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17.A. Systemic steroids alone versus placebo: Impact on recovery to normal or near-normal function

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METHODS

A computerized Ovid search of MEDLINE 1966–2005 was performed. The terms “facial paralysis” and “Bell’s palsy” were exploded, resulting in 1043 articles. These results were limited to English language and therapy-related subheadings yielding 293 trials, which were reviewed. Trials evaluating steroid treatment were reviewed to identify those that met inclusion criteria consisting of: 1) patients with Bell’s palsy (idiopathic facial nerve paralysis), 2) intervention with systemic steroids, 3) treatment within 10 days of onset, 4) outcome measures consisting of normal motor facial recovery [House-Brackmann (HB) or similar scale]. Exclusion criteria included: 1) trials including multiple etiologies of facial paralysis, 2) multiple interventions, 3) treatment initiated after 10 days of onset. The references of these articles were then reviewed and manually cross-checked to ensure all applicable literature was reviewed. This search yielded five randomized controlled trials (RCTs) [1–5] and four systematic reviews [6–9] that met inclusion criteria.

RESULTS

Outcome Measures. The primary outcome measures included: 1) recovery of facial motor function to normal/near normal, and 2) incidence of complications of steroid treatment. The most frequently used assessment tool for facial recovery is the HB system [10]. In this system, a HB grade I–II represents normal or near-normal function, or good recovery. A more detailed analysis of facial recovery was not possible because of trial variations and the lack of stratification. Only one trial [2] stratified recovery based on severity of impairment. Recovery is better in incomplete paralysis; 94% of patients with paresis have full recovery compared with 61% of patients with complete paralysis [11]. Other outcome measures including time to recovery, synkinesis, or crocodile tears (gustolacrimal reflex) were not assessed.

Potential Confounders. Three possible confounding factors between studies include diagnostic certainty, steroid dose, and facial assessment. Bell’s palsy is a diagnosis of exclusion. It is possible that other etiologies of facial paralysis may have been included in the study population; however, all RCTs have sufficient exclusion criteria that make this unlikely. The dose of steroids administered varied widely among the RCTs. One trial administered a total prednisone equivalent dose of 200 mg [1], another 410 mg [2], and a third 4500 mg [5]. Lastly, the assessment method of facial motor recovery varied among trials. In one trial, the method of motor recovery assessment was based on the clinical examination and considered complete or partial, but not otherwise detailed [1] whereas another divided patients into complete return, fair return, and poor return [2]. Despite these variations, it seems that a “successful” outcome (meaning recovery to normal) for the RCTs was comparable.

Study Designs. All five RCTs reported effective randomization of the study population. Two trials were double blinded [2, 5] and one single blinded [1]. Two trials were of lesser quality [3, 4] because they were not blinded and they did not have a placebo-treated control group. The follow-up period was adequate for four trials (6 months minimum), but only 2–3 months for the last [1]. Trial size was small for the majority of RCTs. No trial calculated a priori sample size. Only one of the trials [2] provided outcome stratification based on severity of facial dysfunction. Details of the methods and outcomes of the RCTs are listed in the table “Systemic steroids versus placebo, randomized controlled trials.”

The four meta-analyses used typical methods for analyzing data, assessing homogeneity, and pooling results. Review of the meta-analyses demonstrated mild methodology differences, which produced variations in trial inclusion and exclusion. One systematic review [8] included a trial that had unclear methodology [12] and two systematic reviews [6, 8] included an RCT with 71% completion rate [13]. In the fourth review [7], the authors limited the analysis to the treatment effect of steroids on patients with complete paralysis. This review included one RCT with 71% completion rate [13] and one non-randomized prospective trial [14].

Highest Level of Evidence and Study Results. Five trials were evaluated as level 1 trials, but two were considered lesser quality because of potential bias from lack of blinding [3, 4]. No single RCT demonstrated a statistically significant improvement in recovery with steroid treatment compared with the control group; furthermore, none was adequately powered. No trial demonstrated any significant adverse effects resulting from
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treatment. One trial demonstrated a favorable difference with treatment in the clinical evolution represented by an early worsening of facial strength in the control group [5]. A statistically significant difference in recovery was present at 1 month; however, at 12 months no difference existed. Because the power of individual trials is in question, these studies may fail to uncover any difference that may truly exist.

Four meta-analyses from systematic reviews were assessed. Three of the reviews included all grades of facial impairment in their analysis [6, 8, 9]. One found no benefit [9] and two [6, 8] found evidence of a possible positive treatment effect. The fourth review assessed only patients with complete paralysis and demonstrated a possible benefit with treatment [7]. Each meta-analysis and the trials included in them are listed in the table “Systemic steroids versus placebo, meta-analyses.” The variations in their inclusion criteria, as well as the selection of lower quality trials in the three reviews showing possible benefit, limits the collective interpretation of their findings.

**Applicability.** Based on the inclusion and exclusion criteria of these trials, the population studied likely consisted of patients with Bell's palsy or idiopathic facial nerve paralysis. Bell's palsy has an acute onset of unilateral lower motor neuron facial motor paresis or paralysis not associated with other otologic, neurologic, traumatic, or systemic disease. The results of this review should be applied to patients with Bell's palsy.

**Morbidity/Complications.** No trial indicated significant complications associated with steroid use. The only quantified side effect of steroids was temporary sleep disturbance noted in 3 of 30 patients [5].

**CLINICAL SIGNIFICANCE AND FUTURE RESEARCH**

Five RCTs evaluated the effect of steroid treatment for Bell's palsy by comparing systemic steroids against placebo or no treatment. No RCT demonstrated a statistically significant treatment benefit in facial motor recovery. Four systematic reviews with meta-analyses have been performed. Three suggest a possible benefit, and one does not. The four reviews are inconsistent and demonstrate methodologic variation. Although some evidence suggests steroids may be effective, the collective available evidence is moderate and lacks uniformity. A definitive treatment effect remains unproven.

Additional research is necessary to determine the efficacy of steroids. Trial design will require adequate sample size and stratification. Working from the available natural history data, if a 10% difference in the rate of complete recovery is expected, each control and treatment arm will need 310 patients (Fisher’s exact test, two-tailed analyses, with significance level of 0.05 and power of 80%). If a larger effect is expected, i.e., 20%, then the numbers in each arm decrease to 71 (Fisher’s exact test, two-tailed analyses, with significance level of 0.05 and power of 80%). Future studies need clear stratification based on degree of pretreatment dysfunction, or at the very least stratification into incomplete and complete categories.