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Local interventions for the management of alveolar osteitis (dry socket) (Review)

Daly B, Sharif MO, Newton T, Jones K, Worthington HV

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[Intervention Review]

Local interventions for the management of alveolar osteitis (dry socket)

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ABSTRACT

Background

Alveolar osteitis (dry socket) is a complication of dental extractions and occurs more commonly in extractions involving mandibular molar teeth. It is associated with severe pain developing 2 to 3 days postoperatively, a socket that may be partially or totally devoid of blood clot and in some patients there may be a complaint of halitosis. It can result in an increase in postoperative visits.

Objectives

To assess the effects of local interventions for the prevention and treatment of alveolar osteitis (dry socket) following tooth extraction.

Search methods

The following electronic databases were searched: the Cochrane Oral Health Group Trials Register (to 29 October 2012), the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2012, Issue 10), MEDLINE via OVID (1946 to 29 October 2012) and EMBASE via OVID (1980 to 29 October 2012). There were no restrictions regarding language or date of publication. We also searched the reference lists of articles and contacted experts and organisations to identify any further studies.

Selection criteria

We included randomised controlled trials of adults over 18 years of age who were having permanent teeth extracted or who had developed dry socket post-extraction. We included studies with any type of local intervention used for the prevention or treatment of dry socket, compared to a different local intervention, placebo or no treatment. We excluded studies reporting on systemic use of antibiotics or the use of surgical techniques for the management of dry socket because these interventions are evaluated in separate Cochrane reviews.

Data collection and analysis

Two review authors independently undertook risk of bias assessment and data extraction in duplicate for included studies using pre-designed proformas. Any reports of adverse events were recorded and summarised into a table when these were available. We contacted trial authors for further details where these were unclear. We followed The Cochrane Collaboration statistical guidelines and reported dichotomous outcomes as risk ratios (RR) and calculated 95% confidence intervals (CI) using random-effects models. For some of the split-mouth studies with sparse data it was not possible to calculate RR so we calculated the exact odds ratio instead. We used the GRADE tool to assess the quality of the body of evidence.

Main results

Twenty-one trials with 2570 participants met the inclusion criteria; 18 trials with 2376 participants for the prevention of dry socket and three studies with 194 participants for the treatment of dry socket. The risk of bias assessment identified six studies at high risk of bias, 14 studies at unclear risk of bias and one studies at low risk of bias. When compared to placebo, rinsing with chlorhexidine mouthrinses (0.12% and 0.2% concentrations) both before and after extraction(s) prevented approximately 42% of dry socket(s) with a RR of 0.58 (95% CI 0.43 to 0.78; P < 0.001) (four trials, 750 participants, moderate quality of evidence). The prevalence of dry socket varied from 1% to 5% in routine dental extractions to upwards of 30% in surgically extracted third molars. The number of patients needed to be treated with (0.12% and 0.2%) chlorhexidine rinse to prevent one patient having dry socket (NNT) was 232 (95% CI 176 to 417), 47 (95% CI 35 to 84) and 8 (95% CI 6 to 14) for control prevalences of dry socket of 1%, 5% and 30% respectively.

Compared to placebo, placing chlorhexidine gel (0.2%) after extractions prevented approximately 58% of dry socket(s) with a RR of 0.42 (95% CI 0.21 to 0.87; P = 0.02) (two trials, in 133 participants, moderate quality of evidence). The number of patients needed to be treated with chlorhexidine gel to prevent one patient having dry socket (NNT) was 173 (95% CI 127 to 770), 35 (95% CI 25 to 154) and 6 (95% CI 5 to 26) for control prevalences of dry socket of 1%, 5% and 30% respectively.

A further 10 intrasocket interventions to prevent dry socket were each evaluated in single studies, and therefore there is insufficient evidence to determine their effects. Five interventions for the treatment of dry socket were evaluated in a total of three studies providing insufficient evidence to determine their effects.

Authors' conclusions

Most tooth extractions are undertaken by dentists for a variety of reasons, however, all but three studies included in the present review included participants undergoing extraction of third molars, most of which were undertaken by oral surgeons. There is some evidence that rinsing with chlorhexidine (0.12% and 0.2%) or placing chlorhexidine gel (0.2%) in the sockets of extracted teeth, provides a benefit in preventing dry socket. There was insufficient evidence to determine the effects of the other 10 preventative interventions each evaluated in single studies. There was insufficient evidence to determine the effects of any of the interventions to treat dry socket. The present review found some evidence for the association of minor adverse reactions with use of 0.12%, 0.2% and 2% chlorhexidine mouthrinses, though most studies were not designed to detect the presence of hypersensitivity reactions to mouthwash as part of the study protocol. No adverse events were reported in relation to the use of 0.2% chlorhexidine gel placed directly into a socket (though previous allergy to chlorhexidine was an exclusion criterion in these trials). In view of recent reports in the UK of two cases of serious adverse events associated with irrigation of dry socket with chlorhexidine mouthrinse, it is recommended that all members of the dental team prescribing chlorhexidine products are aware of the potential for both minor and serious adverse side effects.

PLAIN LANGUAGE SUMMARY

What treatments can be used to prevent and treat alveolar osteitis (dry socket)?

Dry socket is a condition that sometimes arises when teeth have been extracted and is more likely to occur following extraction of wisdom teeth in the lower jaw. It is thought to be linked to the loss of some or all of the blood clot that forms at the bottom of a socket after a tooth is taken out, although other factors are probably also involved. Dry socket can be very painful for several days after an extraction and people with this condition can also experience bad breath. The condition can result in more visits to the dentist or dental hospital and other inconveniences such as time lost from work.

This review looked at existing research with the aim of assessing what treatments can be used to prevent and to treat alveolar osteitis (dry socket). The search for existing studies was done on 29 October 2012.

The review team identified 21 trials which met the inclusion criteria for this review: 18 trials (2376 participants) looking at different ways to prevent dry socket and three trials (194) on the treatment of dry socket.

The studies looked at adults over 18 years of age and included (amongst others) people who smoked and took oral contraceptives (both possible risk factors). However, studies involving people who were extremely ill or who had compromised immune systems were not included. Studies which looked at the use of antibiotics to manage dry socket were also not included.

Prevention

It was found that there is some evidence to show that rinsing both before and after tooth extraction with chlorhexidine gluconate rinse (at 0.12% and 0.2% strength) reduced the risk of having a dry socket. Placing chlorhexidine gel (0.2% strength) in the socket of an extracted tooth also reduced the risk of having dry socket.

The risk of developing dry socket depends on many factors, some of which are unknown. Your dentist or dental care professional (DCP) should be able to advise you of your own risk status.

To illustrate the effectiveness of chlorhexidine treatment as a preventive measure: if the risk of contracting alveolar osteitis (dry socket) was 1% (one in a hundred) then 232 people undergoing tooth extractions would need to be treated to prevent one case of dry socket; if the risk was 5%, then the number needed to be treated to prevent one case of dry socket would be 47; if the risk rises to 30%, the number needed to be treated to prevent one case of dry socket would be 8.

In these trials no serious side effects or reactions by patients due to chlorhexidine were reported. However, two serious events associated with the use of chlorhexidine mouthwash for irrigation of dry socket have been reported in the UK. If people have a history of allergies or have had adverse reactions previously to the use of chlorhexidine mouthwashes they should tell their dentist or DCP before using chlorhexidine. They should also tell their dentist or DCP if they experience any unusual symptoms such as rashes, itching or swelling of the lips whilst using chlorhexidine.

It is recommended that all members of the dental team prescribing chlorhexidine products are aware of the potential for both minor and serious side effects, are competent to manage a medical emergency associated with anaphylaxis (toxic shock) and warn patients of the potential for adverse events.

Treatment

There was insufficient evidence to conclude whether any treatments relieved established dry socket or not.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Chlorhexidine rinse for the management of dry socket

Patient or population: Patients with the management of dry socket
Intervention: Chlorhexidine rinse

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control[2]	Chlorhexidine rinse				
Presence of dry socket agreed diagnostic criteria. Follow-up: median 7 days	**Study population**		**RR 0.58** (0.43 to 0.78)	750 (4 studies)	⊕⊕⊕◯ **moderate**[1]	
	300 per 1000	**158 per 1000** (129 to 234)				
	Low					
	10 per 1000	**6 per 1000** (4 to 8)				
	Moderate					
	50 per 1000	**28 per 1000** (22 to 38)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Three trials were assessed as being at high risk of bias and one at unclear risk of bias.
[2] The assumed risk values were set to reflect prevalence rates for routine dental extractions (1% and 5%) and for extraction of mandibular third molars (30%).

BACKGROUND

Teeth are routinely extracted in general dental practice because they are affected by tooth decay or periodontal disease. In spite of the generalised overall improvements in oral health, it is estimated that European dentists in general dental practice extract up to seven teeth per week (McCaul 2001). Alveolar osteitis (dry socket) is a complication that may follow tooth extraction (Noroozi 2009). It tends to occur when the blood clot in an extraction socket is disrupted prematurely leaving bone unprotected and exposed to the oral environment. The socket may become packed with food and bacteria and breakdown products from these are said to lead to further dissolution of the blood clot (Blum 2002; Vezeau 2000). Dry socket typically presents as postoperative pain of increasing severity in and around the extraction site at 1 to 3 days after the extraction. The socket may be partially or totally devoid of a blood clot and the patient may also complain of halitosis (Blum 2002).

Aetiology and prevalence

Dry socket is a complication associated with 0.5% to 5% of routine extractions (Field 1988; Vezeau 2000), and is reported to occur more often after the extraction of mandibular molars, especially impacted wisdom teeth (1% to 37.5%) (Caso 2005; Fridrich 1990; Vezeau 2000). The aetiology of dry socket is not fully understood and a number of mechanisms and factors have been postulated that include: flap extent and design, surgical trauma, experience of the surgeon, perioperative patient stress factors and focal fibrinolytic activity (Caso 2005; Fazakerley 1991; Vezeau 2000). The focal fibrinolytic activity mechanisms were postulated to occur through plasminogen mediated fibrinolysis, non-plasminogen mediated fibrinolysis and leukocyte mediated fibrinolysis (Fazakerley 1991; Vezeau 2000). Women appear to be at higher risk from dry socket compared to men. A number of explanations for this gender difference in prevalence have been suggested e.g. changes that occur in the blood clotting mechanism during the menstrual cycle and the use of oral contraceptives (Garcia 2003; Muhonen 1997). The highest incidence of dry socket is reported in the fourth decade of life (Rood 1981; Rud 1970), but this figure may be artefactual in view of the increased likelihood of tooth loss in later life (Butler 1977). There is some evidence that people who have experienced dry sockets previously may be at greater risk to experiencing dry socket compared to those who have never had a dry socket (Reekie 2006).

Several reviews have suggested a causal relationship between the complexity of the dental extraction and the occurrence of dry socket (Blum 2002; Noroozi 2009; Vezeau 2000). Smoking is considered to be another factor that may increase the risk of developing dry socket after tooth extraction (Sweet 1978). Additional risk factors include: infection around the tooth to be extracted, inadequate oral hygiene (Tjernberg 1979), and poor after care (Noroozi 2009). There is very limited supportive evidence for some of the other reasons that may account for the loss of blood clot from a socket which include forceful spitting, sucking through a straw, coughing or sneezing (Bloomer 2012; Vezeau 2000). While bacterial breakdown and fibrinolysis is widely accepted as a major contributor to the loss of the blood clot, no studies have convincingly demonstrated an unequivocal bacterial cause for dry socket (Alexander 2000; Vezeau 2000).

Symptoms and diagnosis

Two of the key challenges when conducting this review were the multitude of terminologies used for dry socket and the classification of signs and symptoms that were accepted as determining the presence of dry socket. Dry socket was frequently conflated with an infected socket in some studies. A continuous throbbing pain that radiates to the ear, temple and neck is the most common symptom of dry socket (Swanson 1989). Classically, this starts 1 to 3 days post-extraction and may be accompanied by other signs and symptoms e.g. foul taste, bad breath, localised swelling and lymph-node involvement (Blum 2002; Noroozi 2009; Vezeau 2000). The symptoms can persist for up to 10 days after extraction and may include pain so severe that it is not relieved by even the strongest of analgesic medications (Vezeau 2000).

Clinical history and examination are the principal methods of reaching a diagnosis. The clinical picture is of an extraction socket that is visually devoid of a blood clot but other causative factors for severe postoperative pain should be excluded e.g. infected retained roots (Blum 2002; Kolokythas 2010).

Prevention

There have been a number of theories as to the aetiology of dry socket and a range of preventative agents have been advocated according to the prevailing theory of causation at the time including: plaque control, antiseptic rinses, preoperative systemic antibiotics and direct placement of medicaments into the socket (Caso 2005; Goldman 1973; Hall 1971; Hedstrom 2007; Kolokythas 2010; Noroozi 2009; Vezeau 2000). Several studies have reported that preoperative and postoperative antiseptic chlorhexidine rinses can be effective in reducing the incidence of dry socket (Berwick 1990; Hermesch 1998; Larsen 1991; Tjernberg 1979). Other studies have reported on the use of intrasocket antibiotic medicaments (Mitchell 1984; Reekie 2006; Torres-Lagares 2006; Trieger 1991; van Eeden 2006), and intrasocket antifibrinolytic agents (Gersel-Pedersen 1979; Ritzau 1977). Studies have also reported upon the use of flap design to minimise trauma and risk of dry socket (Bello 2011; Haraji 2010; Kirk 2007). The prophylactic use of systemic antibiotics is not generally advocated and there is a consensus that these measures should be reserved for individual patients reporting a history of multiple incidents of dry socket or for the immunocompromised patient (Epstein 2000; Fazakerley

1991). A recent Cochrane review concluded that there is moderate quality evidence that antibiotics may reduce the risk of dry socket by 38% (risk ratio (RR) 0.62; 95% confidence interval (CI) 0.41 to 0.95; P = 0.03) in pooled data of 1429 participants who had surgical removal of third molars (Lodi 2012). This should be balanced against the increased risk of mild and transient adverse events associated with prescribing antibiotics compared to placebo (RR 1.98; 95% CI 1.10 to 3.59; P = 0.02) (Lodi 2012).

Treatment

Forty-five percent of patients with dry socket require multiple postoperative visits, which could have significant consequences for the individual patient as well as societal costs including time off work (Nusair 2007; Vezeau 2000). Treatment options tend to focus on symptomatic relief, which may include the removal of debris from the socket by irrigation with saline or sterile local anaesthetic, and the use of analgesic medication (Blum 2002). Alternative options include the placement of intrasocket medicaments including antibacterials, topical anaesthetics and obtundents or combinations of all three (Blum 2002). These intrasocket medications include zinc oxide and eugenol impregnated cotton pellets (Bloomer 2000), alvogyl (eugenol, iodoform and butamen) (Kaya 2011), dentalone, bismuth subnitrate and iodoform paste (BIPP) on ribbon gauze and metronidazole and lidocaine ointment (Silva 2006). Some studies have also reported the use of lasers for the treatment of dry socket (Jovanovic 2011; Kaya 2011).

Why it is important to do this review

Dry socket is a complication of dental extractions that is associated with severe pain and can result in an increase in postoperative visits. Prevention of dry socket as well as the effective management of its sequelae can help in reducing postoperative morbidity for the individual as well as societal costs, for example, lost time from work and healthcare costs. A systematic review of the current best evidence for the effects of the available interventions could help to inform clinical decision making for the prevention and management of dry socket.

This systematic review will summarise the evidence of local interventions for the management of dry socket. Another Cochrane review summarises the evidence of the effects of systemic antibiotics prescribed to prevent infectious complications following tooth extraction which includes dry socket as one of the primary outcomes (Lodi 2012). A further ongoing Cochrane review will evaluate the evidence for surgical techniques (such as surgical drains, wound irrigation and different flap designs) for the removal of mandibular wisdom teeth, which also includes dry socket as a primary outcome (Coulthard 2003). In order to avoid duplication this review evaluates other 'local' interventions for the prevention and treatment of dry socket.

OBJECTIVES

To assess the effects of local interventions used for the prevention and treatment of alveolar osteitis (dry socket).

METHODS

Criteria for considering studies for this review

Types of studies

We only considered randomised controlled trials (RCTs) for inclusion in this review. All studies included in this review utilised and reported explicit and validated criteria that were used in the diagnosis of dry socket. The diagnosis of dry socket was based on the Blum 2002 criteria i.e. a continuous throbbing pain starting 1 to 3 days post-extraction, a socket that may be partially or totally devoid of blood clot and which may be accompanied by other signs and symptoms such as foul taste, bad breath, localised swelling and lymph-node involvement.

Types of participants

We considered studies that included adults over the age of 18 years who had undergone an extraction (routine or more complex surgical) of one or more permanent teeth under local anaesthesia with or without sedation or under general anaesthesia. We included studies that included participants who were smokers. We excluded participants who were immunocompromised, had any co-morbidities or medical conditions that might influence the healing of oral tissues.

Types of interventions

We considered studies that included any type of local intervention used for the management of dry socket compared to a different local intervention, placebo or no treatment. We included studies that permitted the use of concomitant pain medication provided it was made available equally to both groups. We excluded studies that examined the effectiveness of local interventions to prevent dry socket and then subsequently to treat dry sockets.

We excluded studies which reported upon the use of systemic antibiotics because these are covered in a separate Cochrane review (Lodi 2012). Likewise, we excluded studies evaluating the use of different surgical procedures (including drains and lavage volume) to manage dry socket because these interventions are part of another ongoing Cochrane review (Coulthard 2003)

Types of outcome measures

We considered studies that included outcome measures that were reported according to clinically important time-points i.e. at the end of the intervention and during a follow-up period of up to 2 weeks.

Primary outcomes

For prevention of dry socket.

1. Proportion of participants presenting with a dry socket within 1 week post-treatment.

For treatment of established dry socket.

1. Time to heal dry socket.
2. Pain: its severity and duration from time of administration of intervention to relief of pain assessed using any patient-reported validated pain scale.
3. Swelling: assessed using photography or digital morphometry.
4. Limitation of chewing or swallowing and time to resumption of normal feeding.
5. Fever.

Secondary outcomes

Secondary outcomes assessed were for the treatment of dry sockets.

1. Quality of life as assessed by a validated questionnaire.
2. Patient satisfaction assessed by any validated measure.
3. Costs.

Adverse effects

Any specific adverse effects related to any clinically diagnosed reactions to any of the active interventions were noted and reported as an additional table.

Search methods for identification of studies

Detailed search strategies for each database searched were developed to identify relevant trials. The search strategies were based on the search strategy developed for MEDLINE (OVID) but revised appropriately for each database. The search strategy used a combination of controlled vocabulary and free text terms and was linked with the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomised trials (RCTs) in MEDLINE: sensitivity maximising version (2008 revision) as referenced in Chapter 6.4.11.1 and detailed in box 6.4.c of the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011] (Higgins 2011). Details of the MEDLINE search are provided in Appendix 1. The search of EMBASE was linked to the Cochrane Oral Health Group filter for identifying RCTs.

Electronic searches

The following electronic databases were searched.

- The Cochrane Oral Health Group Trials Register (to 29 October 2012) (Appendix 2)
- The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, 2012, Issue 10) (Appendix 3)
- MEDLINE via OVID (1946 to 29 October 2012) (Appendix 1)
- EMBASE via OVID (1980 to 29 October 2012) (Appendix 4)

Language

There was no language restriction on included studies. Any non-English papers that were identified were translated and assessed for eligibility.

Searching other resources

Handsearching

We did not conduct any additional handsearching outside the Cochrane Collaboration's worldwide handsearching programme (see the Cochrane Master List of journals that have been searched). We examined the reference lists of any potential clinical trials to help identify additional studies not identified by the electronic searches.

Unpublished studies

To identify possible unpublished or ongoing studies, we contacted investigators of several included studies and other researchers, experts and organisations known in this field.

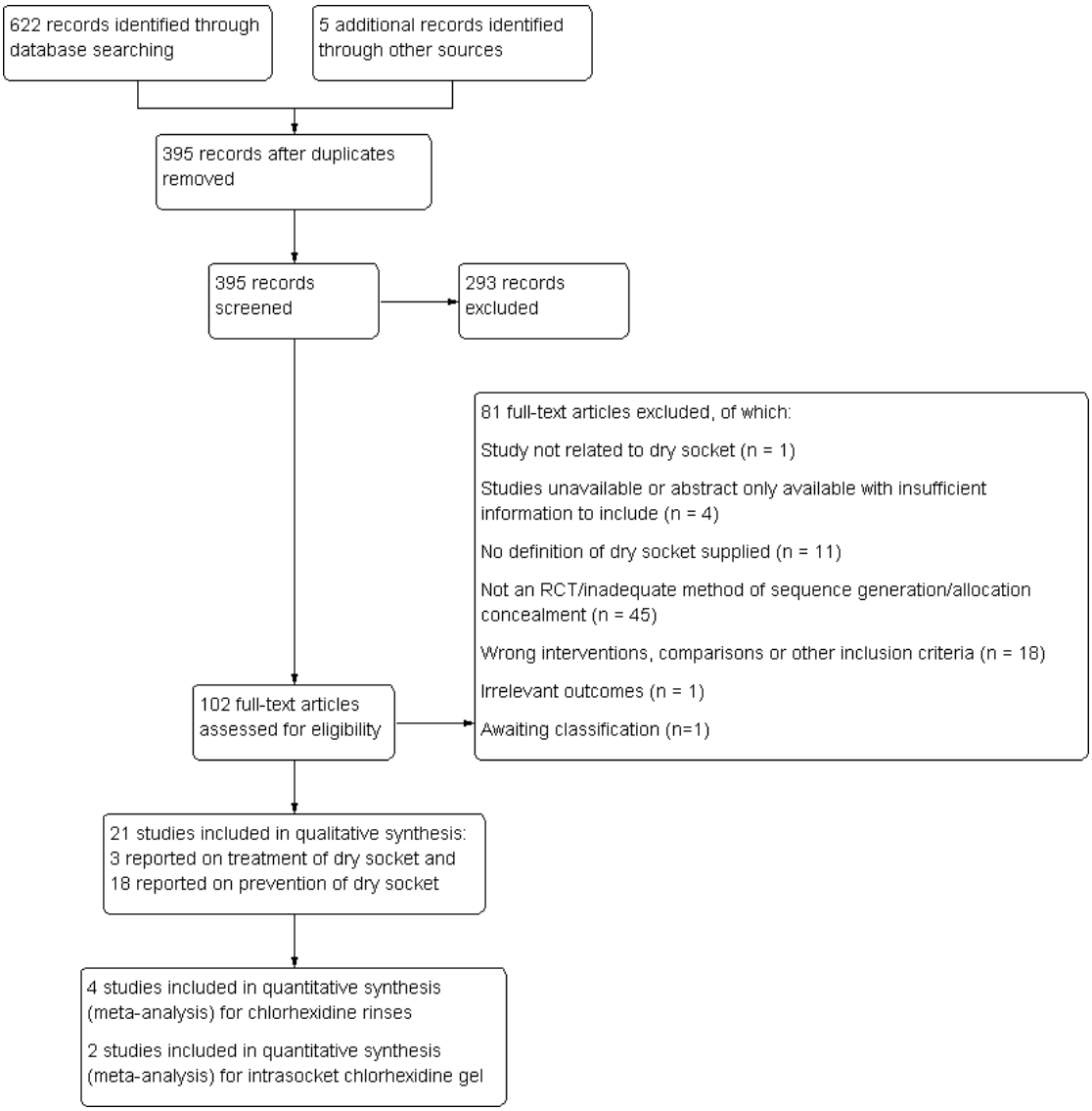
Data collection and analysis

Selection of studies

Two review authors independently assessed the abstracts of retrieved studies. We obtained full copies of studies deemed to be relevant, potentially relevant i.e. those appearing to meet the inclusion criteria, or for which there was insufficient information in the title and abstract to make a clear decision. Two review authors then assessed full text papers independently and any disagreements on the eligibility of included studies were resolved through discussion and consensus. If necessary, a third review author was consulted.

We excluded any studies that did not match the inclusion criteria at this stage or at subsequent stages and noted the reasons for exclusion in the 'Characteristics of excluded studies' table. Figure 1 presents the study flow diagram.

Figure 1. Study flow diagram.



Data extraction and management

Two review authors collected study details and outcomes data independently and in duplicate using a predetermined form designed for this purpose. These were entered into the 'Characteristics of included studies' table and outcome data were entered into additional tables or as forest plots in RevMan and any disagreements were discussed. Data were only included if there was an independently reached consensus. If necessary a third review author was consulted to resolve inconsistencies.

We extracted the following details.

1. Trial methods: (a) method of allocation; (b) masking of participants, operators and outcomes; (c) exclusion of participants after randomisation and proportion of losses at follow-up and number analysed.

2. Participants: (a) country of origin; (b) sample size and sample size calculation; (c) age; (d) gender; (e) inclusion and exclusion criteria.

3. Intervention and control: type and procedural information including dose, mode of local use, time of administration relative to extraction details of any other concomitant medication.

4. Outcomes: primary and secondary outcomes, methods of assessment and completeness of reporting as outlined in the Types of outcome measures section of this review.

If stated, we recorded the sources of funding of any of the included studies.

This information was used to help assess the clinical diversity and generalisability of any included trials.

Assessment of risk of bias in included studies

Studies identified for inclusion in this review were assessed independently by two review authors who graded them using the Cochrane risk of bias tool described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The independent evaluations were compared and discussed and any disagreements were resolved.

We assessed each trial for the following domains.

1. Sequence generation (selection bias)
2. Allocation concealment (selection bias)
3. Blinding of participants and personnel (performance bias)
4. Blinding of outcome assessors (performance bias)
5. Completeness of outcome data
6. Risk of selective outcome reporting
7. Risk of other bias

For each domain a description of what occurred as reported in the journal article was described and a judgement made on the risk of bias: high, unclear or low risk of bias. The judgement was determined using guidance as described in Chapter 8 of the Cochrane Handbook (Higgins 2011).

The assessments for each included study are reported in the corresponding section of the risk of bias tables in RevMan 5 (RevMan 2011).

Overall risk of bias

- Low risk of bias: all domains are judged to be at low risk of bias.
- Unclear risk of bias: one or more domains judged to be at unclear risk of bias.
- High risk of bias: one or more domains judged to be at high risk of bias.

Th overall risk of bias assessment was undertaken without blinding of review authors to the study authors' names or organisations, or the journal type. The independent evaluations were compared and discussed and any disagreements were resolved.

The results of the risk of bias assessment are presented graphically both by domain and by study (Figure 2; Figure 3).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

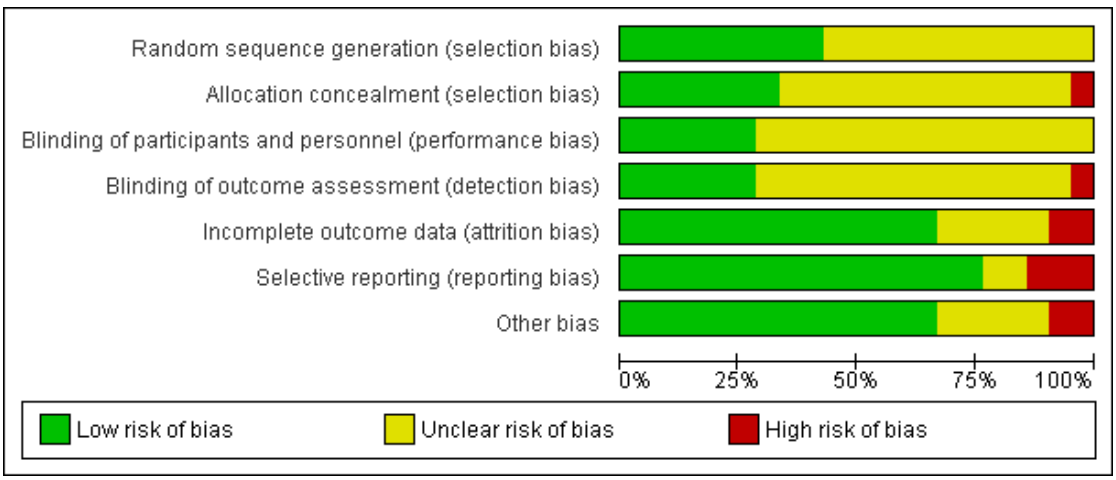
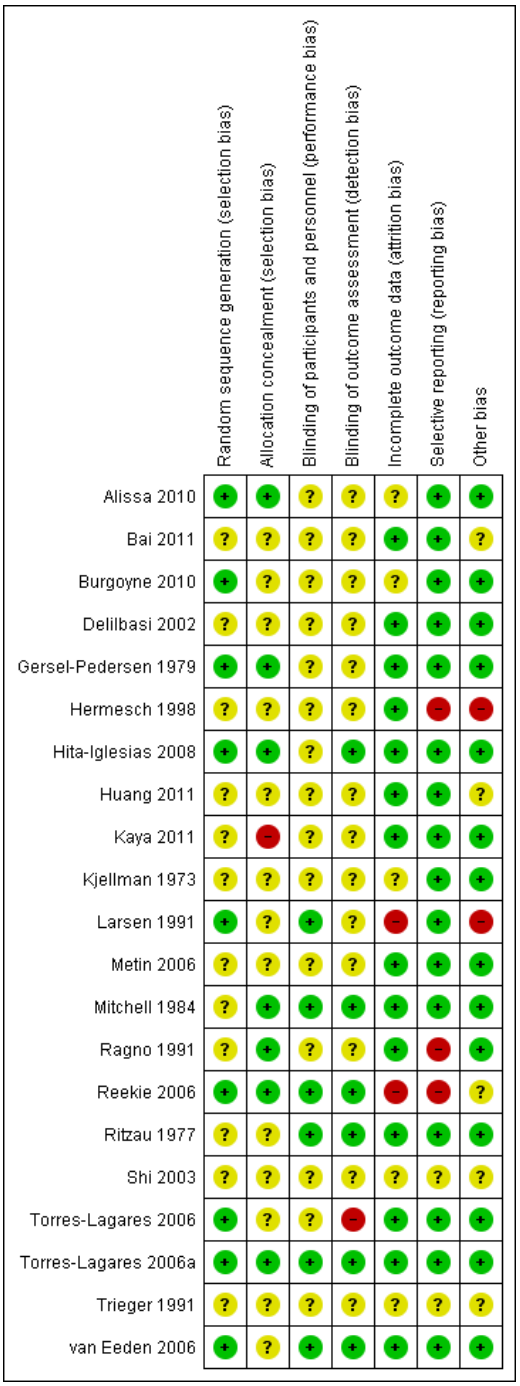


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Measures of treatment effect

The primary measure of intervention effect for the prevention of dry socket was the reduction in incidence of dry socket between the control and intervention groups i.e. proportion of participants presenting with a dry socket within 1 week post-treatment. For the treatment of dry socket the primary measure of intervention effect was the reduction in the time to heal of the socket and reduction in the incidence of pain, swelling, functional limitation (chewing, swallowing and time to resumption of normal feeding) and fever. Secondary measures of intervention effect for the prevention and treatment of dry socket were: quality of life, patient satisfaction and costs between the intervention group and the control.

For each intervention, we recorded data on each patient in both the control and intervention group who experienced the event and the total number of patients involved in both control and intervention arms.

For dichotomous data, we calculated the risk ratio (relative risk), which is the ratio of the risk of an event occurring in the experimental and control group, together with the 95% confidence interval. For the split-mouth studies with sparse data, the risk ratio could sometimes not be calculated, and we calculated the exact odds ratio instead. For continuous outcomes, we used the mean differences and 95% confidence intervals to summarise the data for each group where the mean difference and standard deviations were calculable from the data presented.

If we had identified any data obtained from visual analogue scales and any categorical outcomes we would have converted them into dichotomous data if appropriate prior to analysis.

Unit of analysis issues

The outcomes specified for this review necessitated repeated observations on the participants over a comparatively short period of time during and after the interventions. Therefore, depending on sufficient data being available, we grouped the outcomes and analysed them according to clinically important time-points; at the end of the intervention and during the follow-up period. We analysed the split-mouth studies using 'paired' methods such as those outlined in Elbourne 2002. We calculated risk ratios for the paired differences for whether the site had a dry socket or not, together with the appropriate standard errors and 95% confidence intervals using Stata software version 12.0.

Dealing with missing data

We contacted authors of included studies to obtain missing trial details and data from the reports.

Assessment of heterogeneity

We assessed clinical heterogeneity by examining the characteristics of the studies, the similarity between the types of participants, the interventions and the outcomes as specified in the criteria for included studies. We assessed statistical heterogeneity using a Chi^2 test and the I^2 statistic where I^2 values over 50% indicate moderate to high heterogeneity (Higgins 2003). The Cochrane Handbook also gives a rough guide to heterogeneity measured by I^2 as follows: 0-40% may not be important, 30 to 60% represents moderate heterogeneity, 50 to 90% may be classified as substantial heterogeneity and 75 to 100% represents considerable heterogeneity (Higgins 2011).

In the event that there were insufficient clinically homogeneous trials for any specific intervention or insufficient study data that could be pooled, a narrative synthesis was presented

Assessment of reporting biases

If sufficient trials had been identified for inclusion in this review, we would have assessed publication bias according to the recommendations on testing for funnel plot asymmetry (Egger 1997), as described in section 10.4.3.1 of the Cochrane Handbook (Higgins 2011), and if asymmetry was identified, other possible causes would have been assessed.

Data synthesis

Two review authors analysed the data and reported them as specified in Chapter 9 of the Cochrane Handbook (Higgins 2011). Analysis was conducted at the same level as the allocation. The data for effects related to prevention were analysed and presented separately to those which considered treatment only.

We undertook pooling of data to provide estimates of the efficacy of the interventions if included studies were clinically and statistically homogeneous. We used risk ratios to pool the dichotomous outcomes where possible.

We calculated number needed to treat (NNT) for the pooled estimates using control prevalence rates for dry socket. Dry socket is a complication associated with 0.5% to 5% of routine extraction of teeth affected by periodontal disease and dental decay (Field 1988; Vezeau 2000), however, the prevalence of dry socket post-extraction of mandibular molars, especially impacted wisdom teeth is much higher (1% to 37.5%) (Caso 2005; Fridrich 1990; Vezeau 2000). For the assumed risk of dry socket in the control group for the 'Summary of findings' table, we set prevalence rates to reflect prevalence rates for routine dental extractions (1% and 5%) and for extraction of mandibular third molars (30%).

In general, for the synthesis of any quantitative data, we used the random-effects model unless there were less than three studies, where we used fixed-effect model.

Subgroup analysis and investigation of heterogeneity

The following subgroup analyses were planned if sufficient studies were identified: complexity of the extraction (surgical removal or simple extraction), whether or not prophylactic systemic antibiotics were prescribed and, different types of teeth (third molars, molars, premolars). However, there were insufficient studies to undertake subgroup analyses.

Sensitivity analysis

If a sufficient number of studies with similar characteristics had been included in the review, we would have undertaken sensitivity analyses to assess the robustness of the results by excluding studies at high risk of bias.

Presentation of the main results

We used GRADEPro software to prepare two 'Summary of findings' tables for the main outcomes of this review. We used the mean risk of the outcome in the placebo or the control group as the assumed risk for each outcome and we then calculated the corresponding risk using the risk ratio (or the mean difference) estimate from the meta-analysis. In addition, we assessed the overall quality of the studies using the GRADE approach. In this approach, the quality of a body of evidence involves consideration of within-study risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias, as described in section 12.2.2 of the Cochrane Handbook (Higgins 2011). The quality of the evidence was assessed as: high, moderate, low or very low.

RESULTS

Description of studies

See Characteristics of included studies and Characteristics of excluded studies.

Results of the search

The electronic and other searches retrieved 395 references to studies. Figure 1 presents the study flow diagram. After examination of the titles and abstracts of these references, we eliminated all of those that did not match the inclusion criteria and were clearly ineligible. Full text copies of the remaining studies (n = 102) were obtained and these were then subjected to further evaluation. Several studies were translated; three (Birke 1970; Neugebauer 2004; Neuner 1969) were in German and one each was in Japanese (Anonymous 1966), Russian (Butylin 1977), Serbian (Jovanovic 2011), French (Turcotte 1997), Polish (Banach 1973) and three were in Chinese (Bai 2011; Huang 2011; Wen 2004). We also examined the bibliographical references of all potentially eligible studies and two potentially relevant additional citations were identified (Delilbasi 2002; Kirk 2007). The full details of Babar 2012 were not available at the time of publication of this review.

The search also retrieved two reviews: two with meta-analysis (Caso 2005; Hedstrom 2007) and the remaining five were narrative reviews (Kolokythas 2010; Neuner 1969; Noroozi 2009; Turcotte 1997; Vezeau 2000). Yengopal 2012 was published while the present review was at the editorial stage. All reviews were examined for potentially eligible studies.

Included studies

Twenty-one studies were included in this review. The majority (n = 18) evaluated interventions for the prevention of dry sockets (Alissa 2010; Bai 2011; Delilbasi 2002; Gersel-Pedersen 1979; Hermesch 1998; Hita-Iglesias 2008; Huang 2011; Kjellman 1973; Larsen 1991; Metin 2006; Ragno 1991; Reekie 2006; Ritzau 1977; Shi 2003; Torres-Lagares 2006; Torres-Lagares 2006a; Trieger 1991; van Eeden 2006). The three remaining included studies examined treatment strategies for dry sockets occurring after dental extraction (Burgoyne 2010; Kaya 2011; Mitchell 1984).

All the prevention trials comprehensively addressed the single (primary) outcome of whether a dry socket occurred or not. However, the three treatment trials only provided a limited amount of useable data for the primary and secondary outcomes of this review.

Characteristics of the trial setting and investigators

Thirteen of the studies had been conducted in college/university oral surgery departments: Alissa 2010 (UK); Bai 2011 (China); Burgoyne 2010 (USA); Gersel-Pedersen 1979 (Denmark); Hita-Iglesias 2008 (Spain); Huang 2011 (China); Kaya 2011 (Turkey); Kjellman 1973 (Sweden); Metin 2006 (Turkey); Mitchell 1984 (UK); Ritzau 1977 (Denmark); Torres-Lagares 2006 (Spain) and Torres-Lagares 2006a (Spain). Military clinics were the settings for three of the studies (Hermesch 1998; Ragno 1991; van Eeden 2006). One was a multi-centre study conducted in three dental practices in the UK (Reekie 2006). The settings of the remaining four studies were not stated (Delilbasi 2002; Larsen 1991; Shi 2003; Trieger 1991).

The providers of care for thirteen of the included studies were not stated (Alissa 2010; Burgoyne 2010; Delilbasi 2002; Hita-Iglesias 2008; Huang 2011; Kjellman 1973; Mitchell 1984; Ritzau 1977; Shi 2003; Trieger 1991; Torres-Lagares 2006; Torres-Lagares 2006a; van Eeden 2006). The skill level and number of operators

providing care where stated was variable. Single operators provided care in three of the included studies (Bai 2011; Gersel-Pedersen 1979; Ragno 1991). Either oral and maxillofacial surgeons, general dentists or general dentistry residents provided care for patients in three studies (Hermesch 1998; Kaya 2011; Metin 2006). Larsen 1991 stated that "multiple surgeons with varying levels of experience" with "formal training in third molar removal" were responsible for provision of care. Reekie 2006 stated that four general dental practitioners were providers of care.

There were 18 studies of prevention and three on the treatment of dry socket. Three of the prevention studies were designed as split-mouth studies (Gersel-Pedersen 1979; Trieger 1991; van Eeden 2006), and the remainder were parallel group design. Trials in the treatment review will always be of parallel group design as there would be insufficient patients with more than one dry socket to undertake this type of study design.

Characteristics of the participants

The majority of the prevention studies (n = 16) involved sockets of mandibular third molar teeth in adults. Nine studies reported on mandibular third molars which were extracted under local anaesthesia with/without intravenous sedation (Bai 2011; Gersel-Pedersen 1979; Hermesch 1998; Hita-Iglesias 2008; Huang 2011; Kjellman 1973; Larsen 1991; Torres-Lagares 2006; Torres-Lagares 2006a). A further three studies involved third molar teeth where the patients ages were not specified (Ragno 1991; Shi 2003; Trieger 1991). Three studies investigated prevention of dry socket after mandibular third molar extraction, however, patients below the age of 18 years were enrolled in: Metin 2006 (age 17 to 46 years); Ritzau 1977 (age 17 to 61 years) and van Eeden 2006 (age 16 to 32 years). One further study investigated prevention of dry socket after mandibular third molar extraction, however, patient age was not stated (Delilbasi 2002).

Reekie 2006 investigated prevention of dry socket after non-surgical extraction of one or more molar/premolar teeth under local anaesthetic in adult patients (age 18 to 90 years), while Alissa 2010 also reported on teeth other than third molars.

In the treatment studies, Kaya 2011 reported on treatment of dry socket after mandibular third molar extraction, Burgoyne 2010 reported on premolars and molars and no specific tooth was identified in Mitchell 1984. Burgoyne 2010 investigated the treatment of diagnosed dry socket in 17 to 58 year old patients, Kaya 2011 investigated the treatment of diagnosed dry sockets in adults over 18 years of age and Mitchell 1984 investigated the treatment of diagnosed dry socket, however, age and gender were unspecified.

The number of participants in the prevention studies ranged from 19 to 400 with a median of 86. The number of participants in the treatment studies ranged from 35 to 55 with a median of 52.

Characteristics of the interventions

This section is divided into two main parts: the characteristics of the interventions for the 18 studies looking at the prevention of dry socket and the characteristics of the three trials looking at the treatment of dry socket.

Prevention

The potentially active interventions in this section have been divided into two broad categories: antiseptics and intrasocket interventions.

Antiseptics (rinses)

- Chlorhexidine rinse (pre and post) versus placebo or saline (post) (Delilbasi 2002; Hermesch 1998; Larsen 1991; Ragno 1991)
- Chlorhexidine rinse (pre) versus chlorhexidine rinse (post) (Metin 2006)
- Chlorhexidine gel versus chlorhexidine rinse (both post) (Hita-Iglesias 2008)

Intrasocket interventions

The following interventions were evaluated but only one comparison, intrasocket chlorhexidine gel, was evaluated in more than one trial.

- Acellular dermal matrix patch (1 x 1 cm) versus no treatment (Bai 2011)
- Apernyl versus placebo (Kjellman 1973)
- Artemisia desertorum spreng (Shahaosan or Yunnan) versus placebo control (Shi 2003)
- Chlorhexidine gel versus placebo/no treatment (Torres-Lagares 2006a; Torres-Lagares 2006
- Clindamycin phosphate antibiotic solution patch versus saline patch (Trieger 1991)
- Glucocorticosteroid antibiotic agent versus normal saline (van Eeden 2006)
- Heal-all tissue patch (2 x 2.5 cm) versus no treatment (Huang 2011)
- Metronidazole gel versus placebo gel (Reekie 2006)
- P-hydroxybenzoic acid versus placebo (Ritzau 1977)
- Platelet rich plasma versus control (Alissa 2010)
- Tranexamic acid versus placebo (Gersel-Pedersen 1979)

Treatment

- Alvogyl versus no treatment (Kaya 2011)
- Alvogyl versus SaliCept (Kaya 2011)
- Metronidazole versus placebo (Mitchell 1984)
- SaliCept versus no treatment (Kaya 2011)

- Topical anaesthetic gel (prilocaine-lidocaine) versus eugenol (Burgoyne 2010)

Characteristics of the outcome measures

Prevention

The primary (and only) outcome measure for prevention was the presence/absence of a dry socket. This was clearly reported in all 18 studies for prevention. Minor adverse events were reported in eight of the prevention studies (Delilbasi 2002; Gersel-Pedersen 1979; Hermesch 1998; Kjellman 1973; Metin 2006; Ragno 1991; Ritzau 1977; van Eeden 2006).

Treatment

Although three trials were looking at the treatment of dry socket, there was very little usable data reported. The data from Kaya 2011 were unusable as medians and error bars for pain were presented in graphs. There was no evidence of a difference in pain at 48 hours in Burgoyne 2010 (Table 1).

Mitchell 1984 provided raw data on the duration of treatment and there was a statistically significant reduction in duration of treatment in the metronidazole group (Table 1).

Kaya 2011 (p1574) stated in the text: "The differences in the changes in the clinical signs and symptoms between the control group and all 3 treatment groups were statistically significant (P<0.05) on the third day after treatment" and "Regardless of the treatment the VAS scores changed during the follow-up period (P<0.001); however the intensity of the pain decreased more rapidly in all the treatment groups than for the control group (P<0.05)".

Excluded studies

Eighty-one studies were excluded from this review and the reasons for their exclusion are summarised below:

- Not a randomised controlled trial/inadequate method of sequence generation (n = 45): Annibali 2012; Anonymous 1966; Banach 1973;Bloomer 2000; Bloomer 2012; Birke 1970; Brignardello 2012; Butylin 1977; Christensen 2012; Cooper 2012; Field 1988; Fotos 1992; Garibaldi 1995; Goldman 1973; Goldsmith 2012; Goyal 2012; Hall 1971; Johnson 1988; Jovanovic 2011; Julius 1982; Keskitalo 1973; Krekmanov 1986; Kudiyirickal 2012; Lao 2012; Liu 2011; Long 2012; Malkawi 2011; MacGregor 1975; Mishra 2012; Mitchell 1986; Neugebauer 2004; Neuner 1969; Qi 2012; Ritzau 1978; Sanchis 2004; Sorensen 1987; Swanson 1989; Sweet 1985; Syrjanen 1981; Tjernberg 1979; Tong 2012; Vedtofte 1974; Wen 2004; Yue 2012; Zanetta-Barbosa 1994.
- Dry socket not defined (n = 11): Arakeri 2011; Arenaz-Bua 2010; Daniels 2011; Hooley 1995; Kirk 2007; MacGregor 1973; Majid 2010; Mehlisch 2010a; Mehlisch 2010b; Nordenram 1973; Zuniga 2011.
- Irrelevant outcomes (n = 1): Betts 1995.
- Wrong interventions, comparisons or other inclusion criteria (n = 18): Akota 1998; Altman 2011; Al-Sukhun 2011; Baqain 2012; Bello 2011; Berwick 1990; Bezerra 2011; Butler 1977; Bystedt 1980; Haraji 2010; Hill 2006; Krekmanov 1981; Lopez-Cedrun 2011; Mitchell 1986a; Olusanya 2011; Schatz 1987; Syrjanen 1981a;Torres-Lagares 2010.
- Study not related to dry socket (n = 1): Jolley 1972.
- Study unavailable or abstract available with insufficient information (n = 4): Study unobtainable: Nentwig 1985; Schlund 1968. Abstracts available with insufficient information Olson 1987; Pichler 2001.
- Study awaiting classification (n = 1): Babar 2012.

Further information about the reasons for exclusion of these studies is available in the 'Characteristics of excluded studies' table.

Risk of bias in included studies

For the prevention trials, the risk of bias assessment was undertaken for the primary outcome (whether or not the patient had a dry socket). As both the patients' and outcome assessors' assessment form part of the diagnosis of dry socket, the blinding assessment had to include both (both groups must be blinded for this category to have been assessed as being at low risk of bias). In studies where the operator was not blinded to group allocation, but the patient was blinded, it was difficult to assess the impact on performance bias as it was unclear if personnel had been told not to comment on the intervention being delivered, which could have resulted in inadvertent communication of group allocation.

Allocation

Sequence Generation

Random sequence generation was assessed at low risk of bias in nine studies (43%) (Alissa 2010; Burgoyne 2010; Gersel-Pedersen 1979; Hita-Iglesias 2008; Larsen 1991; Reekie 2006; Torres-Lagares 2006; Torres-Lagares 2006a; van Eeden 2006), and unclear in the remainder.

Allocation concealment

Allocation concealment was considered to be low risk of bias in seven trials (33%) (Alissa 2010; Gersel-Pedersen 1979; Hita-Iglesias 2008; Mitchell 1984; Ragno 1991; Reekie 2006; Torres-Lagares 2006a), and for the remainder of the studies it was deemed as either unclear (13 trials; 62%) or at high risk of bias (one trial; 5%) (Kaya 2011).

Blinding

As both the patients' and outcome assessors' assessment form part of the diagnosis of dry socket, the blinding assessment has to include both (both groups must be blinded for this category to be assessed as being at low risk of bias).

Blinding was considered to be at low risk of bias for both performance and detection bias in five trials (24%) (Mitchell 1984; Reekie 2006; Ritzau 1977; Torres-Lagares 2006a; van Eeden 2006). Blinding (performance bias) was judged as being unclear in 15 trials (71%) and at low risk of bias for six trials (29%). Blinding (detection bias) was judged as being at low risk in six trials (29%), unclear in 14 trials (67%) and at high risk in one trial.

Incomplete outcome data

We assumed that drop-outs in prevention of dry socket studies probably do not have dry socket as they would be returning for treatment. Fifteen (71%) of the trials were considered to be at low risk of bias with respect to incomplete outcome data (Alissa 2010; Bai 2011; Delilbasi 2002; Gersel-Pedersen 1979; Hermesch 1998; Hita-Iglesias 2008; Huang 2011; Kaya 2011; Metin 2006; Mitchell 1984; Ragno 1991; Ritzau 1977; Torres-Lagares 2006; Torres-Lagares 2006a; van Eeden 2006). Four trials (19%) were considered to be at unclear risk with respect to incomplete outcomes (Burgoyne 2010; Kjellman 1973; Shi 2003; Trieger 1991) and two studies were considered at high risk (Larsen 1991; Reekie 2006). Twelve studies analysed the same number of patients as were analysed (Bai 2011; Burgoyne 2010; Delilbasi 2002; Gersel-Pedersen 1979; Huang 2011; Kaya 2011; Kjellman 1973; Metin 2006; Ragno 1991; Ritzau 1977; Torres-Lagares 2006; van Eeden 2006). Where reported, the range in the number of drop-outs was from three (Hita-Iglesias 2008) to 11 (Larsen 1991). One study only assessed patients who returned with pain, so it was assumed that the other patients who did not return did not have dry socket (Reekie 2006).

Selective reporting

Only the reporting of dry socket was considered for this item for the prevention trials. The majority of trials reported this well and were considered at low risk of bias. Two trials were unclear in their reporting (Shi 2003; Trieger 1991), and three were considered to be at high risk of reporting bias (Hermesch 1998; Ragno 1991; Reekie 2006). Hermesch 1998 only reported dry socket for extracted mandibular third molars although non-mandibular third molars were also extracted concurrently. Reekie 2006 as stated above only assessed patients who returned with pain, and Ragno 1991 did not report any data from the questionnaire completed by participants on day 7.

Other potential sources of bias

Two thirds of the trials (n = 14) were considered to be at low risk of bias from other sources. Five trials (24%) were deemed unclear in this respect (Bai 2011; Huang 2011; Reekie 2006; Shi 2003; Trieger 1991). The reporting in the Trieger 1991 trial in general was very poor and it was not possible to make a clear judgement in many domains. Two of the trials in this review were deemed to be at a high risk of bias from other sources. Of the high risk trials, investigators in the Hermesch 1998 trial randomised at an individual participant level but subsequently analysed participants at an extraction site level; similarly Larsen 1991 randomised individuals, however, subsequent analyses were at tooth level.

Overall assessment of bias

All domains had to be assessed as being at low risk of bias for a study to be considered low risk of bias. If any domain was assessed as being at high risk of bias, the study was assessed as high risk of bias, the remainder were assessed as unclear. Figure 2 presents the review authors' judgements about each risk of bias item presented as percentages across all included studies and Figure 3 presents review authors' judgements about each risk of bias item for each included study.

Only one study was assessed as being at low risk of bias overall (Torres-Lagares 2006a), 14 were deemed unclear (Alissa 2010; Bai 2011; Burgoyne 2010; Delilbasi 2002; Gersel-Pedersen 1979; Hita-Iglesias 2008; Huang 2011; Kjellman 1973; Metin 2006; Mitchell 1984; Ritzau 1977; Shi 2003; Trieger 1991; van Eeden 2006), and the six remaining studies were deemed as being at high risk of bias overall (Hermesch 1998; Kaya 2011; Larsen 1991; Ragno 1991; Reekie 2006; Torres-Lagares 2006).

Effects of interventions

See: **Summary of findings for the main comparison** Chlorhexidine rinse for the management of dry socket; **Summary of findings 2** Chlorhexidine gel for the management of dry socket

Prevention

Forest plots have only been included when there was more than one study for a specific comparison.

Primary outcome: prevention of dry socket

Antiseptics (rinses) (comparison 1.1)

Four trials, one at unclear risk of bias (Delilbasi 2002) and three at high risk of bias (Hermesch 1998; Larsen 1991; Ragno 1991), compared rinsing with chlorhexidine at 0.12% concentration

(Hermesch 1998; Larsen 1991; Ragno 1991) and 0.2% concentration (Delilbasi 2002), both pre- and post-extraction, to rinsing with a placebo for the prevention of dry socket. The meta-analysis showed a clear benefit in rinsing with chlorhexidine with a risk ratio (RR) of 0.58 (95% confidence interval (CI) 0.43 to 0.78; P < 0.001). There was no evidence of any heterogeneity (Chi^2 = 3.20, df = 3 (P = 0.36); I^2 = 6%). The number of patients needed to be treated by using the chlorhexidine rinse to prevent one patient having dry socket (NNT) was 232 (95% CI 176 to 417), 47 (95% CI 35 to 84) and 8 (95% CI 6 to 14) for control prevalences of dry socket of 0.01, 0.05 and 0.30 respectively (Analysis 1.1).

One single trial at unclear risk of bias compared rinsing with chlorhexidine (0.2% strength) both pre- and post-extraction, to rinsing just post-extraction (Metin 2006). A further single trial, at unclear risk of bias, compared inserting chlorhexidine gel (0.2%) into the socket with rinsing with chlorhexidine (0.12%) (Hita-Iglesias 2008). As these interventions were evaluated in single studies, there is insufficient evidence to determine their effects. The results for the placement of chlorhexidine gel directly in a socket are presented in the intrasocket section below.

Intrasocket interventions (comparison 1.2)

The other 12 trials investigating intrasocket interventions all compared different interventions with placebo or no treatment as described below.

- Acellular dermal matrix patch (1 x 1 cm) versus no treatment (Bai 2011)
- Apernyl versus placebo (Kjellman 1973)
- Artemisia desertorum spreng (Shahaosan or Yunnan) versus placebo control (Shi 2003)
- Chlorhexidine gel versus placebo/no treatment (Torres-Lagares 2006a; Torres-Lagares 2006)
- Clindamycin phosphate antibiotic solution patch versus saline patch (Trieger 1991)
- Glucocorticosteroid antibiotic agent versus normal saline (van Eeden 2006)
- Heal-all tissue patch (2 x 2.5 cm) versus no treatment (Huang 2011)
- Metronidazole gel versus placebo gel (Reekie 2006)
- P-hydroxybenzoic acid versus placebo (Ritzau 1977)
- Platelet rich plasma versus control (Alissa 2010)
- Tranexamic acid versus placebo (Gersel-Pedersen 1979)

Two trials, one at low risk (Torres-Lagares 2006a) and one at high risk of bias (Torres-Lagares 2006), compared placing chlorhexidine gel in the extracted socket with placebo or no treatment. The meta-analysis showed a benefit for chlorhexidine gel with a RR of 0.42 (95% CI 0.21 to 0.87; P = 0.02), with no evidence of heterogeneity (P = 0.60, I^2 = 0%). The number of patients needed to be treated by chlorhexidine gel to prevent one patient having dry socket (NNT) was 173 (95% CI 127 to 770), 35 (95% CI 25 to 154) and 6 (95% CI 5 to 26) for control prevalences of dry socket 0.01, 0.05 and 0.30 respectively (Analysis 1.2).

The remaining 10 intrasocket interventions to prevent dry socket were each evaluated in single studies, and therefore there is insufficient evidence to determine their effects. The results are shown in 'Additional Table 2'.

Adverse events reported in prevention studies

'Additional Table 3' summarises the adverse events reported in studies for prevention of dry socket. In the 21 trials included in this review, 10 trials with 1267 participants used chlorhexidine either in gel form or as a mouthwash (Delilbasi 2002; Gersel-Pedersen 1979; Hermesch 1998; Hita-Iglesias 2008; Larsen 1991; Metin 2006; Ragno 1991; Torres-Lagares 2006; Torres-Lagares 2006a; van Eeden 2006). Four trials used 0.2% chlorhexidine rinse (Delilbasi 2002; Gersel-Pedersen 1979; Metin 2006; van Eeden 2006), and three trials reported using 0.12% chlorhexidine rinse (Hermesch 1998; Larsen 1991; Ragno 1991). Adverse reactions in relation to the use of chlorhexidine mouthwash were reported in four trials (Delilbasi 2002; Hermesch 1998; Metin 2006; Ragno 1991). Adverse reactions included: staining of teeth, altered taste and bad taste, gastrointestinal complaints, numbness and paraesthesia. Ragno 1991 reported bad taste and stomach upset, though no staining of the teeth was noted. One person in the placebo group of this trial was reported to have had a "severe surgical infection" which the authors concluded was not attributable to the medication received. In contrast, neither Larsen 1991; van Eeden 2006 nor Hita-Iglesias 2008 reported any adverse events associated with the use of chlorhexidine rinse, though it should be noted that Hita-Iglesias 2008 specifically excluded participants with a previous history of chlorhexidine allergy from the trial. Larsen 1991 prescribed dexamethasone (glucocorticoid) IV for all patients immediately before surgery, which could have suppressed allergic symptoms to chlorhexidine but patients were instructed to rinse for 7 days from the day after surgery, so the protective effect of the steroid would have been expected to have reduced over time. In Gersel-Pedersen 1979, all patients were required to rinse with 0.2% chlorhexidine postoperatively three times daily. A foreign body reaction was noted, which the authors attributed to the delivery vehicle of the cones used to deliver the intrasocket medicament. No specific adverse events were reported in relation to the mouthwash, though the authors report that overall 42 patients (36.8%) stated that they experienced an unpleasant taste, general malaise was recorded in 31 patients (25.8%), 19 felt dizzy (16.1%) and 15 (12.5%) felt nausea. It is unclear from the reporting in this study whether these adverse effects were attributable to the after effects of third molar surgery, the delivery vehicle used in the experimental and control group or to the 0.2% mouthwash that was prescribed for all patients. Intrasocket medicaments containing chlorhexidine gels have been developed that are postulated to increase the bioavailability of chlorhexidine in the application

(Hita-Iglesias 2008). No adverse events were reported in the three trials for prevention of dry socket using chlorhexidine 0.2% gels placed in the socket immediately after extraction of the third molar tooth (Hita-Iglesias 2008; Torres-Lagares 2006; Torres-Lagares 2006a). Participants in the Hita-Iglesias 2008 trial who were allocated to the intrasocket gel group topped up the gel in the extraction socket twice daily for 7 days after the extraction. In two trials by Torres-Lagares 2006 and Torres-Lagares 2006a, participants received only one application of the bio-adhesive gel during surgery. All three studies were derived from the same research group and all three excluded participants with a previous history of chlorhexidine allergy.

Of the other trials investigating intrasocket interventions, two reported adverse events: pain and burning sensation associated with apernyl (Kjellman 1973), and hematoma and rash associated with the use of P-hydroxybenzoic acid (Ritzau 1977).

Treatment

Three trials investigated the treatment of dry sockets (Burgoyne 2010; Kaya 2011; Mitchell 1984) with the following: topical anaesthetic gel (prilocaine-lidocaine), alvogyl, SaliCept, and metronidazole. They were compared to no treatment or eugenol. A single study provided data for each comparison, with Kaya 2011 having four arms. The data reported in Kaya 2011 cannot be used as medians are presented with error bars. The treatment comparisons were:

- topical anaesthetic gel (prilocaine-lidocaine) versus eugenol (Burgoyne 2010);
- alvogyl versus no treatment (Kaya 2011);
- SaliCept versus no treatment (Kaya 2011);
- alvogyl versus SaliCept (Kaya 2011); and
- metronidazole versus placebo (Mitchell 1984).

There was no evidence of a difference in pain levels at 48 hours in Burgoyne 2010 (Table 1).

Mitchell 1984 provided raw data on the duration of treatment and there was a statistically significant reduction in duration of treatment in the metronidazole group (Table 1).

Kaya 2011 (p1574) stated in the text: "The differences in the changes in the clinical signs and symptoms between the control group and all 3 treatment groups were statistically significant ($P<0.05$) on the third day after treatment... Regardless of the treatment, the VAS (visual analogue scale) scores changed during the follow-up period ($P<0.001$); however the intensity of the pain decreased more rapidly in all 3 treatment groups than for the control group ($P<0.05$)".

No other outcomes included in the review were reported.

Adverse events reported in treatment studies

None of the three studies that reported on the treatment of dry sockets reported any adverse events.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Chlorhexidine gel for the management of dry socket

Patient or population: Patients with the management of dry socket
Intervention: Chlorhexidine gel

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk [2]	Corresponding risk				
	Control	Chlorhexidine gel				
Presence of dry socket agreed diagnostic criteria. Follow-up: median 7 days	**Study population**		**RR 0.42** (0.21 to 0.87)	133 (2 studies)	⊕⊕⊕◯ **moderate**[1]	
	300 per 1000	**126 per 1000** (63 to 261)				
	Low					
	10 per 1000	**4 per 1000** (2 to 9)				
	Moderate					
	50 per 1000	**21 per 1000** (10 to 44)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] One trial was assessed as being at low risk of bias and the other at high risk of bias. Both were conducted by the same research team.

[2] The assumed risk values were set to reflect prevalence rates for routine dental extractions (1% and 5%) and for extraction of mandibular third molars (30%).

DISCUSSION

Summary of main results

There were 21 studies included in this review that recruited 2570 patients and reported on 17 different interventions. Of the 21 included studies, 18 were for prevention and three for the treatment of dry socket. Although 18 trials were included that looked at interventions for the prevention of dry socket, only two interventions were considered in more than one trial: chlorhexidine rinse and intrasocket chlorhexidine gel. The quality of the trials was mixed.

There was evidence for the effectiveness of rinsing both pre- and post-extraction with 0.12% and 0.2% chlorhexidine compared to placebo with a risk ratio (RR) of 0.58 (95% confidence interval (CI) 0.43 to 0.78; P < 0.001; 750 participants) based on moderate evidence from four trials, one at unclear and three at high risk of bias, but with no evidence of heterogeneity. The number of patients needed to be treated to prevent one patient having dry socket (NNT) varied considerably depending on the prevalence of dry socket. For a 30% prevalence, as in the included studies, the NNT was 8 (95% CI 6 to 14) but if the control prevalence is 1% then the NNT increased to 232 (95% CI 176 to 417) (Summary of findings for the main comparison).

There was moderate evidence from two studies with 133 participants, one at low risk of bias and one at high risk of bias, with no evidence of heterogeneity that chlorhexidine gel (0.2%) placed in an extraction socket is an effective preventative therapy (RR 0.42; 95% CI 0.21 to 0.87; P = 0.02). Once again the NNT varied considerably from 6 (95% CI 5 to 26) for control prevalences of 30% to 173 (95% CI 127 to 770) for control prevalence of 1% (Summary of findings 2).

The remaining interventions for the prevention of dry socket and the interventions for the treatment of dry socket were only looked at in single studies and therefore there is insufficient evidence to determine their effects.

Overall completeness and applicability of evidence

A comprehensive search strategy was employed and it is likely that the majority of published trials are included in this review. It is uncertain how many unpublished trials there are as some of the interventions identified were developed by industry and findings from these trials were not always reported in the past.

Only two studies reported on the prevention of dry socket in molars and premolars (Alissa 2010; Reekie 2006), all other trials reported on prevention following extraction of third molars. The Reekie 2006 trial was also notable in that it was conducted in four general dental practice settings. Trials included in the present review tended to include extractions undertaken by experienced oral surgeons in hospital or military minor oral surgery clinics. However, most extractions in dentistry are undertaken in primary dental care, by general dental practitioners on teeth other than lower third molars. Most extractions do not involve surgical removal of the tooth. It is important that future well designed trials of interventions to treat and prevent dry socket are conducted in primary dental care settings. Such studies should recruit patients who are having a range of tooth type extractions including molar and premolar teeth. It is also important that power calculations inform the sample size of the proposed study to ensure trials are large enough to detect clinically important effects of interventions including hypersensitivity reactions and adverse events.

Three of the trials in this review employed a split-mouth design, with no trials employing a cross-over design. Split-mouth designs are appropriate when the disease is stable and uniformly distributed and the effects of the intervention are short lived or reversible (Antczak-Bouckoms 1990). There is evidence from one trial that development of dry socket increases the risk of developing dry socket in the future (Reekie 2006), therefore this could compromise the use of cross-over studies, however, split-mouth studies appear to be appropriate for looking at the prevention of dry socket. It is also important that participants and observers are blind to the intervention allocation if possible.

There was considerable variation in the design of trials, inclusion and exclusion criteria, definition of dry socket, presurgical regimens, intraoperative procedures and postoperative medications. The generalisability of the trials was compromised in some trials by excluding smokers and women on oral contraceptive therapy. Also, most teeth were third molars. In most trials, the existence of pericoronitis and infection was a cause for exclusion. These exclusion criteria have the potential for studies to include patient groups where the risk factors for dry socket are reduced so dry socket is less likely to happen. This effect was balanced by the predominance of studies that largely reported on extraction of third molars where the prevalence of dry socket is higher compared to extraction of other teeth. Many studies were conducted in a hospital setting with operators who were undertaking these procedures frequently and had high levels of skill. The results may be different from general dental practice where the dentists have less time, are undertaking fewer of these procedures, and so outcomes may be less predictable.

Dry socket is a common consequence of tooth extraction and it is important that this review presents the latest evidence for prevention and treatment. A range of interventions reported in this review reflect prevailing theories of dry socket causation at the time the study was undertaken. This meant that many of the comparisons for the prevention and treatment included small single studies making it difficult to provide strong evidence for any of the interventions used. There is a dearth of evidence in relation to the treatment of dry socket. Recent work has reported on the use of lasers and obtundents in the treatment of dry socket. The studies show promise, though problems with the design of

the studies and reporting precluded their inclusion in this review.

Quality of the evidence

Although the criteria for assessing overall risk of bias were strict (all domains assessed had to be at low risk of bias for the trial to be deemed at low risk of bias), only one study was assessed as being at low risk of bias. Of the remainder, 14 (67%) were assessed as being at unclear risk of bias and six (29%) were assessed at high risk of bias. The quality of reporting could be improved by authors reporting their studies in line with CONSORT and, where possible, undertaking double blind trials with adequate outcome assessment. Some studies had to be excluded as they did not have an adequate definition of dry socket and some appeared to conflate infection with dry socket. There was also variation in the secondary outcomes reported in the trials and many did not match the ones included in the protocol for the present review. There was also generally inadequate reporting of adverse events.

Adverse Effects

Three of the four studies included in the meta-analysis reported some adverse effects associated with the use of 0.12% chlorhexidine (Hermesch 1998; Larsen 1991; Ragno 1991) and 0.2% chlorhexidine (Delilbasi 2002) mouthwash. Adverse effects included: staining of teeth, altered taste, bad taste, numbness and stomach upsets. The use of 0.2% chlorhexidine mouthwash was reported in three further trials (Gersel-Pedersen 1979; Metin 2006; van Eeden 2006). In the trial by Gersel-Pedersen 1979, a range of adverse effects were reported but it was not possible to attribute these with confidence to either the surgery undertaken, the vehicle delivering the intrasocket medicament or the use of 0.2% chlorhexidine mouthwash. Metin 2006 reported altered taste and numbness. van Eeden 2006 reported no adverse effects. No adverse effects were reported in the three included studies for prevention of dry socket that used chlorhexidine 0.2% gels inserted immediately post-extraction of third molar teeth (Hita-Iglesias 2008; Torres-Lagares 2006; Torres-Lagares 2006a). All three studies, however, were derived from the same research group, had small sample sizes and all three excluded participants with a previous history of chlorhexidine allergy.

Immunoglobulin E (IgE) mediated allergic reactions associated with chlorhexidine use have been reported including: urticaria, angioedema and anaphylaxis (Nagendran 2009). Anaphylactic symptoms associated with the use of chlorhexidine have been reported in dental settings (Gagari 1995; Sharma 2009), and other healthcare settings (Nagendran 2009). Immediate hypersensitivity is rare, though late onset hypersensitivity and eczema are well documented events in healthcare settings (Beaudouin 2004). There have been two recent cases in the UK of anaphylaxis associated with irrigation of dry socket with chlorhexidine mouthrinse that have been reported in Coroners' reports and the media but not in the scientific literature (Edwards 2011; Reissner 2011). The present review found some evidence for the association of minor adverse reactions with 0.12% and 0.2% chlorhexidine mouthrinses, though no allergic reactions were reported. All studies in relation to the use of 0.2% chlorhexidine gel excluded participants with a history of chlorhexidine allergy. Most studies in the present review were not designed to detect the presence of hypersensitivity reactions to mouthwash as part of the study protocol. Future trials of chlorhexidine mouthrinses should consider using chlorhexidine-specific IgE serological testing to reduce the risk of allergic reactions (Beaudouin 2004), and to estimate the prevalence of chlorhexidine allergy in the study population. While serious adverse effects and events attributable to rinses are rare, the decision to recommend rinsing with chlorhexidine should be balanced against reported adverse effects of tooth staining, taste alteration and nausea. A recent review of the effect of chlorhexidine mouthrinse on plaque and gingival inflammation concluded that staining was the most common adverse effect, followed by increased calculus formation and change in taste sensation (Van Strydonck 2012). It was also reported that burning sensations, hypersensitivity, mucosal lesions and an anaesthetised sensation were less frequent events (Van Strydonck 2012). While serious adverse effects and events are rare, it is recommended that all members of the dental team prescribing chlorhexidine mouthwashes and gels for the management of dry socket are aware of the potential for side effects, are competent to manage a medical emergency associated with anaphylaxis and warn their patients of the potential for adverse events.

Agreements and disagreements with other studies or reviews

Two systematic reviews concluded that rinsing perioperatively with 0.12% chlorhexidine gluconate was effective in preventing dry socket after the extraction of third molar teeth (Caso 2005; Hedstrom 2007). The findings from the present review are consistent with the findings reported in both these reviews. Hedstrom 2007 concluded that while it could not be determined that perioperative rinsing with 0.12% chlorhexidine prevented dry socket in all extractions, there was evidence that perioperative rinsing with chlorhexidine could prevent dry sockets in lower third molar extractions. Hedstrom 2007 also concluded that there was strong evidence that local treatment with tetracycline seemed to have a clinically relevant effect on dry socket and reported on three trials in this grouping. These three studies did not meet the inclusion criteria for the present review. Yengopal 2012 included a different group of studies to the present review. In contrast to our review, Yengopal 2012 concluded that chlorhexidine had not been conclusively shown to be significantly better than placebo for reducing the incidence of alveolar osteitis (dry socket) after tooth extraction.

The present review reported new findings not reported on in three previous systematic reviews relating to evidence for the effectiveness of 0.2% chlorhexidine gels in the prevention of dry sockets. The three trials on which this new evidence was based were all published after Caso 2005 and Hedstrom 2007. The review by Yengopal 2012 used different inclusion criteria compared to the present review.

AUTHORS' CONCLUSIONS

Implications for practice

There is moderate evidence that rinsing perioperatively with 0.12% and 0.2% chlorhexidine gluconate is beneficial in preventing dry socket. There is moderate evidence that chlorhexidine gel placed in the socket post-extraction may also be beneficial in preventing dry socket. The decision to recommend rinsing with chlorhexidine should be balanced against reported adverse effects of tooth staining, taste alteration and nausea. Adverse events attributable to the rinses were rare but patients need to be aware and informed of the potential for adverse events associated with the use of chlorhexidine. There have been two reported cases of serious adverse event in the UK attributed to rinsing with chlorhexidine mouthwash for established dry socket. It is recommended that all members of the dental team prescribing chlorhexidine mouthwashes and chlorhexidine gels are aware of the potential for adverse effects, are competent to manage a medical emergency associated with anaphylaxis and warn their patients of the potential for adverse events. While an allergic reaction can occur despite a history of previous uneventful use of the allergen, it is also recommended that a full allergy history is taken before the prescription of chlorhexidine mouthwash and gels.

There was no evidence to support any of the interventions included for the treatment of dry socket.

Implications for research

More well designed trials in general dental practice settings with teeth other than third molars and including non-surgical extractions are needed. Further studies comparing rinsing with chlorhexidine with intrasocket chlorhexidine gel to prevent dry socket would help to determine whether one intervention is better than another. Clinicians and researchers in this area need to decide collectively what outcomes should be measured in both prevention and treatment studies. All studies should carefully present data on any adverse events, even if none were observed. More research is required into the effectiveness of treatment of dry sockets.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Alissa 2010

Methods	**Study design:** A randomised, controlled, parallel-group (pilot) study. **Sample size calculation:** A priori sample size calculation suggested needed 34 in each group **Sample size:** N = 23, suggesting 60% power. **Conducted in:** University Dental Hospital of Manchester, Manchester, UK. Patients recruited from consultation clinic **Number of centres:** 1. **Prevention or treatment of dry socket:** Prevention. **Type of teeth:** molars, premolars, canines and incisors, 17 (60.9%) extracted for dental caries and 5 (21.7%) endodontic failure. Extracted under IV sedation **Recruitment period:** January 2005 to April 2008. **Funding source:** Not stated.
Participants	**Inclusion criteria:** • Healthy adults over 18 years of age. • Patients with a demonstrable need for removal of at least one tooth, treated with local anaesthesia and intravenous sedation. • Patients able to consent (written) and willing to complete the requirements of the study protocol. **Exclusion criteria:** • Pregnancy/nursing mothers/having childbearing potential and not using birth control measures. • Platelet dysfunction syndrome or critical thrombocytopenia. • Under treatment with NSAIDs including aspirin, antibiotics, systematic corticosteroids, anticoagulants or immunosuppressive drugs. • Diabetes mellitus. • Cardiovascular disease including a history of rheumatic fever, or other conditions requiring antibiotic prophylaxis. • Neoplasia or haematological malignancy. • Renal, hepatic or endocrine diseases. • Metabolic bone disease such as osteomalacia, hypocalcaemia or hypercalcaemia. • Participation in another trial. **Age group:** Mean = 30.5. **Platelet rich plasma (PRP) Group:** Number randomised 12; analysed 12. **Control Group:** Number randomised 11; analysed 7. **Number evaluated:** 19.
Interventions	**Comparison:** Platelet rich plasma placed in extraction sockets versus control All patients were treated under IV sedation and blood drawn to manufacture the PRP produce before the surgical procedure and before IV sedation administered. All patients had a mucoperiosteal flap raised with two releasing incisions. Extraction with forceps to minimise trauma, elevators used as appropriate. All sockets carefully curetted to remove granulation tissue and/or periapical infections **PRP Group (n = 12):** Platelet rich plasma placed in extraction sockets after extraction

	and curettage **Control Group B (n = 11):** Nothing placed in control sockets. **Co-interventions and concomitant medication:** None stated. Co-codamol analgesic tablets (codeine phosphate 30 mg and paracetamol 500 mg)
Outcomes	**Primary outcome measures:** • Alveolar osteitis: assessed 1 week postoperative using Cheung et al 2001 (range). **Secondary outcome measures:** • Quality of life. A statistically significant improvement associated with use of PRP was observed for two variables: bad taste in mouth (P = 0.03), food stagnation (P = 0. 03) and borderline for change in di • Patient satisfaction: A high level of patient satisfaction in both groups, and no difference between groups. **Adverse outcomes:** • No adverse events reported
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "A computer-generated randomization schedule was created by a statistician" page 127 **Comment:** Probably done.
Allocation concealment (selection bias)	Low risk	**Quote:** "The randomization codes were enclosed in sealed, opaque and sequentially numbered envelopes. The patients allocation to either group was revealed by the investigator just before venous cannulation on the day of the patient's appointment for the extraction." **Comment:** Probably done.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It was probably not possible to blind personnel and participants to group allocation. Strict study criteria required that participants would be blinded to group allocation as they will be involved in reporting of patients symptoms, however as operator is also involved in assessment of outcome, it is unclear the impact of performance bias has on study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	While the criteria for dry socket are clear, it is unclear who and how they made the judgement. Insufficient information to

Alissa 2010 (*Continued*)

		permit judgement of 'high' or 'low' risk, therefore unclear risk
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	In relation to alveolar osteitis, 2 patients from the control group did not attend any of the scheduled appointments following tooth extraction, and given the low event rate it is unclear whether this may introduce a bias. There was no loss in the intervention group
Selective reporting (reporting bias)	Low risk	The report appears to be free of selective reporting.
Other bias	Low risk	The study appears to be free of other sources of bias.

Bai 2011

Methods	**Study design:** Parallel RCT. **Sample size calculation:** Not clear that this was undertaken. **Study size**: 400 participants. **Conducted in:** Stomatological Center of Chinese PLA, the 306 Hospital of Chinese PLA, Beijing, China **Number of centres:** 1. **Prevention or treatment of dry socket:** Prevention. **Type of teeth:** Impacted mandibular third molar, local anaesthesia. **Recruitment period:** 03/2009-06/2010. **Providers of care:** 1 surgeon. **Funding Source:** No funding.
Participants	**Inclusion criteria:** • Participants required to have their impacted mandibular third molar extracted were included. • Aged 18-50. • No acute pericoronitis within a week. • No antibiotics within 3 days before the extraction. • No contra-indications. **Exclusion criteria:** • Acure pericoronitis within a week before the extraction. • Antibiotics administration within 3 days before the extraction. **Age group:** Mean 27.9. **Number randomised in Group 1** = 200; **number analysed** = 200. **Number randomised in Group 2** = 200; **number analysed** = 200. **Number evaluated:** 200.
Interventions	**Comparison:** Acellular dermis matrix versus control. **Group 1 (n = 200):** Acellular dermis matrix (1×1 cm) embedded into the extraction sockets

Bai 2011 (*Continued*)

	Group 2 (n = 200): Nothing embedded into the extraction sockets. **Co-interventions:** Extraction of the teeth (the detailed information was not reported) **Concomitant medication:** Not reported.
Outcomes	**When measured:** 1 week after the extraction. **Primary outcome measures:** • Presence of postoperative alveolitis; disintegration of blood clot; haemorrhage rate; swelling rate (the exact measurement method was not reported); food residue rate; rate of red swollen gingiva. **Secondary outcome measures:** • None reported. **Adverse outcomes:** • None reported.
Notes	Author contact failed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "The participants were randomized into intervention group (n = 200) and control group (n = 200)." **Comment:** The detailed methods of randomisation were not clearly reported
Allocation concealment (selection bias)	Unclear risk	Insufficient reporting to make a judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient reporting to make a judgement.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient reporting to make a judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	None of the participants were reported to have dropped out. All outcomes in relation to dry socket fully reported
Selective reporting (reporting bias)	Low risk	All the outcomes in relation to dry socket were reported clearly
Other bias	Unclear risk	Although the authors reported the gender and the age, the difficulties of the extraction and the detailed information of the tooth impaction were not reported

Burgoyne 2010

Methods	**Study design:** Randomised parallel-group controlled trial. **Study size:** 35. **Sample size calculation:** Not stated. **Prevention or treatment of dry socket:** Treatment. **Type of teeth:** Mandibular third molars, mandibular and maxillary molars and premolars **Conducted in:** Department of Oral and Maxillofacial Surgery, School of Dentistry, Virginia Commonwealth University (Richmond, VA), USA **Number of centres:** 1. **Recruitment period:** Not stated. **Funding source:** Not stated.
Participants	**Inclusion criteria:** • Presenting with alveolar osteitis; diagnosed as pain of increasing severity 2 to 3 days post-extraction, absence of a clot in the socket. **Exclusion criteria:** • Immunocompromised or on immunosuppressant drugs. • Steroids, nonsteroidal anti-inflammatory drugs within 4 hours of examination. • Allergy to eugenol, lidocaine, prilocaine, acetaminophen or codeine. • Medical conditions: Type 1/2 diabetes, glucose 6-phosphate dehydrogenase deficiency. • Pregnancy. • Drugs associated with drug induced methamglobinaemia. **Age:** Gauze strip group: mean = 33, range 19-53. Topical anaesthetic gel: mean = 27, range 17-58. **Number randomised:** 35. **Number analysed:** 35.
Interventions	**Comparison:** Topical anaesthetic gel versus eugenol gauze strip. **Group 1 (n = 15):** 2.5% prilocaine, 2.5% lidocaine (Oraqix; Dentsply Pharmaceutical, York, PA) thermosetting gel syringed into socket **Group 2 (n = 20):** Eugenol on plain gauze into socket. **Co-interventions:** Extraction site irrigated with normal saline. Prescription for 24 tablets of acetaminophen and codeine, 30 mg, taking 1 or 2 tablets every 4 hours if needed for pain. Details recorded quantity and frequency
Outcomes	Self assessment 5, 10, 15 mins after first treatment, and then hourly whilst awake over 48 hours. Assessed at 48 hours and if still in pain re-treated **Primary outcome measures:** • Relief of pain associated with localized alveolar osteitis. Pain measured by VAS: no pain (0) to severe (10) compared at 24 and 48 hours. **Secondary outcome measures:** • None assessed. **Adverse effects:** • None reported.
Notes	The pain outcomes sought were to be assessed during waking hours but it was unclear why the investigators considered pain assessments not recorded while the patients slept as

	"missing data". "Two analyses were performed, one treating the missing data as ignorable and the other inputting pain scores of 0 during sleep". We used the one which ignored the missing data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "control or experimental group by use of a randomization table" page 145 **Comment:** Probably done.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make a clear judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants blinded to allocation and to what they received. Personnel were not blinded to interventions. Strict study criteria required that personnel would be blinded to group allocation as they will be involved in reporting of patients symptoms, however as operator is also involved in assessment of outcome, it is unclear the impact of performance bias has on study. Detail from the study is insufficient to make a judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It is not clear who made outcome assessment, if it was the operator given the low numbers in the trial s/he could remember group allocation, but insufficient information to form a judgement of high risk
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Outcomes assessments not carried out during periods of sleep were considered as "missing data"
Selective reporting (reporting bias)	Low risk	Although the study protocol was unavailable, the report appears to be free of selective reporting
Other bias	Low risk	Appears to be free of other bias.

Delilbasi 2002

Methods	**Study design:** Randomised, placebo-controlled, parallel-group study. **Sample size:** 177. **Power calculation:** Not reported. **Conducted in:** Not stated (Authors based in Turkey and Japan). **Number of centres:** Not stated. **Prevention or treatment of dry socket:** Prevention. **Type of teeth:** Mandibular third molars. **Recruitment period:** Not stated. **Funding source:** Not stated.
Participants	**Inclusion criteria:** • At least 1 impacted mandibular third molar. • Patients in good health. **Exclusion criteria:** • Patients who had pericoronitis or were taking antibiotics for other infections. • Women who were pregnant, breast-feeding, or using oral contraceptives. **Age Group 1**: 24.1; **Group 2:** 24.7; **Group 3:** 24.2. **Number randomised:** 177. **Number analysed:** 177.
Interventions	**Comparison:** **Group 1 (n = 62):** Rinse with 15 mL of CHX solution (Klorhex; Drogsan) for 30 seconds just before tooth removal. Intraoperatively, 15 mL of CHX diluted with 15 mL of sterile saline was used as irrigation. The soft tissue was closed with 3/0 silk suture for transalveolar procedures. The day after surgery, the patients began home use of the CHX solution (15 mL for 30 seconds) twice daily for 7 days **Group 2 (n = 56):** Similarly to Group 1. However, in addition to CHX solution, the patients in Group 2 were prescribed Aug-mentin (500 mg amoxicillin trihydrate, 125 mg clavulanic acid; SmithKline Beecham) twice daily for 5 days postoperatively **Group 3 (n = 59):** Similarly to Group 1, except for the substitution of sterile saline solution (0.09 % NaCl) for CHX **Co-interventions:** All 3 groups were instructed to use only 500 mg paracetamol (Minoset; Roche) for postoperative pain relief
Outcomes	Assessment days 3 and 7 postoperatively. **Primary outcome measures:** • Diagnosis of alveolitis osteitis. **Secondary outcome measures:** • None. **Adverse outcomes:** Adverse events reported for Group 1 n = 62. Allergy: n = 0. Staining of teeth: n = 4. Mucosal irritation: n = 0. Alteration in taste: n = 12. GIS complaints: n = 0. Bad taste: n = 8. No adverse reactions: n = 38. From Table IV page 303
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Delilbasi 2002 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	**Quote:** "...were randomly allocated into 3 groups." **Comment:** No information relating to randomisation process. Insufficient information to make a judgement
Allocation concealment (selection bias)	Unclear risk	Not mentioned and no information to suggest this was done.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants in antibiotic group would not have been blinded to intervention, though personnel were blinded to group allocation. Interventions were in identical bottles, a third operator separate to clinicians undertaking the surgery and doing the assessment, as both personnel and participants would be involved in outcome assessment, unclear impact on performance
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned and no information to suggest this was done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs.
Selective reporting (reporting bias)	Low risk	The report appears to be free of selective reporting.
Other bias	Low risk	The study appears to be free of other sources of bias.

Gersel-Pedersen 1979

Methods	**Study design:** Randomised controlled double-blind split-mouth design. **Sample size:** 120. **Sample size calculation:** Not reported. **Prevention or treatment of dry socket:** Prevention. **Type of teeth:** Bilaterally impacted mandibular third molars - under local anaesthetic **Conducted in:** Department of Oral Surgery, Royal Dental College, Copenhagen, Denmark **Number of centres:** 1. **Recruitment period:** Not stated. **Funding source:** No financial support received.
Participants	**Inclusion criteria:** • Bilateral impacted mandibular third molars without acute pericoronitis. **Exclusion criteria:**

Gersel-Pedersen 1979 (*Continued*)

	• Not reported. **Mean age:** 23.2, range 14-58. **Number randomised:** 120. **Number analysed:** 120.
Interventions	**Comparison:** **Intervention (n = 120):** 4 AMCA (Tranexamic acid 40.0 mg) cones. **Control (n = 120):** 4 placebo (Lactose (n = 30) or Sorbitol (n = 90) 40 mg). **Co-interventions:** The surgical areas were irrigated with 50 ml sterile saline and closure of the wounds was accomplished with 2 silk sutures "Oral hygiene was secured by mouthrinses with chlorhexidine gluconate 0.2%, 3 times a day. The pains were alleviated with tablets containing 500 mg acetylsalicylic acid and 10 mg codeine phosphate." Frequency and quantity not reported
Outcomes	Assessment carried out "...4, 5 or 6 days (mean = 5 days) after the operation..." **Primary outcome measures:** • Presence of alveolitis sicca dolorosa. **Secondary outcome measures:** • None stated. **Adverse effects:** • Foreign body reaction to the vehicle delivery system in the cones.
Notes	2 control groups, 2 teeth per patient.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	**Quote:** "An equal distribution of AMCA/ Tplacebo between right and left side was ensured by randomization corresponding to 120 consecutive numbers."
Allocation concealment (selection bias)	Low risk	**Quote:** "The code was unknown to the author during the study and first broken when all the patients had been treated." **Comment:** Probably done.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned and no information to suggest this was done.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned and no information to suggest this was done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for in analysis.

Gersel-Pedersen 1979 (*Continued*)

Selective reporting (reporting bias)	Low risk	Although the study protocol was unavailable, the report appears to be free of selective reporting
Other bias	Low risk	Appears to be free of other bias.

Hermesch 1998

Methods	**Study design:** Randomised, double-blind, placebo-controlled, parallel-group study **Sample size**: 279. **Sample size calculation:** Not reported. **Conducted in:** A military dental clinic (authors from San Antonio, Texas USA) **Number of centres:** 1. **Prevention or treatment of dry socket:** Prevention. **Type of teeth:** Impacted mandibular third molar - under local anaesthesia with optional intravenous sedation. However, other third molars extracted concurrently **Recruitment period:** Not stated. **Funding source:** Not reported.
Participants	**Inclusion criteria:** • At least 1 impacted mandibular third molar. • Over 18 years of age. • In good health. **Exclusion criteria:** • Pericoronitis. • Medical conditions requiring antibiotic prophylaxis. • Participants taking antibiotics 2 weeks prior. • Pregnant or lactating females. • Allergy to chlorhexidine. **Number randomised:** 279 0.12% CHX n = 140; placebo n = 139. **Number analysed:** 271 0.12% CHX n = 136; placebo n = 135.
Interventions	**Comparison:** **Group 1 (n = 140):** 0.12% chlorhexidine gluconate rinse in 11.6% alcohol. **Group 2 (n = 139):** Placebo rinse containing 11.6% alcohol. **Co-interventions:** Prior to surgery: Daily rinse for 7 days, 15 ml of test product for 30 seconds b.i.d Postoperative: Daily rinse for 7 days,15 ml of test product 30 seconds b.i.d
Outcomes	3-4 days postoperatively telephone contact. Day 7 - clinical evaluation **Primary outcome measures:** • Presence or absence of alveolar osteitis. • Pain not relieved by analgesics. **Secondary outcome measures:** • Not evaluated. **Adverse effects:** • Collected and reported for both intervention groups, but unclear to what extent these were intervention related or essentially postoperative complications (Additional

Hermesch 1998 (*Continued*)

	Table 3).	
Notes	NB: number above = patients, extractions: chlorhexidine 239, placebo 240. Randomisation at individual participant level but analysis of data at extraction site level	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	**Quote:** "Each subject was then randomized to a treatment group within these strata." **Comment:** Method of sequence generation not reported. Unclear.
Allocation concealment (selection bias)	Unclear risk	**Quote:** "Each bottle was labelled with a unique subject number, which allowed for blinding of treatment assignment." **Comment:** Still unclear.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Quote:** "Each bottle was labelled with a unique subject number, which allowed for blinding of treatment assignment." Both the placebo and active interventions were identical in appearance and therefore participants were blinded to group allocation, however it is not clear how bottle labelling ensured blinding of personnel. Strict study criteria required that participants and personnel would be blinded to group allocation, however as operator is also involved in assessment of outcome, it is unclear the impact of performance bias has on study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	All diagnoses were made by one of two attending clinical examiners involved in this study, without knowledge of treatment assignment. However it is not clear how bottle labelling ensured blinding of assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Participants not included in final analysis reported (n = 8) and reasons for exclusion provided. Equal numbers in both intervention groups
Selective reporting (reporting bias)	High risk	271 participants 973 third molars extracted, 51.7% (239 CHX, 240 placebo) were mandibular molars, no data were reported for the non-mandibular molars

Hermesch 1998 (*Continued*)

Other bias	High risk	Randomisation at individual participant level but analysis of data at extraction site level

Hita-Iglesias 2008

Methods	**Study design:** A randomised parallel-group controlled trial. **Sample size:** 73. **Sample size calculation:** Not reported. **Conducted in:** Faculty of Odontology at the University of Seville and the Oral and Maxillofacial Surgery service of the Virgen de Rocio University Hospitals, Seville, Spain **Number of centres:** 1. **Prevention or treatment of dry socket:** Prevention. **Type of teeth:** Mandibular third molars, under local anaesthesia. Difficulty index 4-7 Koerner scale **Recruitment period:** From June - November 2005. **Funding source:** Laboratorios Lacer Barcelona Espan˜ a, donated the chlorhexidine samples used in this study
Participants	**Inclusion criteria:** • Mandibular third molars; difficulty index 4-7 Koerner scale (Koerner 1994), surgical extraction and suture. **Exclusion criteria:** • Antibiotic or analgesic 4 days prior. • AIDs or any type of immuno-suppression. • Pregnant/lactating women • .Allergy to: CHX, articaine, paracetamol or ibuprofen. • Patients requiring simultaneous extraction of 2 third molars. • Any jaw associated pathology. • Operation times > 30 minutes. • Non co-operative patients (psychic-motor dysfunction). **Age:** 18-60 years, mean 29. **Gel Group 1:** randomised 41; analysed 39. **Mouthrinse Group 2:** randomised 32; analysed 31. **Number randomised:** 73. **Number analysed:** 70.
Interventions	**Comparisons:** Chlorhexidine bio-adhesive gel versus mouthrinse. **Group 1 (n = 41):** 0.2% chlorhexidine bio-adhesive gel, placed in wound after extraction then self applied to the wound b.i.d. (day 1-7) beginning same day as intervention **Group 2 (n = 32):** 0.12% chlorhexidine mouthrinse b.i.d. (day 1-7) beginning same day as intervention **Co-interventions:** Ibuprofen 600 mg tds, paracetamol 500 mg with codeine 14.05 mg tds
Outcomes	Subjects evaluated on the 3rd and 7th day postoperatively. **Primary outcome measures:** • Incidence of alveolar osteitis day 1 to day 3.

	Secondary outcome measures: • Not reported. **Adverse effects:** **Quote:** " tolerance to the treatment defined as the frequency that patients developed one or more adverse effects .. assessed on a verbal score 1 (max tolerance) to 5 (max intolerance) during the 3rd and 7th postoperative day" page 443 **Comment:** "Tolerance" was not defined in the report nor the type of "adverse effects" which might constitute maximum intolerance, and the relevant data reported in Table 1 were not readily interpretable
Notes	November 2012: Communication from Dr Torres-Lagares confirmed that Hita-Iglesias 2008; Torres-Lagares 2006 & Torres-Lagares 2006a were separate studies each involving a different group of participants

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "Randomly classified into two groups by means of a simple allocation system using a computer program." **Comment:** Probably done.
Allocation concealment (selection bias)	Low risk	**Quote:** "Having carried out the procedure the envelope corresponding to the patient code was opened." **Comment:** Probably done.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants could not be blinded to group allocation, nor could operators. Strict study criteria required that participants and personnel would be blinded to group allocation as they will be involved in reporting of patients symptoms, however as operator is also involved in assessment of outcome, it is unclear the impact of performance bias has on study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quote:** "All clinical assessment was carried out by a single blind investigator previously trained on diagnostic criteria." **Comment:** Probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The drop-outs/losses to follow-up were reported. Similar numbers in both groups, 2 in gel group, 1 in rinse group

Hita-Iglesias 2008 (*Continued*)

Selective reporting (reporting bias)	Low risk	Although the study protocol was unavailable, the report appears to be free of selective reporting
Other bias	Low risk	Appears to be free of other potential sources of bias.

Huang 2011

Methods	**Study design:** Parallel-group RCT. **Sample size:** 80. **Sample size calculation:** Not reported. **Prevention or treatment of dry socket:** Prevention. **Type of teeth:** Impacted mandibular third molar, local anaesthesia with lidocaine **Conducted in:** Department of Stomatology, the First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China **Number of centres:** 1. **Recruitment period:** 05/2008-07/2010. **Providers of care:** Not reported. **Funding source:** Scientific plan of Cantoon Provience.
Participants	**Inclusion criteria:** • Participants required to have their impacted mandibular third molar extracted were included; 1) aged 18-45; 2) horizontal impacted third mandibular molar on X-ray; 3) agreed to participate and could be followed-up. **Exclusion criteria:** • Have contra-indication and could not be followed-up. **Number Randomised:** 80. **Number evaluated:** 80.
Interventions	**Comparison:** **Group 1 (n = 40):** Acellular dermis matrix (2×2.5 cm) embedded into the extraction sockets **Group 2 (n = 40):** Nothing embedded into the extraction sockets. **Co-interventions:** Extraction of the teeth via flap elevation, bone removing and tooth splitting
Outcomes	**When measured:** 1 week after the extraction. **Primary outcome measures:** • Presence of postoperative alveolitis. **Secondary outcome measures:** • None. **Adverse outcomes:** • None reported.
Notes	Author contact failed.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	**Quote:** "The participants were randomized into two groups with 40 in each group." **Comment:** The detailed methods of randomisation were not clearly reported
Allocation concealment (selection bias)	Unclear risk	It is not clear from the report how allocation concealment was achieved
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants were not blinded to group allocation (placebo received no intrasocket intervention), personnel were not blinded to group allocation. Strict study criteria required that participants and personnel would be blinded to group allocation as they will be involved in reporting of patients symptoms, however as operator is also involved in assessment of outcome, it is unclear the impact of performance bias has on study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It is not clear whether assessors were blinded to group allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	None of the participants dropped out.
Selective reporting (reporting bias)	Low risk	All the outcomes were reported clearly.
Other bias	Unclear risk	Authors stated that the gender and the age in each group were similar at baseline, but the difficulties of the extraction and the detailed information of the tooth impaction were not reported

Kaya 2011

Methods	**Study design:** Randomised parallel-group controlled trial. **Study size:** 104. **Sample size calculation:** Not reported. **Conducted in:** Department of Oral and Maxillofacial Surgery, Atatürk University Faculty of Dentistry, Turkey **Number of centres:** 1. **Prevention or treatment of dry socket:** Treatment. **Type of teeth:** Mandibular permanent first molar. **Recruitment period:** 18-months, January 2008 to July 2009. **Funding source:** Not reported.
Participants	**Inclusion criteria:** • 18 years or older. • The ability to understand verbal and written instructions. • Previously diagnosed, but untreated AO in the mandibular permanent first molar extraction socket. **Exclusion criteria:** • Previous radiotherapy. • Any medical condition that could affect AO treatment (e.g. bone pathologic features, vascular or hematologic disorders, diabetes mellitus). • The use of antibiotics. • Pregnancy or lactation. • An allergy to iodine, eugenol, or paracetamol. • Patients who smoked, used oral contraceptives, were menstruating, or would require a surgical flap to remove the tooth were excluded. **Number randomised:** 104. **Number evaluated:** 104.
Interventions	**Comparison:** **Group 1 (n = 26):** Curettage and irrigation alone. **Group 2 (n = 26):** Curettage and irrigation followed by alvogyl applied directly to the socket **Group 3 (n = 26):** Curettage and irrigation followed by SaliCept patch applied directly to the socket **Group 4 (n = 26):** Curettage and irrigation followed by LLLT irradiation. **Co-interventions:** Patients were allowed 500 mg of acetaminophen as a rescue medication, as required, and were instructed to record how many times daily the medication was used. Additional follow-up visits were organized through the department, as necessary
Outcomes	**Primary outcome measures:** • Pain (VAS) - assessed each morning for 1 week. • Alveolar osteitis - days 3 and 7. **Secondary outcome measures:** • Not stated. **Adverse outcomes:** • Not stated.
Notes	

Risk of bias

Kaya 2011 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "The patients were randomly assigned…" **Comment:** Insufficient information to make a clear judgement.
Allocation concealment (selection bias)	High risk	Not mentioned and no information to suggest this was done.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned and no information to suggest this was done.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned and no information to suggest this was done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for in analysis.
Selective reporting (reporting bias)	Low risk	The report appears to be free of selective reporting.
Other bias	Low risk	The study appears to be free of other sources of bias.

Kjellman 1973

Methods	**Study design:** A randomised parallel-group controlled trial. **Sample size:** 100. **Sample size calculation:** Not reported. **Conducted in:** Department of Oral Surgery at Södersjukhuset Stockholm, Sweden **Number of centres:** 1. **Prevention or treatment of dry socket:** Prevention. **Type of teeth:** Impacted mandibular third molars, degree of difficulty unspecified, under local anaesthesia **Recruitment period:** Not stated. **Funding source:** Not stated.
Participants	**Inclusion criteria:** • Impacted mandibular third molars. **Exclusion criteria:** • Cases that have required relatively major operations on bone tissue. **Number randomised:** 100. **Number evaluated:** 100.

Kjellman 1973 (*Continued*)

Interventions	**Comparison:** **Group 1 (n = 50):** Apernyl cone, consisting of acetylsalicylic acid and p-oxybenzoic acid (preservative) inserted immediately after extraction **Group 2 (n = 50):** Placebo without acetylsalicylic acid inserted immediately after extraction **Co-interventions:** Concomitant pain medication unreported.
Outcomes	Assessments performed on days 1, 2 and 4 postoperatively. **Primary outcome measures:** • The occurrence of postoperative periosteitis "dry socket". **Secondary outcome measures:** • Not evaluated. **Adverse effects:** • Pain and burning sensation.
Notes	Inadequately reported, sparse trial details and incomplete and largely unusable data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "...with the help of a randomising procedure..." **Comment:** Insufficient information to make a clear judgement.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make a clear judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned and no information to suggest this was done.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned and no information to suggest this was done.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Very limited data, reported as graph plots. Insufficient information to make a clear judgement
Selective reporting (reporting bias)	Low risk	Although the protocol was unavailable all of the outcomes specified in the methods section appear to have been reported
Other bias	Low risk	Appears to be free of other potential sources of bias.

Larsen 1991

Methods	**Study design:** A randomised parallel-group controlled trial. **Sample size:** 150. **Sample size calculation:** None reported. **Prevention or treatment of dry socket:** Prevention. **Type of teeth:** Impacted mandibular third molars. **Conducted in:** Not stated. **Number of centres:** Not stated. **Recruitment period:** Not stated. **Funding source:** Procter and Gamble Co, Cin- cinnati, OH.
Participants	**Inclusion criteria:** • Bilaterally impacted mandibular third molars. **Exclusion criteria:** • Acute infection. • Participants on antibiotics. • Those requiring prophylaxis. **Number randomised:** 150. **Number analysed:** 139.
Interventions	**Comparison:** **Group 1 (n = 72):** 0.12% chlorhexidine gluconate 15 mL for 30 seconds a day for 1 week prior to surgery and 1 week after **Group 2 (n = 67):** Placebo rinse (identical appearance). **Concomitant medication:** Preoperative 8 mg dexamethasone IV. Postoperative 325 mg acetaminophen plus 30 mg codeine prn.
Outcomes	Assessment 1 week postoperative or earlier if pain. **Primary outcome measures:** • Presence of dry socket. **Secondary outcome measures:** • None stated. **Adverse effects:** • None stated.
Notes	Sponsored by Procter and Gamble Co, Cincinatti, OH. Randomisation was by patient but analysis by sites which will narrow the confidence intervals slightly

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "using a computer software routine supplied by the sponsor ..." " Within strata subjects were randomly assigned into two groups." **Comment:** Probably done.

Larsen 1991 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Insufficient information to make a judgement of Yes or No.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients were unaware of group allocation, personnel were unaware of group allocation. Active and placebo were identical in appearance
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear who made the assessment of outcome, while operators were blinded to allocation and appearance of placebo was identical, unlikely that they would have known group allocation when making assessment, however insufficient information to make a judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	No data available for drop-outs (11): unreported from which groups, when and the reasons
Selective reporting (reporting bias)	Low risk	Although the study protocol was unavailable, the report appears to be free of selective reporting of the outcomes
Other bias	High risk	Participants were stratified then randomised but subsequent analyses were at tooth level. Although we know how many sites were available for analysis we only know the baseline number of patients

Metin 2006

Methods	**Study design:** Randomised, parallel-group, controlled, double-blind, single-centre trial **Sample size**: 99. **Sample size calculation**: Not reported. **Conducted in:** Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Ondokuz, Mayis, University of Samsun, Turkey **Number of centres:** 1. **Prevention or treatment of dry socket:** Prevention. **Type of teeth:** Impacted mandibular third molars, under local anaesthesia. **Recruitment period:** Not stated. **Funding source:** Not reported.
Participants	**Inclusion criteria:** • Patients requiring surgical removal of impacted mandibular third molars. **Exclusion criteria:** • Acute infection. • Pericoronitis.

	• Patients using antibiotics or requiring antibiotic before treatment. **Number randomised:** 99. **Number analysed:** 99.
Interventions	**Comparison:** Pre & post op chlorhexidine rinse versus post op only. **Group 1 (n = 46):** Rinsed with chlorhexidine 0.2% 15 ml for 30 seconds twice per day for both 1 week prior to and 1 week after surgery **Group 2 (n = 53):** Rinsed with chlorhexidine 0.2% 15 ml for 30 seconds twice per day for 1 week after surgery **Co-interventions:** After removal of the teeth, the surgical sites were rinsed with 10 ml of sterile saline solution, and the soft tissue was closed and sutured with 3-0 silk suture
Outcomes	On the 7th day (or on preceding days if pain was present), the extraction sites were evaluated **Primary outcome measures:** • Incidence of alveolar osteitis. **Secondary outcome measures:** • Not evaluated. **Adverse effects:** Altered taste and numbness page 3. Numbness in the tongue reported in Group 1 and Group 2 45.6% and 13.2%. However, disturbance of taste sensation was seen in 56.5% of the patients in Group 1 and in 11.3% of the patients in Group 2
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "Patients were randomly assigned into two groups." **Comment:** Insufficient information to make a clear judgement.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make a clear judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants may have known their group allocation, it is not clear if personnel knew group allocation. A strict study criteria require that participants and personnel are blinded to group allocation but unclear reporting and unclear impact on performance bias
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It would appear that operators made the assessment of the outcome. It is possible that they may have become aware of group allo-

Metin 2006 (*Continued*)

		cation, but there is insufficient information **Quote:** "The same examiners made all the diagnoses."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants included in the outcome evaluation
Selective reporting (reporting bias)	Low risk	Although the protocol was unavailable all of the outcomes specified in the methods section appear to have been reported
Other bias	Low risk	Appears to be free of other potential sources of bias.

Mitchell 1984

Methods	**Study design:** Randomised, parallel-group, placebo-controlled, double-blind trial **Sample:** 64. **Conducted in:** Oral Surgery Department Newcastle Dental Hospital, UK. **Number of centres:** 1. **Prevention or treatment of dry socket:** Treatment. **Type of teeth:** No tooth specified. **Recruitment period:** Not stated. **Funding source:** Not reported.
Participants	**Inclusion criteria:** • A diagnosed dry socket. **Exclusion criteria:** • None stated. **Number randomised:** 64, 1 lost to follow-up but group allocation not stated. **Group (Metronidazole):** Randomised not reported; 6 lost to follow-up; analysed 26 (18%) **Group (Orabase placebo):** Randomised 32; 3 lost to follow-up; analysed 29 (10%). **Number analysed:** 55.
Interventions	**Comparison:** Metronidazole (10%) versus Orabase alone. **Group 1 (n = 26):** Metronidazole (10%) in carboxymethylcellulose gelatin (Orabase) paste **Group 2 (n = 29):** Orabase paste alone. Dressing syringed into the sockets. **Co-interventions:** Warm saline irrigation at presentation.
Outcomes	Review at 2 days post-intervention initially and then re-application dressing where necessary and review until cure **Primary outcome measures:** • Absence of pain. **Secondary outcome measures:** • Treatment time in days. • Number of visits to effect resolution.

	• Extraction time to start of treatment. **Adverse effects:** • Not reported.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "The patients were randomly allocated to the test or placebo group and the operator was unaware of the code breaker. " **Comment:** Insufficient information on which to base a judgement.
Allocation concealment (selection bias)	Low risk	**Quote:** "The patients were randomly allocated to the test or placebo group and the operator was unaware of the code breaker. " **Comment:** Probably done.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The test and control pastes were packaged in identical 2 ml syringes. Participants and personnel are blinded to group allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Operator unaware of group allocation and code only broken after study was complete
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 drop-out reported but not clear from which group, all other drop-outs fully reported. Unlikely to have had large impact on data analysis
Selective reporting (reporting bias)	Low risk	Although the study protocol was unavailable, the report appears to be free of selective reporting of the outcomes
Other bias	Low risk	Appears to be free of other potential sources of bias.

Ragno 1991

Methods	**Study design:** A randomised, controlled, double-blind, parallel-group study **Sample size calculation:** Not reported. **Conducted in:** Department of Oral and Maxillofacial Surgery, Walter Reed Army Medical Centre, Washington D.C. **Number of centres:** 1. **Prevention or treatment of dry socket:** Prevention. **Type of teeth:** Mandibular third molars, under intravenous sedation and local anaesthesia **Operator:** Resident surgeon for 8 years. **Recruitment period:** July 1987 to April 1989. **Funding source:** Not stated.
Participants	**Inclusion criteria:** • >18 years of age. • Negative medical history. • Not taking any medication apart from birth control pill. • 2 mandibular third molars for extraction. **Exclusion criteria:** • Not stated. **Mean age:** Not reported. **Intervention Group:** Number randomised 40; analysed 40. **Control Group:** Number randomised 40; analysed 40. **Number randomised:** 40 patients, but sites not (80). **Number analysed:** 40 patients, but sites not (80).
Interventions	**Comparisons:** On the day of surgery patients first rinsed with 15 ml of designated solution, teeth were then extracted, surgical sites irrigated with 15 ml of designated solution and soft tissue closed and sutured. The day after surgery patients began home use of solutions **Group 1 (n = 40; 80 surgical sites):** 0.12% CHX rinse, 15 ml twice daily for 7 days postoperatively **Group 2 (n = 40; 80 surgical sites):** Placebo rinse, 15 ml twice daily for 7 days postoperatively **Co-interventions:** None stated. **Concomitant interventions:** None stated.
Outcomes	Postoperative examination on days 3 and 7. **Primary outcome measures:** • Alveolar osteitis. **Secondary outcome measures:** • Postoperative questionnaire day 7, though not reported but presume it relates to adverse events associated with mouthrinse. **Adverse effects:** There were no allergic reactions to the chlorhexidine rinse. 3 participants reported bad taste, 1 reported stomach upset page 526 but no staining noted 1 person in the control had a severe surgical reaction which in the author's opinion was not attributable to the medication
Notes	On the day of the procedure patients first rinsed with 15 ml of their assigned solution for 30 seconds, after the procedure the sites were rinsed with 15 ml of the same solution

Ragno 1991 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	**Quote:** "The patients within each group were randomly assigned.'. **Comment:** Insufficient information to make a judgement.
Allocation concealment (selection bias)	Low risk	**Quote:** "The pharmacist manufactured the placebo and maintained the code for patient assignments"...."Decoding of the patient assignments revealed..." **Comment:** Probably done.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not clear that participants and personnel are blinded to group allocation. Strict study criteria require that participants and personnel are blinded to group allocation, though impact on performance bias is unclear
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clear who assessor was, not clear blinded to group allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patient lost to follow-up.
Selective reporting (reporting bias)	High risk	Postoperative questionnaire completed day 7, no data reported
Other bias	Low risk	Appears to be free of other potential sources of bias.

Reekie 2006

Methods	**Study design:** Randomised, parallel-group, double-blind, placebo-controlled study **Sample size:** 302. **Sample size calculation:** Undertaken. **Conducted in:** 3 dental practices in the UK. **Number of centres:** 3. **Prevention or treatment of dry socket:** Prevention. **Type of teeth:** Routine non-surgical extraction of 1 or more molar or premolar tooth under local anaesthetic **Recruitment period:** 2000-2003. **Funding source:** This study was supported by a grant from the Oral and Dental Research Trust
Participants	**Inclusion criteria:** • Non-surgical extraction of 1 or more molar/premolar tooth under local anaesthetic. **Exclusion criteria:** • Grade 3 mobile teeth. • Participants on warfarin, nicoumalone, phenytoin, fluocil, lithium and cimetidine. • Pregnant/breast feeding women. • Participants with intellectual impairment. **Number randomised:** 302. **Number analysed:** 27. Only patients calling back with pain were examined and assessed. It was assumed all others did not have dry socket
Interventions	**Comparison:** Metronidazole 25% gel versus placebo gel. **Group 1 (n = 152):** 0.25 ml of 25% metronidazole gel (62.5 mg). **Group 2 (n = 150):** Placebo gel (KY jelly). Gel syringed into socket immediately after dental extraction **Mean age:** 49.5, SD 14.77 (range 19 to 93). **Co-interventions:** Not stated.
Outcomes	Assessment made only on participants with severe pain and who phoned the surgery. Only patients with the classical signs of dry socket were reported **Primary outcome measures:** • Presence of dry socket. **Secondary outcome measures:** • None assessed or reported. **Adverse effects:** • Not selected as an outcome but were reported (*see* Notes).
Notes	Adverse events: Reported: 1 participant with nausea and vomiting, 2 complained of a bitter taste.

Risk of bias

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	**Quote:** "Blinding and randomisation was achieved by the manufacturer ....The syringes were allocated a code number derived from a random number sequence." **Comment:** Probably done.
Allocation concealment (selection bias)	Low risk	**Quote:** "Blinding and randomisation was achieved by the manufacturer ..The code constructed by the manufacturer and not broken until the end of the study." **Comment:** Probably done.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel were blinded to group allocation. Placebo and intervention gel had identical appearance
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Code was not broken until after the study, assessors were blinded to group allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	Only patients with pain and who phoned the surgery were "offered an appointment the same day to see a dentist" **Comment:** Incomplete outcome data and judged as potentially at high risk of bias
Selective reporting (reporting bias)	High risk	Only patients with pain and who phoned the surgery were "offered an appointment the same day to see a dentist" **Comment:** Incomplete outcome data and judged as potentially at high risk of bias
Other bias	Unclear risk	**Quote:** "Where more than one extraction was needed only one was randomly chosen to be included in the study." **Comment:** Unclear if this would constitute an element of selection bias

Ritzau 1977

Methods	**Study design:** Randomised, parallel-group, double-blind, placebo-controlled study **Sample size:** 45. **Sample size calculation:** Not reported. **Conducted in:** Royal Dental College in Aarhus, Denmark. **Number of centres:** 1. **Prevention or treatment of dry socket:** Prevention. **Type of teeth:** Impacted mandibular third molars. **Recruitment period:** February to May 1974. **Funding source:** Not stated.
Participants	**Inclusion criteria:** • Partially and totally impacted mandibular third molars. **Exclusion criteria:** • None stated. **Mean age:** 27 range (17 to 61 years). **Number randomised:** 45. **Number analysed:** 45.
Interventions	**Comparison:** Propylic ester of p-hydroxybenzoic acid versus placebo. **Group 1 (n = 24):** Propylic ester of p-hydroxybenzoic acid inserted in each socket **Group 2 (n = 21):** Placebo tablet gel inserted in each socket. **Co-interventions:** Postoperative analgesic tablets containing 10 mg of codeine phosphate, 500 mg of acetyle acid, and 70 mg of magnesium oxide were prescribed, and the number of tablets consumed was recorded Experimental substance or placebo inserted into postoperative socket immediately after removal of impacted third molar
Outcomes	Assessment day 7 postoperatively. Patients also assessed if they returned in pain at any point - the day of return was noted **Primary outcome measures:** • Occurence of alveolitis sicca dolorosa. **Secondary outcome measures:** • Pain. **Adverse outcomes:** • Haematoma and rash.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "PEPH or placebo were inserted at random selection...." **Comment:** Insufficient information to make a judgement.
Allocation concealment (selection bias)	Unclear risk	**Quote:** '"...The code was unknown to the investigators."

Ritzau 1977 (*Continued*)

		Comment: Probably done but randomisation unclear.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients and personnel were blinded to group allocation. Intervention and placebo were identical in appearance
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Patients and personnel were blinded to group allocation. Intervention and placebo were identical in appearance, code for group allocation not broken until after the study completed
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up.
Selective reporting (reporting bias)	Low risk	The report appears to be free of selective reporting of the outcomes
Other bias	Low risk	Appears to be free of other potential sources of bias.

Shi 2003

Methods	**Study design:** A randomised, parallel-group, controlled trial. **Sample size:** 274. **Sample size calculation:** Not reported. **Prevention or treatment of dry socket:** Prevention. **Type of teeth:** Impacted wisdom teeth. **Conducted in:** Not stated (appears to be 4th Medical University, Xi, Shaanxi China) **Number of centres:** Not stated. **Recruitment period:** November to April 2001. **Funding source:** Not stated.
Participants	**Inclusion criteria:** • Impacted wisdom tooth. **Exclusion criteria:** • History of acute pericoronitis in 10 days. • <18 and >65 years of age. • Smoking more than 3 cigarettes. • Oral contraceptives. • Contraindication of tooth extraction. **Number randomised:** 274. **Number analysed:** Not fully reported.
Interventions	**Comparison:** **Group 1 (n = 92):** Shahaosan. **Group 2 (n = 86):** Yunnan white drug. **Group 3 (n = 96):** Blank control.

Shi 2003 (*Continued*)

	Co-interventions: None stated.
Outcomes	Assessments 5-7 days post-extraction. Quote: "incidence and intensity of dry socket in each group were observed and evaluated by scores." **Primary outcome measures:** • Incidence of dry socket. **Secondary outcome measures:** • Self assessed POSSE (Postoperative Symptom Severity Scale) global assessment to include pain and "influence of daily life". Time and frequency of assessment unreported. **Adverse effects:** • No report of any assessment.
Notes	3 different colour capsules, unclear if both A and B are active interventions. Unclear if this was systemic or topical and method and timing of administration not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	**Quote:** "patients with extraction of impacted tooth were randomly divided into 3 groups." **Comment:** Insufficient information to establish the method of sequence generation
Allocation concealment (selection bias)	Unclear risk	Nothing reported, unable to make a clear judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Very limited data reported, unable to make a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Very limited data reported, unable to make a clear judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Very limited data reported, unable to make a clear judgement
Selective reporting (reporting bias)	Unclear risk	Very limited data reported, unable to make a clear judgement
Other bias	Unclear risk	Very limited data reported, unable to make a clear judgement

Torres-Lagares 2006

Methods	**Study design:** Randomised controlled "...prospective, parallel, single-blind clinical trial" **Sample size:** 30. **Sample size calculation:** Not reported. **Conducted in:** Faculty of Odontology of the University of Seville, Spain. **Number of centres:** 1. **Prevention or treatment of dry socket:** Prevention. **Type of teeth:** 1 or 2 impacted mandibular third molars, under local anaesthesia **Recruitment period:** September to December 2001. **Funding source:** Not stated.
Participants	**Inclusion criteria:** • 1 or 2 mandibular impacted third molars; difficulty index 4-7 Koerner scale (Koerner 1994). • No symptoms 10 days pre-surgery. **Exclusion criteria:** • Contra-indications for the intervention. • AIDS. • Smokers. • Immunodepressed patients. • Pregnant/lactating women. • Women taking oral contraceptives. • Allergies to: CHX, lidocaine or paracetamol. • Extraction of both wisdom teeth at one visit. • Bone pathology. • Having ingested any medication 4 days preoperatively. **Number randomised:** 30. **Number analysed:** 30.
Interventions	**Comparison:** **Group 1 (n = 17):** 10 ml of 0.2% CHX bio-adhesive gel applied intra-alveolar post-extraction **Group 2 (n = 13):** No intrasocket medication. **Co-interventions:** "All the patients took, as postoperative treatment, 14.05 mg codeine phosphate and 500 mg of paracetamol on demand..."
Outcomes	Unclear if assessed on days 3 and 7 postoperatively. **Primary outcome measures:** • Development of alveolar osteitis. **Secondary outcome measures:** • None stated. **Adverse effects:** • None stated.
Notes	November 2012: Communication from Dr Torres-Lagares confirmed that Hita-Iglesias 2008; Torres-Lagares 2006 & Torres-Lagares 2006a were separate studies each involving a different group of participants
Risk of bias	

Torres-Lagares 2006 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "The aforementioned allocation into one group or another was carried out by computer before the start of the study." **Comment:** Probably done.
Allocation concealment (selection bias)	Unclear risk	**Quote:** "...an envelope was opened, in which it indicated whether the patient should receive the bio-adhesive gel or not. " **Comment:** No mention of envelope nature (i.e. opaque or not) therefore unable to make a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Patients did not know allocation but operators would have. Strict study criteria required that participants and personnel were blinded to allocation, but unclear the impact on performance bias
Blinding of outcome assessment (detection bias) All outcomes	High risk	Operators detecting presence of dry socket could have remembered group allocation potential for high risk
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed the protocol and analysed.
Selective reporting (reporting bias)	Low risk	The report appears to be free of selective reporting of the outcomes
Other bias	Low risk	Appears to be free of other potential sources of bias.

Torres-Lagares 2006a

Methods	**Study design:** A randomised, controlled, parallel-group, double-blind study **Sample size:** 103. **Sample size calculation:** Not reported. **Conducted in:** Faculty of Dentistry of the University of Seville, Spain. **Number of centres:** 1. **Prevention or treatment of dry socket:** Prevention. **Type of teeth:** Impacted mandibular third molars - under local anaesthesia. **Recruitment period:** January-June 2003. **Funding source:** Laboratorios Lacer, Barcelona, Spain, donated the medication used in this study
Participants	**Inclusion criteria:** • 1 or 2 mandibular impacted third molars; difficulty index 4-7 Koerner scale (Koerner 1994). • No symptoms 10 days pre-surgery. • Aged 18-60 years of age. **Exclusion criteria:** • Contra-indications for the intervention. • AIDS. • Smokers. • Immunodepressed patients. • Pregnant/lactating women. • Women taking oral contraceptives. • Allergies to: CHX, lidocaine or paracetamol. • Extraction of 2 molars at once. • Bone pathology. • Having ingested any medication 4 days preoperatively. **Number randomised:** 103. **Number analysed:** 94.
Interventions	**Comparisons:** 0.2% CHX bio-adhesive gel versus no application. **Group 1 (n = 49):** 10 ml of 0.2% CHX bio-adhesive gel applied intra-alveolar post-extraction **Group 2 (n = 45):** Placebo gel - excipient containing. **Co-interventions:** All the patients took, as postoperative treatment, 14.05 mg codeine phosphate and 500 mg of paracetamol on demand
Outcomes	**Primary outcome measures:** • Developement of alveolar osteitis. **Secondary outcome measures:** • None stated. **Adverse effects:** • None stated.
Notes	No clear statement of when follow-up was done. November 2012: Communication from Dr Torres-Lagares confirmed that Hita-Iglesias 2008; Torres-Lagares 2006 & Torres-Lagares 2006a were separate studies each involving a different group of participants

Torres-Lagares 2006a (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	**Quote:** "The random assignment was carried out by means of a random number list. " **Comment:** Probably done.
Allocation concealment (selection bias)	Low risk	**Quote:** "The allocation of patients into one group or the other was carried out by computer before the start of the study. The gel was identifiable by a patient inclusion code number." **Comment:** Probably done.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote:** "Neither the patient nor the operator knew group allocation, the code list was kept in a sealed enveloped and was not opened until after the study. Placebo did not contain active ingredient."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quote:** "Operator did not know group allocation. The code list was kept in a sealed enveloped and was not opened until after the study."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Number of patients not included in final check-up visit stated, not included in analysis: 5 patients (1 in the control group and 4 in the test group) did not have their final check-up visit
Selective reporting (reporting bias)	Low risk	The report appears to be free of selective reporting of the outcomes
Other bias	Low risk	Appears to be free of other potential sources of bias.

Trieger 1991

Methods	**Study design:** Split-mouth randomised controlled trial. **Prevention or treatment of dry socket:** Prevention. **Type of teeth:** Mandibular bony third molar impactions. **Conducted in:** Setting unreported. **Number of centres:** Not stated. **Recruitment period:** Not stated. **Funding source:** "This study was made possible with a grant from Upjohn, Kalamazoo, Mich."
Participants	**Inclusion criteria:** • Bilateral mandibular third molar bony impactions. **Exclusion criteria:** • No antibiotics 2 weeks prior. **Number randomised:** 172 sites in 86 patients. **Number analysed:** Unclear.
Interventions	**Comparison:** **Group 1 (n = 86):** Gelfoam square saturated with 1 ml clindamycin phosphate solution (150 mg/ml). **Group 2 (n = 86):** Gelfoam square saturated with saline placebo. **Co-interventions:** Comcomitant analgesic medication allowed but no details reported
Outcomes	Not clear when assessments were made and by whom. **Primary outcome measures:** • Dry socket. **Secondary outcome measures:** • Not reported. **Adverse events:** • Unreported and unclear if assessed.
Notes	We assume there were no drop-outs but study poorly reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote**: "...according to a randomized distribution." **Comment:** Insufficient information to make a clear judgement if the sequence generation was adequate
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make a clear judgement if adequate
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Very limited data reported, unable to make a clear judgement

Trieger 1991 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Very limited data reported, unable to make a clear judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Very limited data reported, unable to make a clear judgement
Selective reporting (reporting bias)	Unclear risk	Very limited data reported, unable to make a clear judgement
Other bias	Unclear risk	Very limited data reported, unable to make a clear judgement

van Eeden 2006

Methods	**Study design:** Randomised controlled, split-mouth trial. **Sample size:** 19. **Sample size calculation:** Not reported. **Conducted in:** Military Hospital in South Africa. **Number of centres:** 1. **Prevention or treatment of dry socket:** Prevention. **Type of teeth:** Bilateral impacted mandibular third molars of similar difficulty assessed clinically and radiologically. Carried out under general anaesthesia **Recruitment period:** Not stated. **Funding source:** Not stated.
Participants	**Inclusion criteria:** • Bilateral impactions of similar levels as determined by clinical and radiographic examination. • No pericoronal infection. • No antibiotics. • No anti-inflammatory medication prior to surgery. • No associated co-morbidity. **Exclusion criteria:** • None stated. **Mean age:** 21.4 years (16-32 range). **Number randomised:** 19. **Number analysed:** 19.
Interventions	**Comparison:** Covomycin D versus inert gel foam carrier. **Group 1 (n = 19):** 1 mm Covomycin D (2.0 mg chloramphenicol, 5.0 mg neomycin sulphate and 0.5 mg dexamethasone) delivered within an inert gel foam carrier **Group 2 (n = 19):** Inert gel foam carrier - 1 ml normal saline. **Co-interventions:** Analgesic/anti-inflammatory medication 6 hourly when necessary (Myprodol®) Oral antibiotic medication (amoxicillin 500 mg 8 hourly or in penicillin allergic patients erythromycin 500 mg 6 hourly) for 5 days A 0.2% chlorhexidine gluconate mouthrinse 6 hourly for 5 days

van Eeden 2006 (*Continued*)

Outcomes	Pain scores were recorded at 6-hour intervals from the day of surgery until day 6. The patients were examined clinically on day 6 **Primary outcome measures:** • Development of alveolar osteitis, diagnostic criteria. **Secondary outcome measures:** • None stated. **Adverse effects:** Some of the events may be attributable to intervention or could be normal sequelae of operation
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	**Quote:** "...preselected on a random basis by the flip of a coin." **Comment:** Probably done.
Allocation concealment (selection bias)	Unclear risk	No mention of this. Therefore, insufficient information to make a clear judgement if adequate
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participans were blinded to group allocation. Personnel were blinded to group allocation but as they were not involved in assessment of outcomes, unlikely to have impact
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quote:** "..patients were examined clinically by an independent surgeon blinded to the site of intrasocket medication."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were accounted for at day 6.
Selective reporting (reporting bias)	Low risk	The report appears to be free of selective reporting of the outcomes
Other bias	Low risk	Appears to be free of other potential sources of bias.

AO = alveolar osteitis; CHX = chlorhexidine; RCT = randomised controlled trial.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Akota 1998	The intervention used was an impregnated gauze drain which was specifically excluded from this review
Al-Sukhun 2011	3 analgesics taken systemically to assess their ability to control pain after extraction. They were not local measures
Altman 2011	Not dry socket.
Annibali 2012	Not an RCT. Consensus statement on management of third molars
Anonymous 1966	Not an RCT. Translated from the Japanese by Prof Ken Yaegaki, Nippon Dental University Department of Oral Health, Tokyo, Japan
Arakeri 2011	Dry socket not defined.
Arenaz-Bua 2010	Dry socket not defined, general comments on sequelae.
Banach 1973	Not an RCT (translated from Polish).
Baqain 2012	The intervention was surgical (flap design) which was specifically excluded from the review
Bello 2011	The intervention was wound closure techniques excluded from this review
Berwick 1990	Drop-outs substituted making trial results invalid.
Betts 1995	Evaluated the efficacy of lidocaine jelly for the alleviation of pain experienced during the instrumentation of extraction sites diagnosed with alveolar osteitis. Assessment of pain related to instrumentation only
Bezerra 2011	Systemic amoxicillin antibiotic not local intervention.
Birke 1970	Not an RCT (translated from German).
Bloomer 2000	Quote: "In a consecutive manner, 1 of the 2 lower third molar sockets was packed on each patient. Sockets were packed in a series of 25 on 1 side then changed to a series of 25 on the opposite side throughout the series, totaling 100 patients." Comment: CCT quasi-randomised.
Bloomer 2012	Not an RCT. Expert opinion/commentary.
Brignardello 2012	Study about techniques, not dry socket.
Butler 1977	The interventions were lavage techniques which are excluded from this review
Butylin 1977	Cohort study. Translated from the Russian by Vasiliy Vlassov

(*Continued*)

Bystedt 1980	Interventions were systemic antibiotics.
Christensen 2012	Not an RCT. Expert opinion/commentary.
Cooper 2012	Pain study not dry socket.
Daniels 2011	Dry socket not defined. Pain management study.
Field 1988	Quote: "The trial was 'open' and on arrival extraction cases were consecutively allocated to one of three groups." Comment: CCT quasi-randomised.
Fotos 1992	Quote: "70 randomly selected healthy patients" page 383, "each subject was treated at one extraction site with a saline solution whereas the other site received CHX" page 384. Comment: No evidence of randomisation of participants to intervention
Garibaldi 1995	Quote: "Patients were assigned in sequential (A, B, C, A, B, C, etc) order." Comment: CCT quasi-randomised.
Goldman 1973	CCT non-randomised study.
Goldsmith 2012	Intervention involved surgical techniques which are excluded from the review
Goyal 2012	Not dry socket, instrument evaluation.
Hall 1971	Not an RCT. Expert opinion/commentary.
Haraji 2010	Interventions were envelope versus modified triangular flap designs, which are excluded from this review
Hill 2006	Pain study, not dry socket.
Hooley 1995	No clinical diagnosis of dry socket made, only used pain.
Johnson 1988	CCT non-randomised study.
Jolley 1972	Quote: "The purpose of this was to determine the effectiveness of the gel in controlling pain from ill-fitting dentures after extractions and in other situations" page 72. Comment: Not dry socket.
Jovanovic 2011	Not an RCT (after contact with author).
Julius 1982	Not an RCT. Split-mouth where all left hand sides received intervention and all right hand sides received the control
Keskitalo 1973	Quote: "Alternate patients were treated with Apernyl cones." Comment: CCT quasi-randomised.

(*Continued*)

Kirk 2007	Definition of dry socket not provided.
Krekmanov 1981	Only systemic interventions.
Krekmanov 1986	Unsure if randomised.
Kudiyirickal 2012	Not an RCT, not dry socket, looks at oral facial infections.
Lao 2012	Not dry socket.
Liu 2011	Not dry socket.
Long 2012	The intervention was a surgical technique which is excluded from this review
Lopez-Cedrun 2011	Systemic antibiotics, not a local intervention.
MacGregor 1973	Outcomes specified were pain and swelling, no clinical diagnosis of dry socket
MacGregor 1975	Quote: "Successive patients were entered in to the trials...arrangements were made that there was an equal distribution of experiments and controls." Comment: No evidence of randomisation.
Majid 2010	No definition of dry socket in report. Study refers to generalised sequelae
Malkawi 2011	Cross sectional study, not an RCT.
Mehlisch 2010a	No definition of dry socket. Study refers to pain management
Mehlisch 2010b	No definition of dry socket. Study refers to pain management
Mishra 2012	Not dry socket, dental pain.
Mitchell 1986	Quote: "They were allocated into groups according to a predetermined protocol." Comment: Inadequate method of sequence generation, quasi-randomised CCT
Mitchell 1986a	Systemic intervention, not a local intervention.
Nentwig 1985	Study unobtainable.
Neugebauer 2004	Participants "randomised into two groups". Randomisation at participant level but allocation of intervention 'split-mouth' at extraction socket level. Comment: Open allocation. CCT. Translated from the German language by Mona Nasser.
Neuner 1969	Study to treat pain and there is no mention that it is an RCT (German translation)

(*Continued*)

Nordenram 1973	Outcomes reported were "post-operative complications": pain/swelling/infection but with no independent assessments of classical 'dry socket'
Olson 1987	Abstract only, insufficient information for inclusion.
Olusanya 2011	Systemic antibiotics, not a local intervention.
Pichler 2001	Abstract only, insufficient information for inclusion.
Qi 2012	Not dry socket, pain management study.
Ritzau 1978	Unclear if RCT.
Sanchis 2004	Quote: "We divided the cases into a group of 100 patients who underwent extraction...." Comment: Non-randomised controlled (no treatment) study.
Schatz 1987	Age range of a group of participants outside the inclusion criteria and no subgroup data reported. Open allocation sequence
Schlund 1968	Study unobtainable.
Sorensen 1987	Quote: "Patients were randomly selected and divided so that approximately half would receive....." Comment: Non-RCT.
Swanson 1989	Quote: "One hundred impacted lower third molars were to be operated. They were to be included in the study in the random order in which they came to the surgery by routine booking methods." Comment: CCT quasi-randomised.
Sweet 1985	Quote: "The rinses were chosen by a random-selection technique." Comment: CCT quasi-randomised.
Syrjanen 1981	Controlled study, non-RCT.
Syrjanen 1981a	Does not measure dry socket as an outcome.
Tjernberg 1979	Quote: "Patients referred to the department for the surgical removal of a partially erupted, lower third molar were randomly distributed into two pools." Comment: CCT quasi-randomised.
Tong 2012	Not dry socket.
Torres-Lagares 2010	Patients in the study have bleeding disorders.
Vedtofte 1974	Quote: "The cones were packed in randomly numbered packets and the code was unknown to the investigators." Comment: Inadequate method of randomisation.

(*Continued*)

Wen 2004	Quote: "The method of random-digit dialling was adopted to divide groups." Translated from the Chinese by Dr Nian Fang. "Patients were divided into 2 groups Group A and Group B, with complete randomization according to the visit order....." Comment: Suggestive of quasi-randomisation. Inconsistencies between the English abstract and the translated version of the Chinese paper and lack of clarity in the methodology as reported did not provide any degree of confidence that adequate measures had been taken to satisfactorily randomised the participants or to conceal the allocation sequence in this study
Yue 2012	No dry socket, pain management study.
Zanetta-Barbosa 1994	Following email communication with the principal investigator, "the first patient was decided by a coin toss and the following was always allocated by alternation in the other group." Comment: CCT quasi-randomised.
Zuniga 2011	Dry socket not defined. Pain management study.

CCT= Controlled clinical trial; RCT = randomised controlled trial.

DATA AND ANALYSES

Comparison 1. Prevention of dry socket

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Chlorhexidine rinse versus placebo	4	750	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.43, 0.78]
2 Chlorhexidine gel versus placebo/no treatment	2	133	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.21, 0.87]

Analysis 1.1. Comparison 1 Prevention of dry socket, Outcome 1 Chlorhexidine rinse versus placebo.

Review: Local interventions for the management of alveolar osteitis (dry socket)

Comparison: 1 Prevention of dry socket

Outcome: 1 Chlorhexidine rinse versus placebo

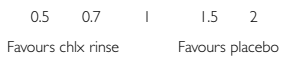
Study or subgroup	Chlorhexidine rinse n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Delilbasi 2002	13/62	14/59		18.5 %	0.88 [0.45, 1.72]
Hermesch 1998	25/136	40/135		40.0 %	0.62 [0.40, 0.96]
Larsen 1991	12/144	28/134		20.3 %	0.40 [0.21, 0.75]
Ragno 1991	10/40	20/40		21.2 %	0.50 [0.27, 0.93]
Total (95% CI)	**382**	**368**		**100.0 %**	**0.58 [0.43, 0.78]**

Total events: 60 (Chlorhexidine rinse), 102 (Placebo)

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 3.20$, df = 3 (P = 0.36); $I^2 = 6\%$

Test for overall effect: Z = 3.66 (P = 0.00026)

Test for subgroup differences: Not applicable

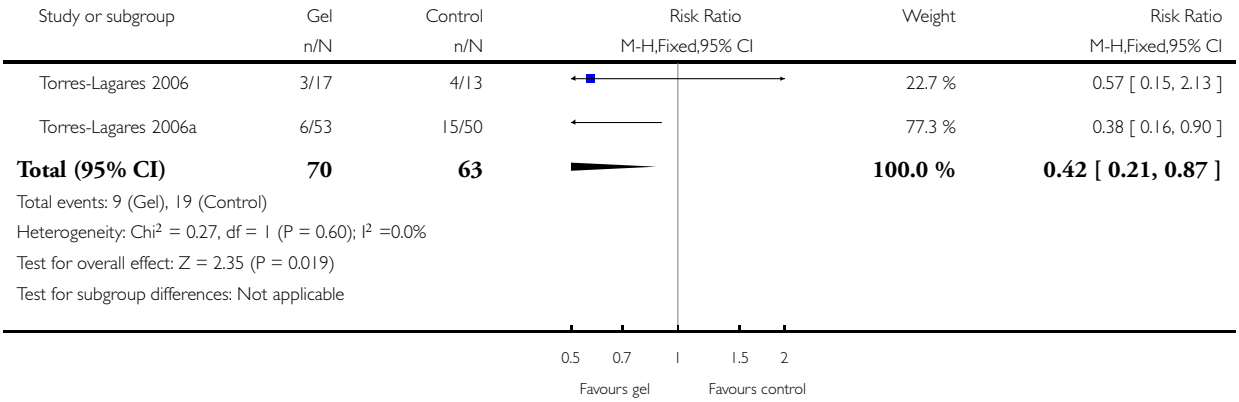


Analysis 1.2. Comparison 1 Prevention of dry socket, Outcome 2 Chlorhexidine gel versus placebo/no treatment.

Review: Local interventions for the management of alveolar osteitis (dry socket)

Comparison: 1 Prevention of dry socket

Outcome: 2 Chlorhexidine gel versus placebo/no treatment



ADDITIONAL TABLES

Table 1. Results for treatment of dry socket (single studies)

Comparison	Data	Effect (95% CI)	P-value
Anaesthetic gel versus eugenol (Burgoyne 2010). Pain at 48 hours.	Anaesthetic gel N = 15, mean = 2.49, SD = 2.51 Placebo N = 20, mean = 2.69, SD = 2.46	Mean difference -0.20 (-1.87 to 1.47)	0.81
Metronidazole versus placebo (Mitchell 1984). Duration of treatment.	Metronidazole N = 26, mean = 5.35, SD = 3.52 Placebo N = 29, mean = 8.52, SD = 8.52	Mean difference -3.17 (-1.04 to -5.300)	0.004

CI = confidence interval; SD = standard deviation.

Table 2. Results for prevention of dry socket (single studies)

Comparison	Data	RR/OR (95% CI)	P-value
Acellular dermal matrix patch versus no treatment (Bai 2011)	Patch 1/200 No patch 15/200	RR 0.07 (0.01 to 0.50)	0.008
Rinsing with chlorhexidine both pre- and post-extraction versus rinsing just post-extraction (Metin 2006)	Pre & post 3/46 Post 6/53	RR 0.58 (0.15 to 2.17)	0.42
Inserting chlorhexidine gel into the socket versus rinsing with chlorhexidine (Hita-Iglesias 2008)	Gel 3/40 Rinse 8/32	RR 0.30 (0.09 to 1.04)	0.06
Glucocorticosteroid antibiotic agent (post) versus normal saline (van Eeden 2006)	Split-mouth CS only = 0 NS only = 3 Both = 0 Neither = 16 Total N = 19	OR (exact) 0 (0 to 2.42)	0.25
Clindamycin phosphate antibiotic solution patch versus saline patch (Trieger 1991)	Split-mouth CP only = 0 S only = 7 Both = 0 Neither = 79 Total N = 86	OR (exact) 0 (0 to 0.69)	0.016
Metronidazole gel (post) versus placebo gel (Reekie 2006)	Met 8/152 Placebo 15/150	RR 0.53 (0.23 to 1.20)	0.13
Apernyl versus placebo (Kjellman 1973)	Apernyl 1/50 Placebo 4/50	RR 0.25 (0.03 to 2.16)	0.21
Platelet rich plasma versus control (Alissa 2010)	PRP 0/12 Control 2/9	RR = 0.15 (0.01 to 2.86)	0.21
Tranexamic acid versus placebo (Gersel-Pedersen 1979)	Split-mouth AMCA Y, placebo Y = 3 AMCA Y, placebo N = 6 AMCA N, placebo Y = 3 AMCA N, placebo N = 108	RR 0.67 (0.30 to 1.48)	0.51

Table 2. Results for prevention of dry socket (single studies) (*Continued*)

P-hydroxybenzoic acid versus placebo (Ritzau 1977)	P-hydro 0/24 Placebo 5/21	RR 0.08 (0.00 to 1.37)	0.08
Heal-all tissue patch versus no treatment (Huang 2011)	Patch 0/40 No patch 6/40	RR 0.08 (0.00 to 1.32)	0.08
Partial versus total wound closure (Bello 2011)	Partial 6/40 Total 4/42	RR 1.58 (0.48 to 5.17)	0.45
Chinese herbs Shahaosan versus placebo (Shi 2003)	Shah 1/92 Placebo 8/96	RR 0.13 (0.02 to 1.02)	0.05
Chinese herbs Yunnan versus placebo (Shi 2003)	Yunn 2/86 Placebo 8/96	RR 0.28 (0.06 to 1.28)	0.10
Chinese herbs Shahaosan versus Yunnan (Shi 2003)	Shah 1/92 Yunn 2/86	RR 0.47 (0.04 to 5.06)	0.53

CI = confidence interval; RR/OR = risk ratio/odds ratio.

Table 3. Adverse events reported in included studies for prevention of dry socket

Author/study	Intervention	Adverse events
Alissa 2010	Platelet rich plasma. Patients all given co-codamol to take postoperatively if needed	No adverse events reported.
Bai 2011	Acellular dermal matrix.	No adverse events reported.
Delilbasi 2002	0.2% chlorhexidine rinse. Paracetamol for postoperative pain relief. Patients rinsed with 15 ml of chlorhexidine solution "just before tooth removal" (page 302). Intraoperatively the surgical site was irrigated with 15 ml of chlorhexidine solution diluted with 15 ml of saline. The day after surgery patients began rinsing with 15 ml chlorhexidine, twice daily for 7 days	Adverse events reported for Group 1 n = 62. Allergy: n = 0. Staining of teeth: n = 4. Mucosal irritation: n = 0. Alteration in taste: n = 12. GIS complaints: n = 0. Bad taste: n = 8. No adverse reactions: n = 38. From Table IV page 303.

Table 3. Adverse events reported in included studies for prevention of dry socket (*Continued*)

Gersel-Pedersen 1979	AMCA cones versus lactose cones. All had 0.2% chlorhexidine 3 times a day.	Foreign body reaction to the vehicle delivery system in the cones
Hermesch 1998	0.12% chlorhexidine rinse. Participants in the experimental group rinsed for 30 seconds twice per day with 15 ml chlorhexidine 7 days preoperatively. On day of surgery supervised rinse before anaesthesia and surgery. Participants suspended rinsing for the remainder of the day and recommenced the next day	Adverse events: Group 1 CHX n = 136 and Group 2 placebo n = 135 Paraesthesia reported: CHX 9, placebo 5. Infection: CHX 4, placebo 3. Trismus: CHX 0, placebo 5. Gingivitis: CHX 1, placebo 3. Glossitis: CHX 2, placebo 2. Abnormal healing: CHX 1, placebo 3. Nausea: CHX 0, placebo 4. Sinusitis: CHX 1, placebo 3. Headache: CHX 1, placebo 2. Dysphagia: CHX 0, placebo 2. Edema (head & neck): CHX 1, placebo 1. Haemorrhage (prolonged): CHX 1, placebo 1. Pain: CHX 1, placebo 1. Pharyngitis: CHX 1, placebo 1. Rash: CHX 1, placebo 1. There were single site observations of each of the following: asthenia, bronchitis, cyst, depression, contact dermatitis, dyspepsia, ecchymosis, fever, herpes simplex, hypalgesia, back pain, rhinitis, stomatitis, and tenosynovitis. All but 2 cases of paraesthesia had resolved by end of study, one in each treatment group. From Table VII page 384
Hita-Iglesias 2008	Chlorhexidine 0.2% gel versus 0.12% chlorhexidine mouthrinse. Participants in the 0.2% chlorhexidine gel group had the gel placed in the socket during surgery and then they were required to apply the gel to the socket twice a day (morning and night-time) for 7 days beginning on the same day as the surgery. Patients in the rinse group rinsed twice a day (morning and night-time) for 7 days beginning on the same day as the surgery	No adverse events reported.
Huang 2011	Intradermal matrix.	No adverse events reported.
Kjellman 1973	Apernyl as alveolar.	Pain and burning sensation page 200.
Larsen 1991	0.12% chlorhexidine rinse versus placebo. All patients received 8 mg dexamethasone (glucocorticoid) IV prior to surgery. Participants were required to rinse twice per day for 30 seconds using 15 ml of the solution for 7 days prior to the surgery. On the day of the surgery they rinsed with the solution	No adverse reactions page 954.

Table 3. Adverse events reported in included studies for prevention of dry socket (*Continued*)

	immediately prior to surgery (using 15 ml) and postoperatively patients were instructed to begin rinsing the day following surgery	
Metin 2006	0.2% chlorhexidine rinse 7 days preoperatively and 7 days postoperatively (group I) versus 7 days postoperatively only (group II)	Altered taste and numbness page 3. Numbness in the tongue reported in group I and group II 45.6% and 13.2%. However, disturbance of taste sensation was seen in 56.5% of the patients in group I and in 11. 3% of the patients in group II
Ragno 1991	0.12% chlorhexidine rinse. Participants rinsed immediately before surgery, the surgical was irrigated intraoperatively and starting the day after the surgery participants were asked to rinse with solution twice daily (15 ml) for 7 days postoperatively	There were no allergic reactions to the chlorhexidine rinse. 3 participants reported bad taste, 1 reported stomach upset page 526 but no staining noted 1 person in the control had a severe surgical reaction which in the author's opinion was not attributable to the medication
Reekie 2006	0.25 ml of 25% metronidazole gel intrasocket intervention.	1 participant with nausea and vomiting, 2 complained of a bitter taste
Ritzau 1977	PEPH (p-hydroxybenzoic acid).	Haematoma and rash.
Shi 2003	Artemisia desertorum spreng (Shahaosan, Yunnan).	No adverse events reported.
Torres-Lagares 2006	0.2% chlorhexidine gel intrasocket versus placebo. Participants in the 0.2% chlorhexidine gel group had the gel placed in the socket during surgery. Note only 1 application of bio-adhesive gel during surgery	No adverse events reported.
Torres-Lagares 2006a	0.2% chlorhexidine gel intrasocket versus placebo. Participants in the 0.2% chlorhexidine gel group had the gel placed in the socket during surgery. Note only 1 application of bio-adhesive gel during surgery	No adverse events reported.
Trieger 1991	Gelfoam clindamycin.	No adverse events reported.
van Eeden 2006	Gelfoam covomycin. 0.2% chlorhexidine advised postoperatively every 6 hours for 5 days	Some of the events may be attributable to intervention or could be normal sequelae of operation

CHX = chlorhexidine.

APPENDICES

Appendix 1. MEDLINE (OVID) search strategy

1. Dry socket/
2. ("alveolar osteitis" or "alveolar ostitis").mp.
3. (alveolalgia or "alveolar periostitis" or "alveolitis sicca dolorosa").mp.
4. ((septic adj4 socket*) or "necrotic socket osteomylitis" or "fibrinolytic alveolitis").mp.
5. ("dry socket$" or dry-socket$ or (infect$ adj5 socket$)).mp.
6. or/1-5
7. exp Tooth Extraction/
8. ("dental extraction$" or (tooth adj3 extract$) or (teeth adj3 extract$) or (teeth adj3 remov$) or (tooth adj3 remov$)).mp.
9. ((dental or oral) and (surgery or surgical)).mp.
10. or/7-9
11. 6 and 10

The above subject search was linked to the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomised trials in MEDLINE: sensitivity maximising version (2008 revision) as referenced in Chapter 6.4.11.1 and detailed in box 6.4.c of the *Cochrane Handbook for Systematic Reviews of Interventions, v*ersion 5.1.0 (updated March 2011) (Higgins 2011).

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. or/1-8
10. exp animals/ not humans.sh.
11. 9 not 10

Appendix 2. The Cochrane Oral Health Group's Trials Register search strategy

The register was searched via the Cochrane Register of Studies, using the following search strategy:

#1 (("dry socket*" or "alveolar osteitis" or "alveolar ostitis" or alveolagia or "alveolar periostitis" or "alveolitis sicca dolorosa" or dry socket* or "septic socket*" or "necrotic socket osteomylitis" or "fibrinolytic alveolitis")) AND (INREGISTER)

#2 ((infect* and socket*)) AND (INREGISTER)

#3 (#1 or #2) AND (INREGISTER)

#4 (extract* or remov* or surg*) AND (INREGISTER)

#5 (#3 and #4) AND (INREGISTER)

Previous searches were conducted using the following strategy on the ProCite version of the register (to January 2012):

(("dry socket*" or "alveolar osteitis" or "alveolar ostitis" or alveolagia or "alveolar periostitis" or "alveolitis sicca dolorosa" or dry-socket* or "septic socket*" or "necrotic socket osteomylitis" or "fibrinolytic alveolitis" or (infect* and socket*)) AND (extract* or remov* or surg*))

Appendix 3. Cochrane Central Register of Controlled Trials (CENTRAL) search strategy

#1 MeSH descriptor Dry Socket this term only
#2 ("alveolar osteitis" in All Text or "alveolar ostitis" in All Text)
#3 ((septic in All Text near/4 socket* in All Text) or "necrotic socket osteomylitis" in All Text or "fibrinolytic alveolitis" in All Text)
#4 (alveolalgia in All Text or "alveolar periostitis" in All Text or "alveolitis sicca dolorosa" in All Text)
#5 ("dry socket*" in All Text or dry-socket* in All Text or (infect* in All Text near/5 socket* in All Text))
#6 (#1 or #2 or #3 or #4 or #5)
#7 MeSH descriptor Tooth Extraction explode all trees
#8 ("dental extraction*" in All Text or (tooth in All Text near/3 extract* in All Text) or (teeth in All Text near/3 extract* in All Text) or (teeth in All Text near/3 remov* in All Text) or (tooth in All Text near/3 remov* in All Text))
#9 ((dental in All Text or oral in All Text) and (surgery in All Text or surgical in All Text))
#10 (#7 or #8 or #9)
#11 (#6 and #10)

Appendix 4. EMBASE (OVID) search strategy

1. Dry socket/
2. ("alveolar osteitis" or "alveolar ostitis").mp.
3. (alveolalgia or "alveolar periostitis" or "alveolitis sicca dolorosa").mp.
4. ((septic adj4 socket*) or "necrotic socket osteomylitis" or "fibrinolytic alveolitis").mp.
5. ("dry socket$" or dry-socket$ or (infect$ adj5 socket$)).mp.
6. or/1-5
7. exp Tooth Extraction/
8. ("dental extraction$" or (tooth adj3 extract$) or (teeth adj3 extract$) or (teeth adj3 remov$) or (tooth adj3 remov$)).mp.
9. ((dental or oral) and (surgery or surgical)).mp.
10. or/7-9
11. 6 and 10

The above subject search was linked to the Cochrane Oral Health Group filter for EMBASE via OVID:

1. random$.ti,ab.
2. factorial$.ti,ab.
3. (crossover$ or cross over$ or cross-over$).ti,ab.
4. placebo$.ti,ab.
5. (doubl$ adj blind$).ti,ab.
6. (singl$ adj blind$).ti,ab.
7. assign$.ti,ab.
8. allocat$.ti,ab.
9. volunteer$.ti,ab.
10. CROSSOVER PROCEDURE.sh.
11. DOUBLE-BLIND PROCEDURE.sh.
12. RANDOMIZED CONTROLLED TRIAL.sh.
13. SINGLE BLIND PROCEDURE.sh.
14. or/1-13
15. ANIMAL/ or NONHUMAN/ or ANIMAL EXPERIMENT/
16. HUMAN/
17. 16 and 15
18. 15 not 17
19. 14 not 18

CONTRIBUTIONS OF AUTHORS

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- The original protocol was only for the treatment of dry socket. We have expanded the scope of the review to incorporate the prevention of dry socket.
- We added the primary outcome for treatment of dry socket: time to heal.
- We reworded 'type of participant' to clarify the inclusion of any extracted teeth.
- We changed analyses from fixed-effect to random-effects as requested by referee.

INDEX TERMS

Medical Subject Headings (MeSH)

Chlorhexidine [therapeutic use]; Dry Socket [prevention & control; *therapy]; Molar, Third [surgery]; Mouthwashes [therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans