Review article

Efficacy of Combination and Single Therapy in Bell's Palsy: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Bell's palsy is an acute, asymmetrical paralysis of facial muscles resulting from peripheral facial nerve dysfunction without a discernible origin. Combination therapy, which leverages the benefits of both antivirals and steroids, may be an effective treatment for Bell's palsy. We aimed to evaluate the effectiveness of steroids antiviral treatments for facial paralysis.

Methods: A systematic search was conducted using the Scopus, PubMed, and Web of Science databases. The search terms used were: (Bell's palsy OR facial palsy) AND (steroids OR corticosteroids) AND antiviral. All selected articles were published between 1990 and Jan 2023. Comprehensive Meta-Analysis (CMA) version 3 was used for statistical analysis and graph construction.

Results: After a full-text evaluation, 14 studies were included. The comparison of patient outcomes between the two treatment groups indicated that combination therapy was more effective than single therapy. Famciclovir, valacyclovir, and acyclovir, respectively, showed the most significant synergistic effect with corticosteroids. According to Egger's test, no significant bias was found in the comparison of the two treatment groups.

Conclusion: Combination therapy (corticosteroid and antiviral) is significantly more effective than single corticosteroid therapy. Among the antiviral agents, famciclovir, valacyclovir, and acyclovir demonstrated the highest efficacy in combination with corticosteroids.

KEYWORDS
Bell's palsy; Steroid; Antiviral; Systematic review; Meta-analysis; Facial paralysis treatment

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INTRODUCTION

Bell's palsy is an acute, asymmetrical paralysis of facial muscles caused by peripheral facial nerve dysfunction without a discernible origin. Additional symptoms may include pain around the ear, extending to the cervical or occipital areas, noise sensitivity, and altered taste perception on the affected side [1, 2].

The prevalence of Bell's palsy is disproportionately higher among pregnant women, diabetics, influenza patients, individuals with the common cold, or those with other upper respiratory conditions [3]. The exact cause of Bell's palsy remains uncertain, with several potential contributing factors suggested, including viral infections, nerve

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ischemia, immune-mediated inflammation, and hereditary factors. Viral etiologies have gained wider acceptance due to the isolation of the herpes simplex virus type 1 genome from the saliva and endoneurial fluid of affected individuals. While the prognosis for Bell's palsy is generally favorable, a significant number of untreated individuals may still exhibit residual symptoms [4].

Two primary pharmacological treatments are available to enhance recovery from Bell's palsy: steroids and antiviral medications. These treatments target the principal pathogenic mechanisms involved in the facial paralysis associated with Bell's palsy, namely, the inflammatory process and viral infection [5, 6].

Initiation of treatment within 72 h of symptom onset is advised. The regimen may consist of prednisolone 25 mg administered twice daily for 10 d, or prednisolone 60 mg daily for five days, with a tapering schedule of 10 mg per day starting on the sixth day. A single daily dose is preferred to minimize adrenal axis suppression [7, 8].

Steroids such as prednisolone, betamethasone, hydrocortisone, methylprednisolone, dexamethasone, and cortisone effectively reduce facial nerve inflammation and edema. These medications have been used to treat Bell's palsy for several decades and remain frequently prescribedearly in the disease course [5, 9]. Herpes simplex virus type 1 reactivation has been suggested as a potential cause of idiopathic peripheral facial nerve palsy, leading to the consideration of glucocorticoids and antiviral agents, such as acyclovir, famciclovir, and valacyclovir, as effective treatments. Although the effectiveness of antivirals for facial paralysis has not been formally confirmed, their use has increased due to the detection of the herpes simplex virus in saliva and the fluid surrounding the facial nerves. Consequently, combination therapy, which leverages the advantages of both antivirals and steroids, may offer a more comprehensive approach to treating Bell's palsy [5, 7, 10, 11].

We aimed to evaluate the effectiveness of combination therapy, specifically antiviral agents paired with corticosteroids, versus corticosteroid monotherapy for the treatment of facial paralysis. By comparing these approaches, the study provides an overview of current therapies, serving as a reference for physicians in their clinical practice.

MATERIALS AND METHODS

This systematic review and meta-analysis were conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A systematic search was performed using the Scopus, PubMed, and Web of Science databases. The search terms included: (Bell's palsy OR facial palsy) AND (steroids OR corticosteroids) AND antiviral. We searched for English-language publications and managed the citations using Endnote software (EndNote 20, Clarivate Analytics, Philadelphia, PA, USA). All selected articles were published between 1990 and Jan 2023. The titles, abstracts, and full texts of the search results were reviewed for screening and study selection based on the inclusion criteria:

Inclusion criteria comprised: (1) studies comparing any type of corticosteroid therapy with the combined treatment of corticosteroids and any type of antiviral agent, and (2) studies that included patients who began therapy within seven days from the onset of the disease. Exclusion criteria encompassed studies on pregnant or breastfeeding women, case reports, review studies, and duplicate studies.

After a thorough review, the selected studies were evaluated for their relevance and quality. This rigorous selection process ensured that only the most pertinent studies were included in the meta-analysis, providing a comprehensive overview of the effectiveness of steroid and antiviral treatments for Bell's palsy.

Quality assessment and data extraction

Studies that met the inclusion criteria were screened, and their statistics were extracted using the Rayyan platform. The quality of each study was evaluated by two authors (ND, XM) using the nine-point Joanna Briggs Institute critical appraisal checklist for studies. Any conflicts between the two authors were initially resolved through consensus, and if disagreements persisted, they were resolved through discussion with a third reviewer (MA). Over half of the quality assessment parameters of the included studies were met. Table 1 provides details on the publication year, country, corticosteroid prescription, antiviral prescription, and disease course of the studies. Additionally, we extracted data on the study design,

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Table 1: Information about the publication year, country, corticosteroid prescription, antiviral prescription, and disease course of the studies

Study name/year	Country	Corticosteroid		Antiviral + Corticosteroid		Antiviral agent	Disease course	Ref
		Event	Total	Event	Total			
Adour et al. 1996	USA	33/46		46/53		Acyclovir	Acute	24
Antunes et al. 2000	Brazil	12/14		15/15		Valacyclovir	Acute	25
Engström et al. 2008	USA	160/210		164/206		Valacyclovir	Acute	26
Hato et al. 2007	Japan	96/107		110/114		Valacyclovir	Acute	27
Kawaguchi et al. 2007	Japan	49/66		69/84		Valacyclovir	Acute	28
Sullivan et al. 2007	Scotland	122/127		115/124		Acyclovir	Acute	29
Vazquez et al. 2008	Mexico	17/19		19/22		Valacyclovir	Acute	30
Yeo et al. 2008	South Korea	35/47		36/44		Acyclovir	Acute	31
Inanli et al. 2001	Turkey	20/22		17/20		acyclovir	Acute	32
Kim et al. 2021	South Korea	108/162		134/173		Acyclovir/ famciclovir	Acute	33
Axelsson et al. 2012	South Korea	147/209		152/206		Valaciclovir	Acute	34
Lee et al. 2013	South Korea	71/107		82/92		famciclovir	Acute	35
Minnerop et al. 2008	Germany	36/67		36/50		Valaciclovir	Acute	36
Kang et al. 2014	South Korea	671/773		510/569		Acyclovir/ famciclovir	Acute	17

the research question, the study count for each type, and the language.

Statistical analysis

To analyze the data statistically and construct graphs, we used Comprehensive Meta-Analysis (CMA) version 3 (Biostat Inc., Englewood, NJ), employing a random effects model plotted on forest plots, as this model is more suitable in cases of heterogeneity than a fixed effects model. The summary estimate was calculated by pooling the standard deviation of the mean with 95% confidence intervals. Heterogeneity was tested using the I-squared (I^2) statistic. We assessed the visual bias of the publications using funnel plots, confirmed by Egger's regression test, with $P< 0.05$ considered statistically significant.

RESULTS

Search outcome and study characteristics

We identified 1017 publications from the Scopus, PubMed, and Web of Science databases. After removing duplicate studies and screening based on inclusion and exclusion criteria, 36 publications were eligible for full-text examination. Following the full-text evaluation, 14 studies were selected (Figure 1). The selected studies were conducted in the following countries: South Korea (4), Japan (2), the United States (2), and one study each from Scotland, Germany, Turkey, Mexico, and Brazil. The designs of the studies included 11 randomized controlled trials (RCTs) and three prospective studies.

Comparison of single and combined therapy for Bell's palsy

Based on the meta-analysis findings presented in Figure 2, there is a significant difference in efficacy between single corticosteroid therapy and combination therapy of corticosteroids with antiviral agents for treating Bell's palsy. The comparison of patient outcomes indicated that the efficacy of combination therapy was superior to that of single therapy. The calculated Odds Ratio (OR) was 1.54, indicating that the efficacy of combination therapy was 1.5 times higher than that of single therapy (95% CI: 1.21-1.97, $P<0.005$).

Comparison of the Efficacy of Three Different Antiviral Agents

Subgroup analysis revealed varying therapeutic effects of different antiviral agents. The comparison of combination therapy involving corticosteroids with three types of antiviral agents—acyclovir, valacyclovir, and famciclovir—and corticosteroid monotherapy indicated differing outcomes (Figure 3). The efficacy of combination therapy was highest with famciclovir, followed by valacyclovir, and then acyclovir, as reflected by the Odds Ratios (OR) of 1.92 (95% CI=1.1 - 3.35, P=0.02), 1.4 (95% CI=1.07 - 1.82, P=0.01), and 1.18 (95% CI=0.54 - 2.56, P=0.67), respectively.

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Publication Bias

A funnel plot was utilized for visual evaluation of data symmetry (Figure 4), and Egger's test was employed to determine bias. According to Egger's test, there was no significant bias in the comparison of the two treatment groups (Egger P=0.46), and the funnel plot was symmetric. Heterogeneity analysis confirmed that the data exhibited no heterogeneity (P>0.05, I^2 = 30).

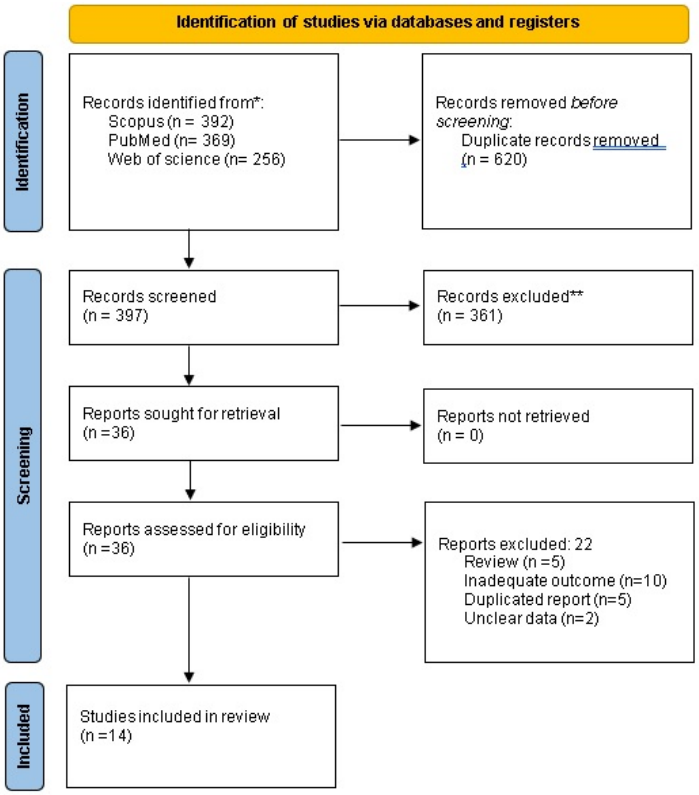

Figure 1: Flowchart of the screening and study selection procedures adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria

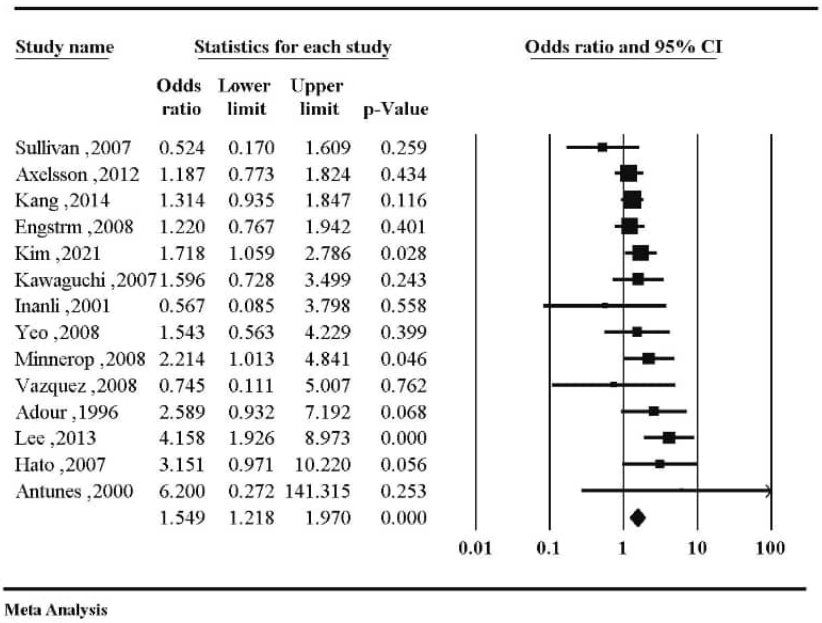

Figure 2: Forest plot of the meta-analysis comparing the pooled odds ratio of single versus combined therapy for Bell's palsy

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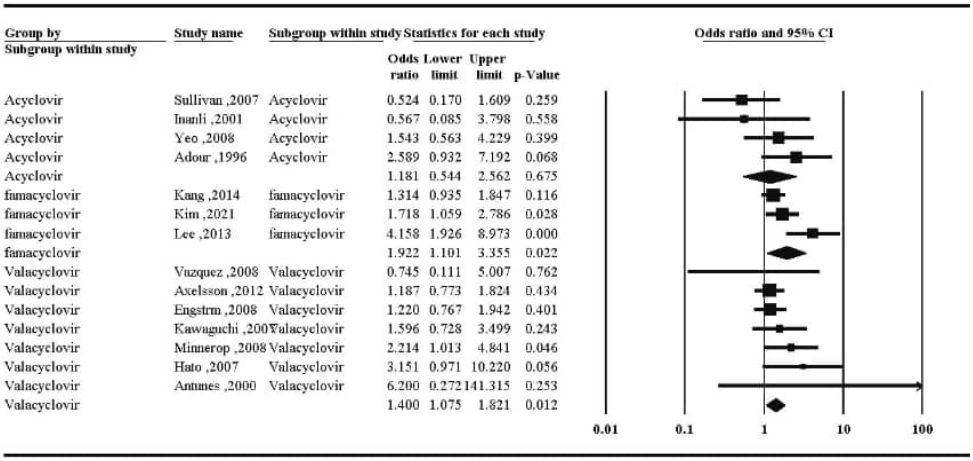

Figure 3: Forest plot of the meta-analysis comparing the efficacy of three different antiviral agents

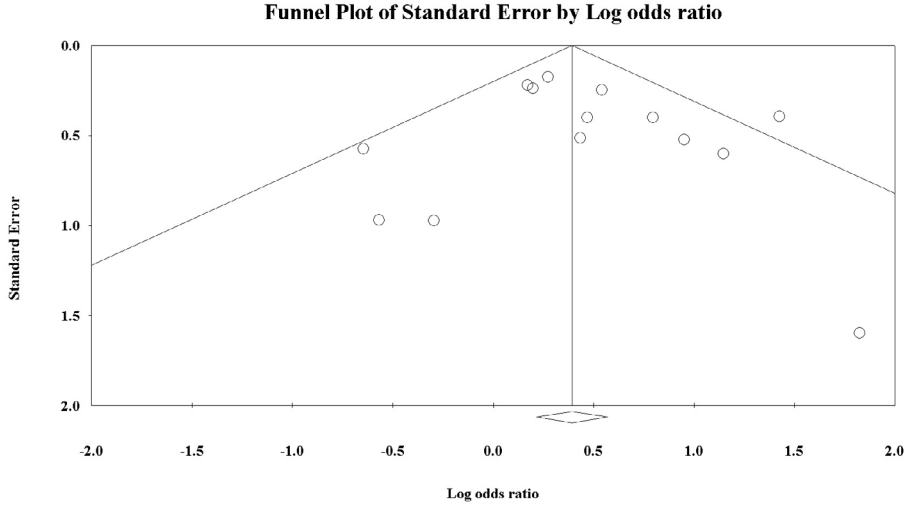

Figure 4: Funnel plot for visual publication bias

DISCUSSION

Bell's palsy is regarded as a neurological condition characterized by an inflammatory reaction and cytotoxic edema resulting from the reactivation of latent herpes or other viruses within the geniculate ganglia [12]. Despite the generally favorable prognosis of Bell's palsy, between 10% and 29% of patients experience persistent facial nerve problems [13]. To reduce the risk of persistent dysfunction and psychological distress, it is crucial to promptly identify and treat individuals at risk for long-term poor functioning. While the administration of steroids in the initial stages appears beneficial to patients, the efficacy of antiviral agents remains uncertain. It is still debated whether monotherapy with steroids or combined therapy with antivirals is more effective. Numerous studies have examined the effectiveness of different therapeutic approaches for individuals suffering from Bell's palsy [14-16]. Comparing different studies is challenging due to the varying standards for defining recovery from Bell's palsy [17].

In this context, our study compared the therapeutic effects of combined therapy with steroids and antiviral agents against those of steroids alone, based on the initial House-Brackmann (H-B) grade of patients with severe Bell's palsy.

Various meta-analyses have reported differing outcomes regarding the effectiveness of combination therapies for Bell's palsy patients. Goudakos JK's study, which included five studies with a total of 709 individuals, found no benefit from the combination of steroids and antivirals compared to steroid

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management alone [18]. However, prednisolone and antiviral drugs provided better therapeutic outcomes, particularly for patients without hypertension or diabetes and those with initially severe Bell's palsy. Combination therapy showed increased benefits in groups categorized by other variables, such as age, ENoG value, and underlying comorbidities [17].

Orally taken antivirals at standard dosages are generally well tolerated and are unlikely to cause adverse health complications. Nevertheless, some adverse effects have been observed. Another studies reported comparable adverse effects in both groups receiving either therapy [18].

Bell's palsy is commonly managed using antiviral drugs such as acyclovir and famciclovir [19]. Although the efficacy of combination treatments was superior to steroid therapies alone, no statistically significant differences were observed [20]. Antiviral agents can provide consistent clinical benefits for individuals suffering from Bell's palsy.

Supporters of antiviral use argue that viruses play a significant role in the etiopathogenesis of Bell's palsy, with reactivation of varicella-zoster virus (VZV) contributing to the pathophysiology in many patients [7, 21]. Valacyclovir, a prodrug of acyclovir, has been proposed to increase recovery rates in patients with facial paralysis due to its high bioavailability, suggesting it is a more potent antiviral agent [22]. However, Goudakos et al. found no benefit to the recovery of facial paralysis from adding either acyclovir or valacyclovir [23]. Our meta-analysis indicated significant differences not only between single and combination therapy but also between different types of antiviral agents in combination therapy.

To our knowledge, our study is the most exhaustive systematic review and meta-analysis conducted thus far concerning efficacy of combination and single therapy in Bell's palsy. The strength of this study includes the use of strict inclusion criteria and adherence to PRISMA guidelines, ensuring a robust and reproducible analysis. The subgroup analysis provided key insights into the efficacy of different antiviral agents in combination with corticosteroids. However, the heterogeneity in patient demographics, disease severity, and treatment protocols among the included studies may have influenced the results. Additionally, the limited number of studies on specific antiviral agents reduces the generalizability of the findings, and reliance on published data could still present some degree of bias despite the absence of significant publication bias in Egger's test.

Future research should focus on large-scale, randomized controlled trials to clarify the role of antiviral agents in treating Bell's palsy, particularly regarding the optimal timing, dosage, and duration of therapy. The efficacy of newer antiviral agents also warrants exploration. Clinically, while combination therapy appears promising, treatment should be personalized based on patient-specific factors, including comorbidities and severity. Ongoing research is essential to refine treatment strategies and improve patient outcomes.

CONCLUSION

Combination therapy with corticosteroids and antiviral agents is significantly more effective than corticosteroid monotherapy. Among the different antiviral agents, famciclovir, valacyclovir, and acyclovir showed the most efficacy in combination with corticosteroids.

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CONFLICT OF INTERESTS

Declarations of interest: none.

ETHICAL DECLARATIONS

All ethical standards have been respected in the preparation of the submitted article.

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