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How should Children with Bell's Palsy (Idiopathic Facial Paralysis) be Treated?

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Introduction

Bell's Palsy (BP) is the most common idiopathic peripheral palsy of a facial nerve cranial nerve VII (Matthew J. Warner et al., 2022). It is characterized by unilateral acute weakness or peripheral paralysis of facial muscles, ear pain, loss of taste, hypogeusia (diminished taste acuity) and excessive tearing or crocodile tears and is shown in Fig.1 (Zohrevandi et al., 2014). Onset of BP is rapid with symptoms progressing over 2-3 days and is often diagnosed based on clinical findings including medical history and physical examination (Matthew J. Warner et al., 2022). The extent of facial motor impairment can range from "mild" through "moderate", "severe", "very severe" to "complete" and is assessed by the House-Brackmann Facial Paralysis Scale (or Facial Nerve Grading System FNGS) (House Brackmann, 1985). In most studies, the incidence, recovery rate and extent of damage due to BP can differ by age group and presence of severe disease at onset. An annual estimated incidence of 6 per 100,000 person-years in children under 14 years, 20 per 100,000 person-years in people aged 15-29 years and 59 per 100,000 person-years in patients older than 65 years has been reported (Danette C Taylor, 2019). Moreover, left untreated, children make an excellent recovery of up to 100% within 12 months, while 25-30% of adults can show delayed or incomplete recovery with serious long-term complications. This can include corneal dryness leading to visual loss, permanent damage to the facial nerve and abnormal growth of nerve fibers (Warner et al., 2022). These complications can not only lead to prolonged periods of functional impairment and facial disfigurement but can also cause psychological distress and significantly impact quality of life (Fu et al., 2011).

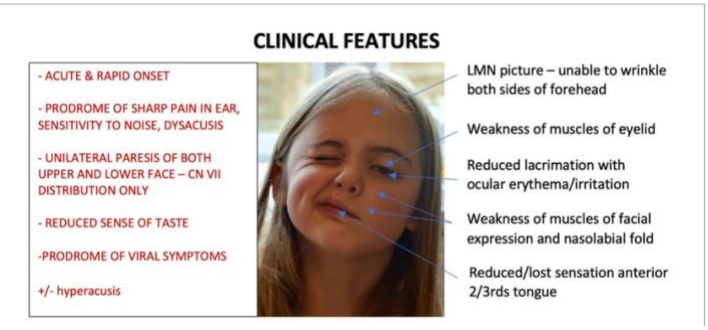

Figure 1. Unilateral paralysis of the face in children (Copp, 2020).

Causes of BP

While the exact etiology of BP remains unknown, five major causes including anatomical, ischemia, cold stimulation, viral infection, and inflammation have been suggested (Zhang et al., 2020a). Numerous lines of evidence have suggested that viral infection promotes an autoimmune reaction and elevates cytokine activity (Zhang et al., 2020b). This further acts against a component of peripheral myelin and causes facial nerve demyelination (Zhang et al., 2020a). This mechanism is clinically consistent with elevated concentrations of chemokines, T and B lymphocytes observed in blood samples from affected BP patients (Kim & Lee, 2020). The known infectious causes of BP include adenovirus, Coxsackie virus, cytomegalovirus, Epstein-Barr virus, influenza, mumps and rubella (Numthavaj et al., 2011). Furthermore, it has also been suggested that virus reactivation in the geniculate ganglion may be related to BP (Zhang et al., 2020b). In this situation, the viruses including varicella zoster virus (VZV), herpes simplex virus type 1 (HSV-1), human herpes virus 6, and the Usutu virus suffer reactivation and subsequent migration to the facial nerve (Zhang et al., 2020b).

Treatment of BP

Treatment for BP can be broadly classified into two main categories: pharmacological and non-pharmacological. The pharmacological treatments include corticosteroids, antiviral therapy or combination treatment including both corticosteroids and antivirals (Warner et al., 2022). While recovery rates have been observed to be better in patients receiving corticosteroids alone than antivirals alone, the effectiveness of combination treatment remails uncertain (Almeida et al., 2009; Madhok et al., 2016). For instance, the use of antivirals in combination with corticosteroids were associated with greater benefit in BP (Almeida et al., 2009.). However, this contrasts with the outcomes of a more recent systematic review which suggested that combined with antiviral agents, corticosteroids have little or no effect on rates of incomplete recovery in BP compared to corticosteroids alone (Madhok et al., 2016). The non-pharmacological interventions explored in BP include botulinum toxin, physiotherapy, hyperbaric oxygen, acupuncture and surgery have also been explored in adults, with scarce evidence in children (Cooper et al., 2017; Holland et al., 2012; Ravikumar et al., 1999; Vaughan et al., 2020).

Many randomized, controlled trials have suggested that the use of oral corticosteroids is linked to faster recovery and improved outcomes for patients with BP and is due to BP to its effects on reducing inflammation, limiting damage to myelin of the facial nerve and ultimately improving outcomes of BP (Sullivan et al., 2009). As such, corticosteroids including prednisolone prescribed within 3 days of BP onset in adults is considered the most common treatment (Numthavaj et al., 2011). While the results supporting the use of corticosteroids in adults has been well established, research on children under 18 years of age have not demonstrated any significant benefit in the use of corticosteroids (Ismail et al., 2013; Karalok et al., 2018). This suggests that the use of corticosteroids might bring about different outcomes in different age groups, presumably due to the differences in mechanism of action of corticosteroids in different subgroups. Interestingly, research now supports the use of antiviral since some studies suggest that infectious viruses e.g. HSV-1 which is able to remain latent and reactivate to trigger inflammation of the facial nerve (Zhang et al., 2020b). Antivirals including acyclovir and valacyclovir have been used with the rationale of eliminating the virus by targeting stages in the replication process (Adour et al., 1996; Zhang et al., 2020b). Nonetheless, there is still lingering uncertainty on the use of antivirals in BP, especially in children. Other treatments can act through different modes of action e.g. Botulinum Toxin acts by relaxing hyperactive muscles and temporarily restoring facial symmetry, hyperbaric oxygen is used to increase the amount of dissolved oxygen, and physiotherapy can be used to increase muscle strength or regain coordination (Cooper et al., 2017; Holland et al., 2012; Ravikumar et al., 1999; Vaughan et al., 2020). Furthermore, if there is no observed improvement in BP outcomes after weeks or months, this can support the use of more invasive treatment options including surgery (Matthew J. Warner et al., 2022). Surgical treatment for BP would require the deroofing of the fallopian canal of the temporal bone through which the facial nerve passes to decompression the nerve and alleviate then damage (Ravikumar et al., 1999).

Uncertainty in Treatment Options in Children

Though corticosteroids are the cornerstone for treatment of BP, the effectiveness of additional treatment with antiviral agents across different age groups remains uncertain. The 2019 update of this Cochrane Review included large-scale randomized controlled trials (RCTs) or quasi-RCTs of antivirals with and without corticosteroids versus control therapies in the years before the review (Madhok et al., 2016). The authors observed that corticosteroids alone were more effective than antivirals and that combination of corticosteroids and antivirals likely has better outcomes in BP compared with corticosteroids alone (Madhok et al., 2016). However, the main evidence arises from trials involving patients aged 14-84 years, with scarce evidence in children under 14 years of age or adults aged 65 or over. Moreover, the differences in prognosis, recovery rates and treatment outcomes in different age groups suggests that recommending similar treatment regimens across different BP age groups may prove clinically ineffective. To overcome any uncertainty around the management of BP in the general population and across specific age groups, this systematic review aims to synthesize data presented in prior Cochrane systematic reviews and more recent publications relating to all established and potential treatments for BP. This will be studied in both the general population and in children under 14 years of age and patients aged 65 years and over. We will aim to integrate any new evidence to provide updated review of the highest quality on the treatment of BP. This will be made available to key stakeholders including patients and clinicians and aim to inform future clinical practice.

Methods

Electronic Search and Inclusion Criteria

A systematic search of four electronic databases will be performed by the Cochrane Neuromuscular Disease. These databases will include MEDLINE, EMBASE and LILACS databases and the Cochrane Database of Abstracts of Reviews of Effects. The main search terms include 'Bell's palsy', 'idiopathic facial paralysis', 'meta-analysis', 'treatment' and terms relating to each specified treatment such as ‘prednisolone’, ‘antivirals’ etc. Furthermore, we will also search the grey literature and review of references of included studies to identify additional materials. We will search for all randomized controlled trials (RCTs) or quasi-RCTs. Interventions under

examination are all known interventions for BP previously subject to systematic review. They include antiviral medication, corticosteroid medication, hyperbaric oxygen, acupuncture, physical therapy botulinum toxin and surgery. We will consider all trials of treatment with any oral antiviral including acyclovir and its prodrug valacyclovir licensed for the treatment of herpes simplex infection. This will include trials in which study participants received antiviral therapy alone or in combination with any other treatment versus placebo or other interventions.

Primary and Secondary Outcomes of Interest

The primary outcome we will study will include incomplete recovery of facial function after 12 months of BP onset which can be measured using a validated rating scale. Results of studies terminated before 12 months will be indicated and included. The secondary outcomes will include motor synkinesis i.e. involuntary muscle contraction, crocodile tears or mass movement, complete palsy, self-assessed quality of life using a validated rating scale, presence and degree of ongoing documented pain using a validated rating scale and adverse events.

Data collection, extraction, and analysis

We will develop standardized data collection forms and discuss them with the author group. We will use these forms to collect data from each primary publication and systematic review. Furthermore, we will assess the quality of included reviews using the relevant PRISMA checklist (Page MJ, 2021) and assess the evidence quality from included trials using the GRADE approach (GRADE 2004). This approach would specify four different grades of quality of evidence: high, moderate, low and very low. Primary studies presented in systematic reviews that could be categorized as randomized trials will start at the highest level and may be downgraded due to study limitations (risk of bias), indirectness of evidence, heterogeneity, imprecision, or publication bias. Collections of observational studies will start at a level of low-grade quality and may be upgraded due to a large magnitude of effect, lack of concern about confounding variables or a dose response gradient. We will extract data from each publication for all outcomes and quality measures and synthesize and present the summary findings initially in a Summary of Comparisons table. This will include relevant meaningful headlines to clearly illustrate treatment effects and quality of evidence.

Measures of treatment effect

To measure the primary outcome i.e., incomplete recovery, we will use the most widely used House-Brackmann scale and treatment effect using Mantel- Haenszel test (House Brackmann, 1985). To calculate the number of participants with incomplete recovery, we would subtract the number of participants with complete recovery from the total number of participants in the reference group. Additionally, to measure adverse events, we will use the number of participants affected with BP as opposed to the number of adverse events observed. Furthermore, we aim to produce a network of evidence to illustrate the relationships between direct and indirect treatment comparisons, as presented in the scientific literature. This is a pictorial representation of the treatment comparisons and will provide a basis from which to conduct the mixed treatment comparison. Subsequently, we will perform a mixed treatment comparison to quantify the available trial evidence and provide estimates of the effect of each intervention relative to the other.

Further Analysis

If we find high levels of heterogeneity (I^2 = 50% or greater), we will primarily use the random-effects model. However, if little or no heterogeneity is observed, we will use the fixed-effects model. Since the disadvantage of using the random-effects model is that it places increased weight onto small studies, we will additionally apply the fixed-effect model in a sensitivity analysis of this review. We will perform sensitivity analyses to explore how missing data can influence the size of effects observed. We will also perform sensitivity analysis by i) repeating the analysis by excluding very large or unpublished studies to investigate how it influences the effect size and ii) excluding trials that had a high or unclear risk of bias to investigate the effects of bias

Results

Two randomized control trials were identified with data on children under 18 years of age. The study by Babl et al., 2022 had a total of 540 subjects of children aged between 6 months and less than 18 years with a diagnosis of Bell's palsy and onset of facial weakness less than 72 hours before randomization. They studied the effects of the use of prednisolone for 10 days to

assess complete recovery of facial function at 1 month of age. Furthermore, facial spasms, motor synkinesis, crocodile tears and adverse effects were also reported. 3 months after treatment, 90% of participants receiving prednisolone recovered completely, compared to only 85% in the placebo or no treatment group. We carried out a risk bias assessment which suggested a very low risk of bias due to random sequence generation, allocation concealment, blinding of personnel and participants, blinding of outcome, incomplete outcome data and selective outcome reporting.

In the second but smaller study by Khajeh et al., 2014 a total of 43 patients with acute unilateral peripheral facial palsy aged 2–18 years were included. They studied the effects of the use of prednisolone alone in comparison with combination therapy receiving both prednisolone and acyclovir for 7 days. Unlike the Babl et al., 2022 study, secondary outcomes including facial spasms, motor synkinesis, crocodile tears and adverse effects were not reported. 3 months after treatment, 90% of participants receiving prednisolone and acyclovir recovered completely, compared to only 65% in the prednisolone group. We carried out a risk bias assessment which suggested a very low risk of bias due to random sequence generation and incomplete outcome data but high risk of bias due to blinding of personnel and participants. The risk of bias due to allocation concealment, blinding of outcome assessment, and selective outcome reporting was unclear.

Discussion

Extensive search of the literature yielded the results of only two randomized clinical trials on management of children with BP. While we are still awaiting to hear from Cochrane about further studies to include in our review, it is difficult to draw conclusions based on two studies. Nonetheless, the results do suggest that prednisolone is more effective than no treatment and that a combination of prednisolone and acyclovir may be a more superior treatment choice for children. However, the sample size in the Khajeh et al., 2014 study is limited and hence should be interpreted with caution and in the context of other available treatments. Yet, it is unclear how other treatment options such as acupuncture, hyperbaric oxygen etc compare with prednisolone or combination of prednisolone and acyclovir. To overcome this, we have

identified 7 other studies which have combined data on adults with children's data that have not been studied in isolation. These studies have looked at the effects of acupuncture, valacyclovir (another antiviral), hyperbaric oxygen and magnetic and oxygen treatment in comparison to prednisolone. Moving forward we aim to contact these study authors to request individual or aggregate data on children aged under 18 years and further perform data extraction and analysis to include in our systematic review.

Conclusion

Initial data extraction suggests that some treatment is better than no treatment for complete recovery to be reached in BP. However, we are yet to await reviewing all studies provided by Cochrane before a definitive conclusion can be drawn. Thus far, the study search undertaken highlights the challenges associated with conducting systematic reviews for treatment of BP in children due to the limited number of trials in the pediatric population. Given that we able to obtain data on children from the above study authors, our article will be the first systematic review to study the effects of all available treatment options to determine the best course of BP management in children.

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