Therapeutic Effect of Steroids on Vestibular Neuritis: Systematic Review and Meta-analysis

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Abstract

Objectives: The present meta-analysis sought to assess further evidence for the efficacy of steroids in vestibular neuritis (VN). Methods: The PubMed, EMBASE and Cochrane Library databases were searched through August 30, 2019. The main outcome measures were 1) complete caloric recovery, 2) improvement of canal paresis (CP) in caloric testing, and 3) dizziness handicap inventory. The follow-up times were divided into short, mid, and long-term. The main outcome measures were 1) complete caloric recovery, 2) improvement of canal paresis (CP) in caloric testing, and 3) dizziness handicap inventory. Results: Among 276 records identified, 5 studies (n = 253) were included in the analysis. The therapeutic effect of steroid on VN was confirmed (Hedges'g = 0.172, 95% CI 0.048 to 0.295, p = .006). This effect was statistically significant on long-term follow-up (Hedges'g = 0.496, 95% CI 0.285 to 0.708, p < .0001). The therapeutic effect of steroids on VN was better than that of non-steroid treatment (Hedges'g = 0.299, 95% CI 0.107 to 0.490, p = .002). However, this effect was obscured by combination of other treatments. The therapeutic effect of steroids on VN was statistically significant regarding complete caloric recovery and improvement in CP (Hedges'g = 0.364, 95% CI 0.181 to 0.547, p < 0.0001; Hedges'g = 0.592, 95% CI 0.315 to 0.5869, p < .0001) Conclusions: The results suggest that corticosteroids are effective at VN recovery, especially in long-term follow-up. More data are required before recommendations can be made regarding management in patients on corticosteroids.

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Short running title: Steroid effect on vestibular neuritis

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Results: Among 276 records identified, 5 studies (n = 253) were included in the analysis. The therapeutic effect of steroid on VN was confirmed (Hedges'g = 0.172, 95% CI 0.048 to 0.295, p = .006). This effect was statistically significant on long-term follow-up (Hedges'g = 0.496, 95% CI 0.285 to 0.708, p < .0001). The therapeutic effect of steroids on VN was better than that of non-steroid treatment (Hedges'g = 0.299, 95% CI 0.107 to 0.490, p = .002). However, this effect was obscured by combination of other treatments.

The therapeutic effect of steroids on VN was statistically significant regarding complete caloric recovery and improvement in CP (Hedges'g = 0.364, 95% CI 0.181 to 0.547, p < 0.0001; Hedges'g = 0.592, 95% CI 0.315 to 0.5869, p < .0001)

Conclusions: The results suggest that corticosteroids are effective at VN recovery, especially in long-term follow-up. More data are required before recommendations can be made regarding management in patients on corticosteroids.

Keywords: Vestibular neuritis, Steroids, Meta-analysis, Recovery of function, Caloric tests

Key points

1. Corticosteroids have a significant therapeutic effect on vestibular neuritis (VN) recovery, especially in long-term follow-up.
2. Corticosteroid treatment was beneficial in evaluating VN recovery by complete caloric recovery, as well as improvement of canal paresis.
3. A negative effect of steroids on VN recovery was found in this meta-analysis according to post-medication dizziness handicap inventory score.
4. When comparing the outcomes of steroid treatment and non-steroid treatment, the steroid treatment had a statistically significant but small therapeutic effect on VN.
5. Although the latest Cochrane review concluded that there is insufficient evidence to support the use of corticosteroids in VN, but this study may present somewhat positive effect of corticosteroids in VN.

INTRODUCTION

Vestibular neuritis (VN) has an incidence of 3.5 per 100,000 persons and is the third most frequent cause of peripheral vestibular vertigo.[1, 2] Treatment of acute VN is based on the following three therapeutic principles: (1) symptomatic therapy, (2) causal therapy, and (3) improvement of central vestibular compensation. Studies in the 1990s indicated that corticosteroids can improve the course of "acute vertigo."[1, 2] Corticosteroids have been used in therapy based on the theoretic viral cause of VN.[3] Corticosteroids can also be effective not only in the peripheral vestibular system, but also in the central vestibular system to restore balance.[4]

However, the latest Cochrane review in 2011 concluded that there is insufficient evidence to support the use of corticosteroids in VN but it stated that corticosteroids had a significant effect on complete caloric recovery at 1 month.[5] After that review, several reports issued newly an interest in the use of corticosteroids for VN.[6, 7] Ismail et al.[6] proposed that corticosteroids may accelerate the recovery of VN. Sjogren et al.[7] describe a critical period when treatment with corticosteroids could be effective. In addition, the Cochrane review published in 2011 proposed the need for future studies, including those addressing health-related quality of life, subjective measures, and objective measures. Therefore, we conducted a systematic review and meta-analysis including more updated literature since the latest Cochrane review was published.[5]

METHODS

Search strategy and data sources

To identify studies eligible for inclusion in this meta-analysis, we conducted a computerized search of clinical studies in PubMed (January 1966 to August 2019), EMBASE (January 1988 to August 2019), and Cochrane Library (database inception to August 2019). To minimize publication bias, references cited in the text of selected articles were further searched. Searches were performed using the keywords as Medical Subject Headings (National Library of Medicine, Bethesda, MD, USA), EMTREE, and natural language. Search terms used in this study were stated in the eAppendix in the Supplement.

This study was conducted according to the Cochrane Handbook for Systematic Reviews of Interventions [8, 9] and the statement by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses group.[10]

Inclusion and exclusion criteria

Two authors (J.H.S. and D.H.L.) independently selected studies for analysis according to the following inclusion criteria: (a) type of participants: patients with VN; (b) type of intervention(s): corticosteroid treatment, combination of corticosteroids plus other treatments (vestibular exercise, valacyclovir et al.); (c) type of comparative treatment: Placebo, no treatment, other treatments (vestibular exercise, valacyclovir et al.) (d) outcome measure(s): Complete caloric recovery (defined as canal paresis in caloric testing return within 20-25%), improvement (as %) of canal paresis (CP) in caloric testing, dizziness handicap inventory (DHI); and (e) type of study: Randomized controlled trials (RCTs). Studies were excluded in the following situations: (a) the study had no original data and/or was an editorial article or conference abstract;(b) there were no proper outcomes data; (c) the article was not written in English; (d) the article was a non-randomized controlled trial, cohort study, case-control study, animal experiment, chemistry, or cell-line study or editorial, commentary, review article, or case report. Two independent authors (J.H.S. and D.H.L.) screened the studies. The studies were identified by title, abstract, and text in the first screening. The full texts of the relevant studies were retrieved for validation before final acceptance in the present systematic review. The search strategy was based on the PRISMA reporting guideline and a flowchart of the study selection process is shown in Figure 1.

Methodological quality assessment

The risk of bias in the selected studies was assessed using an adaptation of the Cochrane Collaboration's tool for assessing the risk of bias (ROB).[10] The criteria involved assessing studies for selection bias caused by random sequence generation and allocation concealment; performance bias caused by blinding of participants and personnel; detection bias caused by blinding of outcome assessment; attrition bias caused by incomplete outcome data; and reporting bias caused by selective outcome reporting. We assigned a judgment related to risk of bias by answering a prespecified question about the adequacy of the study in relation to the entry. A judgment of "green" indicated a low risk of bias, "red" indicated a high risk of bias, and "yellow" indicated an unclear or unknown risk of bias. The methodological quality of the included studies was independently assessed by two researchers (J.H.S. and D.H.L.). Disagreements were resolved by discussion.

Data extraction

Data were extracted in duplicate from all reports and independently recorded on a piloted form by two authors. The data extracted from each study were as follows: (a) patient characteristics (mean age, country, and inclusion and exclusion criteria); (b) intervention characteristics; (c) characteristics of treatment as control; and (d) outcome measures (complete caloric recovery of CP, improvement of CP in caloric test, and DHI score). Other extracted data included author, year of publication, research design, number of samples, outcome variables, and follow up periods.

Statistical analyses

The primary outcome was recovery into the normal range of CP and improvement of CP and DHI score at post-intervention. The standardized mean effect was calculated using Hedges's g value to represent the effect sizes according to the Cochrane Handbook for Systematic Reviews of Intervention.[8] Hedges' g value is a standardized mean difference that was calculated to standardize the values measured by various measurement tools into a single unit. It is also a method to compensate for the shortcomings of the existing Cohen's d value. In this study, the sample size was not large. Therefore, the Hedges' g value was calculated. The Hedges' g values were 0.2 as small, 0.5 as medium, and 0.8 as large. When calculating the total effect size, both the DHI score (with the negative effect size direction) and the other variables (with static effect direction) were included. This combination resulted in a mutually offset effect. Therefore, DHI score was converted to the reverse direction and analyzed.

The estimates were pooled using a fixed-effects model, which assumes that the effect sizes of the populations are the same, and that the differences in effect size are attributable to sampling error.[11] The homogeneity of the studies was identified through Higgin's I statistics and forest plots. The heterogeneity of the studies was tested using the forest plot and Higgins I^2 statistic. Significant heterogeneity was defined as an I^2 value of 25%, 50% and 75% as low, moderate, and high heterogeneity, respectively.[12] When needed, subgroup and

sensitivity analyses were conducted. Funnel plots and Egger's linear regression values for each outcome were prepared and evaluated to assess potential publication bias. All analyses were performed using Cochrane Collaboration's software (RevMan version 5.3.3; Nordic Cochrane Centre, Copenhagen, Denmark) and Comprehensive Meta-Analysis software version 3 (Borenstein M, Hedges L, Higgins J and Rothstein H; Biostat, Englewood, NJ, USA).[13]

Some parts violate the independence assumption when calculating the total effect size. However, since the number of documents included in the analysis was limited, there was minimal information loss by using the effect size as an analysis unit.

Ethical consideration

This article does not contain any studies with human participants or animals performed by any of the authors.

RESULTS

General characteristics of studies

Our initial trial for the literature search yielded 276 citations, 49 of which were duplicate studies. During screening, 209 studies were excluded based on the selection criteria (n = 183 after records title screening and n = 26 after abstract screening). Among the remaining 18 studies, 13 were excluded because of inappropriate study design (n = 9), no original data (n = 1), or because they were not written in English (n = 3). Therefore, five studies (n = 253) met the selection criteria and were included in the final analysis (Figure 1).

The major characteristics of the five articles [6, 14-17] are summarized in Table 1. The year of publication for the identified studies ranged from 1990 to 2018. The follow-up duration ranged from 1 to 12 months. The studies were conducted in Egypt, Germany, Israel, South Korea, and USA.

Three studies [14-16] compared the outcomes of the steroid treatment (ST) group with those of placebo (PL) or non-steroid treatment (NST) group. Three studies [6, 14-18] compared the outcomes among a combination of corticosteroids plus other treatments with those of other treatments alone. In two studies,[6, 17] the outcomes of combined treatment of steroid treatment plus vestibular rehabilitation therapy (ST plus VRT) were compared to those of vestibular rehabilitation therapy alone (VRT only). One study [16] compared the outcomes of combined treatment of ST plus valacyclovir treatment (ST plus VA) with those of valacyclovir treatment alone (VA only). Since the number of studies was small for each comparison group, the results of each follow-up period and comparison group were considered and analyzed as separate studies.

Methodological quality and risk of bias

The assessment of bias is presented in Figure 2. There was a low risk of bias for amount or handling of incomplete outcome data and other bias in five RCTs (100%). Separately, the risk of bias was associated with inadequate generation of randomised sequences and inadequate concealment of allocations prior to assignments. There was also inadequate outcome reporting selection of participants in four studies (80%) and unclear outcome reporting in one study. The risk of bias associated with assessor blinding was unclear in three studies (60%) and low in two studies (20%). In addition, the risk of bias associated with participants and personnel blinding was low in one study (20%) and unclear in others. Although the risk of bias in blinding is generally unclear, this is considered to be due to the nature of the intervention. Overall, most of the included studies were classified as low risk for bias.

Effects of interventions

We calculated Hedges's g value and 95% confidence interval (CI) for all outcomes. The overall effects were weighted by the inverse of the variance on the effects of steroids on VN in five studies. As a result, Hedges's g was 0.172 (95% CI 0.048 to 0.295, p = 0.006), which indicates that the steroid treatment had a small but significant therapeutic effect on VN. The heterogeneity for the overall effect size was moderate ($I^2 = 59.61$) (Figure 3).

In this study, the effects of the intervention on the study group and the control groups were evaluated in the short-term (1 month), mid-term (3 & 6 months), and long-term (12 months) depending on the follow-up period. Hedges's g was 0.106 (95% CI -0.142 to 0.353, p = 0.403, I^2 = 40.97) and -0.059 (95% CI -0.252 to 0.135, p=0.552, I^2 = 38.49) in the short-term and mid-term. There was no statistically significant difference in the effect of steroids in these two groups. However, Hedges's g was 0.496 (95% CI 0.285 to 0.708, p < 0.001, I^2 = 69.76) in the long-term. We found that the steroid treatment had a moderate statistically significant therapeutic effect on long-term follow-up of VN (Figure 4(A)).

To evaluate the possible effect of treatments other than steroids, we divided the comparison design as follows: 1) ST versus NST and 2) combined treatment of ST and others versus other treatments alone. When comparing the outcomes of ST and NST, Hedges's g was 0.299 (95% CI 0.107 to 0.490, p = 0.002, I^2 = 69.01). This finding indicates that the steroid treatment had a statistically significant but small therapeutic effect on VN. When comparing the effect of combined treatment of ST and others versus other treatments alone, Hedges's g was 0.082 (95% CI -0.080 to 0.243, p = 0.322, I^2 = 42.79). This result reflects that there is no statistically significant difference in the therapeutic effect of steroid (Figure 4(B)).

To analyze the possible effect of the outcome variables on the therapeutic effect of steroids on VN, the comparison was made in terms of complete caloric recovery, improvement of CP, and DHI score. When the therapeutic effect was measured in terms of complete caloric recovery and CP improvement, Hedges's g was 0.364 (95% CI 0.181 to 0.547, p < 0.001, I^2 = 11.44) and 0.592 (95% CI 0.315 to 0.869, p < 0.001, I^2 = 65.91), respectively. The results demonstrated that steroids had a significant (medium sized) therapeutic effect on VN, assessed by complete caloric recovery and CP improvement. In contrast, with regard to the DHI score, Hedges's g was -0.323 (95% CI -0.533 to -0.113, p < 0.001, I^2 = 0). This result suggests that steroids had a negative effect (of small effect size) on VN when assessed by DHI score (Figure 4(C)).

Publication bias

No significant asymmetry appeared in the inverted funnel plots of these studies (Figure 5). Funnel plot inspection and Egger's regression test for this analysis did not reveal significant asymmetry (intercept 0.06; 95% CI -3.21 to 3.32, p = 0.09). Therefore, the studies included in this analysis had no publication bias.

Sensitivity analysis

Given the heterogeneity present in our results, we performed a sensitivity analysis in which each trial in the main analysis was removed in turn. These results showed a pooled point estimate of 0.13 to 0.20 (95% CI, 0.01 to 0.32). The results were broadly concordant with the primary analysis.

DISCUSSION

Comparisons to other studies

Our hypothesis is that steroids are involved in the changes during static compensation after vestibular imbalance, that can be ongoing for a long-term period after VN.[2]

Although the latest Cochrane review did not find out enough evidence to support the use of corticosteroids in VN,[5] this meta-analysis demonstrates that administration of corticosteroids to patients with VN is significantly effective over long-term follow-up more than 12 months. Our results showed that corticosteroids have a therapeutic effect on recovery of VN in terms of CP of the caloric test. This result is in accordance with previous studies. Okinaka et al.[19] reported that normalization of lateral semicircular canal paresis in the caloric test was observed in only 42% of the VN patients in long-term follow-up; in addition, 50% of the patients still suffered from canal paresis even 5 or 10 years after initial diagnosis. Bergenius and Perols [20]reported that CP improved at the 7–8-year follow-up, and that CP normalized in 55% of the VN patients. Choi et al.[21]reported that CP improved during the first 1-year of follow-up. Hwang et al.[22] reported that the CP recovery was better in superior VN than it was in overall VN.

Clinical applicability

This study failed to show that steroids had a therapeutic effect on VN in terms of DHI score, which reflects functional recovery after VN. However, a negative effect of steroids on VN recovery was found in this meta-analysis according to DHI score. It is important to recognize potential bias affecting this result. With regard to DHI, three of five studies were analyzed in our meta-analysis.[6, 15, 17]Shupak et al.[15] only presented only post-treatment DHI scores, which were evaluated at 1, 3, 6, and 12 months after VN. Another two studies included baseline DHI scores in their analysis.[6, 17] Therefore, one problem in our design was addressing analysis of DHI. One method was to analyze the amount of DHI change after treatment (from the pretreatment DHI score). The other method was to compare the final DHI score. Our meta-analysis adopted the latter method, because a return to the nondisabled DHI level is considered a significant improvement for patients who experience a severe handicap from VN. However, the limitation of this approach was that the initial status of functional impairment was not considered. Therefore, this approach might have been subject to selection bias. The study of Yoo et al.[17] also might have been subject to selection bias.

An incidental but interesting finding in this study was that the therapeutic effect of steroid treatment was significant despite of its small effect size but disappeared when other treatments (such as vestibular exercise or valacyclovir) were combined with ST and NST. This finding suggests that vestibular exercise or valacyclovir have a therapeutic effect on VN. As the main purpose of this study was not to analyze the effect of vestibular exercise or valacyclovir, we are unable to draw any conclusions regarding these findings. However, our findings suggest that vestibular exercise or valacyclovir can be helpful to patients who cannot take steroids.

Strengths and limitations

The strength of this meta-analysis is that the effect of corticosteroids was analyzed for each period of recovery from acute vestibular syndrome. As previously reported, the effect of steroids on VN patients is likely to vary by time of recovery from acute vestibular syndrome. Therefore, we analyzed the effectiveness of corticosteroids over time as the vestibular function recovers. The second strength is that functional restoration and symptomatic improvement were separately analyzed in this meta-analysis. Patients with compensated peripheral vestibulopathy often have few or no symptoms (even if a permanent functional deficit remains). We analyzed the caloric result and DHI score as a representative functional test and a validated questionnaire, respectively.

This meta-analysis has several shortcomings. First, the potential influence of combined treatment on steroid therapy cannot be excluded. Although we included studies in which the steroid group and non-steroid group underwent the same combined treatment, it is possible that these treatments affected the effect of steroids. Second, there are many types of steroid therapy protocols, which may have differed between studies. This difference between studies was not adjusted in our study. Finally, there were no data regarding the results of the more physiologic vestibular function tests, because no reported controlled studies evaluated rotation chair or video head impulse tests.

CONCLUSIONS

This meta-analysis depicted the possible positive effect of corticosteroids in VN. Corticosteroids have a significant therapeutic effect on VN recovery, especially in long-term follow-up and is beneficial when evaluating VN recovery by complete caloric recovery, as well as improvement of canal paresis. We also found out a negative effect of steroids on VN recovery according to post-medication dizziness handicap inventory score.

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Figure Legends

Figure 1. Flowchart of the process for selecting studies for systematic review and meta-analysis.

Figure 2. Assessment of risk of bias in the included studies.

Figure 3. Forest plot of effect size by steroid treatment for vestibular neuritis

Figure 4. Forest plot of effect size by steroid treatment for vestibular neuritis. (A) Therapeutic effect of steroid was analyzed according to follow-up period after onset. In this analysis, subgroups were classified into short-term (1 month), mid-term (3 & 6 months), and long-term (12 months). (B) The therapeutic effect of steroids was analyzed according to comparator. One comparison design was steroid versus non-steroid groups and the other was combination therapy of steroid and other treatments versus other treatment alone. (C) The therapeutic effect of steroid was analyzed according to outcome measures. In this analysis, outcome variables were complete caloric recovery, improvement of canal paresis, and dizziness handicap inventory score.

a, improvement in lateralization caloric test; b, complete caloric recovery; c, dizziness handicap inventory score; d, after 1month; e, after 3 months; f, after 6 months; g, after 12 months; h, steroid group versus non-steroid group; i, combination therapy of other treatments with the steroid versus other treatment only

Figure 5. Funnel plots of the effects of steroid treatment on vestibular neuritis

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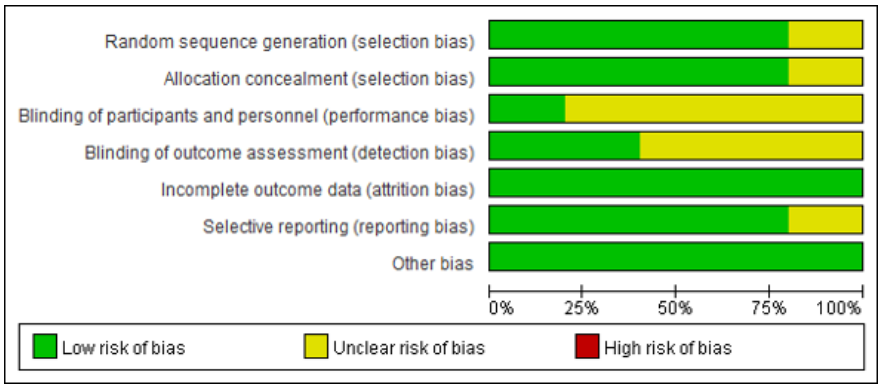
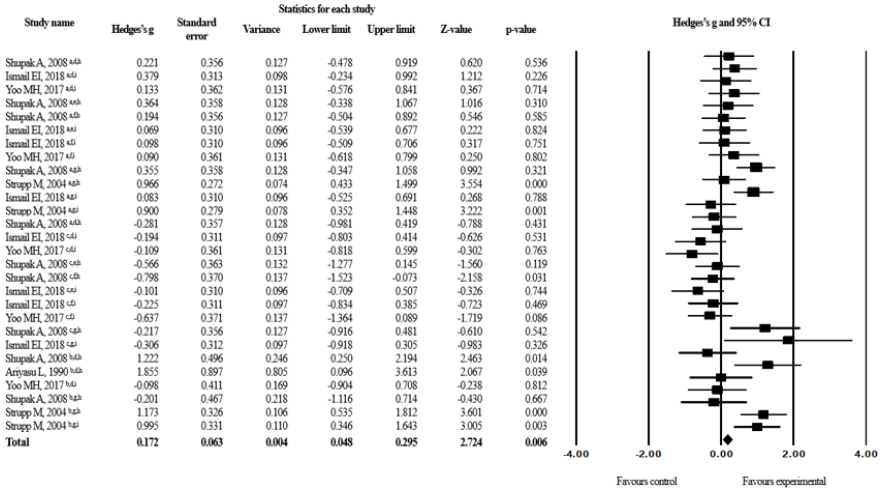
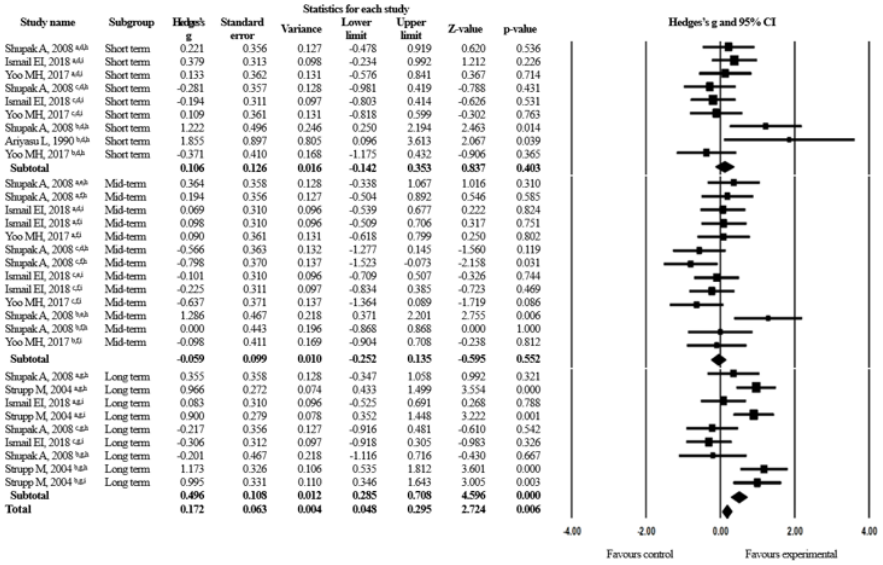
`Figure 1_Metaanalysis_ST_VN.pptx` available at https://authorea.com/users/425311/articles/530151-therapeutic-effect-of-steroids-on-vestibular-neuritis-systematic-review-and-meta-analysis



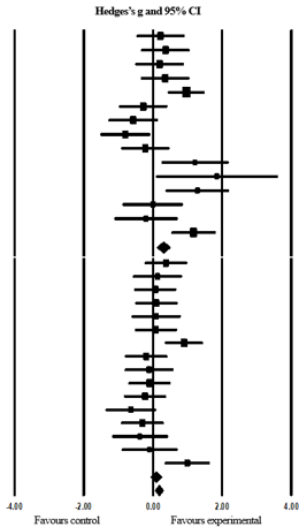


Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-value	p-value
Shupak A, 2008 a,d,h	0.221	0.356	0.127	-0.478	0.919	0.620	0.536
Ismail EI, 2018 a,d,j	0.379	0.313	0.098	-0.234	0.992	1.212	0.226
Yoo MH, 2017 a,d,j	0.133	0.362	0.131	-0.576	0.841	0.367	0.714
Shupak A, 2008 a,e,h	0.364	0.358	0.128	-0.338	1.067	1.016	0.310
Shupak A, 2008 a,f,h	0.194	0.356	0.127	-0.504	0.892	0.546	0.585
Ismail EI, 2018 a,e,j	0.069	0.310	0.096	-0.539	0.677	0.222	0.824
Ismail EI, 2018 a,f,j	0.098	0.310	0.096	-0.509	0.706	0.317	0.751
Yoo MH, 2017 a,f,j	0.090	0.361	0.131	-0.618	0.799	0.250	0.802
Shupak A, 2008 a,g,h	0.355	0.358	0.128	-0.347	1.058	0.992	0.321
Strupp M, 2004 a,g,h	0.966	0.272	0.074	0.433	1.499	3.554	0.000
Ismail EI, 2018 a,g,j	0.083	0.310	0.096	-0.525	0.691	0.268	0.788
Strupp M, 2004 a,g,j	0.900	0.279	0.078	0.352	1.448	3.222	0.001
Shupak A, 2008 a,d,h	-0.281	0.357	0.128	-0.981	0.419	-0.788	0.431
Ismail EI, 2018 c,d,j	-0.194	0.311	0.097	-0.803	0.414	-0.626	0.531
Yoo MH, 2017 c,d,j	-0.109	0.361	0.131	-0.818	0.599	-0.302	0.763
Shupak A, 2008 c,e,h	-0.566	0.363	0.132	-1.277	0.145	-1.560	0.119
Shupak A, 2008 c,f,h	-0.798	0.370	0.137	-1.523	-0.073	-2.158	0.031
Ismail EI, 2018 c,e,j	-0.101	0.310	0.096	-0.709	0.507	-0.326	0.744
Ismail EI, 2018 c,f,j	-0.225	0.311	0.097	-0.834	0.385	-0.723	0.469
Yoo MH, 2017 c,f,j	-0.637	0.371	0.137	-1.364	0.089	-1.719	0.086
Shupak A, 2008 c,g,h	-0.217	0.356	0.127	-0.916	0.481	-0.610	0.542
Ismail EI, 2018 c,g,j	-0.306	0.312	0.097	-0.918	0.305	-0.983	0.326
Shupak A, 2008 b,d,h	1.222	0.496	0.246	0.250	2.194	2.463	0.014
Ariyasu L, 1990 b,d,h	1.855	0.897	0.805	0.096	3.613	2.067	0.039
Yoo MH, 2017 b,d,j	-0.098	0.411	0.169	-0.904	0.708	-0.238	0.812
Shupak A, 2008 b,g,h	-0.201	0.467	0.218	-1.116	0.714	-0.430	0.667
Strupp M, 2004 b,g,h	1.173	0.326	0.106	0.535	1.812	3.601	0.000
Strupp M, 2004 b,g,j	0.995	0.331	0.110	0.346	1.643	3.005	0.003
Total	**0.172**	**0.063**	**0.004**	**0.048**	**0.295**	**2.724**	**0.006**

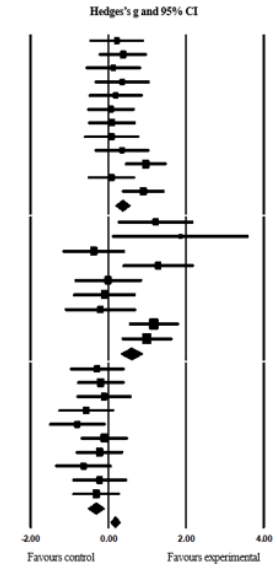


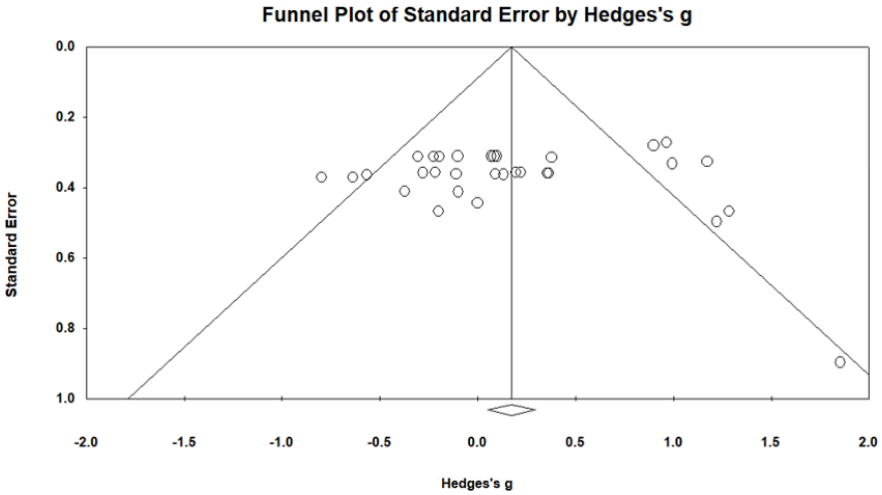
Study name	Subgroup	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-value	p-value
Shupak A, 2008 a,d,h	Short term	0.221	0.356	0.127	-0.478	0.919	0.620	0.536
Ismail EI, 2018 a,d,j	Short term	0.379	0.313	0.098	-0.234	0.992	1.212	0.226
Yoo MH, 2017 a,d,j	Short term	0.133	0.362	0.131	-0.576	0.841	0.367	0.714
Shupak A, 2008 c,d,h	Short term	-0.281	0.357	0.128	-0.981	0.419	-0.788	0.431
Ismail EI, 2018 c,d,j	Short term	-0.194	0.311	0.097	-0.803	0.414	-0.626	0.531
Yoo MH, 2017 c,d,j	Short term	0.109	0.361	0.131	-0.818	0.599	-0.302	0.763
Shupak A, 2008 b,d,h	Short term	1.222	0.496	0.246	0.250	2.194	2.463	0.014
Ariyasu L, 1990 b,d,h	Short term	1.855	0.897	0.805	0.096	3.613	2.067	0.039
Yoo MH, 2017 b,d,j	Short term	-0.371	0.410	0.168	-1.175	0.432	-0.906	0.365
Subtotal		**0.106**	**0.126**	**0.016**	**-0.142**	**0.353**	**0.837**	**0.403**
Shupak A, 2008 a,e,h	Mid-term	0.364	0.358	0.128	-0.338	1.067	1.016	0.310
Shupak A, 2008 a,f,h	Mid-term	0.194	0.356	0.127	-0.504	0.892	0.546	0.585
Ismail EI, 2018 a,e,j	Mid-term	0.069	0.310	0.096	-0.539	0.677	0.222	0.824
Ismail EI, 2018 a,f,j	Mid-term	0.098	0.310	0.096	-0.509	0.706	0.317	0.751
Yoo MH, 2017 a,f,j	Mid-term	0.090	0.361	0.131	-0.618	0.799	0.250	0.802
Shupak A, 2008 c,e,h	Mid-term	-0.566	0.363	0.132	-1.277	0.145	-1.560	0.119
Shupak A, 2008 c,f,h	Mid-term	-0.798	0.370	0.137	-1.523	-0.073	-2.158	0.031
Ismail EI, 2018 c,e,j	Mid-term	-0.101	0.310	0.096	-0.709	0.507	-0.326	0.744
Ismail EI, 2018 c,f,j	Mid-term	-0.225	0.311	0.097	-0.834	0.385	-0.723	0.469
Yoo MH, 2017 c,f,j	Mid-term	-0.637	0.371	0.137	-1.364	0.089	-1.719	0.086
Shupak A, 2008 b,e,h	Mid-term	1.286	0.467	0.218	0.371	2.201	2.755	0.006
Shupak A, 2008 b,f,h	Mid-term	0.000	0.443	0.196	-0.868	0.868	0.000	1.000
Yoo MH, 2017 b,f,j	Mid-term	-0.098	0.411	0.169	-0.904	0.708	-0.238	0.812
Subtotal		**-0.059**	**0.099**	**0.010**	**-0.252**	**0.135**	**-0.595**	**0.552**
Shupak A, 2008 a,g,h	Long term	0.355	0.358	0.128	-0.347	1.058	0.992	0.321
Strupp M, 2004 a,g,h	Long term	0.966	0.272	0.074	0.433	1.499	3.554	0.000
Ismail EI, 2018 a,g,j	Long term	0.083	0.310	0.096	-0.525	0.691	0.268	0.788
Strupp M, 2004 a,g,j	Long term	0.900	0.279	0.078	0.352	1.448	3.222	0.001
Shupak A, 2008 c,g,h	Long term	-0.217	0.356	0.127	-0.916	0.481	-0.610	0.542
Ismail EI, 2018 c,g,j	Long term	-0.306	0.312	0.097	-0.918	0.305	-0.983	0.326
Shupak A, 2008 b,g,h	Long term	-0.201	0.467	0.218	-1.116	0.716	-0.430	0.667
Strupp M, 2004 b,g,h	Long term	1.173	0.326	0.106	0.535	1.812	3.601	0.000
Strupp M, 2004 b,g,j	Long term	0.995	0.331	0.110	0.346	1.643	3.005	0.003
Subtotal		**0.496**	**0.108**	**0.012**	**0.285**	**0.708**	**4.596**	**0.000**
Total		**0.172**	**0.063**	**0.004**	**0.048**	**0.295**	**2.724**	**0.006**

Study name	Sub group	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-value	p-value
Shupak A, 2008 a,d,h	h	0.221	0.356	0.127	-0.478	0.909	0.620	0.536
Shupak A, 2008 a,e,h	h	0.364	0.358	0.128	-0.338	1.067	1.016	0.310
Shupak A, 2008 a,f,h	h	0.194	0.356	0.127	-0.504	0.892	0.546	0.585
Shupak A, 2008 a,g,h	h	0.355	0.358	0.128	-0.347	1.058	0.992	0.321
Strupp M, 2004 a,g,h	h	0.966	0.272	0.074	0.433	1.499	3.554	0.000
Shupak A, 2008 c,d,h	h	-0.281	0.357	0.128	-0.981	0.419	-0.788	0.431
Shupak A, 2008 c,e,h	h	-0.566	0.363	0.132	-1.277	0.145	-1.560	0.119
Shupak A, 2008 c,f,h	h	-0.798	0.370	0.137	-1.523	-0.073	-2.158	0.031
Shupak A, 2008 c,g,h	h	-0.217	0.356	0.127	-0.916	0.481	-0.610	0.542
Shupak A, 2008 b,d,h	h	1.222	0.496	0.246	0.250	2.194	2.463	0.014
Ariyasu L, 1990 b,d,h	h	1.855	0.897	0.805	0.096	3.613	2.067	0.039
Shupak A, 2008 b,e,h	h	1.286	0.467	0.218	0.371	2.201	2.755	0.006
Shupak A, 2008 b,f,h	h	0.000	0.443	0.196	-0.868	0.868	0.000	1.000
Shupak A, 2008 b,g,h	h	-0.201	0.467	0.218	-1.116	0.714	-0.430	0.667
Strupp M, 2004 b,g,h	h	1.173	0.326	0.106	0.535	1.812	3.601	0.000
Subtotal		**0.299**	**0.098**	**0.010**	**0.107**	**0.490**	**3.051**	**0.002**
Ismail EI, 2018 a,d,i	i	0.379	0.313	0.098	-0.234	0.992	1.212	0.226
Yoo MH, 2017 a,d,i	i	0.133	0.362	0.131	-0.576	0.841	0.367	0.714
Ismail EI, 2018 a,e,i	i	0.069	0.310	0.096	-0.539	0.677	0.222	0.824
Ismail EI, 2018 a,f,i	i	0.098	0.310	0.096	-0.509	0.706	0.317	0.751
Yoo MH, 2017 a,f,i	i	0.090	0.361	0.131	-0.618	0.799	0.250	0.802
Ismail EI, 2018 a,g,i	i	0.083	0.310	0.096	-0.525	0.691	0.268	0.788
Strupp M, 2004 a,g,i	i	0.900	0.279	0.078	0.352	1.448	3.222	0.001
Ismail EI, 2018 c,d,i	i	-0.194	0.311	0.097	-0.803	0.414	-0.626	0.531
Yoo MH, 2017 c,d,i	i	-0.109	0.361	0.131	-0.818	0.599	-0.302	0.763
Ismail EI, 2018 c,e,i	i	-0.101	0.310	0.096	-0.709	0.507	-0.326	0.744
Ismail EI, 2018 c,f,i	i	-0.225	0.311	0.097	-0.834	0.385	-0.723	0.469
Yoo MH, 2017 c,f,i	i	-0.637	0.371	0.137	-1.364	0.089	-1.719	0.086
Ismail EI, 2018 c,g,i	i	-0.306	0.312	0.097	-0.918	0.305	-0.983	0.326
Yoo MH, 2017 b,d,i	i	-0.371	0.410	0.168	-1.175	0.432	-0.906	0.365
Yoo MH, 2017 b,f,i	i	-0.098	0.411	0.169	-0.904	0.708	-0.238	0.812
Strupp M, 2004 b,g,i	i	0.995	0.331	0.110	0.346	1.643	3.005	0.003
Subtotal		**0.082**	**0.083**	**0.007**	**-0.080**	**0.243**	**0.990**	**0.322**
Total		**0.172**	**0.063**	**0.004**	**0.048**	**0.295**	**2.724**	**0.006**



Study name	Subgroup	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-value	p-value
Shupak A, 2008 a,d,h	a	0.221	0.356	0.127	-0.478	0.919	0.620	0.536
Ismail EI, 2018 a,d,i	a	0.379	0.313	0.098	-0.234	0.992	1.212	0.226
Yoo MH, 2017 a,d,i	a	0.133	0.362	0.131	-0.576	0.841	0.367	0.714
Shupak A, 2008 a,e,h	a	0.364	0.358	0.128	-0.338	1.067	1.016	0.310
Shupak A, 2008 a,f,h	a	0.194	0.356	0.127	-0.504	0.892	0.546	0.585
Ismail EI, 2018 a,e,i	a	0.069	0.310	0.096	-0.539	0.677	0.222	0.824
Ismail EI, 2018 a,f,i	a	0.098	0.310	0.096	-0.509	0.706	0.317	0.751
Yoo MH, 2017 a,f,i	a	0.090	0.361	0.131	-0.618	0.799	0.250	0.802
Shupak A, 2008 a,g,h	a	0.355	0.358	0.128	-0.347	1.058	0.992	0.321
Strupp M, 2004 a,g,h	a	0.966	0.272	0.074	0.433	1.499	3.554	0.000
Ismail EI, 2018 a,g,i	a	0.083	0.310	0.096	-0.525	0.691	0.268	0.788
Strupp M, 2004 a,g,i	a	0.900	0.279	0.078	0.352	1.448	3.222	0.001
Subtotal		**0.364**	**0.093**	**0.009**	**0.181**	**0.547**	**3.895**	**0.000**
Shupak A, 2008 b,d,h	b	1.222	0.496	0.246	0.250	2.194	2.463	0.014
Ariyasu L, 1990 b,d,h	b	1.855	0.897	0.805	0.096	3.613	2.067	0.039
Yoo MH, 2017 b,d,i	b	-0371	0.410	0.168	-1.175	0.432	-0.906	0.365
Shupak A, 2008 b,e,h	b	1.286	0.467	0.218	0.371	2.201	2.755	0.006
Shupak A, 2008 b,f,h	b	0.000	0.443	0.196	-0.868	0.868	0.000	1.000
Yoo MH, 2017 b,f,i	b	-0.098	0.411	0.169	-0.904	0.708	-0.238	0.812
Shupak A, 2008 b,g,h	b	-0.201	0467	0.218	-1.116	0.714	-0.430	0.667
Strupp M, 2004 b,g,h	b	1.173	0.326	0.106	0.535	1.812	3.601	0.000
Strupp M, 2004 b,g,i	b	0.995	0.331	0.110	0.346	1.643	3.005	0.003
Subtotal		**0.592**	**0.141**	**0.020**	**0.315**	**0.869**	**4.185**	**0.000**
Shupak A, 2008 c,d,h	c	-0.281	0.357	0.128	-0.981	0.419	-0.788	0.431
Ismail EI, 2018 c,d,i	c	-0.194	0.311	0.097	-0.803	0.414	-0.626	0.531
Yoo MH, 2017 c,d,i	c	-0.109	0.361	0.131	-0.818	0.599	-0.302	0.763
Shupak A, 2008 c,e,h	c	-0.566	0.363	0.132	-1.277	0.145	-1.560	0.119
Shupak A, 2008 c,f,h	c	-0.798	0.370	0.137	-1.523	-0.073	-2.158	0.031
Ismail EI, 2018 c,e,i	c	-0.101	0.310	0.096	-0.709	0.507	-0.326	0.744
Ismail EI, 2018 c,f,i	c	-0.225	0.311	0.097	-0.834	0.385	-0.723	0.469
Yoo MH, 2017 c,f,i	c	-0.637	0.371	0.137	-1.364	0.089	-1.719	0.086
Shupak A, 2008 c,g,h	c	-0.217	0.356	0.127	-0.916	0.481	-0.610	0.542
Ismail EI, 2018 c,g,i	c	-0.306	0.312	0.097	-0.918	0.305	-0.983	0.326
Subtotal		**-0.323**	**0.107**	**0.012**	**-0.533**	**-0.113**	**-3.010**	**0.003**
Total		**0.172**	**0.063**	**0.004**	**0.048**	**0.295**	**2.724**	**0.006**





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