Randomized clinical trial of acyclovir plus prednisone *versus* prednisone alone in Bell's palsy

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Abstract

Objective

To determine the effect of treatment with combination of prednisone plus acyclovir versus prednisone alone in time to recovery and outcome in Bell's palsy.

Methods

Between 1995 and 1996 we carried out a randomized, double-blind, placebo-controlled trial on 46 patients with Bell's palsy that developed less than 4 days before study enrolment. Acyclovir or a matched placebo was administered orally, 800mg five times daily for 7 days. Prednisone was administered to both groups of patients orally at 60mg/d for the first 5 days, 50mg, 40mg, 30mg, 20mg, 10mg, daily for other 5 days. Bell's palsy was graded by House-Brackmann facial nerve dysfunction grading system. Facial nerve function evaluation was done monthly for 6 months.

Results

Demographic characteristics were similar for each group. Patients receiving acyclovir plus prednisone had accelerated time to recovery of Bell's palsy, and significantly improved outcome compared with patients receiving prednisone alone (t=4.15, p<0.05, x^2=8.54, p<0.01 respectively).

Conclusions

In patients with Bell's palsy combined acyclovir and prednisone therapy can shorten time to recovery, and improve outcome.

Introduction

Bell's palsy, i.e, idiopathic facial nerve paralysis, is the most common cause of lower motor neurone facial paralysis in the world, and it's incidence is 20 to 30 cases per 100 000 (1,2). The aetiology of this disease is yet unclear. Many events, such as viral infection (3,4,5), ischaemic (6), diabetic vascular disease (7), autoimmune inflammatory (8), or a combination of the preceding factors (9), have been proposed as causes of Bell's palsy. Viral infection is thought to be the most likely cause (3,5,10). Recent evidence has shown that *Herpes simplex* virus (HSV) is the major aetiologic agent in Bell's palsy (11,12,13,14). However, to date, the most widely accepted method of treatment for Bell's palsy is treatment with oral steroids (15,16,17).

Acyclovir is an antiviral agent, and it has been recommended for the treatment of herps zoster (18,19) and recurrent genital herpes (20,21). We did a clinical trial to determine the efficacy and safety of combined therapy of prednisone plus acyclovir versus prednisone alone in treatment of Bell's palsy.

Methods

Patients

From January 1995 to June 1996, 51 patients at the Second Teaching Hospital of Ya'an Medical College with Bell's palsy who met all inclusion criteria were entered voluntarily into a randomized double blind controlled study. This study was approved by the hospital ethical committee. Participants gave written informed consent. Patients were only enrolled if their paralysis had occurred within 4 days of presentation to our unit. Bell's palsy was defined as an acute onset of lower motor

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neurone facial paralysis not associated with any of the following: acute or chronic middle ear disease, cranial or otologic trauma, known central or peripheral neurological disease, autoimmune disease, and herps zoster oticus (Ramsay Hunt syndrome). Patients were entered in to the study only if they had no contraindications to steroid therapy *viz.*, peptic ulcer disease, active tuberculosis, pregnancy, hypertension or diabetes mellitus.

Treatment

All patients received prednisone for 10 days and coded tablets containing either acyclovir or acyclovir placebo for 7 days. The dose of prednisone was 60mg daily for 5 days, 50mg, 40mg, 30mg, 20mg, 10mg daily for other 5 days, Acyclovir was administered orally, 800mg five times daily, for 7 days. Both treatments (prednisone and acyclovir or prednisone and placebo) were administered concurrently. Patients also received other medications according to their needs. All patients received artificial tears and an ophthalmic ointment for eye care.

Evaluation

All the patients had a complete head, neck and cranial nerve examination prior to treatment. The patients were graded by House-Brackmann facial nerve dysfunction grading system (22) (Table 1). Follow-up examinations were performed at weekly intervals for the first month. At the follow-up visits, each patient was examined and graded by the same investigator who initially evaluated the patient. After the first month, patients were examined at monthly intervals until recovery. If the patients believed that their facial function had returned to normal in between appointments, they were asked for the date of recovery. If the investigator agreed that they had recovered to grade III or better, the date the patient provided was used as the end point for assessing resolution. Time to resolution was judged as the period, (in days) that each patient took for recovery of facial nerve function to grade III or better. Good recovery was judged to occur when the patient reached a facial nerve paralysis grade of II or I. If the recovery was only up to grade III within 6 months after the onset of Bell's palsy then it who considered as poor recovery.

Table 1. House-Brackmann facial nerve dysfunction grading system

Grade	Characteristics
I. Normal	Normal facial function in all areas.
II. Mild dysfunction	Gross: slight weakness noticeable on close inspection; may have very slight synkinesis. At rest: normal symmetry and tone. Motion: moderate to good movement of forehead; ability to close eye with minimal effort and slight asymmetry; ability to move corners of mouth with slight asymmetry.
III. Moderate dysfunction	Gross: obvious but not disfiguring difference between two sides noticeable but not severe synkinesis, contracture and/or hemifacial spasm. At rest: normal symmetry and tone. Motion: slight to moderate movement of forehead; ability to close eye with maximal effort; mouth slightly weak with maximal effort.
IV. Moderately severe dysfunction	Gross: obvious weakness and/or disfiguring asymmetry. At rest: normal symmetry and tone. Motion: no movement of forehead; inability to close eye completely with maximal effort; asymmetrical movement of corners of mouth with maximal effort.
V. Severe dysfunction	Gross: only barely perceptible motion. At rest: asymmetry. Motion: no movement of forehead; incomplete closure of eye and only slight movement of mouth.
VI. Total paralysis	No movement.

Statistical analysis

Data are presented as the mean ± SD or as percentage of the group value. We examined overall differences between groups by Students t-test for continuous variables and Chi-square test for categorical variables. Differences were considered statistically significant at $p<0.05$.

Results

Patient characteristics

Of the 51 patients initially randomized, 46(90%) completed initial follow-up and are included in this study, the remaining 5(10%) patients failed to come for follow-up assessments. Of the 46 patients 25 received prednisone plus acyclovir and 21 received prednisone plus acyclovir placebo. There were 24 men and 22 women with a mean age of 39.8 years and a range from 15 to 73 years. There were 24 cases involving the right side and 22 cases affecting the left side. The baseline characteristics of the patients in two groups are shown in Table 2. There were no statistically significant differences between the groups in any of the variables studied.

Table 2. Baseline demographic and clinical characteristics

Characteristic	Acyclovir group (n=25)	Control group (n=21)
Mean age (yr)	39.2	40.3
Sex (M/F)	12/13	10/11
Pain at onset		
Face	16	14
Ear	12	11
Paresthesiae at onset	10	8
Altered hearing at onset	8	6
Tinnitus at onset	8	6
Dysgeusia at onset	11	11
Pre-treatment grade of paralysis		
II	3	2
III	4	4
IV	3	2
V	8	6
VI	7	7

Outcome

The mean time to resolution in the acyclovir and control groups were 42.12 and 53.47 days respectively. These values are statistically significant ($t=4.15$, $p<0.05$). All patients showed recovery of facial nerve function at least up to grade III during the study (Table 3). The acyclovir group has a higher proportion (84%) of patient showing recovery, (grades II or I) compared to the control. The differences in the criteria for good and poor recovery between the two groups was statistically significant ($x^2=8.45$, $p<0.01$).

Table 3. Outcome in the two groups

	Acyclovir group (n=25)	Control group (n=21)
Good recovery (I~II)	21(84)	8(38)
Poor recovery (III)	4(16)	13(62)

The number in parentheses are the percentages

Side-effects

In general, acyclovir was well-tolerated by the patients in that group, and there were no untoward side effects or symptoms. No patient in boths groups suffered any severe side effects of prednisone therapy.

Discussion

Because the aetiology of Bell's palsy is unclear, the treatment methods are widely varied. Several studies (15,16,17) have suggested that prednisone is beneficial in preventing denervation of the facial nerve. In this study the addition of acyclovir to prednisone significantly shortened the time to recovery compared to prednisone alone. There were significant differences between the two groups in the number of days to recovery and the final grade of recovery of the facial paralysis. Hence this clinical trial has shown that the combination of acyclovir and prednisone may have benefits in terms of speed and completeness of recovery in

patients with Bell's palsy. HSV might be the causative agent of Bell's palsy and from the geniculate ganglion it could travel down the nerve axon (3) and cause a seventh nerve paralysis. Studies of autopsy material have shown latent HSV in the geniculate ganglia of humans (23,24). Burgess recently used PCR technique to identify HSV genomes in idiopathic Bell's palsy (13). Murakami *et al*, also using PCR, have isolated the HSV-1 genome from the facial nerve endoneurial fluid and the posterior auricular muscle of patients with the palsy (14). Triggers known to be associated with Bell's palsy are also known to reactivate HSV. These figures including preceding stress, such as upper respiratory tract infection, fever, dental extraction, menstruation or exposure to cold might reactivate latent HSV in the geniculate ganglion. This reactivation of HSV from the geniculate ganglion was a potential cause of Bell's palsy (11,12,24). After virus reactivation, it destroys ganglion cells and spreads into the endoneurial fluid. The virus also infects Schwann cells, leading to demyelination and inflammation of the facial nerve (12) leading to the paralysis of the nerve. Hence, antiviral drugs like acyclovir may be acting by interfering with the actions of the HSV.

We conclude that the concomitant administration of acyclovir and prednisone provides substantial benefit for patient with Bell's palsy.

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