Corticosteroids vs Corticosteroids Plus Antiviral Agents in the Treatment of Bell Palsy

A Systematic Review and Meta-analysis

John K. Goudakos, MD, MSc; Konstantinos D. Markou, MD, PhD

Objective: To review systematically and meta-analyze the results of all randomized controlled trials (RCTs) for the treatment of patients with Bell palsy with corticosteroids vs corticosteroids plus antiviral agents.

Data Sources: A MEDLINE, EMBASE, Cochrane Library, and CENTRAL database search, followed by extensive hand-searching for the identification of relevant studies. No time and language limitations were applied.

Study Selection: Prospective RCTs on the treatment of patients with Bell palsy.

Data Extraction: Odds ratios (ORs), 95% confidence intervals (CIs), and tests for heterogeneity were reported.

Data Synthesis: Five studies were eventually identified and systematically reviewed. Meta-analysis was performed for 4 studies. Regarding the complete recovery rate of facial nerve paralysis 3 months after initiation of therapy, the current systematic review and meta-analysis suggests that the addition of an antiviral agent does not provide any benefit (OR, 1.03 [95% CI, 0.74-1.42]; P=.88). The same conclusion emerged at posterior (fourth, sixth, and ninth) months of assessment. Subgroup analysis, conducted on the basis of time point of therapy initiation, type of antiviral agent, and blindness of assessments did not change the results obtained. The occurrence rate of adverse effects attributable to therapy choice was not significantly different between patients receiving corticosteroids and those following combined treatment.

Conclusion: The present systematic review and meta-analysis, based on the currently available evidence, suggests that the addition of an antiviral agent to corticosteroids for the treatment of Bell palsy is not associated with an increase in the complete recovery rate of the facial motor function.


Bell palsy, or idiopathic facial paralysis, is the most common cause of acute facial paralysis, with an annual incidence reported to range from 20 to 45 cases per 100,000 persons.1,2 The main clinical symptom of Bell palsy is facial motor dysfunction, the degree of which varies from minor weakness to complete paralysis depending on the amount of neural injury.

Genetic factors, vascular ischemia, and inflammation owing to viral infection or autoimmune disorders have been proposed as the possible underlying cause, but the etiology remains unknown.3-5 The theory of viral etiology was first proposed by McCormick,6 who suggested the acute inflammatory neuropathy of the seventh cranial nerve, owing to the presence of herpes simplex virus (HSV) in the geniculate ganglion.7 In 1996, Murakami et al8 isolated the HSV genome from the facial nerve endoneurial fluid of patients with Bell palsy, additionally supporting the viral etiology of the disease.

Considering the natural history of the disease, Peitersen,2 in a retrospective study of 2500 cases of Bell palsy, reported that 70% of the patients presented with complete paralysis of the facial nerve at initial examination, with only 61% of them achieving ultimate recovery. The same study2 also reported that partial regain of facial tone or movement was established in 85% of all patients within 3 weeks, and full recovery was typically achieved within 2 months.

Nowadays, the treatment of choice for Bell palsy has not yet been established. The therapeutic drug choices for the treatment of the idiopathic facial paralysis are (1) corticosteroids, (2) antiviral therapy (acyclovir sodium or valacyclovir hydrochloride), and (3) a combination of corticosteroids with an antiviral agent (combined therapy).

Author Affiliations: First Department of Otorhinolaryngology–Head and Neck Surgery, AHEPA University Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece.
Corticosteroids are considered to be the most widely accepted treatment for Bell palsy. The rationale for early treatment with the use of corticosteroids for patients with Bell palsy is based on the reports of facial nerve swelling during decompression operations. Several nonrandomized controlled trials (non-RCTs) have advocated the use of corticosteroids in facial palsy as the treatment of choice. In 2000, a meta-analysis by Ramsey et al suggested the significant improvement in recovery from facial paralysis in patients with Bell palsy who received corticosteroids. However, a recently published systematic review and meta-analysis indicated that, at present, the beneficial role of corticosteroids in Bell palsy treatment remains in doubt.

The possible association between Bell palsy and viral infection led to the use of an antiviral agent in the therapeutic plan of the disease, either as monotherapy or in combination with corticosteroids. Based on the results of a current systematic review and meta-analysis, insufficient evidence exists to make definitive recommendations regarding the effect of antiviral agents on Bell palsy. Recent multicenter controlled trials have evaluated the combined treatment strategy (corticosteroids plus antiviral agents) vs corticosteroids alone in the therapy of Bell palsy. Conflicting results about the benefit of adding antiviral agents for the recovery of facial nerve paralysis have been presented.

The purpose of the present systematic review and meta-analysis is to address the following question: Among patients with Bell palsy, is the full recovery of facial paralysis significantly different between patients who receive corticosteroids and those who receive combined treatment with corticosteroids and an antiviral agent?

METHODS

SEARCH STRATEGY

We performed a computer literature search in MEDLINE, EMBASE, the Cochrane Library, and CENTRAL electronic databases from January 10 to February 10, 2008, to identify studies that answered the question of interest. For this purpose, we used the following free-text terms: "Bell palsy" or "idiopathic facial nerve paralysis" or "facial palsy" combined with "drug therapy" or "steroids/corticosteroids/cortisone/prednisolone/presolone/methylprednisolone/dexamethasone/glucocorticoids" or "antiviral/acyclovir/valacyclovir" or "treatment" or "therapy" and limited to "human." In addition, extensive hand-searching of the references of all relevant studies was also performed. No time and language limitations were applied.

SELECTION OF STUDIES

All criteria for inclusion or exclusion of studies in the present systematic review were specified prior to the literature search. For a study to be eligible, the following criteria had to be met: (1) the study had to be an RCT, comparing any type of corticosteroid therapy with combined treatment of corticosteroids with any type of antiviral agent, regardless of the route (oral or parenteral), the dose, and the duration of administration of the therapies; (2) the study had to include patients with unilateral facial nerve weakness of no identifiable cause seen within 7 days of the onset of weakness; (3) the follow-up protocol had to include assessments of patients' clinical status at least 3 months after the initial onset of the disease and start of therapy; and (4) the study had to include patients who started therapy within 7 days from the onset of the disease.

The following exclusion criteria were established: (1) any studies that included patients with uncontrolled diabetes mellitus, peptic ulcer disease, supplicative otitis media, herpes zoster, multiple sclerosis, or systemic infection and (2) any study that included pregnant or breastfeeding women were excluded. In case the studies did not offer all the necessary information for the assessment of potential eligibility, the authors of those studies were contacted and asked to provide the missing data.

STUDIES IDENTIFIED

The electronic search resulted in the identification of 262 publications. Of these, 39 were found to be potentially eligible publications. The abstracts of these studies were examined, and 12 articles that could provide data to answer the research question of interest were identified (Figure 1). The full text of these studies was examined thoroughly, resulting in the exclusion of 7 publications. Specifically, these studies were excluded because (1) they did not match with the research question of interest (n=4), (2) the follow-up was less than 3 months (n=2), or (3) their data overlapped those of other publications (n=1); the study with the more extensive sample size was considered eligible in the present systematic review. As a consequence, 5 studies comparing corticosteroids with the combined therapy of corticosteroids plus antiviral agents in patients with Bell palsy were finally identified (Table 1).

Each of us independently assessed eligibility of these studies for the present systematic review. Any disagreement was resolved unanimously by discussion.

DATA EXTRACTION

Both of us performed data extraction, and the following data were recorded from each of the eligible studies: general characteristics (type of study, citation data, number of patients included, and their baseline characteristics), procedural data (type of randomization, inclusion criteria, protocol of follow-up, protocol of corticosteroid therapy or combined treatment and the number of patients who dropped out of the study), and outcome data (facial nerve recovery based on specific grading scale, adverse effects of each therapy strategy). To perform the intention-to-treat analysis, all patients who were initially allocated to each treatment group were analyzed together, regardless of whether they completed or received that treatment.

Figure 1. Flow diagram for study selection.
sweats, and other symptoms attributable to drug choice.

Viral drugs). These adverse effects included dizziness, dyspepsia, nausea, constipation, hunger, vomiting, insomnia, night sweats, and other symptoms attributable to drug choice.

**OUTCOME MEASURES**

The main outcome measure chosen for the systematic review and meta-analysis was the complete recovery of facial motor function 3 months after the initiation of therapy. Assessments of facial motor function at posterior months (at 4, 6, and 9 months) after the therapy started were also conducted. Many facial grading systems have been introduced for the assessment of motor function of facial nerve. In the present systematic review, the House and Brackmann facial nerve grading system, which has been adopted as a standard by the Facial Nerve Disorders Committee of the American Academy of Otolaryngology–Head and Neck Surgery, was chosen for the assessment of the primary outcome. Conversion of scores of other facial grading systems to the scales of the House-Brackmann system, which has been adopted as a standard by the Facial Nerve Disorders Committee of the American Academy of Otolaryngology–Head and Neck Surgery, was chosen for the assessment of the primary outcome. Conversion of scores of other grading systems to the scales of the House-Brackmann system was performed, owing to its universal acceptance for calculation of dysfunction of facial nerve disorders.

Secondary outcome measures included the occurrence rate of adverse effects in each study group attributable to treatment strategies (corticosteroids and corticosteroids plus antiviral agents). These adverse effects included dizziness, dyspepsia, nausea, constipation, hunger, vomiting, insomnia, night sweats, and other symptoms attributable to drug choice.

**QUANTITATIVE DATA SYNTHESIS**

The dichotomous data results for each of the eligible studies for meta-analysis were expressed as an odds ratio (OR) with 95% confidence intervals (CIs). These results were combined for meta-analysis by applying the Mantel-Haenszel model when using the fixed-effects method, and the DerSimonian and Laird model when using the random-effects method.

Revman software (version 4.2 for Windows; Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) was used to combine the results for meta-analysis. Inconsistency of studies (study-to-study variation) was assessed by using the I² statistic (the hypothesis tested was that the studies were all drawn from the same population, ie, from a population with the same effect size). A fixed-effects model was used in which no heterogeneity was present. In the presence of significant heterogeneity (I²<.05), a random-effects model was applied.

Subgroup analyses were performed depending on (1) the duration between disease onset and the start of therapy (early treatment was considered to be the therapy starting within 3 days of the disease onset), (2) the type and dosage of the corticosteroid and antiviral agent used in each study group, and (3) studies in which physicians who performed assessments of the outcomes were actually aware of allocated treatment.

Sensitivity analyses were performed to check the stability of the results obtained by excluding (1) studies that did not report the procedure of randomization and patient allocation clearly and (2) studies that did not provide detailed data regarding the diagnostic criteria of Bell palsy.

**RESULTS**

Five studies fulfilled the inclusion criteria. Characteristics of the eligible studies are listed in Table 1 and Table 2.

**SYSTEMATIC REVIEW**

The eligible studies were published from 1996 to 2007. All studies were RCTs in design, and their sample sizes ranged from 29 to 272 patients. A total of 738 patients were reviewed (corticosteroids group, n=372; combined therapy group, n=366) (Table 1).

Regarding the type of corticosteroid, patients in 4 studies received prednisolone, whereas in 1 study deflazacort was used. In the combined therapy group, the regimen included the corticosteroid plus an antiviral agent, acyclovir or valacyclovir. In all studies the drugs were administered orally. Details about the daily dose and the length of regimen of each study group are presented in Table 2.

In all studies, the procedure of follow-up included assessments of the patients for at least 3 months. The number of patients who were lost during the follow-up period (dropouts) in each study group was reported in 4 of 5 eligible studies. All trials used the full recovery of facial nerve motor function as the main outcome measure. Patients in 4 trials commenced therapy within 3 days of onset of the disease. The initial severity of the facial nerve dysfunction was reported in 3 studies. (Table 2).

The House-Brackmann grading system was used in 3 studies for scoring the facial nerve paralysis and its recovery. The Yanagihara grading system and Facial Paralysis Recovery Profile (FPRP) were used in the remaining 2 studies, and in these 2 studies, the authors reported the conversion of the used grading system (Yanagihara or FPRP) to the scores of House-Brackmann.
system. In 2 studies,15,17 clinicians assessing the recovery profile of the patients were blinded to allocated treatment. Three studies15,18,19 reported that there is no evidence that antiviral agents provide additional recovery benefit for patients with Bell palsy. In contrast, the 2 remaining studies14,17 reported that therapy with corticosteroids plus antiviral agents is superior to corticosteroids alone, regarding the complete recovery of facial motor function of patients with idiopathic acute facial paralysis. Three studies14,15,17 provided data about the adverse effects that occurred in each study group, which could be attributed to treatment strategies.

### META-ANALYSIS

Four14,15,17,19 of 5 eligible studies provided relevant data for quantitative synthesis. The complete recovery rate of facial motor function at 3 months after the initiation of therapy was not significantly different between the corticosteroids group and the combined therapy group (OR, 1.03 [95% CI, 0.74-1.42]; P = .88; heterogeneity, P = .66; fixed-effects model) (Figure 2).

Regarding assessment at 4, 6, and 9 months after initiation of therapy, meta-analysis was not feasible because results from only 1 study were available at each time point.

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### Table 2. Characteristics of the 5 Studies Included in the Systematic Review

<table>
<thead>
<tr>
<th>Source</th>
<th>Corticosteroids Group/Combined Therapy Group</th>
<th>Drug and Dosage</th>
<th>Duration of Follow-up, mo</th>
<th>Dropouts, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sullivan et al,2007</td>
<td>Age, Mean (SD), y: 42.7 (15.9)/43.7 (16.4)</td>
<td>Prednisolone, 25 mg twice a day for 10 days</td>
<td>Steroid plus acyclovir, 400 mg, 5 times a day for 10 days</td>
<td>9/21</td>
</tr>
<tr>
<td>Hato et al,2007</td>
<td>Male: 55.9/51.6</td>
<td>Within 3 d</td>
<td>Steroid plus valacyclovir, 500 mg, twice a day for 5 days</td>
<td>6/52</td>
</tr>
<tr>
<td>Adour et al,1996</td>
<td>Severity of Palsy, Mean (SD): 15.3/14.7</td>
<td>Prednisolone, 20 mg, 3 times a day for 1-5 days; 10 mg, 3 times a day for 6-8 days; 10 mg, once per day for 9-10 days</td>
<td>Steroid plus acyclovir, 2000 mg/d for 10 days</td>
<td>4/20</td>
</tr>
<tr>
<td>Inanli et al,2001</td>
<td>Sex, % Male: 53/52</td>
<td>Within 3 d</td>
<td>Prednisolone, 1 mg/kg for 5 days tapered to 10 mg/d for remaining 5 days</td>
<td>3/10</td>
</tr>
<tr>
<td>Melo et al,2000</td>
<td>Severity of Palsy, Mean (SD): 3.1/3.0</td>
<td>Prednisolone, 1 mg/kg for 12 days</td>
<td>Steroid plus acyclovir, 2400 mg/d for 10 days</td>
<td>6/7</td>
</tr>
</tbody>
</table>

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### Figure 2.

Odds ratio (OR) of complete recovery rate of facial motor function 3 months after the initiation of therapy. CI indicates confidence interval; M-H, Mantel-Haenszel.21 Combined therapy group indicates corticosteroids plus antiviral agents.
point. It should be noted, though, that in the individual studies the observed recovery rate of facial motor function was not considerably different between the corticosteroids group and combined therapy group 4 (OR, 0.48 [95% CI, 0.17-1.38]; P = .17), 6 (OR, 0.76 [95% CI, 0.46-1.25]; P = .29), and 9 months after the initiation of therapy (OR, 1.53 [95% CI, 0.74-3.17]; P = .25).

Sensitivity analysis including only the studies that reported a detailed analysis of randomization procedure and patient allocation suggested that the recovery rate of facial motor function did not differ significantly between the corticosteroids group and combined therapy group (OR, 1.02 [95% CI, 0.71-1.47]; P = .91; heterogeneity, P = .52; fixed-effects model) (Figure 3). Finally, these results did not change substantially by excluding the studies not clearly reporting the diagnostic criteria of Bell palsy (OR, 1.02 [95% CI, 0.71-1.47]; P = .91; heterogeneity, P = .52; fixed-effects model).

Subgroup analysis including only results of studies in which initiation of treatment was performed within 3 days of disease onset did not lead to a significant difference of complete recovery between the study groups (OR, 0.94 [95% CI, 0.63-1.4]; P = .77; heterogeneity, P = .54; fixed-effects model) (Figure 4). In the study by Hato et al, treatment started within 7 days of disease onset, and for this subgroup analysis the results of patients recruited within 3 days were used. In a further subgroup analysis, in which studies administering the same type of antiviral agent (acyclovir or valacyclovir) were analyzed, the rate of patients with complete recovery of facial motor function did not differ significantly (P < .05) between the 2 treatment groups (corticosteroids and corticosteroids plus antiviral agent). Finally, subgroup analysis, based on the type of corticosteroid administrated, could not be performed because all the studies that were included in meta-analysis used the same type of steroid (prednisolone) in similar parenteral dosage.

It should be noted that the recovery rate of facial motor function between the corticosteroid group and combined therapy group was not considerably different, excluding studies in which physicians performing the assessments of the outcome were aware of treatment allocation (OR, 0.99 [95% CI, 0.63-1.57]; P = .97; heterogeneity, P = .28; fixed-effects model).

The occurrence rate of adverse effects attributable to therapy choice did not differ significantly between the study groups (OR, 0.89 [95% CI, 0.50-1.60]; P = .70; heterogeneity, P = .78; fixed-effects model).

### COMMENT

Treatment decisions regarding patients with Bell palsy are doubtful and remain a common problem in medical practice. Corticosteroids have been established as the therapy of choice, despite the fact that the available evidence from RCTs does not exhibit a clear benefit. However, the largest available RCT published recently suggested a benefit from the use of corticosteroids in patients with idiopathic acute facial paralysis.25 The role of anti-
The natural course of Bell palsy, based on analysis of history of numerous cases, indicates that most patients recover within 3 months after the onset of the disease. Regarding the complete recovery rate of the facial nerve paralysis 3 months after the disease occurrence, the current systematic review and meta-analysis suggests that the addition of an antiviral agent does not provide any benefit. This conclusion seems to be in agreement with the results of a recent report dealing with the virologic background of Bell palsy, which indicates that, at first examination, reactivation of the HSV was detected in only 8% of patients. The lack of recovery advantage in patients receiving antiviral agents remained invariable at the 4-, 6-, and 9-month assessments after the therapy initiation.

According to supporters of virus involvement in the etiopathogenesis of Bell palsy, except in the case of HSV, the reactivation of varicella–zoster virus (VZV) is involved in the pathophysiologic course of a considerable proportion of patients. Valacyclovir, a prodrug of acyclovir, has been proposed as the antiviral agent that can improve the recovery rate of facial paralysis owing to its high bioavailability, which implies a much higher antiviral activity. However, in the present study, a subgroup analysis, based on the type of antiviral agent (acyclovir or valacyclovir), did not detect a benefit in the recovery of facial paralysis by adding either of the 2 agents.

The rationale for early (within 3 days of onset of disease) treatment with corticosteroids in patients with Bell palsy was based on its theoretical effect on early occurring cytotoxic edema, being proposed as a prevention strategy to neural degeneration of facial nerves and as a therapy method for complete recovery of facial paralysis. However, the results of the present meta-analysis do not confirm this assumption because the subgroup analysis on the basis of the timing of therapy initiation (within or not within 3 days of disease onset) supports the conclusion that early treatment does not provide any recovery advantage in patients with Bell palsy. The lack of benefit from the addition of antiviral agents to the therapeutic plan of patients with Bell palsy was also confirmed in the sensitivity analysis by excluding the studies that did not clearly report the diagnostic criteria of disease or the procedure of randomization and patient allocation.

The accurate diagnosis of the acute idiopathic facial nerve paralysis depends on the exclusion of other causes that have similar symptoms. Particularly, zoster sine herpete, which can mimic the signs and symptoms of Bell palsy, which is caused by VZV, has an incidence rate ranging from 29% to 34% among patients with Bell palsy. Consequently, data are needed regarding the virologic backgrounds of all participating patients and obtained by means of serologic and polymerase chain reaction examinations. In the present systematic review, only 1 study excluded patients with VZV reactivation.

The results of the present systematic review are liable to certain limitations. In 2 studies, the investigators who were administering the treatment and assessing the outcome were not aware of study-group assignments. Moreover, because facial functional outcome assessments are semisubjective, a level of bias in the final outcome assessment scores should be considered in all trials. Revealing the statistical significance of treatment benefit in studies of Bell palsy requires a large number of patients owing to the variable and spontaneous recovery profile of patients.

In the present systematic review, time-to-event analysis was not incorporated in any of the eligible studies. Time-to-event analysis and estimation of the relative risk are considered to be the most appropriate methods for comparison of the recovery of facial nerve motor function between the 2 groups so that the time interval between the intervention and the event (recovery of facial nerve) will not be disguised. None of the eligible studies in the present systematic review reported their results on the basis of the intention-to-treat analysis. The rationale of the specific analysis is to provide the pragmatic estimate of the benefit of a change to treatment policy rather than an estimate of potential benefit to patients receiving treatment exactly as planned. The results of the eligible studies in the present review were included in the quantitative data synthesis after their calculation on the basis of intention-to-treat analysis.

The current systematic review and meta-analysis suggests that addition of an antiviral agent to corticosteroids for the treatment of patients with Bell palsy is not associated with an increase in the complete recovery rate of facial motor function. Additional well-designed RCTs are needed to assess the potential value of antiviral addition to the recovery of facial palsy with more confidence. However, based on the currently available evidence, the addition of an antiviral agent to corticosteroids for the treatment of patients with Bell palsy is not justified.

Submitted for Publication: June 4, 2008; final revision received November 3, 2008; accepted November 16, 2008.

Correspondence: John K. Goudakos, MD, MSc, First Department of Otolaryngology–Head and Neck Surgery, AHEPA Hospital, Aristotle University of Thessaloniki, 54636 Thessaloniki, Greece (jgoudakos@gmail.com).

Author Contributions: Both authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Goudakos. Acquisition of data: Goudakos. Analysis and interpretation of data: Goudakos and Markou. Drafting of the manuscript: Goudakos. Critical revision of the manuscript for important intellectual content: Goudakos and Markou. Statistical analysis: Goudakos. Obtained funding: Goudakos. Administrative, technical, and material support: Goudakos and Markou. Study supervision: Goudakos and Markou.

Financial Disclosure: None reported.

Additional Contributions: K. K. Adour, M. L. Antunes, N. Hato, S. Inanli, and F. M. Sullivan contributed to this study.


