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

FM Sullivan,¹* IRC Swan,² PT Donnan,³ JM Morrison,⁴ BH Smith,⁵ B McKinstry,⁶ RJ Davenport,⁷ LD Vale,⁸,⁹ JE Clarkson,¹⁰ R Hernández,⁹ K Stewart,¹¹ V Hammersley,⁶ S Hayavi,⁴ A McAteer,⁵ D Gray⁵ and F Daly³

¹Scottish School of Primary Care, University of Dundee, UK
²Department of Otolaryngology, University of Glasgow, UK
³Community Health Sciences, University of Dundee, UK
⁴Division of Community Based Sciences, University of Glasgow, UK
⁵Centre of Academic Primary Care, University of Aberdeen, UK
⁶Community Health Sciences, University of Edinburgh, UK
⁷Department of Clinical Neurosciences, University of Edinburgh, UK
⁸Health Services Research Unit, University of Aberdeen, UK
⁹Health Economics Research Unit, University of Aberdeen, UK
¹⁰Dental Health Services Research Unit, University of Dundee, UK
¹¹St John’s Hospital, Livingston, UK

*Corresponding author

Executive summary

Health Technology Assessment 2009; Vol. 13: No. 47
DOI: 10.3310/hta13470
Executive summary: Aciclovir and/or prednisolone for the early treatment of Bell’s palsy: the BELLS study

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**

How to obtain copies of this and other HTA programme reports

An electronic version of this publication, in Adobe Acrobat format, is available for downloading free of charge for personal use from the HTA website (www.hta.ac.uk). A fully searchable CD-ROM is also available (see below).

Printed copies of HTA monographs cost £20 each (post and packing free in the UK) to both public and private sector purchasers from our Despatch Agents.

Non-UK purchasers will have to pay a small fee for post and packing. For European countries the cost is £2 per monograph and for the rest of the world £3 per monograph.

You can order HTA monographs from our Despatch Agents:
– fax (with credit card or official purchase order)
– post (with credit card or official purchase order or cheque)
– phone during office hours (credit card only).

Additionally the HTA website allows you either to pay securely by credit card or to print out your order and then post or fax it.

Contact details are as follows:

HTA Despatch
Email: orders@hta.ac.uk
c/o Direct Mail Works Ltd
Tel: 02392 492 000
4 Oakwood Business Centre
Fax: 02392 478 555
Downley, HAVANT PO9 2NP, UK
Fax from outside the UK: +44 2392 478 555

NHS libraries can subscribe free of charge. Public libraries can subscribe at a very reduced cost of £100 for each volume (normally comprising 30–40 titles). The commercial subscription rate is £300 per volume. Please see our website for details. Subscriptions can be purchased only for the current or forthcoming volume.

Payment methods

Paying by cheque
If you pay by cheque, the cheque must be in pounds sterling, made payable to Direct Mail Works Ltd and drawn on a bank with a UK address.

Paying by credit card
The following cards are accepted by phone, fax, post or via the website ordering pages: Delta, Eurocard, Mastercard, Solo, Switch and Visa. We advise against sending credit card details in a plain email.

Paying by official purchase order
You can post or fax these, but they must be from public bodies (i.e. NHS or universities) within the UK. We cannot at present accept purchase orders from commercial companies or from outside the UK.

How do I get a copy of HTA on CD?

Please use the form on the HTA website (www.hta.ac.uk/htacd.htm). Or contact Direct Mail Works (see contact details above) by email, post, fax or phone. HTA on CD is currently free of charge worldwide.

The website also provides information about the HTA programme and lists the membership of the various committees.
NIHR Health Technology Assessment programme

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. ‘Health technologies’ are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the ‘National Knowledge Service’.

The HTA programme is needs led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, from the public and consumer groups and from professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA programme then commissions the research by competitive tender.

Second, the HTA programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Third, through its Technology Assessment Report (TAR) call-off contract, the HTA programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

The final reports from HTA projects are peer reviewed by a number of independent expert referees before publication in the widely read journal series Health Technology Assessment.

Criteria for inclusion in the HTA journal series

Reports are published in the HTA journal series if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in Health Technology Assessment are termed ‘systematic’ when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

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.

Editor-in-Chief: Professor Tom Walley CBE
Series Editors: Dr Aileen Clarke, Professor Chris Hyde, Dr John Powell,
Dr Rob Riemsmma and Professor Ken Stein

ISSN 1366-5278
© 2009 Queen’s Printer and Controller of HMSO
This monograph may be freely reproduced for the purposes of private research and study and may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising.
Applications for commercial reproduction should be addressed to: NETSCC, Health Technology Assessment, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.
Published by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk), on behalf of NETSCC, HTA.
Printed on acid-free paper in the UK by Henry Ling Ltd, The Dorset Press, Dorchester.