

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Sullivan FM, Swan IRC, Donnan PT, et al. Early treatment with prednisolone or acyclovir in Bell's palsy. *N Engl J Med* 2007;357:1598-607.

0 Project Title

Bell's palsy: Early aciclovir and/or prednisolone in Scotland
"BELLS"
A multicentre factorial trial of the early administration of steroids
and/or antivirals for Bell's Palsy

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2 Planned investigation

(a) Research objectives

1. To describe the resolution of neurological deficit and cosmetic, psychological and functional recovery in each of four groups of patients: those treated with prednisolone, aciclovir, both, or neither.
2. To determine which group of patients have the greatest reduction in neurological disability scores on the House and Brackmann grading system at 3 and 9 months after randomisation.
3. To compare self-reported health status (including assessments of pain) at 3 and 9 months after randomisation.
4. To compare the incremental cost per neurological deficit resolved and incremental cost per QALY in the study groups.

(b) Existing research

Bell's palsy is an acute unilateral paralysis of the facial nerve first described by the Scottish surgeon Sir Charles Bell (1774–1842)^[1]. Its cause is unknown but animal studies have suggested the possibility that reactivation of herpes viruses may be responsible for demyelination^[2,3]. It affects 25–35 people per 100,000 in the population per annum, most commonly in the age group 30–45^[4]. The condition presents disproportionately amongst pregnant women and people who have diabetes, influenza, a cold, or some other upper respiratory ailment. On average every year a General Practitioner will see one or two patients who have developed the condition. A recent UK study using the general practice research database (GPRD) showed that 36% of patients were treated with oral steroids and 19% were referred to hospital^[5]. Although most recover well, 30% of patients have a poor recovery with continuing facial disfigurement, psychological difficulties and sometimes facial pain (though the presence and course of pain is unclear from current knowledge)^[6]. In the absence of an established aetiology, treatment continues to be based upon the established pathophysiology: swelling and entrapment of the nerve.

Two recent Cochrane reviews concerning the treatment of Bell's palsy have examined the effectiveness of oral prednisolone and aciclovir^[7,8]. These found that insufficient data exist to conclude that either or both therapies are effective. Many of the studies included in the reviews either failed to randomise patients or, when correctly randomised, were erroneously interpreted in a favourable light^[9,10]. In addition high dose steroid therapy has numerous potential side effects including peptic ulceration hypertension and confusional states. Antiviral therapy is expensive and should be reserved for circumstances where definite benefits are likely to be obtained. Current recommendations suggest that aciclovir needs to be started within 48 hours, though more recent studies of viral replication in patients with Bell's palsy suggest that this might be extended^[11].

(c) Research methods

Design

A randomised 2 × 2 factorial design to assess whether prednisolone and/or aciclovir commenced within the first 72 hours of onset of Bell's palsy results in the same level of disability and pain after 9 months as treatment with placebo^[12].

Recruitment

In order to establish whether aciclovir or steroids are an effective therapy, initial treatment needs to be given in the first 72 hours of the onset of symptoms.

Because Bell's palsy is a comparatively rare condition only a coordinated approach across a large population will provide sufficient numbers to allow a satisfactory power to be achieved in this study. Our pilot work with the Scottish research networks led to almost 100% participation rates. We intend to approach every medical and dental practice in Scotland and to enhance recruitment through existing networks of influence which will encourage referral of a higher proportion of cases than would be expected from more anonymised exhortation. The Scottish School of Primary Care is able to coordinate recruitment through several networks which overlap in their membership:

- general medical practices already associated with existing primary care research networks, $n = 273$;
- networks of practices already involved in undergraduate and postgraduate teaching, $n = 482$;
- general medical practice out of hours co-operatives, $n = 89$;
- NHS24 which will cover most of Scotland by the time the study commences (we have arranged to amend their referral scripts and train their nurses);
- the Medical Research Council General Practice Research Framework (MRC GPRF), $n = 90$;
- Scottish Dental Practice Based Research Network dental practices, $n = 270$;
- A&E departments across Scotland.

We will also advertise the study with articles in the free, weekly medical press. Clinicians throughout Scotland will be reminded on a quarterly basis to recruit into the study any patients who present with Bell's palsy. As soon as a suitable patient presents to the GMP, GDP, A&E or Out of Hours Co-op clinician within 72 hours of onset, they will telephone the nearest ENT unit and arrange with the ENT surgeon on call for the patient to be seen immediately. When the patient is seen by the ENT surgeon the criteria for study entry will be confirmed, consent will be obtained and the randomisation centre will be contacted. All consultant ENT surgeons in Scotland have been contacted and with one exception have agreed to take part in the study. We will ensure that randomisation is secure by telephone randomisation which will be centrally controlled by the Health Services Research Unit (HSRU) in Aberdeen^[13]. When an eligible patient has given consent to participation, the doctor will telephone the computerised randomisation service, via a hot-key, and receive instructions about which numbered pack is to be supplied. The on-call ENT Registrar will immediately supply the medication from the supplies available in the unit.

The HSRU computer will notify the study coordinator of the patient's study details by an immediate email. This mechanism has been extensively used in multicentre trials before. The coordinator will arrange for the nearest research assistant to visit within the next three days to complete the baseline assessments and arrange follow-up.

(d) Planned interventions

Patients will be randomised to receive two identical preparations for 10 days simultaneously, creating four patient groups: (1) prednisolone (50mg per day) and placebo, (2) aciclovir (2000 mg per day) and placebo, (3) prednisolone and aciclovir, and (4) placebo and placebo. Each patient will be supplied with two bottles of medication (marked by a code).

(e) Planned inclusion and exclusion criteria

Inclusion criteria:

- Adults (16 or older) with unilateral facial nerve weakness of no identifiable cause seen within 72 hours of the onset of weakness

Exclusion criteria:

- Pregnancy
- Uncontrolled diabetes (HbA1c > 8%)
- Peptic ulcer disease
- Suppurative otitis media
- Herpes zoster
- Multiple sclerosis
- Sarcoidosis and other rarer conditions
- Inability to give informed consent

and two further exclusions identified during the processes of MREC application

- Breast-feeding
- Patients with systemic infection

(f) Ethical arrangements

Risks and anticipated benefits

- No adverse events have been reported for the interventions in this study when administered in similar settings. There is a theoretical risk of adverse events from the prednisolone which should be greatly reduced by adherence to the exclusion criteria above.
- The potential benefits include faster and/or more complete resolution of neurological deficit and cosmetic, psychological and functional recovery.

Informed consent

- will be obtained before entry to the study.

Actions where informed consent is not possible

- Unless the person is able to provide informed consent they will not enter the study.

Proposed time period for retention of documentation

- At least 20 years in electronic format in which all study documentation will be retained. (“Personal Information in Medical Research”, MRC 2000, 2003; also “MRC Population Data Archiving and Access Project, Consultants’ Report, Draft 2”, MRC 2002.)

(g) Sample size

This has been calculated using the primary endpoint of incomplete recovery of facial motor function (House and Brackmann Grade III or greater) nine months after randomisation.

Design

2 × 2 factorial randomized controlled trial with the following treatments:

1)	Aciclovir	(A)
2)	Steroids	(B)
3)	Aciclovir + Steroids	(AB)
4)	Placebo	(O)

Main effect of Aciclovir = $\frac{1}{2} (A + AB) - \frac{1}{2} (B + O)$

Note that this assumes A and B have independent effects and do not interact.

The literature is sparse about likely effect sizes. One systematic review suggests a Relative Risk (of incomplete recovery) $RR = 0.86$ (95% CI: 0.47 to 1.59) or 22% on steroids compared with 26% in the control group. Other results are few and contradictory; Adour suggests 24% on steroids compared with 7.5% on aciclovir plus steroids, while De Diego suggests 6.4% on steroids and 22% on aciclovir alone^[14,15]. Hence the literature gives effect sizes from 4% to 17%. We regard a difference in incomplete recovery of 10% or more to be clinically meaningful and so, in the table below, sample sizes are given for differences in percentage with incomplete recovery from 10% to 15%.

Table

Sample size required to show various differences in % with incomplete recovery at 9 months with 80% power at the 5% significance level (two-sided)

Trt 1	Trt 2				
% incomplete recovery	% incomplete recovery	Difference	Relative Risk	n per group	Total
22%	32%	10%	0.69	328	656
22%	34%	12%	0.65	235	470
22%	37%	15%	0.59	157	314

If we simultaneously randomize approximately 240 patients per treatment (a total of 480) this would allow detection of differences of the order of 12%. Since the study design is factorial the power is the same for each pair-wise comparison of treatments (assuming no interaction). Note that we will also treat the House-Brackmann scale as ordinal as well as binary which serves to increase power.

The ability to detect an interaction if it exists is an attractive feature of the factorial design. If there is a significant interaction the overall efficiency of the design is maintained as long as the two drugs do not act antagonistically to cancel each other out, which is unlikely. With an interaction it is still possible to assess each drug separately, albeit with reduced power (72% instead of 80%) for the effect size (12%) or alternatively to detect effect sizes > 15% with the same power.

For clarity of numbers: we will seek to recruit 720 patients commencing treatment within 72 hours after onset, of whom 480 have commenced treatment within 48 hours after onset.

The incidence of Bell's palsy in Scottish adults is 33 per 100,000 per year and with an eligible population of 4.3 million for Scotland the expected number per year in Scotland would be 1,419 after one year, and 2,129 over 18 months^[16]. We have piloted a notification process for early cases in 4 primary care research networks covering 1.4 million patients in Scotland. During 1 month of observation 74 cases of Bell's palsy were seen and 35 of these within 48 hours. Based on this, we believe we are able to recruit approximately 1/3rd of those who develop Bell's palsy within 48 hours (710) and 50% by 72 hours and that 70% (a conservative estimate) will attend for review at 9 months. From Adour's work and others we believe that at least 50% of patients will have fully recovered by 3 months, so a smaller number will require to be visited at 9 months^[17]. We will require 18 months of a recruitment period to achieve 480 completed examinations at 9 months. If we collaborate with another coordinating centre of an equivalent size, this could be reduced to 9 months.

For the analyses, results will be stratified and analysed according to whether treatment started within 48 hours.

(h) Statistical analyses

Reporting will adhere to revised CONSORT criteria^[18].

The baseline characteristics in each treatment group will be described. The following will be used to adjust the results: severity at initial presentation, age and gender. The main outcome of incomplete recovery (House-Brackmann \geq III) will be compared between treatment groups using chi-squared tests and also tests for linear trends as the nerve function scale is ordinal. We will use logistic regression to adjust for the prespecified confounding factors above. All analyses will be based on an intention-to-treat principle. Similar methods will be used for the ordinal scale for pain. The mean or median HUI score will be compared using t-tests or Mann-Whitney tests, depending on the distributions found. Two-sided tests will be implemented throughout, using SPSS for data analysis.

Generally, sub-group analyses should be avoided in randomized controlled trials, or at least specified before data collection. It is intended to carry out formal tests of interaction between treatment and severity of House-Brackmann scale to assess whether treatment effects are greater in those most severely affected. The results of such analyses will be treated with caution and as hypothesis-generating^[19].

(i) Outcome measures

Following the email alert from HSRU to the research coordinator, patients will then be seen at their GP surgery or at home within three days by the research assistants for more detailed assessment. At this first post-randomisation visit the degree of facial nerve denervation will be recorded by a digital camera and the other study instruments administered. Patients will be reassessed by questionnaire and digital camera at 3 and 9 months post-randomisation. We will capture facial appearances in digital images in standard positions (at rest, forced smile, bared teeth and buried eyelashes). These will be assessed blindly by a panel of 3 experts in otorhinolaryngology, neurology and plastic surgery.

The key outcome measure to be used in research objectives 1, 2 and 4 is the House-Brackmann grading system for facial nerve function shown below^[20]. It has been validated against electrophysiological studies.

Grade	Definition
I	<i>Normal symmetrical function in all areas</i>
II	<i>Slight weakness noticeable only on close inspection Complete eye closure with minimal effort Slight asymmetry of smile with maximal effort Synkinesis barely noticeable, contracture, or spasm absent</i>
III	<i>Obvious weakness, but not disfiguring May not be able to lift eyebrow Complete eye closure and strong but asymmetrical mouth movement with maximal effort Obvious, but not disfiguring synkinesis, mass movement or spasm</i>
IV	<i>Obvious disfiguring weakness Inability to lift brow Incomplete eye closure and asymmetry of mouth with maximal effort Severe synkinesis, mass movement, spasm</i>
V	<i>Motion barely perceptible Incomplete eye closure, slight movement corner mouth Synkinesis, contracture, and spasm usually absent</i>
VI	<i>No movement, loss of tone, no synkinesis, contracture, or spasm</i>

The Health Utilities Index version 3 (HUI3) will be used to assess research objectives 1 and 3. The HUI3 represents a global assessment of overall health status. It has eight dimensions: vision; hearing; speech; ambulation; dexterity; emotion; cognition and pain. For details see www.fhs.mcmaster.ca/hug/. It is designed for use in clinical practice and research, health policy evaluations, and general population surveys. It is constructed for self-administration by persons 14 years of age and older, and for administration by a trained interviewer in person or by telephone. It takes about 5 to 10 minutes to administer.

Pain measures will be used to achieve research objective 3.

The presence and duration of facial pain will be determined by a simple set of screening questions, based on a validated chronic pain case definition questionnaire^[21]. The global severity of any pain will be assessed using a visual analogue scale, and the Chronic Pain Grade, a simple validated measure of intensity and pain-related disability, providing classification into four hierarchical grades of severity (Grade I low-intensity-low disability; Grade IV high disability-severely limiting)^[22,23].

Measure	Baseline	3 months	9 months
House-Brackman	720	576	138
Health Utilities Index	720	576	504
Chronic pain grade	720	576	504
Costs	720	576	504

(j) Economic evaluation

The cost-effectiveness of early treatment can be evaluated by calculating the incremental cost per additional neurological deficit resolved. However, it is not clear what incremental cost per additional deficit resolved decision makers should consider good or poor value for money. The results of the trial will be rendered more informative by also translating the resolution of a neurological deficit into a quality-adjusted life-year equivalent by estimating the duration of the effect and the impact on the patient's quality of life. This will be achieved by using the Health Utilities Index to measure quality of life at baseline, three months and nine months^[24]. Unresolved deficits will have resource implications for the NHS and thus it is appropriate to subtract any savings that result from successful treatment from the cost of that treatment. These savings will be estimated by comparing the use of health care resources by those with resolved and unresolved deficits.

We will obtain permission from participating patients to review their primary care records and extract data on treatments in practice and elsewhere. Other variables to be collected are patient demographic data, blood pressure, current drug therapy, concomitant medical conditions. The numbers of patients undergoing tarsorrhaphy or attending outpatient clinics for corneal ulceration will also be collected from patient records. Scottish morbidity register (SMR1) data on outpatient attendances will also be obtained^[25].

No electrophysiological studies are proposed because these are normally unavailable to GPs within the timeframe of therapy initiation and because of uncertainty as to what useful information they add to the clinical decision, which is usually based on clinical examination and an assessment of the patient's psychological state.

(k) Independent supervision

In accordance with the HTA's research governance framework we will form an independent Trial Steering Committee (TSC) under the chairmanship of Prof Chris van Weel (Catholic University, Nijmegen) and a Data Monitoring and Ethics Committee (DMEC) under the chairmanship of Dr Marion Campbell (HSRU, University of Aberdeen). We are continuing our efforts to identify a suitable patient representative through health councils and the Cochrane collaboration.

3 Project timetable and milestones

Month	Activity
-3	<i>MREC Submission</i>
	<i>Inform practices via local research, teaching and training networks, the MRC GP Research Framework, two direct mailshots to every medical and dental practice and out of hours cooperatives in Scotland. Train NHS24 nurses and ENT registrars. General advertisement via medical press.</i>
1	<i>Project specific training of research team to use study instruments</i>
	<i>Pilot study instruments and recruitment process.</i>
2	<i>Begin patient recruitment. Monthly reminders to health professionals. Data entry by research secretary.</i>
5	<i>Begin 3 month assessments.</i>
6	<i>Provide first interim report and prepare conference submissions.</i>
11	<i>Begin 9 month assessments.</i>
12	<i>Provide second interim report.</i>
18	<i>Complete patient recruitment. Provide third interim report.</i>
21	<i>Complete 3 month assessments</i>
24	<i>Provide fourth interim report.</i>
27	<i>Complete 9 month assessments. Final analysis and writing up.</i>
31	<i>Provide final report and submit papers.</i>

4 Expertise

The research team comprises multidisciplinary expertise in health economics, medical statistics, neurology, otorhinolaryngology, general medical and dental practice. They will work within the framework of the Scottish School of Primary Care (SSPC) which coordinates primary care research throughout Scotland.

Prof Sullivan, the lead investigator, has experience of participating in 6 and leading 1 randomised controlled trial. He has 15 years experience of other types of research in primary care. As the clinical director of one of the research networks, TayRen, and head of department in one of the participating universities he will be able to positively influence recruitment in the East of Scotland.

Prof Morrison contributes expertise in the detection and assessment of psychological distress in primary care. She also has experience of participating in and leading RCTs in primary care. She will be able to influence the recruitment of study subjects by general practitioners in teaching and research networks in the West of Scotland.

Dr Smith is a primary care career scientist with expertise in the epidemiology of pain in the community. As a respected researcher in the north-east of Scotland he will be able to influence the recruitment of study subjects by general practitioners in teaching and research networks in Grampian and Highland.

Dr McKinstry has experience of leading two randomised controlled trials in telephone triage and hypertension, and is taking part in another. He has 15 years experience of other types of research in primary care. He is a working general practitioner and Medical Director of Lothian and Borders Primary Care Research Network and can therefore facilitate recruitment in this area.

Mr Swan is one of two postgraduate training directors in ENT in Scotland. He is able to train and support all Scottish ENT registrars likely to see patients eligible for study. He has already secured agreement from the clinical directors of 12/14 Scottish ENT units to participate.

Dr Donnan is a senior medical statistician who has advised on the study methodology and will remain in daily contact with the principal investigator and research fellow as the study proceeds.

Dr Vale is a senior health economist with longstanding interests in community interventions.

Dr Davenport is a neurologist who has provided advice on the study methodology and will be a member of the panel of photographic reviewers providing independent assessment of the key outcome variable.

Dr Clarkson is the director of the Scottish Dental Practices Research Network. She will be able to increase the recruitment of study subjects by general dental practitioners in teaching and research networks throughout Scotland.

5 Trial process

The Trial may be separated into eight stages as follows.

-1	approvals, advertisement, awareness-raising
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This stage covers trial administration (MREC approvals, appropriate LREC approvals, DDX certification, etc) and advice of the existence of the trial to all relevant persons with a potential role, including GPs, A&E departments, NHS24, dentists (stage 1) and ENT consultants, registrars and nurses (stage 2).

Stages 0 to 6 are taken from the patient's point of view and are as follows.

0	onset (or symptoms noticed)
1	seek advice (visit GP, dentist or A&E; or contact NHS24)

These experts need to be sufficiently aware of the trial and its design to refer the patient onward to

2	visit the nearest ENT acute receiving clinic
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of which there are 14 identified so far; of these, 13 have agreed to collaboration. Here diagnosis is confirmed and, if appropriate, consent, randomisation and the commencement of treatment follow. It is herethat the first written record is taken from the patient. The Trial Coordinator is advised of the new recruitment, and the appropriate local RA is informed.

It is crucial to the design of the trial that the time delay from onset to first administration of treatment should not exceed 72 hours.

On receipt of notification from the Coordinator, the local RA arranges

3	baseline visit by local RA to the patient
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to take place at the patient's home or GP surgery (if preferred) within 3 days (72 hours) of the ENT visit. At this point photographs of the patient's condition are taken and further details are recorded. This is followed two or three days later by

4	a telephone contact
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to enquire about the patient's condition, to check adherence to the treatment and their general progress on the trial. The two final stages are

5	3-month visit
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at which follow-up photographs and further details are taken. The final stage of patient involvement is

6	9-month visit
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if deemed necessary.

It is anticipated that recruitment will commence on 1st February 2004 and continue for 18 months up to 31st July 2005. The last recruit's 9-month visit will therefore take place on or about 30th April 2006. That 27-month period is also the approximate period of employment of the local RAs. The trial is scheduled to end 6 months later on 31st October 2006.

6 Justification of support requested

Study Coordinator

A single, full-time post-doctoral health services researcher is required to coordinate all the components of the study, visit each of the centres and arrange meetings of the study team. This post will be full-time for the duration of the study and the postholder will be experienced in multi-centre health services research. They will be supported in this role by the Scottish Clinical Trials coordinators group based at HSRU in Aberdeen. They will also be responsible for visiting the study subjects in their own region of Scotland, i.e. Tayside, Fife and Forth Valley.

Centre Coordinators

In the 3 other centres, Glasgow, Edinburgh and Aberdeen the baseline, 3-month and 9-month visits will be conducted by centre coordinators working respectively full-time (covering all West of Scotland NHS boards), half-time (covering Edinburgh, Lothian and Borders) and half-time (covering Grampian and Highland).

Secretary

A half-time research secretary will be responsible for correspondence with patients and practitioners, data entry, typing reports and minutes of meetings, and general office administration.

Statistician

For a total of 1 day per month throughout the study and three months at the end of the study a post-doctoral statistician will be required to assist with analysis of the data and assist the principal investigators in completing the report to the HTA and preparation of papers for publication.

Health Economist

For three months at the end of the study a post-doctoral health economist will be required to assist with the analysis of the economic data and assist the principal investigators in completing the report to the HTA and preparation of papers for publication.

Randomisation Service

The Health Services Research Unit in Aberdeen have experience of 24 hour factorial randomisation for clinical trials. This will be accessed by an 0800 number from the ENT Department where the patient is first seen and data on entry of study subjects will be sent every day to the study coordinator with monthly summary statistics provided.

Office equipment

- One laptop PC for the study coordinator to use on site visits and conferences as well as daily trial management (e.g. Dell C640-256Mb, CD, 20 GB)
- Printer: e.g. HP LaserJet 1200

- Other equipment will be supplied by the study sites

Postage + Stationery

- 3,000 initial requests to participate to all medical and dental practices as well as A/E units and out of hours co-operatives. Production of laminated sheets to go in every participating site's consulting areas.
- 1,500 reminders to participants. Monthly reminders to practices and hospitals.

Cameras

For baeline assessment and follow-up of patients at 3 and 9 months the research coordinators in each centre will need a camera.

- Four Canon A40 8Mb USB cameras for onward transmission of digital images to the three assessors.

Travel to patients' homes and conference expenses

- This has been costed on the assumption of a return car journey of 10 miles either of the patient to the practice or the coordinator to the patient's home.

7 References

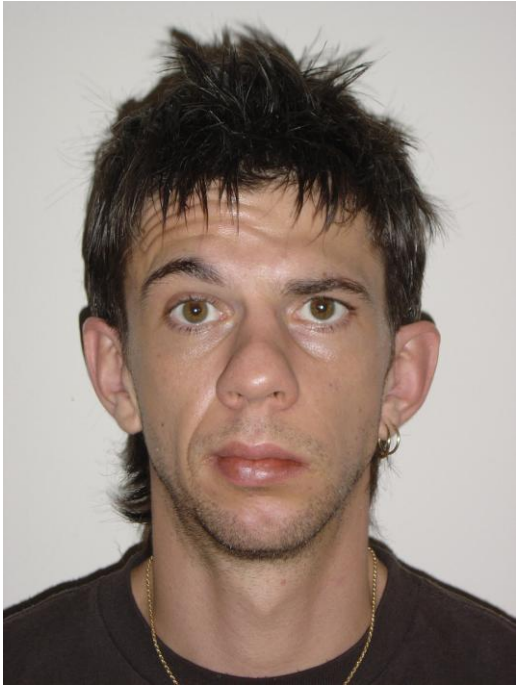
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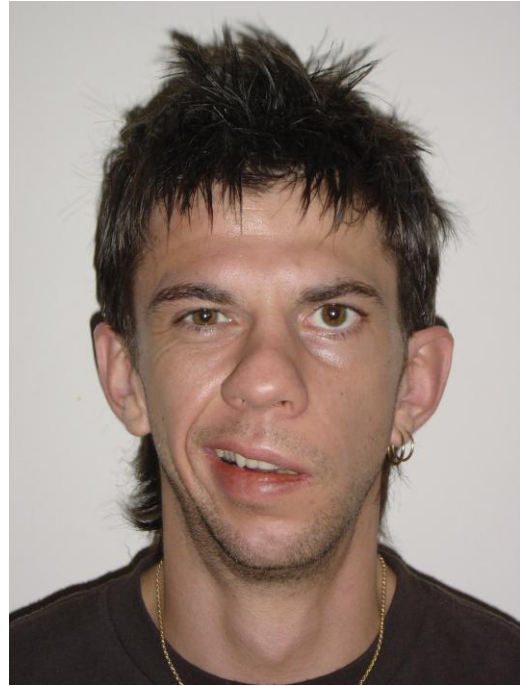
House Brackmann grading system

Grade	Definition
I	<i>Normal symmetrical function in all areas</i>
II	<i>Slight weakness noticeable only on close inspection Complete eye closure with minimal effort Slight asymmetry of smile with maximal effort Synkinesis barely noticeable, contracture, or spasm absent</i>
III	<i>Obvious weakness, but not disfiguring May not be able to lift eyebrow Complete eye closure and strong but asymmetrical mouth movement with maximal effort Obvious, but not disfiguring synkinesis, mass movement or spasm</i>
IV	<i>Obvious disfiguring weakness Inability to lift brow Incomplete eye closure and asymmetry of mouth with maximal effort Severe synkinesis, mass movement, spasm</i>
V	<i>Motion barely perceptible Incomplete eye closure, slight movement corner mouth Synkinesis, contracture, and spasm usually absent</i>
VI	<i>No movement, loss of tone, no synkinesis, contracture, or spasm</i>

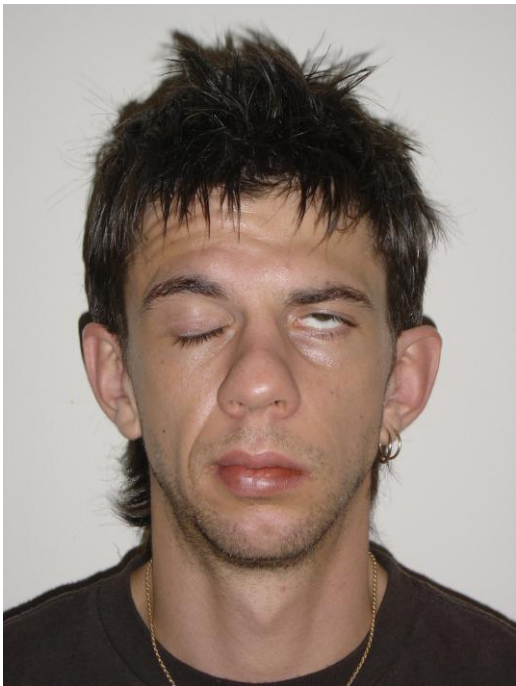
Posed portrait photographs (example at baseline)



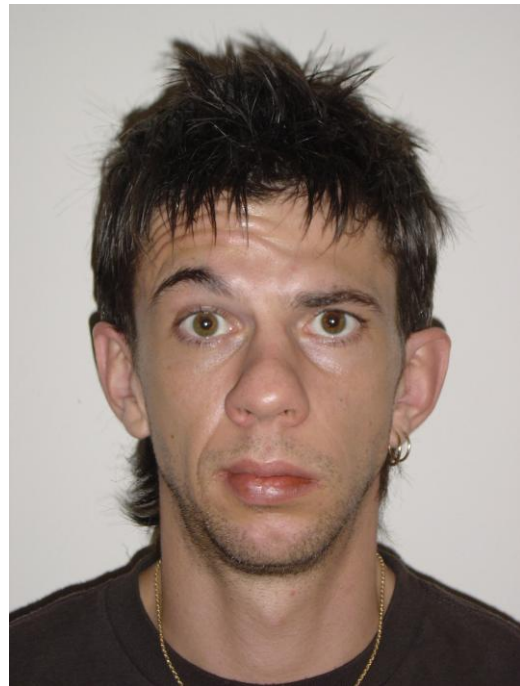
(i) At rest



(ii) Smiling



(iii) Eyes tightly closed



(iv) Eyebrows raised

Table. Baseline Characteristics of the Patients					
	Prednisolone- Placebo (N = 127)	Aciclovir- Prednisolone (N = 124)	Placebo- Placebo N = 122	Acyclovir- Placebo (N = 123)	Total (N = 496)
Sex – no. (%)					
Male	71 (55.9)	64 (51.6)	63 (51.6)	55 (44.7)	253
Female	56 (44.1)	60 (48.4)	59 (58.4)	68 (55.3)	243
Age – yr *	42.7 ± 15.9	43.7 ± 16.4	43.4 ± 16.3	46.3 ± 16.7	44.0 ± 16.4
Score on House-Brackmann scale †	3.5 ± 1.2	3.4 ± 1.2	3.8 ± 1.2	3.8 ± 1.3	3.6 ± 1.3
Score on Health Utilities Index Mark 3 ‡	0.80 ± 0.24	0.80 ± 0.21	0.76 ± 0.20	0.79 ± 0.21	0.79 ± 0.22
Score on Derriford Appearance Scale 59 §	72 ± 37	70 ± 37	76 ± 40	75 ± 41	73 ± 39
Score on Brief Pain Inventory ¶	11 ± 20	10 ± 17	18 ± 23	14 ± 19	13 ± 20
Time between onset of symptoms and start of treatment – no. (%)					
Up to 24 hr	59 (46.5)	61 (49.2)	71 (58.2)	76 (61.8)	267 (53.8)
Up to 48 hr	50 (39.4)	45 (36.3)	34 (27.9)	30 (24.4)	159 (32.1)
Up to 72 hr	13 (10.2)	12 (9.7)	5 (4.1)	13 (10.6)	43 (8.7)
Unknown (but ≤ 72 h)	5 (3.9)	6 (4.8)	12 (9.8)	4 (3.3)	27 (5.4)

* ± values are mean ± SD.

† Data are missing for 12 patients on the House-Brackmann scale, which ranges from 1 to 6, with higher scores indicating worse facial paralysis.

‡ Data are missing for 13 patients on the Health Utilities Mark 3, which ranges from –0.36 to 1.00 (as assessed by the patient) with 1 being full health; negative scores indicate a quality of life that is considered worse than death.

§ Data are missing for 13 patients on the Derriford Appearance Scale 59, which ranges from 8 to 262, with higher scores indicating more distress and dysfunction.

¶ Data are missing for 7 patients on the Brief Pain Inventory, which ranges from 0 to 110, with higher scores indicating greater severity.