

Acyclovir with Steroid and Steroid Alone in the Treatment of Idiopathic Facial Nerve Palsy: A Randomised Double-blinded Clinical Study from a Tertiary Care Centre, Chennai, India

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ABSTRACT

Introduction: Idiopathic palsy of facial nerve is an acute disease which causes lower motor neuron palsy characterised by facial asymmetry leads to psychological effects and limits one's social life. Steroids are very effective in the management of Bell's palsy. The usage of antiviral is still in debate due to the idiopathic aetiology of Bell's palsy.

Aim: To evaluate the efficacy of acyclovir with steroid and steroid alone in the management of Bell's palsy with respect to the recovery time.

Materials and Methods: The randomised double-blinded clinical study was conducted in the Department of Otorhinolaryngology, Chettinad Hospital and Research Institute, Chennai, Tamil Nadu, India, from September 2021 to February 2022 among 100 patients with idiopathic facial nerve palsy. Patients were divided into two groups, 50 patients in each. One group treated with acyclovir (400 mg oral five times daily) and methylprednisolone (1 mg/kg/day), and other group treated with steroid alone. Both the groups received physiotherapy in the Department of Physiotherapy and

taught about home facial exercises. The patients were on regular follow-up for six months to monitor the time of the recovery. House-Brackmann grading system was used for initial assessment and monitor the recovery of the patient. The improvement of House-Brackmann grade to I or II was considered a satisfactory recovery. The association between two groups were assessed by Chi-square test (χ^2), repeated measures and paired t-test. The statistical significance was considered when p-value <0.05.

Results: Out of 100 patients, 52 patients were male and 48 were female, while the age range was 19-58 years. At two months, 43 (86%) patients recovered in the combination group and 41 (82%) in the steroid alone group (p-value=0.038). At six months, 48 (96%) patients recovered in the combination group and 42 (84%) in the steroid alone group (p-value=0.178). The overall recovery rate was higher in the combination group (96%) compared to steroid alone group (84%).

Conclusion: The combination of acyclovir with steroids in the treatment of Bell's palsy has better recovery compared to steroid alone therapy.

Keywords: Antiviral drug, House-brackmann grading system, Methylprednisolone

INTRODUCTION

Idiopathic palsy of facial nerve affects 20-30 per 100000 persons per year and has a high healing rate of 70%. It affects both men and women equally [1]. Nicolaus Friedreich postulated that paralysis a figure or the cause of facial nerve palsy is exposure to cold surrounding [2]. It is a type of lower motor neuron palsy caused by an unknown aetiology, otherwise called Bell's palsy. The causes may be ischaemia, immunology, and recently virus-induced [3]. Herpes Simplex Virus (HSV), belonging to the family Herpes viridiae, is believed to be the cause of Bell's palsy. Its reactivation in geniculate ganglion causes neural inflammation, cytotoxic oedema followed by obstruction of microcirculation in the fallopian canal [4]. The HSV genes were isolated from geniculate ganglia, endoneural fluid, and postaural muscles [5]. Other viruses like Epstein-Barr virus, Varicella zoster virus, and cytomegalo virus also cause facial nerve palsy.

Ram Say Hunt syndrome is caused by Varicella zoster virus. The characteristics are ear vesicles, acute facial nerve palsy sometimes involvement of vestibulocochlear nerve. It also occurs without skin lesions called Zoster sine herpete which resembles Bell's palsy [6]. Even though the recovery rate is high, 30% of the patients have the severe form of Bell's palsy and they do not undergo complete recovery [7].

Pharmacological management and physiotherapy play a major role in the treatment and recovery of Bell's palsy. Medical treatment includes immunosuppressants, antiviral, and antibiotics [8]. Steroids are the mainstay of the treatment. Steroids have an anti-inflammatory property

which reduces neural inflammation and oedema thereby, improving the facial nerve function [9]. Kastle DA et al., analysed variations in the management of acute bell's palsy and concluded that compared to neurologists, Otorhinolaryngologists prescribe higher doses of steroids, most frequently antivirals and rarely imaging [2].

Acyclovir, a bacteriostatic, is the most commonly prescribed antiviral drug. Acyclovir inhibits HSV Deoxyribonucleic Acid (DNA) polymerase, thus, blocking DNA replication [10]. Because the HSV reactivation in the aetiology of Bell's palsy, the combination of the antiviral drug with steroid is effective. Yeo SG et al., compared acyclovir (2400 mg/day) with steroid (methyl prednisolone 1 mg/kg/day) and steroid alone in the Bell's palsy and found that the overall recovery rate is greater in the combination group (93.1%) compared to steroid alone group (85.1%), but statistically not significant [1]. Hato N et al., administered oral prednisolone (60-40 mg/day) with valacyclovir (1000 mg/day) and steroid with placebo for five days, and found that the recovery rate is higher in the combination of steroid with valacyclovir group (95.7%) compared to steroid with placebo group (88.6%) [11]. Yeo SG et al., compared the efficacy of acyclovir with famciclovir and concluded that famciclovir was helpful in treating the severe facial nerve palsy [3]. Despite these evidences, some otorhinolaryngologists recommend a combination of acyclovir with steroids while others suggests steroids alone.

The present study aimed to compare the efficacy of acyclovir with steroids and steroids alone in patients with idiopathic facial palsy along with physiotherapy. The primary outcome was to measure

the early and complete recovery of facial nerve function and the secondary outcome was the prevention of contractures.

MATERIALS AND METHODS

This randomised double-blinded clinical study was conducted in the Department of Otorhinolaryngology, Chettinad Hospital and Research Institute, Chennai, Tamil Nadu, India, from September 2021 to February 2022. The Institutional Ethics Committee approval was obtained (IHEC-I/0007/21) from the Chettinad University.

Inclusion criteria: Patients belonging to both gender, age between 18-60 years with acute symptoms of facial nerve palsy without any underlying cause were included in this study.

Exclusion criteria: Patients with facial palsy due to other causes like abnormalities of brain, neoplasm, acute or chronic middle ear disease, temporal bone fracture, surgery, and patients with uncontrolled diabetes mellitus (random blood sugar more than 200 mg/dL), duodenal ulcer were excluded from this study. All these patients were excluded based on history, clinical examination and investigations. Acute and chronic middle ear diseases were excluded by performing otoendoscopy or microscopic examination, while neoplasms and temporal bone fractures were excluded based on the Computed Tomography (CT) imaging of temporal bone.

Sample size calculation: The superiority margin was 0.05 (i.e., $\delta=0.05$) and the true difference in mean between treatment groups was 1 (i.e., $d=1$) with a standard deviation of 1.8 [1]. For achieving an 80% power (i.e., $1-\beta=0.8$) at the 5% level of significance (i.e., $\alpha=0.05$) with equal allocation (i.e., $k=1$), the sample size for treatment agents and the active control were 50 in each group ($N=100$).

After obtaining informed consent, detailed history of the symptoms, duration, and characteristics were taken. Thorough clinical examination including general and systemic examination along with ear, nose, and throat examination were carried out. Grading of facial nerve palsy was done using the House-Brackmann grading system [12].

Study Procedure

Patients with Bell's palsy were divided randomly into two equal study groups. Randomisation was done using a systematic sampling method. Every odd number was randomised to steroid with acyclovir group whereas even numbers were assigned to steroid alone group.

- Acyclovir with steroid (n=50): Patients were treated with acyclovir and steroid (1 mg/kg/day).
- Steroid alone (n=50): Patients were treated only with Methylprednisolone (1 mg/kg/day).

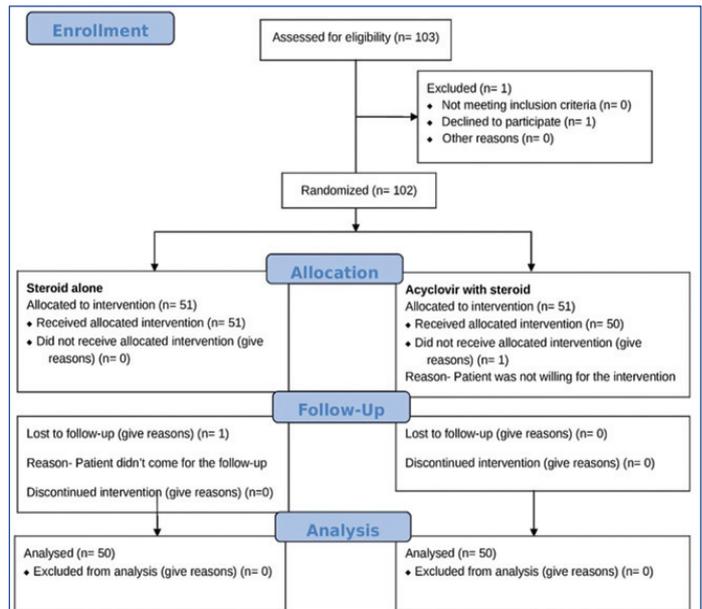
The dose for Acyclovir was 400 mg oral five times daily and methylprednisolone was 1 mg/kg/day. All the patients were tested for random blood sugar levels before prescribing methylprednisolone. Capillary blood sugar levels were measured by glucometer at the time of presentation and all the patients with facial palsy had normal random blood sugar (below 200 mg/dL). Both groups received physiotherapy, which included galvanic electrical stimulation, facial massage in the Department of Physiotherapy while they came for review. The patients were taught facial expression exercises to practice in their home. Patients were asked to come for review after one week for reassessment. After that, they were followed regularly at two month and six month [Table/Fig-1].

House-Brackmann grading was used for monitoring the recovery of facial nerve palsy [13] [Table/Fig-2]. House-Brackmann grades of I or II were considered as complete recovery of facial palsy, and grade III or IV as partial recovery.

STATISTICAL ANALYSIS

Statistical analysis was carried out using Statistical Package for the Social Sciences (SPSS) version 26.0 and Microsoft excel software.

The tests used are frequency tables and descriptive statistics. The association between two groups were assessed by Chi-square test (χ^2), repeated measures and paired t-test. The statistical significance was considered when p-value <0.05.



[Table/Fig-1]: Consolidated Standards of Reporting Trials (CONSORT) flow diagram showing patient progress through the study phases.

Degree of injury	Grade	Definition
Normal (1°)	I	Normal symmetrical function in all areas.
Mild dysfunction (barely noticeable) (1-2°)	II	Slight weakness noticeable only on close inspection. Complete eye closure with minimum effort. Slight asymmetry of smile with maximal effort. Synkinesis barely noticeable, contracture or spasm absent.
Moderate dysfunction (obvious difference) (2-3°)	III	Obvious weakness, but not disfiguring. May not be able to lift eyebrow. Complete eye closure and strong but asymmetric mouth movement with maximal effort. Obvious, but not disfiguring synkinesis, mass movement or spasm.
Moderately severe dysfunction (3°)	IV	Obvious disfiguring weakness. Inability to lift eyebrow. Incomplete eye closure and asymmetry of the mouth with maximal effort. Severe synkinesis, mass movement, spasm.
Severe dysfunction (3-4°)	V	Motion barely perceptible. Incomplete eye closure, slight movement of the corner of the mouth. Synkinesis, contracture and spasm usually absent.
Total paralysis	VI	No movement, loss of tone, no synkinesis, contracture or spasm.

[Table/Fig-2]: House-Brackmann grading of facial nerve palsy.

RESULTS

This study included 100 patients, of which 52 were males and 48 were females. The age group was 19-58 years, with mean age 35.28 years [Table/Fig-3]. During the first visit, majority of the patients belonged to grade III (n=16) and grade IV (n=18) in the acyclovir with steroid group; and grade III (n=24) and grade IV (n=18) in the steroid alone group [Table/Fig-4].

Groups	Mean age (years) (Mean±SD)	p-value	Male/Female	p-value
Acyclovir with steroid	34.54±11.45	0.51	Male: 24 (48%) Female: 26 (52%)	0.42
Steroid alone	36.02±10.70		Male: 28 (56%) Female: 22 (44%)	

[Table/Fig-3]: Distribution of age and gender.

Time interval	Grade II	Grade III	Grade IV	Grade V	Mean±SD	p-value
At presentation						
Acyclovir with steroid	12	16	18	4	3.28±0.93	0.13
Steroid alone	4	24	18	4	3.44±0.76	
At 2 months						
	Complete recovery (Grade I and II)		Partial recovery (Grade III and IV)		Mean±SD	0.038
Acyclovir with steroid	43		7		1.74±0.69	
Steroid alone	41		9		1.70±0.95	
At 6 months						
	Complete recovery (Grade I and II)		Partial recovery (Grade III and IV)		Mean±SD	0.178
Acyclovir with steroid	48		2		1.22±0.58	
Steroid alone	42		8		1.34 ±0.63	

[Table/Fig-4]: House-Brackmann grading at presentation, 2 months and 6 months.

At the end of two months, 43 (86%) patients recovered completely in acyclovir with steroid group [Table/Fig-4] and 41 (82%) patients recovered completely in the steroid alone group (p-value=0.038). At the end of six months, 48 (96%) patients recovered completely in the the acyclovir with steroid group and 42 (84%) patients recovered completely in the other (p-value=0.178).

The combination of acyclovir with steroid in the treatment of Idiopathic facial palsy showed early recovery compared to steroid alone and also prevents the contractures of facial muscles [Table/Fig-5].

Groups	Time interval			p-value
	At presentation (1) (Mean±SD)	At 2 months (2) (Mean±SD)	At 6 months (3) (Mean±SD)	
Acyclovir with steroid	3.28±0.93)	1.74±0.69)	1.22±0.58)	1 vs 2≤0.05 1 vs 3≤0.05 2 vs 3≤0.05
Steroid alone	3.44±0.76)	1.70±0.95)	1.34±0.63)	1 vs 2≤0.05 1 vs 3≤0.05 2 vs 3≤0.05

[Table/Fig-5]: Comparison within two groups.

Author's of the study	Year and place of study	Drugs and dosage	Assessment tool or parameters	Final outcome
Yeo SG et al., [1]	2008, South Korea	Among 91 patients, one group (44) was treated with oral prednisolone (1 mg/kg per day and tapered doses) for 10 days with oral acyclovir (2400 mg/day) for 5 days. The other group (47) was treated with oral prednisolone (1 mg/kg per day and tapered doses) for 10 days.	Complete recovery from facial paralysis, using House-Brackmann grade.	The recovery rate with steroid and acyclovir (93.1%) was greater than that of patients treated with steroid alone (85.1%), but the difference was not statistically significant.
Kim HJ et al., [3]	2016, South Korea	Among 702 patients, one group (457) was treated with Acyclovir (1000 to 2400 mg/day) for 5 days with oral prednisolone (80 mg/day and tapered doses) for 12 days. The other group (245) was treated with famciclovir (750 mg/day) for 7 days with oral prednisolone (80 mg/day and tapered doses) for 12 days.	Facial palsy recovery was assessed by House-Brackmann grading and electroneurography.	Treatment with steroid plus famciclovir was more effective than treatment with steroid plus acyclovir in patients with severe facial palsy.
Hato N et al., [11]	2007, Japan	Among 221 patients, one group (114) was treated with oral valacyclovir (1000 mg/day) and oral prednisolone for 5 days. The other group (107) was treated with oral prednisolone and placebo for 5 days.	Recovery of palsy was defined by using Yanagihara 40-point scoring system with a score higher than 36 without facial contracture or synkinesis.	The valacyclovir and prednisolone therapy (96.5%) was more effective in treating Bell's palsy compared to oral prednisolone and placebo therapy (86.6%).
Hato N et al., [15]	2003, Japan	Among 480 patients, one group (94) was treated with oral prednisolone (60-40 mg/day) and oral acyclovir (2000 mg/day) started within 3 days of onset of facial palsy. The other group (386) was treated with oral prednisolone alone.	Recovery of palsy was defined by using Yanagihara 40-point scoring system with a score higher than 36 without facial contracture or synkinesis.	The early diagnosis and treatment within 3 days of onset of facial palsy resulted in maximum efficacy with combination of acyclovir with oral prednisolone compared to steroid alone.
Numthavaj P et al., [16]	2011, Thailand	A network meta-analysis included 6 studies (1805 patients). This study included acyclovir or valacyclovir with prednisolone or prednisolone alone.	Recovery was monitored by House-Brackman Facial Recovery scale, Facial Palsy Recovery Index, Yanagihara score, Sunnybrook scale.	Antiviral therapy with corticosteroid may lead to slightly higher recovery rate but not statistically significant.
Gagyor I et al., [17]	2019, Germany	Systemic review included 2488 patients and studies the combination of antivirals with steroids and steroids alone or placebo.	Facial palsy recovery was assessed by House-Brackmann grading.	The combination of antivirals and corticosteroids probably reduced the late sequelae of Bell's palsy compared with corticosteroids alone.
Kim Y et al., [18]	2021, Republic of Korea	Among 335 patients with severe Bell's palsy, with 162 patients treated with oral prednisolone (1 mg/kg/day followed by tapered doses) alone and 173 patients treated with combinations of oral prednisolone and acyclovir (1000–2400 mg/day for 5 days) or famciclovir (750 mg/day for 7 days).	Facial palsy recovery was assessed by House-Brackmann grading and electroneurography.	The Combination therapy with steroids and antiviral agents resulted in significantly higher favorable recovery rates than steroids alone in severe Bell's palsy patients.

DISCUSSION

Steroids, vasodilators, and blood circulation supplements are effective in the treatment of facial palsy [7]. Methylprednisolone plays a major role in the early recovery and prevention of synkinesis. It produces anti-inflammatory response by preventing release of proinflammatory mediators like prostaglandins and leukotrienes through indirect inhibition of phospholipase [14].

The use of antiviral drugs in the recovery of facial palsy is still debatable. The most commonly used antiviral drug is acyclovir which blocks Deoxyribonucleic Acid (DNA) replication by inhibiting Herpes Simplex Virus (HSV) DNA polymerase [10]. The present study aimed to compare the efficacy of acyclovir with steroid combination and steroid alone in the treatment of idiopathic facial palsy in terms of complete early recovery and prevention of complications. At the end of the study, the combination of acyclovir with steroids showed complete early recovery of idiopathic facial nerve palsy and fewer complications when compared to steroids alone.

The addition of antiviral drugs such as acyclovir, valacyclovir, and famciclovir with oral steroids aided in the early and higher recovery

Kang HM et al., [19]	2014, Korea	In a total of 1342 patients with Bell's palsy, 569 patients were treated with acyclovir (1000-2400 mg/day for 5 days) or famciclovir (750 mg/day for 7 days) and oral prednisolone (1 mg/kg/day followed by tapered doses) and 773 patients were treated with oral prednisolone alone.	Facial palsy recovery was assessed by House-Brackmann grading and electroneurography.	Treatment with a steroid plus antiviral agent resulted in significantly higher recovery rates than steroid therapy alone.
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[Table/Fig-6]: Compilation of similar studies [1,3,11,15-19].

rate when compared to oral steroids alone. The most commonly used antiviral was acyclovir and its dosage ranges from 1000-2400 mg/day for 5 days. The least effective dose of acyclovir was 1000 mg/day. The other antivirals used are famciclovir (750 mg/day for 7 days) and valacyclovir (1000 mg/day for 5 days) [Table/Fig-6] [1,3,11,15-19]. The most common side effects of oral antiviral drugs are headache, nausea, and malaise, but the present study patients did not report any side-effects [14].

The current study showed the combination of acyclovir with oral prednisolone in the treatment of idiopathic facial palsy aided in early and complete recovery of facial weakness compared to steroids alone while patients receiving physiotherapy at the end of two months.

Limitation(s)

There are newer antiviral drugs available on the market nowadays like famciclovir, valacyclovir, etc., which have higher oral bioavailability with excellent efficacy. This study only compared the efficacy of acyclovir with steroids.

CONCLUSION(S)

The present study compared the two groups i.e, acyclovir with steroid and steroid alone in the management of idiopathic facial nerve palsy and on regular follow-up for six months to observe the early recovery of facial palsy. There was complete and early recovery of Bell's palsy while using acyclovir with steroid, compared to steroid alone along with physiotherapy. Future studies are recommended to evaluate the efficacy of various available antivirals and other modalities of treatment in Bell's palsy for the better outcome.

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