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Corticosteroids for Bell's palsy (idiopathic facial paralysis) (Review)

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[Intervention Review]

Corticosteroids for Bell's palsy (idiopathic facial paralysis)

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ABSTRACT

Background

Inflammation and oedema of the facial nerve are implicated in causing Bell's palsy. Corticosteroids have a potent anti-inflammatory action that should minimise nerve damage. This is an update of a review first published in 2002 and last updated in 2010.

Objectives

To determine the effectiveness and safety of corticosteroid therapy in people with Bell's palsy.

Search methods

On 4 March 2016, we searched the Cochrane Neuromuscular Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and LILACS. We reviewed the bibliographies of the randomised trials and contacted known experts in the field to identify additional published or unpublished trials. We also searched clinical trials registries for ongoing trials.

Selection criteria

Randomised trials and quasi-randomised trials comparing different routes of administration and dosage schemes of corticosteroid or adrenocorticotrophic hormone therapy versus a control group receiving no therapy considered effective for this condition, unless the same therapy was given in a similar way to the experimental group.

Data collection and analysis

We used standard Cochrane methodology. The main outcome of interest was incomplete recovery of facial motor function (i.e. residual facial weakness). Secondary outcomes were cosmetically disabling persistent sequelae, development of motor synkinesis or autonomic dysfunction (i.e. hemifacial spasm, crocodile tears) and adverse effects of corticosteroid therapy manifested during follow-up.

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Main results

We identified seven trials, with 895 evaluable participants for this review. All provided data suitable for the primary outcome meta-analysis. One of the trials was new since the last version of this Cochrane systematic review. Risk of bias in the older, smaller studies included some unclear- or high-risk assessments, whereas we deemed the larger studies at low risk of bias. Overall, 79/452 (17%) participants allocated to corticosteroids had incomplete recovery of facial motor function six months or more after randomisation; significantly fewer than the 125/447 (28%) in the control group (risk ratio (RR) 0.63, 95% confidence interval (CI) 0.50 to 0.80, seven trials, n = 895). The number of people who need to be treated with corticosteroids to avoid one incomplete recovery was 10 (95% CI 6 to 20). The reduction in the proportion of participants with cosmetically disabling sequelae six months after randomisation was very similar in the corticosteroid and placebo groups (RR 0.96, 95% CI 0.40 to 2.29, two trials, n = 75, low-quality evidence). However, there was a significant reduction in motor synkinesis during follow-up in participants receiving corticosteroids (RR 0.64, 95% CI 0.45 to 0.91, three trials, n = 485, moderate-quality evidence). Three studies explicitly recorded the absence of adverse effects attributable to corticosteroids. One trial reported that three participants receiving prednisolone had temporary sleep disturbances and two trials gave a detailed account of adverse effects occurring in 93 participants, all non-serious; the combined analysis of data from these three trials found no significant difference in adverse effect rates between people receiving corticosteroids and people receiving placebo (RR 1.04, 95% CI 0.71 to 1.51, n = 715).

Authors' conclusions

The available moderate- to high-quality evidence from randomised controlled trials showed significant benefit from treating Bell's palsy with corticosteroids.

PLAIN LANGUAGE SUMMARY

Corticosteroids for Bell's palsy

Review question

What are the effects of corticosteroids on Bell's palsy?

Background

Bell's palsy is a paralysis or weakness of muscles in the face, usually on one side, with no certain cause. Symptoms usually recover, although not always. Reducing inflammation of the facial nerve using corticosteroid medicines (steroids) is thought to limit nerve damage. This is an update of a review first published in 2002 and last updated in 2010.

Study characteristics

We identified seven clinical trials involving 895 people with one-sided mild, moderate or severe Bell's palsy of unknown cause. All of these trials reported rates of incomplete recovery (the proportion of people left with facial weakness) and we were able to combine the results. People in the studies were aged from 2 to 84 years. They were treated with corticosteroids or placebo (inactive treatment), either alone or in combination with other therapies. One trial only involved children, from 24 months to 74 months old. The duration of the included studies for adults and children ranged from 157 days to 12 months.

Key results and quality of the evidence

Incomplete recovery

According to moderate quality to high quality evidence, corticosteroids reduced the number of people left with facial weakness after Bell's palsy compared to placebo (a pretend medicine). This finding was based on data from seven studies involving 895 participants with Bell's palsy of varying degrees of severity. We calculated that to stop one person from being left with facial weakness, 10 people need to be treated.

Five studies provided data on long-term after-effects of Bell's palsy following treatment. Two of the studies (75 participants) looked at persistent effects on facial appearance after six months or more. The effect was nearly the same for corticosteroids and placebo, showing that participants who had corticosteroids benefited slightly, although this evidence was low quality. Data from three studies (485 participants) showed clearly that people who received corticosteroids developed less motor synkinesis (unwanted facial movements) and crocodile tears (watery eyes when eating or chewing), compared with people who received placebo alone. This finding was based on moderate-quality evidence.

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Side effects

Three studies reported that no side effects could be attributed to corticosteroid treatment. Based on moderate-quality evidence from three studies (715 participants), numbers experiencing side effects were similar with corticosteroids and placebo.

The evidence is current to March 2016.

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SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Corticosteroids compared to placebo or no treatment for Bell's palsy

Patient or population: people with Bell's palsy
Settings: primary and secondary care
Intervention: corticosteroids
Comparison: placebo or no treatment

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 or no treatment	Corticosteroids				
Incomplete recovery ≥ 6 months after randomisation House-Brackmann grading system and Sunnybrook scale Follow-up: 157 days to 12 months	**281 per 1000**	**177 per 1000** (140 to 225)	**RR 0.63** (0.50 to 0.80)	895 (7 studies)	⊕⊕⊕⊕ **high**[1]	NNTB 10, 95% CI 6 to 20
Cosmetically disabling persistent sequelae ≥ 6 months after randomisation Clinical assessment Follow-up: mean 6 months	**216 per 1000**	**208 per 1000** (86 to 495)	**RR 0.96** (0.4 to 2.29)	75 (2 studies)	⊕⊕◯◯ **low**[2,3]	-
Motor synkinesis and crocodile tears Clinical assessment Follow-up: 9 to 12	**260 per 1000**	**167 per 1000** (117 to 237)	**RR 0.64** (0.45 to 0.91)	485 (3 studies)	⊕⊕⊕◯ **moderate**[4]	-

months						
Adverse effects Follow-up: 9 to 12 months	**127 per 1000**	**133 per 1000** (91 to 192)	**RR 1.04** (0.71 to 1.51)	715 (3 studies)	⊕⊕⊕◯ **moderate**[5]	3 other studies recorded that no adverse effects occurred with corticosteroid treatment

*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; **NNTB:** number needed to treat for an additional beneficial outcome; **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] Two trials excluded participants who were found to have clinical evidence of herpes zoster infection (Lagalla 2002; Taverner 1954). In addition, two studies did not use a scoring system such as the House-Brackmann or Sunnybrook scale to assess facial motor function, relying upon clinical examination, electromyographic tests or photographs (May 1976; Taverner 1954). Taverner 1954 reported outcomes at five months rather than at six months or more. However, we felt that these limitations did not compromise the generalisability of the findings.
[2] We downgraded twice: first for imprecision - there was a low number of events and pooled RR allowed the possibility of both no effect and the chance of harm; second for publication bias - of the seven included studies, five did not provide data on the presence of cosmetically disabling sequelae six months or more after randomisation.
[3] We downgraded once for imprecision. There was a low number of events.
[4] We downgraded the quality of the evidence to moderate because of publication bias.
[5] We downgraded for publication bias - only three of seven studies provided data on adverse effects.

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BACKGROUND

Description of the condition

Bell's palsy is an acute, generally unilateral, paralysis or weakness of facial musculature consistent with peripheral facial nerve dysfunction, of no detectable cause (Niparko 1993). Additional symptoms frequently include pain around or behind the ear sometimes extending into the occipital or cervical region. Impaired tolerance to ordinary levels of noise and disturbed sense of taste on the same side may also be present (Burgess 1984).

Epidemiological studies have reported an annual incidence of 23 to 25 per 100,000 per year (Martyn 1997; Victor 1994), but one study using a general practitioner (GP) database has suggested it may be even higher at 37 per 100,000 per year (Morales 2013). Bell's palsy affects men and women more or less equally. Until recently was thought to be most common in the 30- to 45-year age group (Bateman 1992; Brandenberg 1993; Katusic 1986; Peitersen 1982; Peitersen 2002; Yanagihara 1988), although the one more recent primary care database study suggested a peak in people over 70 years of age (Morales 2013). The condition presents disproportionately among pregnant women and people who have diabetes, influenza, a cold, or some other upper respiratory ailment. On average, every year a British GP will see one or two people who have developed the condition. Both sides of the face are affected equally often (Prescott 1988).

The aetiology of Bell's palsy is still debated. A viral infection, vascular ischaemia, autoimmune inflammatory disorders and heredity have been proposed as underlying causes (Adour 1982; Burgess 1984; Lackner 2010). A viral aetiology has gained popularity since the isolation of herpes simplex virus-1 (HSV-1) genome from the facial nerve endoneurial fluid of people with Bell's palsy (Lackner 2010; Murakami 1996). The prognosis is on the whole favourable. One of the largest series of people with Bell's palsy including those who were not receiving specific therapy, showed that 85% of people with Bell's palsy began to recover within three weeks of onset (Peitersen 1982). For the remaining 15%, partial recovery occurred three to six months later. The same series showed that normal facial expression reappeared in 71% of cases, 13% had insignificant sequelae, and the remaining 16% had permanently diminished function with aberrant innervation (expressed as motor synkinesis or autonomic dysfunction) and post-paralytic spasms.

Description of the intervention

The treatment of Bell's palsy used to be highly controversial. Corticosteroids were the treatment of choice, based mainly on non-randomised comparisons (Adour 1972). The authors of numerous clinical series both espoused and condemned corticosteroid therapy with, what appeared to them, equally convincing arguments (Burgess 1984). Four systematic reviews found a significant trend favouring corticosteroid treatment in improving the recovery of facial motor function (de Almeida 2009; Grogan 2001; Ramsey 2000; Williamson 1996). However, their conclusions were affected by including trials of poor quality in the pooled estimate. de Almeida 2009, a state-of-the-art, high-quality systematic review, differed from our methodology in the way they collected data, in the inclusion of a non-randomised trial that we excluded (Martinez 1990), and in the exclusion of a trial that we included in our analysis (Taverner 1954).

How the intervention might work

Corticosteroids are known to have an anti-inflammatory mode of action, which reduces oedema and inflammation of the facial nerve in the acute presentation of Bell's palsy.

Why it is important to do this review

The purpose of this systematic review was to collect and analyse the available evidence from randomised controlled trials concerning the use of corticosteroids for improving the outcome of people with Bell's palsy. This is an update of a review first published in 2002 and last updated in 2010. We updated the review to assess the quality of the evidence regarding the benefit of corticosteroids in Bell's palsy using current methodology, integrate any new evidence and to determine whether further research would be likely to change the estimate of effect or its certainty.

OBJECTIVES

To determine the effectiveness and safety of corticosteroid therapy in people with Bell's palsy.

METHODS

Criteria for considering studies for this review

Types of studies

Trials of the use of corticosteroid therapy for the treatment of recent-onset Bell's palsy in which an attempt had apparently been made to conduct a randomised or quasi-randomised comparison between corticosteroid therapy and a placebo, or open control group. As in the previous version of the review, we used study quality as an exclusion criteria excluding trials with a high risk of bias in several domains.

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Types of participants

Participants of any age with clinically diagnosed Bell's palsy, irrespective of the time of evolution of symptoms. We included all participants considered to have Bell's palsy or acute idiopathic facial nerve paralysis by the study authors, irrespective of the ancillary studies they performed to rule out other causes of facial paralysis. We included in the analysis all participants considered eligible by the authors of the studies, irrespective of associated conditions.

Types of interventions

We included trials using any corticosteroid or adrenocorticotrophic hormone therapy, irrespective of the route of administration (oral or parenteral) and length of therapy. We excluded trials in which a drug considered 'effective' for this condition was given to the control group, unless it was given in a similar way to the experimental group. The exception was studies in which control and treatment groups received concomitant antiviral therapy; these are not included in this review, but in the updated Cochrane review 'Antiviral treatment for Bell's palsy (idiopathic facial paralysis)' (Gagyor 2015).
We excluded trials comparing different types of corticosteroids or different dosage schemes, unless the trial included a placebo group.

Types of outcome measures

Primary outcomes

- Incomplete recovery of facial motor function six months or more after randomisation.

Secondary outcomes

- Cosmetically disabling persistent sequelae of facial paralysis (poor recovery of facial motor function as defined by the authors of the studies) six months or more after randomisation.
- Motor synkinesis or autonomic dysfunction during follow-up (including facial spasm, motor synkinesis and crocodile tears).
- Adverse effects attributable to the use of corticosteroids.

Search methods for identification of studies

Electronic searches

On 4 March 2016, we searched the Cochrane Neuromuscular Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL in the *Cochrane Register of Studies Online*), MEDLINE (January 1966 to February 2016), EMBASE (January 1980 to February 2016) and LILACS (January 1982 to February 2016). The detailed search strategies are in the appendices: Cochrane Neuromuscular Specialised Register (Appendix 1), CENTRAL (Appendix 2), MEDLINE (Appendix 3), EMBASE (Appendix 4) and LILACS (Appendix 5).
On 21 June 2016, we searched ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform (ICTRP) (who.int/trialsearch/) for ongoing studies. We searched both using the term "Bell's Palsy".

Searching other resources

We reviewed the bibliographies of the randomised trials and contacted the study authors and known experts in the field to identify additional published or unpublished data.

Data collection and analysis

Selection of studies

Six review authors scrutinised published and unpublished papers retrieved by the literature searches to select papers for inclusion. At least two review authors independently assessed each paper for relevance, eligibility and quality. There were no disagreements about inclusion. We applied no language limitations.

Data extraction and management

Review authors collected and analysed data in pairs (FG and VM, DS and MS, IG and FS). We collected data on the following.

- Methods: study design, study duration, number of study centres and location, study setting, withdrawals, and date of study.
- Participants: number (n), mean age, age range, gender, severity of condition, diagnostic criteria, baseline characteristics, inclusion criteria and exclusion criteria.
- Interventions: intervention, comparison, concomitant medications.
- Outcomes: primary and secondary outcomes specified and collected, and time points reported; definition of recovery status.
- Notes: funding for trial and notable conflicts of interest of trial authors.

All six review authors had a selection of papers to read, review for quality and extract data from. At least two review authors assessed each trial. All review authors agreed data extraction.
Two review authors (IG and VM) inputted data into Review Manager 5 (RevMan 2014).

Assessment of risk of bias in included studies

IG completed the 'Risk of bias' table. FS and FD individually reviewed the 'Risk of bias' assessments. We assessed bias by scoring studies as at high, low or unclear risk of bias using methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

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Measures of treatment effect

When comparing studies using different symptom scores to assess outcomes, we used the House-Brackmann scale when available as this was the most widely used or had comparisons to other scales available. When assessing adverse effects, we reported the number of participants affected, as opposed to the number of events, to facilitate data comparison.

We used dichotomous outcomes and we analysed data as risk ratios (RR) with a corresponding 95% confidence interval (CI). We calculated a treatment effect using the Mantel-Haenszel method (Egger 2007).

Unit of analysis issues

Where a single trial included multiple trial arms, we included only arms relevant to this review. If two comparisons (e.g. drug A versus placebo and drug B versus placebo) had been combined in the same meta-analysis, our preference would be to combine groups to create a single comparison if appropriate, or otherwise use one of the other approaches described in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Dealing with missing data

One of the trial authors, who is also a review author (FS), provided unpublished trial data. We also contacted a previous study team member (P Lockhart) for additional information on other studies and received a response. We either extracted the number of participants who completed a treatment originally allocated and the number with the outcome, and considered the potential effect of missing data when presenting results, or reported intention-to-treat analyses as presented in trial reports. Where data were unavailable we contacted the original authors, when there was no response, we calculated the numbers from the rates and percentages presented in the papers. We undertook no sensitivity analyses for missing values. For some trials, we calculated either number in the analysis or the number experiencing an event using the percentage experiencing an event.

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity among the trials in each analysis, using the thresholds in the *Cochrane Handbook for Systematic Reviews of Interventions* as guidance (Higgins 2011):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

We interpreted the I^2 statistic in the context of its CI, the Chi^2 test, P value and the size of the effect.

Assessment of reporting biases

Since we were unable to pool more than 10 trials, we could not create a funnel plot to explore possible small-study biases.

Data synthesis

We used a fixed-effect model for our analysis and performed a sensitivity analysis with a random-effects model.

If the review had included more than one comparison that could not be included in the same analysis, we would have reported the results for each comparison separately.

Throughout we have utilised the following notations:

OS: corticosteroid treatment alone

OO: placebo or no treatment only

Using these notations, we conducted the following comparison: OS versus OO.

'Summary of findings' table

At this update, we added a 'Summary of findings' table. We used the following outcomes: incomplete recovery, cosmetically disabling persistent sequelae six months or more after randomisation, motor synkinesis and crocodile tears, and adverse effects.

Under the GRADE approach, the levels of quality of evidence are high, moderate, low or very low. Assessors start at high quality and may downgrade the evidence for the pre-specified outcomes depending on five GRADE considerations, which are: study limitations, consistency of effect, imprecision, indirectness and publication bias. We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We used GRADEpro software (GRADEpro 2008). We have justified all decisions to downgrade or upgrade the quality of studies using footnotes and have made comments to aid readers' understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We did not undertake any subgroup analyses for this review. The protocol detailed possible subgroup analyses, although none were appropriate for the included studies.

Sensitivity analysis

We carried out the following sensitivity analyses.

- Repeated the analyses excluding smaller and underpowered studies.
- Repeated the analyses excluding studies with short-term follow-up (less than nine months).

RESULTS

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Description of studies

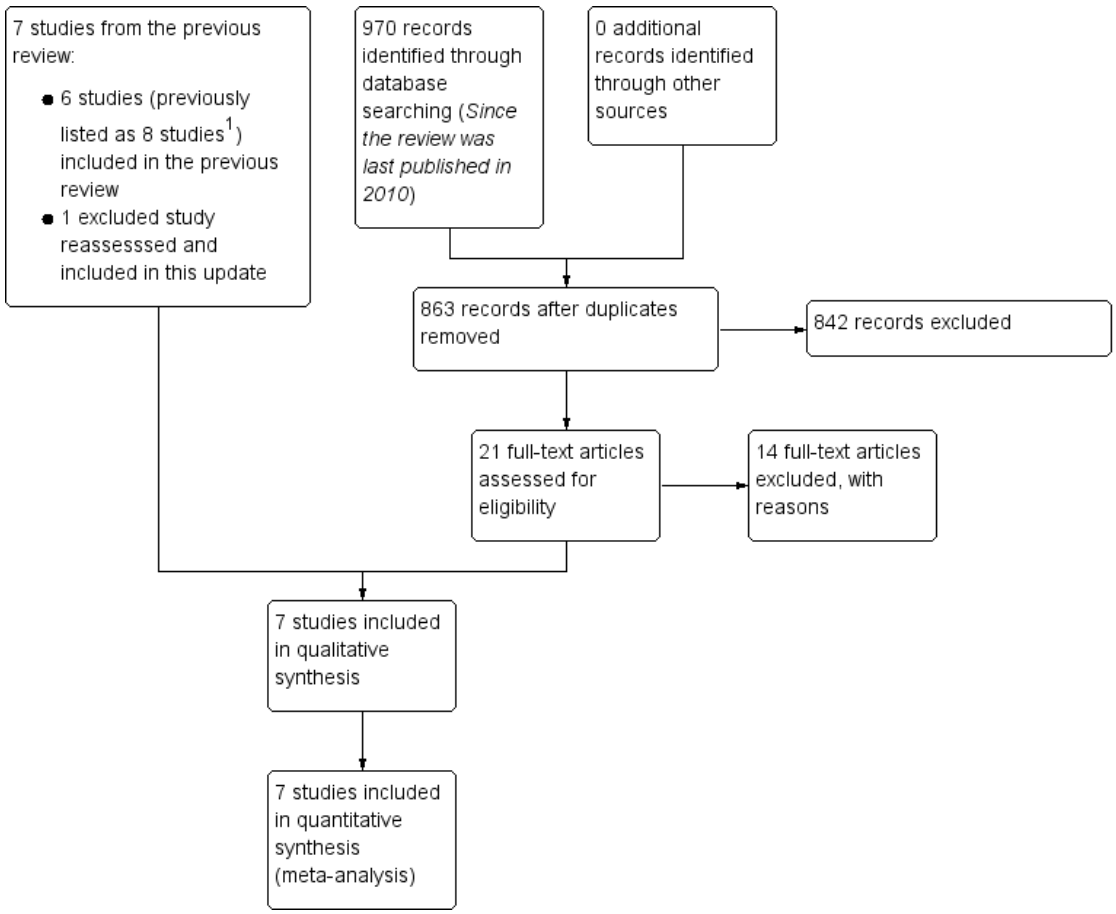
Results of the search

In the updated searches for this review, we found 59 references in the Cochrane Neuromuscular Specialised Register, 81 in CENTRAL, 818 in MEDLINE, 117 in EMBASE and 15 in LILACS. There were seven completed randomised controlled trials comparing corticosteroids with no active control when this review was first written. In subsequent updates, review authors identified five other potentially relevant trials (Austin 1993; Bento 1991; Engström 2008; Lagalla 2002; Sullivan 2007).

In all, seven trials including 895 evaluable participants met our inclusion criteria (Austin 1993; Engström 2008; Lagalla 2002; May 1976; Sullivan 2007; Taverner 1954; Unuvar 1999).

See Figure 1 for a flow chart illustrating the study selection process for this update.

Figure 1. Study flow diagram illustrating the study selection process for this update.1. The previous version of this review listed comparisons involving participants treated with antiviral therapy from Sullivan 2007 and Engström 2008 as two additional separate studies. These two comparisons are not included in this update.



The previous update of this review, Salinas 2010, listed seven excluded studies (Akpinar 1979; Austin 1993; Bento 1991; Bento 1994; Brown 1982; Martinez 1990; Wolf 1978). We have linked two references previously listed as separate trials (Bento 1991 and Bento 1994) under one trial identifier in this update (Bento 1991). We included Austin 1993, previously excluded because of potential attrition bias, as current practice is to include all trials eligible

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according to the selection criteria.

Authors of the last version of this review included groups receiving antiviral therapy and considered the different comparisons from Engström 2008 and Sullivan 2007 as separate studies (Engström 2008b and Sullivan 2007b). We did not consider the two antiviral-treated participant groups from those trials in this updated review. These comparisons are included in the companion Cochrane review, 'Antiviral treatment for Bell's palsy (idiopathic facial paralysis)' (Gagyor 2015). In this update, we included only the comparisons of corticosteroid versus placebo or corticosteroids versus no treatment.

Included studies

Summary details of the included trials are given in Characteristics of included studies.

Austin 1993 recruited 107 participants whose symptoms had occurred within five days of presentation to the study centre. Of these, 31 participants did not return for initial follow-up. The 76 remaining participants subsequently entered a double-blinded randomised controlled study allocating them to a corticosteroid treatment group (prednisone) or a placebo group. The trial authors gave no details about binding or randomisation. Assessment of participants occurred within five days of onset and at "regular intervals until they experienced recovery from their acute paralysis". Final follow-up was at six months after recovery. The trial authors stated, "to be included in the analysis, patients must have completed follow up until their acute recovery occurred." Investigators measured disease status using the House-Brackmann grading system. At first evaluation, participants underwent various tests including blood tests, an audiogram, a nerve excitability test using the maximal stimulation technique and, if indicated, electroneurography. Treatment with prednisone was started at 30 mg twice daily for the first five days followed by a reducing dose stated by the trial authors.

The study reported final outcomes on 53 participants at six months after recovery. The primary outcome was time to recovery, for which trial authors found no statistically significant difference between the two groups. Secondary outcomes included facial paralysis grade at onset versus grade at recovery. There was a statistically significant difference in incomplete recovery rates favouring the treatment group: 5/23 participants receiving prednisone had incomplete recovery at six months versus 10/30 participants receiving placebo (RR 0.65, 95% CI 0.26 to 1.65). Investigators found no significant difference in persistence of pain during recovery, with 3/23 participants in the prednisone group still experiencing pain at six months, compared with 4/30 participants in the placebo group (RR 0.98, 95% CI 0.24 to 3.95).

Engström 2008 had a factorial design that randomised 829 participants into four treatment groups using a two-stage computerised process. The four treatment groups were prednisolone with placebo, prednisolone with valaciclovir, valaciclovir with placebo, and double placebo. Treatment started within 72 hours of symptom onset. The trial was double-blind (administrator and participant) for assessment of recovery status until the end of follow-up. Participants were assessed at onset, after two weeks (11 to 17 days) and after 1, 2, 3, 6 and 12 months. Trialists measured disease status using the House-Brackmann grading system and the Sunnybrook scale, defining complete recovery status as a Sunnybrook score of 100 and a House-Brackmann grade of I. Data analysis included an assessment of treatment interaction.

The study reported a positive effect on recovery time due to prednisolone (comparing recovery rates at 12 months in the prednisolone group with the placebo group). For this review, we analysed the corticosteroid-placebo combination (OS) versus the double placebo combination (OO) 12 months after the onset of facial palsy. Using the Sunnybrook definition, 50/210 participants had an incomplete recovery with prednisolone compared with a greater proportion (73/206) in the placebo group (RR 0.67, 95% CI 0.50 to 0.91).

Lagalla 2002 randomised 62 participants within three days of onset of Bell's palsy to high-dose prednisone, 1 g daily for three days, then 0.5 g daily for three days, administered intravenously, using saline solution as a placebo. The age range was 15 to 84 years. Exclusion criteria included peptic ulcer disease, pregnancy, severe hypertension, other neurological conditions, diseases of the ear and previous treatment. As in Taverner 1954, investigators excluded participants with herpes zoster oticus from the analyses (four of the participants initially randomised in Lagalla 2002). The investigators monitored participants for 12 months. They assessed recovery of facial motor function using the House-Brackmann scale. The trial authors reported the development of disabling synkinesis at 12-month follow-up.

Lagalla 2002 reported final outcomes on 58 participants at 12 months. In the prednisolone group, 5/30 participants had incomplete recovery, compared with 8/28 participants in the placebo group (RR 0.58, 95% CI 0.22 to 1.57).

May 1976 included 51 participants within two days of Bell's palsy onset and reported outcomes using clinical assessment and photographic documentation without a validated scoring system. The trial report did not specify the age range of participants in this double-blinded study. In the intervention group, participants received prednisone 410 mg in descending doses over 10 days. The placebo intervention was vitamins. Trialists excluded people with chronic otitis media, trauma, loss of lacrimation, or recurrent or bilateral palsy.

May 1976 was the only study that stated that there was no benefit from corticosteroids for the recovery of Bell's palsy (RR 1.16, 95% CI 0.57 to 2.36).

Sullivan 2007 recruited 551 participants to be treated within 72 hours of onset. Participants were randomised by a dedicated remote telephone-computerised mechanism in a two-stage process into four treatment groups in a factorial design: prednisolone with placebo, prednisolone with aciclovir, aciclovir with placebo or dou-

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ble placebo. Participants received prednisolone 25 mg twice daily for 10 days. The trial was blinded for administrator, participant and assessment of recovery status until the end of follow-up. Assessments took place at onset, after three months and, if participants were still unwell, again after nine months. The investigators measured recovery status on the House-Brackmann scale, with complete recovery defined as House-Brackmann grade I. Data analysis included an assessment of treatment interaction.

Sullivan 2007 reported final outcomes on 496 completed participants at three and nine months. In the corticosteroid (OS) group, 5/127 participants had incomplete recovery, compared with 18/122 participants in the placebo (OO) group (RR 0.27, 95% CI 0.10 to 0.70).

Taverner 1954 was a double-blind trial that included 26 participants with a range of ages from 12 to 76 years within 10 days of onset of Bell's palsy. Participants received either oral cortisone acetate 1 g in descending doses over eight days or placebo tablets. Participants were monitored for up to 157 days. The trial excluded participants with other neurological conditions or diseases of the ear. Taverner 1954 included participants with herpes zoster oticus. These participants were allocated in equal numbers to each treatment arm, and trial authors excluded them from the analyses. The trialists did not used a validated scoring system to measure outcomes.

Taverner 1954 used the recovery of facial motor function as the main outcome measure and reported a small, non-significant benefit of corticosteroids compared with placebo; CIs allowed for effects in either direction (RR 0.86, 95% CI 0.27 to 2.71).

Unuvar 1999 conducted a non-blinded, randomised controlled trial on children with severe to complete presentation of Bell's palsy (House-Brackmann grades IV to V). They randomised 42 children with an age range of 24 to 74 months using a computer-generated random sequence into two groups. All participants entered the trial within three days of onset of Bell's palsy and received either methylprednisolone 1 mg/kg daily for 10 days then gradually withdrawn over three to five days or no specific treatment. They excluded participants with other neurological conditions, diseases of the ear or systemic diseases. The primary outcome was the recovery of facial motor function measured on the House-Brackmann facial grading system.

Unuvar 1999 reported a benefit from the treatment with corticosteroids although wide CIs allowed for the possibility of both no effect and a large effect (RR 0.14, 95% CI 0.01 to 2.61).

Ongoing studies

We identified one trial report on the World Health Organization International Clinical Trials Registry Platform search portal (Babl 2015). From the website, it appeared that the study has now started recruitment; we will assess this trial fully in future review updates. See Characteristics of ongoing studies.

Excluded studies

Akpinar 1979 compared three groups of 10 participants each; two groups received different dosage regimens of corticosteroids, and the other received placebo. It was unclear who diagnosed the participants with Bell's palsy and there were varying dosage regimens of corticosteroids used. Two studies were not randomised or quasi-randomised (Brown 1982; Martinez 1990). It was not possible to extract complete information on the specified outcomes for one study (Wolf 1978). Finally, we excluded Bento 1991 as number of participants and outcome events by treatment groups was not provided; in addition, 50% of the participants were lost to follow-up.

Risk of bias in included studies

Figure 2 summarises the 'Risk of bias' assessment for each included study.

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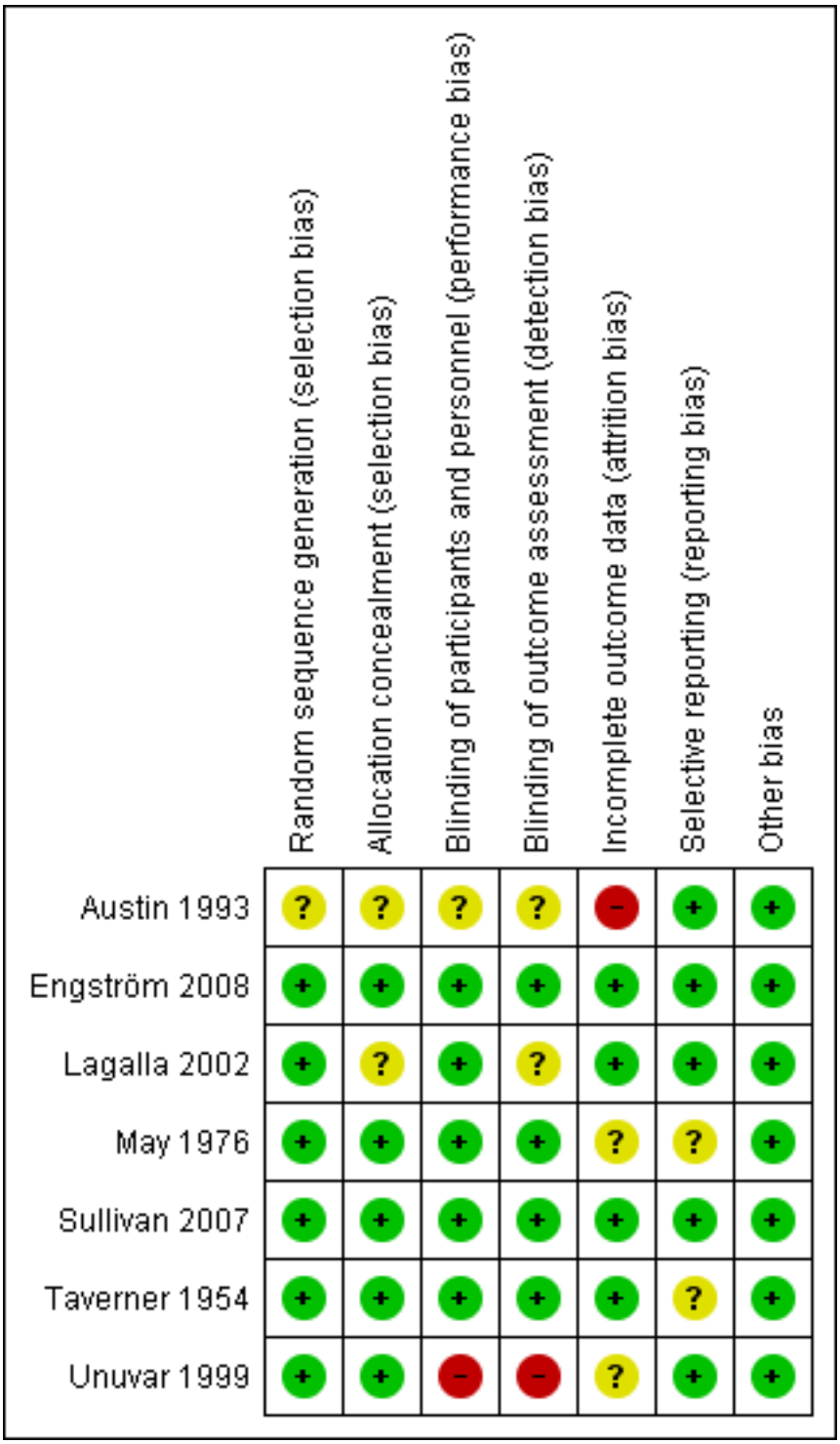
Figure 2. 'Risk of bias' summary: review authors' judgements about each methodological quality item for each included study. Green (+) = low risk of bias; yellow (?) = unclear risk of bias; red (-) = high risk of bias.



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Allocation

All included trials reported the method of randomisation. Four used randomisation centralised at a pharmacy, in accordance with a master sheet of random numbers (May 1976; Taverner 1954), or an automated permuted block technique (Engström 2008; Sullivan 2007). One study used a random number list (Lagalla 2002), and another used a computer-based program (Unuvar 1999). It was not clear from the reports if there was adequate allocation concealment in Lagalla 2002 or Unuvar 1999. We considered none of the trials to be at high risk of bias for random sequence generation or allocation concealment.

Blinding

Five trials were double-blind, using placebo in the control group (Engström 2008; Lagalla 2002; May 1976; Sullivan 2007; Taverner 1954). Two of these trials used lactose as the placebo (Sullivan 2007; Taverner 1954), one used vitamins (May 1976), and one used a saline solution (Lagalla 2002). Two trials did not specify what was used as placebo, but they stated that this was formulated to have the same size, smell and colour (Engström 2008; Unuvar 1999). In the trial using vitamins as placebo, the experimental group received similar looking capsules containing prednisone plus vitamins. The trial using saline solution as placebo gave intramuscular vitamins to all participants for 15 days (Lagalla 2002). In one trial, it was not clear from the report if the physicians administering the drug were blinded (Lagalla 2002). There were no serious imbalances in baseline prognostic factors between groups.

Incomplete outcome data

Engström 2008, Sullivan 2007; and Taverner 1954 had drop-out rates of less than 10%. No participants dropped out in May 1976. Lagalla 2002 included drop-outs in analyses on an intention-to-treat basis, by assuming that drop-outs had a poor outcome. Austin 1993 had a drop-out rate of 50% for outcomes six months after recovery. Unuvar 1999 did not report on attrition.

Selective reporting

All studies reported their intended primary outcomes. Engström 2008 reported all primary outcomes, with secondary outcomes reported in subsequent publications (Axelsson 2012; Berg 2012).

Other potential sources of bias

We identified no other potential sources of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Corticosteroids compared to placebo or no treatment for Bell's palsy

As all trials reported different intervals and lengths of follow-up, we performed analyses on data reported at the end of the study periods. These were 157 days (Taverner 1954), six months (May 1976; Austin 1993), nine months (Sullivan 2007), and 12 months (Engström 2008; Lagalla 2002; Unuvar 1999).

Primary outcome

Incomplete recovery of facial motor function six months or more after randomisation

All seven trials, with 895 participants, provided data for the outcome complete recovery of facial motor function at six months' follow-up or more (we included data from Taverner 1954, which reported at five months). The number of people with incomplete recovery at six months' follow-up was lower in the corticosteroid group compared to the control group (RR 0.63, 95% CI 0.50 to 0.80) (Analysis 1.1; Figure 3).

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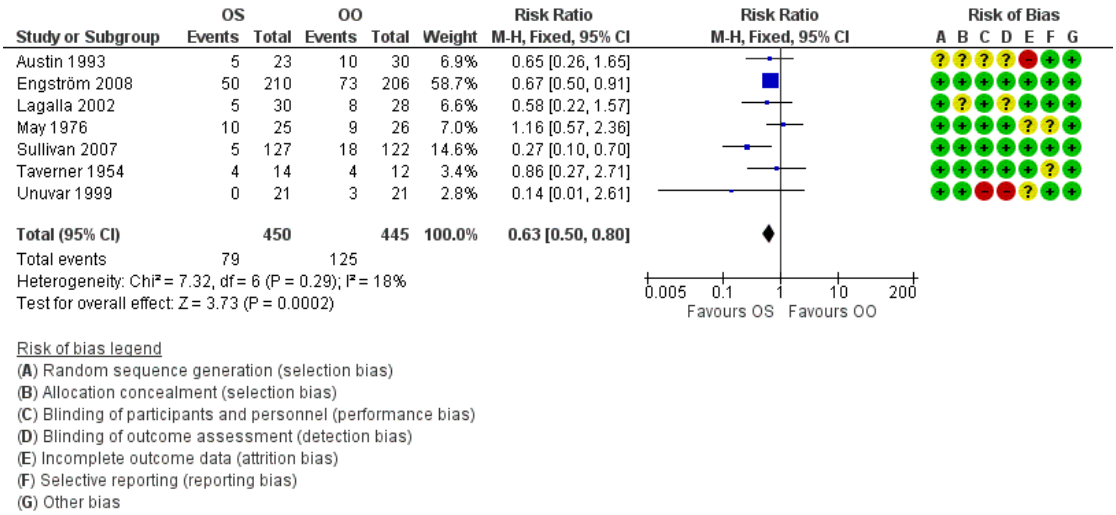
Figure 3. Forest plot of comparison: 1 Corticosteroid (OS) versus placebo or no treatment (OO), outcome: 1.1 Incomplete recovery ≥ 6 months after randomisation.



The tests for statistical heterogeneity were marginally significant (Chi^2 = 7.32, P value = 0.29, I^2 = 18%). This small degree of heterogeneity was due to the differences in the findings between the large studies (Engström 2008; Sullivan 2007), and small, underpowered studies (Austin 1993; Lagalla 2002; May 1976; Taverner 1954; Unuvar 1999). There were better outcomes in two of the studies (Engström 2008; Sullivan 2007).

The number of people who need to be treated with steroids to avoid one person with incomplete recovery was 10 (95% CI 6 to 20).

Sensitivity analyses

We removed smaller underpowered studies (Austin 1993; Lagalla 2002; May 1976; Taverner 1954; Unuvar 1999) from the main analysis leaving the two largest studies (Engström 2008; Sullivan 2007). This analysis confirmed the size and direction of effect, but with higher statistical heterogeneity (RR 0.59, 95% CI 0.44 to 0.79, Chi^2 = 3.32, I^2 = 70%).

We analysed the main outcome for the studies that had the longest follow-up (i.e. between nine and 12 months) (Engström 2008; Lagalla 2002; Sullivan 2007). This did not significantly change the result.

Secondary outcomes

Cosmetically disabling persistent sequelae six months or more after randomisation

Two trials with 75 participants provided data on the number of participants with severe paralysis, or what may be judged as cosmetically disabling sequelae, at six months' follow-up or more (May 1976; Taverner 1954). When we combined the data, the number of participants with cosmetically disabling sequelae was similar in the corticosteroid group and the control group (RR 0.96, 95% CI 0.40 to 2.29) (Analysis 1.2; Figure 4)

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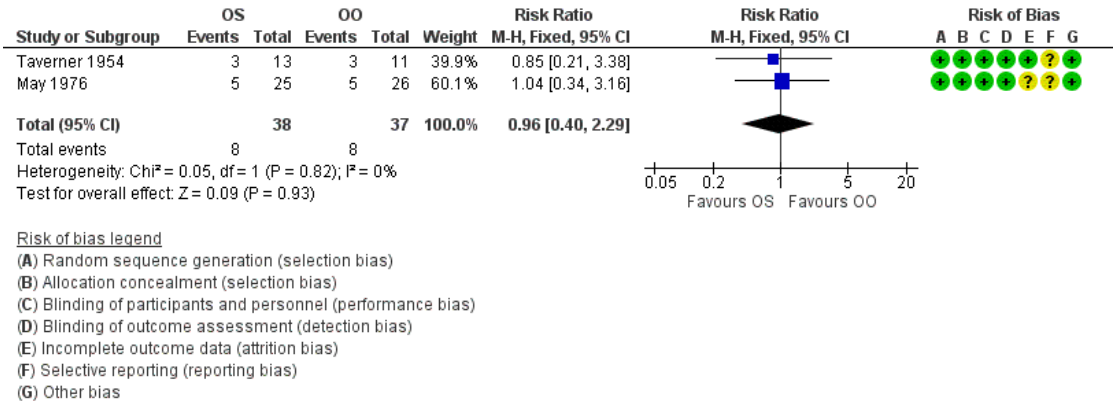
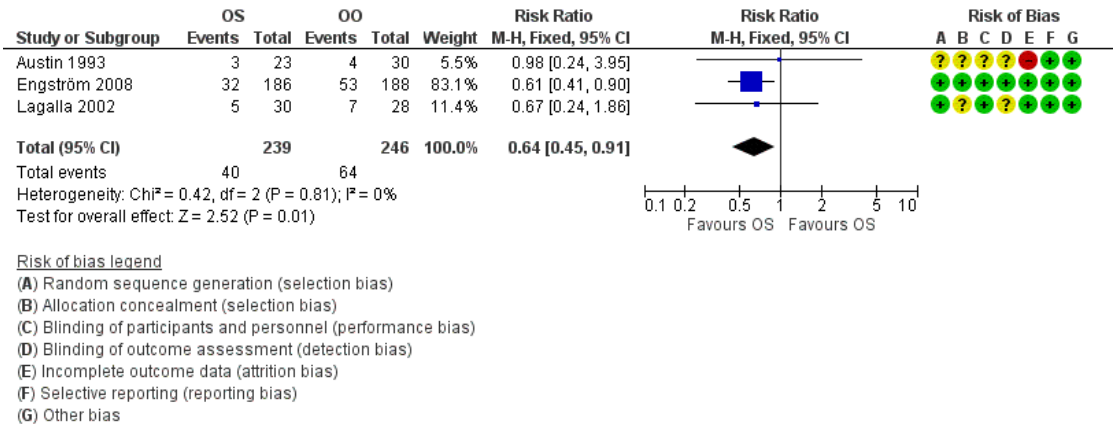
Figure 4. 1.2 Cosmetically disabling persistent sequelae ≥ 6 months after randomisation.



Motor synkinesis or crocodile tears during follow-up

Three trials, with 485 evaluable participants, reported separate data on motor synkinesis or crocodile tears during follow-up (Austin 1993; Engström 2008; Lagalla 2002). Two trials reported the occurrence of disabling synkinesis at 12 months' follow-up (Engström 2008; Lagalla 2002); the other trial reported at six months' follow-up (Austin 1993). After pooling these data, we found a significant reduction in the number of people with motor synkinesis in the corticosteroid group (40/241) compared to the placebo group (64/248) (RR 0.64, 95% CI 0.45 to 0.91) (Analysis 1.3; Figure 5). We found no statistical heterogeneity (Chi^2 = 0.42, df = 2 (P = 0.81), I^2 = 0%).

Figure 5. Forest plot of comparison: 1 Corticosteroid (OS) versus placebo or no treatment (OO), outcome: 1.3 Motor synkinesis and crocodile tears.



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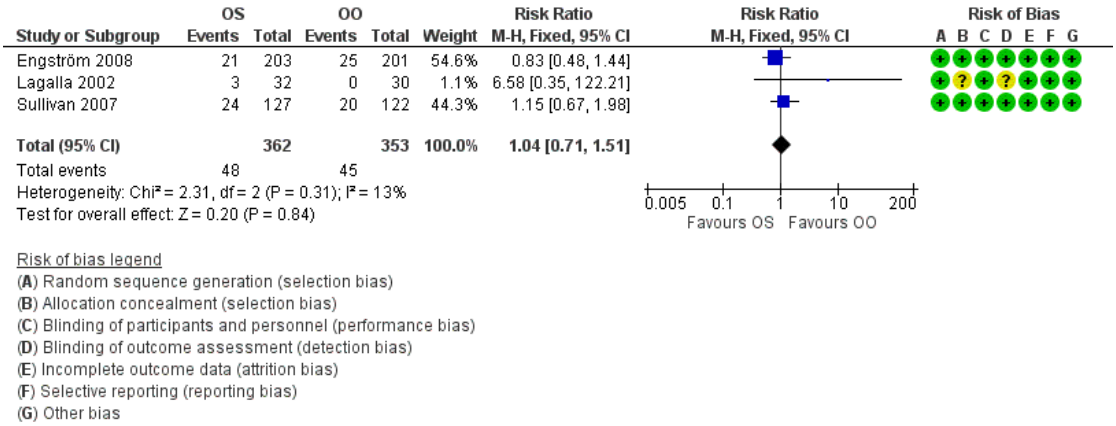
Adverse effects attributable to the use of corticosteroids

Three studies explicitly recorded the absence of adverse effects attributable to the experimental treatment (May 1976; Taverner 1954; Unuvar 1999). One trial reported that three participants receiving prednisone had temporary sleep disturbances (Lagalla 2002). Another reported "no severe side effects of steroid therapy", although there were single reported cases of mood swings, dyspepsia and minor conjunctivitis by individual participants (Austin 1993). Two trials gave a detailed account of 93 adverse effects (Engström 2008; Sullivan 2007), all of them non-serious, with no significant difference between people receiving corticosteroids and people receiving placebo (RR 1.04, 95% CI 0.71 to 1.51). Three deaths occurred; all were deemed to be unrelated to treatment, all were in the groups not receiving prednisolone. One man with a history of recurrent atrial fibrillation had a transient relapse while taking prednisolone and valaciclovir (Figure 6).

Figure 6. Forest plot of comparison: 1 Incomplete recovery of facial motor function, outcome: 1.4 Adverse effects.



Subgroup analyses

In this updated version of the review, we did not perform any subgroup analyses.

DISCUSSION

Summary of main results

High-quality evidence from randomised controlled trials indicated benefit from the use of corticosteroids in Bell's palsy.

Two trials reached a statistically significant difference favouring the use of prednisolone (Engström 2008; Sullivan 2007). Meta-analysis of the complete high-quality randomised controlled trial literature convincingly supported a beneficial effect of prednisolone for reducing the numbers of participants with incomplete recovery. Moderate-quality evidence indicated that participants who received corticosteroid treatment had less motor synkinesis and crocodile tears than the placebo group.

Based on these two studies, low-quality evidence revealed no important differences between corticosteroids and placebo in cosmetically disabling persistent sequelae, but wide CIs allowed for the possibility of an effect in either direction.

The included studies did not report differences in the occurrence of adverse effects between corticosteroids and placebo and additionally no serious adverse effects were reported. However, corticosteroids have well-known adverse effects, of which the incidence rises markedly with prolonged dosages above 10 mg of prednisolone or its equivalent per day (Dollery 1999). Usually corticosteroid courses in Bell's palsy are short and the dose quickly reduces, making the likelihood of adverse effects in practical use less than in longer-term indications.

Overall completeness and applicability of

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evidence

No new studies have been published since the previous Cochrane review (Salinas 2010). The two most recent, well-powered studies (Engström 2008; Sullivan 2007), with five smaller studies (Austin 1993; Lagalla 2002; May 1976; Taverner 1954; Unuvar 1999), provided a significant result based on the evidence provided. These studies sufficiently address the objectives of this review in that they investigate all relevant participants, interventions and outcomes. The findings are in accordance with suggested current clinical practice (Madhok 2009).

Quality of the evidence

For the main outcome of this review (incomplete recovery six months or more after randomisation), all seven studies combined provided high-quality evidence. In addition, for motor synkinesis and crocodile tears, data from three studies provided moderate-quality evidence. Cosmetically disabling persistent sequelae six months or more after randomisation was the only analysis performed where the quality of evidence was low. For adverse effects, the evidence was moderate quality. Reasons for downgrading the quality of evidence were that in one study participants and assessors were not blinded to the treatment that they received (Unuvar 1999), and in another study, loss to follow-up was 50%, representing incomplete outcome data (Austin 1993). Two studies excluded participants who were found after randomisation to have clinical evidence of herpes zoster infection (Lagalla 2002; Taverner 1954). Two studies did not use a standardised scale for assessment of facial motor function (May 1976; Taverner 1954). We considered the effects of these factors on the quality of the evidence insufficient for further downgrading for indirectness of evidence. The results of the majority of studies in this review were consistent with each other, apart from those of one older, smaller study (May 1976).

Potential biases in the review process

To help ensure that decisions about which studies to include in this review were reproducible, two review authors repeated the process (we divided the studies into three groups). There was no distinction made on the experience and expertise of each author in the reviewing pairs. On applying the eligibility criteria and assessing the relevance of studies, review authors were aware of the names of the study authors, institutions, journal of publication and results. FS and FD did not assess their own trial (Sullivan 2007). There were no final disagreements about which studies should be included. According to previous practice in this review, we excluded several studies and a published abstract that provided insufficient information. Therefore, there might be some risk of publication and selective reporting bias due to data from some studies being unavailable.

Agreements and disagreements with other studies or reviews

Our results are coincident with three previous systematic reviews, which found that corticosteroids significantly improved the prognosis of people with Bell's palsy (de Almeida 2009; Ramsey 2000; Williamson 1996). All three reviews, even though of good quality, included a study that lost 50% of participants to follow-up (Bento 1991). Only one of them, de Almeida 2009, was carried out after the publication of the largest trials included in our review (Engström 2008; Sullivan 2007). Two of them (de Almeida 2009; Ramsey 2000) also included a non-randomised study in the analyses (Martinez 1990; Shafshak 1994). A Practice Parameter published by the American Academy of Neurology concluded that corticosteroids were safe and probably effective in improving facial functional outcomes in people with Bell's palsy (Grogan 2001). This Practice Parameter was published, also, before the publication of Sullivan 2007 and Engström 2008.

AUTHORS' CONCLUSIONS

Implications for practice

According to high-quality evidence, 10 people with Bell's palsy need to be treated with corticosteroids to avoid one incomplete recovery. The available evidence from randomised controlled trials shows that corticosteroids significantly reduce the frequency of incomplete recovery from Bell's palsy.

Implications for research

Further research on Bell's palsy treatment should consider giving corticosteroids to those participants acting as controls.

There should be no further studies that do not include corticosteroids as a treatment for Bell's palsy. No participants should be given placebo or no treatment in any future studies. There is an adequate body of evidence to support the use of corticosteroids in the treatment of Bell's palsy.

ACKNOWLEDGEMENTS

We would like to thank the authors of previous editions of this review and we are very grateful for their hard work and enthusiasm. Our thanks are also extended to Angela Gunn who provided the search results and to Cochrane Neuromuscular for their extensive technical assistance and support.

The review has some sections in common with the Cochrane review 'Antiviral treatment for Bell's palsy (idiopathic facial paralysis)' (Gagyor 2015), which has been completed in parallel with this review by the same authors.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

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

Austin 1993

Methods	Double-blind, randomised, controlled study
Participants	107 people were initially randomised; 76 completed follow-up until acute recovery and were included in the study analyses Participants were treated within 5 days of onset Sex: male 39 (51%), female 37 (49%) Age: mean 36.8 years, range 18 to 70 years 37 cases (49%) right side palsy and 39 cases (51%) left side palsy
Interventions	• Prednisone (n = 35): in a scheduled dosage (30 mg twice daily for 5 days reducing to 20 mg twice daily on day 6, 15 mg twice daily on day 7, 10 mg twice daily on day 8, 5 mg twice daily on day 9, and 5 mg once daily on day 10) • Equivalent placebo (n = 31)
Outcomes	Primary outcome: • time to resolution in days of facial function as defined by the House-Brackmann scale Secondary outcomes: • distribution of facial nerve grade at 6 months after recovery, in addition to • crocodile tears and • anxiety during follow-up Follow-up up to 9 months
Funding	Not stated
Conflicts of interest	Not stated
Date conducted	1 October 1989 to 31 December 1990
Notes	Good recovery defined as grade I or II of the House-Brackmann scale

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated to be randomised at the pharmacy but details not given
Allocation concealment (selection bias)	Unclear risk	Allocation of participants not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "The study was blinded to both the patient and the clinical investigators". Further details of blinding not given

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Austin 1993 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "The study was blinded to both the patient and the clinical investigators". Further details of blinding not given
Incomplete outcome data (attrition bias) All outcomes	High risk	107 participants randomised, 31 did not attend for follow-up assessment. 76 allocated to prednisone or placebo Analysis 6 months after resolution of Bell's palsy included 53 participants (23 prednisolone and 30 placebo), representing over 50% loss to follow-up at this point. Reasons for additional drop-outs at 6 months not described
Selective reporting (reporting bias)	Low risk	All primary outcomes reported
Other bias	Low risk	Single-centre study

Engström 2008

Methods	Randomised, placebo-controlled trial with 4 treatment groups
Participants	829 participants randomised within 72 hours of facial palsy onset No contraindications to corticosteroid or antiviral use Sex: male 341 (41%), female 488 (59%) Age: mean 40 years, range 31-54 years
Interventions	Participants allocated into 1 of 4 treatment groups: • prednisolone with placebo • valaciclovir with prednisolone • valaciclovir with placebo • double placebo Dosages: valaciclovir 1000 mg 3 times daily for 7 days; prednisolone 60 mg daily for 5 days
Outcomes	Primary outcome: • recovery of facial function, as assessed at visits with the Sunnybrook scale and the House-Brackmann scale Complete recovery was taken as Sunnybrook scale 100 and House-Brackmann scale grade I Other outcomes: • degree of pain, as recorded during the first 2 months • adverse effects recorded for the first month • frequency of severe pain, synkinesis, facial spasm and residual facial symptoms at 12 months Follow-up at 2 weeks, and 1, 2, 3, 6 and 12 months after randomisation, according to recovery

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Engström 2008 (*Continued*)

	Final outcomes reported at 12 months	
Funding	Uppsala University; GlaxoSmithKline (Sweden); Pfizer AB (Sweden); Acta Otolaryngologica Foundation; Rosa and Emanuel Nachmanssons Foundation; Stig and Ragna Gorthon Foundation; Torsten Birger Segerfalk Foundation; Margit Arstrups Foundation; County Council of Skaˊ ne; Helsinki University Central Hospital Research Funds	
Conflicts of interest	One author was paid by GlaxoSmithKline for a lecture on Bell's Palsy	
Date conducted	May 2001 to September 2006	
Notes	Multicentre	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Generated by computer number generator. Sequentially numbered identical containers allocated to participants on entry into the trial, by the recruiting physician
Allocation concealment (selection bias)	Low risk	Allocation sequence double-blind and generated by a computer number generator in random permuted blocks of 8
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study drugs issued in identical containers. All participants blinded to treatment group until study completion. All study personnel and data analysts blinded to treatment group until study completion
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All study personnel and data analysts blinded to treatment group until study completion
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers lost to follow-up and reasons given: • 213 randomised to corticosteroids: 3 did not receive the drug, 24 lost to follow-up at 12 months (12.7%); 210 analysed • 209 randomised to placebo: 3 did not receive the placebo; 18 lost to follow-up at 12 months; 206 analysed 'Modified' intention-to-treat analyses used. All randomised participants who received at least 1 dose of study medication included, but participants who did not start

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Engström 2008 (*Continued*)

		therapy excluded. Last observation carried forward method used for the modified intention-to-treat analysis, and missing data points imputed in the post-baseline follow-up visits from the last observation available for each participant
Selective reporting (reporting bias)	Low risk	All primary outcomes reported. Other outcomes reported in another paper due to space constrictions
Other bias	Low risk	No other biases identified

Lagalla 2002

Methods	Randomised, placebo-controlled, double-blind trial
Participants	62 participants within 3 days of onset of onset of Bell's palsy; 4 people excluded after randomisation because of acute herpes zoster infection Sex: male 34, female 28 Age: mean (± SD) 47.5 (± 19) years, range 15 to 84 years Participants with contraindications to corticosteroids (peptic ulcer disease, pregnancy, severe hypertension), or previously treated excluded. No losses to follow-up 34 cases left palsy, 28 cases right palsy
Interventions	• Prednisone: 1 g daily intravenously in saline solution for 3 days and then 0.5 g for the other 3 days • Placebo: saline solution All participants received intramuscular vitamins for 15 days
Outcomes	Primary outcome: • recovery of facial function Used House-Brackmann scale for assessment. "Good recovery" was grades I or II Secondary outcomes: • motor synkinesis and crocodile tears Follow-up at 1, 3, 6 and 12 months Final outcomes reported at 6 and 12 months
Funding	Not stated
Conflicts of interest	Not stated
Date conducted	Not stated
Notes	Single centre

Risk of bias

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Lagalla 2002 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random list used to generate random sequence
Allocation concealment (selection bias)	Unclear risk	Not stated by authors
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were blinded to the treatment. Saline solution was used as a placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers lost to follow-up and reasons given: 62 people randomised, 4 excluded after randomisation (2 in each group) because of herpes zoster infection; the remaining 58 completed study Trial authors stated: "Comparative statistics was carried out on an intention-to-treat basis, by assuming that drop-outs had a poor outcome. Data analysis concerning basal features included all patients enrolled. The analysis of clinical grading changes included data from only 58 subjects"
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes reported
Other bias	Low risk	No other bias identified

May 1976

Methods	Double-blind, placebo-controlled, randomised trial with 2 treatment groups
Participants	51 participants within 2 days of onset of Bell's palsy People with chronic otitis, trauma, loss of lacrimation, and bilateral or recurrent palsy, and herpes zoster excluded Sex: male 28, female 23 Age: ranges not clearly stated "30 years or less and 31 years or older"
Interventions	• Prednisone: 410 mg in descending doses over 10 days, plus vitamins • Placebo: vitamins alone
Outcomes	Primary outcome: • complete recovery of facial function Assessment made clinically using photographs (examples given in the paper) at 6 months

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	after onset Secondary outcomes: • pain • taste • hyperacusis • time to recovery No adverse effects reported
Funding	Not stated
Conflicts of interest	Not stated
Date conducted	1972 to 1974
Notes	Single centre

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random stratified sequence generated by a statistician, administered in a pharmacy
Allocation concealment (selection bias)	Low risk	Allocation of treatment group unknown to both participants and physicians
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded. Placebo was similar-looking tablets containing vitamins
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors blinded to treatment group
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information on loss to follow-up rates
Selective reporting (reporting bias)	Unclear risk	Primary outcomes reported, adverse effects not reported
Other bias	Low risk	No other bias identified

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Sullivan 2007

Methods	Double-blind, placebo-controlled, randomised, factorial trial
Participants	552 participants randomised and 496 included in final outcome assessment Referred for assessment and treatment within 72 hours of paralysis onset All participants aged ≥ 16 years and no contraindications to corticosteroids or antiviral therapy Sex: male 253 (51%), female 243 (49%) Age: mean (± SD) 44 (± 16.4) years
Interventions	Participants allocated to 1 of 4 treatment groups to receive: • aciclovir • prednisolone • aciclovir with prednisolone • placebo Participants received prednisolone 25 mg twice daily for 10 days or aciclovir 400 mg 5 times daily for 10 days, both treatments or neither treatment, depending on allocation
Outcomes	Primary outcome: • recovery rated on House-Brackmann scale, where recovery was grade I Secondary outcomes: • health-related quality of life • Health Utilities Index Mark 3 • facial appearance (Derriford Appearance Scale) • pain • adverse effects • frequency of incomplete recovery at end of study Follow-up at 3 and 9 months Final outcomes reported at 9 months
Funding	Supported by a grant (02/09/04) from the Health Technology Assessment Programme of the National Institute for Health Research (Department of Health, England). The Scottish Executive (Chief Scientist Office and National Health Service Education for Scotland) funded the Scottish School of Primary Care during the study. Practices were reimbursed for their contributions through national Support for Science mechanisms
Conflicts of interest	Drs Sullivan and Donnan reported receiving grant support from GlaxoSmithKline for projects unrelated to the trial. No other potential conflict of interest relevant to this article reported
Date conducted	June 2004 to June 2006
Notes	Multicentre: 17 hospitals

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

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Sullivan 2007 (*Continued*)

Random sequence generation (selection bias)	Low risk	Quote: "... patient was randomly assigned to a study group by an independent, secure, automated telephone randomisation service"
Allocation concealment (selection bias)	Low risk	All parties blinded to allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants not receiving active drug received placebo. All administered medication was identical and in identical containers
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors blinded to treatment group
Incomplete outcome data (attrition bias) All outcomes	Low risk	Frequency and reason for drop-outs documented: 138 assigned to prednisolone, of whom 127 completed the trial: 3 received an incorrect drug and 11 were lost to follow-up (4 withdrew consent, 2 sought active treatment, 1 did not provide primary outcome data, 4 could not be contacted after the 1st visit) 141 assigned to placebo of whom 122 completed the trial: 19 were lost to follow-up (6 withdrew consent, 3 could not be contacted, 3 sought active treatment, 1 did not provide primary outcome data, 3 could not be contacted after the 1st visit, 2 died, 1 withdrawn by investigator)
Selective reporting (reporting bias)	Low risk	All planned outcome measures reported
Other bias	Low risk	No other potential sources of bias identified

Taverner 1954

Methods	Double-blind, randomised controlled trial
Participants	26 participants within 10 days of onset of Bell's palsy Sex: male 13 and female 13 Age: range 12 to 76 years
Interventions	• Cortisone acetate: orally in descending doses over 8 days (200 mg in divided doses daily for the first 3 days, 100 mg daily for 3 days and 50 mg daily for 2 days) • Placebo: same number of lactose tablets for the same period

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Taverner 1954 (*Continued*)

Outcomes	Primary outcomes: • recovery of facial function (clinical assessment) • signs of denervation on electromyographic examination Secondary outcome: • duration of recovery Final outcome reported at 157 days
Funding	Medical Research Council supplied cortisone acetate
Conflicts of interest	Not stated
Date conducted	August 1953 to June 1954
Notes	Single-centre study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation centralised in pharmacy, in accordance with a master sheet of random numbers
Allocation concealment (selection bias)	Low risk	Central allocation in pharmacy
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Assessors and participants both blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors and participants both blinded (the point to which assessors were blinded was not clear)
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 people excluded from analysis because of herpes of the external meatus
Selective reporting (reporting bias)	Unclear risk	Adverse effects not reported
Other bias	Low risk	No other bias identified

Unuvar 1999

Methods	Randomised controlled trial
Participants	42 children within 3 days of onset of Bell's palsy Sex: male 21, female 21 Age: mean (± SD) 56.9 (± 4.7) months, range 24 to 74 months Children with chronic neurological conditions, other reasons for facial palsy and acute

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Unuvar 1999 (*Continued*)

	otitis media excluded
Interventions	• Oral methylprednisolone: 1 mg/kg daily, for 10 days, and then withdrawn in 3 to 5 days • Control: no specific treatment (no placebo used)
Outcomes	Primary outcome: • recovery of facial motor function (House-Brackmann scale) Secondary outcome: • adverse effects Follow-up at 4, 6 and 12 months
Funding	Not stated
Conflicts of interest	Not stated
Date conducted	Not stated
Notes	Single-centre study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence
Allocation concealment (selection bias)	Low risk	Participants allocated to groups by concealed computer-generated random sequence
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants not blinded to the treatment that they were receiving
Blinding of outcome assessment (detection bias) All outcomes	High risk	Assessors not blinded to the treatment that participants were receiving
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up not reported
Selective reporting (reporting bias)	Low risk	Outcomes given by authors
Other bias	Low risk	No other potential biases were identified

n: number of participants; SD: standard deviation.

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

Study	Reason for exclusion
Akpinar 1979	Allocation to treatment group was according to the day of admission, which is a method that is highly susceptible to bias. It was not clear who diagnosed participants with Bell's palsy and they used varying dosage regimens of corticosteroids. Follow-up 3 weeks
Bento 1991	Did not provide the number of participants and outcome events by treatment groups. 50% of participants lost to follow-up
Brown 1982	Not randomised or quasi-randomised. There was no placebo group or open control group
Martinez 1990	Not randomised or quasi-randomised. 27% of participants lost to follow-up
Wolf 1978	Unable to extract complete information on the specified outcomes

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

Babl 2015

Trial name or title	Bell's palsy in children: a multi-centre, double-blind, randomised, placebo-controlled trial to determine whether prednisolone improves recovery at 1 month
Methods	Randomised control trial (computer-generated randomisation schedule), parallel assignment
Participants	Participants aged 6 months to 18 years, weight $\geq$ 5 kg, diagnosed with Bell's palsy by their treating doctor and have an acute onset of symptoms of Bell's palsy for < 72 hours prior to randomisation
Interventions	• Prednisolone 1 mg/kg/day (dosing based on weight categories) up to a maximum of 50 mg/day for 10 days • Placebo: oral liquid with the same ingredients as the intervention solution minus the active drug
Outcomes	Primary outcome: • complete recovery at 1-month post-randomisation, where recovery was defined as a House-Brackmann facial grading score of I. Recovery assessed by a specialist clinician in a face-to-face setting
Starting date	1 July 2015
Contact information	Prof Franz Babl Emergency Research Department, Murdoch Children's Research Institute, Royal Children's Hospital, VIC, Australia +61399366748 franz.babl@rch.org.au
Notes	www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12615000563561

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DATA AND ANALYSES

Comparison 1. Corticosteroid (OS) versus placebo or no treatment (OO)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incomplete recovery ≥ 6 months after randomisation	7	895	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.50, 0.80]
2 Cosmetically disabling persistent sequelae ≥ 6 months after randomisation	2	75	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.40, 2.29]
3 Motor synkinesis and crocodile tears	3	485	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.45, 0.91]
4 Adverse effects	3	715	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.71, 1.51]

Analysis 1.1. Comparison 1 Corticosteroid (OS) versus placebo or no treatment (OO), Outcome 1 Incomplete recovery ≥ 6 months after randomisation.

Review: Corticosteroids for Bell's palsy (idiopathic facial paralysis)

Comparison: 1 Corticosteroid (OS) versus placebo or no treatment (OO)

Outcome: 1 Incomplete recovery ≥ 6 months after randomisation

Study or subgroup	OS n/N	OO n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Austin 1993	5/23	10/30		6.9 %	0.65 [0.26, 1.65]
Engström 2008	50/210	73/206		58.7 %	0.67 [0.50, 0.91]
Lagalla 2002	5/30	8/28		6.6 %	0.58 [0.22, 1.57]
May 1976	10/25	9/26		7.0 %	1.16 [0.57, 2.36]
Sullivan 2007	5/127	18/122		14.6 %	0.27 [0.10, 0.70]
Taverner 1954	4/14	4/12		3.4 %	0.86 [0.27, 2.71]
Unuvar 1999	0/21	3/21		2.8 %	0.14 [0.01, 2.61]
Total (95% CI)	**450**	**445**		**100.0 %**	**0.63 [0.50, 0.80]**

Total events: 79 (OS), 125 (OO)

Heterogeneity: Chi^2 = 7.32, df = 6 (P = 0.29); I^2 =18%

Test for overall effect: Z = 3.73 (P = 0.00019)

Test for subgroup differences: Not applicable

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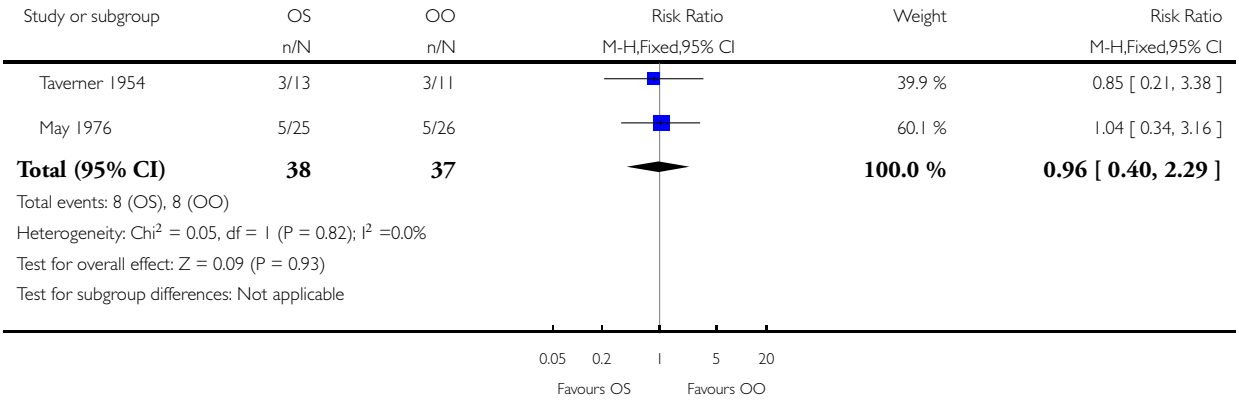
Analysis 1.2. Comparison 1 Corticosteroid (OS) versus placebo or no treatment (OO), Outcome 2 Cosmetically disabling persistent sequelae ≥ 6 months after randomisation.

Review: Corticosteroids for Bell's palsy (idiopathic facial paralysis)

Comparison: 1 Corticosteroid (OS) versus placebo or no treatment (OO)

Outcome: 2 Cosmetically disabling persistent sequelae ≥ 6 months after randomisation



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Analysis 1.3. Comparison 1 Corticosteroid (OS) versus placebo or no treatment (OO), Outcome 3 Motor synkinesis and crocodile tears.

Review: Corticosteroids for Bell's palsy (idiopathic facial paralysis)

Comparison: 1 Corticosteroid (OS) versus placebo or no treatment (OO)

Outcome: 3 Motor synkinesis and crocodile tears

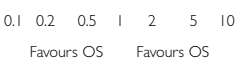
Study or subgroup	OS n/N	OO n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Austin 1993	3/23	4/30		5.5 %	0.98 [0.24, 3.95]
Engström 2008	32/186	53/188		83.1 %	0.61 [0.41, 0.90]
Lagalla 2002	5/30	7/28		11.4 %	0.67 [0.24, 1.86]
Total (95% CI)	**239**	**246**		**100.0 %**	**0.64 [0.45, 0.91]**

Total events: 40 (OS), 64 (OO)

Heterogeneity: Chi^2 = 0.42, df = 2 (P = 0.81); I^2 =0.0%

Test for overall effect: Z = 2.52 (P = 0.012)

Test for subgroup differences: Not applicable



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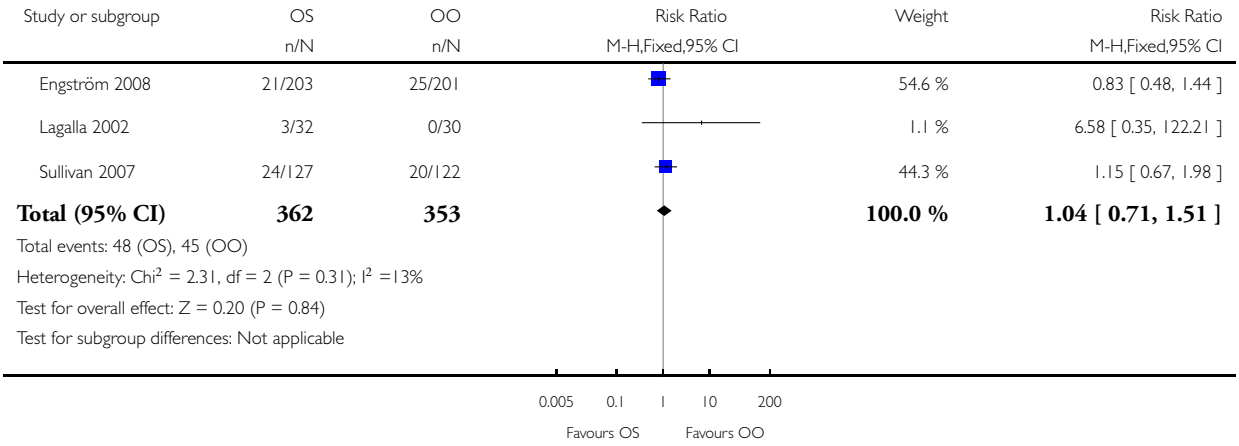
Analysis 1.4. Comparison 1 Corticosteroid (OS) versus placebo or no treatment (OO), Outcome 4 Adverse effects.

Review: Corticosteroids for Bell's palsy (idiopathic facial paralysis)

Comparison: 1 Corticosteroid (OS) versus placebo or no treatment (OO)

Outcome: 4 Adverse effects



APPENDICES

Appendix 1. Cochrane Neuromuscular Specialised Register (CRS) search strategy

#1 MeSH DESCRIPTOR Facial Nerve Diseases [REFERENCE] [STANDARD]
#2 MeSH DESCRIPTOR Bell Palsy [REFERENCE] [STANDARD]
#3 MeSH DESCRIPTOR Facial Paralysis [REFERENCE] [STANDARD]
#4 MeSH DESCRIPTOR Hemifacial Spasm [REFERENCE] [STANDARD]
#5 (((bell* or facial* or hemifacial* or cranial*) NEAR3 (pals* or paralys* or paresi* or spasm*))) AND (INREGISTER) [REFERENCE] [STANDARD]
#6 #1 or #2 or #3 or #4 or #5 [REFERENCE] [STANDARD]
#7 MeSH DESCRIPTOR Steroids [REFERENCE] [STANDARD]
#8 steroid or steroids [REFERENCE] [STANDARD]
#9 MeSH DESCRIPTOR Adrenal Cortex Hormones [REFERENCE] [STANDARD]
#10 MeSH DESCRIPTOR Adrenocorticotropic Hormone [REFERENCE] [STANDARD]
#11 MeSH DESCRIPTOR Prednisone [REFERENCE] [STANDARD]
#12 MeSH DESCRIPTOR Prednisolone [REFERENCE] [STANDARD]
#13 MeSH DESCRIPTOR Glucocorticoids [REFERENCE] [STANDARD]
#14 MeSH DESCRIPTOR Cortisone [REFERENCE] [STANDARD]
#15 corticosteroid* or adrenocorticotroph* or prednisone or prednisolone or glucocorticoid* or cortisone or methylprednisone [REFERENCE] [STANDARD]
#16 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 [REFERENCE] [STANDARD]

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#17 #6 and #16 [REFERENCE] [STANDARD]

Appendix 2. CENTRAL (CRSO) search strategy

Search run on Fri Mar 4 2016

#1 ((Bell or "Bell's" or Bells or facial or hemifacial or cranial) NEAR (palsy or palsies or paralysis or paresis or spasm or spasms)):TI,AB,KY 555
#2 (steroid* or corticosteroid* or adrenocorticotroph* or corticotropin or prednisone or prednisolone or glucocorticoid* or cortisone or methylprednisone or "adrenal cortex hormone*"):TI,AB,KY 37189
#3 (steroid* or corticosteroid* or adrenocorticotroph* or corticotropin or prednisone or prednisolone or glucocorticoid* or cortisone or methylprednisone or "adrenal cortex hormone*"):TI,AB,KY 37189
#4 #1 AND #2 98
#5 sr-neuromusc:cc 5823
#6 #4 not #5 44

Appendix 3. MEDLINE (OvidSP) strategy

Database: Ovid MEDLINE(R) <1946 to February Week 4 2016>
Search Strategy:
---
1 randomized controlled trial.pt. (407164)
2 controlled clinical trial.pt. (90097)
3 randomized.ab. (304430)
4 placebo.ab. (155333)
5 drug therapy.fs. (1823046)
6 randomly.ab. (215472)
7 trial.ab. (313777)
8 groups.ab. (1364056)
9 or/1-8 (3457470)
10 exp animals/ not humans.sh. (4191570)
11 9 not 10 (2944190)
12 facial nerve diseases/ (1409)
13 Bell Palsy/ (977)
14 Facial Paralysis/ or hemifacial spasm/ (11784)
15 ((bell$ or facial$ or hemifacial$ or cranial$) adj3 (pals$ or paralys$ or paresi$ or spasm$)).tw. (14759)
16 or/12-15 (19812)
17 steroid$.tw. or steroids/ (195309)
18 corticosteroid$.tw. or adrenal cortex hormones/ (111371)
19 adrenocorticotroph$.tw. or corticotropin/ (47991)
20 prednisone.tw. or prednisone/ (46046)
21 prednisolone.tw. or prednisolone/ (38861)
22 glucocorticoid$.tw. or glucocorticoids/ (87141)
23 cortisone.tw. or cortisone/ (22428)
24 methylprednisone.tw. (209)
25 or/17-24 (448308)
26 11 and 16 and 25 (892)
27 remove duplicates from 26 (886)

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Appendix 4. EMBASE (OvidSP) strategy

Database: Embase <1980 to 2016 Week 09>
Search Strategy:
---
1 crossover-procedure.sh. (46158)
2 double-blind procedure.sh. (126385)
3 single-blind procedure.sh. (21564)
4 randomized controlled trial.sh. (393423)
5 (random$ or crossover$ or cross over$ or placebo$ or (doubl$ adj blind$) or allocat$).tw,ot. (1223922)
6 trial.ti. (193286)
7 or/1-6 (1370827)
8 (animal/ or nonhuman/ or animal experiment/) and human/ (1446761)
9 animal/ or nonanimal/ or animal experiment/ (3498115)
10 9 not 8 (2901774)
11 7 not 10 (1261401)
12 limit 11 to embase (1041826)
13 exp facial nerve paralysis/ (20154)
14 Bell palsy/ (2578)
15 hemifacial spasm/ (2209)
16 ((bell$ or facial$ or hemifacial$ or cranial$) adj3 (pals$ or paralys$ or paresi$ or spasm$)).tw. (18906)
17 or/13-16 (28552)
18 corticosteroid/ or corticosteroid$.tw. (233317)
19 glucocorticoid/ or glucocorticoid$.tw. (101570)
20 corticotropin/ or corticotrophin$.tw. (58083)
21 prednisolone/ or prednisolone.tw. (106302)
22 prednisone/ or prednisone.tw. (142280)
23 or/18-22 (552861)
24 12 and 17 and 23 (133)
25 remove duplicates from 24 (131)

Appendix 5. LILACS IAHx strategy

("Bell palsy" or "paralisis de Bell" or "paralisia de Bell" or "facial paralysis" or "paralisis facial" or "paralisia facial" or "hemifacial spasm" or "espasmo hemifacial") and (MH:D06.472.040$ or steroids or esteroides or cortisone or cortisona or corticoesteroides or corticosteroides or corticosteroid$ or glucocorticoid$ or prednisolone or prednisolona or prednisone or prednisona or methylprednisone) and ((PT:"Randomized Controlled Trial" or "Randomized Controlled trial" or "Ensayo Clínico Controlado Aleatorio" or "Ensaio Clínico Controlado Aleatório" or PT:"Controlled Clinical Trial" or "Ensayo Clínico Controlado" or "Ensaio Clínico Controlado" or "Random allocation" or "Distribución Aleatoria" or "Distribuição Aleatória" or randon$ or Randomized or randomly or "double blind" or "duplo-cego" or "duplo-cego" or "single blind" or "simples-cego" or "simples cego" or placebo$ or trial or groups) AND NOT (B01.050$ AND NOT (humans or humanos or humanos)))

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Appendix 6. Clinical trials registries search strategies

ClinicalTrials.gov and World Health Organization International Clinical trials Registry
Bell's palsy

WHAT'S NEW

Last assessed as up-to-date: 4 March 2016.

Date	Event	Description
4 July 2016	New citation required but conclusions have not changed	New author team. One new trial was found, with no change to previous conclusions. We made the following corrections and revisions: • more detailed documentation of methods and additional sections to comply with current standards • amendments and corrections in the results section • inclusion of additional study data in our primary analysis, which changed the RR for incomplete recovery from 0.71 (95% CI 0.61 to 0.83) to 0.63 (95% CI 0.50 to 0.80) • we largely presented available data analyses, reporting intention-to-treat data only when trialists used this approach • removal of comparisons involving antiviral co-medication, which are analysed in a separate Cochrane review • inclusion of an analysis of adverse events • inclusion of a 'Summary of findings' table and of comments on the quality of evidence in the text of the review
4 March 2016	New search has been performed	Searches updated and integrated

HISTORY

Protocol first published: Issue 1, 2000

Review first published: Issue 1, 2002

Date	Event	Description
25 February 2009	New citation required and conclusions have changed	New trials have been added leading to a substantial change in the conclusion of the review
16 July 2008	Amended	Converted to new review format.

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(*Continued*)

23 June 2008	New citation required and conclusions have changed	Substantive amendment
28 February 2006	New search has been performed	February 2006 We updated the search of the Cochrane Neuromuscular Disease Group specialised register (November 2005) , MEDLINE (January 1966 to November 2005), EMBASE (January 1980 to November 2005) and LILACS (January 1982 to November 2005). No new randomised controlled trials were found

CONTRIBUTIONS OF AUTHORS

All six review authors worked in pairs on study selection and data extraction.

IG and VM agreed data input into Review Manager 5.

IG performed risk of bias assessments; FS and FD reviewed them.

IG and VM drafted the revised review.

FD assisted with calculations.

VM and IG revised the review after editorial review.

All authors approved the final draft.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- New source of support, Other.

External sources

- No sources of support supplied

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

A new author team updated this review: Vishnu B Madhok, Ildiko Gagyor, Fergus Daly, Dhruvashree Somasundara, Michael Sullivan, Fiona Gammie, Frank Sullivan.

The review authors added a 'Summary of findings' table and added some sections to the Methods to comply with current Cochrane standards.

Changes from the previous update of this review

When looking at Engström 2008 and Sullivan 2007, we excluded participants that were given antiviral therapy with corticosteroids or antiviral therapy alone as these are reported in a separate review (Gagyor 2015).
As a result, in this update we deleted the comparisons from those trials that the previous review authors designated Sullivan b and Engström b.
We assume that the total number of events given in Engström a (i.e. 213) was incorrect, and changed the figure to 210.
In the previous Cochrane review, authors used intention-to-treat numbers. We decided to perform available-case analysis unless the trialists reported intention-to-treat data.
We deleted Sullivan b from Table 1.2 "cosmetically disabling persistent sequelae" for the reasons above. Sullivan a did not contribute data to this table.
In Analysis 1.3, "motor synkinesis of or autonomic dysfunction during follow up", we deleted Engström b for the reasons above.
In Analysis 1.3, we changed the data for Engström a - the previous Cochrane review correctly gave the number of participants reporting synkinesis at 12 months in the OS group as 32. We continued to use this event rate, but changed the total sample number from 290 to 186 in accordance with the information given.
We deleted what was previously Analysis 1.4 "incomplete recovery of patients with Bell's Palsy" as the numbers of participants was negligible (only 22 participants from two studies Sullivan a and May 1976), after we removed the data from Sullivan b.
We checked the numbers for May 1976; Taverner 1954; and Unuvar 1999. We found that the numbers included for Taverner were incorrect and updated these in Analysis 1.1.
The previous Cochrane review excluded Lagalla 2002 from the main meta-analysis giving the reason that the paper did not provide primary outcome data on complete recovery. We decided to include this study given that we could use information on page 109 (results section) of the paper to calculate the data for input into Analysis 1.1. In the prednisolone group, 32 participants, 83%, had complete recovery, hence 17% (five participants) had incomplete recovery. In the placebo group, there were 30 participants, of whom 25% (eight participants) had incomplete recovery.
Based on our changes to Analysis 1.1, the RR changed from 0.51 (95% CI 0.32 to 0.80) to 0.65 (95% CI 0.50 to 0.83).
We added a table of adverse effects (Analysis 1.4).
We checked the data for each of the included studies and made significant amendments and corrections in the Effects of interventions section.
In the Objectives, we deleted the reference to 'early' use of corticosteroids in Bell's palsy.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Inflammatory Agents [*therapeutic use]; Bell Palsy [*drug therapy]; Cortisone [*analogs & derivatives; therapeutic use]; Glucocorticoids [adverse effects; *therapeutic use]; Methylprednisolone [therapeutic use]; Prednisolone [therapeutic use]; Prednisone [therapeutic use]; Randomized Controlled Trials as Topic; Recovery of Function; Vitamins [therapeutic use]

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MeSH check words

Humans

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