CHX 0.12% | 141 | | | 25/141 | 82.27 |
| Haraji et al.[27] | 2014 | RCT | 45 (24/21) | 22.1 (17-31) | 3 days | Iran | CHX 0.2% gel | 45 | Impacted mandibular third molars | NR | 6/45 | 86.67 |
| | | | | | | | Control | 45 | | | 16/45 | 64.44 |
| Shaban et al.[28] | 2014 | RCT | 41 (14/27) | 24.15 (18-35) | 1 week | Iran | CHX 0.2% gel | 41 | Impacted mandibular third molars | Amoxicillin 500mg Acetaminophen 500mg every 8 hrs for 7 days | 2/41 | 95.12 |
| | | | | | | | Control | 41 | | | 9/41 | 78.05 |
| Ahmedi et al.[29] | 2014 | RCT | 25 | 18-30 | 1 week | Republic of Kosovo | CHX 1% gel | 25 | Impacted mandibular third molars | Ibuprofen 400mg every 8 hrs in case of pain | 1/25 | 96 |
| | | | | | | | Saline solution | 25 | | | 7/25 | 72 |
| Younus et al.[30] | 2014 | RCT | 100 (60/40) | 23.16 (17-32) | 1 week | Pakistan | CHX 0.2% gel | 50 | Impacted mandibular third molars | Flurbiprofen 100mg for 3 days | 3/50 | 94 |
| | | | | | | | CHX 0.2% | 50 | | | 9/50 | 82 |
| Sánchez et al.[31] | 2014 | RCT | 102 | NR | 1 week | Peru | CHX 0.12% | 51 | Third mandibular molars | Paracetamol 500mg every 8 hrs for 3 days | 9/51 | 82.35 |
| | | | | | | | Hydrogen peroxide 1.5% | 51 | | | 15/51 | 70.59 |

was a very significant difference (*p*<0.0001; mean diffe-rence=0.40; 95% confidence interval=0.26, 0.63; random effects model; I²=45%), favoring the use of chlorhexidine as a intra-alveolar gel for AO prevention. (Figure 5)

### Subgroup analysis

Revealed that, in 8 studies,[12,16, 21-23,25,27,28] that applied 0.2% chlorhexidine as an intra-alveolar gel, there was a

significant difference (*p*=0.001; mean difference=0.43; 95% confidence interval=0.26, 0.72; random effects model; I²=58%), favoring the use of 0.2% chlorhexidine as intra-alveolar gel for AO prevention.

Three studies[14,19,20] revealed that when using 0.12% chlorhexidine intra-alveolar gel there was a significant difference (*p*=0.07; mean difference=0.23; 95% confidence

interval=0.08, 0.67; random effects model; $I^2$=0%), favoring the use of 0.12% chlorhexidine as a intra-alveolar gel for AO prevention. (Figure 5)

## DISCUSSION.

After extracting permanent teeth, AO incidence is high, severely affecting patients' health; therefore, having an effective prevention method is important.[2,3]

Multiple studies have recommended the use of CHX in gel form, mouthwash or as an irrigant to prevent AO. This is because CHX is an effective antiseptic against aerobic and anaerobic bacteria, both Gram positive and Gram negative, and against yeasts. Furthermore, it can have high affinity with the microorganisms' cellular wall and change the surface structures, altering their permeability and resulting in the precipitation of proteins and nucleic acids.[2,3] Therefore, this systematic review and meta-analysis is carried out based on primary studies in order to explicitly assess whether CHX is effective in reducing AO incidence in patients undergoing permanent tooth extractions.

Results showed that using 0.02% CHX as an intra-alveolar irrigant, 0.12% CHX as post-orthodontic mouthwash and CHX gel (0.2% and 0.12%) significantly decreased AO incidence in patients undergoing permanent tooth extractions, compared with the control treatment. However, it is not yet possible to conclude which form of CHX is most effective for AO prevention.

The application of CHX gel has longer-lasting pharmacological efficacy compared to CHX in mouthwash form, as it does not depend on patient's compliance and no side effects were observed when applying CHX gel.[3] In the present study it was not possible to determine which of these two methods is more effective due to lack of information, as only one study[26] described a comparison between these two forms of CHX and their application, and their success rates regarding OA prevention were very similar (85.63% for 0.2% CHX gel and 82.27% for 0.12% CHX as mouthwash). Consequently, this was not included in the meta-analysis.

A comparison was made regarding whether the application of 0.2% CHX gel has advantages over using 0.2% CHX as an intra-alveolar irrigant for AO prevention, based on one study[30] that assessed this comparison. Since there was limited information available, it was not possible

to determine which method is most effective, although a noticeable difference between both methods in terms of their success rate is observed (94% for 0.2% CHX gel and 82% for 0.2% CHX as an intra-alveolar irrigant).

Furthermore, it was also not possible to determine whether the application of 0.2% CHX mouthwash has advantages over using intra-alveolar antibiotics for AO prevention, because only one study[18] reported this comparison. However, a minor difference between both methods is observed in terms of their success rate (94% for 0.2% CHX mouthwash and 96% for the use of intra-alveolar antibiotics).

In addition, the application of 1%[29] and 0.1%[24] CHX gel, ornidazole gel[23] and intra-alveolar eugenol[20] was observed, obtaining favorable results for AO prevention. However, due to the lack of studies analyzing this, a conclusion on whether these methods are more effective than applying 0.2% CHX gel could not be drawn.

Heterogeneity among the studies was zero ($I^2$=0) for 0.02% CHX as an intra-alveolar irrigant and for 0.12% CHX mouthwash, while it was moderate for CHX gel ($I^2$=45%). Regarding the latter, the variation in results among the studies may be due to differences in the selection criteria for patients, such as: age, smoking habits, extracted teeth and the postoperative medication administered.

Regarding age, it is known that the risk of suffering AO is higher in elderly patients. As for smoking, it is widely known it can interrupt the formation of blood clots by decreasing vascularization and bleeding potential, consequently increasing the risk of developing AO. In relation to which tooth is extracted, it is known that there is an increased risk of suffering AO in extracted posterior and mandibular teeth. Regarding postoperative medication, it is well known that the use of antibiotics does not reduce the risk of developing AO.[1-7]

One of the strengths of the present systematic review was the selection of studies, as a comprehensive search was carried out in the most important databases and rigorous inclusion criteria were used. Although this analytical process was carried out with care, there were some limitations in the meta-analysis: first of all, the inclusion and exclusion criteria were inconsistent for factors such as age-gender composition and the degree of difficulty of the dental extraction; secondly, the diagnostic criteria for

AO were not the same, possibly because these have been updated in recent years; thirdly, the sample size of some of the studies included in this meta-analysis was limited; and fourthly, the inclusion of studies with a high risk of bias.

According to the information provided above, it is not advisable to generalize the results of the present study. For this reason, conducting randomized controlled trials of a higher quality and scale is recommended in order to obtain more valid conclusions where the inclusion and exclusion criteria, as well as the AO diagnostic standards, are more accurate. In addition, as some of the included studies described other methods for AO prevention, these interventions were evaluated individually and there is insufficient evidence to confirm their effectiveness. Therefore, more studies that assess the role of these interventions and compare them with the efficacy of CHX in all its forms are required, in order to provide adequate suggestions to prevent the development of AO after permanent teeth are extracted.

## CONCLUSION.

The use of chlorhexidine is effective in preventing AO, however, more studies that compare the efficacy of chlorhexidine gel with chlorhexidine as an irrigant or as mouthwash are needed.

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