

SYSTEMATIC REVIEW

Bioadhesive chlorhexidine gel for reduction of alveolar osteitis incidence: Systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Introduction: Alveolar osteitis (AO) creates severe and self-limiting pain, which needs to be treated with several postoperative visits, leading to increases in patient's morbidity and costs. Hence, the most basic and best treatment could be prevention. The aim of this study was to investigate the efficacy of bioadhesive chlorhexidine (CHX) gel in reducing AO occurrence with published studies. **Materials and Methods:** Medline/PubMed, Scopus, EBSCO, Ovid and Cochrane central registry for control trial were searched up to 28 February 2014 using "alveolar osteitis" and "chlorhexidine" as key words for systematic review and meta-analysis. Inclusion criteria were prospective and randomized controlled trials (RCTs) published on this topic. From the chosen studies, the eligible articles were reviewed. Data were analyzed using Review Manager 5.2 software. **Results:** Out of 43 studies, seven eligible trials with 593 participants were selected. Bioadhesive 0.2% CHX gel prevented approximately 72% of AO (Odd ratio (OR) = 0.28, 95% confidence Interval (CI): 0.18-0.44; $P < 0.001$). **Conclusion:** Bioadhesive 0.2% CHX gel may be effective as a post-medication to reduce incidence of AO.

Key words: Alveolar osteitis, chlorhexidine, systematic review

Introduction

Alveolar osteitis (AO) known as dry socket and is identified as a severe pain in or around the site of an extracted tooth, intensifying any time between the first and third postoperative days, accompanying with partial or total blood clot loss in the alveolar socket.^[1] AO is a common complication following surgical removal of impacted mandibular third molar (up to 30%) and extraction of any other teeth (up to 70%).^[2-6] This is a

multifactorial condition and the exact causative agent is not clear; however, fibrinolytic cascade and bacterial factors have been reported as the main ones.^[1,7]

AO leads to severe pain, which needs several postoperative visits to be treated, leading to increase in patient's morbidity and costs. Owing to the proposed microbial origin, prevention of AO has focused on systemic and topical antimicrobial therapies.

Chlorhexidine (CHX), povidone iodine, 9-aminoacridine, metronidazole, tetracycline, and clindamycin in both systemic and localized regimens have been utilized as preventatives with varying degrees of success.^[1,6,8] Of them, the most extensively tested therapy was CHX due to its broad spectrum of activity versus oral aerobes and anaerobes, general tolerability, and absence of resistance development.^[9,10] On the contrary, a number of authors found it ineffective.^[7,11,12]

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The introduction of bioadhesive CHX gel turned lights on a new line of investigation.^[13-15] The gel could be more effective than mouthwash because when positioned intra-alveolar provides more bioavailability and prolonged release of the active substance and also can act directly on the alveolus.^[14-16]

Several studies regarding local interventions, especially, the use of CHX for prevention of AO have been performed, but no one has focused particularly on bioadhesive CHX gel.^[7,11,12,17] On the other hand, it has been reported that short-term use of CHX mouthwash can cause some adverse effects such as an irritation or a burning sensation in oral mucosa and also discoloration of teeth or mucosa.^[18,19] It seems that CHX gel due to the local placement within the alveolar socket and a single-dose administration may alleviate such adverse effects.

The aim of present study was to systematically review pervious randomized controlled trials (RCTs) on the efficacy of bioadhesive CHX gel in reducing of AO occurrence.

Materials and Methods

Search strategy

Electronic searches were performed using “alveolar osteitis” and “chlorhexidine” as key words for title and abstract in medical subject headings (MeSH) word search. References of each article were also reviewed.

Electronic databases

This review study has been searched up to 28 February 2014 in Medline/PubMed, Scopus, EBSCO, Ovid and Cochrane central registry for controlled trial by searching mentioned key words. A total of 43 studies were found. PubMed query translation was “dry socket” [MeSH] or “alveolar osteitis” [MeSH], and “chlorhexidine” [MeSH]. The search through Medline and Cochrane central register for control trial listed out 37 and 17 articles, respectively, which all overlapped with the results found in PubMed.

Inclusion/exclusion criteria

Inclusion criteria were limited to the journal articles in prospective RCTs in English language. Articles were excluded if they did not fulfill one or all of the inclusion criteria, if no control group (e.g. placebo (any material different from CHX gel), rinse, and no intervention) was used, and if the outcome of interest was other than incidence of AO.

Outcome measurement

The outcome measure was set on incidence of AO.

Data extraction

For data extraction, we designed a check list, regarding AO and CHX gel including author, year, country, sample size, study design, and main outcomes of each study [Table 1]. Two authors [Mahmood Reza Kalantar Motamedi and Saber Khazaei], who were not blinded, performed all searches and review procedures from the beginning to the end, independently. In the case of disagreement between evaluators, it reassessed by discussion and a final consensus was agreed on. Figure 1 provides information on the number of papers identified through the search strategy. Moreover, cross-references were screened to identify further trials that probably were missed through the search strategy. However, no additional trials were found.

Data analysis

The data were analyzed using review manager software (version 5.2). Inverse-variance weighting was implemented to calculate the random effect summary estimates and to produce a forest plot using the number of participants with events and total number of participants in experimental and control groups of each study.

Results

Out of initial 43 articles, seven letters to the editor (comments on previous studies), nine reviews, nine studies due to lacking relevance to the subject, and 10 articles because they had evaluated CHX rinse

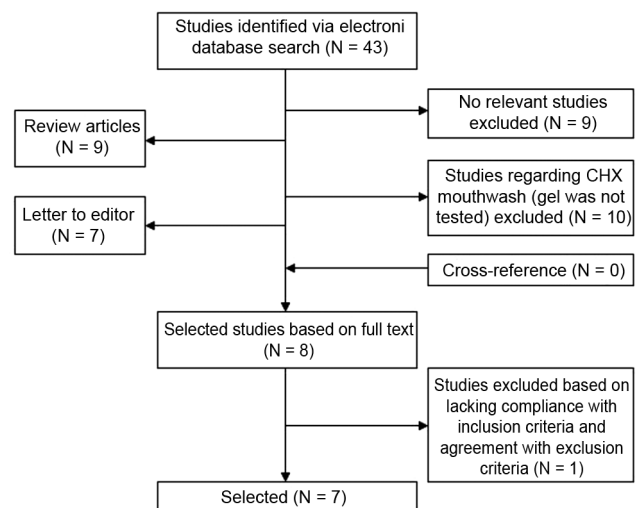


Figure 1: Flow chart of the article selection

Table 1: Characteristics of selected studies

First author/ year	Country	Study type	Experimental material	Control material	Outcome		Patient/Socket		Tooth type
					Aspect	Definition	Experimental	Control	
Hita-Iglesias/2008 ¹	Spain	Non-blind, parallel group, RCT	0.2% CHX gel placed in the socket twice a day during the first postoperative week	0.12% CHX rinse placed in the socket twice a day during the first postoperative week	Incidence of AO in the third and seventh postoperative days	Blum's criteria	N=41 patients, 14 males (34.2%); Mean age: 28; AO: Three (7.5%); smokers: 16 (39.9%); contraceptives: Six (14.6%); analgesics: Yes; antibiotics: Yes	N=32 patients, five males (15.6%); Mean age: 26; AO: Eight (25%); smokers: 10 (31.3%); contraceptives: Two (6.3%); Analgesics: Yes; antibiotics: Yes	Impacted mandibular third molar
Torres-Lagares/2006	Spain	Double-blind, parallel group, RCT	0.2% CHX gel placed in the socket immediately following extraction	Placebo gel	Incidence of postoperative AO	Blum's criteria	N=53 patients, 20 males (37.7%); Mean age: 27.8; SD (8.4); AO: six (11%); smokers: 12 (22.6%); contraceptives: Seven (13.2%); analgesics: Yes; antibiotics: No	N=50 patients, 14 males (28%); Mean age: 25.7; SD (8.6); AO: 15 (30%); smokers: 14 (28%); contraceptives: Three (6%); analgesics: Yes; antibiotics: No	Impacted mandibular third molar
Torres-Lagares/2010	Spain	Double-blind, parallel group, RCT	0.2% CHX gel placed in the socket immediately following extraction	Placebo gel	Incidence of postoperative AO	Blum's criteria	N=14 patients, 11 males (78.6%); Mean age: 32.5; SD (16.67); AO: One (7%); smokers: Four (28.5); contraceptives: No; analgesics: Yes; antibiotics: No	N=24 patients, 22 males (91.6%); Mean age: 32; SD (11.90); AO: Four (17%); smokers: 12 (50%); contraceptives: No; analgesics: Yes; antibiotics: No	Impacted mandibular third molar
Torres-Lagares/2006	Spain	Single-blind, parallel group, RCT	0.2% CHX gel placed in the socket twice a day during the first post-operative week	No intervention	Incidence of postoperative AO	Blum's criteria	N=17 patients, five males (29.4%); Mean age: 29; SD (10.24); AO: Three (17.64%); smokers: No; contraceptives: No; analgesics: No; antibiotics: Yes	N=13 patients, four males (30.7%); Mean age 26.3; SD (5.96); AO: Four (13.76%); smokers: No; contraceptives: No; analgesics: No; antibiotics: Yes	Impacted mandibular third molar
Haraji/2013	Iran	Double-blind, Split-mouth, RCT	0.2% CHX gel placed in the socket immediately following extraction	Placebo gel	Incidence of AO in the third postoperative day	Blum's criteria	N=45 sockets; AO: Six (6.67%); analgesics: No; antibiotics: No	N=45 sockets; AO: 16 (17.8%); analgesics: No; antibiotics: No	Impacted mandibular third molar
Haraji/2013	Iran	Double-blind, Split-mouth, RCT	0.2% CHX gel placed in the socket immediately following extraction	Placebo gel	Incidence of AO in the first or third postoperative days	Blum's criteria	N=80 sockets; AO: Nine (11.3%); analgesics: No; antibiotics: No	N=80 sockets; AO: 26 (32.5%); analgesics: No; antibiotics: No	Impacted mandibular third molar
Babar/2012	Pakistan	Non-blind, parallel-group, RCT	0.2% CHX gel placed in the socket immediately following extraction	Placebo gel	Incidence of AO in the 1-3 postoperative days	Blum's criteria	N=50 patients, 38 males (76%); AO: Four (8%); smokers: no; Contraceptives: Not mentioned; analgesics: Yes; antibiotics: No	N=50 patients, 27 males (54%); AO: 14 (28%); smokers: No; contraceptives: Not mentioned; analgesics: Yes; antibiotics: No	Impacted mandibular third molar

Note: In the studies of Haraji *et al.*, owing to the use of a split-mouth design, the variables such as gender, age, contraceptives ingestion, and smoking were equal in the experimental and control groups. Baber *et al.*, did not mention the mean age of control and experimental groups; CHX = Chlorhexidine, AO = Alveolar osteitis, RCT = Randomized controlled trial, SD = Standard deviation;

(CHX gel was not tested) were excluded. Among eight remained articles, the full texts were obtained, and they were considered based on compliance with exclusion/inclusion criteria. Finally, seven RCTs^[13-16,20-22] fully met the criteria for detailed analysis. The reasons for excluding the one study was that Rodríguez-Pérez *et al.*, did not used any placebo gel, in fact, they compared two different amounts of CHX gel (1 and 0.2%) without using another control group using some materials different from CHX gel.^[23]

CHX (0.2% concentrations) after surgery prevented 72% of AO (OR = 0.28, 95% confidence interval (CI): 0.18-0.44; $P < 0.001$) (seven trials, 593 participants) [Figure 2]. Also, the prevalence of dry socket varied from 6.67 to 32.5% in surgically extracted third molars. Out of the selected RCTs, two studies had a split-mouth design and five did not have. Four and two trials were performed in Spain and Iran, respectively, with same study authors [Table 1].

Discussion

This meta-analysis study was carried out to review and study the efficacy of bioadhesive CHX gel compared with placebo used to reduce the incidence of AO in patients who were candidate for bilateral tooth extractions. Considering this searching strategy, seven articles met the criteria for final evaluation. Based on these studies, a single-dose administration of 0.2% bioadhesive CHX gel reduces the incidence of AO.

Several factors can increase the risk of AO incidence such as tobacco smoking,^[7,24,25] drinking,^[26] herpes,^[26]

level of tooth impaction,^[1,26] periodontal problems,^[1,27] poor oral hygiene,^[7,28,29] surgical site,^[24,30] preoperative infection,^[24,31] aging,^[25,29] female gender,^[24,25,32] use of local anesthesia with a vasoconstrictor,^[24,33] ingestion of oral contraceptives,^[1,25,34] traumatic exodontias,^[25,26] and lack of experience in the surgeon.^[3,7,24,25] However, the results are controversial^[25] and statistical analyses are mostly inadequate as only a few studies have conducted multivariable analyses.^[7,27,35,36] In a great number of previous studies, such risk factors were included. Therefore, when evaluating the role of CHX in reducing AO incidence, these risk factors can serve as confounding variables. Most of the selected studies included analgesic and antibiotic medications, contraceptive pills, and smoker patients.^[13-16,22] In two included trials with split-mouth design,^[20,21] the main risk factors comprised smoking and receiving contraceptives; however, due to the use of split-mouth design, the role of confounding variables might be controlled. Haraji *et al.*,^[20,21] were in this opinion as well, which stated due to the split-mouth design, the variables gender, age, receiving contraceptives, different oral hygiene, and smoking were equal in the treatment and control groups.

It is worth mentioning, Haraji *et al.*,^[20,21] extracted the teeth with similar surgery difficulty index in both sides of a mouth. This may lead to a further accurate and calibrated split-mouth evaluation. However, of the Haraji's *et al.*,^[20,21] limitations, although most of confounders were limited in their studies, enrolling only patients who could tolerate postoperative pain without analgesic consumption might be questionable, as the results might not be generalizable to the routine clinical practice.

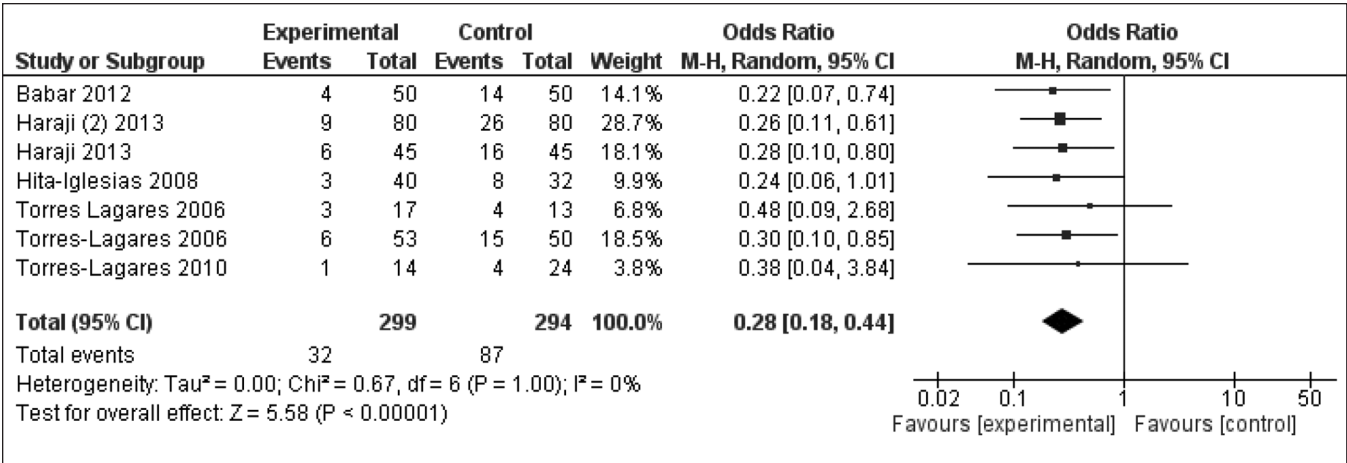


Figure 2: Forest plot of comparison between CHX gel versus placebo; CHX = Chlorhexidine; M-H = Mantel-Haenszel, 95% CI: 95% confidence interval, df: degree of freedom

A proposed responsible factor regarding incidence of AO was microbial agents that may contribute to fibrinolysis and consequent blood clot disintegration.^[1] Several studies have focused on reducing the incidence of AO by decreasing bacterial count in oral cavity.^[7] Therefore, the fact that CHX can reduce the frequency of AO might be due to its broad spectrum of activity versus oral aerobes and anaerobes.^[9,10]

A limitation of our study was that only relevant studies in PubMed/Medline, Scopus, EBSCO, Ovid and Cochrane library were searched. The authors suggest for future surveys to utilize split-mouth design with a more control on included AO risk factors.

In conclusion, bioadhesive CHX gel can reduce incidence of AO.

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