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For Bell's palsy, start steroids early; no need for an antiviral

Practice changer

A 10-day course of corticosteroids (prednisolone 25 mg twice daily) started within 72 hours significantly improves the chances of complete recovery. There is no added benefit from acyclovir.¹

Strength of recommendation

A: Based on a large, well-designed randomized controlled trial

Sullivan FM, Swan IR, Donnan PT, et al. Early treatment with prednisolone or acyclovir in Bell's palsy. *N Engl J Med* 2007; 357:1598–1607.

cyclovir, largely on the basis of pathophysiologic reasoning, because we've had no clear guidance from outcome studies. Until now, outcome studies have had mixed findings, and have been inconclusive.² Most outcome studies have lacked the statistical power to either detect or to rule out potential benefits convincingly. The study by Sullivan and colleagues is the first to have a sufficiently large study sample from which to draw more definitive conclusions based on patient-oriented outcomes.

FAST TRACK

Adding acyclovir to prednisolone does not improve chances of full recovery

PURLs methodology

This study was selected and evaluated using FPIN's Priority Updates from the Research Literature (PURL) surveillance system methodology. The criteria and findings leading to the selection of this study can be accessed at www.jfponline.com/purls.

ILLUSTRATIVE CASE

A 45-year-old man presents to your outpatient clinic within 24 hours after onset of left-sided facial nerve weakness and inability to smile on one side of his face. He asks for a therapy to help improve his symptoms quickly, as his daughter is getting married in a few months, and he will be in the wedding pictures.

Is there a treatment that will hasten his complete recovery?

BACKGROUND

■ Insufficient statistical power until now

Many of us treat patients with Bell's palsy with both corticosteroids and antiviral medications, such as acyclovir or vala-

Steroid plus antiviral makes sense, pathophysiologically

Corticosteroids are thought to decrease inflammation of the facial nerve during an episode of facial paralysis. Some have postulated that herpes simplex virus type I may be a cause of facial nerve paralysis, hence the treatment with antivirals.³

Most of our PURL surveillance system clinician reviewers said that they prescribe both corticosteroids and antivirals.

Guidelines: "probably, possibly"

For example, a report of the Quality Standards Subcommittee of the American Academy of Neurology concluded that benefit from both steroids and antivirals has not been well established in patients with Bell's palsy. However, the report states that evidence suggests that steroids are safe and *probably* effective, while antivirals are also safe and *possibly* effective.⁴

In contrast, UpToDate suggests treating all patients seen within a week of symptom onset with corticosteroids (prednisone 60–80 mg daily) plus valacyclovir (1 g 3 times daily) for 1 week.⁵

CLINICAL CONTEXT

■ Quality of life, risk of permanent harm

Bell's palsy, defined as an acute peripheral facial weakness of unknown cause, has an annual incidence of 20 to 32 per 100,000. Most patients recover completely, with or without treatment, but 20% to 30% can have permanent facial weakness or paralysis.

The time to resolution is a quality of life issue for those in whom disease does not resolve spontaneously.⁶

We think that this study provides convincing evidence that acyclovir is not indicated for Bell's palsy and that corticosteroids are.

STUDY SUMMARY

■ 10-day treatment, starting promptly

This double-blind, placebo-controlled, randomized, multifactorial trial compared recovery of facial nerve function for patients randomized to receive 10 days of treatment with prednisolone (25 mg twice daily), acyclovir (400 mg 5 times daily), both agents, or placebo (lactose).

Inclusion criteria

Patients had to be at least 16 years of age (average age=44), with unilateral facial nerve weakness of no identifiable cause (eg, a diagnosis of Bell's palsy). They were recruited mostly through their family doctors (75%) but also through emergency rooms and dental offices, and were referred to otolaryngologists at 17 Scottish hospitals within 72 hours.

The degree of initial facial paralysis was moderate to severe, based on the House-Brackmann scale, a widely used system for grading recovery from

FIGURE

Facial weakness or paralysis may be permanent



Although most patients with Bell's palsy recover completely, with or without treatment, 20% to 30% can have permanent facial weakness or paralysis.

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facial nerve paralysis. After the onset of symptoms, most patients (53.8%) initiated treatment within 24 hours, 32.1% within 48 hours, and 14.1% within 72 hours. Patients were assessed at baseline, 3 months, and 9 months.

Exclusion criteria

Exclusion criteria included pregnancy, breastfeeding, uncontrolled diabetes (Hb A_{1c} >8.0%), peptic ulcer disease, suppurative otitis media, herpes zoster, multiple sclerosis, systemic infection, sarcoid or other rare disorder, and inability to give informed consent.

Primary outcome: Complete recovery

The study was designed to test the effectiveness of prednisolone and acyclovir's effects on facial nerve recovery. The House-Brackmann scale was used to score recovery. The scale divides patients into 1 of 6 categories depending on the severity of facial nerve dysfunction, with grade 1 describing normal function and grade 6 indicating total paralysis.

FAST TRACK

Most of our clinician reviewers said they prescribe both corticosteroids and antivirals

CONTINUED

TABLE

Complete recovery was significantly higher in the group that received prednisolone without an antiviral

	ACYCLOVIR ARM		PLACEBO ARM	
	ACYCLOVIR + PREDNISOLONE	ACYCLOVIR + PLACEBO	PLACEBO + PREDNISOLONE	PLACEBO + PLACEBO
Number of patients who completed therapy	124	123	127	122
% complete recovery* at 9 months	92.7%	78.0%	96.1%	85.2%

* Grade 1 on House-Brackmann scale, indicating normal function.
 Source: Adapted from Sullivan et al.¹

FAST TRACK

This study included twice as many patients as were included in the Cochrane systematic reviews

The scale was applied to photographs of patients taken while smiling, raising eyebrows, at rest, and closing eyes. The photographs were assessed and graded independently by 3 experts: an otolaryngologist, a neurologist, and a plastic surgeon. They were unaware of the study group assignment or stage of assessment.

Of 496 patients who completed the study, 357 recovered fully at 3 months, with no further treatment needed. Of the remaining patients, 80 had fully recovered at 9 months and 59 still had some facial-nerve deficit. At 3 months, there was a significant difference in recovery rates in prednisolone comparison groups: 83% with prednisolone vs 63.6% without prednisolone, a difference of 19.4 percentage points (95% confidence interval [CI], 11.7 to 27.1; $P < .001$, number needed to treat [NNT]=5). There was no significant difference in recovery rates in acyclovir comparison groups: 71.2% with acyclovir vs 75% not treated with acyclovir, a difference of 4.5% percentage points (95% CI, -12.4 to 3.3; unadjusted $P = .30$; adjusted $P = .50$). At 9 months, the rates of complete recovery were 94.4% in prednisolone treated groups vs 81.6% in no prednisolone treatment groups (NNT=8) (TABLE).

Adverse events

Adverse events included an expected range of minor symptoms associated with use of prednisolone and acyclovir, such as dizzi-

ness and vomiting. During the study, 3 patients died under circumstances unrelated to treatment: 2 were receiving double placebo and 1 received only acyclovir.¹

WHAT'S NEW

A treatment based on patient-oriented evidence

Neither corticosteroids nor antivirals are new treatments for Bell's palsy. What is new is that we know what works (corticosteroids) and what does not work (antivirals). This randomized controlled trial finally gives us the evidence on patient-oriented outcomes that we need to make confident recommendations, primarily because it enrolled twice as many patients as all trials compiled for the Cochrane systematic reviews on this topic.^{7,8}

As an interesting side note, this is a good case study of how pathophysiologic reasoning sometimes leads us to good medical practice (corticosteroids in this case) and sometimes does not (antivirals in this case).

Isn't it good to know that we can actually help patients with Bell's palsy with corticosteroids and that antivirals are not necessary?

CAVEATS

Valacyclovir

Hato et al,⁹ in a Japanese study, showed that valacyclovir reaches a level of bio-

availability that is 3 to 5 times more than acyclovir and may add some benefit to recovery when used in conjunction with prednisolone, particularly in more severe cases of Bell's palsy.

The Hato study was a prospective, multicenter, randomized, placebo-controlled study that investigated the effects of valacyclovir (1000 mg/d for 5 days) and prednisolone in comparison with the effects of placebo and prednisolone for the treatment of Bell's palsy.

The study outcomes included complete recovery from palsy; patients were followed until recovery occurred or more than 6 months in cases with severe prognosis. The patients in the Hato study had an average Yanagihara score of 15 when rating their facial palsy (which falls between House–Brackmann grades 4 and 5).

The overall rate of recovery of those treated with valacyclovir and prednisolone (96.5%) was significantly better ($P<.05$) than the rate among those treated with placebo and prednisolone (89.7%). In cases of complete or severe palsy, the rates of patients treated with both agents vs prednisolone alone who recovered were 95.7% ($n=92$) and 86.6% ($n=82$) ($P<.05$; NNT=11).

One big difference between the Sullivan and Hato studies is that the patients recruited for the Hato study had much more severe facial palsy (rated between 4 and 5) than in the Sullivan study (average=3.6), which suggests that there may be a use for valacyclovir in treating patients with complete facial palsy.⁶ Patients were all recruited from tertiary care centers as opposed to mainly from primary care settings as in the Sullivan study, consistent with the greater severity of cases in the Hato study.

Outcome assessors were not blinded to treatment assignments or stage of assessment in the Hato study, raising major concerns about the validity of the findings given the nature of facial paralysis as an outcome measure. We find the Sullivan study a more rigorous and convincing study. Nonetheless, future research

may verify their findings and support the use of valacyclovir in the most severe cases of Bell's palsy. For now, we are not convinced.

CHALLENGES TO IMPLEMENTATION

■ Easy to put into practice

Thankfully, some changes in practice are easy to implement. This is one of them. For those who prefer to prescribe prednisone, the dose of prednisolone used in the study, 25 mg bid, is equivalent to 60 mg of prednisone. ■

PURL surveillance system methodology

This study was selected and evaluated using FPIN's Priority Updates from the Research Literature (PURL) surveillance system methodology. Both the methodology and the criteria and findings leading to the selection of this study as a PURL can be accessed at www.jfponline.com/purls.

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FAST TRACK

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25 mg twice daily
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