CLINICAL RESEARCH STUDY

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Antiviral Treatment of Bell's Palsy Based on Baseline Severity: A Systematic Review and Meta-analysis

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ABSTRACT

PURPOSE: We conducted a systematic review with meta-analysis to evaluate the efficacy of antiviral agents on complete recovery of Bell's palsy.

METHODS: We searched CENTRAL, Embase, MEDLINE, International Pharmaceutical Abstracts, and sources of unpublished literature to November 1, 2014. Primary and secondary outcomes were complete and satisfactory recovery, respectively. To evaluate statistical heterogeneity, we performed subgroup analysis of baseline severity of Bell's palsy and between-study sensitivity analyses based on risk of allocation and detection bias.

RESULTS: The 10 included randomized controlled trials (2419 patients; 807 with severe Bell's palsy at onset) had variable risk of bias, with 9 trials having a high risk of bias in at least 1 domain. Complete recovery was not statistically significantly greater with antiviral use versus no antiviral use in the random-effects meta-analysis of 6 trials (relative risk, 1.06; 95% confidence interval, 0.97-1.16; $I^2 = 65\%$). Conversely, random-effects meta-analysis of 9 trials showed a statistically significant difference in satisfactory recovery (relative risk, 1.10; 95% confidence interval, 1.02-1.18; $I^2 = 63\%$). Response to antiviral agents did not differ visually or statistically between patients with severe symptoms at baseline and those with milder disease (test for interaction, $P = .11$). Sensitivity analyses did not show a clear effect of bias on outcomes.

CONCLUSIONS: Antiviral agents are not efficacious in increasing the proportion of patients with Bell's palsy who achieved complete recovery, regardless of baseline symptom severity.

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KEYWORDS: Antiviral; Bell's palsy; Facial nerve

Bell's palsy is a unilateral paralysis of the facial nerve of unknown cause with an annual incidence of 11 to 40 cases per 100,000 individuals.[1] Reactivation of herpes simplex and herpes zoster is postulated to account for the majority of cases of Bell's palsy.[2-4] After reactivation, inflammation of the facial nerve leads to nerve compression, resulting in clinical symptoms.

On the basis of these mechanisms, antivirals and corticosteroids have been used in the treatment of Bell's palsy for decades. Corticosteroids reduce facial nerve edema and have been demonstrated in numerous high-quality randomized controlled trials to accelerate the rate of recovery and increase the proportion of patients achieving complete recovery.[5] Conversely, despite the proposed viral cause of Bell's palsy, antiviral agents have shown a relatively weak and ultimately inconclusive effect on outcomes in clinical trials.[6-9] In 2012, the American Academy of Neurology recommended shared decision-making regarding antiviral agents for Bell's palsy in

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light of the inability to rule out a modest effect based on the available evidence at that time.[10]

Bell's palsy with initial severe symptoms (defined as grade V or VI on the House-Brackmann grading scale) carries a worse prognosis than milder forms of the disease, with up to 50% of patients failing to achieve complete recovery beyond 9 months even with corticosteroids.[11,12] Some authors have advocated for the use of antiviral agents in severe Bell's palsy at baseline because of the disappointing recovery rate with corticosteroids alone in such patients.[13,14] Thus, we conducted a systematic review with meta-analysis to evaluate the efficacy of antiviral agents with or without corticosteroids on complete recovery of Bell's palsy, with a priori subgroup analysis based on severity of disease.

CLINICAL SIGNIFICANCE

- Antiviral agents did not increase the likelihood of complete recovery, regardless of baseline symptom severity.
- Effects of antiviral agents on "satisfactory recovery" should be interpreted in the context of variability in outcome scale, threshold for achieving this outcome, and issues with biases in performance, detection, and selective outcome reporting.

LITERATURE REVIEW

We searched Cochrane Central Register of Controlled Trials (CENTRAL), Embase, MEDLINE, and International Pharmaceutical Abstracts up to November 1, 2014, for relevant trials in the English language. The following search terms were combined: *Bell's palsy, facial nerve, cranial nerve, palsy, paralysis, paresis, antiviral, aciclovir, acyclovir, famciclovir, valaciclovir,* and *valacyclovir*. The World Health Organization International Clinical Trials Registry Platform was searched on November 1, 2014, for unpublished or ongoing trials. We also screened the bibliographies of relevant articles for additional studies.

Two reviewers (RDT and KJW) screened all studies by title or abstract for those requiring further retrieval and reviewed these studies for eligibility. We included all randomized or quasi-randomized controlled trials comparing the use of antiviral agents with placebo or no antiviral therapy in individuals with Bell's palsy. Trials were eligible irrespective of background therapy, such as corticosteroids, as long as there was equal opportunity to receive these cointerventions in both groups. We excluded trials reported only as abstracts. One review author (RDT) extracted and collected relevant data in an electronic spreadsheet data extraction form. Both reviewers (RDT and KJW) independently performed a risk of bias assessment using methods described in the *Cochrane Handbook*.[15] Briefly, for the domains of selection, performance, detection, attrition, reporting, and miscellaneous biases, we rated trials at low, high, or unclear risk.

Our primary outcome for meta-analysis was complete recovery of facial palsy, denoted as grade I on the House-Brackmann grading scale, or as defined by any comparable alternative scale, such as the Sunnybrook facial nerve rating scale and Yanagihara facial nerve grading scale.[16] Our secondary outcome was satisfactory recovery according to study investigators, for which we combined the primary outcome as defined by the original study report, similar to what has been done in previous meta-analyses on this topic.[9] Study authors were contacted for any methodology clarifications or outcome data missing from the available reports.

STATISTICAL ANALYSIS

All statistical analyses were performed using Review Manager version 5.2. We present dichotomous data as relative risk (RR) with 95% confidence intervals (CIs). Whenever possible, we present data according to the intention-to-treat population. Patients lost to follow-up before the end of trial were assumed not to have achieved complete recovery. Where insufficient data were reported in original trials for intention-to-treat analysis, we used the per-protocol population as presented in the study report.

We assessed for statistical heterogeneity with visual inspection of the forest plot and calculation of the I^2 statistic. We defined I^2 <25% as low heterogeneity, 25% to 50% as moderate heterogeneity, and >50% as large heterogeneity. When meta-analysis was possible because of acceptable clinical and methodological heterogeneity, we report the

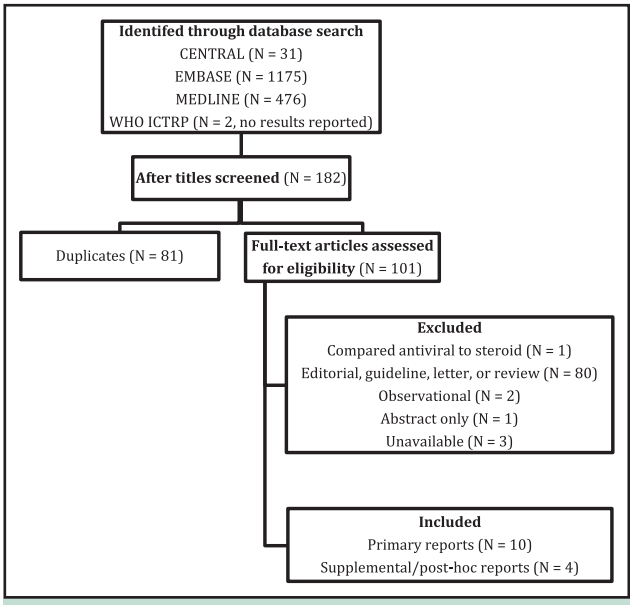

Figure 1 PRISMA flow diagram for identified studies. CENTRAL = Cochrane Central Register of Controlled Trials; WHO ICTRP = World Health Organization International Clinical Trials Registry Platform.