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Corticosteroids as standalone or add-on treatment for sore throat (Review)

Hayward G, Thompson MJ, Perera R, Glasziou PP, Del Mar CB, Heneghan CJ

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[Intervention Review]

Corticosteroids as standalone or add-on treatment for sore throat

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ABSTRACT

Background

Sore throat is a common condition associated with a high rate of antibiotic prescriptions, despite limited evidence for the effectiveness of antibiotics. Corticosteroids may improve symptoms of sore throat by reducing inflammation of the upper respiratory tract.

Objectives

To assess the clinical benefit and safety of corticosteroids for symptoms of sore throat in adults and children.

Search methods

We searched *The Cochrane Library*, the Cochrane Central Register of Controlled Trials (CENTRAL 2012, Issue 5) which includes the Acute Respiratory Infections (ARI) Group's Specialised Register, the Database of Reviews of Effects and the NHS Health Economics Database, MEDLINE (1966 to November Week 4, 2012) and EMBASE (1974 to June 2012).

Selection criteria

We included randomised controlled trials that compared steroids to either placebo or standard care in adults and children (older than three years of age) with sore throat. We excluded studies of hospitalised participants, those with infectious mononucleosis, sore throat following tonsillectomy or intubation, or peritonsillar abscess.

Data collection and analysis

Two review authors independently reviewed and selected trials from searches, assessed and rated study quality, and extracted relevant data.

Main results

We included eight trials involving 743 participants (369 children and 374 adults). All trials gave antibiotics to both placebo and corticosteroid groups; no trials assessed corticosteroids as standalone treatment for sore throat. In addition to any effect of antibiotics and analgesia, corticosteroids increased the likelihood of complete resolution of pain at 24 hours by more than three times (risk ratio (RR) 3.2, 95% confidence interval (CI) 2.0 to 5.1, $P < 0.001$, I^2 statistic 44%) and at 48 hours by 1.7 times. Fewer than four people need to be treated to prevent one person continuing to experience pain at 24 hours. Corticosteroids also reduced the mean time to onset of pain relief and the mean time to complete resolution of pain by 6 and 14 hours, respectively, although significant heterogeneity was present. At 24 hours, pain (assessed by visual analogue scores) was reduced by an additional 14% by corticosteroids. No difference in rates of recurrence, relapse or adverse events were reported for participants taking corticosteroids compared to placebo, although reporting of adverse events was poor.

Authors' conclusions

Oral or intramuscular corticosteroids, in addition to antibiotics, increase the likelihood of both resolution and improvement of pain in participants with sore throat. Further trials assessing corticosteroids in the absence of antibiotics and in children are warranted.

PLAIN LANGUAGE SUMMARY

Corticosteroids as standalone or add-on treatment for sore throat

Sore throat is a common condition. Patients often receive antibiotics for sore throat, which is thought to contribute to resistance to antibiotics in individuals and the community. Sore throats are painful because of the inflammation of the lining of the throat. Corticosteroids reduce inflammation and because they act on the upper respiratory tract in other conditions, may also be beneficial in sore throat.

This systematic review combined the results of eight trials which looked at this question, including a total of 743 participants. Patients taking corticosteroids were three times more likely to experience complete resolution of their sore throat symptoms by 24 hours compared to those taking placebo. In addition, corticosteroids improved the time to onset of symptom relief and the time to complete resolution of symptoms, although the trials were not consistent for these outcomes. Adverse events, relapse rates and recurrence rates were not different for corticosteroid compared to placebo groups. Limitations of the review include the absence of any trials set in Europe and the fact that only two trials addressed the question in children. As all the included trials also gave antibiotics to all participants, we recommend that future research should examine the benefit of corticosteroids in patients who are not also taking antibiotics.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Corticosteroids compared to placebo for sore throat

Corticosteroids compared to placebo for sore throat

Patient or population: patients with sore throat
Settings: emergency departments and General Practice
Intervention: corticosteroids
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Corticosteroids				
Complete resolution of sore throat pain at 24 hours Patient report	**Study population**		**RR 3.16** (1.97 to 5.08)	286 (4 studies)	⊕⊕⊕⊕ **high** [1,2]	
	12 per 100	**39 per 100** (241 to 622)				
	Moderate					
	11 per 100	**34 per 100** (211 to 544)				
Complete resolution of sore throat pain at 48 hours Patient report	**Study population**		**RR 1.65** (1.32 to 2.06)	209 (3 studies)	⊕⊕⊕⊖ **moderate** [3]	
	47 per 100	**77 per 100** (618 to 965)				
	Moderate					
	524 per 1000	**87 per 100** (692 to 1000)				
Mean time to onset of pain relief in hours Patient report	The mean time to onset of pain relief in hours in the control groups was **14 hours**	The mean time to onset of pain relief in hours in the intervention groups was **6.3 lower** (9.29 to 3.35 lower)		609 (6 studies)	⊕⊕⊕⊖ **moderate** [4]	

Mean time to complete resolution of sore throat pain Patient report	The mean time to complete resolution of pain in the control groups was **46 hours**	The mean time to complete resolution of pain in the intervention groups was **14 hours fewer** (25 to 4 fewer)		500 (5 studies)	⊕⊕⊕⊖ **moderate** [5]
Mean absolute reduction in sore throat pain at 24 hours Visual analogue scale or McGrath scale	The mean absolute reduction in pain at 24 hours in the control groups was **3.6 VAS units (max 10, min 0)**	The mean absolute reduction in pain at 24 hours in the intervention groups was **1.3 greater** (0.61 to 2.06 greater)		617 (6 studies)	⊕⊕⊕⊕ **high**
Recurrence/relapse of symptoms Patient report	**Study population**		**RR 0.56** (0.24 to 1.34)	353 (3 studies)	⊕⊕⊕⊖ **moderate** [6]
	8 per 100	**4 per 100** (18 to 100)			
	Moderate				
	7 per 100	**36 per 100** (16 to 87)			
Number of days missed from work or school Patient report	The mean number of days missed from work or school in the control groups was **0.7 days**	The mean number of days missed from work or school in the intervention groups was **0.3 fewer** (0.87 fewer to 0.27 more)		92 (1 study)	⊕⊕⊕⊖ **moderate** [7]

*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 (CI)) 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
VAS: visual analogue scale

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] Total number of cases < 300.
[2] RR > 2.
[3] Total number of cases < 300.
[4] High heterogeneity, multiple possible contributing factors.
[5] High heterogeneity.
[6] Low overall numbers of events in each group, 95% CI includes no effect.

7 Single study only.

BACKGROUND

Description of the condition

Sore throat is a very common reason for people to seek medical care, accounting for approximately nine consultations for every 100 patients registered with a General Practioner (GP) in the UK (Gulliford 2009). Sore throat is a term which can refer both to a patient's complaint of pain in the throat due to an infection but also includes pathological conditions such as tonsillitis or pharyngitis. Many sore throats are caused by viral infections such as rhinovirus, coronavirus and adenovirus. The main bacterial pathogen is Group A beta-haemolytic streptococcus (GABHS), found in approximately 10% of adult and 15% to 30% of sore throats in children (Bisno 2001; Linder 2005). Although antibiotics have only a small benefit for sore throat (Del Mar 2011), the rate of antibiotic prescribing for this condition remains high with an estimated rate of 40% to 50% of UK consultations in 2006 (Gulliford 2009; Linder 2001). In part, this may be due to attempts by clinicians to reduce symptoms in patients with sore throat and also to reduce the risk of known complications of streptococcal throat infection such as peritonsillar abscess, rheumatic fever and glomerulonephritis. However, the incidence of these complications is currently very low in high-income countries, for example, hospital admission for peritonsillar abscess occurs in less than 4 per 100,000 people and the effects of antibiotics overall in patients with sore throats is small (Howie 1985; Little 2002; NICE 2008; Petersen 2007; Sharland 2005). Furthermore, unnecessary antibiotic use contributes to the development of antimicrobial resistance (SMAC 1998).

Description of the intervention

Corticosteroids are a group of steroid hormones which are secreted naturally by the adrenal cortex and are also synthetically produced. They are hormones that are involved in a large range of physiological systems in the human body, particularly those related to inflammation and immune response. Synthetic corticosteroids are widely used in clinical practice in topical, oral and parenteral forms. The intervention we will examine is the use of corticosteroids administered locally (for example, sprays into the throat), or systemically (by oral or parenteral administration) to participants suffering from sore throats.

How the intervention might work

The discomfort experienced by people with sore throat is due to inflammation in the oropharyngeal mucosa. This results in pain and particularly pain with swallowing saliva or ingesting food or drink. Therefore, reducing the level of inflammation could lead to fewer symptoms. Analgesics which are currently used for sore throat include topical agents with mild local anaesthetic properties, as well as oral agents such as non-steroidal anti-inflammatory drugs. Corticosteroids are widely used to reduce inflammation in many conditions, both locally (for example, topical corticosteroids for eczema, steroid joint injections for inflamed joints), as well as systemically (for example, oral steroids for rheumatoid arthritis). Moreover, corticosteroids decrease inflammation in the respiratory tract epithelium (Mygind 2001) and improve symptoms and other outcomes in other upper respiratory tract infections such as acute sinusitis (Zalmanovici 2011) and viral croup (Russell 2011). They may also provide short-term relief from the symptoms of sore throat in infectious mononucleosis (Candy 2011). The question that we will address is whether corticosteroids offer any relief for symptoms in adults and children with sore throats.

Why it is important to do this review

There are currently few therapeutic options for managing sore throats in adults and children. There is wide consensus that antibiotics are overused for treating sore throat in primary care and contribute to growing antibiotic resistance (NICE 2008). However, there are currently few other therapeutic options available for management of sore throat in adults and children. Oral and topical analgesics are often recommended or prescribed for sore throat, with unclear benefit (NICE 2008). If corticosteroids provided significant symptomatic benefit in people with sore throat they could potentially fill this therapeutic vacuum. If corticosteroids reduce symptoms, then it is possible that after testing in the absence of antibiotics, and if found to be effective still without adverse effects, then they might be used to reduce the demand for or use of antibiotics for this condition.

Although corticosteroids are widely used in clinical practice, they can cause side effects. It is therefore important to determine how frequently these occur in treating patients with sore throat and whether they are outweighed by any benefits. This systematic review attempts to resolve this for sore throat in adults and children.

OBJECTIVES

To assess the clinical benefit and safety of corticosteroids on reducing the symptoms of sore throat in adults and children.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) comparing corticosteroids to placebo or to standard clinical management.

Types of participants

We included adults and children (older than three years of age) with sore throat. Specifically sore throat includes the following.

1. Clinical signs of acute tonsillitis - inflammation of the tonsils.
2. Pharyngitis - inflammation of the oropharynx.
3. Clinical syndrome of sore throat (painful throat, odynophagia).

We excluded studies of hospitalised participants but included studies examining outpatients seen in the Emergency Department setting. We excluded studies of participants with infectious mononucleosis, sore throat following tonsillectomy or intubation, or peritonsillar abscess.

Types of interventions

Studies which used corticosteroids versus standard clinical care or placebo in the control group were included. All routes and types of corticosteroid administration were included. Trials reporting combined interventions were included if they allowed a direct comparison between corticosteroids and usual care.

Types of outcome measures

Primary outcomes

1. Resolution or improvement of any patient-related symptoms
2. Mean time to onset of symptom and pain relief

Secondary outcomes

1. Reduction in pain measured by visual analogue scales
2. Adverse events
3. Days missed from school or work
4. Relapse rates

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2012, Issue 5, part of *The Cochrane Library,* www.thecochranelibrary.com (accessed 5 June 2012) which includes the Acute Respiratory Infections (ARI) Group's Specialised Register, MEDLINE (1966 to May week 4, 2012) and EMBASE (1974 to June 2012). We also searched the Database of Abstracts of Reviews of Effects (DARE) and the NHS Health Economics Database (accessed from *The Cochrane Library*, 5 June 2012).

We searched MEDLINE and CENTRAL, combining our search strategy with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision), Ovid format (Lefebvre 2011) (Appendix 1). We adapted the search strategy to search EMBASE (Appendix 2).

Searching other resources

To increase the yield of relevant studies, we searched the references of all identified studies. We looked for any ongoing trials registered with the World Health Organization (WHO) International Clinical Trials Register (inception to 6 June 2012). There were no language or publication restrictions.

Data collection and analysis

Selection of studies

Two review authors (GH, MT) independently reviewed the titles and abstracts from the electronic searches. We obtained the full-text articles and assessed them for relevance. We resolved disagreements by discussion with a third review author (CH).

Data extraction and management

Two review authors (GH, MT) independently extracted data from included trials. We documented disagreements and resolved them by discussion with a third review author (CH). A statistician (RP) independently reviewed all data extracted from original publications to verify the quality of methods and analysis used. We selected the data closest to a single-dose regime as our conservative strategy in those studies using different dosing regimes. Where studies reported results from both oral and intramuscular corticosteroid use, we used oral data for our overall analyses and the intramuscular data in appropriate subgroup analysis. Where necessary, we extracted data from graphs using the programme Grab It XP in Microsoft Excel.

Assessment of risk of bias in included studies

Two review authors (GH, MT) independently assessed the methodological quality. We documented and resolved any disagreements by discussion with a third review author (CH). The specific aspects of methodological quality assessed included allocation concealment, randomisation, blinding, treatment adherence, percentage participation and comparability of groups on baseline characteristics.

Measures of treatment effect

We expressed dichotomous outcomes as risk ratios (RR) and calculated 95% confidence intervals (CIs). We expressed continuous variables as a mean difference (MD) if reported on the same scale or as a standardised mean difference (SMD) if reported using different continuous scales and calculated 95% CIs.

Dealing with missing data

We considered that incomplete outcome data had been addressed if more than 80% of participants were included in the analysis. All of our trials satisfied this criteria. Where data were missing (for example, change from baseline data where baseline and endpoint values were provided) we calculated this using the formula suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Assessment of heterogeneity

We used the I^2 statistic (Higgins 2003) to quantify the level of statistical heterogeneity for each outcome. We performed a fixed-effect meta-analysis where no heterogeneity was present. We considered possible explanations where substantial heterogeneity (I^2 statistic above 50%) was detected and, where applicable, we used a random-effects model to test the robustness of the findings, or considered not combining the results and presenting a descriptive analysis instead.

Assessment of reporting biases

We compared data previously published as an abstract with the full paper where possible. We assessed the extent to which common outcomes were reported by each paper and looked for incomplete reporting of outcomes.

Subgroup analysis and investigation of heterogeneity

We performed subgroup analyses for the following groups.

1. Children/adults.
2. Proven bacterial pathogen.
3. Route of corticosteroid administration.
4. Presence/absence of exudate.
5. Severity of sore throat.

We performed subgroup analyses only where each subgroup contained two or more studies, because analyses of small subgroups can often produce misleading results.

Sensitivity analysis

Where we found heterogeneity we explored the causes, in particular, by examining the characteristics (methodological and clinical) of the included trials. We used a sensitivity analysis to understand the impact of any differences on the results.

RESULTS

Description of studies

Results of the search

We retrieved 712 references from our searches. Assessment of the titles and abstracts resulted in 12 potentially relevant papers, for which the full text was obtained.

Included studies

Participants

The eight studies included in the review involved 743 participants (369 participants aged 5 to 21 years and 374 participants aged 12 to 65 years): 348 (47%) had exudative sore throat, 330 (44%) were group A beta-haemolytic streptococcus (GABHS) positive. Two trials included only adult participants (Kiderman 2005; Tasar 2008), two trials included only children (Bulloch 2003; Olympia 2005) (age range 5 to 18 years) and the remainder included both age groups.

Patients were recruited from Emergency Department and General Practice settings in four countries: USA (Marvez-Valls 1998; Niland 2006; O'Brien 1993; Olympia 2005; Wei 2002), Canada (Bulloch 2003), Israel (Kiderman 2005) and Turkey (Tasar 2008).

Interventions

In all included trials antibiotics were administered to both corticosteroid and placebo groups. Corticosteroids used included betamethasone 2 ml (estimated dose 8 mg) (Marvez-Valls 1998), dexamethasone (up to 10 mg) (Bulloch 2003; Niland 2006; O'Brien 1993; Olympia 2005; Tasar 2008; Wei 2002) or prednisone 60 mg (Kiderman 2005). Corticosteroids were administered either intramuscularly (Marvez-Valls 1998; O'Brien 1993; Tasar 2008), orally (Bulloch 2003; Kiderman 2005; Niland 2006; Olympia 2005) or both (Wei 2002). Six trials (Bulloch 2003; Marvez-Valls 1998; O'Brien 1993; Olympia 2005; Tasar 2008; Wei 2002) used a single dose of corticosteroids and two trials (Kiderman 2005; Niland 2006) prescribed more than one dose of corticosteroids to a subgroup of participants.

Outcomes

Outcome measures included complete resolution of pain at 24 hours (Kiderman 2005; Niland 2006; Tasar 2008; Wei 2002) and 48 hours (Kiderman 2005; Niland 2006; Tasar 2008), mean time to onset of pain relief (Bulloch 2003; Marvez-Valls 1998; O'Brien 1993; Olympia 2005; Tasar 2008; Wei 2002), mean time to complete resolution of pain (Bulloch 2003; Marvez-Valls 1998; O'Brien 1993; Olympia 2005; Tasar 2008), reduction in visual analogue scale pain score (Bulloch 2003; Kiderman 2005; Marvez-Valls 1998; O'Brien 1993; Olympia 2005; Wei 2002), recurrence/relapse rates (Bulloch 2003; Kiderman 2005; Niland 2006), adverse events (Bulloch 2003; O'Brien 1993; Olympia 2005; Tasar 2008) and number of days missed from school or work (Marvez-Valls 1998).

Seven trials prescribed antibiotics to both intervention and placebo arms and allowed simple analgesia. One trial (Bulloch 2003) only prescribed antibiotics to those testing positive for GABHS on direct antigen testing. In four trials analgesia use was recorded (Niland 2006; O'Brien 1993; Olympia 2005; Wei 2002) and in all cases no significant differences were reported. Two trials restricted analgesia to paracetamol for 24 or 72 hours, recording no difference in use (Wei 2002) and not reporting usage (Tasar 2008) respectively. Four trials reported outcomes for bacterial pathogen positive and negative participants separately (Bulloch 2003; Marvez-Valls 1998; Olympia 2005; Wei 2002).

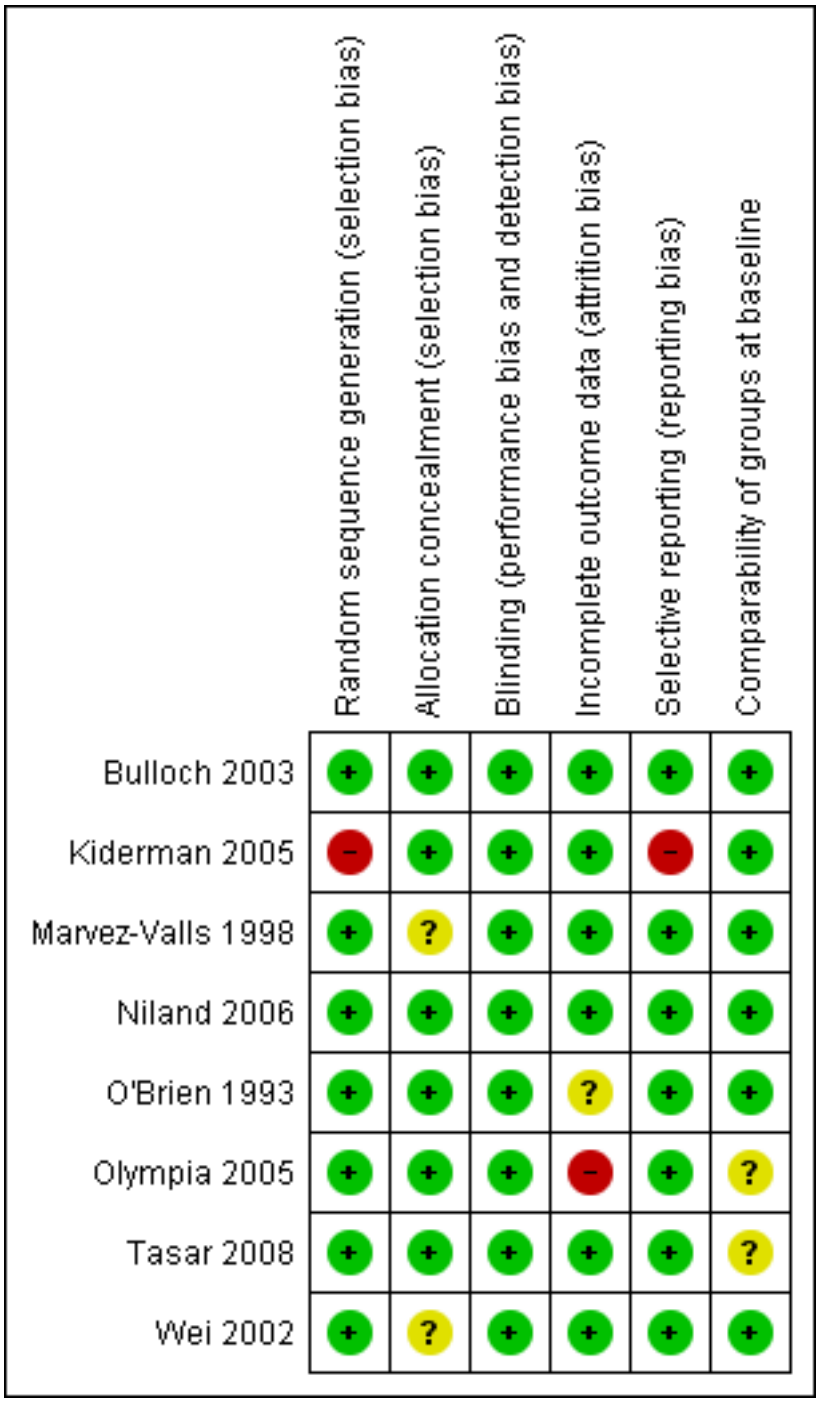
Excluded studies

We excluded four studies. One was an abstract duplicating the trial reported elsewhere (Olympia 2003) and one did not include a placebo comparison group (Marvez-Valls 2002). One study was conducted in hospitalised participants (Hahn 1951) and the final study did not randomise participants (confirmed by personal communication) and thus was not considered a RCT (Ahn 2003).

Risk of bias in included studies

See Figure 1 for a summary of our assessment.

Figure 1. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

We judged there to be a low risk of selection bias from poor allocation concealment in six studies (Bulloch 2003; Kiderman 2005; Niland 2006; O'Brien 1993; Olympia 2005; Tasar 2008). In the other two studies (Marvez-Valls 1998; Wei 2002) no method of allocation concealment was reported, although in both the method was described as double-blind and placebo-controlled.

We judged that in seven studies there was low risk of selection bias due to poor randomisation (Bulloch 2003; Marvez-Valls 1998; Niland 2006; O'Brien 1993; Olympia 2005; Tasar 2008; Wei 2002). One trial (Kiderman 2005) used a random number table generated using an electronic spreadsheet to prepare treatment packages but then used chance selection to assign participants to placebo or steroid arms. We felt that the risk was unclear in this case.

Blinding

We judged that all of the included trials were at low risk of bias as all used a double-blind design. However, only three studies (Bulloch

2003; Kiderman 2005; Marvez-Valls 1998) explicitly stated that their outcome assessors were blinded to the intervention.

Incomplete outcome data

The study with the highest number of participants lost to follow-up was by Olympia 2005, where 83% of participants provided outcome data. The authors aimed to obtain a daily follow-up assessment until complete resolution of sore throat and excluded any child who did not meet this criterion, which is a stricter criterion than that employed by other trials (Bulloch 2003; Wei 2002) and accounted for over 70% of those lost to follow-up.

Three studies reported no loss to follow-up (Kiderman 2005; Marvez-Valls 1998; Tasar 2008).

Selective reporting

All of the included studies measured appropriate and common outcomes and reported all of the outcomes assessed. In the only paper to have previously published an abstract on the research, no additional outcomes were reported (Olympia 2005). Participants in one trial (Kiderman 2005) were randomised to either a one-day course or a two-day course of either prednisolone or placebo but they then failed to report the data for these two groups separately, despite reporting in the text that prednisolone had a significantly greater effect in the two-day group compared to the one-day group.

Effects of interventions

See: **Summary of findings for the main comparison** Corticosteroids compared to placebo for sore throat

Complete resolution of symptoms at 24 and 48 hours

Four trials reported this outcome at 24 hours (Kiderman 2005; Niland 2006; Tasar 2008; Wei 2002) and three at 48 hours (Kiderman 2005; Niland 2006; Tasar 2008). At 24 hours the participants treated with corticosteroids were three times more likely to experience complete resolution of pain (risk ratio (RR) 3.16, 95% confidence interval (CI) 1.97 to 5.08; P < 0.001; I^2 statistic 44%) (Analysis 1.1; Figure 2). The number needed to treat is 3.7 (95% CI 2.8 to 5.9). Subgroup analysis of oral versus intramuscular drug routes revealed a significant benefit in both routes with a greater effect size for the intramuscular route, although the test for subgroup differences did not reach significance (oral: RR 2.56, 95% CI 1.53 to 4.27; intramuscular: RR 4.68, 95% CI 2.08 to 10.52) (Analysis 1.2; Figure 3). No other subgroup comparisons were possible. At 48 hours the likelihood of complete resolution of pain was 1.7 times greater in the corticosteroid group (RR 1.65, 95% CI 1.32 to 2.06; P < 0.0001; I^2 statistic 0%) (Analysis 1.3; Figure 4). The number needed to treat is 3.3 (95% CI 2.4 to 5.6). No other subgroup comparisons were possible.

Figure 2. Forest plot of comparison: 1 Corticosteroids versus placebo, outcome: 1.1 Complete resolution of pain at 24 hours.

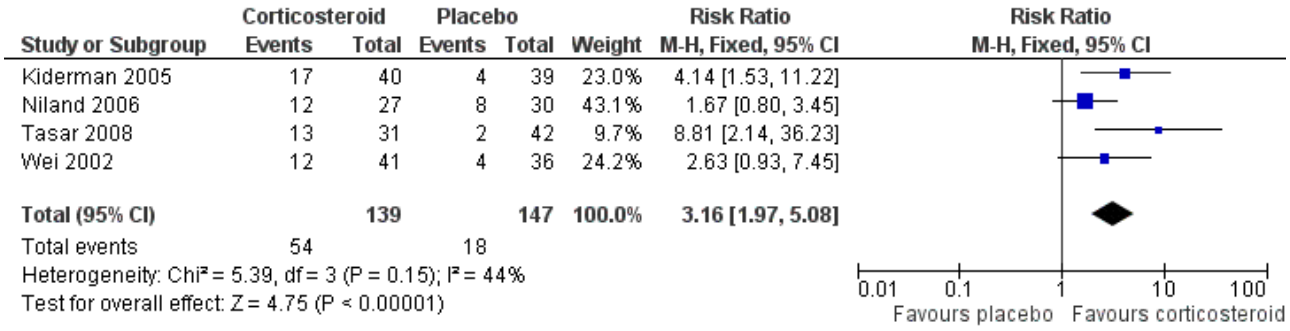


Figure 3. Forest plot of comparison: 1 Corticosteroids versus placebo, outcome: 1.2 Complete resolution of pain at 24 hours: route of corticosteroid administration.

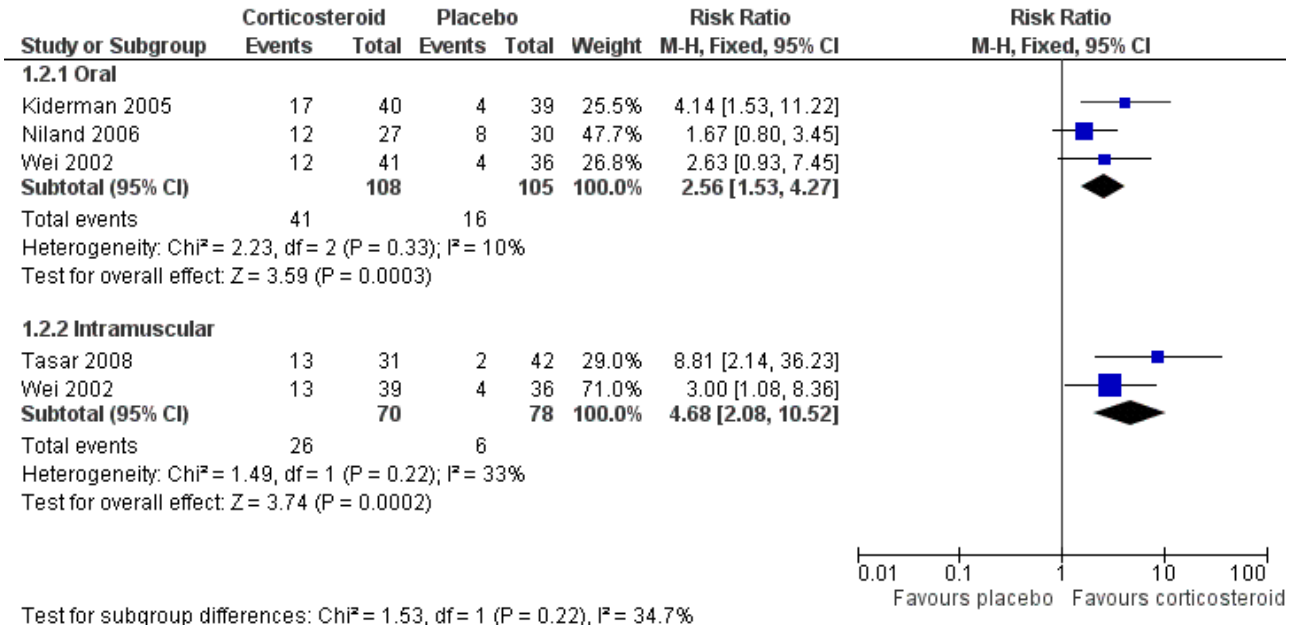
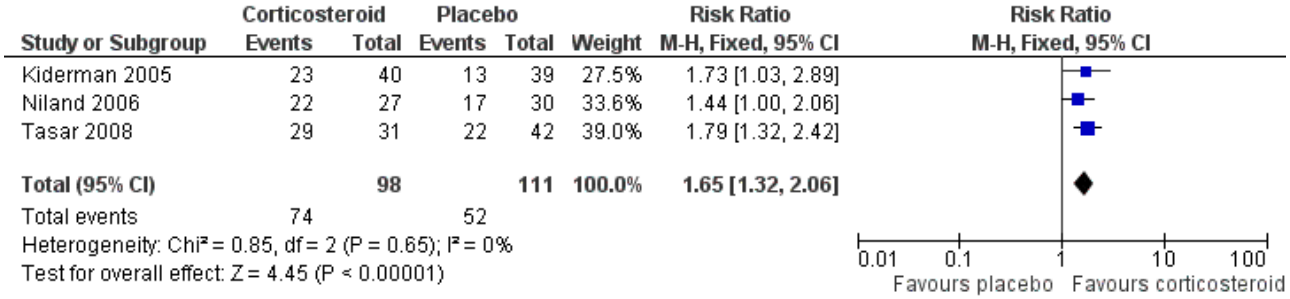


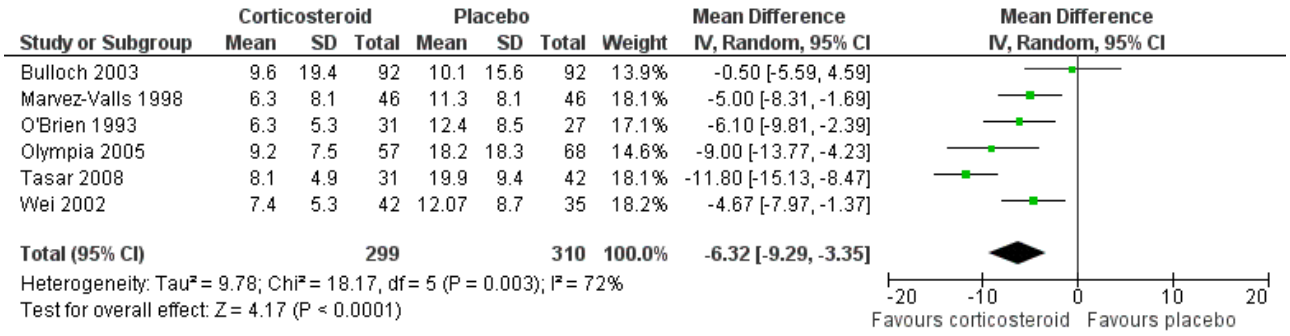
Figure 4. Forest plot of comparison: 1 Corticosteroids versus placebo, outcome: 1.3 Complete resolution of pain at 48 hours.



Time to onset of pain relief

In a pooled analysis of six trials the mean time to onset of pain relief was 6.3 hours earlier in participants taking corticosteroids compared to placebo (mean difference (MD) -6.32, 95% CI -9.29 to -3.35; P < 0.001; I^2 statistic 72%) (Analysis 1.4; Figure 5). High heterogeneity was evident in this analysis. We therefore performed a sensitivity analysis which excluded each trial in turn (leave-one-out method). This demonstrated a range of MD from 5.1 to 7.2 hours with no loss of significance. The majority of the heterogeneity arose from the trial by Tasar 2008, which also showed the largest benefit and smallest variability. Excluding this trial resulted in a mean benefit of 5.1 hours.

Figure 5. Forest plot of comparison: 1 Corticosteroids versus placebo, outcome: 1.4 Mean time to onset of pain relief.



A number of subgroup analyses were possible for this outcome. In participants with bacterial pathogen positive sore throat (Analysis 1.5), exudative sore throat (Analysis 1.6) or severe sore throat (Analysis 1.7) the size and direction of effect was greater than trials where < 50% of participants had exudate, trials which did not select for severe sore throat, or in participants in whom bacterial pathogens were not detected. However, in no case did the test for subgroup differences reach significance. Analysis of intramuscular versus oral routes of administration showed a non-significant trend towards a greater effect with intramuscular administration (Analysis 1.8) but both subgroups showed high heterogeneity.

Time to complete resolution of pain

The mean time to complete resolution of pain was reduced by 14.4 hours in participants given corticosteroids (MD -14.41, 95% CI -24.99 to -3.84; P = 0.008; I^2 statistic 78%) (Analysis 1.9). This analysis showed high heterogeneity and sensitivity analysis (leave-one-out method) revealed a MD ranging from 11 to 21 hours (P ≤ 0.05). The trial by Bulloch 2003 appeared to be the main contributor to the heterogeneity in this analysis and removing this trial resulted in a mean time to complete pain resolution of 21 hours (MD -21.01, 95% CI -26.42 to -15.61, P < 0.001, I^2 statistic 9%). Analysis of scores on the visual analogue scale (VAS) for pain suggests that participants in this study may have experienced less severe sore throat initially.

Reduction in pain measured by visual analogue scale

We performed a pooled analysis of the absolute reduction in pain visual analogue scale (VAS) score for those studies reporting this outcome (Analysis 1.10). The results indicate that participants who received corticosteroids experienced a 1.4 cm or 14% greater reduction in VAS score at 24 hours than those in the placebo group (MD 1.34, 95% CI 0.61 to 2.06). However, this result had high heterogeneity (I^2 statistic 67%). One reason for this may be that the included trials used different versions of the VAS. Three studies (Kiderman 2005; Marvez-Valls 1998; Wei 2002) used a 10 cm (0 to 10-point) VAS. One study (Olympia 2005) used a McGrath Facial Affective scale which was scored between 1 to 0 and includes nine faces, one study used a 15 cm VAS with a score between 0 and 3.0 (O'Brien 1993) and one study used a colour analogue scale equivalent to a 10 cm VAS (Bulloch 2003). The trial by Bulloch 2003 was the main contributor to the high heterogeneity.

Adverse events

This outcome was reported in detail by only one trial of 125 participants (Olympia 2005). Five participants (4%; three corticosteroid and two placebo) were hospitalised for fluid rehydration and three participants (2%; one corticosteroid and two placebo) developed peritonsillar abscess. Three trials reported no side effects attributable to dexamethasone (O'Brien 1993), no complications of Group A beta-haemolytic streptococcus (GABHS) infections were identified in either group (Bulloch 2003) and there were no participants with additional complaints or requiring additional medications (Tasar 2008).

Recurrence/relapse rates

Three trials (Bulloch 2003; Kiderman 2005; Niland 2006) reported rates of recurrence or relapse. Pooled analysis showed a non-significant trend towards a lower risk of relapse in the corticosteroid group (RR 0.56, 95% CI 0.24 to 1.34; P = 0.19; I^2 statistic 23%) in a very small number of cases (Analysis 1.11). The rates of attendance for further care within five days reported in a single trial involving 118 participants (Wei 2002) were 0/39 for intramuscular dexamethasone, 3/42 for oral dexamethasone and 6/37 for placebo (P = 0.032).

Days missed from work or school

Only one trial provided data for this outcome (Marvez-Valls 1998) and showed no significant differences between corticosteroid and placebo groups (Analysis 1.12). Kiderman 2005 recorded no significant differences in time taken off work or studies between the two groups at any follow-up period but did not provide any supporting data. Niland 2006 reported no difference in the number of days missed from work or school with a significance value of P = 0.68, but did not provide any further data.

DISCUSSION

Summary of main results

In participants with sore throat, oral or intramuscular corticosteroids in addition to antibiotics significantly increase the proportion experiencing complete resolution of pain at 24 and 48 hours. Fewer than four people need to be treated with corticosteroids to prevent one person continuing to experience pain at 24 hours. Corticosteroids decrease the mean time to onset of pain relief by 6.3 hours and the mean time to complete resolution of symptoms by 14.4 hours. However, both of these analyses were associated with high heterogeneity. Corticosteroids reduce the subjective rating of pain at 24 hours by an additional 14%, again associated with high heterogeneity.

Subgroup analyses revealed a greater effect size for intramuscular versus oral corticosteroids in both the proportion of participants achieving complete pain resolution at 24 hours and the mean time to onset of pain relief, although tests for subgroup effects did not reach significance. The effect on mean time to onset of pain relief was greater in those participants with severe, exudative and bacterial pathogen positive sore throat.

A small number of trials reported the outcomes of adverse events, relapse or recurrence rates or days missed from work or school and found no difference in the likelihood of these outcomes between participants receiving corticosteroids and those receiving placebo.

Overall completeness and applicability of evidence

This systematic review includes eight trials from General Practice and Emergency Department settings. Most of the trials were performed in the USA and only one in Europe. Therefore, additional trial data are warranted in European populations, who may differ in consultation patterns and clinical practice (including antibiotic prescribing), before the results can be generalised to these populations.

Only two of the included trials included children and these trials had inconsistent results, so we were not able to draw firm conclusions about the clinical benefit of corticosteroids in this population. Children commonly present with sore throat and it will be important to develop a clearer understanding of whether corticosteroids also provide benefit in this population.

The most important limitation to applicability of the evidence is that all participants in the included trials received antibiotics in addition to either corticosteroid or placebo groups, so evidence is lacking for the effectiveness of corticosteroids in the absence of antibiotics.

Quality of the evidence

Whilst we included only randomised, double-blind, placebo-controlled trials, in a number of cases the trials did not specify their methods of randomisation or allocation concealment. Trials reported a variety of outcome measures, in some cases with inadequate reporting, no standard deviations, or use of graphical representation only. Significant heterogeneity was evident in a number of our analyses. This heterogeneity, and the relatively small number of patients in some analyses, resulted in a GRADE quality score of 'moderate' for the majority of our analyses, with two analyses (complete resolution of pain at 24 hours and mean absolute reduction in visual analogue scale (VAS) score) graded as high quality.

The outcome measures of mean time to onset of pain relief and to complete resolution were limited by recall bias as they rely on participants' subjective recall and recording. The mean time could also be skewed by a few participants who had sore throat pain for especially long or short periods. A median time may have been more appropriate, although there were insufficient data for us to calculate this. Included studies were also under-powered to detect rare adverse effects of corticosteroid therapy, as well as relapse rates and days missed from work or school.

Finally, the limited number of trials meant that we were unable to assess publication bias using funnel plots, although we attempted to address this issue by using citation searching.

Agreements and disagreements with other studies or reviews

Four systematic reviews addressing the question of corticosteroids in sore throat have been published, including one by the current review authors (Hayward 2009; Korb 2010; Mullarkey 2011; Wing 2010).

Korb 2010 used a similar search strategy to this review but did not search the Database of Reviews of Effects (DARE), the NHS Health Economics Database or the WHO international database of controlled trials. They included the same eight trials included in the current review but did not document excluded trials. Although they did not perform a meta-analysis, they drew similar conclusions to this review regarding a small but significant beneficial effect of corticosteroids using a descriptive analysis.

Wing 2010 performed an extensive search of the literature, including conference proceedings. In addition to the eight trials included in this review, they identified two further poor quality trials. One (Hahn 1951) achieved a Jadad score (Jadad 1996) of zero and in fact did not contribute any data to the meta-analyses. We excluded this trial as it was performed in hospitalised participants. The second study (Ahn 2003) was single-blind and required estimation of standard deviations, scoring two on the Jadad scale. We excluded this study as personal communication with the trial authors revealed that it was not a randomised trial. However, their results including this poor quality trial are also in line with our review. They reported mean time to clinically meaningful pain relief as 4.5 hours (mean difference (MD) -4.54, 95% confidence interval (CI) -7.19 to -1.89, I^2 statistic 81%, $P < 0.001$), compared to 6.3 hours in our review but failed to address the high heterogeneity in this analysis. They also present a meta-analysis of absolute VAS scores at 24 hours and demonstrate a mean difference (MD) of -0.9 on a 0 to 10 VAS (MD -0.9, 95% CI -1.5 to -0.3, I^2 statistic 74%, $P = 0.003$). This is a difficult finding to interpret as it does not take account of the baseline VAS score, which is variable between studies. The trial authors argue that a reduction of 1.3 points is a clinically meaningful change and hence that this is not significant. In our analysis, which accounted for baseline scores by assessing change from baseline, we found that the reduction from baseline was greater in the corticosteroid group by 14% or 1.4 cm.

Mullarkey 2011 performed a systematic review as a single author and limited the search to adult participants presenting to Emergency Departments. The trial author identified five of our included studies and one systematic review (Hayward 2009) but no additional studies. No meta-analysis was attempted and the quality of studies was not fully assessed. A descriptive analysis was supportive of a benefit of corticosteroids as an adjunct in management of acute pharyngitis.

AUTHORS' CONCLUSIONS

Implications for practice

Our findings suggest that in participants with sore throat, pain can be reduced and resolution hastened by use of a single dose of oral or intramuscular corticosteroids in conjunction with antibiotic therapy.

Our finding that the duration of pain is reduced by 6.3 hours seems modest. However, the decision to use any treatment

involves balancing the potential benefits and harms of the therapy. Although our included studies were probably not sufficiently powered to detect adverse effects of short courses of oral corticosteroids, a recent review has suggested that courses shorter than one week are unlikely to be harmful (Richards 2008). In this context, onset of pain relief six hours earlier may be an acceptable benefit to many patients.

We could not fully assess the optimal formulation, route of administration or dosing regimen of corticosteroids due to small sample sizes. Two studies which directly compared intramuscular and oral routes found no differences (Marvez-Valls 2002; Wei 2002) and no significant differences were seen in our subgroup comparisons. As oral corticosteroids may be more acceptable to patients and appear to be equally beneficial as intramuscular preparations, we would suggest that the oral route is used. In terms of dosing regimen, only two trials compared a single dose of dexamethasone with multiple doses. One (Kiderman 2005) reported that there was a significant benefit of two days compared to one day of treatment but failed to provide any supporting data. The second (Niland 2006) found no difference in outcomes between one and three-day courses of treatment.

Implications for research

Future trials of corticosteroids for sore throat are needed in non-USA populations and in children or adolescents. Outcomes assessed should include the number of patients who experience resolution of symptoms at 24, 48 and 72 hours, measured using standardised pain scores. Additional outcomes should include effects of corticosteroids on antibiotic use, days missed from school/college or work, as well as longer-term measures such as re-attendance with sore throats. Trials should also be sufficiently powered to assess adverse outcomes. Trials should compare single versus multiple dose regimens and oral versus intramuscular routes. Use of severity criteria such as the Centor criteria at baseline may facilitate classification of severity.

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CHARACTERISTICS OF STUDIES

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

Bulloch 2003

Methods	Randomised, double-blind, placebo-controlled trial
Participants	184 children (92 in each group) aged 5 to 16 years (mean 9.74) presenting with erythema of the pharynx, onset of symptoms within the previous 48 hours and one chief complaint of sore throat, odynophagia or dysphagia

Bulloch 2003 *(Continued)*

Interventions	Dexamethasone 0.6 mg/kg orally (maximum of 10 mg) or placebo orally. All participants with a positive direct antigen test for *Streptococcus pyogenes* group A antigen from pharyngeal swabs were treated with penicillin V
Outcomes	Reduction in pain visual analogue scale. Time to onset of pain relief, time to complete pain resolution, percentage recurrence
Notes	Analgesia unregulated and unrecorded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation table with groups of 10 held at a central pharmacy. 2 lists used for those positive and negative on direct antigen testing. Attempted to enrol consecutive children but missed some eligible children when the Emergency Department was too busy to allow for enrolment
Allocation concealment (selection bias)	Low risk	Placebo with identical appearance and taste used
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind design. Randomisation code known only pharmacy and not broken until all participants recruited. Outcome assessors blinded to treatment groups
Incomplete outcome data (attrition bias) All outcomes	Low risk	5/184 failed to complete
Selective reporting (reporting bias)	Low risk	Main outcome measures in similar trials included. No outcome measures assessed were not reported. Data and confidence intervals (CIs) clearly reported
Comparability of groups at baseline	Low risk	Comparable

Kiderman 2005

Methods	Randomised, double-blind, placebo-controlled trial
Participants	79 participants aged 18 to 65 years (mean 33.9) complaining of severe sore throat and at least 2 out of: tonsillar/pharyngeal exudate, dysphagia, fever, lymphadenopathy
Interventions	Prednisolone 60 mg orally for either 1 or 2 days or placebo orally. Antibiotics (penicillin V, amoxicillin or erythromycin) prescribed at General Practitioner's discretion
Outcomes	Reduction in visual analogue scale score. Percentage of participants pain-free at various time points. Percentage recurrence. Complete resolution of pain at 24 and 48 hours. Days missed from school or work
Notes	Data from 1 and 2-day arms not presented separately. Analgesia unregulated and unrecorded

Risk of bias

Bias	Authors' judgement	Support for judgement

Kiderman 2005 *(Continued)*

Random sequence generation (selection bias)	High risk	Treatment packages prepared using a random number table generated using an electronic spreadsheet. Chance selection of treatment package then used to assign participants to groups
Allocation concealment (selection bias)	Low risk	Placebo drug identical to active tablets
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and doctors (who were also outcome assessors) blinded to treatment given
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants lost to follow-up
Selective reporting (reporting bias)	High risk	No data reported for 1 dose versus 2 doses of prednisolone, despite text reporting of a significant dose effect
Comparability of groups at baseline	Low risk	Comparable

Marvez-Valls 1998

Methods	Randomised, double-blind, placebo-controlled trial
Participants	92 participants aged 14 to 65 (mean 29.1) presenting with symptoms of sore throat or odynophagia, dysphagia, fever or cervical lymphadenopathy AND appearances of exudative pharyngitis
Interventions	Dexamethasone 2 ml IM (8 mg is an approximate dosage based on US formularies) or saline 2 ml IM. Antibiotics given to all participants. 1.2 million units benzathine penicillin IM or a 10-day course of erythromycin 500 mg twice daily
Outcomes	Reduction in pain visual analogue scale. Time to onset of pain relief. Time to complete pain resolution. Days missed from school/work. Percentage recurrence
Notes	Analgesia unrecorded and unregulated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised list for assignment of participants
Allocation concealment (selection bias)	Unclear risk	Not specifically commented upon
Blinding (performance bias and detection bias) All outcomes	Low risk	Physician and patient blinded to the study drug used. Follow-up phone calls made by blinded individuals
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up

Marvez-Valls 1998 *(Continued)*

Selective reporting (reporting bias)	Low risk	
Comparability of groups at baseline	Low risk	Comparable

Niland 2006

Methods	Randomised, double-blind, 3-arm, prospective, placebo-controlled trial
Participants	90 participants aged 4 to 21 years (median 7.7) with a positive direct streptococcal antigen test
Interventions	Dexamethasone 0.6 mg/kg/day orally for 1 or 2 days versus oral placebo. 45 received IM and 45 received oral antibiotics (type at discretion of physician)
Outcomes	Time to return of general health. Time to return of normal activity level. Days missed from school or work. Time to complete pain resolution. Number with complete pain resolution at 24 and 48 hours. Percentage recurrence
Notes	Convenience sample. Analgesia use recorded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block randomisation in blocks of 9, stratified by IM or oral antibiotics
Allocation concealment (selection bias)	Low risk	Masked liquid suspension
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and administering personnel blinded to the study drug. Blinding of outcome assessor not explicitly stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	6/90 lost to follow-up
Selective reporting (reporting bias)	Low risk	All outcomes reported
Comparability of groups at baseline	Low risk	Comparable apart from gender - shown to have no influence on results

O'Brien 1993

Methods	Prospective, randomised, double-blind, placebo-controlled trial
Participants	58 participants aged 12 to 65 years (mean 26.3) with visible tonsillar exudate, severe odynophagia or dysphagia and either fever or cervical adenopathy

O'Brien 1993 *(Continued)*

Interventions	Dexamethasone 10 mg IM (10 mg/ml) or 1 ml saline IM. 10-day course of either penicillin V or erythromycin supplied to all participants
Outcomes	Reduction in pain visual analogue scale. Time to onset of pain relief. Time to complete pain resolution
Notes	Analgesia recorded but not regulated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers table
Allocation concealment (selection bias)	Low risk	Syringes containing the 2 preparations were indistinguishable
Blinding (performance bias and detection bias) All outcomes	Low risk	Physicians, nurses and participants blinded to the study drug
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Primary outcome at 24 hours - 7/58 lost to follow-up. Secondary outcome of time to complete pain resolution - 32/58 participants lost to follow-up
Selective reporting (reporting bias)	Low risk	All outcomes reported
Comparability of groups at baseline	Low risk	Comparable

Olympia 2005

Methods	Prospective, randomised, double-blind, placebo-controlled trial
Participants	125 children aged 5 to 18 years (mean 11.9) with odynophagia or dysphagia, moderate to severe pharyngeal erythema or swelling as determined by the Emergency Department physician and McGrath Facial Affective Scale (FAS) score of 'F' (0.75) or higher
Interventions	Dexamethasone 0.6 mg/kg orally single dose or oral isotonic sodium chloride solution as placebo. Antibiotics (penicillin G IM, amoxicillin or azithromycin orally) given if rapid streptococcal antigen test positive or culture positive for group A beta-haemolytic streptococcus
Outcomes	Reduction in McGrath FAS score. Time to onset of pain relief. Time to complete pain resolution. Fever Associated symptoms. Need for further medical care
Notes	Analgesia use recorded. Convenience sample of participants

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation using a computerised random numbers table in groups of 30

Olympia 2005 *(Continued)*

Allocation concealment (selection bias)	Low risk	Both steroid and placebo medications flavoured and coloured with cherry syrup
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind design, although specific blinding not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	25/150 lost to follow-up
Selective reporting (reporting bias)	Low risk	Abstract published 2 years earlier did not report any additional outcomes
Comparability of groups at baseline	Unclear risk	Comparable

Tasar 2008

Methods	Prospective, randomised, double-blind, placebo-controlled trial
Participants	73 participants aged 18 to 65 years (mean 31.3) with sore throat or odynophagia and 2 of the Centor criteria (absence of cough, tonsillar exudates, tender anterior cervical lymphadenopathy, fever)
Interventions	Dexamethasone 8 mg intramuscularly (IM) versus the same volume of saline IM. All participants received 500 mg azithromycin daily for 3 days
Outcomes	Time to onset of pain relief. Time to complete pain resolution. Percentage with complete pain resolution at 24 and 48 hours
Notes	Paracetamol allowed for 3 days, unrecorded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Low risk	No visual difference between the 2 drugs
Blinding (performance bias and detection bias) All outcomes	Low risk	Physicians administering the drugs were blinded to the contents. No comment on blinding of outcome assessors. However, drugs were prepared and randomised by the pharmacy
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	All intended outcomes reported
Comparability of groups at baseline	Unclear risk	Comparable

Wei 2002

Methods	Randomised, double-blind, 3-arm, placebo-controlled trial
Participants	118 participants aged 15 years or more (mean age 28) with clinical diagnosis of acute pharyngitis or tonsillitis and pharyngeal erythema with or without exudate
Interventions	3 arms: 1) 10 mg intramuscular (IM) dexamethasone and placebo tablet, 2) 10 mg oral dexamethasone and IM placebo, 3) IM and oral placebo
Outcomes	Reduction in pain visual analogue scale. Percentage with complete pain resolution at 24 hours. Time to return to normal activity. Ability to take liquids and solids. Percentage recurrence
Notes	Paracetamol allowed for the first 24 hours as required - usage recorded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation scheme prepared by section of biostatistics and held by a central pharmacy
Allocation concealment (selection bias)	Unclear risk	Not specifically mentioned
Blinding (performance bias and detection bias) All outcomes	Low risk	Physician administering the treatment was blinded to the content. Blinding of outcome assessor not specifically commented upon
Incomplete outcome data (attrition bias) All outcomes	Low risk	7/118 participants did not provide 12-hour follow-up. 2/118 participants did not provide 24-hour follow-up
Selective reporting (reporting bias)	Low risk	Intended outcomes reported
Comparability of groups at baseline	Low risk	Comparable

FAS: facial affective scale
IM: intramuscular
VAS: visual analogue scale

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

Study	Reason for exclusion
Ahn 2003	Not randomised
Hahn 1951	Hospitalised participants
Marvez-Valls 2002	No placebo or usual care control group
Olympia 2003	Abstract reporting results of included study

DATA AND ANALYSES

Comparison 1. Corticosteroids versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete resolution of pain at 24 hours	4	286	Risk Ratio (M-H, Fixed, 95% CI)	3.16 [1.97, 5.08]
2 Complete resolution of pain at 24 hours: route of corticosteroid administration	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Oral	3	213	Risk Ratio (M-H, Fixed, 95% CI)	2.56 [1.53, 4.27]
2.2 Intramuscular	2	148	Risk Ratio (M-H, Fixed, 95% CI)	4.68 [2.08, 10.52]
3 Complete resolution of pain at 48 hours	3	209	Risk Ratio (M-H, Fixed, 95% CI)	1.65 [1.32, 2.06]
4 Mean time to onset of pain relief	6	609	Mean Difference (IV, Random, 95% CI)	-6.32 [-9.29, -3.35]
5 Mean time to onset of pain relief by bacterial pathogen positive/negative	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 Bacterial pathogen positive	4	208	Mean Difference (IV, Random, 95% CI)	-5.30 [-8.03, -2.58]
5.2 Bacterial pathogen negative	4	247	Mean Difference (IV, Random, 95% CI)	-3.92 [-9.20, 1.36]
6 Mean time to onset of pain relief in exudative/not sore throat	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 Exudative	2	150	Mean Difference (IV, Random, 95% CI)	-5.49 [-7.96, -3.02]
6.2 Not exudative	2	261	Mean Difference (IV, Random, 95% CI)	-3.05 [-7.04, 0.93]
7 Mean time to onset of pain relief in severe/not severe sore throat	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
7.1 Severe sore throat	2	183	Mean Difference (IV, Random, 95% CI)	-7.19 [-10.12, -4.27]
7.2 Trials not only selecting patients with severe sore throat	4	423	Mean Difference (IV, Random, 95% CI)	-5.74 [-10.12, -1.36]
8 Mean time to onset of pain relief by route of corticosteroid administration	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
8.1 Oral corticosteroids	3	386	Mean Difference (IV, Random, 95% CI)	-4.79 [-9.03, -0.54]
8.2 Intramuscular corticosteroids	4	297	Mean Difference (IV, Random, 95% CI)	-6.94 [-10.27, -3.61]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9 Mean time to complete resolution of pain	5	500	Mean Difference (IV, Random, 95% CI)	-14.41 [-24.99, -3.84]
10 Mean absolute reduction in pain VAS/Mcgrath scale at 24 hours	6	617	Mean Difference (IV, Random, 95% CI)	1.34 [0.61, 2.06]
11 Recurrence/relapse of symptoms	3	353	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.24, 1.34]
12 Number of days missed from work or school	1	92	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-0.87, 0.27]

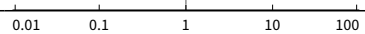
Analysis 1.1. Comparison 1 Corticosteroids versus placebo, Outcome 1 Complete resolution of pain at 24 hours.

Study or subgroup	Corticosteroid n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Kiderman 2005	17/40	4/39		23.03%	4.14[1.53,11.22]
Niland 2006	12/27	8/30		43.09%	1.67[0.8,3.45]
Tasar 2008	13/31	2/42		9.66%	8.81[2.14,36.23]
Wei 2002	12/41	4/36		24.22%	2.63[0.93,7.45]
Total (95% CI)	**139**	**147**		**100%**	**3.16[1.97,5.08]**
Total events: 54 (Corticosteroid), 18 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=5.39, df=3(P=0.15); I^2=44.31%					
Test for overall effect: Z=4.75(P<0.0001)					

Favours placebo — Favours corticosteroid

Analysis 1.2. Comparison 1 Corticosteroids versus placebo, Outcome 2 Complete resolution of pain at 24 hours: route of corticosteroid administration.

Study or subgroup	Corticosteroid n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Oral					
Kiderman 2005	17/40	4/39		25.49%	4.14[1.53,11.22]
Niland 2006	12/27	8/30		47.7%	1.67[0.8,3.45]
Wei 2002	12/41	4/36		26.81%	2.63[0.93,7.45]
Subtotal (95% CI)	**108**	**105**		**100%**	**2.56[1.53,4.27]**
Total events: 41 (Corticosteroid), 16 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.23, df=2(P=0.33); I^2=10.48%					
Test for overall effect: Z=3.59(P=0)					
1.2.2 Intramuscular					
Tasar 2008	13/31	2/42		28.99%	8.81[2.14,36.23]
Wei 2002	13/39	4/36		71.01%	3[1.08,8.36]
Subtotal (95% CI)	**70**	**78**		**100%**	**4.68[2.08,10.52]**
Total events: 26 (Corticosteroid), 6 (Placebo)					



Favours placebo — Favours corticosteroid

Study or subgroup	Corticosteroid n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=1.49, df=1(P=0.22); I²=32.93%					
Test for overall effect: Z=3.74(P=0)					
Test for subgroup differences: Chi²=1.53, df=1 (P=0.22), I²=34.68%					

Favours placebo 0.01 0.1 1 10 100 Favours corticosteroid

Analysis 1.3. Comparison 1 Corticosteroids versus placebo, Outcome 3 Complete resolution of pain at 48 hours.

Study or subgroup	Corticosteroid n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Kiderman 2005	23/40	13/39		27.45%	1.73[1.03,2.89]
Niland 2006	22/27	17/30		33.58%	1.44[1,2.06]
Tasar 2008	29/31	22/42		38.96%	1.79[1.32,2.42]
Total (95% CI)	**98**	**111**		**100%**	**1.65[1.32,2.06]**
Total events: 74 (Corticosteroid), 52 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.85, df=2(P=0.65); I²=0%					
Test for overall effect: Z=4.45(P<0.0001)					

Favours placebo 0.01 0.1 1 10 100 Favours corticosteroid

Analysis 1.4. Comparison 1 Corticosteroids versus placebo, Outcome 4 Mean time to onset of pain relief.

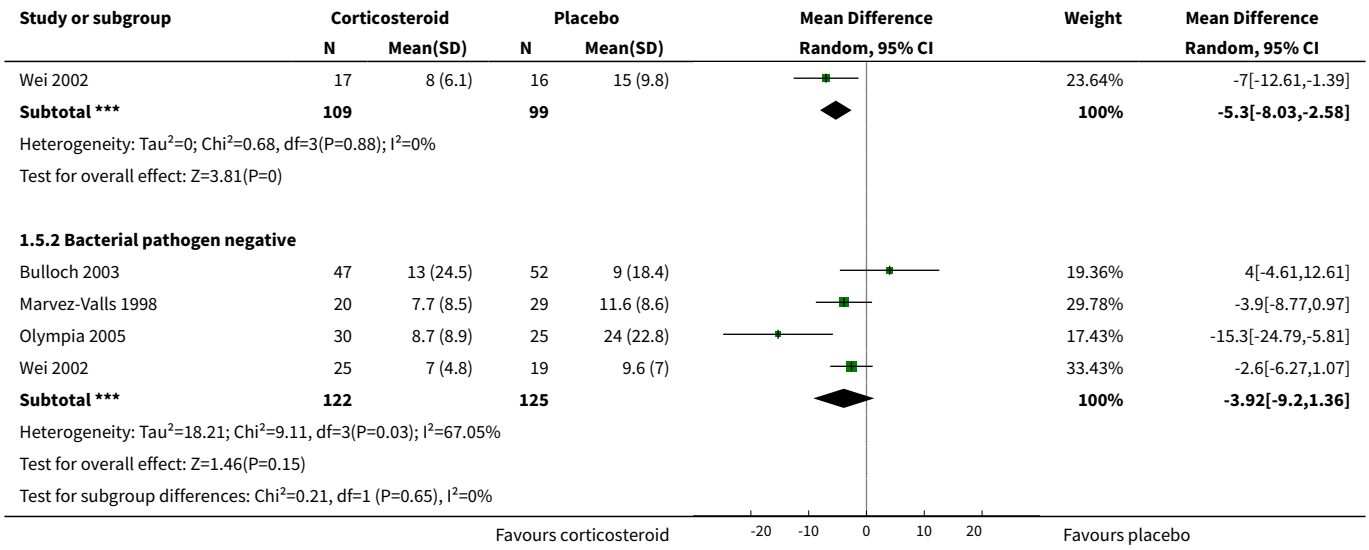
Study or subgroup	Corticosteroid N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Bulloch 2003	92	9.6 (19.4)	92	10.1 (15.6)		13.87%	-0.5[-5.59,4.59]
Marvez-Valls 1998	46	6.3 (8.1)	46	11.3 (8.1)		18.13%	-5[-8.31,-1.69]
O'Brien 1993	31	6.3 (5.3)	27	12.4 (8.5)		17.14%	-6.1[-9.81,-2.39]
Olympia 2005	57	9.2 (7.5)	68	18.2 (18.3)		14.6%	-9[-13.77,-4.23]
Tasar 2008	31	8.1 (4.9)	42	19.9 (9.4)		18.1%	-11.8[-15.13,-8.47]
Wei 2002	42	7.4 (5.3)	35	12.1 (8.7)		18.16%	-4.67[-7.97,-1.37]
Total ***	**299**		**310**			**100%**	**-6.32[-9.29,-3.35]**
Heterogeneity: Tau²=9.78; Chi²=18.17, df=5(P=0); I²=72.49%							
Test for overall effect: Z=4.17(P<0.0001)							

Favours corticosteroid -20 -10 0 10 20 Favours placebo

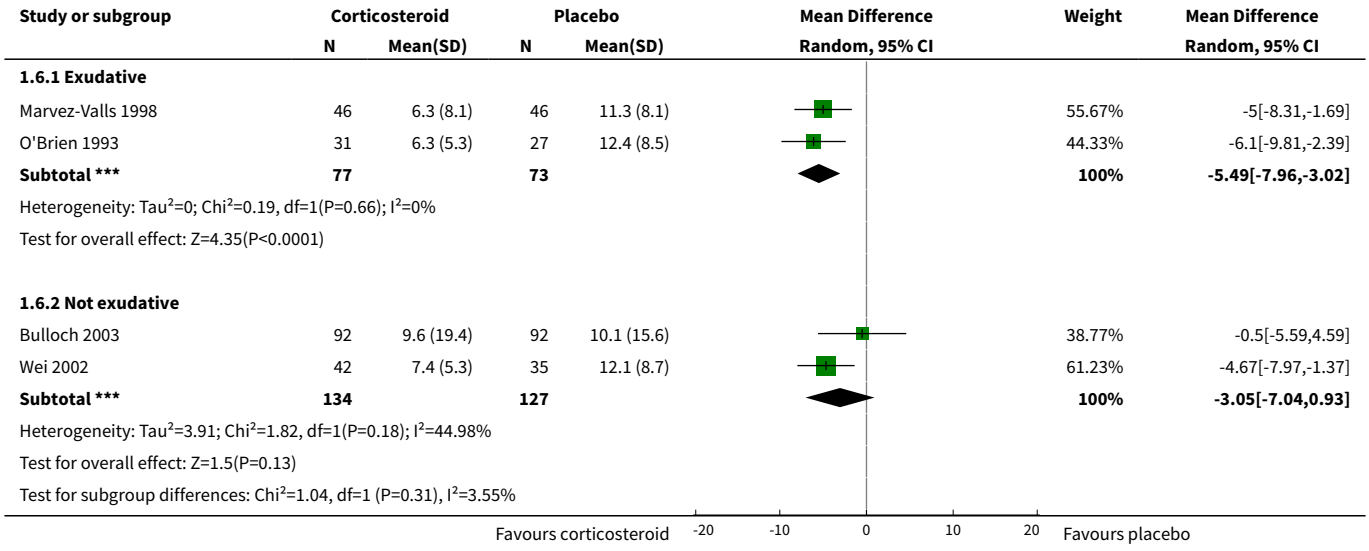
Analysis 1.5. Comparison 1 Corticosteroids versus placebo, Outcome 5 Mean time to onset of pain relief by bacterial pathogen positive/negative.

Study or subgroup	Corticosteroid N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.5.1 Bacterial pathogen positive							
Bulloch 2003	45	6 (11.1)	40	11.5 (11.3)		32.65%	-5.5[-10.27,-0.73]
Marvez-Valls 1998	20	7.7 (8.5)	29	11.6 (8.6)		31.42%	-3.9[-8.77,0.97]
Olympia 2005	27	9.7 (5.6)	14	14.8 (14.3)		12.28%	-5.1[-12.88,2.68]

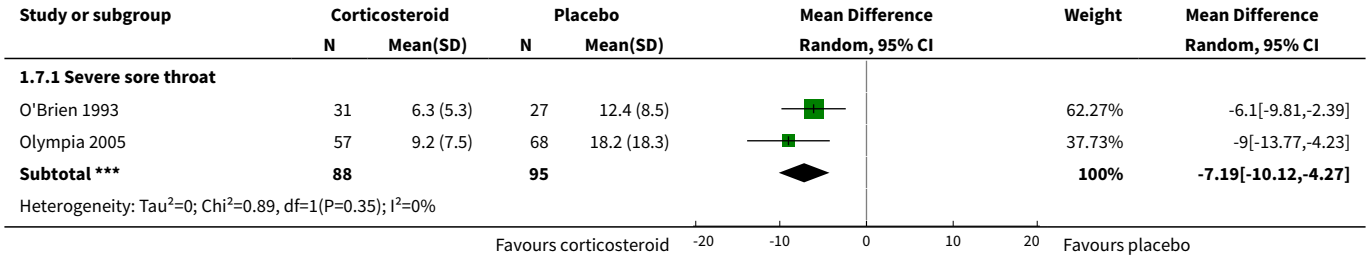
Favours corticosteroid -20 -10 0 10 20 Favours placebo

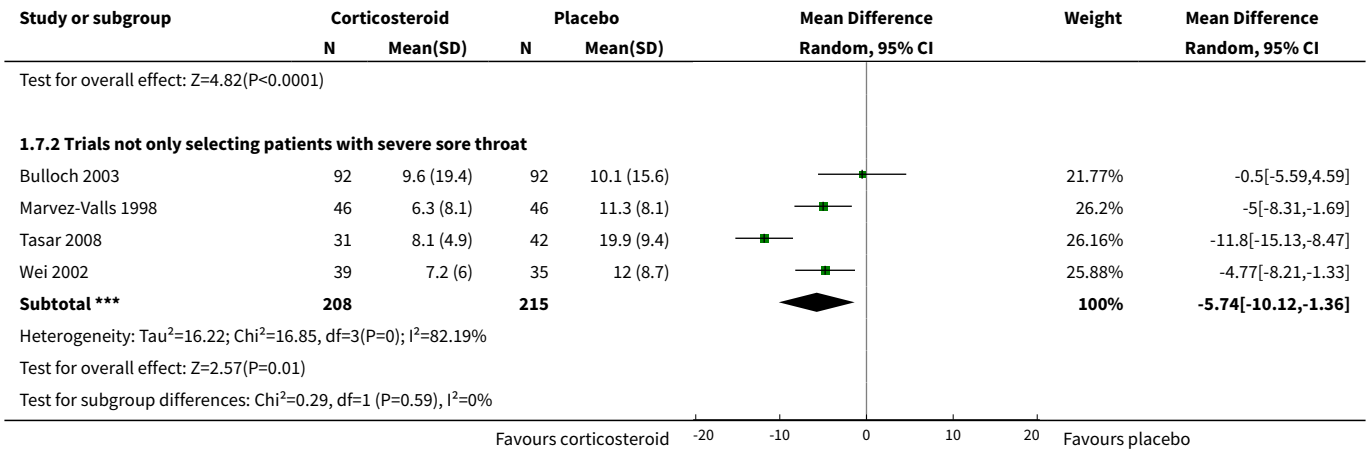


Analysis 1.6. Comparison 1 Corticosteroids versus placebo, Outcome 6 Mean time to onset of pain relief in exudative/not sore throat.

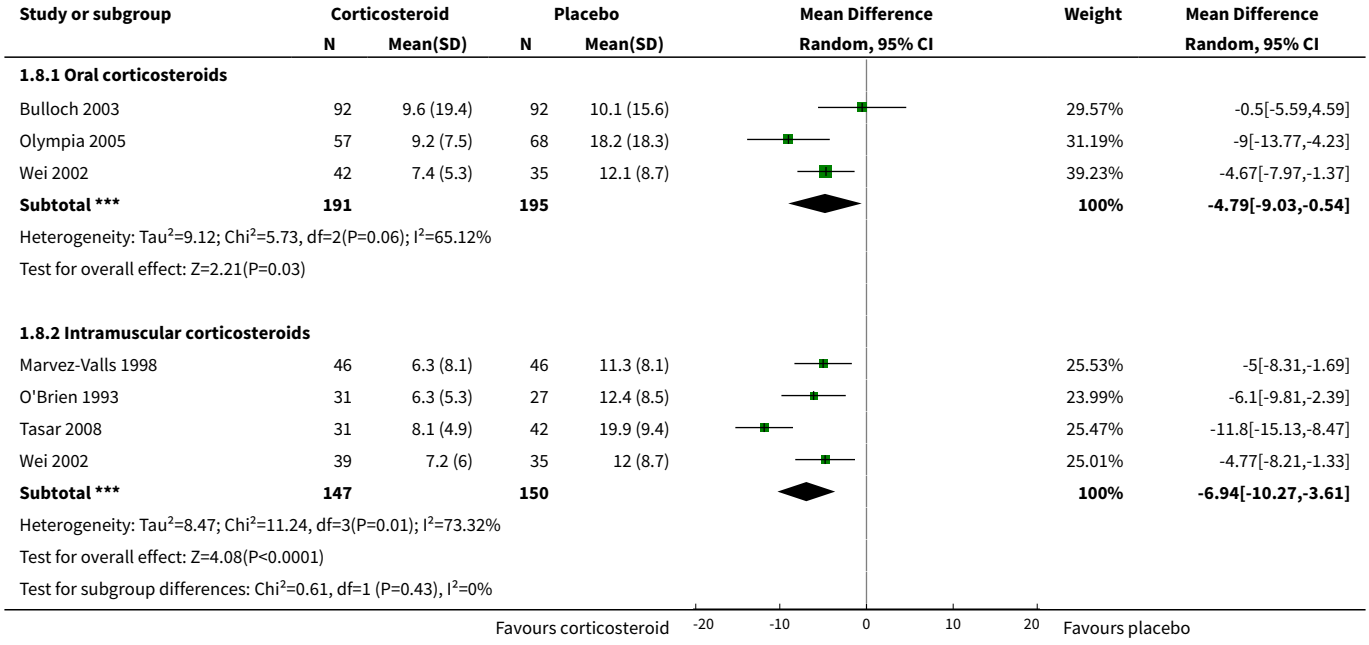


Analysis 1.7. Comparison 1 Corticosteroids versus placebo, Outcome 7 Mean time to onset of pain relief in severe/not severe sore throat.

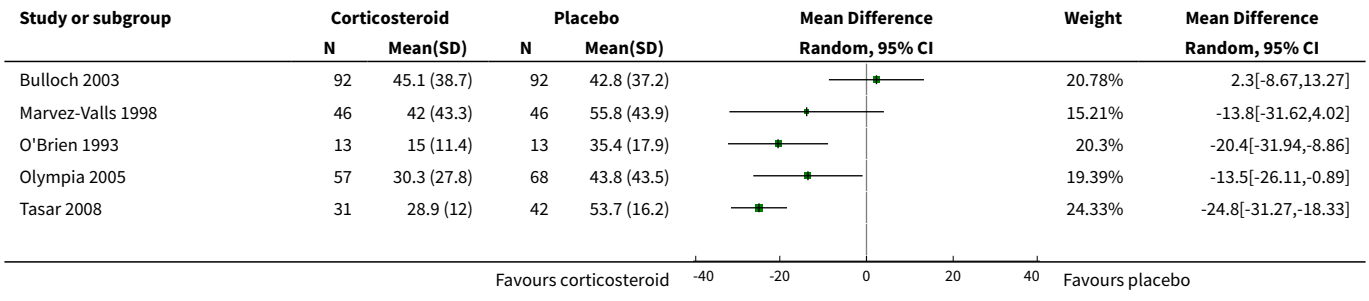




Analysis 1.8. Comparison 1 Corticosteroids versus placebo, Outcome 8 Mean time to onset of pain relief by route of corticosteroid administration.



Analysis 1.9. Comparison 1 Corticosteroids versus placebo, Outcome 9 Mean time to complete resolution of pain.



Study or subgroup	Corticosteroid N	Corticosteroid Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Total ***	**239**		**261**			**100%**	**-14.41[-24.99,-3.84]**
Heterogeneity: Tau^2=108.78; Chi^2=18.2, df=4(P=0); I^2=78.02%							
Test for overall effect: Z=2.67(P=0.01)							

Favours corticosteroid -40 -20 0 20 40 Favours placebo

Analysis 1.10. Comparison 1 Corticosteroids versus placebo, Outcome 10 Mean absolute reduction in pain VAS/Mcgrath scale at 24 hours.

Study or subgroup	Corticosteroid N	Corticosteroid Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Bulloch 2003	92	2.6 (2.8)	92	2.5 (2.3)		20.76%	0.1[-0.64,0.84]
Kiderman 2005	40	5.4 (2.7)	39	3 (2.9)		14.96%	2.4[1.16,3.64]
Marvez-Valls 1998	46	5.5 (2.7)	46	3.9 (2.7)		16.42%	1.6[0.5,2.7]
O'Brien 1993	31	6 (2.7)	27	4 (3)		12.61%	2[0.52,3.48]
Olympia 2005	57	5.8 (2.6)	68	4.3 (3)		17.83%	1.5[0.52,2.48]
Wei 2002	42	4.6 (1.9)	37	3.6 (2.6)		17.43%	1[-0.02,2.02]
Total ***	**308**		**309**			**100%**	**1.34[0.61,2.06]**
Heterogeneity: Tau^2=0.52; Chi^2=14.12, df=5(P=0.01); I^2=64.6%							
Test for overall effect: Z=3.62(P=0)							

Favours placebo -5 -2.5 0 2.5 5 Favours corticosteroid

Analysis 1.11. Comparison 1 Corticosteroids versus placebo, Outcome 11 Recurrence/relapse of symptoms.

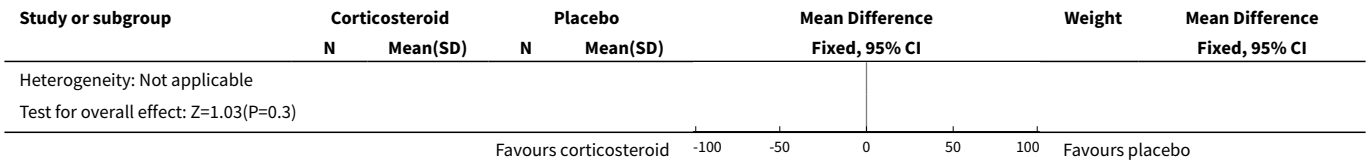
Study or subgroup	Corticosteroid n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bulloch 2003	6/92	6/92		45.97%	1[0.33,2.99]
Kiderman 2005	1/40	5/39		38.79%	0.2[0.02,1.59]
Niland 2006	0/60	1/30		15.24%	0.17[0.01,4.04]
Total (95% CI)	**192**	**161**		**100%**	**0.56[0.24,1.34]**
Total events: 7 (Corticosteroid), 12 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.59, df=2(P=0.27); I^2=22.82%					
Test for overall effect: Z=1.31(P=0.19)					

Favours corticosteroid 0.005 0.1 1 10 200 Favours placebo

Analysis 1.12. Comparison 1 Corticosteroids versus placebo, Outcome 12 Number of days missed from work or school.

Study or subgroup	Corticosteroid N	Corticosteroid Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Marvez-Valls 1998	46	0.4 (1.4)	46	0.7 (1.4)		100%	-0.3[-0.87,0.27]
Total ***	**46**		**46**			**100%**	**-0.3[-0.87,0.27]**

Favours corticosteroid -100 -50 0 50 100 Favours placebo



APPENDICES

Appendix 1. MEDLINE and CENTRAL search strategy

MEDLINE (Ovid)

1 exp Tonsillitis/
2 tonsillit*.tw.
3 exp Pharyngitis/
4 pharyngit*.tw.
5 exp Laryngitis/
6 laryngit*.tw.
7 pharyngotonsillit*.tw.
8 sore throat*.tw.
9 exp Streptococcus/
10 Streptococcal Infections/
11 (streptococc* or gabhs).tw.
12 ("s. pyogenes" or "s pyogenes").tw.
13 ("s. pneumoniae" or "s pneumoniae").tw.
14 or/1-13
15 exp Glucocorticoids/
16 glucocorticoid*.tw,nm.
17 exp Hydroxycorticosteroids/
18 hydroxycorticosteroid*.tw,nm.
19 exp Pregnenediones/
20 hydrocortisone.tw,nm.
21 hydroxypregnenolone.tw,nm.
22 pregnenolone.tw,nm.
23 tetrahydrocortisol.tw,nm.
24 cortodoxone.tw,nm.
25 cortisone.tw,nm.
26 corticosterone.tw,nm.
27 triamcinolone.tw,nm.
28 prednisone.tw,nm.
29 prednisolone.tw.
30 paramethasone.tw,nm.
31 methylprednisolone.tw,nm.
32 dexamethasone.tw,nm.
33 clobetasol.tw,nm.
34 beclomethasone.tw,nm.
35 betamethasone.tw,nm.
36 budesonide.tw,nm.
37 corticosteroid*.tw,nm.
38 steroid*.tw,nm.
39 (efcortesol or hydrocortone or solu-cortef).tw,nm.
40 (betnelan or betnesol).tw,nm.
41 (medrone or solu-medrone or depo-medrone).tw,nm.
42 kenalog.tw,nm.
43 (novolizer or pulmicort or symbicort).tw,nm.
44 (beclometasone or aerobec or asmabec or beclazone or becodisks or becotide or clenil modulite or qvar or becloforte).tw,nm.
45 (deflazacort or calcort).tw,nm.
46 or/15-45

47 14 and 46

Appendix 2. Embase.com search strategy

#51 #47 AND #50149019 Dec 2010
#50 #48 OR #4989794519 Dec 2010
#49 random*:ab,ti OR placebo* OR factorial*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR 'cross-over':ab,ti OR volunteer*:ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR ((singl* OR doubl*) NEAR/2 (blind* OR mask*)):ab,ti AND [embase]/lim86727719 Dec 2010
#48 'randomised controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp AND [embase]/lim23386119 Dec 2010
#47 #14 AND #46672519 Dec 2010
#46 #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35
OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #4554074719 Dec 2010
#45 deflazacort:ab,ti OR calcort:ab,ti AND [embase]/lim39019 Dec 2010
#44 beclometasone:ab,ti OR aerobec:ab,ti OR asmabec:ab,ti OR beclazone:ab,ti OR becodisks:ab,ti OR becotide:ab,ti OR 'clenil modulite':ab,ti OR qvar:ab,ti OR becloforte:ab,ti AND [embase]/lim41819 Dec 2010
#43 novolizer:ab,ti OR pulmicort:ab,ti OR symbicort:ab,ti AND [embase]/lim28919 Dec 2010
#42 kenalog:ab,ti AND [embase]/lim11619 Dec 2010
#41 medrone:ab,ti OR 'solu medrone':ab,ti OR 'dep medrone':ab,ti AND [embase]/lim1319 Dec 2010
#40 betnelan:ab,ti OR betnesol:ab,ti AND [embase]/lim2619 Dec 2010
#39 efcortesol:ab,ti OR hydrocortone:ab,ti OR 'solu cortef':ab,ti AND [embase]/lim2419 Dec 2010
#38 steroid*:ab,ti AND [embase]/lim15167519 Dec 2010
#37 corticosteroid*:ab,ti AND [embase]/lim6537519 Dec 2010
#36 budesonide:ab,ti AND [embase]/lim360919 Dec 2010
#35 betamethasone:ab,ti AND [embase]/lim376819 Dec 2010
#34 beclomethasone:ab,ti AND [embase]/lim257019 Dec 2010
#33 clobetasol:ab,ti AND [embase]/lim74619 Dec 2010
#32 dexamethasone:ab,ti AND [embase]/lim3776219 Dec 2010
#31 methylprednisolone:ab,ti AND [embase]/lim1045419 Dec 2010
#30 paramethasone:ab,ti AND [embase]/lim6319 Dec 2010
#29 prednisolone:ab,ti AND [embase]/lim1621519 Dec 2010
#28 prednisone:ab,ti AND [embase]/lim1833919 Dec 2010
#27 triamcinolone:ab,ti AND [embase]/lim461019 Dec 2010
#26 corticosterone:ab,ti AND [embase]/lim1766619 Dec 2010
#25 cortisone:ab,ti AND [embase]/lim504419 Dec 2010
#24 cortodoxone:ab,ti AND [embase]/lim519 Dec 2010
#23 tetrahydrocortisol:ab,ti37919 Dec 2010
#22 pregnenolone:ab,ti AND [embase]/lim393619 Dec 2010
#21 hydroxypregnenolone:ab,ti AND [embase]/lim50019 Dec 2010
#20 hydrocortisone:ab,ti AND [embase]/lim1104419 Dec 2010
#19 'pregnane derivative'/de AND [embase]/lim52719 Dec 2010
#18 hydroxycorticosteroid*:ab,ti AND [embase]/lim62919 Dec 2010
#17 'hydroxycorticosteroid'/exp AND [embase]/lim24019 Dec 2010
#16 glucocorticoid*:ab,ti AND [embase]/lim4210419 Dec 2010
#15 'glucocorticoid'/exp AND [embase]/lim38055619 Dec 2010
#14 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #1310695919 Dec 2010
#13 's. pneumoniae':ab,ti OR 's pneumoniae':ab,ti OR 's. pyogenes':ab,ti OR 's pyogenes':ab,ti AND [embase]/lim761119 Dec 2010
#12 'streptococcus infection'/exp AND [embase]/lim1848919 Dec 2010
#11 streptococc*:ab,ti OR gabhs:ab,ti AND [embase]/lim5434219 Dec 2010
#10 'streptococcus'/exp AND [embase]/lim6479619 Dec 2010
#9 'sore throat':ab,ti OR 'sore throats':ab,ti AND [embase]/lim280919 Dec 2010
#8 'sore throat'/de AND [embase]/lim581219 Dec 2010
#7 pharyngotonsillit*:ab,ti AND [embase]/lim30119 Dec 2010
#6 laryngit*:ab,ti AND [embase]/lim102019 Dec 2010
#5 'laryngitis'/exp AND [embase]/lim320319 Dec 2010
#4 pharyngit*:ab,ti AND [embase]/lim349219 Dec 2010
#3 'pharyngitis'/exp AND [embase]/lim1233519 Dec 2010
#2 tonsillit*:ab,ti AND [embase]/lim297819 Dec 2010
#1 'tonsillitis'/exp AND [embase]/lim631419 Dec 2010

FEEDBACK

Corticosteroids as standalone or add-on treatment for sore throat, 25 October 2014

Summary

Just wanted to point out a possible typo under participants section:

(369 participants aged 5-21 years and 374 participants aged *12* to 65)

Thanks,

Jane Barr

I agree with the conflict of interest statement below:
I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Corticosteroids as standalone or add-on treatment for sore throat, 1 October 2013

Summary

I think that the use of Relative Risks in relation to pain resolution may have resulted in misleading subgroup comparisons in this review (for example in relation to oral and IM corticosteroids). The Relative Risks of persistent pain are (RR (Non-event) 0.73; 95% CI 0.61 to 0.86) and (RR (Non-event) 0.68; 95% CI 0.56 to 0.83) for oral and IM treatment respectively. These are almost identical.

Odds ratios have the advantage that sub-group analysis is unchanged by whether the outcome is measured as persistent pain or resolution of pain.

Chris Cates
ccates@sgul.ac.uk

I agree with the conflict of interest statement below:

I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

WHAT'S NEW

Date	Event	Description
2 June 2014	Feedback has been incorporated	Two feedback comments added to the review

HISTORY

Protocol first published: Issue 1, 2010
Review first published: Issue 10, 2012

Date	Event	Description
5 August 2010	Amended	Contact details updated.
16 June 2010	Amended	Contact details updated.

CONTRIBUTIONS OF AUTHORS

Gail Hayward (GH) wrote the review. All review authors, GH, Matthew Thompson (MT), Carl Heneghan (CH), Rafael Perera (RP), Paul Glasziou (PG), Chris Del Mar (CDM) revised the manuscript.

DECLARATIONS OF INTEREST

None declared.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- British Society of Antimicrobial Chemotherapy, UK.

  A Systematic Review Grant was awarded (GA722SRG)

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [*administration & dosage]; Anti-Bacterial Agents [*administration & dosage]; Drug Therapy, Combination [methods]; Pharyngitis [*drug therapy]; Randomized Controlled Trials as Topic; Tonsillitis [drug therapy]

MeSH check words

Adolescent; Adult; Child; Child, Preschool; Humans; Middle Aged; Young Adult