A randomised controlled trial of the use of aciclovir and/or prednisolone for the early treatment of Bell's palsy: the BELLS study

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Executive summary

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Executive summary

The cause of Bell's palsy is unknown although vascular, inflammatory and viral aetiologies have been suggested. There are 11 to 40 cases per 100,000 people each year, most commonly in the age range 30–45. Up to 30% of patients have continuing facial disfigurement, psychological difficulties and sometimes facial pain. Treatment has been controversial and highly variable.

Methods

We conducted a 2 × 2 factorial randomised double-blind trial. The primary outcome was recovery of facial function assessed by the House–Brackmann scale. Secondary outcomes included health status, pain, self-perceived appearance and cost-effectiveness.

Patients

We recruited adults (aged 16 years or older) with unilateral facial nerve weakness of no identifiable cause presenting to primary care, the accident and emergency department (A&E) or NHS24 within 72 hours of symptom onset.

Study design

The study was conducted throughout mainland Scotland with referrals mainly from general practice to 17 hospital trial sites. An otolaryngologist confirmed eligibility, and patients were randomly assigned to treatment by an independent, secure, automated telephone service using a permuted block randomisation technique with block sizes of four or eight, and no stratification.

Patients were randomised into four groups to receive active preparations or placebo for 10 days: (1) prednisolone (50 mg per day, 2 × 25-mg capsules) and aciclovir (2000 mg per day, 5 × 400-mg capsules); (2) prednisolone and placebo (lactose, indistinguishable); (3) aciclovir and placebo; and (4) placebo and placebo. The patient took the first dose before leaving hospital, and the remaining doses at home over the next 10 days.

A researcher visited patients at their home or their doctor's surgery within the next 3–5 days to complete the baseline assessments, record any adverse events and arrange follow-up. Repeat patient visits to assess recovery occurred at 3 months and, if recovery was incomplete at this visit, again at 9 months.

Outcome measurements

The primary outcome measure was the House–Brackmann grading system for facial nerve function. It assigns patients to six categories (I to VI) on the basis of their degree of facial function: grade I indicates normal function. Assessment was based on digital photographic images in four standard portrait poses, graded independently by three experts masked to treatment allocation.

Secondary outcomes were quality of life (QoL) measured by the Health Utilities Index Mark 3 (HUI3), the Derriford Appearance Scale (DAS59), the Brief Pain Inventory (BPI) and incremental cost per cure and incremental cost per quality-adjusted life-year (QALY), with QALYs based on patient responses to HUI3.

Subgroup analyses included outcome dependent on delay between onset of symptoms and commencement of treatment, and on severity at onset; there was an additional analysis of concordance between expert assessors.

Safety evaluation and compliance

Medication use was reviewed at the first visit and during two subsequent telephone calls. Adverse events were reviewed then and at subsequent visits.

Statistical analysis

Primary and secondary analyses were based on intention-to-treat. Subgroup and additional analyses were made post hoc.

Complete recovery (House–Brackmann grade I) at 3 and 9 months was compared initially between those who did and did not receive prednisolone

using a two-sided Fisher's exact test. This was repeated for aciclovir. We tested the data for any interaction between the groups prior to these tests. Pre-specified secondary analyses compared HUI3, DAS59 and BPI scores. Our analysis was adjusted for all baseline characteristics measured: age, gender, interval between onset and receiving treatment, and scores on the House–Brackmann scale, HUI3, DAS59 and BPI.

Decision economic modelling was used to compare cost-effectiveness. The time horizon of the model was 9 months, and outcomes were the cumulative proportion of cases cured, mean QALYs gained and mean costs. Costs were reported in 2006–7 pounds sterling. NHS costs were based on costs of treatments and costs of subsequent health services collected from general practice notes. QALYs were based on responses to HUI3 with the assumption that the 3-month score of those cured at 3 months was carried forward to the 9-month assessment. Two-arm models were developed for prednisolone versus no prednisolone and aciclovir versus no aciclovir comparisons, respectively. A further four-arm model was developed to compare prednisolone alone, aciclovir alone, aciclovir and prednisolone, and no treatment (placebo) strategies.

Power calculation

A difference in complete recovery of 10% or more was considered to be clinically meaningful. Randomising 240 patients per treatment (a total of 480) would provide 80% power to detect a difference of the order of 12% at the 5% level. Since the study design was factorial the power is the same for each pair-wise comparison of treatments.

Results

Study population

Of 752 patients referred, 132 were ineligible and 551 of the 620 patients eligible were randomised. Fifty-five patients dropped out of the study before a final determination of their House–Brackmann status. Thus final outcomes were available for 496 patients.

The study was balanced for gender; the mean age of patients was 44 years; and the degree of initial facial paralysis was moderate to severe. One half of patients initiated treatment within 24 hours of onset of symptoms, one-third within 24–48 hours and the remainder within 48–72 hours.

Of 496 completed patients, 357 had recovered by 3 months. A further 80 had recovered at 9 months, leaving 59 with a residual facial nerve deficit.

There was no significant prednisolone–aciclovir interaction at 3 months or at 9 months ($p = 0.32$, $p = 0.72$ respectively).

There were significant differences in complete recovery at 3 months between the prednisolone comparison groups (83.0% for prednisolone, 63.6% for no prednisolone, a difference of + 19.4%; 95% confidence interval (CI): + 11.7% to + 27.1%, $p < 0.001$). The number needed to treat (NNT) in order to achieve one additional complete recovery was 6 (95% CI: 4 to 9). There was no significant difference between the aciclovir comparison groups (71.2% for aciclovir and 75.7% for no aciclovir, a difference of –4.5% (95% CI: –12.4% to + 3.3%, $p = 0.30$, adjusted 0.50). Nine-month assessments of patients recovered were 94.4% for prednisolone compared with 81.6% for no prednisolone, a difference of + 12.8% (95% CI: + 7.2% to + 18.4%, $p < 0.001$); the NNT is 8 (95% CI: 6 to 14). Proportions recovered at 9 months were 85.4% for aciclovir and 90.8% for no aciclovir, a difference of –5.3% (95% CI: –11.0% to + 0.3%, $p = 0.07$, adjusted 0.10).

The formally correct analysis for the 2×2 factorial design is to follow two independent (two-arm) comparisons, being (1) study outcomes for those patients treated with prednisolone, and those not; and (2) study outcomes for those patients treated with aciclovir, and those not.

However, it is helpful for clinicians to be provided with a single simple comparison of the four treatment options available to trial participants (prednisolone with aciclovir, prednisolone alone, aciclovir alone, and placebo) supported by an expression of prednisolone–aciclovir interaction. This four-arm analysis does not provide the most powerful scrutiny of the data, but it does provide an easily interpreted assessment of treatment options. For this study, the results of the four-arm analysis are included to support and confirm those of the two-arm analyses.

When we explored outcome differences by individual treatment (the four-arm model) there were significant differences at 3 and 9 months. At 3 months the recovery rate was 86.3% in the prednisolone treatment group, 79.7% in the aciclovir–prednisolone group, 64.7% in the placebo

group and 62.5% in the aciclovir group. At 9 months the recovery rates were respectively 96.1%, 92.7%, 85.3% and 78.1%. The increase in recovery rate conferred by the addition of the treatment prednisolone (both for prednisolone over placebo and for aciclovir–prednisiolone over aciclovir) is highly statistically significant ($p < 0.001$).

There were no significant differences in our secondary measures apart from HUI3 at 9 months in those treated with prednisolone.

From the two-arm model, the mean cost of prednisolone was £232 and the mean cost of no prednisolone was £248. Prednisolone was more effective in terms of cure and provided on average slightly more QALYs (0.718 versus 0.717). A probabilistic analysis suggested that prednisolone was likely (over 70%) to be considered cost-effective at a £20,000 or £30,000 cost per QALY threshold. The aciclovir versus no aciclovir two-arm model showed that aciclovir was on average more costly than no aciclovir (£253 versus £246) and not likely to be more effective in terms of cure and QALYs (0.717 versus 0.718). It was unlikely to be considered cost-effective at a £20,000 or £30,000 cost per QALY threshold (15% and 18%, respectively). The four-arm model showed prednisolone alone to be more effective and less costly than the other strategies (over 70% probability of being cost-effective for £20,000 and £30,000 thresholds).

Adverse events included the expected range of minor side effects with the drugs used (nausea, dyspepsia, constipation, rash). There were three deaths during follow-up (two in the placebo-placebo group and one in the aciclovir-placebo group) all unrelated to treatment. No serious adverse events were reported. No suspected unexpected serious adverse reactions were reported. There was no instance of a requirement for unblinding of patients or their practitioners or of study personnel. An analysis of the frequency of adverse events showed no differences whatsoever between the treatment groups.

Discussion

This is the largest randomised controlled trial of the effectiveness of treatment for Bell's palsy. We have confirmed the generally favourable outcome for Bell's palsy, with 63% of patients recovered with no treatment at 3 months, increasing to 85% after 9 months. Treatment within 72 hours of onset with prednisolone increased these rates to 83% and 94% respectively. Aciclovir alone produced no benefit over placebo and there was no benefit from its addition to prednisolone.

This study provided robust evidence to support the early use of oral prednisolone in Bell's palsy as an effective treatment which may be considered cost-effective by NHS commissioners. Most patients recover fully without any treatment. Therefore, for some clinicians and their patients, the option of offering 'no treatment' may remain an appropriate strategy, but they can now have a more fully informed discussion regarding the use of steroids. Treatment with aciclovir, either alone or with steroids, had no effect on outcome.

Trial registration

This trial is registered as ISRCTN71548196.

Publication

Sullivan FM, Swan IRC, Donnan PT, Morrison JM, Smith BH, McKinstry B, *et al*. A randomised controlled trial of the use of aciclovir and/or prednisolone for the early treatment of Bell's palsy: the BELLS study. *Health Technol Assess* 2009;**13**(47).

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The research reported in this issue of the journal was commissioned by the HTA programme as project number 02/09/04. The contractual start date was in November 2003. The draft report began editorial review in September 2007 and was accepted for publication in March 2009. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA programme or the Department of Health.

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