Systematic Review

A Network Meta-Analysis to Compare the Efficacy of Steroid and Antiviral Medications for Facial Paralysis from Bell´s Palsy

Xiying Fu, MD[1], Linda Tang, MD[2], Can Wang, MD[3], Ming Li, MD[3], Huijie Wu, MD[3], Jinyao Li, MD[3], Qianqian Ma, MD[3], Wei Yang, MD[3]

From: [1]Department of Endocrinology, the Second Hospital of Jilin University, Changchun, Jilin, China; [2]Research Center, the Second Hospital of Jilin University, Changchun, Jilin, China; [3]Department of Neurology, the Second Hospital of Jilin University, Changchun, Jilin, China

Address Correspondence:
Wei Yang, MD
Department of Neurology,
The Second Hospital of Jilin University
No.218 Ziqiang Street
Nanguan District, Changchun
130041, Jilin, China
E-mail: wei88linda@yahoo.com

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Background: Background: Facial paralysis is the most common cranial nerve injury. Bell's palsy is the name commonly used to describe an acute peripheral facial paralysis of unknown origin. The annual incidence of Bell's palsy is 20-30 cases per 100,000 persons, regardless of age and gender.

Objective: Our objective was to appraise the efficacy of steroid and antiviral treatments for facial paralysis.

Study Design: We conducted a network meta-analysis of studies of steroid and antiviral treatments for facial paralysis.

Setting: Second Hospital of Jilin University.

Methods: We performed a systematic search of PubMed and Embase databases to retrieve relevant studies. The efficacy outcome was overall recovery, measured in terms of the odds ratio (OR) and a corresponding 95% confidence interval (CI). The comprehensive ranking for each treatment with respect to overall recovery is presented as the value of the surface under the cumulative ranking curve (SUCRA).

Results: A total of 23 articles representing 4,623 patients were eligible for our study. In terms of overall recovery, no significant differences were found in the pairwise meta-analysis. From the results of the network meta-analysis, antiviral combined with steroid treatment was superior to placebo treatment (OR = 3.25; 95% CI, 1.23-8.61), but neither steroid nor antiviral therapy alone resulted in significant benefit compared with placebo. According to the SUCRA, antiviral combined with steroid treatment was the most effective, with a SUCRA value of 0.96, and the probability of ranking first was 90%. Only a small difference was observed between the efficacies of steroid and antiviral treatments (SUCRA values of 0.55 and 0.36, respectively), and they were both better than the placebo (SUCRA value of 0.134).

Limitations: The major limitation of our study is that, due to the limited number of related studies in the last several years, we were not able to evaluate the safety of these therapies.

Conclusions: Antiviral combined with steroid therapy is significantly better than antiviral or steroid therapy alone with respect to overall recovery, and the efficacies of single antiviral medications or single steroid treatments are nearly equal. In addition, all 3 therapies are more effective than placebo, according to the SUCRA values.

Key words: Facial paralysis, Bell´s palsy, steroids, antiviral drugs, efficacy, overall recovery, network meta-analysis, SUCRA

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Facial paralysis is the most common cranial nerve injury. Bell's palsy is the name commonly used to describe an acute peripheral facial paralysis of unknown origin. The annual incidence of Bell's palsy is 20-30 cases per 100,000 persons, regardless of age and gender. The reactivation of the herpes simplex virus has been widely recognized as the main cause of Bell's palsy, but this has not been proven (1). In addition, other viruses – such as herpes zoster virus, human immunodeficiency virus, Epstein Barr Virus, and hepatitis B virus – might be associated with the occurrence of Bell's palsy. In terms of the main clinical symptoms of Bell's palsy, facial asymmetry and facial motor dysfunction can cause dysfunction of the muscles on one side of the face, which, in turn, can cause remarkable disruption in patients' social lives. The underlying mechanism of Bell's palsy is not completely understood, and the cure for this disease is complicated. According to previous studies, 70% of patients experience complete recovery within 6 months of treatment; up to 30% of patients, however, do not recover completely and remain afflicted by residual symptoms such as paresis, synkinesis, and facial spasms (2).

Two main pharmacological treatments have been used to improve the recovery of Bell's palsy: steroids and antivirals. These treatments target the presumed pathogenetic mechanisms underlying the facial paralysis associated with Bell's palsy: inflammation and viral infection (3). Steroids, including prednisolone, betamethasone, hydrocortisone, methylprednisolone, dexamethasone, and cortisone, are a group of agents that can effectively decrease inflammation and swelling of the facial nerve. Therefore, they have been used to treat Bell's palsy for decades and continue to be widely used in the early stages of treatment. Antivirals – in particular, acyclovir, famciclovir, and valacyclovir – have also been used to treat Bell's palsy because of the suspicion that, in most patients, Bell's palsy is caused by the herpes simplex virus. The efficacy of antivirals in treating facial paralysis has not yet been validated, but they have gained popularity since the herpes simplex virus was found in patients' saliva and facial nerve endoneurial fluid (4). Combination therapy (antivirals and steroids), which takes advantage of the virtues of both antivirals and steroids, has been suggested as an effective treatment for Bell's palsy (5).

Some placebo-controlled and head-to-head studies have been conducted to compare the different therapies for Bell's palsy, as shown in the studies cited previously, but randomized clinical trials (RCTs) can only compare 2 or 3 therapies. Additionally, small sample sizes have prevented these studies from achieving conclusive results, and some studies have produced inconsistent results (6,7). Therefore, the best therapy for the treatment of Bell's palsy remains unclear, and a comprehensive comparison of the efficacies of these therapies is needed. In this study, a systematic review and a network meta-analysis (NMA), which integrates the evidence from direct and indirect comparisons, were performed to compare the overall recovery rates associated with 1 to 12 months of steroid drugs, antiviral agents, or the combination of both for the treatment of Bell's palsy. This study offers a complete overview of the effectiveness of current therapies and can be used as a reference by physicians engaged in clinical practice.

Methods

Search Strategy and Study Selection

We performed a systematic search in the Embase and PubMed databases from inception to 2016 without any restrictions on language or type of publication. The following keywords and subject terms were used in the search: "facial paralysis," "Bell´s palsy," "steroid," "corticosteroids," "prednisolone," "antiviral drugs," "acyclovir," and "valacyclovir."

Studies that met the following selection criteria were included: (1) those with patients who were treated for facial paralysis diseases caused by Bell´s palsy; (2) RCTs with at least a 1-month follow-up period; (3) comparisons of the efficacy between placebo and antiviral or steroid treatments; and (4) studies in which the mean age of patients was over 18 years. Studies were excluded if they (1) did not have sufficient data related to this study; (2) did not have relevant outcomes; or (3) included patients who were diagnosed with Ramsay Hunt syndrome.

Outcome Measures and Data Extraction

Overall recovery was chosen as the indicator of efficacy, representing the number of patients who recovered after receiving the relevant treatments. The following information from each study was extracted: first author; publication year; number of patients treated with steroids, antiviral drugs, or combination treatment and placebo; basic patient characteristics (average age, gender); length of the follow-up period; and efficacy outcome. These data are presented in Table 1. Two independent reviewers extracted the data from original studies, and any discrepancy between the 2

Table 1. *Characteristics of the studies included in the network meta-analysis.*

First Author	Year	Blinding	Total n	Follow-up Mos.	Men (%)	Mean Age	Treatment 1			Treatment 2		
							Drug Type	n	Recovery Number	Drug Type	n	Recovery Number
Adour (17)	1996	Double	99	4	49.42	43.2	Antiviral + Steroid	53	53	Steroid	46	46
De Diego (18)	1998	-	101	3	55.40	43.0	Antiviral	54	45	Steroid	47	44
Hato (21)	2007	Single	221	6	52.48	50.3	Antiviral + Steroid	114	110	Steroid	107	96
Sullivan (23)	2007	Double	496	3, 9	51.03	44.0	Antiviral + Steroid	251	237	Steroid	245	200
Sullivan (23)	2007	Double	496	3, 9	51.01	44.0	Antiviral + Steroid	247	211	Antiviral	249	226
Roh (26)	2008	-	44	1, 3, 6	56.82	50.5	Steroid	22	22	Placebo	22	21
Yeo (27)	2008	Double	91	2, 6	45.05	41.4	Steroid	47	40	Antiviral + Steroid	44	41
Engstrom (24)	2008	Double	829	1, 2, 3, 6, 12	58.76	40.25	Placebo	206	134	Steroid	210	160
							Antiviral	207	132	Antiviral + Steroid	206	165
Lee (1)	2013	Double	206	6	49.05	47.7	Steroid	107	71	Antiviral + Steroid	99	82
Kawaguchi (22)	2007	-	150	6	30.56	50.3	Steroid	66	55	Antiviral + Steroid	84	78
Lagalla (20)	2002	Double	62	12	54.84	47.5	Steroid	32	27	Placebo	30	23
Taverner (9)	1954	Double	26	-	50.00	39.9	Steroid	14	10	Placebo	12	8
Taverner (10)	1966	Single	70	3	-	39.9	Steroid	34	27	Placebo	36	22
Taverner (11)	1967	Single	381	3	49.87	41.2	Steroid	216	178	Placebo	165	12
Minnerop (25)	2008	-	117	12	51.28	32.0	Steroid	67	61	Antiviral + Steroid	50	48
Ekstrand (14)	1979	-	42	3, 6, 12	-	-	Steroid	30	15	Placebo	12	2
Ferreira (30)	2016	Single	73	6	47.95	42.4	Steroid	42	27	Placebo	31	20
Abdelghany (29)	2013	Double	603	12	52.96	45.82	Steroid	198	148	Antiviral	203	114
							Antiviral + Steroid	202	148	-		
Austin (16)	1993	Double	76	-	-	36.8	Steroid	23	5	Placebo	30	10
Antunes (19)	2002	-	46	-	-	-	Steroid	17	2	Placebo	17	2
							Antiviral + Steroid	15	0	-		
Tekle-Haimanot (15)	1987	-	59	-	-	-	Steroid	30	11	Placebo	29	11
Wolf (13)	1978	-	239	12	-	-	Steroid	107	13	Placebo	132	26
Shahidullah (28)	2011	-	68	3	70	33	Steroid	34	26	Antiviral + Steroid	34	33
May (12)	1976	Double	51	6	54.9	-	Steroid	25	25	Placebo	26	26

reviewers was resolved by a third reviewer and a group discussion.

Statistical Analyses

First, a pairwise meta-analysis was performed to compare the efficacies of treatments that had been directly compare, using a fixed-effects model. The heterogeneity of the included pairwise comparisons was analyzed using Cochran's *Q* formula and Higgins' I^2 statistic. A *P* value < 0.05 indicated that there was heterogeneity, which required a random-effects model.

Next, we conducted an NMA based on a Bayesian framework. Overall recovery is represented by an odds ratio (OR) and a corresponding 95% confidence interval (CI). Generally, a 95% CI that excludes one represents a statistically significant result. Cumulative ranking probability plots have been suggested as a comprehensive and reliable way to present ranking probabilities graphically (8). A rankogram for a specific treatment is a graphical plot of the probabilities associated with all possible ranks (where the total number of positions in the ranking is equal to the total number of treatments in the network); this is slightly different from an absolute rankogram. The surface under the cumulative ranking curve (SUCRA) is used to present the probability of each treatment's ranking and thereby determine the best one. A higher SUCRA value represents better performance on a certain outcome measure. Furthermore, the consistency of a result was evaluated using the node-splitting method. A *P* value > 0.05 suggests that the study's assumption of consistency was satisfactory. A net heat plot was used to draw patterns and provide more information on the consistency of the network comparison. The R 3.3.3 and WinBUGS (version 1.4.3) software packages were used to conduct all of the above analyses for this study.

Results

Included Articles

As shown in the flow chart (Fig. 1), 179 studies were retrieved from the electronic databases. After removing 134 irrelevant articles and duplicates, 45 studies were determined to be eligible. Twenty-two studies were discarded according to the selection criteria. Ultimately, 23 studies were involved in our NMA.

Main Characteristics of the Included Articles

A total of 23 articles were eligible for our study, and the primary characteristics of each trial are shown in Table 1 (1,9-30). All 3 treatments (antiviral, steroid, and antiviral plus steroid) were included among these

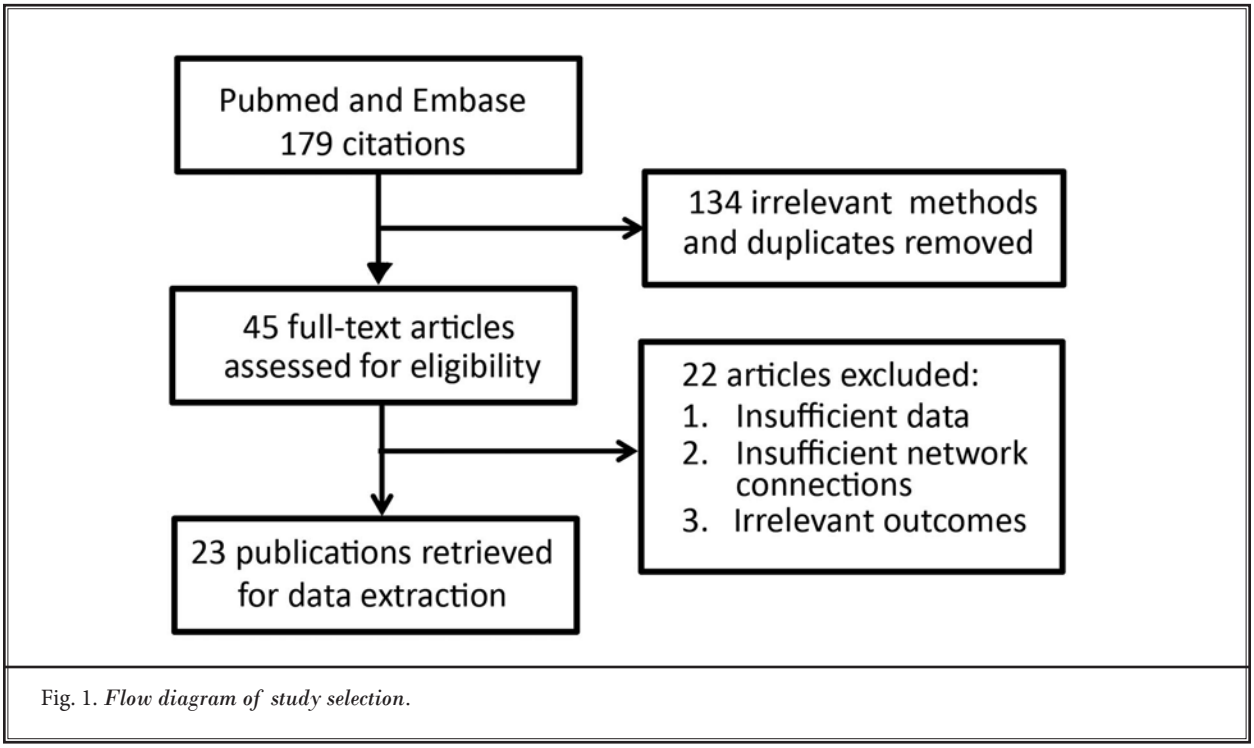


Fig. 1. *Flow diagram of study selection.*

studies. Antiviral drugs mainly include acyclovir, famciclovir, and valacyclovir; steroids include prednisolone, cortisone, betamethasone, hydrocortisone, deflazacort, and methylprednisolone. Among the 23 included studies, 11 RCTs were double-blind, 4 were single-blind, and 8 did not specify type of trial with regard to blinding. The total number of patients was 4,623, and the follow-up time ranged from 1 to 12 months. The comparisons and the number of studies in each pair are graphed in Fig. 2.

Pairwise and Network Meta-Analysis Results

As shown in Table 2, no significant differences were observed among all direct comparisons with respect to overall recovery. However, in terms of ORs, combination treatment (antiviral plus steroid) had a tendency toward higher overall recovery.

Figure 3 shows the network comparison results. Compared with placebo therapy, combination treatment (antiviral + steroid) resulted in 3.25 higher odds of OR value (95% CI, 1.23-8.61). Other pairs of comparisons indicated no statistically significant differences between the treatments.

Cumulative Ranking Probability

The analyzed probability of ranking with respect to overall recovery is presented by the SUCRA, as shown in Table 3 and Fig. 4. With a SUCRA value of 0.96, combination treatment showed the best efficacy and had the highest probability of ranking first (90%). Steroids and antiviral drugs had similar SUCRA values (0.54 and 0.36, respectively), but they were prone to be in second and third place, respectively (59% and 36% for rank probability). Placebo treatment had the worst efficacy, with a SUCRA value of 0.13 and a high probability of being the last choice of treatment (66% probability of ranking in last place).

Consistency Assessment

An assessment of the consistency between the di-

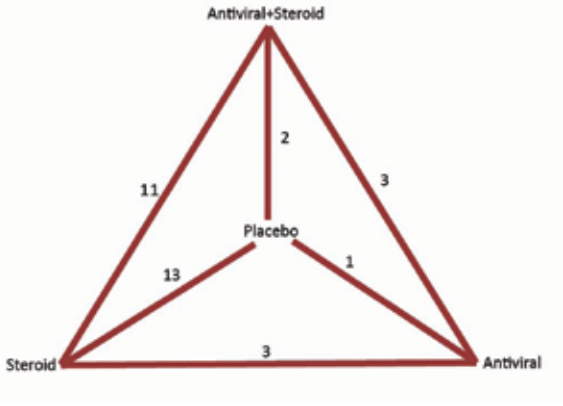


Fig. 2. *Comparison network of included interventions.*

Table 2. Meta-analysis results for pairwise comparisons.

Drug 1	Drug 2	OR (95% CI)
Antiviral + Steroid	Antiviral	1.41 (0.39-6.12)
Placebo	Antiviral	1.10 (0.11-14.02)
Steroid	Antiviral	2.40 (0.56-9.43)
Placebo	Antiviral + Steroid	1.15 (0.14-13.70)
Steroid	Antiviral + Steroid	0.47 (0.22-1.03)
Steroid	Placebo	1.77 (0.70-4.46)

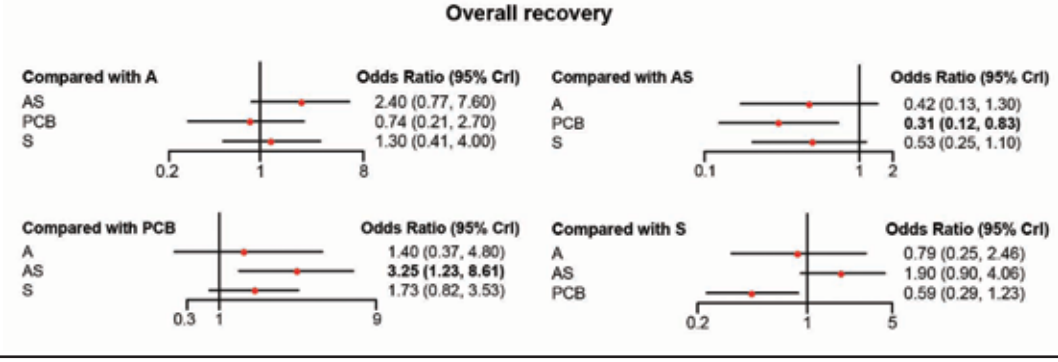


Fig. 3. *Forest plot for overall recovery.*

Table 3. *Rank probability and surface under the cumulative ranking curve results.*

Rank	1	2	3	4	SUCRA
Antiviral	0.06	0.27	0.36	0.31	0.36
Antiviral + Steroid	0.90	0.09	0.01	0.00	0.96
Placebo	0.01	0.05	0.29	0.66	0.13
Steroid	0.04	0.59	0.34	0.03	0.54

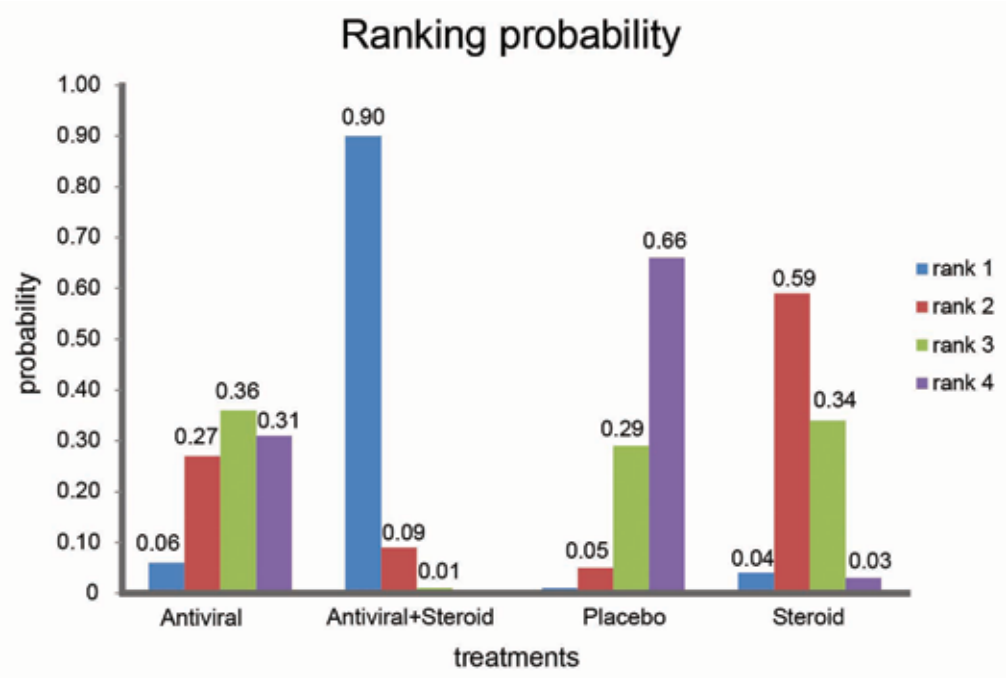


Fig. 4. *Ranking probability of the 3 treatments in terms of overall recovery.*

rect and indirect sources of evidence was conducted by the splitting node method and *P* value measurements (Fig. S1). No significant differences were found between the direct and indirect sources of evidence comparing any 2 treatments; all *P* values > 0.05. Moreover, a heat map (Fig. 5) was used to show the consistency of the results of the NMA. The contribution of direct evidence is represented by the gray squares. The conclusion was almost the same as the result from the node-splitting graph: there were no significant inconsistencies between direct and indirect sources of evidence for any treatment comparisons.

Publication Bias

The funnel plot is used to test for publication bias. One dot represents an included study. No distinct asymmetry pattern was found in the comparison-adjusted funnel graph presented in Fig. S2. Consequently, there is no evidence of publication bias in our study.

Discussion

Facial paralysis from Bell's palsy severely threatens the outward appearance and mental health of patients. In recent years, Bell's palsy has aroused the interest of many researchers, and many studies have been carried out to evaluate the efficacy of different therapies in treating facial paralysis (4,31,32). In this study, an NMA was launched to comprehensively assess the performance of 3 therapies (antiviral, steroid, and antiviral + steroid) for the treatment of Bell's palsy. The results of the proposed NMA indicate that antiviral + steroid treatment is superior to the other 2 therapies with

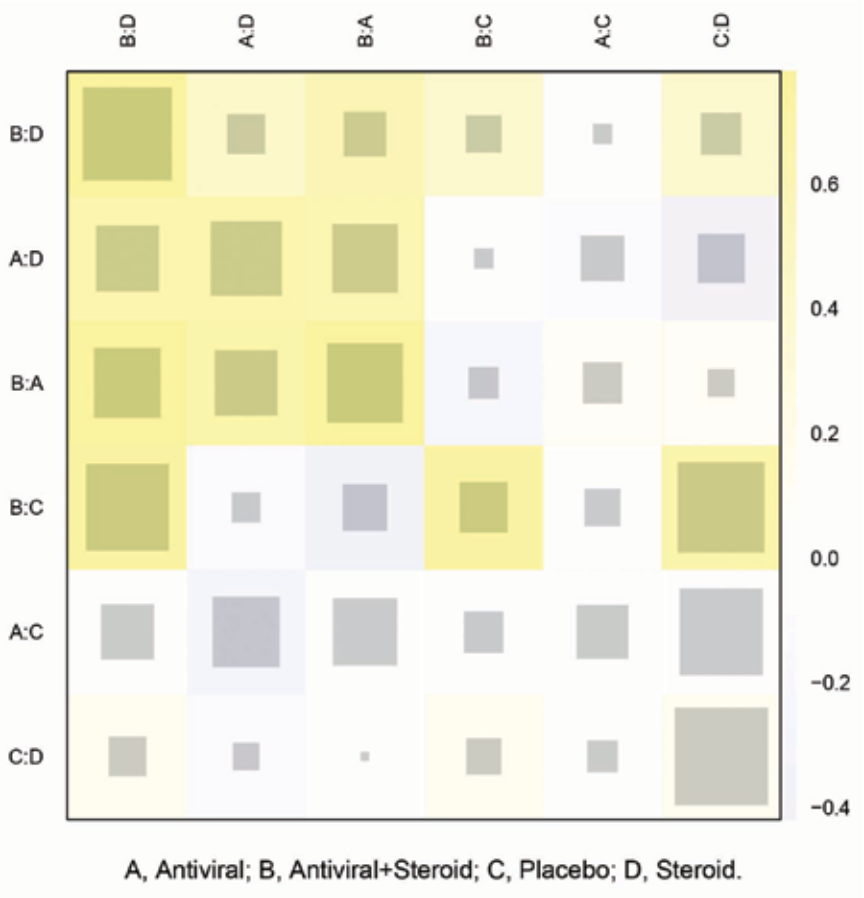


Fig. 5. *Net heat plot. The size of the gray squares indicates the contribution of the direct evidence (column) to the network evidence (row). The colors are associated with changes in inconsistency between direct and indirect evidence (row). Blue colors indicate increased inconsistency, and warm colors indicate decreased inconsistency.*

respect to overall recovery, and that the efficacies of antiviral or steroid treatments alone are nearly equal. In addition, the SUCRA values indicate that all 3 therapies are better than placebo treatment.

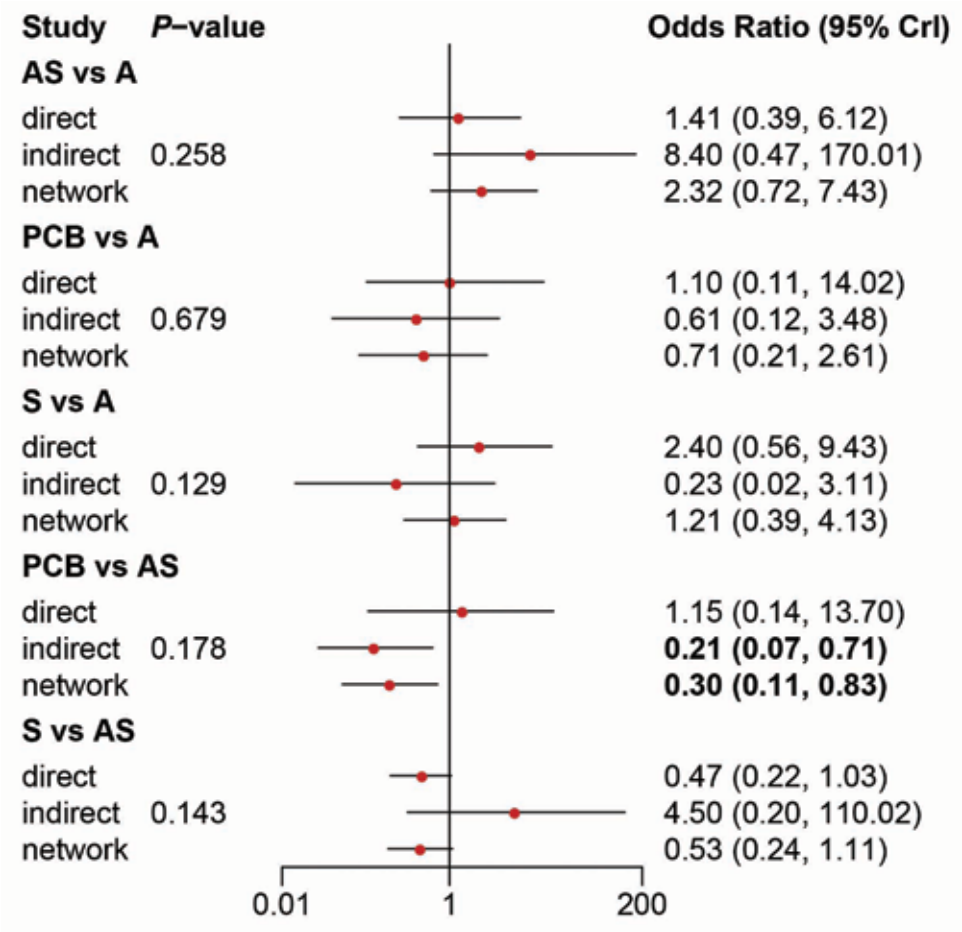
Some pairwise meta-analyses have been conducted in previous studies comparing treatments for Bell's palsy, resulting in some contradictory conclusions with respect to the efficacies of different treatments for overall recovery. For instance, Salinas et al compared the efficacies of steroids vs placebo therapy for the treatment of Bell's palsy in terms of overall recovery, and argued that steroids did not show a significant benefit over placebo (7); in contrast, Ramsey et al reported that steroids were more effective than placebo (33). This divergence will cause a dilemma among patients and clinicians. Lockhart et al conducted a meta-analysis to evaluate the efficacy of antiviral agents for the treatment of Bell's palsy and concluded that there was no significant difference between antiviral and placebo treatments with respect to overall recovery (6). Most of these meta-analyses were placebo-controlled comparisons and did not provide relative rankings for all therapies. Through this study, our NMA has overcome the limitations of previous meta-analyses. First, by organizing all therapies into a network comparison, a relative ranking of all therapies can be easily obtained from the SUCRA values. Meanwhile, the abovementioned contradictions can be eliminated by simultaneously considering direct and indirect sources of evidence.

In this NMA, we used overall recovery as the efficacy outcome to assess 3 treatments for Bell's palsy (antiviral, steroid, and antiviral + steroid). Overall, the

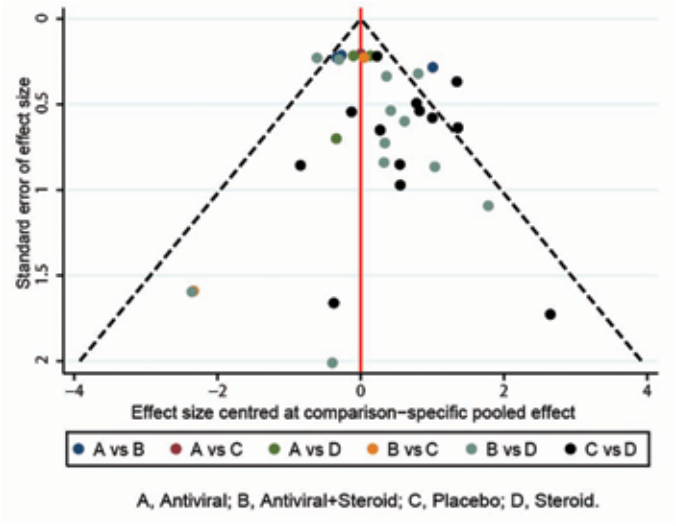
results of our NMA were consistent with those of previous works. We found that antiviral + steroid treatment outperformed placebo, consistent with the study of Salinas et al (7). They reported that antiviral + steroid treatment was dramatically superior to placebo treatment. In addition, our NMA demonstrated that there were no significant differences between the comparisons of antiviral vs placebo and antiviral vs steroid treatments; these conclusions are consistent with our previous study (7). We also obtained the relative ranking of the 3 therapies from the SUCRA values. Antiviral + steroid treatment was clearly the most satisfactory, with a 90% probability of ranking first and a SUCRA value of 0.96. The efficacies of steroid or antiviral treatments alone were nearly equal, with SUCRA values of 0.54 and 0.36, respectively, and both performed better than placebo therapy, whose SUCRA value was only 0.13.

In conclusion, this NMA provides extensive insight compared with previous works. Our study connected all treatments of facial paralysis from Bell's palsy in a network comparison and obtained a comprehensive ranking of their efficacies in terms of overall recovery. However, due to an insufficient number of related studies in the last several years, we were not able to evaluate the safety of these therapies; this is the major limitation of our study. Further studies should be conducted to provide more evidence for the evaluation of treatments for Bell's palsy.

Supplemental 1 Node-splitting results in terms of overall recovery.



Supplementa 2. Publication bias.



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