Combined antiviral agents with corticosteroids versus corticosteroids alone in the treatment of Bell's palsy: a systematic review

ORIGINAL ARTICLE BY

Tanapak Wisetmongkolchai, M.D.[1]; Rewadee Wongarmart, M.D.[2]; Nattapon Seenoikhao, M.D.[3]; Kittima Taprungsirikul, M.D.[4]; Prapaporn Supannanon , M.D.[5]

[1]Nong Rua Hospital, Thailand; [2]At Samat Hospital, Thailand; [3]Ban Muang Hospital, Thailand; [4]Ban Phai Hospital, Thailand; [5]Na Thom Hospital, Thailand;

Accepted: April 2017
Latest revision: March 2018
Printed: April 2018

Correspondence to: Rewadee Wongarmart; r.wongarmart@gmail.com

ABSTRACT

OBJECTIVE

To compare the efficacy between using combined antiviral agents with corticosteroids and corticosteroids alone for treatment of Bell's palsy.

METHODS

We systematically searched through electronic databases including The Cochrane Library, MEDLINE, Scopus, CINAHL, ClinicalTrials.gov as well as other sources than database such as Google scholar and hand searching of published randomized controlled trials (RCTs). We considered of participants were diagnosed with unilateral facial paralysis without any identifiable causes, who started therapy within seven days from the onset of the disease, and who satisfied the author's requirement for eligibility and inclusion. We assessed participants who received any types of corticosteroids therapy alone versus the combination of corticosteroids with acyclovir, valacyclovir or famciclovir, regardless of routes, dosages and duration of administration of the therapies. The primary outcome was the incomplete recovery of facial function.

RESULTS

We included ten RCTs with a total of 1,850 participants, who received combined antiviral agents with corticosteroids (n=922) and corticosteroids (n=928). Our study showed combined antiviral agents with corticosteroids statistically significant reduced incomplete recovery of facial function than corticosteroids alone for Bell's palsy treatment (relative risk (RR), 0.74; 95% confidence interval (CI), 0.61 to 0.90; I^2=38%). Combined famciclovir with corticosteroids showed a significant benefit more than corticosteroids alone (RR, 0.44; 95% CI, 0.27 to 0.71). It also showed combined antiviral agents with the cumulative dose of prednisolone greater than 400 mg but less than 500 mg significantly reduced in incomplete recovery of facial function (RR, 0.73; 95% CI, 0.55 to 0.98) than both cumulative doses that lesser than or equal 400 mg and at least 500 mg of prednisolone (RR, 0.77; 95% CI, 0.55 to 1.07), (RR, 1.04; 95% CI, 0.48 to 2.26) respectively.

CONCLUSION

In conclusion, there was evidence of a benefit of famciclovir in combination with greater than 400 mg but less than 500 mg of prednisolone for Bell's palsy treatment.

INTRODUCTION

Bell's palsy or idiopathic facial paralysis is defined as an acute unilateral paralysis of the facial nerve first recognized by the Scottish surgeon; Sir Charles Bell.[1] The annual incidence of Bell's palsy is 20 per 100,000 populations and the incidence tends to increase with age.[2] The etiology is still unclear but genetic, vascular, infectious and immunological causes have all been hypothesized.[3] In addition, previous studies found that herpes infection as the etiology of the paralysis based on serological evidence.[4,5] Positive serology for herpes simplex virus (HSV) has been reported in 20-79% of participants.[4,5] Concerning that HSV can cause inflammation of the facial nerve in the infected patients.[6] Although most of the participants will completely or near normal recover, the rest will have persistent moderate to severe weakness, facial contracture or synkinesis.[7] the major aims of treatment for Bell's palsy are to recover and prevent the sequelae. Nowadays, the treatment of choices for the Bell's palsy are corticosteroids and a combination of an antiviral agent with corticosteroids (combined therapy).[8] Corticosteroids are recommended for treatment of Bell's palsy by many physicians to reduce facial nerve inflammation.[8]

Bell's palsy suspected to be caused by herpes infection. Therefore, antiviral agents (e.g., acyclovir, valacyclovir and famciclovir) when administered with corticosteroids may be obtained the additional benefit for Bell's palsy treatment. There were three systematic reviews published in 2009 and no consensus was found.[9-11] Even though the therapeutic effects of combined therapies are controversial, some physicians still prescribe combined antiviral agents with corticosteroids for Bell's palsy.

Since those reviews three further studies have been published: three of them were RCTs. Two of studies suggested that greater outcome for Bell's palsy participants occurred if they were treated with antiviral agents and corticosteroids in combination instead of corticosteroids alone.[12,13] The remaining studies showed no significance.[14] Subgroup analysis by type of antiviral agents and cumulative dose of corticosteroids was not analyzed by three recent systematic reviews. Therefore, we included three new RCTs and analyzed subgroups by type of antiviral agents and cumulative dose of corticosteroids in our study.

METHODS

SEARCH STRATEGIES

We searched for studies through The Cochrane Library, MEDLINE, Scopus, CINAHL and ClinicalTrials.gov without any language restriction. We used a combination of Medical Subject Headings (MeSH) for MEDLINE and Cochrane Library searching (("Bell Palsy"[Mesh]) AND "Antiviral Agents"[Mesh]) AND "Steroids"[Mesh] and used keyword "bell's palsy AND antiviral drugs AND steroid", "bell's palsy AND antiviral drugs ", "bell's palsy AND steroid", "bell's palsy AND acyclovir AND steroid", "bell's palsy AND valacyclovir AND steroid" , "bell's palsy AND famciclovir AND steroid", "bell's palsy AND corticosteroids AND antiviral drugs " in Scopus, CINAHL, ClinicalTrials.gov and other database like Google scholar. We checked the references of

included studies and hand searched for additional studies which were relevant. Overall, 132 titles and abstracts were reviewed.

INCLUSION CRITERIA

PARTICIPANTS

Studies in the participants with unilateral facial nerve weakness of no identifiable causes had seen within seven days of the onset.

INTERVENTIONS

Treatment with corticosteroids plus antiviral agents and corticosteroids alone which started within seven days from the onset of the disease, regardless of types, routes, dosages and durations of administration of the therapies.

OUTCOMES

The primary outcome was the incomplete recovery of facial function at the end of the study measured using a validated rating scale. Duration of studies included in this systematic review was at least three months. Secondary outcomes included motor synkinesis and adverse events.

EXCLUSION CRITERIA

Studies in the participants with uncontrolled diabetes mellitus, herpes zoster, peptic ulcer disease, suppurative otitis media, multiple sclerosis, pregnancy, and breastfeeding women were excluded.

STUDY SELECTION

This systematic review is searched and considered the design of each trial; randomized controlled, involving acyclovir, valacyclovir or famciclovir combined with any corticosteroids therapy in the treatment of Bell's palsy. All inclusion and exclusion criteria of RCTs were specified prior to the literature selection. For a study to be eligible, the

DATA EXTRACTION

Data were extracted and recorded from five review authors individually. We extracted data was as follows criteria for diagnosis, inclusion and exclusion criteria, the language of publication, interventions, number of participant, date, and duration of the study and outcomes. We extracted data into simple standard forms.[15]

QUALITY OF REPORTING AND RISK OF BIAS

The five authors evaluated the quality and risk of bias of the included studies with Cochrane risk of bias tool to assess the quality of selected studies. Moreover, we used the domain base-evaluation following The Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0.15 The Domain base-evaluation evaluated in random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias) and selective reporting (reporting bias) and others bias. They classified the study into low risk, high risk and unclear risk for each bias tool. Potential publication bias was assessed by using a funnel plot.

DATA ANALYSES

To standardize the reporting of our results, we calculated relative risk (RR) with 95% confidence

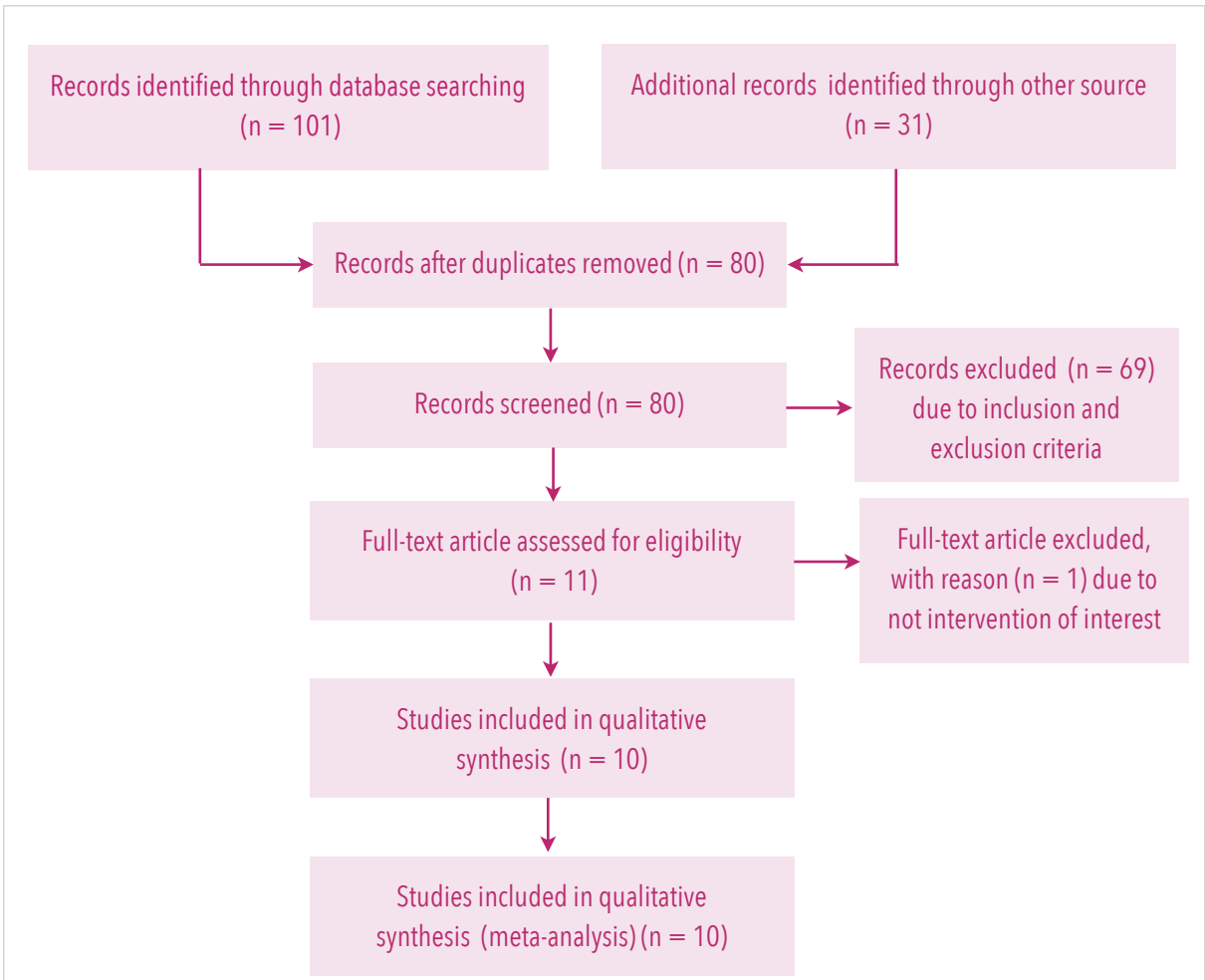


Figure 1. Process of study selection.

interval (CI) from dichotomous data in each group for every trial. All analyses were performed with Revman 5.3.0 (RevMan, the programme provided by the Cochrane Collaboration) statistical software using fixed effect model meta-analyses to assess the effectiveness of combined antiviral agents with corticosteroids compared with corticosteroids alone for Bell's palsy treatment in achieving incomplete recovery of facial function, motor synkinesis occurrence rate and adverse events. The chi-square and I^2 statistics were used to evaluate statistical heterogeneity across trials. The statistical test of heterogeneity was significant if $P<0.05$ and heterogeneity was considered high if the I^2 statistics was more than 50%. We considered to use a random effect model for the meta-analysis when heterogeneity was statistical significance from the I^2 statistics.

Table 1. Characteristics of the included study

Source	Combined group/corticosteroids alone group					Intervention		Outcomes	Duration of Follow-up (Mo)
	N	Age (Y) (Mean±SD)	Sex (% Male)	Initial Severity of Palsy	Therapy Start*	Combined Therapy Group	Corticosteroids Group†		
Ho yun, 2013	99/107	46.7±16.2/ 48.6±15.1	50.5/47.7	HB≥5	First 7 days	Corticosteroids plus famciclovir (750 mg/d) for 7 days	Methylprednisolone, 64 mg/d for 4 days 48 mg/d for 2 days 32 mg/d for 2 days 16 mg/d for 2 days	HB≤II	6
Axelsson, 2012	206/209	NR	NR	SB 0-20, 18.9/18; SB 21-40, 36/34; SB ≥40, 45.1/47.8	First 3 days	Corticosteroids plus valaciclovir two 500-mg tablets 3 times daily for 7 days	Prednisolone, 60 mg/d for 5 days,tapering by 10 mg/ day for 5 days	SB=100 (HB =I)	12
Shahidullah, 2011	34/34	31.1±9.6/ 35.1±1.7	64.7/76.5	HB, 4.4±1.0/ 4.3±1.2	Early treatment group (≤3 day), late treatment group (>3 d)	Corticosteroids plus famciclovir 250 mg, 3 times daily for 5 days.	Prednisolone 60 mg/day for 7 days.	HB=1	3
Engström, 2008	206/210	42/40	61/61	HB, 4/4	First 3 days	Corticosteroids plus valaciclovir 1000 mg 3 times daily for 7 days	Prednisolone 60 mg/day for 5 days	HB=1	12
Vázquez, 2008	22/19	42.5±20.8/ 40.1±18.5	36.4/42.1	FGS, 39.4±12.7/ 33.5±15.6	First 3 days	Corticosteroids plus valacyclovir, 2000 mg/day for 7 days	Prednisone for 1 mg/kg, single dose for first 7 days lowered of a 10 mg every 3 days within 14 days.	FGS>90	6
Yeo, 2008	44/47	42.7±15.7/ 40.2±18.4	47.7/ 42.6	HB, 3.76±1.3/ 3.6±0.9	Early treatment group (≤3 day), late treatment group (>3 d)	Corticosteroids plus acyclovir 2,400 mg/d for 5 days.	Prednisolone 1 mg/kg per day (maximum, 80 mg/d) for 4 days, reduced to 60 mg/day on days 5-6, 40 mg on days 7-8, 20 mg on days 9-10	HB≤II	6
Hato, 2007	114/107	52.3/48.4	52/53	YH, 14.7/15.3	First 7 days	Corticosteroids plus valacyclovir, 500 mg, twice a day for 5 days	Prednisolone, 20 mg, 3 times a day for 5 days;10 mg, 3 times a day on day 6-8;10 mg, once per day on day 9-10	YH>36 (HB=I)	6
Sullivan, 2007	124/127	43.7±16.4/ 42.7±15.9	51.6/55.9	HB,3.4±1.2/ 3.5±1.2	Within 3 days	Corticosteroids plus acyclovir, 400 mg, 5 times a day for 10 days	Prednisolone, 25 mg twice a day for 10 days	HB=I	9

Table 1. (Continued)

Source	N	Combined group/corticosteroid alone group				Intervention		Outcomes	Duration of Follow-up (Mo)
		Age (Y) (Mean±SD)	Sex (% Male)	Initial Severity of Palsy	Therapy Start[a]	Combined Therapy Group	Corticosteroids Group[b]		
Inanli, 2001	20/22	38/42	70/59	NR	First 4 days	Corticosteroids plus acyclovir, 800 mg, 3 times a day for 10 days	Prednisolone 1 mg/kg per day tapering to terminated within12 days	HB ≤2	3
Adour, 1996	53/46	41.9±14.1/ 44.6±15.1	55/ 43	FPRP; 3.0/3.1	First 3 days	Corticosteroids plus acyclovir, 2000 mg/day for 10 days	Prednisolone,30 mg, 2 times a day for 5 days; 5 mg, 2 times a day at day 6-10	FPRI=10 (HB=I)	4

Abbreviation: NR; not reported, HB; House-Brackmann Scale, SB; Sunnybrook score, FPRP; Facial Paralysis Recovery Profile, FPRI; Facial Paralysis Recovery Index, FGS; Facial Grading System

*Time after disease onset that therapy initiated.

† Combined therapy: corticosteroids plus antiviral agents.

RESULTS

The literature search retrieved 101 citations and additional 31 citations were identified through other sources like manual searches reference lists of articles and Google scholar. Of these, 80 citations after duplicates removed were identified. After screened titles and abstracts, 69 citations were excluded and then 11 full-text articles assessed for eligibility according to inclusion and exclusion criteria. Ultimately, ten articles were included as eligible (Fig. 1).

All studies were RCTs regarding study design and performed between 1996 and 2013. The included studies assigned 1,850 participants, who received combined antiviral agents with corticosteroids (n=922) and corticosteroids (n=928).

STUDY CHARACTERISTICS

All ten trials provided a comparison of disease outcome after combined antiviral drugs with corticosteroids treatment and corticosteroids alone. Four trials compared acyclovir combined prednisolone and prednisolone alone, four trials compared valacyclovir combined prednisolone, and two trial compared famciclovir combination to corticosteroids and corticosteroid alone (Table 1).

RISK OF BIAS ASSESSMENT

Ten trials were assessed using Cochrane risk of bias tool. Here are the results of the assessment of the 10 included studies (Fig. 2 and Fig. 3).

SEQUENCE GENERATION, ALLOCATION CONCEALMENT, AND BLINDING

Four studies were randomized, double-blind and placebo-controlled trial.[16-19] Four studies did not adequately describe methods of random sequence generation.[13,14,20,21] Three of these and one more studies did not adequately describe methods of allocation concealment.[12,14,20,21] Two studies did not adequately describe methods of blinding of participants and personnel.[12,21] Two studies did not

adequately describe methods of blinding of outcome assessment.[14,21] Three studies were not blind or placebo use,[13,20,21] two of these studies did not conceal of allocation.[13,21]

INCOMPLETE OUTCOME DATA

All studies reported frequencies and reasons for failure to complete follow up.

SELECTIVE OUTCOME REPORTING

All studies were the low risk of bias in the domain of selective reporting.

OTHER POTENTIAL SOURCE OF BIAS

One study stated participants were diagnosed with Bell's palsy but did not give any further information.[16] And one study reported modified intention to treat.[19] Visually our funnel plot which constructed from the ten trials included in the analysis appeared to be symmetrical (Fig. 8).

CLINICAL OUTCOMES

PRIMARY OUTCOME

The primary outcome was the incomplete recovery of facial function. The meta-analysis of ten studies showed a statistically significant difference between combined antiviral agents with corticosteroids and corticosteroids alone for Bell's palsy treatment, RR 0.74 (95% CI, 0.61 to 0.90; chi-square 14.60; I^2=38%) (Fig. 4).

We analyzed subgroup of these trials by type of antiviral agents. Four trials compared acyclovir plus prednisolone and prednisolone alone, there was no significant reduction in the rate of incomplete recovery, RR 0.79 (95% CI, 0.47 to 1.34).[16,18,20,21] Four trials provided data valacyclovir plus prednisolone versus prednisolone.[14,17,19,22] The relative risk of incomplete recovery was again non-significant, RR 0.83 (95% CI, 0.66 to 1.04). The remaining trials showed comparison of famciclovir plus corticosteroids and corticosteroids alone.[12,13] This analysis showed a significant improvement in facial function, RR 0.44 (95% CI, 0.27 to 0.71) (Fig. 4).

We also analyzed subgroup by cumulative dose of corticosteroids. Two RCTs were not included in this analysis due to limited information of cumulative dose of corticosteroids.[19,20] Therefore, there were eight RCTs were analyzed. Two trials, combined therapies with lesser than or equal 400 mg of prednisolone were no significant association with a reduction in the risk of incomplete recovery (RR, 0.77; 95% CI, 0.55 to 1.07).[16,17] Three trials showed significant RR reduction in incomplete recovery of facial function in participants treated with combined antiviral agents with greater than 400 mg but less than 500 mg of prednisolone (RR, 0.73; 95% CI, 0.55 to 0.98).[13,14,22] And two trials gave data combined therapies with at least 500 mg prednisolone showed no significant improvement of facial function (RR, 1.04; 95% CI, 0.48 to 2.26).[18,21] One trial was no significant difference in rates of incomplete recovery between combined antiviral agents with 448 mg of methylprednisolone and methylprednisolone alone (RR, 0.51; 95% CI, 0.31 to 0.85) (Fig. 5).[12]

SECONDARY OUTCOMES

The secondary outcome was motor synkinesis. Two trials showed a significant reduction in motor

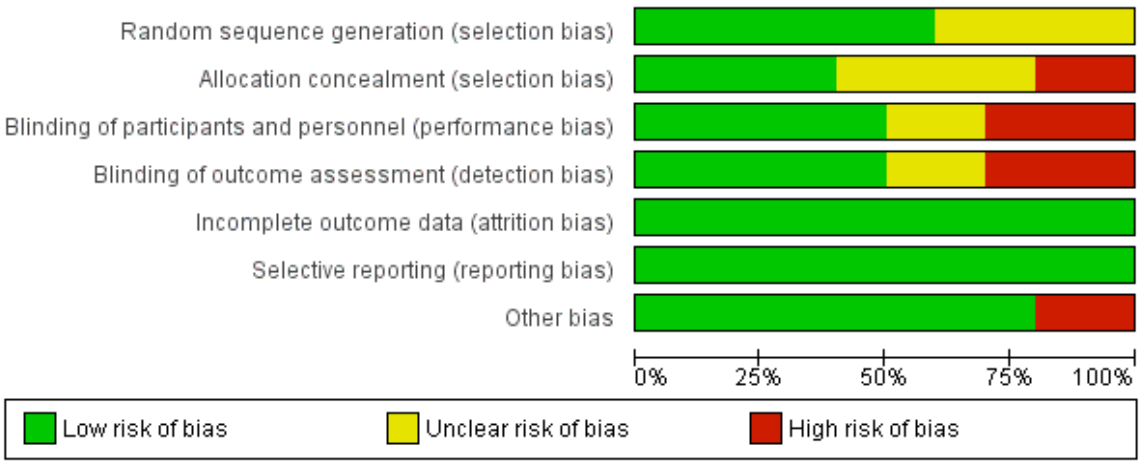


Figure 3. Risk of bias graph

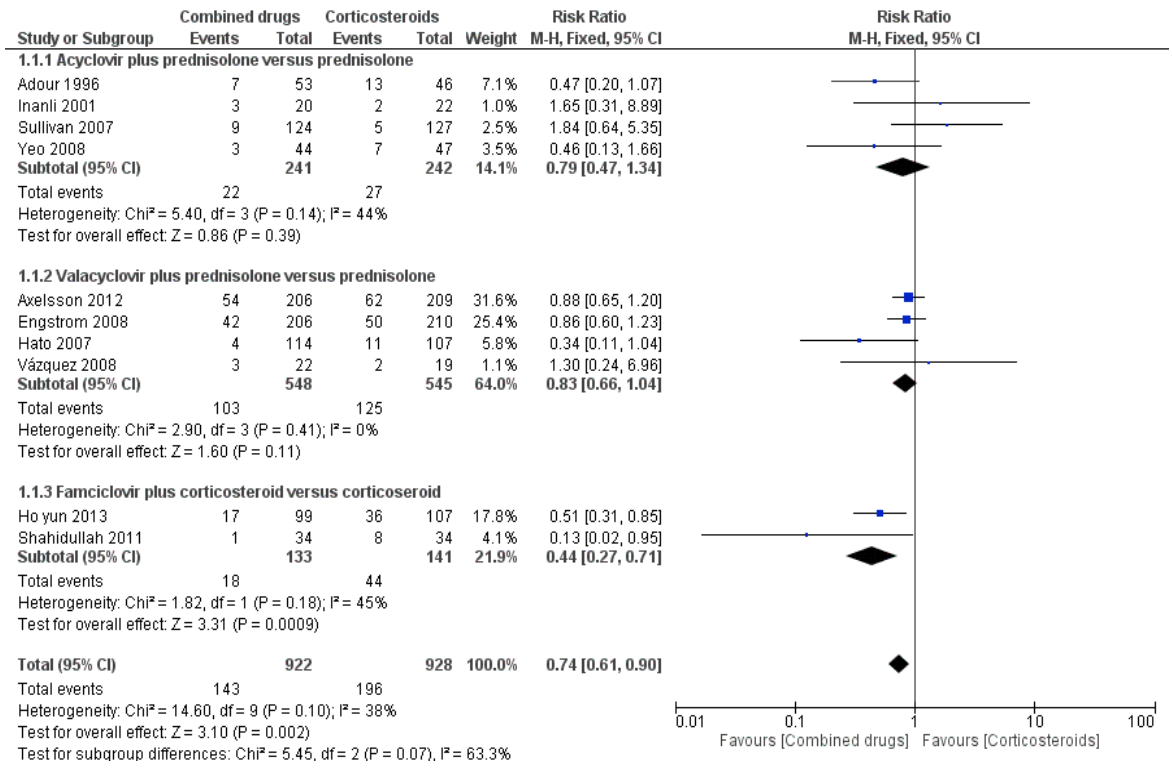


Figure 4. Forest Plot; Combined drugs vs corticosteroids alone; primary outcome, incomplete recovery of facial function

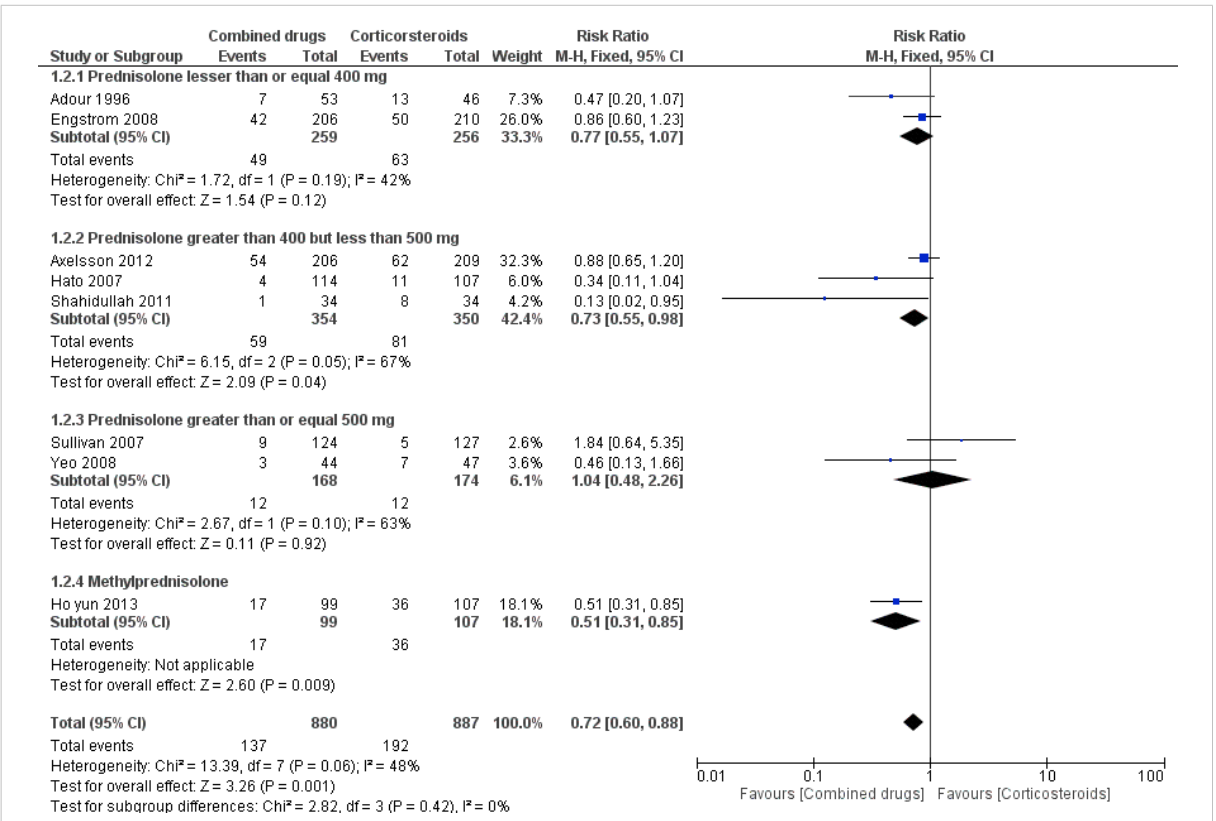


Figure 5. Forest Plot; Combined drugs vs corticosteroids alone; primary outcome, incomplete recovery of facial function with subgroup analysis dosage of corticosteroids

synkinesis occurrence rate, RR 0.56 (95% CI, 0.36 to 0.87; chi-square 0.24; I^2=0%) (Fig. 6).[14-16] Three trials gave data for adverse events, there were not significantly different between two groups, RR 1.18 (95% CI, 0.83 to 1.69; chi-square 0.30; I^2=0%) (Fig. 7).[17,18,22]

DISCUSSION

Our systematic review, a meta-analysis of ten RCTs showed a statistically significant difference between combined antiviral agents with corticosteroids and corticosteroids alone for Bell's palsy treatment. These results were influenced by the two trials suggesting that combined famciclovir with corticosteroids treatment had a significant higher rate of recovery of Bell's palsy.[12,13] There was no significant reduction in the incomplete recovery rate in acyclovir or valacyclovir plus prednisolone versus prednisolone alone. These results may due to mechanisms of the drug. Mechanisms of famciclovir are superior oral bioavailability and longer intracellular half-life than other antiviral agents.[23,24]

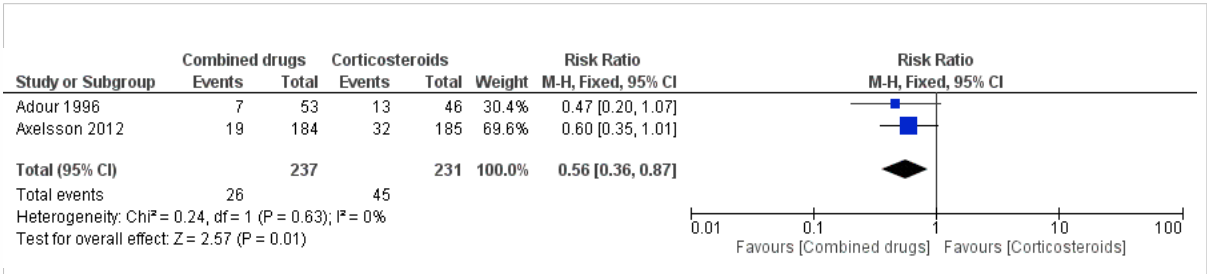


Figure 6. Forest Plot of Comparison

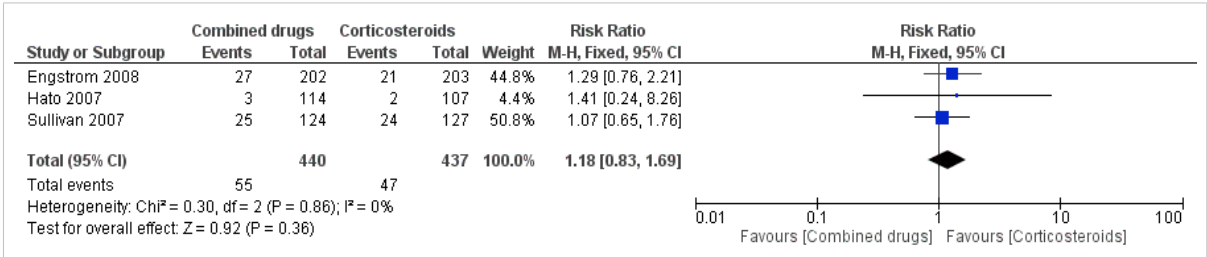


Figure 7. Forest Plot of Comparison

When combined antiviral agents with the different cumulative dose of corticosteroids were subgroup analyzed, the participants receiving greater than 400 mg but less than 500 mg of prednisolone were significantly more likely to recover than those receiving other doses of prednisolone. There was a significant reduction in incomplete recovery in combined antiviral agents with 448 mg of methylprednisolone, but there was only one RCT included in this analysis.[12] Therefore, there was no sufficient data to support using of combined antiviral agents with methylprednisolone for Bell's palsy treatment. From the minimal data for comparison of motor synkinesis, the results of two studies with separate comparisons were significant. Other secondary outcomes including adverse events which were reported by three studies were not significant.

STRENGTH AND LIMITATION OF THE REVIEW

This systematic review has much strength. Five authors searched for eligible RCTs by screening all titles and abstracts and read full-text articles to assess relevant studies, thus, we got eligible studies and can be assured not to missed important data. The data extraction has been performed by individual reviewers and independently. Furthermore, our included studies were considered as high methodological quality with a low risk of bias and the results from these studies can be trusted. This study examined the risk of bias of each study thoroughly using Cochrane risk bias tool.

The limitations of this systematic review are various data of initial severity at the onset of disease and time to start treatment. These factors may affect facial recovery rate. Our study may have

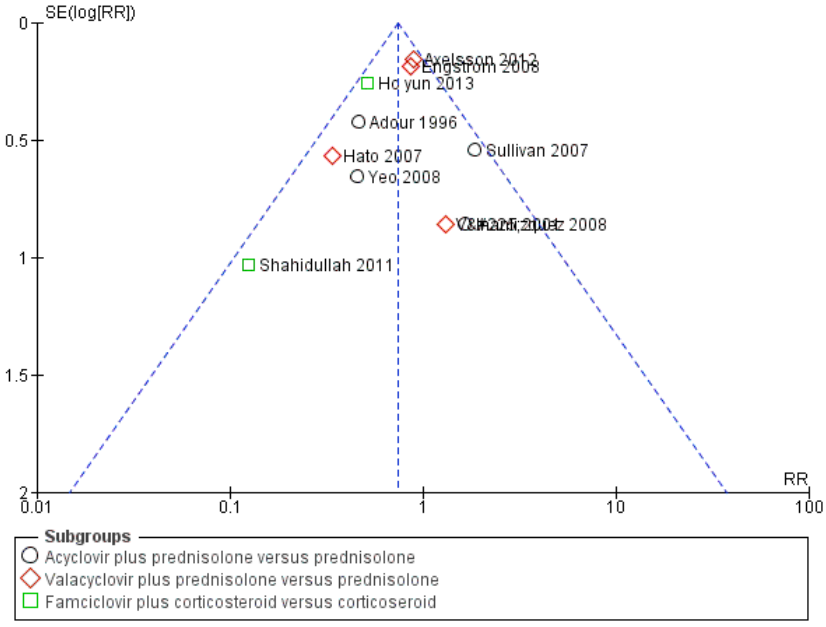


Figure 8. Funnel Plot of Comparison

inadequate power for some outcomes such as adverse events of combined antiviral agents with corticosteroids therapy and reduction rate of motor synkinesis due to few literature.

COMPARISON WITH OTHER STUDIES

There were three systematic reviews studied combined antiviral agents with corticosteroids versus corticosteroids. The Cochrane systematic review included seven RCTs with 1,987 participants. The rate of incomplete recovery was significantly less with the combined treatment than with corticosteroids alone which would suggest a beneficial effect from antiviral agents but this analysis showed moderate heterogeneity.[9] One review suggested a borderline significant risk reduction of borderline superior effect of the combined therapy over corticosteroids alone.[10] The last review included five RCTs with 738 participants and showed no benefit of using antiviral agents with corticosteroid compared with corticosteroid alone.[11] In our study, we included ten RCTs with 1,850 participants. Five RCTs were included in Cochrane systematic review and John R systematic review, two RCTs also included in John R systematic review and three more RCTs were newly added to our systematic review. Two RCTs in Cochrane systematic review.[25,26] and nine RCTs in John R systematic review were excluded from our studies because they did not meet our inclusion criteria.[26-34] In John R systematic review, two RCTs had missing information which published only abstract and no available full-text publication.[35,36] Finally, combined antiviral agents with corticosteroid

showed statistically significant to reduce incomplete recovery of facial function (RR 0.74, 95% CI, 0.61 to 0.90). Our results were similar to John R systematic review which found a benefit of antiviral agents with corticosteroid (RR 0.75, 95% CI, 0.56 to 1.00), but our study slightly more precise (95% CI, 0.61 to 0.90 versus 95% CI, 0.56 to 1.00 respectively). In addition, our study analyzed subgroups of these trials by type of antiviral agents and dosage of corticosteroids which the recent three systematic reviews did not report. In an analysis, famciclovir presented a significant effect on the outcome of incomplete recovery (RR 0.44, 95% CI, 0.27 to 0.71). The cumulative dose of prednisolone greater than 400 mg but less than 500 mg and methylprednisolone 448 mg showed a significant reduction in a risk of incomplete recovery (RR, 0.73; 95% CI,0.55 to 0.98, RR, 0.51; 95% CI, 0.31 to 0.85 respectively).

CONCLUSION AND IMPLICATIONS

In conclusion, this systematic review and meta-analysis of ten RCTs showed a statistically significant increase recovery rate of Bell's palsy in combined famciclovir with greater than 400 mg but less than 500 mg of prednisolone compared to prednisolone alone. Combined therapy with 448 mg of methylprednisolone also showed significant improvement of facial function. Though these results showed significant, only one randomized controlled trial was included in this analysis. Therefore, the data to support using of combined antiviral agents and methylprednisolone for the treatment of Bell's palsy were insufficient.

ACKNOWLEDGMENTS & DECLARATION

The authors would like to thank Dr. Thammasorn Jeeraaumponwat for his advice and suggestion. We also would like to thank Khon Kaen Medical Education Center, Khon Kaen Hospital for all support during conduct the current study.

COMPETING INTERESTS: This study has no competing on interest.
FUNDING: None

REFERENCES

1. Petruzzelli GJ, Hirsch BE. Bell's palsy. A diagnosis of exclusion. Postgrad Med. 1991 Aug;90(2):115–8, 121–2, 125–7.
2. Rowlands S, Hooper R, Hughes R, Burney P. The epidemiology and treatment of Bell's palsy in the UK. Eur J Neurol Off J Eur Fed Neurol Soc. 2002 Jan;9(1):63–7.
3. Bauer CA, Coker NJ. Update on facial nerve disorders. Otolaryngol Clin North Am. 1996 Jun;29(3):445–54.
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 Jan 1;124(1 Pt 1):27–30.
5. MacDougall C, Guglielmo BJ. Pharmacokinetics of valaciclovir. J Antimicrob Chemother. 2004 Jun;53(6): 899–901.
6. Stjernquist-Desatnik A, Skoog E, Aurelius E. Detection of herpes simplex and varicella-zoster viruses in patients with Bell's palsy by the polymerase chain reaction technique.

Ann Otol Rhinol Laryngol. 2006 Apr;115(4): 306–11.
7. Holland NJ, Weiner GM. Recent developments in Bell's palsy. BMJ. 2004 Sep 4;329(7465):553–7.
8. Murthy JMK, Saxena AB. Bell's palsy: Treatment guidelines. Ann Indian Acad Neurol. 2011 Jul;14(Suppl1):S70–2.
9. Lockhart P, Daly F, Pitkethly M, Comerford N, Sullivan F. Antiviral treatment for Bell's palsy (idiopathic facial paralysis). Cochrane Database of Systematic Reviews [Internet]. John Wiley & Sons, Ltd; 1996 [cited 2014 Nov 17].
10. De Almeida JR, Al Khabori M, Guyatt GH, Witterick IJ, Lin VYW, Nedzelski JM, et al. Combined corticosteroid and antiviral treatment for Bell palsy: a systematic review and meta-analysis. JAMA. 2009 Sep 2;302(9):985–93.
11. 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 Jun;135(6):558–64.
12. 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 Apr;126(4):336–41.
13. Shahidullah M, Haque A, Islam MR, Rizvi AN, Sultana N, Mia BA, et al. Comparative study between combination of famciclovir and prednisolone with prednisolone alone in acute Bell's palsy. Mymensingh Med J MMJ. 2011 Oct;20(4):605–13.
14. 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 Off J ENT-UK Off J Neth Soc Oto-Rhino-Laryngol Cervico-Facial Surg. 2012 Aug;37(4):283–90.
15. Cochrane Handbook for Systematic Reviews of Interventions [Internet]. [cited 2014 Nov 17].
16. Adour KK, Ruboyianes JM, Von Doersten PG, Byl FM, Trent CS, Quesenberry CP, et al. Bell's palsy treatment with acyclovir and prednisone compared with prednisone alone: a double-blind, randomized, controlled trial. Ann Otol Rhinol Laryngol. 1996 May;105(5):371–8.
17. Engström M, Berg T, Stjernquist-Desatnik A, Axelsson S, Pitkäranta A, Hultcrantz M, et al. Prednisolone and valaciclovir in Bell's palsy: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet Neurol. 2008 Nov; 7(11):993–1000.
18. Sullivan FM, Swan IRC, Donnan PT, Morrison JM, Smith BH, McKinstry B, et al. Early Treatment with Prednisolone or Acyclovir in Bell's Palsy. N Engl J Med. 2007;357(16):1598–607.
19. Vázquez MC, Sánchez N, Calvo J, Perna A. Eficacia de los antivirales en la parálisis de Bell. Rev Méd Urug. 2008;167–74.
20. Inanli S, Tutkun A, Ozturk O, et al. Idiopathic facial paralysis treatment with acyclovir and prednisolone alone. Turkish Arch Otolaryngol. 2001;39(1):19-24.
21. 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 Jun;29(3):163–6.
22. Hato N, Yamada H, Kohno H, Matsumoto S, Honda N, Gyo K, et al. Valacyclovir and prednisolone treatment for Bell's palsy: a multicenter, randomized, placebo-controlled study. Otol Neurotol Off Publ Am Otol Soc Am Neurotol Soc Eur Acad Otol Neurotol. 2007 Apr;28(3):408–13.
23. Perry CM, Wagstaff AJ. Famciclovir. Drugs. 1995 Aug 1;50(2):396–415.
24. Crumpacker C. The pharmacological profile of famciclovir. Semin Dermatol. 1996 Jun;15(2 Suppl 1):14–26.
25. De Diego JI, Prim MP, De Sarriá MJ, Madero R, Gavilán J. Idiopathic facial paralysis: a randomized, prospective, and controlled study using single-dose prednisone versus acyclovir three times daily. The Laryngoscope. 1998 Apr;108(4 Pt 1):573–5.
26. Kawaguchi K, Inamura H, Abe Y, Koshu H, Takashita E, Muraki Y, et al. 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. The Laryngoscope. 2007 Jan;117(1):147–56.
27. Austin JR, Peskind SP, Austin SG, Rice DH. Idiopathic facial nerve paralysis: a randomized double blind controlled study of placebo versus prednisone. The Laryngoscope. 1993 Dec;103(12):1326–33.
28. Bento RF, Bogar P, Lorenzi MC. Treatment comparison between dexamethasone and placebo for idiopathic facial palsy. Eur Arch Oto-Rhino-Laryngol Off J Eur Fed Oto-Rhino-Laryngol Soc EUFOS Affil Ger Soc Oto-Rhino-Laryngol - Head Neck Surg. 1994 Dec;S535–6.
29. Lagalla G, Logullo F, Di Bella P, Provinciali L, Ceravolo MG. Influence of early high-dose steroid treatment on Bell's palsy evolution. Neurol Sci Off J Ital Neurol Soc Ital Soc Clin Neurophysiol. 2002 Sep;23(3): 107–12.
30. Martínez G. C, Abarca B, Alvarado CL, Almonte C, Acevedo M, Leyton R. Parálisis de Bell: evaluación del tratamiento esteroidal. Bol Hosp S Juan Dios. 1990 Feb; 37(1):13–7.
31. May M, Wette R, Hardin WB, Sullivan J. The use of steroids in Bell's palsy: a prospective controlled study. The Laryngoscope. 1976 Aug;86(8):1111–22.
32. Tekle-Haimanot R. Idiopathic facial paralysis (Bell's palsy) in 167 Ethiopians, with a controlled therapeutic trial in 59

patients. Ethiop Med J. 1987 Jan;25(1):23–7.
33. Unüvar E, Oğuz F, Sidal M, Kiliç A. Corticosteroid treatment of childhood Bell's palsy. Pediatr Neurol. 1999 Nov;21(5):814–6.
34. Wolf SM, Wagner JH, Davidson S, Forsythe A. Treatment of Bell palsy with prednisone: a prospective, randomized study. Neurology. 1978 Feb;28(2):158–61.
35. Antunes LM, Fukuda Y, Testa JRG. Tratamento clínico da paralisia de Bell: estudo comparativo com o uso de valaciclovir mais deflazacort versus deflazacort versus placebo. Acta AWHO. 2000 Jun;19(2):68–75.
36. Roy, A, Jose, J, Kamath, V, Matthew, T. Efficacy of acyclovir and methylprednisolone versus methylprednisolone alone in the treatment of bell's palsy. J Neurol Sci. 2005 Jan 1;238:S207.