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Bell's palsy -
study design, prognosis and quality-of-life

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In loving memory of my father Nils-Owe Pettersson

Women don't want to hear what you think.
Women want to hear what they think – in a deeper voice.
Bill Cosby

ABSTRACT

Background: Bell's palsy is an acute peripheral facial nerve dysfunction with unknown etiology, causing weakness or paralysis of the mimic muscles of the face. The disease can cause disfigurement of the face, impair the ability to eat, drink and speak, and seriously affect the patient's quality of life. Physicians have searched for tests or clinical signs that can predict the outcome of Bell's palsy but none have proven powerful enough. Studies also show several methodological differences and interpretation of results is difficult. In addition, validated instruments measuring quality of life aspects in these patients in Swedish have not been available.

Aims: To examine the effect of different analysis methods on a Bell's palsy study, to find prognostic clinical signs for non-recovery in Bell's palsy using the Sunnybrook facial grading scale, and to translate and validate the Facial Disability Index (FDI) and Facial Clinimetric Evaluation (FaCE) scale questionnaires in Swedish.

Data: Data for papers I-III were extracted from a prospective, controlled multi-center study including 829 patients with Bell's palsy. Patients were randomized to treatment with prednisolone and/or valacyclovir or placebo. In paper IV, 93 patients with stable peripheral facial palsy had their facial function assessed with House-Brackmann and Sunnybrook scales and answered FDI and FaCE-scale questionnaires on two occasions with a 2-week interval.

Results and conclusions: The choice of statistical method and definition of complete recovery substantially influence the calculated rate of recovery. These results emphasize the caution that must be exercised when interpreting clinical results in reported Bell's palsy studies. Early deterioration in Sunnybrook scores between baseline and first follow-up at days 11-17 is found to be a negative prognostic factor for complete recovery at 12 months. Early prednisolone treatment reduces this deterioration and improves outcome in patients with early deterioration. Sunnybrook grading at 1 month can accurately predict non-recovery (Sunnybrook< 70) at 12 months in Bell's palsy. A prediction model and a simple-to-use risk curve for identifying patients at risk for sequelae based on the Sunnybrook score at 1 month are presented and both can be used in clinical practice. The Swedish versions of the FDI and FaCE-scale show high reliability and validity, and the questionnaires can be used for clinical evaluation and for studies on patients with peripheral facial palsy in Sweden.

LIST OF CONTENTS

LIST OF PUBLICATIONS

This thesis is based on the following papers, which will be referred to in the text by their roman numerals:

I.   Berg T, **Marsk E**, Engström M, Hultcrantz M, Hadziosmanovic N, Jonsson L.
The effect of study design and analysis methods on recovery rates in Bell's palsy.
Laryngoscope. 2009 Oct;119:2046-50

II.   **Marsk E**, Hammarstedt L, Berg T, Engström M, Jonsson L, Hultcrantz M.
Early deterioration in Bell's palsy: prognosis and effect of prednisolone.
Otol Neurotol. 2010 Dec;31:1503-7.

III.   **Marsk E**, Bylund N, Jonsson L, Hammarstedt L, Engström M, Hadziosmanovic N, Berg T, Hultcrantz M.
Prediction of nonrecovery in Bell's palsy using Sunnybrook grading.
Laryngoscope. 2012 Apr;122:901-6.

IV.   **Marsk E**, Hammarstedt-Nordenvall L, Jonsson L, Engström M, Hultcrantz M.
Validation of a Swedish version of the Facial Disability Index (FDI) and the Facial Clinimetric Evaluation (FaCE) scale.
Unpublished manuscript. Submitted.

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ABBREVIATIONS

AUC	area under the curve
CI	confidence interval
DNA	deoxyribo nucleic acid
EMG	electromyography
ENoG	electroneurography
ENT	ear, nose and throat
FaCE-scale	facial clinimetric evaluation scale
FDI	facial disability index
HSV	herpes simplex virus
ICC	intraclass correlation
IQR	inter quartile range
ITT	intention to treat
LOCF	last observation carried forward
MRI	magnetic resonance imaging
PCR	polymerase chain reaction
ROC	receiver operating characteristic
SF-36	short form 36 item questionnaire

INTRODUCTION

Background

Peripheral facial palsy is the most frequent cranial neuropathy and can originate from various kinds of damage to the seventh cranial nerve, including its motor nucleus (Roob et al. 1999). A peripheral palsy of the facial nerve can cause not only a distressing disfigurement of the face, but also impair the ability to communicate by facial expression and articulation. An impairment of the motor function of the facial mimic muscles may also cause an inability to eat, drink and speak in an agreeable manner, thereby causing embarrassment and social isolation. This may seriously affect the individual's possibilities to function in his or her social environment.

Bell's palsy is the most common form of peripheral facial palsy in adults (Peitersen 2002). For decades, physicians have searched for tests or clinical signs that can predict the outcome of Bell's palsy. However, studies show several methodological differences and interpretation of the results is difficult. The main purpose of this thesis is to examine prognostic signs for recovery in Bell's palsy and to study the effect of different analysis methods on Bell's palsy trials.

Although several studies regarding Bell's palsy have been performed in Sweden, validated instruments for measuring quality of life aspects in this patient group in Swedish are still lacking. The second purpose of this work is therefore to translate and validate two instruments for measuring quality of life status in patients with peripheral facial palsy.

Anatomy

The greater part of the VIIth cranial nerve, also termed the facial nerve, is composed of motor fibers to the mimic muscles regulating facial expression. The facial nerve also carries parasympatic fibers to the submandibular, sublingual, and lacrimal glands, taste fibers from the anterior two-thirds of the tongue, sensory fibers from membranes of the pharynx, nose and hard and soft palate, and sensation from the skin in the region of the external ear (May M 2000).

Signals for voluntary movement of the facial mimic muscles originate in the motor cortex and pass via the corticobulbar tract in the internal capsule to the facial motor nuclei in the caudal lateral pons. The majority of the fibers cross over in the pons and reach the facial nucleus of the opposite side, but some diverge toward the ipsilateral facial nucleus. Facial nuclei therefore receive input from both sides of the cerebral cortex (Malone and Maisel 1988). The forehead and the orbicularis

15

oculi muscles receive fibers from both the contralateral and ipsilateral motor cortex, while the lower muscles of facial expression receive fibers from only the contralateral motor cortex. This explains why central (upper motor neuron) and peripheral (lower motor neuron) lesions present differently (Malone and Maisel 1988; May M 2000).
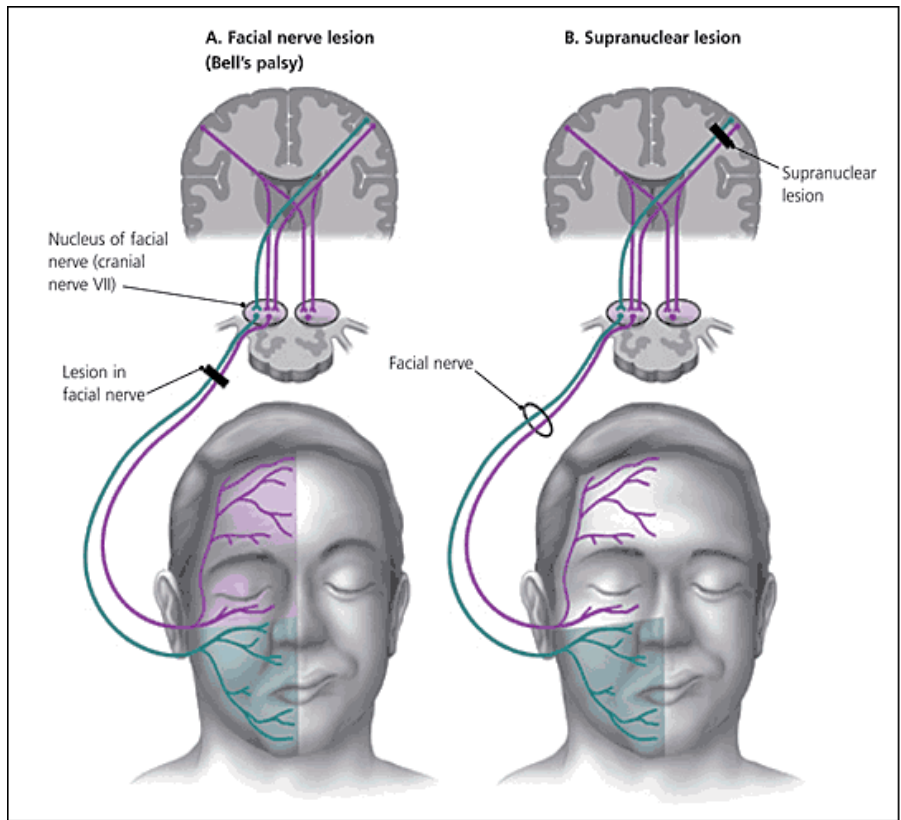
Figure 1. *Central and peripheral facial palsy. From Am Fam Physician. 2007 Oct 1;76:997-1002. Bell's palsy: Diagnosis and Management, Tiemstra and Khatkhate*

Before emerging from the pons, fibers make a loop around the nuclei of cranial nerve VI and traverse through the internal auditory canal together with cranial nerve VIII (the vestibulo-cochlerar nerve). The sensory root of the facial nerve runs separate from the motor root between the brainstem and the internal acoustic canal and is often called nervus intermedius (Gilchrist 2009).

After entering its own bony circuitous tunnel, the fallopian canal, the nerve makes two bends, thus dividing the canal into three segments: the labyrinthine, the tympanic (horizontal), and the mastoid (vertical) (Roob et al. 1999). The labyrinthine part ends at the geniculate ganglion where the nerve makes its first external genu. Within the canal, some visceral motor fibers become the greater petrosal nerve, which leads to the sphenopalatine ganglia from where it supplies the lacrimal, nasal and palatine

glands. In the tympanic segment, a second branch of the facial nerve arises; the nerve to the stapedius muscle that regulates the stapedial reflex and thus protects the inner ear from harmful noise. The facial canal then makes its second external bend in the mastoid segment, where visceral branches form the chorda tympani, which provides innervation to the submandibular and sublingual salivary glands and taste to the anterior two thirds of one side of the tongue (Gilchrist 2009).

The facial nerve leaves the skull through the stylomastoid foramen between the mastoid and the styloid processes. Following its emergence from the skull, it gives off the posterior auricular nerve to provide sensation to the periauricular area. The facial nerve then runs in an arciform course to supply the motor branch of the stylohyoid muscles and the posterior belly of the digastric muscle, before entering the posterior border of the parotid gland. There it finally divides into its terminal branches, the temporofrontal, zygomatic, buccal, marginal mandibular and cervical branches that regulate the movement of the face (Malone and Maisel 1988).

The labyrinthine section of the fallopian canal has been claimed to be the narrowest part (Dumitru et al. 1988) and the nerve is believed to be most vulnerable to stretch and compression at this point (Fisch and Felix 1983).
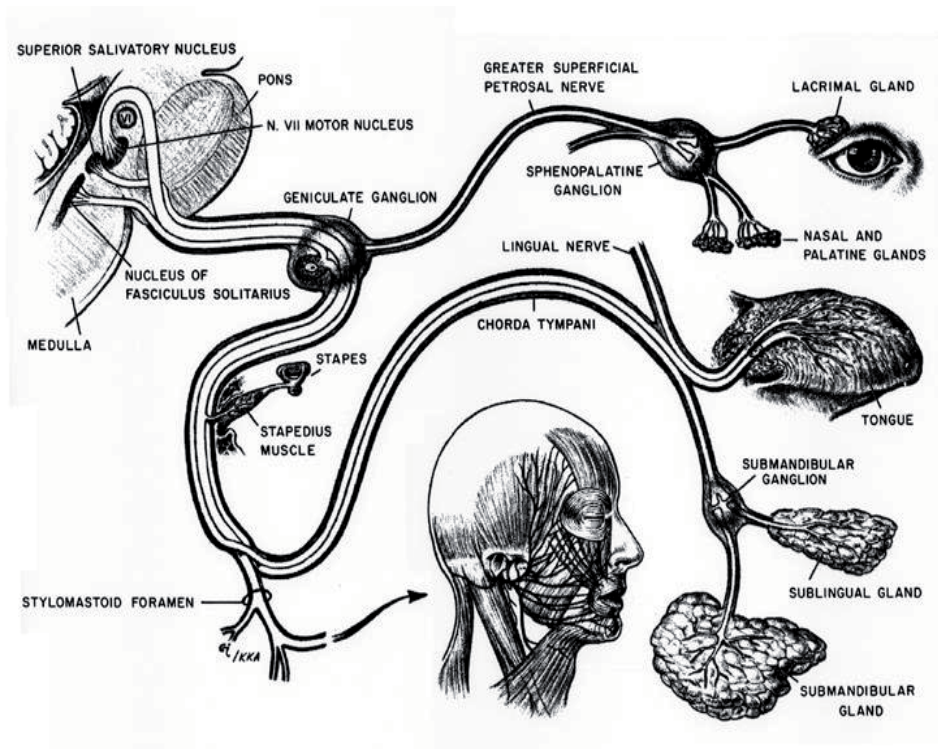

Figure 2. *Facial nerve. Pictures by Dr Kedar K, Dr Adour K, and Steadman E.*

Etiology of peripheral facial palsy

The long intra- and extra-cranial course of the facial nerve exposes the nerve to a broad battery of diseases potentially causing peripheral facial palsy. The etiology of peripheral facial palsy can be infections, trauma, vascular lesions and tumors among others (Valls-Sole 2007). Most frequently identifiable causes of peripheral facial palsy are listed in Table I.

TABLE I. *Identifiable etiologies of peripheral facial palsy. Modified from Roob et al. Eur Neurol 1999;41:3-9*

Traumatic and post-surgical
Temporal bone fracture
Middle ear surgery
Mastoidectomy
Parotid gland surgery
Penetrating wound

Tumor and other compression
Neuroma/neurinoma
Meningioma
Choleasteatoma
Parotid gland tumor
Hemangioma
Metastasis

Infection and inflammation, demyelination
Herpes zoster (Ramsey Hunt syndrome)
Lyme disease
Herpes simplex

Human immunodeficiency virus
CMV
Mycoplasma
Meningitis
Guillain-Barré syndrome
Idiopathic cranial polyneuropathy
Otitis media (acute and chronic)
Heerford syndrome (sarcoidosis)
Melkersson-Rosenthal syndrome

Pontine lesions
Inflammatory - demyelinating (multiple sclerosis)
Vascular
Tumor

Miscellaneous
Diabetes mellitus

Bell's palsy

Bell's palsy is unilateral weakness or paralysis of the face due to acute peripheral facial nerve dysfunction with no readily identifiable cause and with some recovery of function within six month (May and Hughes 1987). Named after Sir Charles Bell (1774-1842), who in the 1820s described the syndrome along with the anatomy and function of the facial nerve, it is the most common cause of peripheral facial palsy (Holland and Weiner 2004).

The average annual incidence of Bell's palsy is 25–30 per 100,000 individuals (Yanagihara 1988; Peitersen 2002) with the highest incidence in patients aged 15-45 (Peitersen 2002). No gender, side, annual or seasonal differences have been noted in most studies (Peitersen 1982; Yanagihara 1988) and no racial predilection has been established (Dumitru et al. 1988).

The onset of Bell's palsy is sudden and usually evolves rapidly during a period of 1 to 7 days (Chow et al. 2002; Tiemstra and Khatkhate 2007; Melvin and Limb 2008), but it may also progress more slowly, reaching maximum weakness up to 1 to 3 weeks after onset (Adour et al. 1985; May and Hughes 1987; Linder et al. 2010).

Etiology of Bell's palsy

The etiology of Bell's palsy remains obscure and there are no clinical, radiological or laboratory tests that can diagnose the disease. On the contrary, diagnosis should be made after exclusion of all other possible causes of peripheral facial palsy. Several theories concerning the etiology have been proposed including genetic, vascular, infective, and autoimmune processes (Roob et al. 1999). Herpes simplex type I (HSV-1) and varicella zoster are two viruses believed to be a plausible etiologic factor for the majority of reported Bell's palsies (Dumitru et al. 1988). McCormick (McCormick 1972) published a hypothesis suggesting that reactivation of HSV-1 causes inflammation and edema in the bony fallopian canal and results in peripheral facial palsy due to compression. His theory was supported by earlier results from serological studies of HSV antibodies by Adour and co-workers (Adour et al. 1975). In a histopathological study of the facial nerve performed by Liston and Kleid, (Liston and Kleid 1989), the entire nerve was found to be infiltrated by inflammatory cells. Myelin breakdown, axonal changes, and edema were present, suggesting viral neuritis. Increased numbers of HSV genome fragments detected by polymerase chain reaction (PCR) were seen in the saliva of patients with Bell's palsy (Furuta et al. 1998). PCR also identified such fragments in human geniculate ganglia at autopsy (Takasu et al. 1992; Burgess et al. 1994). Murakami et al. detected HSV-1 DNA in endoneurial fluid from the facial nerve and posterior auricular muscle from patients with Bell's palsy during decompression surgery (Murakami et al. 1996). Varicella zoster virus infection has also been suggested as the cause of Bell's palsy, even without eruptions of the skin, so-called zoster sin herpete (Adour 1994; Furuta et al. 2000; Lee et al. 2012).

However, other studies have failed to support the viral theory (Rowlands et al. 2002; Linder et al. 2005; Stjernquist-Desatnik et al. 2006) and the etiology of Bell's palsy still remains unclear.

Treatment

Medical treatment

The medical treatment of Bell's palsy used to be highly controversial and different therapeutic regimens have been suggested over the decades. Because the disease is known to be associated with edema and inflammation of the facial nerve (Yanagihara et al. 2000), corticosteroid treatment, particularly in the early stages, has been an obvious possibility (Kennedy 2010). This was believed to reduce edema, swelling and subsequent compression of the nerve within the facial canal (Roob et al. 1999). However, the proposal of corticosteroids as the treatment of choice was mainly based on non-randomized comparisons (Adour et al. 1972). Since then, numerous authors of clinical series have both espoused and condemned corticosteroid therapy with, what appeared to both proponent groups, to be equally convincing arguments (Burgess et al. 1984).

With growing support for herpes simplex virus as an etiology for Bell's palsy (McCormick 1972; Murakami et al. 1996) the use of antiviral agents emerged. Antiviral medication was intended to eradicate the infectious agent, and corticosteroids could then reduce the swelling of the facial nerve. Results of studies by Hato et al report that a combination of valacyclovir and prednisolone was more effective than prednisolone alone for complete recovery (Hato et al. 2007). However, other randomized clinical trials could not verify these results (Sullivan et al. 2007; Engstrom et al. 2008).

The latest Cochrane database review concluded that the available evidence from randomized controlled trials shows significant benefit from treating Bell's palsy with corticosteroids (Salinas et al. 2010). Corticosteroids alone improve rate of recovery and the proportion of people who make a full recovery, and reduce cosmetically-disabling sequelae, motor synkinesis, and autonomic dysfunction compared with placebo or no treatment (Holland and Bernstein 2011). Treatment is likely to be more effective when started within 72 hours of onset, and less effective after 7 days (Holland and Bernstein 2011).

Furthermore, high-quality evidence from randomized controlled trials of herpes simplex antivirals for the treatment of Bell's palsy showed no significant benefit from antivirals compared to placebo. (Lockhart et al. 2009). There is no evidence of a clinically-important additive effect of adding antivirals to corticosteroid therapy (Engstrom et al. 2008; Holland and Bernstein 2011).

Some authors have recommended prednisolone treatment to prevent progression of paresis from a mild to severe form (Adour 1991), but it is still unclear whether early prednisolone treatment could prevent deterioration of incomplete palsy to complete clinical paralysis (May et al. 1976; Linder et al. 2010).

Surgical treatment

Decompression surgery: As the proposed pathophysiology involves entrapment of the nerve, some surgeons have suggested surgical decompression of the nerve as a suitable management option. In 1932, Balance and Duel reported the first recorded attempt at surgical decompression of the facial nerve for Bell's palsy (Duel 1934). Over the following decades, different proposed methods for decompression operations have been reported and their timing has also varied from three months to surgery immediately after onset of palsy (Fisch and Esslen 1972; May and Hawkins 1972) .

Since randomized controlled trials have produced only very low-quality evidence, there is insufficient evidence to support surgical decompression for the management of Bell's palsy (McAllister et al. 2011). This, together with the inherent danger of damaging the facial nerve and other ear structures during the decompression procedure, has made this surgery rare in the management of Bell's palsy. In Sweden today, decompression surgery is rarely undertaken in the management of the disease.

Reconstructive surgery/treatment: Other surgical procedures can be categorized into dynamic versus static, and are mainly undertaken by plastic reconstructive surgeons. In cases where facial muscles can be re-innervated, nerve transfer to 'babysit' facial muscles can be performed. These dynamic procedures include ipsilateral nerve grafts, nerve transfers and cross-facial nerve grafts. This concept of facial reanimation implies that there is a possibility of preventing, minimizing, or slowing down the denervation effects on the facial musculature, and the techniques are believed to be best employed as soon as possible after onset of facial paralysis (Rosson and Redett 2008). Other dynamic procedures include regional and free muscle transfers.

Static procedures, undertaken when sequelae are already obvious, involve facial slings to eyelids and mouth, gold/platinum weights to upper eyelids, eyelid procedures, brow lifts and botox (Rosson and Redett 2008). Optimal reconstruction of the completely paralyzed face usually requires multiple surgeries with both dynamic and static procedures (Robey and Snyder 2011).

Physical therapy

Bell's palsy is commonly treated by various physical therapy strategies and advice. Exercise therapy is the most commonly used, but thermal methods, electrotherapy, massage and biofeedback are other forms that have been used (Peitersen 2002; Beurskens and Heymans 2004; Teixeira et al. 2011).

The effectiveness of facial exercise therapy for facial palsy has been debated in systematic reviews and the mechanism of action is still not totally explained. The

Cochrane Database Systematic Review made by Teixeira and co-workers in 2011 concludes that high-quality evidence to support significant benefit or harm from any physical therapy for idiopathic facial paralysis is lacking. There is, however, low-quality evidence that tailored facial exercises can help improve facial function, mainly for people with moderate paralysis and chronic cases, and that facial exercise reduces sequelae in acute cases (Teixeira et al. 2011).

In their systematic review and meta-analysis, Pereira et al. concluded that mime therapy can improve functionality for patients with facial palsy (Pereira et al. 2011). Baricich et al. also found low-level evidence that mime therapy could be effective in improving functional outcome in patients with peripheral facial palsy. However, evidence of specific treatment addressed to specific cause is lacking and no evidence is available on the timing of intervention with respect to time of onset. Well-designed randomized controlled trials are therefore required to evaluate the effect of rehabilitation in patients with facial palsy (Baricich et al. 2012).

Sequelae and recovery rates

Most Bell's palsy patients are believed to recover well but persistent peripheral facial palsy can be a devastating handicap. Apart from negatively affecting facial appearance, weakness of the facial musculature can result in difficulty in eating, drinking, speaking, and conveying intimate human emotions and communication signals. Disabling secondary defects also include eye dryness and irritation, taste disturbances, stapedius muscle problems resulting in over-sensitivity to loud noise, muscle spasm, and facial pain. The most troublesome sequelae for patients are the associated movements, so-called synkinesis, and contractures that give the patient a feeling of stiffness in the facial muscles (Peitersen 2002). The social and psychological consequences of peripheral facial palsy can be significant (Macgregor 1990).

Earlier Bell's palsy trials have reported varying rates of facial recovery in both treated and untreated patients. In the large, non-controlled study on the spontaneous course of Bell's palsy that included 1,701 cases studied over a period of 25 years, Peitersen reported that about 70% of the patients recovered without medical treatment within 6 months (Peitersen 2002). Sequelae were slight in 12% of the patients, mild in 13% and severe in 4%. He concluded that no treatment, even that including prednisone, was able to improve prognosis.

In contrast, two recent large Bell's palsy trails both concluded that prednisolone does improve restitution of facial function, (Sullivan et al. 2007; Engstrom et al. 2008). Sullivan and coworkers reported complete recovery of facial function in over 90% of patients treated with prednisolone (Sullivan et al. 2007) and in the

study of Engström et al., the corresponding proportions of patients with complete recovery were 72% (Engstrom et al. 2008). In two recent Japanese trials, treatment with prednisolone resulted in recovery rates of 80% and 90% respectively (Kawaguchi et al. 2007) (Hato et al. 2007). In the retrospective clinical study by Mantsopoulos, 73% of patients treated with prednisolone had a satisfactory outcome (Mantsopoulos et al. 2011) compared to the prospective study by Takemoto et al. where full recovery was seen in 94% of patients treated with both prednisolone and valaciclovir (Takemoto et al. 2011).

All above-mentioned studies have methodological differences with different facial grading systems, different follow-up times and different statistical methods and definitions of complete recovery. The impact of study design on recovery rates has been a subject of discussion because studies with similar treatments report varying recovery rates (Gilden and Tyler 2007; Davenport et al. 2008).

Are there any prognostic factors for outcome?

A leading prognostic problem is the difficulty in predicting the final grade of denervation early enough in the development of the disease. Bell's palsy lesions may result in temporary neural blockade (neurapraxia) or axonal destruction with Wallerian degeneration (axonotmesis, neurotmesis). Early in disease evolution, the prognosis is uncertain because the pathologic process producing paralysis may continue for 1-3 weeks (Linder et al. 2010).

Electrophysiology
Several electrophysiological methods have been used in the prognosis of Bell's palsy, including minimal- and maximal nerve excitability testing, blink reflex, electromyography (EMG) and electroneurography (ENoG) (Chow et al. 2002). Among these tests, ENoG has shown to be the most powerful tool in predicting the prognosis of Bell's palsy and other acute peripheral facial palsies (Thomander and Stalberg 1981; May et al. 1983; Valls-Sole 2007; Mantsopoulos et al. 2011; Takemoto et al. 2011).

ENoG for prognostic purposes in Bell's palsy was popularized by Fisch (Fisch 1984). The procedure includes stimulating the facial nerve peripherally, recording the compound muscle action potential of the affected side, and expressing that as a percentage of the non-affected side. Individuals who demonstrate complete palsy and 10% or less of the normal evoked response within the first 2 weeks were believed to have an 80% risk of unsatisfactory recovery (Dumitru et al. 1988).
Although ENoG has the advantage of recordable quantitative and reproducible results, reliable results are dependent on skilled personnel being able to operate the

special equipment with a standardized method since this can influence the test results (Gantz et al. 1984). Furthermore, ENoG cannot give precise information on the type of injury that occurred in the nerve (Fisch 1984). Wallerian degeneration in the distal segment of the nerve takes at least 72 hours to become apparent after an acute injury to the facial nerve. It is therefore recommended that ENOG should not be performed until at least 3 days after the onset of facial palsy. Some users choose to establish ENoG as a prognostic indicator between 5 to 14 days after onset (Chow et al. 2002; Kress et al. 2004; Valls-Sole 2007). Patients with an uncertain prognosis were also recommended daily serial tests to assess prognosis, particularly between the seventh and fourteenth day after onset of the palsy (Esslen 1977; Fisch 1984; Chow et al. 2002). This can cause a severe problem in the clinical setting, since access to these neurophysiological tests is often limited (Kasse et al. 2005).

As a result, other factors that can predict prognosis have been sought in studies based on clinical evaluation of acute symptoms and signs, concurrent medical diseases, age, and radiological investigations.

Clinical parameters for prognosis
Many reports have examined the influence of different parameters on the final outcome of Bell's palsy. Epidemiologic factors include: age (Kerbavaz et al. 1983; Peitersen 2002; Ikeda et al. 2005; Kasse et al. 2005), clinical severity of the initial palsy (Katusic et al. 1986; Gavilan et al. 1988; Smith et al. 1988; Peitersen 2002; Ikeda et al. 2005), severity of palsy 1 month after onset (Ikeda et al. 2005), early beginning of remission (Smith et al. 1988), otalgia or postauricular pain (Katusic et al. 1986; Gavilan et al. 1988; Smith et al. 1988; Peitersen 2002; Berg et al. 2009), and previous ipsilateral palsy (Gavilan et al. 1988).

Old age is often referred to as a negative prognostic factor, but in the work of Mantsopoulos et al., age was not statistically significant in the long-term prognosis of Bell's palsy (Mantsopoulos et al. 2011).
The work of Katusic et al. identified hypertension as an important risk factor for incomplete recovery (Katusic et al. 1986). Peitersen, on the other hand, did not find more frequent or severe palsies in hypertensive patients (Peitersen 2002).

MRI
In the literature, some claim magnetic resonance imaging (MRI) data to be a valid method of predicting outcome (Brugel et al. 1993; Kress et al. 2004), but MRI has mainly been deemed to be an unreliable method for prognostification (Kohsyu et al. 1994; Brandle et al. 1996; Engstrom et al. 1997; Mineta et al. 1997; Burmeister et al. 2011).

Although several studies have investigated these clinical predictive factors, many factors remain inconclusive and not powerful enough in the clinical situation. Additional clinical prognostic tools are therefore needed (Yeo et al. 2007; Ushio et al. 2008).

Grading scales

Clinicians require an objective, reliable and valid clinical tool to accurately describe a patient's facial function, to monitor status over time, and to assess and communicate the course of recovery and the effects of treatment (Croxson et al. 1990; Ross et al. 1996). For a grading system to have clinical usefulness, it must be easy to administer, require little time or equipment, yet be sensitive enough to detect clinically important changes (Ross et al. 1996). Secondary defects such as synkinesis, contracture, and hemifacial spasms may affect facial appearance and function and can be considered in the assessment. In the review of House in 1983, facial grading scales were divided into three different categories: gross, regional (weighted or unweighted) and specific (House 1983).

The general scales are called 'gross' because they consider overall facial function. The primary purpose of gross scales is description; they categorize patients in a simple and practical way without specific details about facial function. Gross scales have been proposed by Botman and Jongkees (Botman and Jongkees 1955), May (May 1970), Peitersen (Peitersen 1982) and House (House and Brackmann 1985).

In a regional system, the assessor scores different areas of facial function independently. In a weighted regional scale, certain areas of the face are considered less important because they are deemed to be less functionally or cosmetically relevant. Regional scales have been devised by several authors (Yanagihara 1976; Lewis and Adour 1995; Ross et al. 1996). In addition to these main systems, different specific scales that address the presence or absence of various associated symptoms also exist (Stennert et al. 1977; Burres and Fisch 1986; Murty et al. 1994).

The House-Brackmann system, based on a 6-graded score where I is normal function and VI total paralysis, offers a gross evaluation of facial motor function and evaluation of sequelae. Its basic purpose is to rate patient's facial function according to general categories and not to give specific details about facial function (House 1983; House and Brackmann 1985). In 1985, the Facial Nerve Disorder Committee of the American Academy of Otolaryngology - Head and Neck Surgery adopted the House-Brackmann grading scale as a universal standard for grading facial nerve recovery (House and Brackmann 1985). It has since become the most used scaling system for facial nerve disorders in the USA and Europe. However, the scale has

been criticized for not being sensitive enough to document clinically significant changes in facial function over time (Ross et al. 1996) and for being prone to inter-observer variation (Croxson et al. 1990; Kanerva et al. 2006).

TABLE II. *The House-Brackmann facial grading scale*

Grade	Description	Characteristics
I	Normal	Normal facial function in all areas
II	Mild dysfunction	Slight weakness noticeable on close inspection; may have very slight synkinesis
III	Moderate dysfunction	Obvious but not disfiguring difference between 2 sides; noticeable but not severe synkinesis, contracture or hemifacial spasm; complete eye closure with effort
IV	Moderately severe dysfunction	Obvious weakness or disfiguring asymmetry; normal symmetry and tone at rest; incomplete eye closure
V	Severe dysfunction	Only barely perceptible motion; asymmetry at rest
VI	Total paralysis	No movement

In 1996, Ross et al. proposed a grading system, the Sunnybrook facial grading system, that reports results in a more continuous manner and with a wider response range than the House-Brackmann grades (Ross et al. 1996). This regionally-weighted system includes evaluation of resting symmetry, degree of voluntary movements, and synkinesis to form a composite score from 0 to 100, where 0 is complete paralysis and 100 indicates normal function (Ross et al. 1996).

Due to its demonstrated improved sensitivity and reliability, use of the Sunnybrook facial grading system has been advocated when the intention is to monitor change in facial function (Chee and Nedzelski 2000; Kanerva et al. 2006). The intra-rater and inter-rater reliability of the system has been reported to be high when applied both by novice and expert users (Hu et al. 2001).

The regional unweighted Yanagihara system assesses 10 areas of facial function. Each function is scored from 0 to 4, giving a maximum score of 40. The scale does not include any secondary effects. The Yanagihara scale is the most widely used system in Japanese studies for evaluating facial nerve function in peripheral facial palsy (Satoh et al. 2000).

TABLE III. *The Sunnybrook Facial Grading scale*

Sunnybrook Facial Grading System

Resting Symmetry

Compared to normal side

Eye (choose one only)

normal	0
narrow	1
wide	1
eyelid surgery	1

Cheek (naso-labial-fold)

normal	0
absent	2
less pronounced	1
more pronounced	1

Mouth

normal	0
corner drooped	1
corner pulled up/out	1

Total ☐

Total x 5 ☐

Resting symmetry score

Symmetry of Voluntary Movement

Degree of muscle excursion compared to normal side

Standard Expressions	No movement	Slight movement	Movement with mild excursion	Movement almost complete	Normal movement	
Brow lift	1	2	3	4	5	
Gentle eye closure	1	2	3	4	5	
Open mouth smile	1	2	3	4	5	
Snarl	1	2	3	4	5	
Lip pucker	1	2	3	4	5	
	Gross Asymmetry	Severe Asymmetry	Moderate Asymmetry	Mild Asymmetry	Normal Asymmetry	Total

Voluntary movement score:

Total x 4

Vol mov't score | **Resting - symmetry score** | **-Synk score** | **= Composite score**

Synkinesis

Degree of involuntary muscle contraction associated with each expression

	No synkinesis	Mild synkinesis	Moderate synkinesis	Severe synkinesis
Brow lift	0	1	2	3
Gentle eye closure	0	1	2	3
Open mouth smile	0	1	2	3
Snarl	0	1	2	3
Lip pucker	0	1	2	3
				Total

Synkinesis score:

Total

27

Peripheral facial palsy and quality-of-life

Health-related quality-of-life is the component of overall life quality that is determined primarily by the person's health and may be influenced by clinical intervention. It is a broad multi-dimensional concept that usually includes self-reported measures of physical and mental health.

Most of the measurement methods used in Bell's palsy today are the above-mentioned physician-ranking scales that quantify impairment of facial posture and movement. Although both the House-Brackmann and Sunnybrook scales describe the severity of facial palsy, neither capture the patient's perception of their outcome and neither address how this handicap may affect the patient's quality-of-life.

Facial nerve dysfunction may be classified into two components: facial impairment, which describes the anatomical abnormality, and facial disability, which pertains to the functional and social deficits caused by the impairment (Saito and Cheung 2010).

A number of existing patient-reported instruments measure quality-of-life outcomes in peripheral facial palsy patients. These validated instruments measure and describe facial disability related to dysfunction. The most used and best-validated questionnaires are the Facial Disability Index (FDI) and the Facial Clinimetric Evaluation (FaCE) scale (Ho et al. 2012). FDI, developed by physical therapists at the Facial Nerve Center of the University of Pittsburgh, includes aspects of the mouth, eye and entire face, as well as the influence of the palsy on emotions and everyday activity (VanSwearingen and Brach 1996). Patients report their impairment and disability by answering 10 questions divided into two domains: physical function and social/well-being function. The FaCE-scale, developed by researchers at the Baylor College of Medicine, Houston, Texas, also measures facial impairment and disability (Kahn et al. 2001). The 15-item scale includes six domains: facial movement, facial control, oral function, eye comfort, lacrimal control, and social function. Both FDI and FaCE questionnaires have been used in several clinical studies over the years (Coulson et al. 2004; Lee et al. 2007; Mehta and Hadlock 2008).
Despite many research studies on peripheral facial palsy from Sweden, validated questionnaires in Swedish regarding quality-of-life aspects in peripheral facial palsy are still lacking. Using these quality-of-life questionnaires in a language other than English requires a rigorous translation and revalidation in the new language (Guillemin et al. 1993).

AIMS OF THE THESIS

The overall aim of the research project was to examine the effect of different analysis methods on a Bell's palsy study and to find clinical prognostic parameters to detect those patients at risk for suffering sequelae from the disease. An instrument in Swedish for subjective measurement of the impact the facial palsy has on patients' quality-of-life was also needed.

Specific aims were:

1. To investigate how the choice of analysis method and the definition of recovery affect recovery rates in a Bell's palsy study.

2. To assess if early deterioration of Bell's palsy is a negative prognostic factor for facial outcome at 12 months and if prednisolone treatment can prevent this early deterioration.

3. To develop a prognostic model using clinical parameters, including the Sunnybrook scale, to find patients with a poor prognosis as early as possible in the disease.

4. To translate and validate a Swedish version of the FDI and FaCE-scale quality-of-life questionnaires in a Swedish cohort of patients with peripheral facial palsy.

MATERIALS AND METHODS

Patients

Papers I-III
Data for the first three papers were extracted from the 'Scandinavian Bell's palsy study'. This controlled trial included patients with acute unilateral peripheral facial palsy from 16 public otorhinolaryngological centers in Sweden and Finland. Patients aged 18 to 75 years with onset of palsy within 72 hours were included from May 2001 to September 2006 with final follow-up in September 2007.

Exclusion criteria were systemic anti-herpetic medication within the previous 2 weeks, ongoing systemic steroid medication, allergy to anti-herpetic medication, pregnancy, breastfeeding, other neurological diseases, signs of Borreliosis, diabetes, badly-controlled hypertension, current or a history of serious heart disease, history of renal or hepatic disease, gastric or duodenal ulcer, history of glaucoma, acute otitis or history of ipsilateral chronic otitis, psychiatric disease, or any other condition that risked being influenced by the study medication or that might have affected completion of the study.

In total, 839 of the 1,953 screened patients met the inclusion criteria and were randomized into four treatment arms. Ten patients did not take the intended study drug and were excluded. Consequently, 829 patients (341 women, 488 men) were included in the modified intention-to-treat (ITT) analysis. Baseline assessment was performed before treatment start and included otorhinolaryngological examination, grading of facial function, measurement of ipsilateral pain, documentation of concurrent medication, and serum analysis for antibodies to *Borrelia burgdorferi*. Baseline characteristics of the four treatment groups were similar with regard to median age, gender, side of palsy, time from onset of palsy to treatment start, and median scores of facial function. Patients were randomly assigned to one of four treatment groups; placebo plus placebo, prednisolone plus placebo, valacyclovir plus placebo, or prednisolone plus valacyclovir within 72 hours after onset of palsy. Of these, 206 received placebo plus placebo, 210 prednisolone plus placebo, 207 valacyclovir plus placebo, and 206 prednisolone plus valacyclovir. Study design was factorial with four analysis groups; 416 of the patients were given prednisolone whereas 413 were not. Similarly, 413 received valacyclovir and 416 did not.

Paper IV
Swedish versions of the FDI and FaCE-scale were tested on 93 consecutive patients examined between May 2011 and June 2012. The study was performed at two different Otorhinolaryngology centers; the Karolinska University Hospital in Stockholm and Uppsala University Hospital in Uppsala, Sweden.

Inclusion criteria were age 18 or older and a history of peripheral facial nerve palsy of more than 4 months. Patients were excluded if they were non-Swedish speaking, required assistance to complete the form, or had primary signs of facial dysfunction other than peripheral facial nerve palsy. They were also excluded if cancer in the head and neck region was the cause of palsy, since head and neck cancer and its treatment were assumed to cause a reduction in the patient's quality-of-life independently of the facial palsy. Patients with other serious illnesses (severe heart failure, spread malignancies and diseases causing severe chronic pain), which could also be expected to reduce their overall quality-of-life, were similarly excluded. Vestibular schwannoma patients with facial palsy were included if they did not have serious balance or vertigo problems.

Methods

Papers I-III
The included 829 patients were randomly assigned to four treatment arms. Prednisolone (5 mg tablets or its placebo) was given at 60 mg daily for five days, then tapering 10 mg per day with a total treatment time of 10 days. Valacyclovir (or its placebo) was given as two 500 mg tablets three times daily for 7 days.

Follow-up visits were scheduled for day 11 to 17 and at 1, 2, 3, 6, and 12 months. If recovery was complete (Sunnybrook score =100) at 2 or 3 months, the next follow-up was at the final 12-month visit. At the final 12-month visit, 743 patients of the included 829 were examined (90%).

Sunnybrook and House-Brackmann facial grading scales were used to assess the facial function at all visits. The Sunnybrook scale was used as the main grading system to evaluate facial function in the studies.

Paper IV
Translation process
Translation was performed according to internationally accepted guidelines and with permission from the American original authors. English versions of the FDI and FaCE-scale were translated independently by two professional otolaryngologists with excellent knowledge of English but with Swedish as their native language. A bicultural expert compared the two translated scales and a consensus version was obtained. The Swedish version was then separately translated back into English by two native English-speaking medical physicians with excellent knowledge of Swedish. A professional medical translator then compared the original English version with the back-translations. This translator found no conceptual differences in the back-translations compared with the original version and the Swedish versions of the FDI and FaCE-scale were thus approved in format and content.

Pilot study

The Swedish versions of both questionnaires were tested in a pilot study on five professional physicians with knowledge of peripheral facial palsy and five patients with the same characteristics as the intended study population. Professionals and patients completed the questionnaires in the presence of the main author, who observed whether or not they had problems reading or responding to the items. The main author then asked questions about the measure's relevance as well as ease of understanding and completion. This testing allowed for corrections in the final layout of the questionnaires that made it easier for the patients and doctors to read, understand and answer.

Validation process

Clinical information (etiology of the palsy, duration, co-morbidity, therapy received) was collected from the patient or from the patient's medical records. All subjects' facial function was graded with House-Brackmann facial grading scale and Sunnybrook facial grading scales.

Patients agreeing to participate filled in the FaCE-scale, the FDI and the Medical outcomes Study Short Form 36 Item Questionnaire (SF-36) during the clinical visits. For the retest, the FDI and the FaCE-scale were sent home to the patients two weeks later, who then returned them by mail to the examining physician. No treatment for their palsy was given to the study patients during this two-week interim period.

Statistical Analysis

Paper I

Facial function recovery rates were assessed with four different analysis methods used in similar Bell's palsy studies (Hato et al. 2003; Kawaguchi et al. 2007; Sullivan et al. 2007):

1. **Last observation carried forward, Sunnybrook = 100.**
   Recovery defined as Sunnybrook score of 100 at 12 months based on the intention-to-treat principle and last-observation-carried-forward method (n = 829).

2. **Last observation carried forward, House-Brackmann = I.**
   Recovery defined as House-Brackmann grade I at 12 months based on the intention-to-treat principle and last-observation-carried-forward method (n = 829).

3.   **Complete-case analysis, House-Brackmann = I.**
     Recovery defined as House-Brackmann grade I in patients followed until re-
     covery plus those remaining at the 12-month follow-up (n = 782) (47 patients
     were lost to follow-up before recovery and excluded).

4.   **Complete-case analysis, House-Brackmann ≤ II**
     Recovery defined as House-Brackmann ≤ grade II in patients followed until
     recovery plus those remaining at the 12-month follow-up (n = 797) (32 pa-
     tients were lost to follow-up before recovery and were excluded).

Fisher's exact test was used to compare categorical values. Results are given with
continuous variables as median values with interquartile range (IQR; 25th–75th
percentiles) and dichotomous data as proportions with 95% confidence interval. All
computations were carried out using SAS software version 9.1 (SAS Institute Inc.,
Cary, NC) and R version 2.4.1 (The R Foundation for Statistical Computing).

Paper II
To identify patients with early deterioration of palsy, deterioration from baseline to
the first follow-up at days 11 to 17 was registered by Sunnybrook facial grading and
House-Brackmann grading scores.

Outcome of palsy at 12 months in patients exhibiting deterioration from baseline to
the first follow-up visit was compared with subjects whose palsy did not deteriorate
during this time interval.

The effect of prednisolone on deterioration of palsy from baseline to first follow-up
was evaluated with the Sunnybrook grading system by comparing the number of
patients deteriorating during this interval in subjects receiving prednisolone and in
those not given the drug. The effect of the drug compared with no treatment on the
outcome of palsy at 12 months in patients with early deterioration was also assessed
with the Sunnybrook scaling system.

Data are presented as median values and interquartile range (IQR; 25th-75th per-
centile). Missing data for patients were handled using the last-observation-carried-
forward (LOCF) method where missing values (facial gradings) were replaced with
the last available observation for each patient.

Because the data set was not normally distributed, comparison analyses were perfor-
med using non-parametric methods. The Kruskal-Wallis test was used to compare
median facial grading values between the deteriorating and the non-deteriorating
groups. The $\chi 2$ (chi-2) test was used to compare proportions of complete recovery.

The Kaplan-Meier method was used to estimate survival curves, and the log-rank test was used to compare survival distribution of the samples. $P < 0.05$ was considered statistically significant. STATA software (version 9; StataCorp LP, College Station, TX, USA) was used for all statistical analyses.

Paper III
Prediction model
To develop and validate a clinical prognostic mathematical model, the data set that included 829 patients was randomly divided into a *training data set* comprising 500 patients (60%) and a *validation data set* of 329 patients (40%).

Univariate and multivariate logistic regression analyses with facial function at 12 months as main outcome were performed using the training data set (n = 500). Potential prognostic factors of outcome were first analyzed by univariate logistic regression analysis that included patient characteristics at baseline: treatment (prednisolone or no prednisolone), gender, time from onset to inclusion, age, side of palsy, and pain. Statistically significant predictors for non-recovery were then analyzed for their independent predictive values using multivariate logistic regression.

Data from days 11 to 17 that included Sunnybrook scores, pain, deterioration from baseline to days 11 to 17, and previously mentioned baseline variables were then tested in a multivariate model. Finally, a third multivariate model was constructed. This included the variables described for the baseline, days 11 to 17 models, and Sunnybrook scores at 1 month.

Missing values were replaced with the LOCF method. In addition to LOCF, data obtained by the complete-case analysis method (743 patients) were also analyzed in all models. The logistic regression models obtained with the training data set were also tested on the validation data set (n = 329).

ROC and AUC
To evaluate the diagnostic performance of the logistic regression models, receiver operating characteristic (ROC) curves were constructed to discriminate between patients with Sunnybrook scores ≥70 and Sunnybrook scores <70 (non-recovery) at 12 months. ROC analysis curves show the relationship between sensitivity on the y-axis and specificity on the x-axis for different cut-off levels of test positivity. The area under the ROC curve (AUC) provides a measure of the overall discriminative power of a model. Values can range from 0.5 (no predictive power, expected by chance alone) to 1 (perfect prediction).

Results are presented with numbers of observations, odds ratios with 95% confidence intervals (CI), AUC (95% CI), sensitivity, and specificity. P values ≤0.05 were

considered significant. Statistical analyses were carried out using the SAS version 9.2 statistical program (SAS Institute, Cary, NC).

Paper IV
Descriptive statistics are given as number, mean values with standard deviation, median with minimum to maximum values, or valid percentage.

To estimate the internal consistency of the FDI and FaCE-scale when examining all the items and the items in each domain, Cronbach's α coefficient was calculated. Internal consistency is considered satisfactory if Cronbach's α exceeds 0.70, although ≥0.80 is recommended. Test-retest reliability was calculated through the intraclass correlation coefficient (ICC) by repeated FDI and FaCE-scale scoring (by test and retest) with intervals of 2 weeks.

Cross-sectional validity was tested with Spearman's rho statistics by comparing FDI and FaCE-scale scores to House-Brackmann and Sunnybrook grading scores. Construct validity was assessed by creating subscale matrices for the FDI domain and FaCE-scale domain as well as total scores to compare with related domains in SF-36.

SF-36 results were calculated using Quality Metric Health Outcomes™ scoring software 4.0. Statistical calculations were made in STATA® version 10 (StataCorp LP, USA), Statistica 10.0 (Stat Soft Inc Tulsa OK, USA) and IBM SPSS Statistics 19 (IBM Inc USA). A p-value less than 0.05 was regarded statistically significant.

RESULTS

Recovery rates (Paper I)

Of the 829 included patients, 341 (41%) were women, and the median age was 40 years (IQR 31–54). The baseline median Sunnybrook and House-Brackmann scores (for the 829 patients in the intention-to-treat analysis) were 39 (IQR 23–54) and 4 (IQR 3–5) respectively.

With recovery defined as Sunnybrook scale score 100, analysis of the 829 patients based on the intention-to-treat principle and last-observation-carried-forward method showed that 300 of the 416 patients (72%) in the prednisolone group had recovered at 12 months, compared with 237 of 413 patients (57%) who did not receive prednisolone ($p < 0.0001$; Fig 3). For valacyclovir, the corresponding values at 12 months were 271 of 413 (66%) for the valacyclovir group and 266 of 416 (64%) in the no-valacyclovir group ($p = 0.66$).

When House-Brackmann grade I was defined as recovery, recovery rates at 12 months in the 829 intention-to-treat patients were 324 of 416 (78%) for those receiving prednisolone and 266 of 413 (64%) for patients not receiving prednisolone ($p < 0.0001$; Fig. 3). In the valacyclovir group, 297 of 413 (72%) recovered, whereas in patients not treated with valacyclovir this figure was 293 of 416 (70%) ($p = 0.65$).

With recovery defined as House-Brackmann grade I in patients followed until recovery (39 patients had House-Brackmann grade I before 12 months) plus the remaining patients with a 12-month follow-up (n = 782), 335 of 389 patients (86%) in the prednisolone group had recovered compared with 277 of 393 (70%) in the no-prednisolone group ($p < 0.0001$; Fig. 3). The corresponding rates for valacyclovir/no-valacyclovir groups were 307 of 386 (80%) and 305 of 396 (77%), respectively ($p = 0.44$).

When definition of recovery was House-Brackmann I or II in patients followed until recovery, plus the remaining patients with a 12-month follow-up (n = 797), recovery rates were 380 of 396 (96%) in prednisolone-treated patients and 353 of 401 (88%) in those not treated with prednisolone ($p < 0.0001$; Fig. 3). The corresponding recovery in the valacyclovir group was 363 of 393 (92%) and in the no-valacyclovir group, 370 of 404 (92%) ($p = 0.70$).
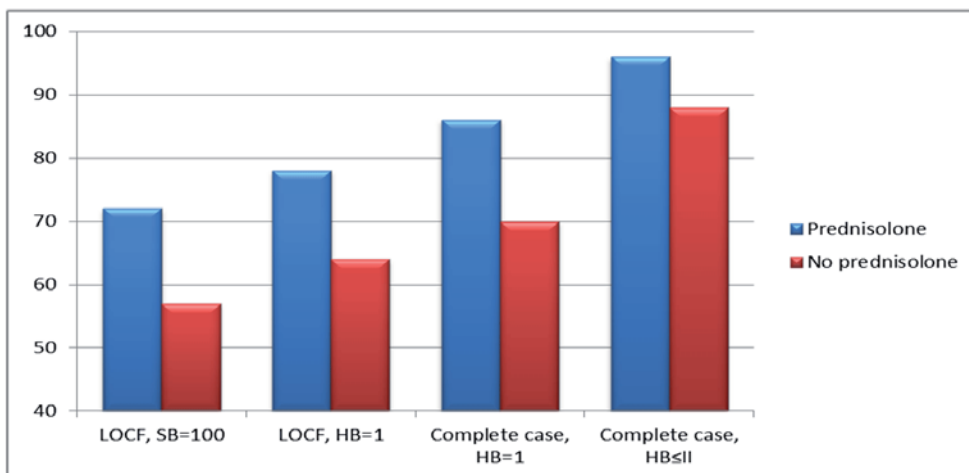
Figure 3. *Recovery rates in Bell's palsy patients receiving prednisolone and not receiving prednisolone. Last-observation-carried-forward (LOCF) method with recovery defined as Sunnybrook scale score of 100 and House-Brackmann grade I, and complete-case analysis method with recovery defined as House-Brackmann grade I and ≤ grade II, respectively.*

Early deterioration (Paper II)

Early deterioration of palsy and outcome at 12 months
In 236 (28%) of the 829 patients, palsy deteriorated from baseline to the first follow-up at days 11 to 17. Deterioration was indicated by a drop of ≥30 Sunnybrook scores in 34 patients (4%), a drop of 20 to 29 scores in 44 patients (5%), 5 to 19 scores in 112 patients (14%), and less than 5 in 46 (6%) of the 829 patients. Median time for inclusion of the 236 patients with deterioration from baseline to days 11 to 17 was 24 hours (IQR, 16.5-36 h) compared with 32 hours (IQR, 24-48 h) in the 593 patients whose condition did not initially deteriorate.

The proportion of patients with complete recovery at 12 months was 106 (45%) of 236 subjects whose palsy deteriorated from baseline to days 11 to 17 compared with 433 (73%) of 593 patients with no initial deterioration ($p < 0.0001$), Table IV.

TABLE IV. *Number of Bell's palsy patients with early deterioration or no early deterioration. Values are Sunnybrook scores at 12 months and the number of patients (%) with complete recovery at 12 months. Total number is 829 patients.*

	Early deterioration	No early deterioration	*p*
Sunnybrook	n=236	n=593	
Score at 12 months, median (IQR)	96 (72-100)	100 (99-100)	<0.0001
Complete recovery (Sunnybrook =100), n (%)	106 (45)	433 (73)	<0.0001

In the 176 patients included between 49 and 72 hours ('late inclusion'), the conditions of 29 (16%) deteriorated from baseline to days 11 to 17 compared with those of 147 patients (84%) that did not deteriorate. The proportion of patients with complete recovery among the 'late included' whose conditions deteriorated between baseline and days 11 to 17 was 15 (52%) of 29 compared with 112 (76%) of 147 in late included patients with no initial deterioration ($p = 0.007$).

Effect of Prednisolone on Early Deterioration and Outcome at 12 months
As shown in Table V, 105 patients with initial deterioration of palsy had been randomized to prednisolone, whereas 131 patients with initial deterioration did not receive prednisolone. Baseline Sunnybrook scorings were similar in the 2 groups.

The number of patients with complete recovery at 12 months was 64 (62%) of the 105 patients in the prednisolone group compared with 41 (31%) of the 131 patients

in the non-prednisolone group ($p < 0.0001$). Figure 4 shows that early prednisolone treatment gave a significantly higher recovery rate among the patients with early deterioration ($p = 0.001$).

Among the 593 patients whose condition did not deteriorate between baseline and days 11 to 17, 311 (52%) were randomized to prednisolone and 282 (48%) received no prednisolone. At 12 months, 236 (76%) of the patients treated with prednisolone and with no initial deterioration showed complete recovery compared with 196 (70%) of 282 patients with no initial deterioration and who did not receive prednisolone ($p = 0.08$; Table V and Fig. 4).

TABLE V. *Number of Bell's palsy patients with early deterioration or no early deterioration and treated or not treated with prednisolone. Complete recovery defined as Sunnybrook =100.*

| | Early deterioration | | | No early deterioration | | |
	Prednisolone	No prednisolone	p	Prednisolone	No prednisolone	p
Sunnybrook Score at baseline, median (IQR)	n=105	n=131		n=311	n=282	
	45 (29-62)	43 (29-58)	0.5	35 (22-51)	37 (19-51)	0.94
Score at 12 months, median (IQR)	100 (88-100)	88 (62-100)	0.0001	100 (100-100)	100 (96-100)	0.024
Complete recovery n (%)	64 (62)	41 (31)	0.0001	236 (76)	196 (70)	0.081
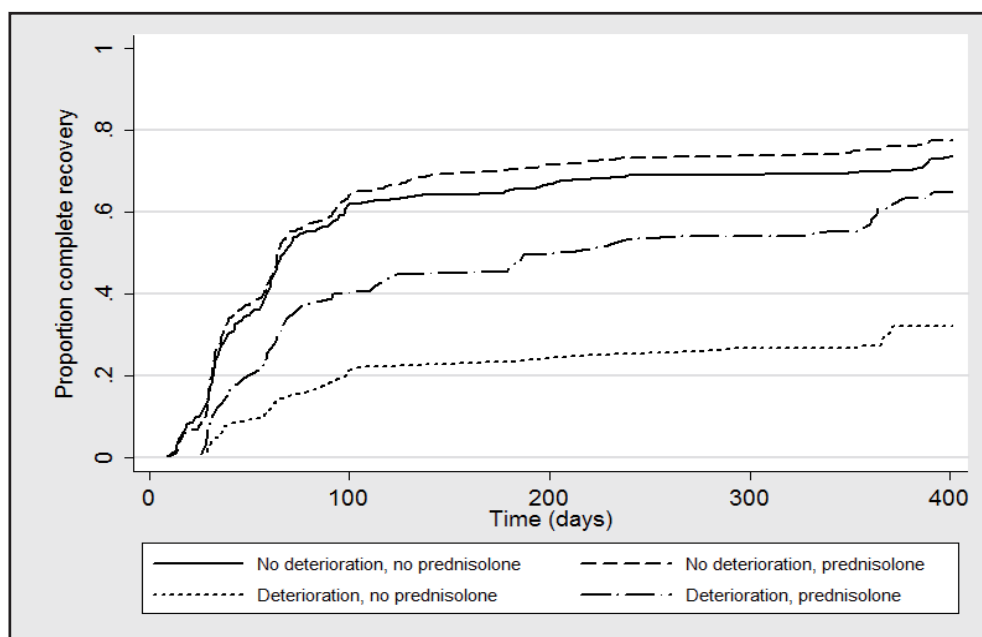
Figure 4. *Kaplan-Meier estimates of patients who made a complete recovery (Sunnybrook=100). Curves represent patients with early deterioration or no early deterioration and treated or not treated with prednisolone.*

Sunnybrook grading at 1 month (Paper III)

Among the seven baseline variables analyzed in the univariate regression analysis, treatment (prednisolone or no prednisolone) ($p = 0.0005$), age ($p = 0.04$) and Sunnybrook score at baseline ($p = 0.0002$) were statistically significant prognostic factors for non-recovery. Gender, time from onset of palsy to treatment start, side of palsy, and pain at baseline were not significantly correlated with non-recovery.

In the multivariate regression analysis of baseline data: treatment, age, and Sunnybrook score at baseline were independent significant predictive factors and were used to create the baseline model. In the multivariate analysis of data obtained from days 11 to 17, the variables treatment and age lost their predictive ability when analyzed together with Sunnybrook score at days 11 to 17. Sunnybrook score at days 11 to 17 was the only variable that was a significant predictive factor (odds ratio 0.94, 95% CI 0.92-0.96). Multivariate analysis at 1 month also showed the Sunnybrook score as the only significant factor for non-recovery (odds ratio 0.92, 95% CI 0.91-0.95). Sunnybrook scores at these time points during recovery were therefore used to develop the days 11 to 17 and 1-month models for clinical practice.

Figure 5 shows the ROC curve for the 1-month model for the training and validation data sets. The AUC value for non-recovery in the training data set (n = 500) was 0.74 for the baseline model and 0.83 for the days 11 to 17-model. The corresponding value at 1 month was excellent with AUC 0.94 (sensitivity 0.91, specificity 0.85). Validation of the models in the independent validation data set (n = 329) showed good calibration and discriminative ability for predicting non-recovery (AUC 0.74 at baseline, 0.87 at days 11 to 17, and 0.94 at 1 month).

The predicted probability for a Sunnybrook score <70 (non-recovery) at 12 months was also calculated for the total data set (for patients receiving prednisolone or no prednisolone) using the presented 1-month model. As shown in Figure 6, the risk for non-recovery predicted at 1 month differs greatly depending on the Sunnybrook score at that time point, both in patients treated and not treated with prednisolone.
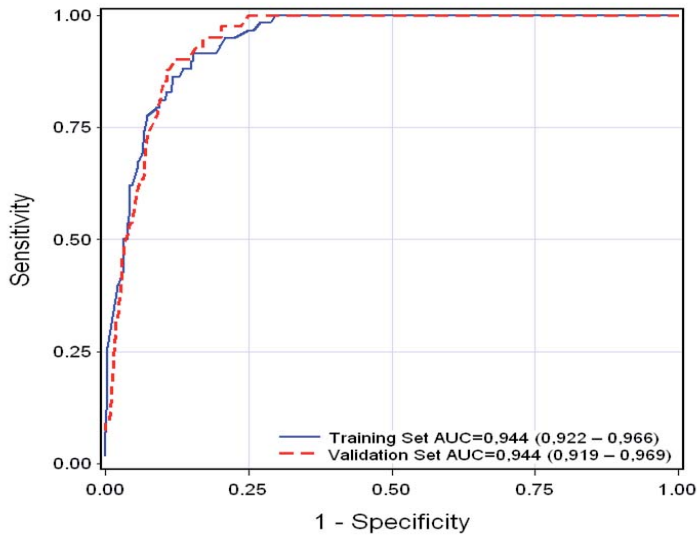
Figure 5. *Receiver operating characteristics for Sunnybrook scores at 1 month for the training and the validation set. AUC and CI are shown for both sets.*
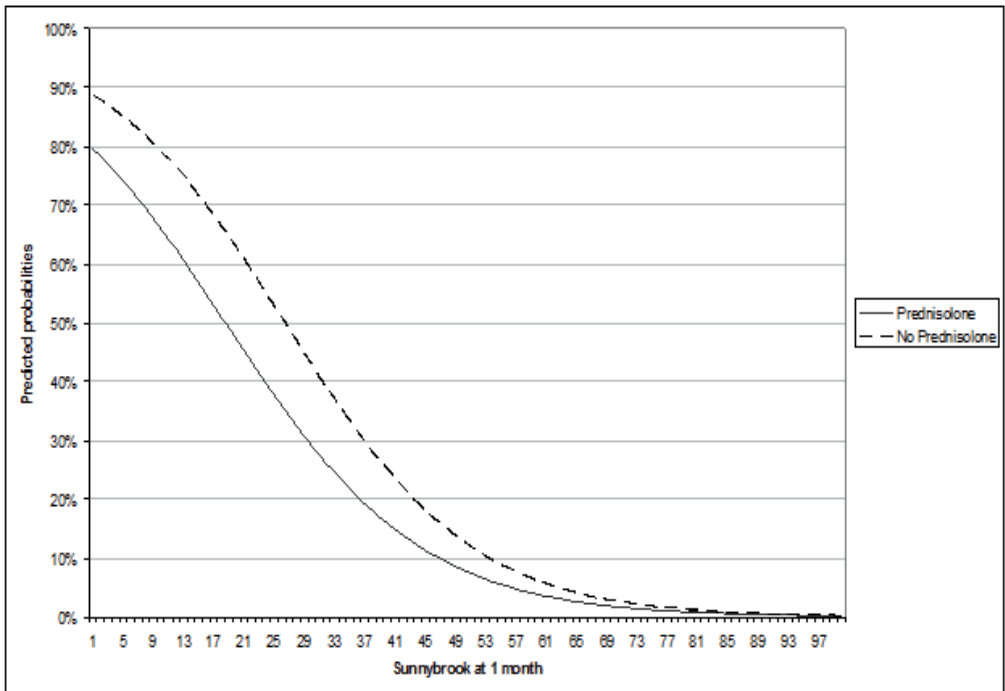

Figure 6. *Predicted probabilities for patients with non-recovery defined as Sunnybrook <70 at 12 months according to the 1-month Sunnybrook score. The predicted fraction of patients with non-recovery at 12 months treated with prednisolone (full line) or not treated with prednisolone (dashed line) on the basis of Sunnybrook score at 1 month is shown.*

40

Validation of the FDI and FaCE-scale (Paper IV)

A total of 93 patients were included in the study. Forty-nine (53%) were women and 44 men (47%). The mean age was 56.9 years (range 26-89 years, median 59). The mean duration of palsy was 51.9 months with median duration 22 months (range 4-696 months). The majority of patients (78.5%) were diagnosed with Bell's palsy. The mean Sunnybrook total score was 62.7 with a median of 65.0 (range 1-100). Corresponding scores for House-Brackmann were 3.1 (mean), 3.0 (median) and 1-6 (range). (One patient had recovered objectively with a Sunnybrook score of 100 and a House-Brackmann score of 1, but still experienced subjective sequelae and was therefore included).

The internal consistency of the FDI and FaCE-scale was tested by Cronbach's α, as shown in Table VI. For the FDI domains, Cronbach's α results were excellent, with scores ranging from 0.82 to 0.87. For the FaCE-scale, Cronbach's α scores for Domains and Total scores were also excellent; 0.76 to 0.92.

Table VI. *Internal consistency reliability (Cronbach's α) and test-retest reliability (intraclass correlations coefficient, ICC and 95% CI=confidence interval) for FDI domains, FaCE-scale domains and total scores.*

	Internal consistency Cronbach's α		Test-retest ICC	95% CI
FDI	Test	Retest		
Physical function	0.87	0.86	0.93	0.90–0.96
Social/well-being function	0.82	0.80	0.91	0.86–0.94
FaCE-scale				
Social function	0.89	0.91	0.93	0.90–0.96
Total	0.92	0.92	0.97	0.96–0.98

A plot of the patients' test and retest total scores for the FaCE-scale is shown in Figure 7. The degree of agreement was similar when using the test and retest scores from FDI domains physical function and social/well-being function (data not shown). The intraclass correlation coefficient (ICC) was used as a measure of relia-
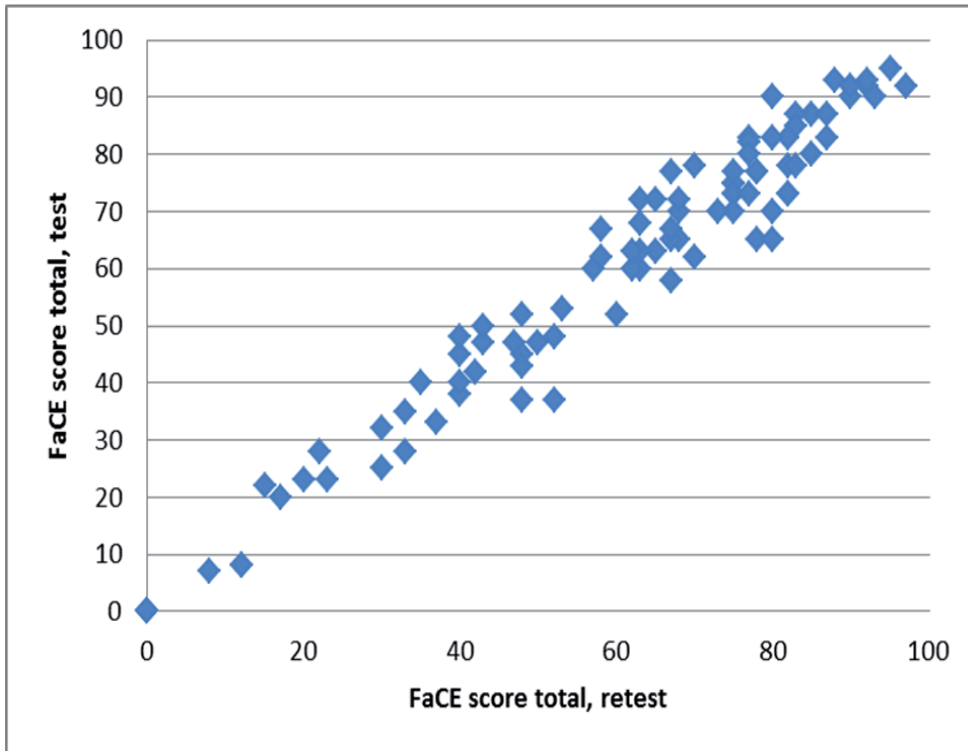
Figure 7. *FaCE scale: plot of the patients' test and retest total scores.*

bility. Retest forms were returned by 88 patients (94.6 %). The FDI scores showed excellent reliability with ICC results of 0.93 for physical function and 0.91 for social/well-being function. ICC results for the FaCE-scale were also excellent; ICC ranged from 0.83 to 0.97 (Table VI).

Cross-sectional validity was tested by comparing FDI and FaCE-scale scores (domain and total) with Sunnybrook and House-Brackmann scores. Positive correlation was found between the FDI/FaCE-scale scores (Figure 8) and Sunnybrook grading, whereas a negative correlation was found between FDI/FaCE-scale and House-Brackmann scores. This latter finding was expected due to the House-Brackmann scale design.

In FaCE-scale, facial movement score showed best correlation with House-Brackmann and Sunnybrook scores (-0.81 and 0.85), but oral function and social function scores also correlated well. FDI showed good correlation with House-Brackmann and Sunnybrook scores in physical function (-0.61 and 0.63), but lower correlation with the social/well-being function (-0.38 and 0.40).
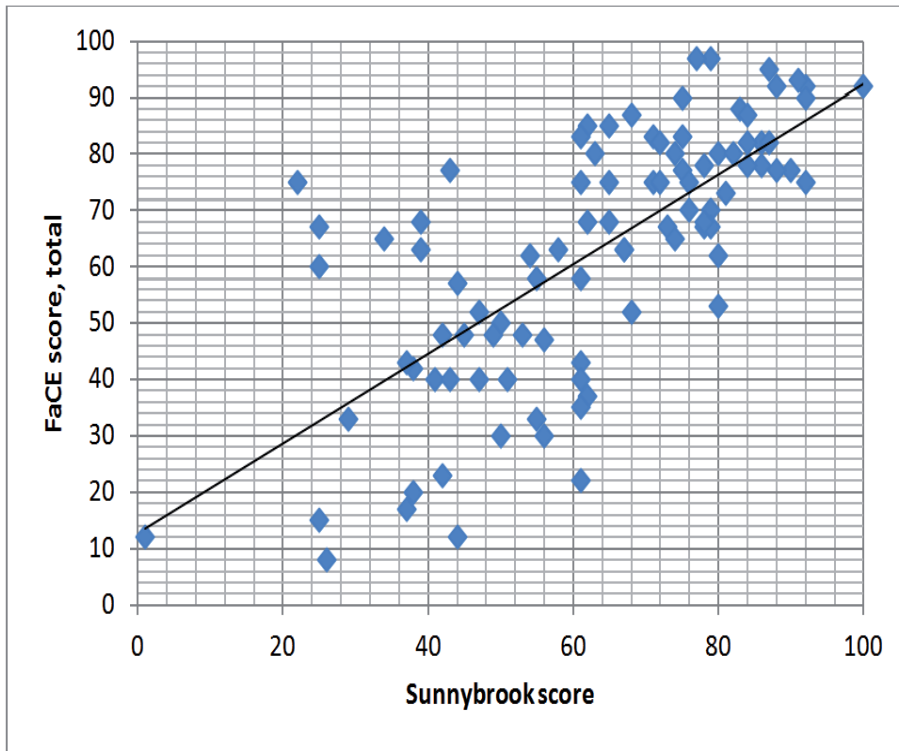
Figure 8. *Plot of the patients' total FaCE-scale scores and Sunnybrook facial grading scores.*

DISCUSSION

The disfiguring facial expressions associated with Bell's palsy can cause significant functional, aesthetic, and psychological disturbances to the patient (Yeo et al. 2007). The terms used to describe satisfactory and unsatisfactory recovery from the disease are often poorly defined and the reported studies have important methodological differences (Dumitru et al. 1988). The findings in this work show that caution must be exercised when interpreting clinical results in Bell's palsy studies reported in the literature.

The possible sequelae from which Bell's palsy patients might suffer can be a hindrance to an active social life and most patients and their caregivers thus worry about the prognosis. An accurate prognosis of the peripheral facial palsy is therefore useful for counseling these patients and guiding further treatment. In this work, deterioration between baseline and days 11-17 as well as facial function at 1 month after onset measured with the Sunnybrook facial grading scale were shown to be of prognostic value for the outcome of Bell's palsy.

Only through patient-reported outcome instruments can we truly evaluate the success of surgical and non-surgical interventions in patients with peripheral facial palsy (Ho et al. 2012). To date, instruments in Swedish for measuring quality-of-life aspects in this patient group have been lacking. Therefore, two validated patient-reported outcome instruments for measuring quality-of-life and patient satisfaction in peripheral facial palsy have been translated to Swedish and validated.

Why differences in reported recovery rates?

Earlier Bell's palsy trials have reported varying rates of facial recovery in both treated and untreated patients. However, the studies have several methodological differences that make comparing results difficult.

This thesis highlights the impact of different statistical analysis methods on calculated recovery rates in a Bell's palsy study. The choice of method substantially influences the rate of recovery, which varies from 72% to 96% in patients treated with prednisolone and from 66% to 92% in patients receiving valacyclovir. A variety of factors can affect recovery rates.

Reasons for different outcomes
Inclusion and exclusion criteria in a study determine which patients may be evaluated and that might influence the severity of palsy at baseline. This will affect the prognosis of the palsy (Gilden and Tyler 2007) and thereby also recovery rates.

The method used to assess facial function is another factor that impinges on recovery rates (Hato et al. 2008). Grading facial function from photos (Sullivan et al. 2007; Hato et al. 2008) or videos has a lower sensitivity for minor sequelae and most probably results in higher recovery rates compared with live grading.

The grading system used to measure facial function can also impact the outcome. Recovery rates were shown to be lower when using the Sunnybrook scale compared to the House-Brackmann scale (72% and 78% respectively in groups treated with prednisolone and 57% and 64% in the groups not treated with prednisolone). This could be caused by the fact that the regional-weighted Sunnybrook scale succeeds in reporting results in a more continuous manner and with a wider response range than House-Brackmann grading scale (Ross et al. 1996). The gross House-Brackmann scale is the most widely used scale (Coulson et al. 2005) and has been shown to be easy to use, but it displays only a moderate degree of inter-observer reliability and fair sensitivity (Chee and Nedzelski 2000). A system with only 6 different categories does not allow documenting minor changes during a short time period, neither as deterioration nor improvement in function (Linder et al. 2010).

Investigators have therefore advocated that the Sunnybrook grading scale should be applied whenever accurate and precise documentation of facial function is required, both in patient counseling and in research (Chee and Nedzelski 2000).

Follow-up times differ in the literature and can presumably influence reported outcome. In studies, patients with Bell's palsy were followed at 3 months (Gavilan et al. 1988), 6 months (Ikeda et al. 2005), 9 months (Sullivan et al. 2007) or 1 year (Smith et al. 1988; Engstrom et al. 2008). It has been shown that no great improvement can be expected more than 1 year after onset of Bell's palsy (Mantsopoulos et al. 2011), but 12 months have been estimated to be required as follow-up period to achieve a steady state in the facial muscles (Peitersen 2002).

Missing data and dropouts in a clinical trial can be dealt with by several different methods, but none is fully adequate (Streiner 2002; Lane 2008). In the Scandinavian Bell's palsy trial, the intention-to-treat principle was applied and the last-observation-carried-forward method used for missing data (Engstrom et al. 2008). The rationale behind this approach is that it is conservative; it operates against the hypothesis that people will improve over time, and thus under-estimates rather than over-estimates the degree of improvement (Streiner 2002; Lane 2008). Statisticians have, however, warned that imputing missing values with last observation carried forward can introduce bias (Lane 2008; Simpson et al. 2008).

In contrast to last-observation-carried-forward, the complete-case analysis method excludes dropout patients and only includes patients with complete data. The recovery rate (with recovery defined as House-Brackmann grade I) in the prednisolone group was 86% with complete-case analysis and 78% with the last-observation-carried-forward method. Thus, the complete-case analysis resulted in higher recovery rates than last-observation-carried-forward. Criticism of the complete-case analysis method is that it reduces the sample size and the power of the study. It may also produce biased results unless data are missing completely at random (Fielding et al. 2008).

Prognostic factors

The work in this thesis first focused on the prognostic value of Sunnybrook scores at 3 months after onset of palsy. This time point was previously used at the ENT department in Stockholm for assessing the severity of remaining palsy and for selecting patients at risk for sequelae. In the Scandinavian Bell's palsy trial, 334 observations were done at 3 months. This '3-months-group' was divided into different subgroups according to the severity of the remaining facial palsy using the 3-month visit Sunnybrook scores. Scores of the same patients at baseline, 11-17 days, and

1-, 2-, 6-, and 12-months visits were checked. These are shown as a graph in Figure 9. It can be seen that the best two groups start to improve directly with median scores at the second visit exceeding baseline scores. All other groups deteriorate in median scores from the initial visit to the next, with the worst groups improving very slowly.
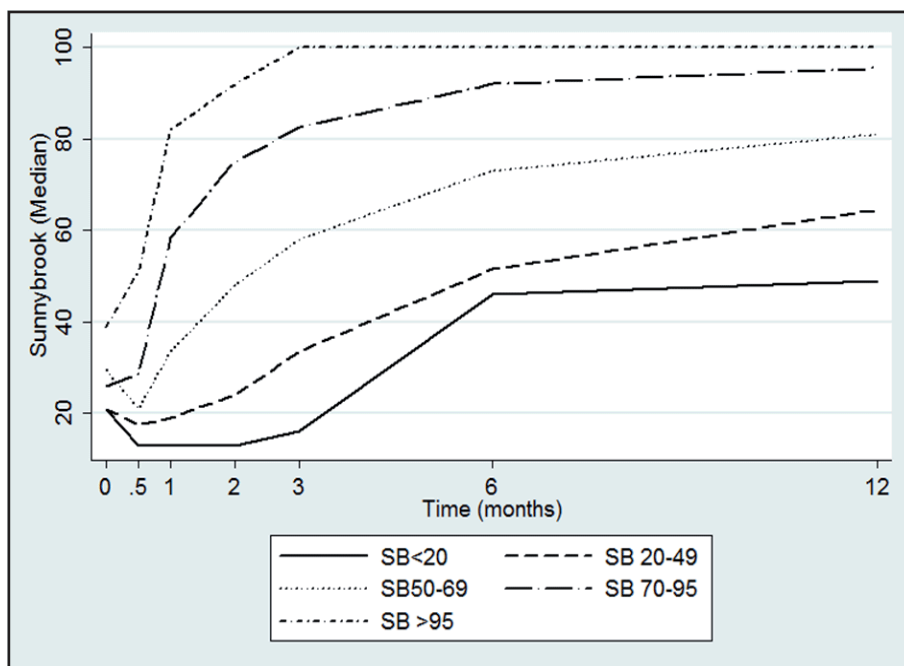

Figure 9. *Median Sunnybrook scores at different time points after onset of palsy. Patients are grouped after severity of palsy at 3 months using their Sunnybrook score at that time point. n=334.*

The finding of this drop in initial score in the groups with worst outcome prompted us to evaluate what effect this early deterioration has for outcome in Bell's palsy.

Early deterioration
When focusing on different prognostic factors in predicting the outcome of Bell's palsy, data from the Scandinavian Bell's palsy trial were again used in the assessments. This study dataset is unique due to the magnitude of patients included, a follow-up period of 1 year, a low percentage of patients lost to follow-up, and use of the sensitive regional and weighted Sunnybrook scale. The study was summarized with a low risk of bias in the Cochrane report by Lockhart et al. (Lockhart et al. 2009). All these factors favor usage of the dataset for implementation of clinical predictive studies concerning non-recovery from Bell's palsy.

Bell's palsy has a high spontaneous recovery, but up to 30% of patients experience sequelae (Peitersen 2002). Since sequelae can be severe, patients are often seriously worried about their disease throughout its clinical course, and they expect physicians to be able to predict the outcome of their palsy.

Early deterioration of Bell's palsy, defined as deterioration in Sunnybrook scores from baseline (within 72 h) to days 11 to 17, was found to be a negative prognostic factor for complete recovery at 12 months. Early deterioration was demonstrated in 28% of patients. It may be speculated that this early deterioration was partly due to these patients seeking medical care earlier (median of 24 h after onset) than patients with no initial deterioration (median of 32 h after onset), resulting in an assessment of their facial function being made before the palsy reached its maximum weakness. However, the time for the initial clinical assessment during the first 72 hours does not seem to entirely explain the poorer outcome in the deteriorating group; 15 (52%) of 29 patients with early deterioration and initially examined late (between 49 and 72 hours after onset of palsy) had similar complete recovery rates to those with early deterioration but examined between 0 and 72 hours (106 of 236 patients, 45%).

Our findings of early deterioration as a negative prognostic factor are in agreement with the report by Linder et al. (Linder et al. 2010). They found that in patients with an initial drop of facial score plus paralysis (severe palsy), 30% had delayed improvement and incomplete recovery. In an earlier study by May et al. (May et al. 1976), 12 (24%) of 51 Bell's palsy patients progressed from incomplete to a complete palsy. Both studies used regional grading systems similar to the Sunnybrook system used in paper II.

Sunnybrook score at 1 month
Sunnybrook grading at 1 month showed the ability to accurately predict non-recovery at 12 months in Bell's palsy. The risk of not reaching full recovery (Sunnybrook < 70) was evaluated based on age, gender, time to inclusion, prednisolone treatment, side of palsy, pain at inclusion and Sunnybrook score at baseline, days 11-17, and 1 month. A prediction model is presented that identifies Bell's palsy patients at 1 month with a high risk for non-recovery at 12 months. The accuracy of the ROC model was excellent at 1 month (AUC = 0.94) and the main predictor for non-recovery was the Sunnybrook score at 1 month. The predictive value of Sunnybrook grading at baseline was weaker than at days 11 to 17 and at 1 month, which is reflected by the AUC values for the prediction model (AUC = 0.74 at baseline, 0.83 at days 11 to 17, and 0.94 at 1 month). The improvement in predictive capability over time may be explained by the palsy being unstable in its early stage and then stabilizing.

The presented model is validated and simple to use for early identification of patients with a high risk for poor outcome. It may be used for planning and the need for follow-up visits.

Why the necessity to predict outcome early?
It is important to identify patients at risk for suffering sequelae early for several reasons. Some of the patients with inadequate improvement of facial function will require plastic reconstructive intervention to achieve better facial symmetry (Bulstrode and Harrison 2005). Today, surgical nerve crossover techniques can be used to improve facial function (Rosson and Redett 2008). This surgery is best carried out before the muscles on the paralyzed side become atrophied. The time interval when surgery needs to be performed is preferably within 9 months after onset of palsy (Terzis and Tzafetta 2009). It is therefore important to early predict those patients who risk suffering sequelae and to identify candidates for surgery.

Furthermore, patients with Bell's palsy worry about the risk for permanent facial deformity and are eager to determine their chances of recovery. It is important to save patients with good prognosis some mental distress whenever possible. In addition, outpatient clinic resources may be scarce, so unnecessary visits to the doctor should be avoided if possible. The presented results show that 1 month after onset of palsy is an optimal time point for clinical prediction of non-recovery in Bell's palsy. By examining patients with Bell's palsy at this time, those at risk of suffering sequelae could be identified and clinical resources, e.g. surgery, physical therapy and speech therapy, allocated to these patients.

Prognostic clinical signs and tests in literature
The predictive value of facial function at 1 month is in accordance with the reported findings of Ikeda et al., who found that the House-Brackmann grading at 1 month had a statistical significance for the prognosis of facial paralysis (Ikeda et al. 2005). Our findings of the high predictive capacity of Sunnybrook at 1 month are, however, in contrast to those of Takemoto and co-workers (Takemoto et al. 2011). They reported that Yanagihara grading at baseline as well as the worst grading score during recovery are not significant predictable variables. These contradictive results may be due to the difference in grading systems used (Yanagihara scale is not weighted), fewer patients included in their study, the time points for the predictive evaluation, and different definitions of non-recovery.

In the early acute setting, there are no electrical, radiologic, or clinical tests that can accurately predict the final facial outcome for the individual patient (Adour et al. 1985; Peitersen 2002; Lee et al. 2006; Yeo et al. 2007; Ushio et al. 2008). It is known that ENoG is a useful test to assess the prognosis of Bell's palsy (Fisch

1984). However, test equipment for ENoG is relatively expensive and can be difficult to use (Ikeda et al. 2005). Furthermore, the test should not be performed as a prognostic indicator until at least 3-14 days after the onset of palsy (Chow et al. 2002; Kress et al. 2004; Valls-Sole 2007), and it is not always reliable in predicting outcome (Qiu et al. 1996; Lee et al. 2006). Moreover, access to this method can be very limited and as a result, other clinical factors that can accurately predict prognosis have been sought after.

Clinical indicators for poor prognosis have been proposed, including severity of initial facial palsy, old age, presence of pain, hypertension, and diabetes mellitus (Danielides et al. 1996; Peitersen 2002; Ikeda et al. 2005; Hsieh et al. 2009). However, these factors are inconclusive and not powerful enough in the clinical situation. Additional clinical prognostic tools are therefore needed (Yeo et al. 2007; Ushio et al. 2008; Burmeister et al. 2011).

Age was not a predicting factor for non-recovery in this work. In other studies, the influence of age on outcome has been reported to be significant (Adour and Wingerd 1974; Danielides et al. 1996; Peitersen 2002; Ushio et al. 2008). With increasing age there is an increase in vascular degeneration which leads to a decrease of the peripheral blood supply. This has been an argument for possible decrease in facial nerve recovery in older patients with Bell's palsy (Danielides et al. 1996). However, several studies show that age was not among the most important variables in predicting prognosis of Bell's palsy (Gavilan et al. 1988; Yeo et al. 2007; Takemoto et al. 2011). This latter observation is in agreement with the presented results.

The importance of presented results
The impact of study design on recovery rates in Bell's palsy has recently been debated (Gilden and Tyler 2007; Davenport et al. 2008; Hato et al. 2008). The presented results show that the analysis method and definition of recovery used in a Bell's palsy study can substantially affect calculated recovery rates at 12 months. Therefore, comparison of recovery rates between different studies has to be carefully interpreted. If the study design is not taken into account, important methodological differences may be overlooked and comparisons between recovery rates in untreated patients (Peitersen 2002) and patients treated with prednisolone (Sullivan et al. 2007) may result in erroneous conclusions (Romijn et al. 2008).

Case history, clinical investigations and laboratory tests have to be combined in order to estimate outcome correctly (Hyden et al. 1982). The finding that early deterioration is a risk factor for non-recovery, together with the presented prognostic model and 1 month-risk curve, may be an additional tool for identifying patients at risk for sequelae and may help clinicians in their work.

49

Corticosteroid treatment

Among patients treated with prednisolone, the number with early deterioration was lower compared with patients not given prednisolone. In patients with early deterioration, prednisolone medication compared with no prednisolone resulted in a larger proportion with complete recovery at 12 months.

The background for early deterioration is unclear. The pathological process in Bell's palsy is most probably related to an inflammatory reaction with edema along the facial nerve in the fallopian canal. Owing to its anti-inflammatory effect, steroid treatment may reduce this inflammation and prevent further nerve damage.

Whether early corticosteroid treatment could prevent deterioration from paresis to complete clinical paralysis has so far not been sufficiently documented (Linder et al. 2010), but it seemed prudent to treat patients early to prevent further deterioration of a palsy to complete paralysis (Linder et al. 2010). Adour et al suggested an association between early prednisolone treatment and less severe disease (Adour et al. 1996). However, May et al found no beneficial effect of early steroid treatment on disease progression or final outcome (May et al. 1976).

Patients with incomplete acute Bell's palsy should start to improve their facial function early (3-weeks after onset) and are expected to recover completely within 3 months (Peitersen 2002). Some argue that only patients with severe palsy should be prescribed steroid treatment (Sathirapanya and Sathirapanya 2008) since those with incomplete palsy are expected to recover without treatment. At the initial visit, however, it is not possible to predict if the conditions of these patients are likely to deteriorate to a paralysis (severe or complete palsy) (Linder et al. 2010). Prednisolone treatment, when compared with no prednisolone medication, resulted in a lower number of patients with early deterioration and a higher proportion with complete recovery. The reported high percentage of patients with early deterioration (May et al. 1976; Linder et al. 2010), plus our findings that prednisolone may reduce progression and improve outcome in the deteriorating group, justifies early corticosteroid treatment even in patients with an initially mild Bell's palsy.

Peripheral facial palsy and quality-of-life

The face is the primary source of identification for human beings, displaying emotions effectively and enhancing communication between individuals. Patients with facial palsy suffer a profound loss because of the impairment of this system (Byrne 2004). The effect that altered facial motion has on those suffering from facial palsy is significant. Depressive symptoms are reported in 65% of those with facial neuromotor disorders, an incidence three to five times that of the general population

(VanSwearingen et al. 1998). Finding ways to measure the impairment and disability that the patient with peripheral facial palsy experience is therefore of great importance.

The FDI and FaCE-scale were translated into Swedish and validated in patients with peripheral facial palsy. The two questionnaires showed very good psychometric properties with high validity and reliability. No major difficulties were observed in the translation and cultural adaptation of the questionnaires. The instruments were easily understood by patients and straightforward to fill in. Compliance was high and missing response values very low.

The majority of scales used today are physician-ranking scales used to quantify impairments of facial resting posture and movement (Ho et al. 2012). More recently, outcomes have been analyzed with respect to patient satisfaction, functional outcome and quality-of-life (Coulson et al. 2004; Ryzenman et al. 2005; Saito and Cheung 2010).

The systematic review of Ho et al. identified only three patient-reported outcome instruments for quality-of-life that were developed and validated for facial palsy patients and in which FDI and FaCE-scale were considered applicable for the general facial paralysis population (Ho et al. 2012). In English, both the FDI (VanSwearingen and Brach 1996) and FaCE-scale (Kahn et al. 2001) are proven to be valid and reliable specific questionnaires. FDI was recently translated into Spanish (Gonzalez-Cardero et al. 2012) but FaCE-scale has not been translated and validated in other languages.

Both the translated FDI and FaCE-scale showed very good to excellent internal validity with Cronbach's α scores between 0.76 and 0.92 for domain and total score. The response rate for the retest was as high as 95% for the patients who responded to the second questionnaire. Both questionnaires had good reliability with intra-class correlation scores ranging from 0.83 to 0.97, and good sensitivity, i.e. the ability to discriminate between patients with varying degrees of impairment. Both questionnaires also showed good cross-sectional validity with high correlation with the House-Brackmann and Sunnybrook facial grading scales. The strong correlation between the FaCE-scale facial movement domain score and House-Brackmann ($r = -0.81$) agrees with the results ($r = -0.55$ and -0.69) of the original FaCE-scale validation performed by Kahn et al. (Kahn et al. 2001).

Social function domains showed lower correlation values with House-Brackmann and Sunnybrook scoring systems than did physical domains. Lower values for social function domain correlation with House Brackmann were also reported by Kahn et al. (Kahn et al. 2001) in the original study.

Relationship between severity of palsy and subjective distress

Studies have shown that there is no clear relationship between degree of disfigurement and degree of subjective distress (Bradbury et al. 2006). For example, Cross et al. found no association between the severity of facial impairment and the level of psychological distress measured in 29 patients experiencing facial paralysis for at least one year after acoustic tumor surgery (Cross et al. 2000). In the report by Lee et al., social disability measured by the FaCE-scale could not be predicted by the severity of facial paralysis in 56 patients with facial weakness after vestibular schwannoma surgery (Lee et al. 2007). This illustrates the difficulty in measuring social aspects of the disease with only objective physician-graded instruments.

The reasons for low correlation between social function and objective physical measurements in this work, as in the literature, can be several. Factors that mediate individual responses such as personal resilience, strong family and social support, and the development of effective coping strategies are some examples. Patients who have had their palsy for a longer time can adapt to the handicap and accept their situation. Many of the patients included in the present study spontaneously reported that they would have answered the social domain questions differently if they had been asked the same questions earlier during their disease. Further, patients undergoing vestibular schwannoma surgery are informed about the risk for peripheral facial palsy beforehand, and have time to mentally prepare for possible sequelae.

The extent of the psychological problems due to the patients' facial palsy has probably not been fully understood by clinicians. Ikeda and colleagues (Ikeda et al. 2003) evaluated 131 patients with peripheral facial palsy and scored 20-30% of the patients 'cured' with the Yanagihara and House-Brackmann scales. Yet, the same patients experienced the persistence of minor dyskinesia and did not rate themselves as cured. It has been suggested that the long-term sequelae of facial nerve paralysis has been underestimated by clinicians (Smith et al. 1994). It is therefore of great importance that the physician takes the social and psychological aspects of the disease in account when handling the patient.

The Swedish versions of the FDI and FaCE-scale questionnaires showed high reliability and validity and can be used for clinical studies on patients with peripheral facial palsy in Sweden. The inclusion of self-report measures in the assessment process, and a focus on issues drawn from these patients' reports, could be directly fed back into clinical treatment strategies. Psychological support is sometimes asked for by patients with peripheral palsy in distress, but many patients included in this work revealed that they withheld requests for psychological counseling since that option never was presented by the doctor, and also seemed impossible to ask for. This should be taken into account when planning future treatment options for these patients.

Limitations

The number of physicians involved in the Scandinavian Bell's palsy study was 49. Early stage assessments were often done by less experienced physicians, although help was available from more senior colleagues. To reduce these problems, the Sunnybrook scale was used as the main facial grading system. This system has good repeatability and has reliable agreement between observers, even with novice users (Kanerva et al. 2006). The Scandinavian Bell's palsy study included 829 patients. Of these, 719 had their facial function assessed at 1 month. In our prediction model, we used imputed data for missing values (n = 829) in the follow-up visits. To overcome the possible influence of this statistical method, we therefore also analyzed data with complete-case analysis (n = 743). The two methods gave similar results.

Facial function was assessed at baseline and at days 11 to 17 in the early stage. Daily assessments would have made it possible to study if the difference between rapid and slow progression was related to the outcome of palsy. We found no correlation between the severity of early deterioration, measured by progression in Sunnybrook grades, and outcome. However, the subgroups studied were comparatively small.

Results are presented with the Sunnybrook facial grading system, but in the Scandinavian Bell's palsy study, facial function was also assessed by House-Brackmann grading. As could be expected (according to earlier argumentation), the number of patients with early deterioration was greater with the more sensitive Sunnybrook scale compared with the gross House-Brackmann system. Nevertheless, when analyzed, the overall result for early deterioration and facial grading score at 1 month as a significant negative prognostic factor for complete recovery was similar for both grading systems.

The quality-of-life questionnaires were not tested for responsiveness to change (Heffernan and Jenkinson 2005). Testing patients in the early stage of facial palsy and re-examining at different time points during follow-up would allow analysis of how the FDI and FaCE-scale's scores change in relation to changes in House-Brackmann and Sunnybrook scores over time. This has not previously been tested, even in the original English versions, and might therefore be a study for the future.

CONCLUSIONS

- Calculated recovery rates at 12 months in a Bell's palsy study are substantially affected by the choice of analysis method and definition of recovery.

- Deterioration in facial function in Bell's palsy from baseline (within 72 h) to days 11 to 17 is a negative prognostic factor for recovery at 12 months. Early prednisolone treatment reduces progression of palsy and improves outcome in patients with early deterioration.

- Sunnybrook grading at 1 month accurately predicts non-recovery (defined as Sunnybrook < 70) at 12 months in Bell's palsy. A simple-to-use risk curve for non-recovery at 12 months that can be used in the clinical setting is presented.

- Swedish versions of the FDI and FaCE-scale questionnaires showed high reliability and validity. Both can be applied as useful tools for clinical evaluations and future studies in Swedish patients with peripheral facial palsy.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Bells pares definieras som ansiktsförlamning av okänd orsak. Sjukdomen drabbar ca 25-30 per 100 000 personer och år. Förlamningen debuterar relativt snabbt och sjukdomen kännetecknas av svaghet eller total förlamning av muskulaturen som sköter mimiken i halva ansiktet. Patienten blir svag i mungipan, får svårt att stänga ögat och blir svag i pannan. Många får problem att dricka, äta och prata och vissa kan även få påverkad hörsel, smak och känna smärta bakom ena örat. Prognosen är oftast mycket god men ca 30 % får kvarstående besvär. Många av dessa mår fysiskt och psykiskt väldigt dåligt av sina kvarvarande symtom.

Man har länge letat efter kliniska tecken som kan förutspå vilka som kommer drabbas av kvarstående förlamning. Inga studier har dock kunna hitta tillräckligt starka faktorer. Studier har även presenterat stora skillnader i utläkningsgrad hos patienter trots liknande behandling. Det har inte funnits någon enkät för mätning av sjukdomens påverkan på livskvalitet på svenska.

Målet med avhandlingen

- Att undersöka hur val av design, statistiska analys-metoder och definition av utläkning kan påverka den framräknade utläkningsgraden i en Bells pares studie.

- Att finna kliniska faktorer som kan vara till hjälp för att förutspå vilka med Bells pares som inte kommer läka ut.

- Att översätta och validera två amerikanska livskvalitets-enkäter till svenska.

Resultatet av avhandlingsarbetet visar att val av analysmetod och definition av utläkning påtagligt påverkar graden av framräknad utläkning av Bells pares. I det använda materialet skilde sig utläkningsgraden mellan 72% och 96%. Detta kan förklara skillnader i presenterade utläkningsgrader i olika studier med likande behandling. Resultaten visar att försiktighet måste användas vid jämförelse av olika studier av Bells pares för att inte felaktiga slutsatser ska dras.

Försämring av ansiktsfunktionen mellan det akuta besöket och första återbesöket (vid 11-17 dagar) är ett prognostiskt dåligt tecken för utläkning. Behandling med kortisontabletter inom 72 timmar från förlamningens debut kan bromsa denna tidiga försämring och påverka utläkningen positivt.

Ansiktsfunktionen vid 1 månad efter insjuknandet mätt med den objektiva Sunnybrook-skalan, kan användas för att förutspå risken för att patienten ska drabbas av dålig utläkning. En riskkurva baserad på en framtagen prediktionsmodell presenteras. Denna riskkurva kan användas i det kliniska arbetet för att tidigt kunna identifiera patienter som löper risk för att få kvarstående besvär. Dessa patienter skulle i så fall snabbare kunna få hjälp med åtgärder såsom sjukgymnastik eller nerv-kirurgi.

Två amerikanska livskvalitet-enkäter har översatts till svenska. Dessa är lättanvända och pålitliga. De kan med fördel användas i det dagliga kliniska arbetet och i framtida studier på patienter med ansiktsförlamning i Sverige.

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