Combined Corticosteroid and Antiviral Treatment for Bell Palsy

A Systematic Review and Meta-analysis

John R. de Almeida, MD
Murtadha Al Khabori, MD
Gordon H. Guyatt, MD, MSc, FRCPC
Ian J. Witterick, MD, MSc, FRCSC
Vincent Y. W. Lin, MD, FRCSC
Julian M. Nedzelski, MD, FRCSC
Joseph M. Chen, MD, FRCSC

Context New evidence has emerged regarding the use of corticosteroids and antiviral agents in Bell palsy.

Objective To estimate the association of corticosteroids and antiviral agents with the risk of unsatisfactory facial recovery in patients with Bell palsy.

Data Sources The search included MEDLINE, EMBASE, CENTRAL, PsychInfo, CINAHL, Web of Science, PAPERSFIRST, PROCEEDINGSFIRST, and PROQUEST to identify studies up to March 1, 2009.

Study Selection and Data Extraction Eligible studies were randomized controlled trials comparing treatment with either corticosteroids or antiviral agents with a control and measuring at least 1 of the following outcomes: unsatisfactory facial recovery (≥4 months), unsatisfactory short-term recovery (6 weeks to <4 months), synkinesis and autonomic dysfunction, or adverse effects. Two reviewers extracted data on study characteristics, methods, and outcomes. Disagreement was resolved by consensus.

Results Eighteen trials involving 2786 patients were eligible. Regression analysis identified a synergistic effect when corticosteroids and antiviral agents were administered in combination compared with alone (odds ratio for interaction term, 0.54 [95% confidence interval {CI}, 0.35-0.83]; $P=.004$). Meta-analysis using a random-effects model showed corticosteroids alone were associated with a reduced risk of unsatisfactory recovery (relative risk [RR], 0.69 [95% CI, 0.55-0.87]; $P=.001$) (number needed to treat to benefit 1 person, 11 [95% CI, 8-25]), a reduced risk of synkinesis and autonomic dysfunction (RR, 0.48 [95% CI, 0.36-0.65]; $P<.001$) (number needed to treat to benefit 1 person, 7 [95% CI, 6-10]), and no increase in adverse effects. Antiviral agents alone were not associated with a reduced risk of unsatisfactory recovery (RR, 1.14 [95% CI, 0.80-1.62]; $P=.48$). When combined with antiviral agents, corticosteroids were associated with greater benefit (RR, 0.48 [95% CI, 0.29-0.79]; $P=.004$) than antiviral agents alone. When combined with corticosteroids, antiviral agents were associated with greater risk reduction of borderline significance compared with corticosteroids alone (RR, 0.75 [95% CI, 0.56-1.00]; $P=.05$).

Conclusions In Bell palsy, corticosteroids are associated with a reduced risk of unsatisfactory recovery. Antiviral agents, when administered with corticosteroids, may be associated with additional benefit.

JAMA. 2009;302(9):985-993 www.jama.com

BELL PALSY OR IDIOPATHIC FACIAL paralysis, an acute weakness or paralysis of the facial nerve, has a lifetime risk of 1 in 60.[1] The annual incidence of Bell palsy is 20 to 30 per 100 000 population.[2] While 71% of untreated patients will completely recover and 84% will have complete or near normal recovery,[3] the remainder will have persistent moderate to severe weakness, facial contracture, or synkinesis.[1] Initial severity is associated with a poor prognosis with as few as 61% of cases of complete pareses and as many as 94% of cases of incomplete pareses having complete recovery,[3] usually within 4 months of presentation.[3,4]

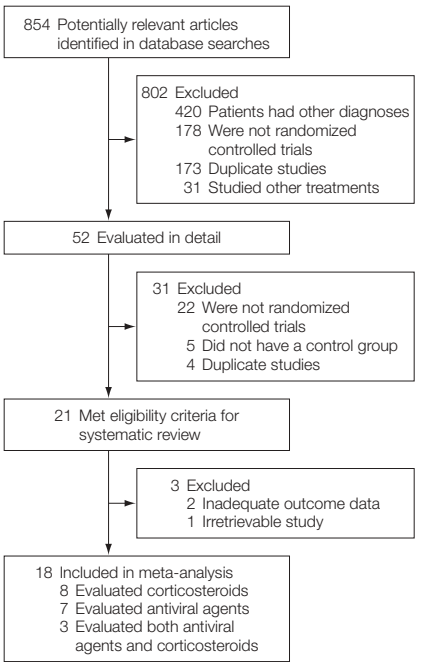
A herpes infection likely causes this disorder.[5-9] Swelling of the nerve at the meatal foramen has been observed intraoperatively,[10] and sampling of endoneurial fluid during nerve decompression for Bell palsy has yielded DNA of herpes sim-

For editorial comment see p 1003.

CME available online at www.jamaarchivescme.com and questions on p 1010.

Author Affiliations: Department of Otolaryngology–Head and Neck Surgery, Sunnybrook Hospital (Drs de Almeida, Lin, Nedzelski, and Chen), Department of Medical Oncology and Hematology, Princess Margaret Hospital (Dr Al Khabori), and Department of Otolaryngology–Head and Neck Surgery, Mount Sinai Hospital (Dr Witterick), University of Toronto, Toronto, Ontario, Canada; and Departments of Clinical Epidemiology and Biostatistics (Drs de Almeida, Al Khabori, and Guyatt) and Medicine (Dr Guyatt), CLARITY Research Group (Dr Guyatt), McMaster University, Hamilton, Ontario, Canada.
Corresponding Author: Gordon H. Guyatt, MD, MSc, FRCPC, McMaster University, Health Sciences Center, 2C12, 1200 Main St W, Hamilton, ON, Canada L8N 3Z5 (guyatt@mcmaster.ca).
Clinical Review Section Editor: Mary McGrae McDermott, MD, Contributing Editor. We encourage authors to submit papers for consideration as a Clinical Review. Please contact Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

Figure 1. Selection of Studies for Meta-analysis



The search was conducted with the MEDLINE, EMBASE, CENTRAL, CINAHL, PsychInfo, Web of Science, PAPERSFIRST, PROCEEDINGSFIRST, and PROQUEST databases to identify studies up to March 1, 2009.

plex virus type 1 (HSV-1).[9] Varicella zoster virus (VZV) reactivation is also associated with Bell palsy[11,12] and may be responsible for as many as one-third of idiopathic facial paralyses.[13]

The goal of treatment for Bell palsy is preventing sequelae. Both corticosteroids and antiviral agents are used as treatment strategies. In a large observational study from the United Kingdom, 36% of patients with Bell palsy were prescribed corticosteroids, 0.6% were prescribed antiviral agents, and 0.4% were prescribed a combination, suggesting the clinical community is unconvinced of the benefit of these agents.[14] However, recent Cochrane systematic reviews have failed to show benefit for either treatment.[15,16] Prior systematic reviews demonstrated a modest effect of corticosteroids,[17,18] but either included non–randomized controlled trials (non-RCTs)[17] or excluded trials meeting their own eligibility criteria.[18] Several RCTs recently have been completed,[19-25] including 2 large trials (N=839 and N=551)[19,23] that both demonstrated benefit with corticosteroids but not with antiviral agents.

We conducted a systematic review and meta-analysis, including the most recent evidence of the association of corticosteroid and antiviral agent therapy with the risks of unsatisfactory facial recovery, synkinesis and autonomic dysfunction, and adverse effects in patients with Bell palsy.

METHODS

We searched MEDLINE, EMBASE, CENTRAL, CINAHL, PsychInfo, and Web of Science to March 1, 2009, for relevant trials in any language. Our search included the gray literature (conference proceedings, dissertations, and theses) through PAPERSFIRST, PROCEEDINGSFIRST, and PROQUEST. We screened bibliographies of relevant articles, involved experts (V.Y.W.L., J.M.N., J.M.C.), and checked the clinical trial registry (www.clinicaltrials.gov) for additional studies. Medical Subject Headings and keywords for methods (RCTs), patient population (Bell palsy and idiopathic facial nerve paralysis occurring at all ages), and interventions (corticosteroids and antiviral agents) were used to identify studies.

Two reviewers (J.R.D., M.A.) independently screened all studies by title or abstract for those requiring further retrieval (full text or abstract), and then independently reviewed these studies for eligibility (FIGURE 1). The inclusion criterion was a RCT study design of patients diagnosed with Bell palsy. Included studies compared treatment with corticosteroids or antiviral agents against a control (placebo, no treatment, supportive treatment, an active treatment present in both groups) and reported at least 1 of the outcomes of facial recovery, synkinesis and autonomic dysfunction, major adverse effects, and/or minor adverse effects. Disagreements regarding trial eligibility were resolved by consensus.

Studies in non-English languages were translated. Two reviewers (J.R.D., M.A.) extracted data and resolved inconsistencies by consensus. We attempted to contact primary authors for further information regarding study inclusion, methods, outcomes, and verification of trial results. We recorded patient eligibility, number of patients, and treatment in each group. We addressed methodological quality including adequacy of random sequence generation, allocation concealment, blinding, loss to follow-up, selective reporting, or other biases. Judgments regarding the presence of methodological biases were made according to the Cochrane criteria guidelines.[26] As suggested by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group, we considered issues of risk of bias, precision, consistency, directness, and publication bias in determining the quality of evidence for each outcome.[27]

The primary outcome measure was unsatisfactory facial recovery (≥4 months); secondary outcomes included unsatisfactory short-term recovery (6 weeks to <4 months), synkinesis and autonomic dysfunction, major life-threatening adverse effects, and minor adverse effects. When outcomes were reported at multiple time points, we used the earliest time point for the short-term outcome and the latest time point for the primary outcome.

To explain variability in the primary outcome, we defined 5 a priori hypotheses: treatment modality (larger effect in combination vs corticosteroid or antiviral agent monotherapy), initial severity (greater benefit in moderate vs severe paresis), dose (smaller benefit in cumulative dose of <450 mg vs ≥450 mg of prednisone equivalent for corticosteroids and smaller benefit for <4000 mg/d of acyclovir or <3000 mg/d of valacyclovir vs ≥4000 mg/d of acyclovir or ≥3000 mg/d valacyclovir), time to treatment (larger benefit in studies in which patients were treated within 72 hours vs studies in which patients were not necessarily treated within 72 hours), and blinding.

Studies used a variety of measurement instruments including the House-Brackmann, Facial Paralysis Recovery

Profile/Index, Sunnybrook, Yanagihara, Modified Adour Mechelse, and instruments[28-32] not previously described to measure recovery and initial severity (eTable [available at http://www.jama.com] and TABLE 1). We defined unsatisfactory recovery as failure to achieve complete or near normal recovery. In 2 studies, investigators reported outcomes using 2 instruments, one of which was the House-Brackmann. For these studies, we report the House-Brackmann results.

We measured interrater agreement for study inclusion and assessment of methodological quality (weighted κ). We report outcomes using relative risks (RR) with 95% confidence intervals (CIs). Pooled estimates of effect were derived using a random-effects model with Mantel-Haenszel statistics. Study heterogeneity was determined using the I^2 statistic in which 0% to 40% may be unimportant heterogeneity, 30% to 60% indicates moderate, 50% to 90% indicates substantial, and 75% to 100% indicates considerable heterogeneity[44] and the *P* value from the χ^2 test. Trials with factorial design were treated as 2 separate trials (combined therapy vs monotherapy, placebo and monotherapy, or placebo vs double placebo).

To explore the interaction between corticosteroids and antiviral agents, we used logistic regression analysis with study, corticosteroid treatment, antiviral agent treatment, and an interaction term for corticosteroid and antiviral agent treatment as covariates. For other a priori hypotheses, we calculated *z* scores to test for interactions.[45] We estimated event rates (baseline risk for unsatisfactory recovery) in untreated patients from previous observational data,[3] and from the median control group event rate for all other outcomes. Corresponding risks with 95% CIs were computed by multiplying treatment effect (RR) and control event rates. The absolute risk reduction was calculated as the difference of baseline and corresponding risk. The number of patients needed to treat for 1 patient to experience benefit (NNTB) or harm (NNTH) were computed by taking the reciprocal of the absolute risk reduction or absolute risk increase.[46]

Publication bias was evaluated using funnel plots and the Egger statistic for unsatisfactory recovery. Regression analysis was performed using SPSS version 15.0 (SPSS Inc, Chicago, Illinois), meta-analyses were performed using Review Manager version 5.0.17 (Nordic Cochrane Center, Copenhagen, Denmark), and Egger statistical analyses were performed using Stata version 10.0 (StataCorp, College Station, Texas).

RESULTS

Of 854 identified studies, 18 were eligible for inclusion (Figure 1). Of these, 8 evaluated corticosteroids, 7 evaluated antiviral agents, and 3

Table 1. Study Characteristics of Randomized Controlled Trials Included in the Meta-analysis

Source	Randomization Groups	No. of Patients Randomized
Adour et al,[33] 1996	Placebo plus prednisone	46
	Acyclovir plus prednisone	53
Antunes et al,[34] 2000	Double placebo	17
	Placebo plus deflazacort	14
	Valacyclovir plus deflazacort	15
Austin et al,[35] 1993	Placebo	41
	Prednisone	35
Bento et al,[36] 1991	Placebo	20
	Dexamethasone	20
Engström et al,[19] 2008	Double placebo	209
	Placebo plus prednisolone	213
	Valacyclovir plus placebo	207
	Valacyclovir plus prednisolone	210
Hato et al,[20] 2007	Placebo plus prednisone	107
	Valacyclovir plus prednisone	114
Inanli et al,[37] 2001	Prednisone alone	22
	Acyclovir plus prednisone	20
Kawaguchi et al,[21] 2007	Placebo plus prednisolone	66
	Valacyclovir plus prednisolone	84
Lagalla et al,[38] 2002	Placebo plus polyvitamin therapy	28
	Prednisone plus polyvitamin therapy	30
Martinez et al,[39] 1990	No placebo	45
	Prednisone	42
May et al,[40] 1976	Vitamins	26
	Vitamins plus prednisone	25
Roy et al,[22] 2005	Methylprednisolone alone	32
	Acyclovir plus methylprednisolone	32
Sullivan et al,[23] 2007	Double placebo	141
	Placebo plus prednisolone	138
	Acyclovir plus placebo	138
	Acyclovir plus prednisolone	134
Tekle-Haimanot,[41] 1987	Vitamins	29
	Prednisone	30
Unüvar et al,[42] 1999	No placebo	21
	Methylprednisolone	21
Vazquez et al,[24] 2008	Placebo plus prednisone	19
	Valacyclovir plus prednisone	22
Wolf et al,[43] 1978	No placebo	132
	Prednisone	107
Yeo et al,[25] 2008	Prednisone alone	47
	Acyclovir plus prednisone	44

evaluated both corticosteroids and antiviral agents. Interrater agreement for study inclusion was excellent ($\kappa = 0.88$).

The 18 trials included 2786 patients (mean, 155 patients; range, 40-829), 2078 in corticosteroid trials, and 2134 in antiviral agent trials. Median follow-up was 6 months (range, 10 weeks-12 months). Trials were conducted in 12 countries and 5 continents. Thirteen studies were published in English, 2 in Portuguese,[34,36] 2 in Spanish,[24,39] and 1 in Turkish.[37] All but 3 trials[33,34,39] attempted to rule out other causes of acute facial paralysis. One trial involved exclusively pediatric patients,[42] 6 trials included pediatric patients,[22,34,36,39,42,43] and the remainder included only patients older than 14 years.

Eight trials compared corticosteroids with a control (placebo, supportive treatment, or no treatment),[35,36,38-43] 7 compared the combination of antiviral agents and corticosteroids with a corticosteroid control (with or without placebo),[20-22,24,25,33,37] 2 used a factorial design,[19,23] and 1 used a 3-group design comparing the combination of antiviral agents and corticosteroids vs corticosteroids and placebo vs double placebo (eTable [available at http://www.jama.com] and Table 1).[34]

We attempted to contact 16 primary authors,[19-25,33-39,41,42] and established contact with 9.[20-24,33,35,36,38] Information regarding study inclusion was sought and retrieved from 3 trials.[21,22,24] Methodological information was sought from 13 trials[20-22,25,33-39,41,42] and retrieved from 7.[20-22,33,35,36,38] Further outcome results were requested from investigators for 15 trials[19-23,25,33-39,41,42] and obtained from 4.[20-22,38] Attempts to verify trial results was successful in 4[20,22,23,33] of 5 trials.[20,22,23,33,34] Unpublished results were obtained for the primary outcome in 1 trial,[21] unsatisfactory recovery (short term) in 3 trials,[20-22] and major adverse effects in 1 trial.[22]

TABLE 2 reports risk of bias[26] for each trial. Interrater agreement for assessment of methodological quality ranged from 0.58 to 1.00 for the 6 categories with an overall agreement of 0.75. The lowest agreement was in the category of other bias, while perfect agreement was achieved in the areas of adequate sequence generation and allocation concealment. Although all studies describe randomization, 6 did not adequately describe methods of random sequence generation,[25,34,37,39,41,43] and 7 did not adequately describe allocation concealment.[25,34,37,39,41-43] Ten studies used blinding methods for outcome adjudication.[19,23-25,33-36,38,40] Five trials described the type of analysis[19-21,23,38]; one described adherence to the intention-to-treat principle.[23] Five trials described a modified intention-to-treat analysis.[19-21,24,38] One trial described a

Table 2. Assessment of Study Quality

Source	Adequate Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data Addressed	Free of Selective Reporting	Free of Other Bias	Description of Other Bias
Adour et al,[33] 1996	Yes	Yes	Yes	Unclear	No	No	Use of per-treatment analysis
Antunes et al,[34] 2000	Unclear	Unclear	Yes	Yes	No	No	Poorly described statistical methods
Austin et al,[35] 1993	Yes	Yes	Yes	No	No	No	Prognostically imbalanced groups; more severe pareses in control group
Bento et al,[36] 1991	Yes	Yes	Yes	No	Yes	No	Poorly described statistical methods
Engström et al,[19] 2008	Yes	Yes	Yes	No	Yes	No	Premature trial termination; modified intention-to-treat analysis; industry funding
Hato et al,[20] 2007	Yes	Yes	No	No	Yes	No	Postrandomization exclusion of patients with varicella zoster virus
Inanli et al,[37] 2001	Unclear	Unclear	No	Yes	Yes	Yes	
Kawaguchi et al,[21] 2007	Yes	Yes	No	Yes	Yes	No	Postrandomization exclusion of patients with varicella zoster virus
Lagalla et al,[38] 2002	Yes	Yes	Yes	Yes	No	No	Postrandomization exclusion of patients with varicella zoster virus
Martinez et al,[39] 1990	Unclear	Unclear	No	No	Yes	Yes	
May et al,[40] 1976	Yes	Yes	Yes	Yes	No	Yes	
Roy et al,[22] 2005	Yes	Yes	No	Yes	Yes	Yes	
Sullivan et al,[23] 2007	Yes	Yes	Yes	Yes	Yes	Yes	
Tekle-Haimanot,[41] 1987	Unclear	Unclear	No	Yes	Yes	No	Poorly described statistical methods
Unüvar et al,[42] 1999	Yes	Unclear	No	Yes	Yes	Yes	
Vazquez et al,[24] 2008	Yes	Yes	Yes	Yes	No	No	Modified intention-to-treat analysis
Wolf et al,[43] 1978	Unclear	Unclear	No	Unclear	Yes	Yes	
Yeo et al,[25] 2008	Unclear	Unclear	Yes	Yes	Yes	Yes	

per-treatment analysis.[33] In 4 trials, the loss to follow-up exceeded 20%.[20,35,36,39] Methods of statistical analysis were well described in all but 3 trials.[34,36,41]

TABLE 3 summarizes the quality of evidence for each outcome. The quality of evidence was high for the effects of corticosteroids on unsatisfactory facial recovery and on synkinesis and autonomic dysfunction. The quality of the evidence was moderate for other outcomes.

Fifteen studies reported unsatisfactory recovery for corticosteroids and/or antiviral agents.[19-21,23-25,33-35,38-43] Regression analysis revealed a positive interaction between corticosteroid and antiviral agent use (OR for interaction term, 0.54 [95% CI, 0.35-0.83]; $P=.004$). Corticosteroid therapy alone was associated with reduced risk of unsatisfactory recovery in 10 studies (FIGURE 2 and Table 3).[19,23,34,35,38-43,47] When patients also were treated with antiviral agents, corticosteroids were associated with a further reduction in the risk of unsatisfactory recovery in 2 studies compared with antiviral agents alone.[19,23,47]

Although not effective alone,[19,23,47] antiviral agents were associated with a reduction in risk of borderline statistical significance when given with corticosteroids compared with corticosteroids alone (FIGURE 3 and Table 3). Eight studies contributed to the pooled estimate.[19-21,23-25,33,34,47] Using a fixed-model analysis, antiviral agents were associated with a significant risk reduction when given in combination with corticosteroids compared with corticosteroids alone (RR, 0.75 [95% CI, 0.59-0.97]; $P=.03$; $I^2=10\%$; $P=.36$ for heterogeneity). We found no evidence of publication bias based on visual inspection of funnel plots or Eg-

Table 3. Evidence Profile for Corticosteroids and Antiviral Agents in Bell Palsy

	Evidence Profile	RR (95% CI)	*P* Value	Risk Without Treatment	Risk With Treatment (95% CI)	NNTB (95% CI)	Quality of Evidence
Primary Outcome							
Unsatisfactory recovery							
Corticosteroids without antiviral agents	No serious methodological limitations, consistent, direct, precise, no publication bias detected	0.69 (0.55-0.87)	.001	29/100 population[a]	20 (16-25)/ 100 population	11 (8-25)	High[b]
Antiviral agents without corticosteroids	No serious methodological limitations, consistent, direct, imprecise,[c] no publication bias detected	1.14 (0.80-1.62)	.48	29/100 population[a]	33 (23-47)/ 100 population	25 (NNTB 17 to ∞ – NNTH 6)	Moderate
Corticosteroids with antiviral agents (vs antiviral agents alone)	No serious methodological limitations, inconsistent,[d] direct, precise, no publication bias detected	0.48 (0.29-0.79)	.004	33/100 population[e]	16 (10-26)/ 100 population	6 (4-14)	Moderate
Antiviral agents with corticosteroids (vs corticosteroids alone)	No serious methodological limitations, inconsistent,[d] direct, precise, no publication bias detected	0.75 (0.56-1.00)	.05	20/100 population[e]	15 (11-20)/ 100 population	20 (11-∞)	Moderate
Secondary Outcomes							
Corticosteroids							
Major adverse effects	No serious methodological limitations, consistent, direct, imprecise,[c] no publication bias detected	0.56 (0.09-3.39)	.44	0/1000 population[f]	0/1000 population	NA	Moderate
Minor adverse effects	Serious methodological limitations,[g] consistent, direct, precise, no publication bias detected	1.23 (0.93-1.64)	.15	9/100 population[f]	11 (8-15)/ 100 population	NNTH 50 (NNTB 100 to ∞ – NNTH 17)	Moderate
Synkinesis and autonomic dysfunction	No serious methodological limitations, consistent, direct, precise, no publication bias detected	0.48 (0.36-0.65)	<.001	27/100 population[f]	13 (10-17)/ 100 population	7 (6-10)	High[b]
Antiviral agents							
Major adverse effects	No serious methodological limitations, consistent, direct, imprecise,[c] no publication bias detected	0.97 (0.27-3.74)	.67	0/1000 population[h]	0/1000 population	NA	Moderate
Minor adverse effects	Serious methodological limitations,[g] consistent, direct, precise, no publication bias detected	1.02 (0.79-1.33)	.87	9/100 population[h]	9 (7-12)/ 100 population	∞ (NNTB 50 to ∞ – NNTH 33)	Moderate
Synkinesis and autonomic dysfunction	No serious methodological limitations, consistent, direct, precise, no publication bias detected	0.75 (0.51-1.11)	.15	27/100 population[h]	20 (14-30)/ 100 population	14 (NNTB 8 to ∞ – NNTH 33)	Moderate

Abbreviations: CI, confidence interval; NA, not estimable; NNTB, number of patients needed to treat for 1 patient to benefit; NNTH, number of patients needed to treat for 1 patient to be harmed; RR, relative risk.

[a] Risk is derived from a large observational study describing the natural history of patients not treated for Bell palsy. Unsatisfactory recovery is reported in this study as 29% (overall) and stratified by initial severity of paresis.[3]

[b] Graded as high and may be upgraded due to strength of effect.

[c] Quality of evidence downgraded due to a large 95% CI with the possibility of harm.

[d] Consistency was downgraded for combined therapy because there is a differential effect in combined therapy vs monotherapy.

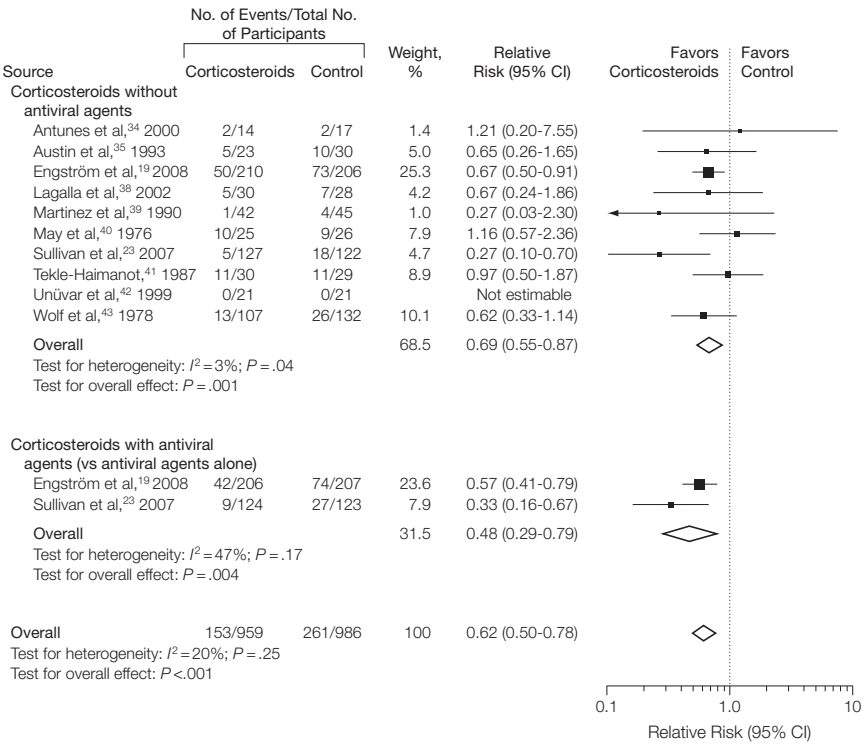
[e] The risk of unsatisfactory recovery for corticosteroids alone or antiviral agents alone are the corresponding risks from the lines above.

[f] Risk was derived from the median control group event rate for each secondary outcome.

[g] Only 2 studies describe rigorous monitoring of minor adverse effects.

[h] Risk for those treated with antiviral agents is the same as for those treated with corticosteroids listed above for all secondary outcomes.

Figure 2. Unsatisfactory Facial Recovery for Corticosteroids Given With or Without Antiviral Agents



The size of the point estimates indicate the relative weight of each trial in the meta-analysis as determined by the inverse variance method. CI indicates confidence interval.

ger statistics (corticosteroids, $P = .80$; antiviral agents, $P = .31$).

A significant interaction was observed between higher doses (≥450 mg) and lower doses (<450 mg) of corticosteroids (TABLE 4). Corticosteroids were associated with a larger effect at higher doses than at lower doses ($P = .02$ for interaction). There was no significant interaction in other subgroup analyses. However, a nearly statistically significant difference in effect was observed ($P = .06$ for interaction) when corticosteroids were used to treat moderate paresis compared with severe paresis.

In the 4 trials that assessed the association of corticosteroids with the outcome of short-term unsatisfactory recovery,[19,23,36,38,47] corticosteroids were associated with a significant benefit (RR, 0.70 [95% CI, 0.55-0.89]; $P = .003$; $I^2 = 60\%$; heterogeneity, $P = .03$). In the 8 trials that assessed the association of antiviral agents with short-term unsatisfactory recovery, antiviral agents were not associated with a benefit (RR, 0.97 [95% CI, 0.84-1.12]; $P = .69$; $I^2 = 19\%$; heterogeneity, $P = .26$).[19-23,25,33,34,47]

Meta-analysis of 3 studies showed a RR reduction in synkinesis and autonomic dysfunction in patients treated with corticosteroids (Table 3).[19,38,43] Meta-analysis of 2 trials showed no reduction in synkinesis and autonomic dysfunction among patients treated with antiviral agents.[19,33]

Few major adverse effects were associated with corticosteroid or antiviral agent treatment in the 9 trials that reported this outcome.* Eight major adverse effects were reported in 2122 patients. Three deaths were reported (all of which occurred in 1 trial)[23]; 2 of these deaths occurred in the double placebo group and 1 in the combined antiviral agent and placebo group. None were attributed to treatment. One episode of recurrent atrial fibrillation was described in a patient receiving antiviral agents.[19] In one trial, 4 patients receiving corticosteroids developed gastric ulceration.[22] Avascular necrosis of the hip was not reported in any studies. Neither corticosteroids nor antiviral agents were associated with an increased risk of major adverse effects compared with control groups (Table 3).

In the 7 corticosteroid trials that reported minor adverse effects,[19,23,35,38,39,42,43] there was no apparent association with an increase in the risk of minor adverse effects (Table 3). Four trials reported minor adverse effects for antiviral agents.[19,20,22,23] There was no apparent association with an increase in the risk of adverse effects in patients taking antiviral agents. Only 2 studies described rigorous monitoring methods for minor adverse effects.[19,23]

*References 19, 20, 22, 23, 35, 38, 39, 42, 43.

COMMENT

Recent evidence from large RCTs indicates that Bell palsy may best be managed with corticosteroids and that antiviral agents may be of no benefit. This systematic review has shown a possible incremental benefit of adding antiviral agents to corticosteroid therapy and a synergistic effect when these 2 agents are given in combination.

Based on the GRADE criteria,[27] high-quality evidence suggests that corticosteroids alone reduce the risk of unsatisfactory recovery by 9% in absolute terms, with a NNTB of 11 (95% CI, 8-25). Corticosteroid therapy combined with antiviral agents reduced the risk of unsatisfactory recovery compared with antiviral agents alone. Corticosteroids were also associated with a 14% absolute risk reduction of synkinesis and autonomic dysfunction (NNTB, 7; 95% CI, 6-10) (moderate quality of evidence). Corticosteroids were not associated with an increased risk of adverse effects.

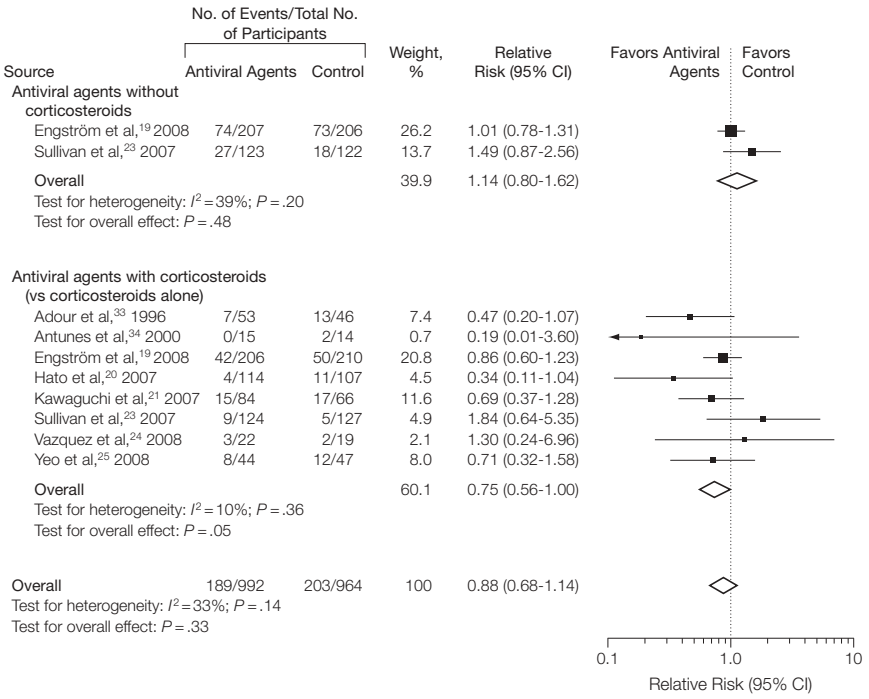
Moderate-quality evidence suggests that antiviral agents given without corticosteroids were not associated with benefit. However, antiviral agents com-

bined with corticosteroids are associated with reduced risk of unsatisfactory recovery (of borderline significance) compared with corticosteroids alone.

Corticosteroids and antiviral agents appear to be associated with larger effects when administered together than when given separately. We view this apparent difference in effect as credible but not definitive.[49] The conclusion is based on 1 of 5 a priori hypotheses with a specified direction. Some of the results come from within-study comparisons[19,23]; the effect is not likely to be due to chance, is relatively large, has biological plausibility, and is consistent across studies.

Corticosteroids were associated with greater benefit when prescribed at doses of greater than 450 mg compared with doses lower than 450 mg. This subgroup effect has limited credibility because it is based on between-study comparisons, has not been supported by external evidence, and is inconsistent among studies. Furthermore, the lower dose subgroup effect is based on small studies with meth-

Figure 3. Unsatisfactory Facial Recovery for Antiviral Agents Given With or Without Corticosteroids



The size of the point estimates indicate the relative weight of each trial in the meta-analysis as determined by the inverse variance method. CI indicates confidence interval.

Table 4. Subgroup Analysis of Unsatisfactory Facial Recovery After Treatment With Corticosteroids and Antiviral Agents

	Subgroup	No. of Studies	No. of Patients With Unsatisfactory Recovery/Total		RR (95% CI)	I^2, %	*P* Value[a]	*P* Value for Interaction Between Subgroups[b]
			Treatment	Control				
Corticosteroids								
Initial severity[c]	Moderate	3[23,39,40,48]	9/210	28/188	0.31 (0.15-0.63)	0	.42	.06
	Severe	4[23,39-41,48]	16/103	29/129	0.87 (0.40-1.92)	49	.14	
Dose[d]	<450 mg	4[34,35,40,41]	28/92	32/102	0.96 (0.63-1.46)	0	.80	.02
	≥450 mg	6[19,23,38,39,42,43]	125/867	229/884	0.56 (0.46-0.70)	8	.37	
Time to treatment	Within 72 h	5[19,23,38,40,42]	121/743	208/733	0.58 (0.42-0.80)	47	.09	.38
	Not within 72 h	5[34,35,39,41,43]	32/216	53/253	0.73 (0.49-1.08)	0	.70	
Blinding	Blinded	6[19,23,34,35,38,40]	128/759	220/759	0.60 (0.46-0.78)	31	.18	.45
	Not blinded	4[39,41-43]	25/200	41/227	0.73 (0.47-1.13)	0	.39	
Antiviral agents								
Initial severity[c]	Moderate	3[20,23,33,48]	20/231	19/216	0.83 (0.30-2.28)	50	.16	.91
	Severe	3[20,23,33,48]	26/164	28/159	0.76 (0.26-2.22)	78	.01	
Dose[e]	Low dose	7[20,21,23-25,33,34]	73/579	80/548	0.81 (0.52-1.25)	44	.08	.52
	High dose	1[19]	116/413	123/416	0.95 (0.77-1.18)	0	.47	
Time to treatment	Within 72 h	4[19,23,25,33]	162/735	161/730	1.00 (0.76-1.31)	32	.19	.06
	Not within 72 h	4[20,21,25,34]	27/257	42/234	0.61 (0.39-0.94)	0	.57	
Blinding	Blinded	6[19,23-25,33,34]	170/794	175/791	0.96 (0.75-1.23)	24	.24	.09
	Not blinded	2[20,21]	19/198	28/173	0.57 (0.30-1.07)	18	.14	

Abbreviations: CI, confidence interval; RR, relative risk.
[a] Based on the χ^2 test.
[b] Based on *z* scores.
[c] Subgroup analysis contains within and between study level data. All patients not accounted for because subgroup data not available for every patient. Severity is defined by primary author. See eTable (available at http://www.jama.com) for further details.
[d] Dose is in an equivalent to prednisone.
[e] Low dose is suitable for treatment of herpes simplex virus, high dose is suitable for treatment of varicella zoster virus.

odological limitations while the higher dose subgroup is based on larger more rigorous studies.

Patients with complete or severe initial paresis have a poorer prognosis than those with incomplete paresis.[2] Our results suggest that corticosteroids are associated with a smaller benefit in patients with severe than in those with moderate severity pareses, however the test for interaction was not statistically significant. The effect was substantial, in the predicted direction (1 of 5 a priori hypotheses), and was based primarily on within-study comparisons. However, results were inconsistent across studies.

We found no difference in the effect of corticosteroids on unsatisfactory recovery when patients are treated within 72 hours vs later. This finding was the result of between-study comparisons of studies that restricted enrollment to those presenting within 72 hours vs those that enrolled patients presenting both before and after 72 hours of onset. Thus, the subgroup analysis is weak. If time to treatment data were available for individual patients, a more powerful analysis would be possible.

The etiologic basis for Bell palsy may be due not only to reactivation of herpes simplex virus, but also due to reactivation of VZV.[12] Adequate treatment of VZV requires a higher dose of antiviral agents.[12] We did not find improved facial recovery in patients treated with higher doses of antiviral agents, although only 1 study used a dose appropriate for treatment of VZV.[19]

Our meta-analysis has limitations. First, 2 trials[19,23] contributed almost half of the patients in the meta-analysis. In this review, however, results were consistent across multiple studies. We also chose a random-effects model which, although it gives a higher weight to large studies, it has a lower large to small study gradient in weight than fixed-effects models if there is variation between studies. Second, our meta-analysis may be underpowered for some outcomes such as minor adverse effects of corticosteroids and synkinesis and autonomic dysfunction for antiviral agents. These associations had substantial, but nonsignificant treatment effects. Third, included studies were not blinded by author or journal source. Given reviewer familiarity with the literature, complete anonymity would be difficult to achieve. However, we used criteria delineated by the Cochrane group[26] to assess methodological quality. Fourth, our primary outcome is subjective and susceptible to biased assessment, particularly in nonblinded studies. However, blinded and nonblinded studies showed similar results. Finally, there was considerable heterogeneity in the instruments used to measure outcomes. One study, however, showed moderate to good agreement (chance-corrected agreement of 0.65 on a scale from 0 to 1.0) between 3 of the grading systems used in this review (Sunnybrook, House Brackmann, Yanagihara).[50] Our results were consistent across studies with different measurement instruments.

A recent study suggested that corticosteroid monotherapy may be more cost-effective than combining antiviral agents and corticosteroids.[51] This analysis was based on trial results that did not demonstrate a synergistic effect of corticosteroids and antiviral agents.[23] Our results suggest a possible incremental benefit of antiviral agents in addition to corticosteroids, with an absolute risk reduction of 5% compared with corticosteroids alone. This effect, however, is not definitive and did not quite reach statistical significance. Moreover, the cost of roughly $20 per day for acyclovir (4000 mg) and valacyclovir (3000 mg) is not insignificant. The higher value that patients place on the uncertain incremental benefit of combining antiviral agents and corticosteroids compared with corticosteroids alone is likely to determine their inclination to use antiviral agents in addition to corticosteroids. Further primary studies are needed to definitively establish—or refute—an incremental benefit of combined therapy compared with corticosteroid monotherapy.

Author Contributions: Dr de Almeida had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: de Almeida, Al Khabori, Guyatt, Witterick, Lin, Nedzelski, Chen.
Acquisition of data: de Almeida, Al Khabori.
Analysis and interpretation of data: de Almeida, Al Khabori, Guyatt, Witterick, Lin, Nedzelski, Chen.
Drafting of the manuscript: de Almeida, Guyatt, Chen.
Critical revision of the manuscript for important intellectual content: de Almeida, Al Khabori, Guyatt, Witterick, Lin, Nedzelski, Chen.
Statistical analysis: de Almeida, Al Khabori, Guyatt.
Administrative, technical, or material support: Guyatt, Witterick, Lin, Nedzelski, Chen.
Study supervision: Guyatt, Chen.
Financial Disclosures: Dr Witterick reported being a member of the advisory board for Schering Canada and Abbott Laboratories and a consultant for Alcon Canada. No other authors reported financial disclosures.
Funding/Support: Dr de Almeida is supported by an educational grant for graduate studies from the Albert and Temmy Latner Family Foundation in conjunction with Dr Jeremy Freeman and the Samuel Lunenfeld Research Institute at Mount Sinai Hospital, Toronto, Ontario, Canada.
Role of the Sponsor: None of the funding organizations or sponsors had any role in the design and conduct of the study; the collection, management, analysis, or interpretation of the data; or the preparation, review, or approval of the manuscript.
Additional Information: eTable is available at http://www.jama.com.
Additional Contributions: We thank Adalberto Loloya, MD, MSc candidate, McMaster University, Hamilton, Ontario, Canada, and Rahit Eskicioglu, PhD, Department of Computer Sciences, University of Manitoba, Winnepeg, Canada, for translations of articles. We also thank Sachin Sud, MD, Interdeparmental Division of Critical Care, University of Toronto, Toronto, Ontario, Canada, for verification of publication bias analyses. We also thank the following authors for clarifications regarding trial data: Kedar Adour, MD, Department of Head and Neck Surgery, Kaiser Permanente Medical Center, Oakland, California; Ricardo Bento, MD, Department of Otolaryngology, University of Sao Paolo School of Medicine, Sao Paolo, Brazil; Naohito Hato, MD, Department of Otolaryngology, Ehime University School of Medicine, Ehime, Japan; Kazuhiro Kawaguchi, MD, Department of Otolaryngology, Yamagata University School of Medicine, Yamagata, Japan; Gianni Lagalla, MD, Department of Neurosciences, University of Ancona, Torrette, Italy; Ajit Roy, MD, Department of Neurology, St John's Medical College, Bangalore, India; Frank Sullivan, PhD, and Fergus Daly, PhD, Scottish School of Primary Care, University of Dundee, Dundee, Scotland; and Maria Vazquez, MD, Faculty of Medicine, Universidad de la Republica, Montevideo, Uruguay. None of these individuals received compensation for their contributions.

REFERENCES

1. Holland NJ, Weiner GM. Recent developments in Bell's palsy. *BMJ*. 2004;329(7465):553-557.
2. Hauser WA, Karnes WE, Annis J, Kurland LT. Incidence and prognosis of Bell's palsy in the population of Rochester, Minnesota. *Mayo Clin Proc*. 1971;46(4):258-264.
3. Peitersen E. The natural history of Bell's palsy. *Am J Otol*. 1982;4(2):107-111.
4. Cawthorne T, Wilson T. Indications for intratemporal facial nerve surgery. *Arch Otolaryngol*. 1963;78:429-434.
5. Adour KK, Bell DN, Hilsinger RL Jr. Herpes simplex virus in idiopathic facial paralysis (Bell palsy). *JAMA*. 1975;233(6):527-530.

6. Stjernquist-Desatnik A, Skoog E, Aurelius E. Detection of herpes simplex and varicella-zoster viruses in patients with Bell's palsy by the polymerase chain reaction technique. *Ann Otol Rhinol Laryngol*. 2006; 115(4):306-311.
7. Theil D, Arbusow V, Derfuss T, et al. Prevalence of HSV-1 LAT in human trigeminal, geniculate, and vestibular ganglia and its implication for cranial nerve syndromes. *Brain Pathol*. 2001;11(4):408-413.
8. Furuta Y, Fukuda S, Suzuki S, et al. Detection of varicella-zoster virus DNA in patients with acute peripheral facial palsy by the polymerase chain reaction, and its use for early diagnosis of zoster sine herpete. *J Med Virol*. 1997;52(3):316-319.
9. Murakami S, Mizobuchi M, Nakashiro Y, et al. Bell's palsy and herpes simplex virus. *Ann Intern Med*. 1996; 124(1 pt 1):27-30.
10. Fisch U, Esslen E. Total intratemporal exposure of the facial nerve. *Arch Otolaryngol*. 1972;95(4): 335-341.
11. Furuta Y, Ohtani F, Sawa H, et al. Quantitation of varicella-zoster virus DNA in patients with Ramsay Hunt syndrome and zoster sine herpete. *J Clin Microbiol*. 2001;39(8):2856-2859.
12. Hato N, Murakami S, Gyo K. Steroid and antiviral treatment for Bell's palsy. *Lancet*. 2008;371 (9627):1818-1820.
13. Sweeney CJ, Gilden DH. Ramsay Hunt syndrome. *J Neurol Neurosurg Psychiatry*. 2001;71(2):149-154.
14. Rowlands S, Hooper R, Hughes R, Burney P. The epidemiology and treatment of Bell's palsy in the UK. *Eur J Neurol*. 2002;9(1):63-67.
15. Salinas RA, Alvarez G, Ferreira J. Corticosteroids for Bell's palsy (idiopathic facial paralysis). *Cochrane Database Syst Rev*. 2004;4(4):CD001942.
16. Allen D, Dunn L. Aciclovir or valaciclovir for Bell's palsy (idiopathic facial paralysis). *Cochrane Database Syst Rev*. 2004;3(3):CD001869.
17. Grogan PM, Gronseth GS. Practice parameter. *Neurology*. 2001;56(7):830-836.
18. Ramsey MJ, DerSimonian R, Holtel MR, Burgess LP. Corticosteroid treatment for idiopathic facial nerve paralysis. *Laryngoscope*. 2000;110(3 pt 1): 335-341.
19. Engström M, Berg T, Stjernquist-Desatnik A, et al. Prednisolone and valaciclovir in Bell's palsy. *Lancet Neurol*. 2008;7(11):993-1000.
20. Hato N, Yamada H, Kohno H, et al. Valacyclovir and prenisolone treatment for Bell's palsy. *Otol Neurotol*. 2007;28(3):408-413.
21. Kawaguchi K, Inamura H, Abe Y, et al. Reactivation of herpes simplex virus type 1 and varicella-zoster virus and therapeutic effects of combination therapy with prednisolone and valacyclovir in patients with Bell's palsy. *Laryngoscope*. 2007;117(1):147-156.
22. Roy A, Jose J, Karnath V, et al. Efficacy of acyclovir and methylprednisolone versus methylprednisolone alone in the treatment of Bell's palsy. *J Neurol Sci*. 2005;238(suppl 1):S207.
23. Sullivan FM, Swan IRC, Donnan PT, et al. Early treatment with prednisolone or acyclovir in Bell's palsy. *N Engl J Med*. 2007;357(16):1598-1607.
24. Vazquez MC, Sanchez N, Calvo J. Eficacia de los antivirales en la paralysis de Bell [in Spanish]. *Rev Med Urug*. 2008;24(3):1-8.
25. Yeo SG, Lee YC, Park DC, Cha CI. Acyclovir plus steroid vs steroid alone in the treatment of Bell's palsy. *Am J Otolaryngol*. 2008;29(3):163-166.
26. Higgins J, Altman DG. Assessing risk of bias in included studies. In: Higgins J, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions 5.0.1*. Oxford, England: Cochrane Collaboration; 2008: chap 8.
27. Guyatt GH, Oxman AD, Vist GE, et al; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926.
28. House JW, Brackmann D. Facial nerve grading system. *Otolaryngol Head Neck Surg*. 1985;93 (2):146-147.
29. Adour KK, Swanson PJ Jr. Facial paralysis in 403 consecutive patients. *Trans Am Acad Ophthalmol Otolaryngol*. 1971;75(6):1284-1301.
30. Ross BG, Fradet G, Nedzelski JM. Development of a sensitive clinical facial grading system. *Otolaryngol Head Neck Surg*. 1996;114(3):380-386.
31. Yanagihara N, Hato N, et al. Assessment of facial nerve function following acoustic neuroma surgery: facial nerve grading system. In: Kanzaki J, Tos M, Sanna DA, eds. *Acoustic Neuroma: Consensus on Systems for Reporting Results.* Tokyo, Japan: Springer; 2003:91Y8.
32. Martinez C, Abarca B, Aillach E, et al. Paralisis de Bell: evolucion natural [in Spanish]. *Bol Hosp San Juan Dios*. 1988;35:273-278.
33. Adour KK, Ruboyianes JM, Von Doersten PG, et al. Bell's palsy treatment with acyclovir and prednisone compared with prednisone alone. *Ann Otol Rhinol Laryngol*. 1996;105(5):371-378.
34. Antunes ML, Fukuda Y, Testa JRG. Clinical treatment of Bell's palsy. *Acta AWHO*. 2000;19(2): 68-75.
35. Austin JR, Peskind SP, Austin SG, Rice DH. Idiopathic facial nerve paralysis. *Laryngoscope*. 1993; 103(12):1326-1333.
36. Bento RF, Lorenzi MC, Bogar P, et al. Treatment comparison between dexametasona and placebo at idiopathic facial palsy. *Rev Bras Otorinolaringol*. 1991; 57(4):196-202.
37. Inanli S, Tutkun A, Ozturk O, et al. Idiopathic facial paralysis treatment with acyclovir and prednisolone alone. *Turkish Arch Otolaryngol*. 2001;39 (1):19-24.
38. Lagalla G, Logullo F, Di Bella P, et al. Influence of early high-dose steroid treatment on Bell's palsy evolution. *Neurol Sci*. 2002;23:107-112.
39. Martinez GC, Abarca B, Alvarado CL, et al. Paralisis de Bell: evaluacion del tratamiento esteroidal [in Spanish]. *Bol Hosp San Juan Dios*. 1990;37(1): 13-17.
40. May M, Wette R, Hardin WB Jr, Sullivan J. The use of steroids in Bell's palsy. *Laryngoscope*. 1976; 86(8):1111-1122.
41. Tekle-Haimanot R. Idiopathic facial paralysis (Bell's palsy) in 167 Ethiopians, with a controlled therapeutic trial in 59 patients. *Ethiop Med J*. 1987;25(1): 23-27.
42. Unüvar E, Oğuz F, Sidal M, et al. Corticosteroid treatment of childhood Bell's palsy. *Pediatr Neurol*. 1999;21(5):814-816.
43. Wolf SM, Wagner JH, Davidson S, et al. Treatment of Bell palsy with prednisone. *Neurology*. 1978; 28:158-161.
44. Deeks JJ, Higgins JPT, Altman DG. Analyzing data and undertaking meta-analyses. In: Higgins J, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions 5.0.1.* Oxford, UK: The Cochrane Collaboration; 2008:chap 9.
45. Altman DG, Bland JM. Interaction revisited. *BMJ*. 2003;326(7382):219.
46. Altman DG. Confidence intervals for the number needed to treat. *BMJ*. 1998;317(7168):1309-1312.
47. Madhok V, Falk G, Fahey T, Sullivan FM. Prescribe prednisolone alone for Bell's palsy diagnosed within 72 hours of symptom onset. *BMJ*. 2009; 338:b255.
48. Sullivan F, Swan I, Daly F. Prenisolone or acyclovir in Bell's palsy. *N Engl J Med*. 2008;358(3):306-307.
49. Guyatt G, Jaeschke R, Prasad K, Cook DJ. Summarizing the evidence. In: Guyatt G, Rennie D, Meade MO, Cook DJ, eds. *Users' Guides to the Medical Literature.* 2nd ed. New York, NY: McGraw Hill Medical; 2008:537.
50. Berg T, Jonsson L, Engstrom M. Agreement between Sunnybrook, House Brackmann, Yanagihara facial nerve grading systems in Bell's palsy. *Otol Neurotol*. 2004;25(6):1020-1026.
51. Hernández RA, Sullivan F, Donnan P, Swan I, Vale L; BELLS Trial Group. Economic evaluation of early administration of prednisolone and/or acyclovir for the treatment of Bell's palsy. *Fam Pract*. 2009;26(2): 137-144.