Original Article
Steroid-antivirals treatment versus steroids alone for the treatment of Bell's palsy: a meta-analysis

Yabing Dong[1,2], Yong Zhu[1,2], Chuan Ma[1,2], Huaqiang Zhao[1]

[1]College of Stomatology, Shandong University, Number 44, Wen Hua Xi Lu, Jinan 250012, Shandong Province, China; [2]Shandong Provincial Key Laboratory of Oral Biomedicine, Number 44, Wen Hua Xi Lu, Jinan 250012, Shandong Province, China

Abstract: Background: To illustrate whether the steroid-antivirals treatment could acquire a better recovery in patients with Bell's palsy than the steroids alone treatment. Materials and methods: We conducted an exhaustive search over Pub med/Medline, Ovid, Elsevier search engines and the Cochrane library thereby collecting the randomized controlled trials in the treatment of patients with Bell's palsy with steroid-antivirals and steroids. The qualities of relevant articles were assessed by GRADE, which was used to present the overall quality of evidence as recommended by the Cochrane Handbook for Systematic Reviews of Interventions. Results: Two investigators evaluated these papers independently, and resolved the disagreements by discussion. At last 8 eligible papers (1816 patients included: 896 treated with steroid-antivirals and 920 treated with steroids alone) match the criteria. Owing to the result (chi^2 = 12.57, P = 0.08, I^2 = 44%) presented by the formal test for heterogeneity, the fixed effect meta-analysis model was chosen. The facial muscle recovery between the steroids-antivirals group and the steroids alone group show significant differences (OR = 1.52, 95% CI: 1.20-1.94), while the statistical outcome of adverse effect shows no statistical significance (OR = 1.28, 95% CI: 0.71-2.31). Conclusions: The present meta-analysis indicates that the steroid-antivirals treatment could improve the recovery rate in patients with Bell's palsy when comparing with the steroid alone treatment. Clinical significance: This meta-analysis showed that the steroid-antivirals treatment achieved the better outcomes in patients with Bell's palsy. Clinicians should consider that steroid-antivirals therapy is an *alternative* choice for the patients with Bell's palsy.

Keywords: Steroid-antivirals, steroids, Bell's palsy, meta-analysis

Introduction

Bell's palsy is an acute peripheral facial paresis caused by unknown factors. [1] Usually, the diagnosis is established without difficulty in patients presenting with unexplained unilateral isolated facial weakness [2]. It affects 11 to 40 people per 100,000 in the population per annum, most commonly in the age group 30 to 45 [3]. The etiology of Bell's palsy remains indistinct, but the reactivation of herpes simplex virus (HSV) which can be detected by the polymerase chain reaction (PCR) to analyze the saliva of patients with Bell's palsy for the presence of shed HSV-1 in about 31-79% of patients of Bell's palsy might be one reason [4-6]. Moreover, the injection of HSV into the auricle or tongue could induce Bell's palsy in an animal model [7]. Thus, patients are prescribed with antivirals, such as aciclovir, famciclovir and valaciclovir [8]. Inflammation and edema of the facial nerve are implicated in causing Bell's palsy and steroids have a potent anti-inflammatory action which should minimize nerve damage and thereby improve the outcome [9, 10]. Therefore, steroids was used to treat Bell's palsy and ended up with significantly improving outcomes [11].

Some studies showed that the addition of antiviral agents could effectively enhance the curative effect of steroids [12-14]. However, Kawaguchi K et al and Engstrom, M et al found that the combination of prednisolone and valacyclovir did not achieve significantly better performance than prednisolone alone [15, 16]. With the dispute existing, the present meta-analysis was made to illustrate whether the steroid-antivirals treatment could acquire a better recovery in patients with Bell's palsy than the steroids alone treatment.

Table 1. Search strategies for collecting papers

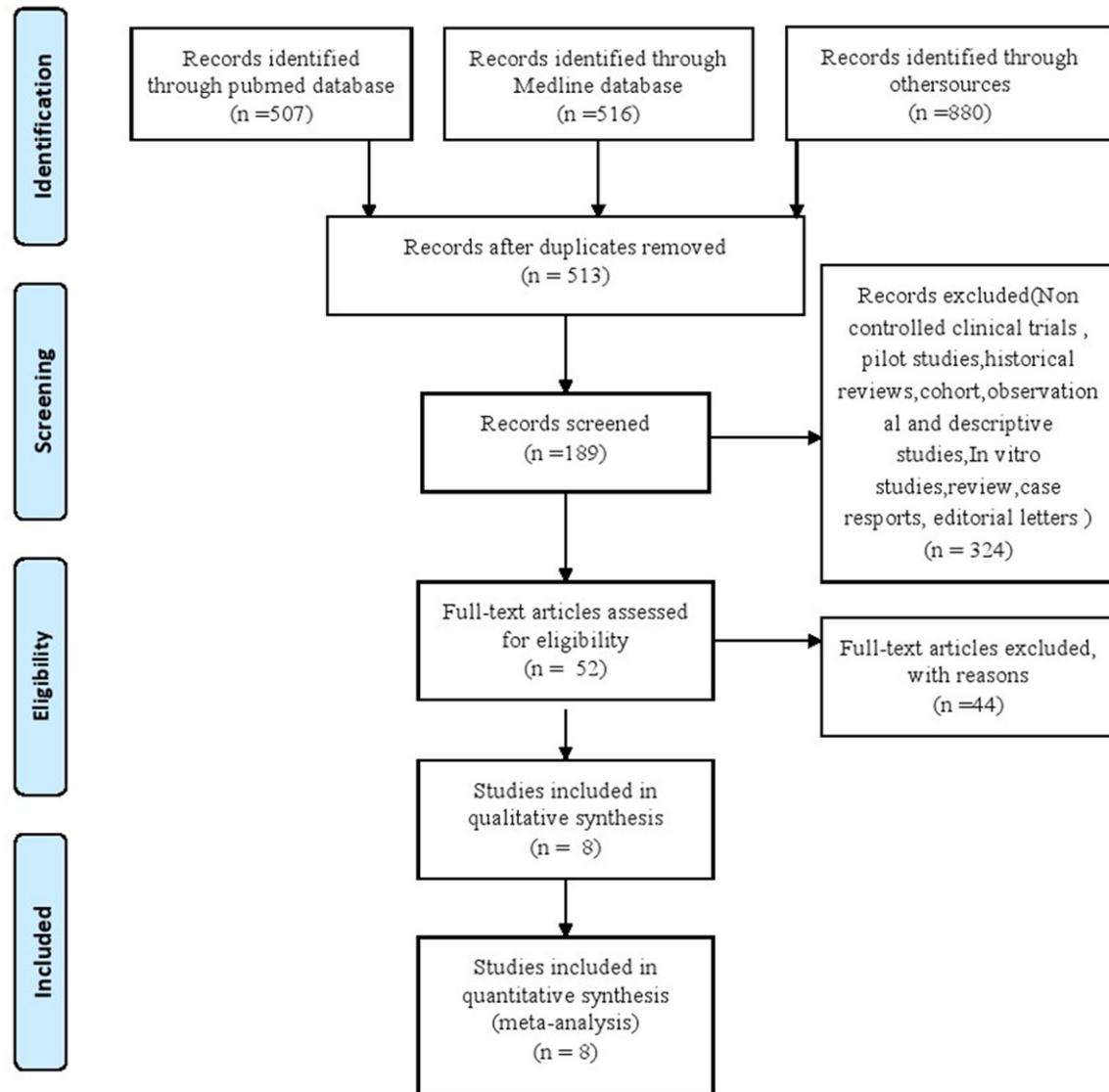|	Search MeSH terms
1#	"bell's palsy," or "bell palsy," or "bell's palsies," or "idiopathic facial paralyses," or "idiopathic facial paralysis," or "herpetic facial paralysis
2#	"acyclovir," or "valacyclovir," or "famcyclovir," or "famciclovir." or "antiviral agents"
3#	"Steroids", or "methylprednisolone", or "Prednisolone"
4#	1# and 2#
5#	1# and 3#
6#	4# or 5#

Figure 1. Flow Chart of Study Selection Process.

Materials and methods

Search strategy and study selection

We searched the electronic databases Pubmed, Medline, Web of science and the Cochrane library to collect the eligible original papers from 1984 (the year that aciclovir was licensed for clinical use) to July 2014 using the following Medical Subject Heading (MeSH) terms: "bell's palsy", "bell palsy", "bell's palsies", "idiopathic facial paralyses", "idiopathic facial paralysis",

"herpetic facial paralysis", "acyclovir", "valacyclovir", "famcyclovir", "famciclovir", "Antiviral agents", "steroids", "methylprednisolone", "prednisolone". Search strategies for both databases are described in the **Table 1**.

The eligible papers were limited to the following criteria:

(a) Randomized controlled trials (RCT) or controlled clinical trials (CCTs);

(b) The original papers were written in English;

(c) Studied subjects aged 15 years or older with sufficient data;

(d) At least 25 patients in total were included;

(e) An assessment of facial muscle recovery determined by a recognized scoring system, such as the House-Brackmann grade, Yanagihara score or the facial paralysis recovery index.

No controlled clinical trials, editorial letters, pilot studies, historical reviews, cohort, observational and descriptive studies, case reports, In vitro studies, review, editorial letters were excluded. In addition, animal studies were also excluded.

Furthermore, we reviewed citations in the retrieved articles to search for additional relevant studies. The criteria of collecting papers were reviewed by two authors (Y.B.D and Y.Z) and checked by another author (C.M).

Two investigators evaluated these papers independently, and then resolved the disagreements by discussion. Literature selection was present in the PRISMA flow chart, a four-phase flow diagram, (**Figure 1**) according to the PRISMA guidelines [17, 18].

Data extraction & quality assessment (QA)

Data extraction was independently carried out by two investigators (Y.B.D and Y.Z) using a standardized data extraction form which included (a) study design, (b) year of publication, (c) sample size, (d) patient characteristics (i.e. gender, age, type of treatment, study style, Mean disease score and so on), (e) type of intervention and comparator, (f) outcomes, and (g) follow-up time. Quality of studies was assessed by

two independent investigators (Y.B.D and Y.Z) based on a modified Jadad score, which takes into account of randomization technique, allocation concealment, blinding, intention to treat, and patient attrition [19]. All controversies between the two reviewers were resolved by discussion.

Statistical analyses

The outcome of facial muscle recovery from Bell's palsy and the adverse effects were summarized. Odds ratio (OR) and 95% CI (confidence intervals) were employed to evaluate each outcome for the proportion of patients with at least partial facial muscle recovery who were treated with steroid-antivirals compared with those who received steroids alone. The OR would be considered statistically significant at the $P < 0.05$ level if the 95% CI does not include the value 1. Heterogeneity of the trails was assessed by I^2, which gives a better measure of the consistency opposed to random error or chance between trials in a meta-analysis. According to I^2 values (low: 0-25%; moderate: 25-50%; high: 50-75%; extreme: 75-100%) , we calculated the OR using fixed effect model or random effect model (Mantel-Haenszel method) [20]. The test seeks to determine whether there are genuine differences underlying the results of the studies (heterogeneity), or whether the variation in findings is compatible with chance alone (homogeneity) [21].

The meta-analysis was carried out with the RevMan 5.2 software (http://ims.cochrane.org/revman/download). Effect sizes were calculated as Hedges' adjusted with 95% CI.

Results

Search results

We searched 298 potentially relevant papers in relation to Bell's palsy. 189 articles were available after duplicates removed. We excluded 137 articles because of the inconformity to the criteria (a), (b) and (c). Finally, after assessing the full-text articles for eligibility, we adopted 8 studies in total in the present meta-analysis [11-14, 16, 22-24]. The cross-sectional or RCT studies were included based on our eligibility criteria. The detailed steps of paper collection are shown in the Flow Chart (**Figure 1**).

Table 2. Characteristics of the included studies

Author	N	% Male Participants	Age	Type of treatment		Study style	Mean disease severity score	Full time (month)
				Intervention (dosage)	Control (dosage)			
Adour, Kedar K (1996)	99	55[*,a] 43[#,a]	44.6[*,a] 41.9[#,a]	Valaciclovir 2000 mg/d × 10 d Prednisolonee 60 mg/d × 5 d 50 mg/d × 6 d, 40 mg/d × 7 d, 30 mg/d × 8 d 20 mg/d × 9 d 10 mg/d × 10 d	Prednisolone with the same dosage	RCT (double blind)	House-Brackmann grade (II-V)	4
Axelsson, S (2012)	415	50.7[*,a] 52[#,a]	18-75	Valaciclovir 3000 mg/d × 7 d Prednisolonee 60 mg/d × 5 d 50 mg/d × 6 d, 40 mg/d × 7 d, 30 mg/d × 8 d 20 mg/d × 9 d 10 mg/d × 10 d	Prednisolone with the same dosage	RCT (double blind)	Sunnybrook facial grading system severe-moderate	12
Engstrom, M (2008)	416	61[*,a] 1[#,a]	18-75	Valaciclovir 3000 mg/d × 7 d Prednisolone 60 mg/d × 5 d 50 mg/d × 6 d, 40 mg/d × 7 d, 30 mg/d × 8 d 20 mg/d × 9 d 10 mg/d × 10 d	Prednisolone with the same dosage	RCT (double blind)	House-Brackmann grade (II-V)	12
Lee, H. Y (2013)	206	47.7[*,a] 50.5[#,a]	48.6[*,a] 48.7[#,a]	Famciclovir 750 mg/d × 7 d Methylprednisolone 64 mg/d × 4 d 48 mg/d × 5-6 d, 32 mg/d × 7-8 d, 16 mg/d × 9-10 d	Methylprednisolon with the same dosage	RCT (double blind)	House-Brackmann grade ≥ V	6
Minnerop, M. (2008)	117	50.7[*,a] 52[#,a]	40.6[*,a] 42.6[#,a]	Valaciclovir 750 mg/d × 7 d Prednisolone (1 mg/kg body weight) for 4 days and tapered subsequently over the following 8 days	Prednisolone with the same dosage	RCT (not blind)	House-Brackmann grade (II-V)	3
Yeo, S. G (2008)	91	42.6[*,a] 47.7[#,a]	40.2[*,a] 42.7[#,a]	Acyclovir 2400 mg/d × 5 d Prednisone, at a dose of 1 mg/kg per day (maximum, 80 mg/d) × 4 days 60 mg/d × 5-6 d, 40 mg/d × 7-8 d, 20 mg/d × 9-10 d	Prednisolone with the same dosage	RCT (double blind)	House-Brackmann grade (II-V)	6
Hato, N. (2007)	221	47[*,a] 48[#,a]	52.3[#,a] 48.4[*,a]	Valacyclovir 1,000 mg/d × 5 d Prednisolonee 60 mg/d × 5 d 50 mg/d × 6 d, 40 mg/d × 7 d, 30 mg/d × 8 d 20 mg/d × 9 d 10 mg/d × 10 d	Prednisolone with the same dosage	RCT (singleblind)	House-Brackmann grade (II-V)	6

[*]: the steroids alone group; [#]: the steroids-antivirals group; [a]: mean age.

Steroid-Antivirals compared to Steroids Alone for Bell's palsy

Patient or population: patients with Bell's palsy
Settings:
Intervention: Steroid-Antivirals
Comparison: Steroids Alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Steroids Alone	Steroid-Antivirals				
summary of findings Follow-up: mean 6 months	Study population		OR 1.52 (1.20 to 1.94)	1816 (8 studies)	⊕⊕⊕⊖ moderate	
	768 per 1000	835 per 1000 (799 to 866)				
	Moderate					
adverse effect Follow-up: mean 7.5 months	Study population		OR 1.28 (0.71 to 2.31)	522 (2 studies)	⊕⊕⊕⊖ moderate	
	81 per 1000	102 per 1000 (59 to 170)				
	Moderate					

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; OR: Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Figure 2. Summary of findings table and adverse effect using GRADE methodology.
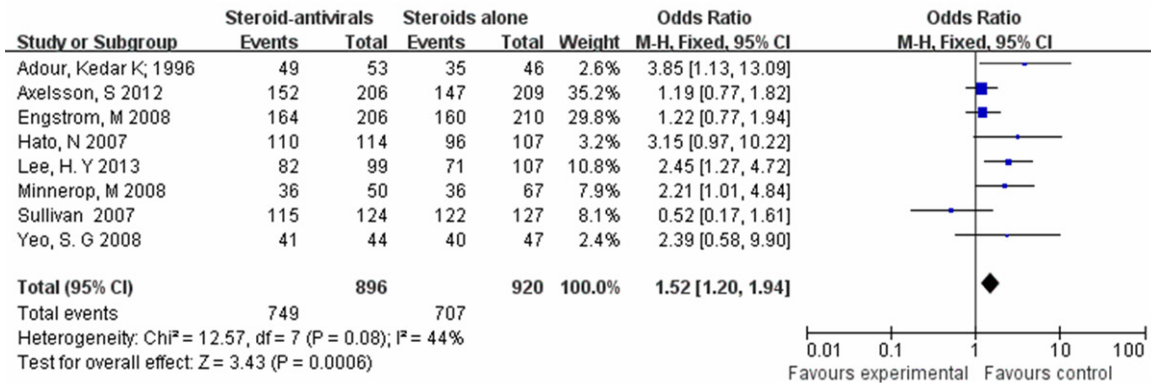
Figure 3. The steroids-antivirals group versus the steroids alone group (fixed effects model).
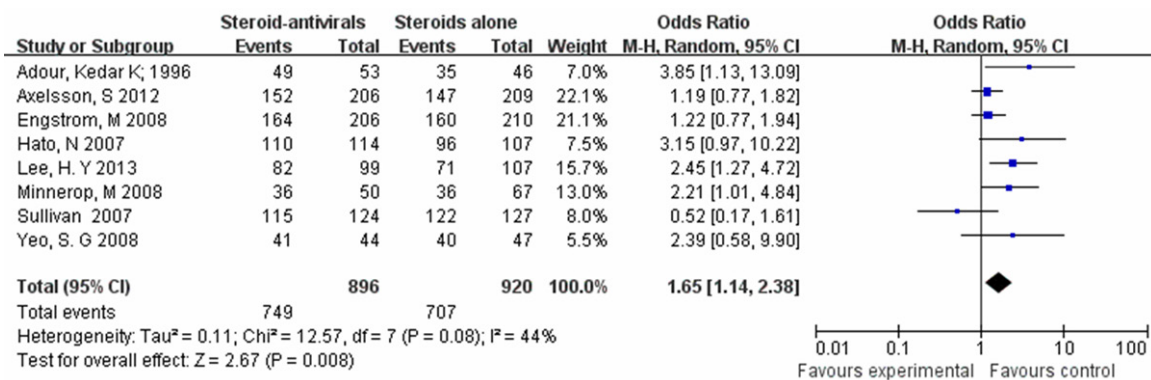

Figure 4. The steroids-antivirals group versus the steroids alone group (random effects model).

Description of included studies

The 8 eligible papers include 896 patients treated with steroid-antivirals and 920 patients treated with steroids alone. The RCTs showed a low risk of bias according to the Cochrane Collaboration's tool for assessing the risk of bias [25]. The quality score of studies ranged from 6 to 8 according to the Newcastle-Ottawa Scale [26]. General characteristics of the patients in the articles are present in **Table 2**, and the patients were followed up at the longest follow-up point. The retrieved studies and the levels of evidence were described referring to Oxford Centre for Evidence-based Medicine [27]. The study quality was also estimated according to the GRADE system, which was used to present the overall quality of evidence as recommended by the Cochrane Handbook for Systematic Reviews of Interventions [28]. **Figure 2** shows the outcomes of 'summary of findings', which was moderate for the new outcome.

Results of the meta-analysis

Owing to the result (chi^2 = 12.57, P = 0.08, I^2 = 44%) presented by the formal test for heterogeneity, the fixed effect meta-analysis model was chosen. The pooled proportion of patients recovery was 83.6% (749/896) among those who received steroids-antivirals, while the steroids alone group was 76.8% (707/920). There were significant differences in facial muscle recovery between the steroids-antivirals group and steroids alone group (OR = 1.52, 95% CI: 1.20-1.94) (**Figure 3**).

To assess the effect of study quality on our results, we further performed a sensitivity analysis by changing the effect model into random effect model. Consistently with the fixed effect model, the differences between the steroids-antivirals group and the steroids alone group stayed statistically significant (OR = 1.65, 95% CI: 1.14-2.38) (**Figure 4**).

Study or Subgroup	steroid-antivirals Events	Total	steroid alone Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Engström 2008	27	202	21	203	93.4%	1.34 [0.73, 2.45]	
Minnerop, M 2008	0	50	1	67	6.6%	0.44 [0.02, 11.00]	
Total (95% CI)		252		270	100.0%	1.28 [0.71, 2.31]	
Total events	27		22				

Heterogeneity: Chi² = 0.44, df = 1 (P = 0.51); I² = 0%
Test for overall effect: Z = 0.81 (P = 0.42)

0.01 0.1 1 10 100
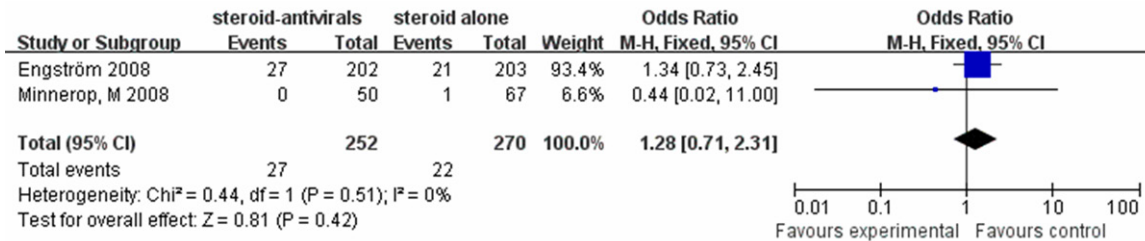Favours experimental Favours control

Figure 5. The adverse effect of steroids-antivirals group versus the steroids alone group (fixed effects model).

Two studies (Engström 2008 and Minnerop 2008) [13, 16] reported the adverse effects of the two therapies, such as headache and fatigue and so on. There was a low heterogeneity among the trials (I² = 0%). So we calculate the statistically outcome using the fixed effect model, and no statistically significant difference was observed (OR = 1.28, 95% CI: 0.71-2.31) (**Figure 5**).

Discussion

In general, Bell's palsy affects each individual differently. The treatments for Bell's palsy are different. Recent studies have shown that steroids such as the steroid prednisone which was used to reduce inflammation and swelling are effective in treating Bell's palsy [9]. Some studies showed that the addition of antiviral agents such as acyclovir could effectively enhance the curative effect of steroids [12-14].

Taking account of the different treatments for Bell's palsy, we performed a Meta-analysis to get a better treatment for the patients with Bell's palsy. Eight randomized controlled trials include 1816 patients in our meta-analysis. A high facial recovery rate at least partial recovery were achieved, no matter the patients were given steroid-antivirals or steroids alone. Our pooled odds ratio for facial muscle recovery (OR = 1.52, 95% CI: 1.20-1.94) (**Figure 3**) indicate that the steroid-antivirals treatment improves the recovery rate in patients with Bell's palsy. The quality of this study was moderate which was estimated by the GRADE system, supporting the new outcome.

Furthermore, oral antivirals are well tolerated if administered at standard doses. The rate of adverse effects of antiviral agents is low in all cases. We observe the adverse effects of included studies. Two trials (Engström 2008

and Minnerop 2008) reported the adverse effect of two therapies [13, 16]. The similar complications were presented in both groups. The statistically outcome shows no statistically significant difference between the steroid-antivirals group and the steroid alone group (OR = 1.28, 95% CI: 0.71-2.31) (**Figure 5**).

Several meta-analysis studies reported the different outcomes about whether combination treatment is effective on patients with Bell's palsy. Goudakos JK's study included 5 studies with 709 patients reporting no benefit of the steroid-antivirals treatment (OR = 1.03; 95% CI: 0.74-1.42) when compared with the steroid alone group [29]. But the small numbers in this meta-analysis may lead to lack of power. Numthavaj P' net meta-analysis suggests that the current practice of treating Bell's palsy with antiviral treatment plus corticosteroid may lead to slightly higher recovery rates compared with treating with prednisone alone. But their pooled estimates were quite heterogeneous. Moreover this study does not quite reach statistical significance [30]. The heterogeneity of included studies is moderate according to I² values (I² = 44%) in our Meta-analysis. Then the fixed effect meta-analysis model was chosen. At last we got the significant differences between the steroids-antivirals group and steroids alone group.

The two latest studies in our Meta-analysis which were double blind, had an effect on the result [14, 23]. The House-Brackmann grade of the facial muscle paralysis in Lee, H. Y's study is severe to complete. And Yeo, S. G's study shows that physical therapy in the department of rehabilitation was adopted to treat the patients [23]. All of these may have a great effect on the last outcome. So sensitivity analysis was performed showing similar findings (OR = 1.76, 95% CI: 1.25-2.46) (**Figure 4**), that the steroid-antivirals treatment improves the recovery rate in patients with Bell's palsy.

The steroid-antivirals treatment could improve the recovery rate in patients with Bell's palsy in our Meta-analysis. Given the truly existing heterogeneity detected between the low number of studies, before making final conclusion, caution is still needed to determine whether the steroid-antivirals treatment can achieve a better curative effect than the steroids alone on patients with Bell's palsy.

Conclusions

There were significant differences in facial muscle recovery between the steroids-antivirals group and the steroids alone group. This meta-analysis shows that the steroid-antivirals treatment achieves a recovery rate in patients with Bell's palsy than the steroid alone treatment, supporting the routine addition of antivirals to steroids in Bell's palsy. Clinicians should consider that steroid-antivirals therapy is a better choice for the patients with Bell's palsy.

Acknowledgements

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Huaqiang Zhao, Department of Oral and Maxillofacial Surgery, College of Stomatology, Shandong University, Number 44, Wen Hua Xi Lu, Jinan 250012, Shandong Province, China. Tel: +86 13506402199; Fax: +86 531 82950154; E-mail: zhaohq@sdu.edu.cn

References

[1] Hauser WA, Karnes WE, AnnisL J, Kurland T. Incidence and prognosis of Bell's palsy in the population of Rochester, Minnesota. Mayo Clin Proc 1971; 46: 258-64.

[2] Katusic SK, Beard CM, Wiederholt WC, BergstralhL ET, Kurland T. Incidence, clinical features, and prognosis in Bell's palsy, Rochester, Minnesota, 1968-1982. Ann Neurol 1986; 20: 622-7.

[3] Lockhart P, Daly F, Pitkethly M, Comerford N. Sullivan F. Antiviral treatment for Bell's palsy (idiopathic facial paralysis). Cochrane Database Syst Rev 2009: CD001869.

[4] Murakami S, Mizobuchi M, Nakashiro Y, Doi T, Hato N, Yanagihara N. Bell palsy and herpes simplex virus: identification of viral DNA in endoneurial fluid and muscle. Ann Intern Med 1996; 124: 27-30.

[5] Furuta Y, Fukuda S, Chida E, Takasu T, Ohtani F, Inuyama Y, Nagashima K. Reactivation of herpes simplex virus type 1 in patients with Bell's palsy. J Med Virol 1998; 54: 162-6.

[6] Abiko Y, Ikeda M, Hondo R. Secretion and dynamics of herpes simplex virus in tears and saliva of patients with Bell's palsy. Otol Neurotol 2002; 23: 779-83.

[7] Sugita T, Murakami S, Yanagihara N, Fujiwara Y, Hirata Y, Kurata T. Facial nerve paralysis induced by herpes simplex virus in mice: an animal model of acute and transient facial paralysis. Ann Otol Rhinol Laryngol 1995; 104: 574-81.

[8] Allen D, Dunn L. Aciclovir or valaciclovir for Bell's palsy (idiopathic facial paralysis). Cochrane Database Syst Rev 2004: CD001869.

[9] Kim IS, Shin SH, Kim J, Lee WS, Lee HK. Correlation between MRI and operative findings in Bell's palsy and Ramsay Hunt syndrome. Yonsei Med J 2007; 48: 963-8.

[10] Jackson CG, von Doersten PG. The facial nerve. Current trends in diagnosis, treatment, and rehabilitation. Med Clin North Am 1999; 83: 179-95, x.

[11] Sullivan FM, Swan IR, Donnan PT, Morrison JM, Smith BH, McKinstry B, Davenport RT, Vale LD, Clarkson JE, Hammersley V, Hayavi S, McAteer A, Stewart K, Daly F. Early treatment with prednisolone or acyclovir in Bell's palsy. N Engl J Med 2007; 357: 1598-607.

[12] Adour KK, Ruboyianes JM, Von Doersten PG, Byl FM, Trent CS, Quesenberry CP Jr, Hitchcock T. Bell's palsy treatment with acyclovir and prednisone compared with prednisone alone: a double-blind, randomized, controlled trial. Ann Otol Rhinol Laryngol 1996; 105: 371-8.

[13] Minnerop M, Herbst M, Fimmers R, Kaabar P, Matz B, Klockgether T, Wullner U. Bell's palsy: combined treatment of famciclovir and prednisone is superior to prednisone alone. J Neurol 2008; 255: 1726-30.

[14] Lee HY, Byun JY, Park MS, Yeo SG. Steroid-antiviral treatment improves the recovery rate in patients with severe Bell's palsy. Am J Med 2013; 126: 336-41.

[15] Kawaguchi K, Inamura H, Abe Y, Koshu H, Takashita E, Muraki Y, Matsuzaki Y, Nishimura H, Ishikawa H, Fukao A, Hongo S, Aoyagi M. Reactivation of herpes simplex virus type 1 and

varicella-zoster virus and therapeutic effects of combination therapy with prednisolone and valacyclovir in patients with Bell's palsy. Laryngoscope 2007; 117: 147-56.

[16] Engstrom M, Berg T, Stjernquist-Desatnik A, Axelsson S, Pitkaranta A, Hultcrantz M, Kanerva M, Hanner P, Jonsson L. Prednisolone and valaciclovir in Bell's palsy: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet Neurol 2008; 7: 993-1000.

[17] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 2009; 6: e1000100.

[18] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009; 6: e1000097.

[19] Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996; 17: 1-12.

[20] Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959; 22: 719-48.

[21] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557-60.

[22] Hato N, Yamada H, Kohno H, Matsumoto S, Honda N, Gyo K, Fukuda S, Furuta Y, Ohtani F, Aizawa H, Aoyagi M, Inamura H, Nakashima T, Nakata S, Murakami S, Kiguchi J, Yamano K, Takeda T, Hamada M, Yamakawa K. Valacyclovir and prednisolone treatment for Bell's palsy: a multicenter, randomized, placebo-controlled study. Otol Neurotol 2007; 28: 408-13.

[23] Yeo SG, Lee YC, Park DC, Cha CI. Acyclovir plus steroid vs steroid alone in the treatment of Bell's palsy. Am J Otolaryngol 2008; 29: 163-6.

[24] Axelsson S, Berg T, Jonsson L, Engström M, Kanerva M, Stjernquist-Desatnik A. Bell's palsy - the effect of prednisolone and/or valaciclovir versus placebo in relation to baseline severity in a randomised controlled trial. Clin Otolaryngol 2012; 37: 283-90.

[25] Higgins JPT and Green S. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from: www.cochrane-handbook.org., 2011.

[26] Wells GA, Shea B, O'Connell D, Peterson D, Welch V, Losos M, Tugwell M. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa Hospital Research Institute (OHRI). http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp., 2012.

[27] Philips B, Ball C, Sackett D, Badenoch D, Straus S, Haynes B, Dawes M. Oxford Centre for Evidence-based Medicine Levels of Evidence. Available: http://www.cebm.net/index.aspx?o=1025, 2009.

[28] Higgins J, C.R., Cumpston M, Chandler J. Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0. Available: http://www.cochrane.org/training/cochrane-handbook., 2013.

[29] Goudakos JK, Markou KD. Corticosteroids vs corticosteroids plus antiviral agents in the treatment of Bell palsy: a systematic review and meta-analysis. Arch Otolaryngol Head Neck Surg 2009; 135: 558-64.

[30] Numthavaj P, Thakkinstian A, Dejthevaporn C, Attia J. Corticosteroid and antiviral therapy for Bell's palsy: a network meta-analysis. BMC Neurol 2011; 11: 1.