No effect of corticosteroid treatment for idiopathic facial paralysis

Kristian Friesgaard Christensen, Therese Ovesen & Christer Swan Andreassen

ABSTRACT

INTRODUCTION: This retrospective cohort study aimed to determine if the effect of corticosteroid treatment on idiopathic facial palsy (IFP) could be reproduced in patients treated in a strictly clinical setting.

MATERIAL AND METHODS: A total of 43 patients diagnosed with IFP in the period 2004-2009 were included and patient files were reviewed. Treatment with corticosteroids was introduced as standard treatment for this disease in December 2006, ensuring groups of similar size. In all, 20 patients had received prednisolone and 23 patients had not. Baseline characteristics were registered and severity of facial palsy according to the House-Brackmann grading system (HB) was determined before treatment and at follow-up.

RESULTS: Change in HB score did not differ between participant groups (delta HB: 3 (range: 0-5), and 3 (range: 1-5), patients treated with steroids versus patients receiving no treatment, respectively, p = 0.69). When dividing patients into sub-groups according to age (age >/≤ 40 years), no difference was found for change in HB score between treatment groups for either age group (age ≤ 40 years; p = 0.59, and age > 40 years; p = 0.12). The effect of steroid treatment on outcome was larger among older than among younger patients (p = 0.03).

CONCLUSION: Treatment with prednisolone does not improve short-term outcome in patients with IFP in an unselected clinical setting. Further studies should evaluate the possible effect of age on treatment outcome.

FUNDING: not relevant.

TRIAL REGISTRATION: not relevant.

Idiopathic facial paralysis (IFP), also known as Bell's palsy, is an acute paralysis of the facial nerve of unknown aetiology, leading to partial or complete inability to control facial muscles on the affected side (**Figure 1**). The annual incidence is 11-40 per 100,000 in adults [1]. Nearly 70% regain muscle function completely without treatment, whereas the remaining 30% suffer from sequelae such as persisting pain and facial muscle weakness [2]. Reactivation of herpes simplex virus type 1 (HSV-1) in the geniculate ganglion has been suggested as a possible mechanism in the pathophysiology of IFP, as has local arteriolar constriction and reduced nerve blood flow, both leading to demyelination of the facial nerve followed by oedema and inflammation [3-6]. However, trials investigating the effect of corticosteroids and/or antiviral agents in the treatment of IFP have reported conflicting results. Recently, two trials showed that corticosteroids improve the prognosis of IFP, whereas neither study found any effect of antiviral agents, and their use in the treatment of the disease was questioned [7, 8].

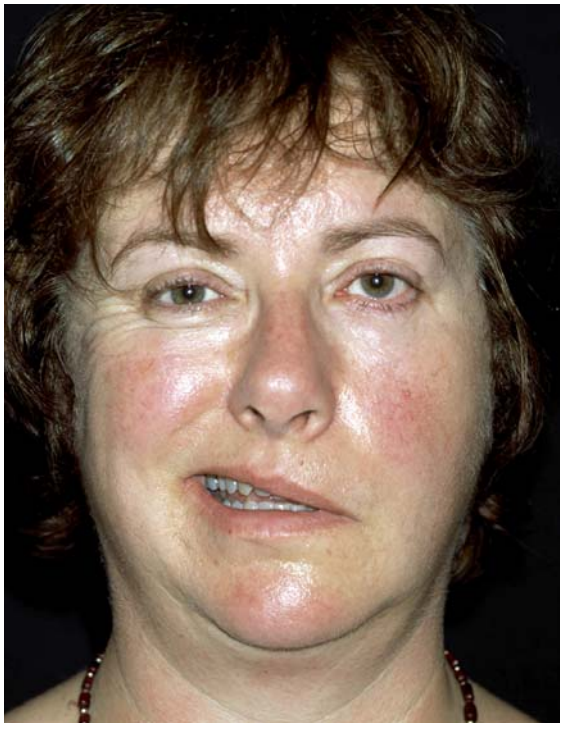
In contrast, a synergistic effect of valaciclovir in combination with prednisolone compared with prednisolone alone has been reported [4]. The effect of corticosteroids in combination with antiviral drugs in the treatment of IFP was also evaluated in two meta-analyses, which reached opposing conclusions [9, 10]. A recent meta-analysis found no difference between treatment with antiviral drugs and placebo, and, furthermore, concluded that complete recovery was less likely to occur in patients treated with antiviral agents than in those treated with corticosteroids [11]. Also, the effect of prednisolone is more pronounced in patients older

ORIGINAL ARTICLE

Department of Otorhinolaryngology, Head and Neck Surgery, Aarhus University Hospital, Aarhus

Dan Med J 2012;59(4):A4416

FIGURE 1



Patient with idiopathic facial palsy of grade five according to the House-Brackmann Facial Grading System.
Photo: Scanpix Danmark.

than 40 years of age than in younger patients. In fact, prednisolone had no effect on recovery in younger patients [12].

The aim of this retrospective cohort study was to evaluate the effect of treatment with corticosteroids on IFP in an unselected patient population treated in a strictly clinical setting at the Department of Otorhinolaryngology, Head & Neck Surgery, at Aarhus University Hospital, and to compare the findings to those reported in prospective studies.

MATERIAL AND METHODS

We identified patients diagnosed with unilateral peripheral facial paralysis at the Department of Otorhinolaryngology, Head and Neck Surgery, Aarhus University Hospital, between 1 January 2004 and 31 December 2009 (**Figure 2**). Patient files were reviewed and subjects excluded according to the following criteria: severe head trauma, Ramsay Hunt syndrome, *Borrelia* infection, acute otitis media, pregnancy or breastfeeding, diabetes mellitus, dysregulated hypertension, severe heart disease, stroke, multiple sclerosis, peptic ulcer, immunodeficiency or – suppression, organ transplantation, cancer, and age < 16 years. As prednisolone was established as the standard treatment for IFP in December of 2006 owing to results reported in prospective studies, the period chosen ensured observation periods of comparable length and thus also participant groups of similar size [7, 8].

Age, gender, serology (*Borrelia burgdorferi*, varicella zoster virus (VZV), and HSV), and time from disease onset to initiation of treatment were registered. Furthermore, disease severity evaluated according to the House-Brackmann grading system (HB score) was determined before treatment was initiated and at follow-up [13]. The HB grading system ranges from I to VI; grade I is designated normal facial function, and a score of VI equals complete paralysis of muscles innervated by the facial nerve. A total of 29 patients had not been given an HB score at the initial examination and were therefore graded by a trained otorhinolaryngologist (TO) blinded to patient identity and participant group based on the clinical description obtained from patient files. Patients included after December 2006 were treated with 50 mg of prednisolone orally for ten days, whereas subjects included earlier received no treatment at all in the majority of cases. To evaluate the effect of age, patients were divided into two groups using the median age as cut point, thereby enabling comparison of similar age-groups as in the study by Axelsson et al and equal group sizes [12]. All statistical analyses were conducted using STATA version 9.2 (StataCorp, TX, USA). Comparison between groups was performed using the Mann-Whitney U-test, whereas distributions were compared using Fischer's exact test or χ^2 test. For all statistical analyses, a 5% limit of significance was applied.

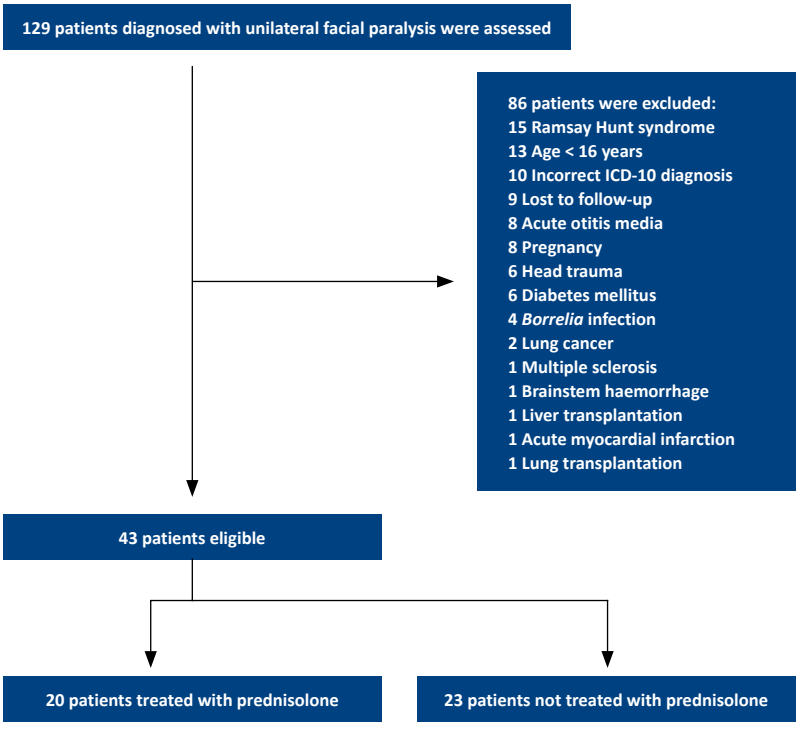
Trial registration: not relevant.

RESULTS

A total of 129 patients were identified with peripheral facial palsy during the study period. In all, 86 patients were excluded according to the exclusion criteria (Figure 2). Consequently, 43 patients were diagnosed with IFP, of whom 20 received prednisolone (steroid treatment group (STG)) and 23 patients did not (no steroid treatment group (NSTG)). Participant groups did not differ with regard to age, gender, time from onset of symptoms to initiation of treatment, observation time, or HB score at baseline. The majority of the NSTG patients received no treatment at all. However, six subjects were treated with aciclovir and one was given penicillin. In the STG, one subject was treated with aciclovir and two were given penicillin in addition to prednisolone. The distribution of patients treated with either antiviral agents or antibiotics did not differ between the study groups (χ^2: p = 0.2). Serological analyses performed on all participants were negative for *B. burgdorferi*, VZV, and HSV antibodies.

FIGURE 2

Flow chart of the 129 patients diagnosed with unilateral facial paralysis who were screened according to the in- and exclusion criteria stated in the study protocol.



ICD = International Classification of Diseases.

TABLE 1

Demographic data, time to treatment, follow-up period, and House-Brackmann score for patients with idiopathic facial nerve paralysis either treated or not treated with prednisolone at baseline and at clinical control.

	Treatment group		
	steroid	no steroid	p value
n	20	23	-
Age, median (range), years	38 (19-85)	41 (21-74)	0.56
Male/female, n	9/11	12/11	0.64
Time to treatment/initial examination, median (range), hours	24 (12-408)	24 (12-672)	0.99
Follow-up, median (range), days	59.5 (14-399)	63 (17-273)	0.87
House-Brackmann score, baseline, median (range)	4 (2-6)	5 (2-6)	0.57
House-Brackmann score, clinical control, median (range)	1 (1-3)	2 (1-4)	0.099
Change in House-Brackmann score, median (range)	3 (0-5)	3 (1-5)	0.69

Change in HB score showed no difference between the STG and the NSTG, and the groups had similar HB scores at follow-up (**Table 1**). HB scores according to age and participant group are presented in **Table 2**. The degree of facial palsy at the initial examination was more severe in the older age group. Severity of palsy at the initial examination did not differ between the two participant groups, neither when comparing patients younger than 41 years of age, nor when comparing the group of patients who were 41 years or older. Also, for the youngest patient group, HB scores did not differ at follow-up when comparing participant groups. In contrast, for patients 41 years or older, HB scores at follow-up were lower for patients treated with prednisolone than for untreated patients. However, the change in HB score did not differ between participant groups for either age group. Comparing patients receiving prednisolone, the change in HB score was greater for older patients than for patients 40 years or younger (Table 2 and **Figure 3**). No correlation was found between age and change in HB score for the STG (Spearman: rho = 0.37, p = 0.1). At follow-up, no complaints regarding side-effects in the STG were recorded from patient files.

DISCUSSION

In this retrospective follow-up study, we sought to evaluate the effect of treatment with prednisolone on recovery after IFP in a clinical setting. Overall, we found no effect of treatment with steroids on short-term recovery after IFP.

Our study has some limitations. First, a selection bias may have been introduced as the patients referred to the department probably suffered from more severe degrees of IFP as milder cases are more likely to be treated by primary sector physicians [4]. In our study, the median HB score at baseline was five, whereas HB scores before treatment were lower in the studies by both Sulllivan et al (HB = 3, 6) and Engstrøm et al (HB = 4). Second, primary sector physicians might consider the possibility of a cerebral insult to be a more serious event in older patients presenting with onset of unilateral facial palsy and thus admit these patients to a neurological department. Also, older patients with IFP may be less concerned with cosmetic sequelae and would in such case not be referred to an otorhinolaryngologist. As the effect of prednisolone has been shown to be related to age, a higher proportion of participants over 40 years of age may have strengthened the trend observed following treatment with prednisolone in the group of older patients. However, the age distribution in our study is similar to that of the study first describing the association with age and, therefore, the lack of significance in our study may probably be attributed to small study size [12].

Studies evaluating the relationship between the period from symptom onset to initiation of treatment with prednisolone and outcome after IFP report opposing findings. A recent study found improved effect of corticosteroids given within two days of disease onset

TABLE 2

House-Brackmann scores for patients with idiopathic facial paralysis divided into age-groups arranged according to treatment group (± steroid).

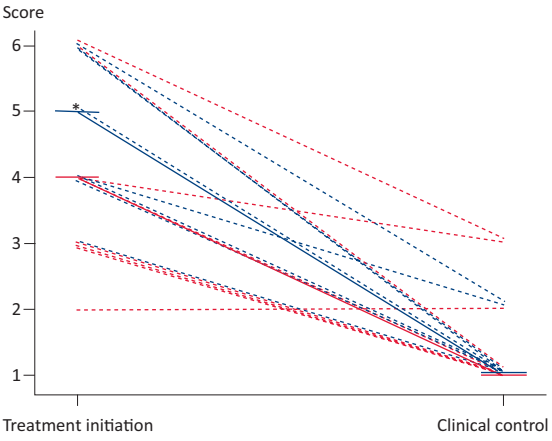
	Age < 41 years				Age ≥ 41 years			
	all	steroid treatment group	no steroid treatment group	p value	all	steroid treatment group	no steroid treatment group	p value
n	20	10	10	-	23	10	13	-
House-Brackmann score, baseline, median (range)	4 (2-6)*	4 (2-6)	4 (2-6)	0.78	5 (3-6)*	5 (4-6)	5 (3-6)	0.95
House-Brackmann score, clinical control, median (range)	-	1 (1-3)	1 (1-3)	0.89	-	1 (1-2)	2 (1-4)	0.02
Change in House-Brackmann score, median (range)	-	2 (0-5)*[a]	3 (1-5)	0.59	-	4 (2-5)*[a]	3 (1-4)	0.12

*) $p < 0.05$ when comparing all participants ≥ 41 years of age with all participants < 41 years of age.

*a) $p < 0.05$ when comparing age-groups (age ≥/< 41 years) for participants receiving steroid treatment for idiopathic facial paralysis.

FIGURE 3

House-Brackmann score at initiation of corticosteroid treatment and at clinical control for individual patients suffering from idiopathic facial paralysis according to age group.



*) p < 0.05 when comparing median HB scores at treatment initiation.

compared with treatment administered later, whereas other studies have included patients treated within three days of symptom onset [7, 8, 12]. In our study, seven patients, equally distributed between the two participant groups, received treatment three days after symptom onset, which may have weakened the effect of treatment. However, the effect of corticosteroids on outcome has been demonstrated following treatment initiation as late as seven days after symptom onset, and as 42 (98%) of the patients in our study were treated within five days of symptom onset, an effect on outcome would be expected based on these reports [14, 15]. One patient in our study did not receive treatment until 17 days after onset of IFP, and in this case any effect of treatment with steroids is doubtful. However, as this was the only treatment option available shown to improve outcome and as the drug has few adverse effects when administered in small doses over a short period of time, it was administered by the clinician.

For the 29 patients assigned an HB score based on the clinical description obtained from patient files, the score may be biased in either direction. However, all 29 patient files were considered sufficient for HB score allocation by the blinded observer. Furthermore, these patients were equally distributed in the two study groups. Finally, inter-observer variability might have affected HB scores for all other patients as initial examination was performed by various clinicians.

Nine patients were lost to follow-up, of whom six were treated with prednisolone and three were not. One explanation for this finding may be that patients treated with prednisolone experienced an improvement in symptoms owing to treatment and therefore did not consider further controls necessary. Inclusion of these patients would probably have altered the results towards an effect of steroid treatment. Patients lost to follow-up did not differ from participating subjects with regard to initial HB score or age.

As observation time was relatively short compared with other studies, our study only evaluated the short-term effect of corticosteroids on IFP [7, 8]. Recovery following IFP occurs up to twelve months after the disease presents, and longer follow-up could, therefore, have affected our results.

Ten patients were treated with either penicillin or aciclovir. However, as none of the participants presented with clinical signs of *Borrelia* or HSV/VZV infection, and, further, as serology was found to be negative, treatment with antibiotics or antiviral medication should be considered a result of overtreatment.

In our study, patients in the older age group experienced more severe facial palsy at initial examination, a finding supported by a recent prospective study [12]. A correlation has been shown between the HB score and increased signal intensity on magnetic resonance imaging, and it has been proposed that inflammation and oedema adjacent to the nerve cause the described findings [5]. The effect of prednisolone observed in older patients may imply that oedema and inflammation are more pronounced in this sub-group of patients. Alternatively, loss of axons due to age may have left more space for oedema, thereby relieving the remaining axons from the higher pressure occurring in younger individuals.

Subjects were excluded from our study if an infection with VZV was present. However, the infection, which may induce facial palsy, can occur without the formation of vesicles and may be related to the most severe cases of IFP resulting in sequelae such as persisting facial muscle weakness [4]. As mentioned earlier, an association between HSV-1 and IFP has been sought. HSV-1 DNA has been detected in endoneural fluid of the facial nerve in patients with IFP, and the impact of HSV-1 on facial nerve function has been demonstrated in animal studies [3, 16]. However, as all participants in our study presented with negative serology for HSV and VZV, an underlying viral aetiology is unlikely.

A synergistic effect of valaciclovir and prednisolone was recently reported; however, the study had several weaknesses [4]. First, investigators were not blinded, and second, 25% of the participants were excluded retrospectively. Although these findings were somewhat supported by a large meta-analysis, opposing results were reported in yet another meta-analysis, which also found

that low study quality favoured combination therapy [9, 10]. In our study, only one subject in the STG was treated with combination therapy, and so it is unlikely that combination therapy has affected our outcome.

In this retrospective population-based cohort study evaluating the short-term effect of prednisolone on recovery after IFP in a strictly clinical setting, no difference was found between patients treated with prednisolone and those receiving no treatment. Thus, the effect of corticosteroids reported in previous prospective studies could not be reproduced. Nonetheless, we recommend treatment with prednisolone for IFP within three days as it has been shown to have a positive effect on outcome in large prospective studies, and as the treatment has few side-effects when given over a short period of time. Further studies should evaluate the effect of age on treatment outcome as this may have implications for clinical practice.

CORRESPONDENCE: *Christer Swan Andreassen*, Øre-næse-hals-afdeling H, Aarhus Universitetshospital, 8000 Aarhus C, Denmark.
E-mail: christer.andreassen@ki.au.dk

ACCEPTED: 2 February 2012

CONFLICTS OF INTEREST: none

LITERATURE

1. Bateman DE. Facial palsy. Br J Hosp Med 1992;47:430-1.
2. Peitersen E. The natural history of Bell's palsy. Am J Otol 1982;4:107-11.
3. Wakisaka H, Hato N, Honda N et al. Demyelination associated with HSV-1-induced facial paralysis. Exp Neurol 2002;178:68-79.
4. Hato N, Yamada H, Kohno H et al. Valaciclovir and prednisolone treatment for Bell's palsy: A multicenter, randomized, placebo-controlled study. Otol Neurotol 2007;28:408-13.
5. Song MH, Kim J, Jeon JH et al. Clinical significance of quantitative analysis of facial nerve enhancement on MRI in Bell's palsy. Acta Otolaryngol 2008;128:1259-65.
6. Cawthorne T. The pathology and surgical treatment of Bell's palsy. J Laryngol Otol 1951;44:565-72.
7. Sullivan FM, Swan IR, Donnan PT et al. A randomized 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;13:1-130.
8. Engstrøm M, Berg T, Stjernquist-Desatnik A et al. Prednisolone and valacyiclovir in Bell's palsy: a randomized, double-blind, placebo-controlled, multicenter trial. Lancet Neurol 2008;7:993-1000.
9. Almeida JR, Al Khabori M, Guyatt GH et al. Combined corticosteroid and antiviral treatment for Bell palsy. JAMA 2009;302:985-93.
10. Quant EC, Jeste SS, Muni RH et al. The benefits of steroids versus steroids plus antivirals for treatment of Bell's palsy: a meta-analysis. BMJ 2009;339:1-7.
11. Lockhart P, Daly F, Pitkethly M et al. Antiviral treatment for Bell's palsy (idiopathic facial paralysis). Cochrane Database Syst Rev 2009;(4): CD001869.
12. Axelsson S, Berg T, Jonsson L et al. Prednisolone in Bell's palsy related to treatment start and age. Otol Neurotol 2011;32:141-6.
13. Vrabec JT, Backous DD, Djalilian HR et al. Facial nerve grading system 2.0. Otolaryngol Head Neck Surg 2009;140:445-50.
14. Adour KK, Winger J, Bell DN et al. Prednisolone treatment for idiopathic facial paralysis (Bell's palsy). N Engl J Med 1972;287:1268-72.
15. Sathirapanya P, Sathirapanya C. Clinical prognostic factors treatment outcome in Bell's palsy: a prospective study. J Med Assoc Thai 2008;91:1182-8.
16. Murakami S, Mizobuchi M, Nakashiro Y et al. Bell's palsy and herpes simplex virus: identification of viral DNA in endoneuronal fluid and muscle. Ann Intern Med 1996;124:27-30.