

3,4-diaminopyridine Treatment for Lambert-Eaton Myasthenic Syndrome in Adults: A Meta-analysis of Randomized Controlled Trials

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Abstract

Background: Lambert-Eaton myasthenic syndrome (LEMS) is a rare autoimmune disorder of neuromuscular transmission. The objective was to examine the efficacy and safety of 3,4-diaminopyridine (3,4-DAP) in LEMS.

Methods: We searched several databases to identify relevant studies, including PubMed, EMBASE, Cochrane Neuromuscular Disease Group Specialized Register and the Cochrane Controlled Trials Register. The primary outcome Quantitative Myasthenia Gravis (QMG) muscle score and secondary outcome compound muscle action potentials (CMAP) amplitude were pooled by meta-analysis.

Results: Six randomised controlled trials (RCT) involving 115 patients with LEMS were included. A meta-analysis of the primary outcome showed a significant improvement of 2.33 (95% CI, -2.81 to -1.85, $p < 0.001$) in QMG muscle score after treatment with 3,4-DAP. Moreover, a meta-analysis of the secondary outcome showed that the overall mean CMAP amplitude improved significantly in LEMS patients with 3, 4-DAP treatment, compared with placebo treatment (mean difference 1.63 mV, 95% CI, 0.85 to 2.41, $p < 0.001$). The overall assessment of all included trials showed low risk of bias and low heterogeneity.

Conclusions: The pooled results demonstrated that 3,4-DAP had a significant effect on LEMS treatment, with improvements in muscle strength score and CMAP amplitude, which are moderate to high evidence from randomized controlled trials.

Introduction

Lambert-Eaton Myasthenic Syndrome (LEMS) is a rare autoimmune neuromuscular junction dysfunction resulted from antibodies generated against the voltage-gated calcium channels (VGCC) on the presynaptic nerve terminals, thereby suppressing the release of neurotransmitters such as acetylcholine [1–3]. The onset age of LEMS patients mainly ranges from 20 to 50 years [4], although childhood and infancy have been reported [5, 6]. It has been reported that about 60% of LEMS patients are tumor-related [7]. Among LEMS patients, small-cell lung cancer (SCLC) is the most common type, but other types of tumors, including non-small cell lung cancer, mixed lung cancer, thymoma, prostate cancer, have also been reported [7, 8]. Based on the prevalence of SCLC, the prevalence of LEMS was estimated to be 1 in 100,000 in the United States [4]. LEMS is characterized by limb girdle muscles weakness, easy fatigability, absent deep tendon reflexes with posttetanic potentiation, and autonomic alterations, such as dry mouth and erectile dysfunction. Activities related to daily functions, such as rising from a chair, climbing stairs, health, and self-care management, are also involved [9]. It has been extensively documented in biopsied intercostal muscles that reducing the quantitative release of ACh plays a vital role in the pathophysiology of LEMS [10].

The LEMS is initially diagnosed on the basis of typical clinical characteristics, including the classic triad of proximal muscle weakness, autonomic nerve dysfunction and decreased tendon

reflexes [11]. Confirmation diagnosis of LEMS also requires the combination of specific VGCC antibody detection and characteristic electrophysiological results. The detection of positive VGCC antibody provides reliable evidence for the diagnosis of LEMS. Positive VGCC antibody has been observed in 100% of LEMS patients with SCLC and 90% of LEMS cases without potential malignancy [12]. Lambert and Eaton [13] first proposed the classic electrophysiological triad of LEMS, including low resting compound muscle action potentials (CMAP) amplitude, decreased response of low-frequency repetitive nerve stimulation, and increased response after high frequency stimulation or short exercise.

Over the past few decades, many symptomatic treatments have been tried, including guanidine, pyridazine, 4-aminopyridine and 3,4-diaminopyridine (3,4-DAP, amifampridine), the last of which have proven to be the most effective [14]. With the exception of 3,4-DAP, these drugs have not been studied in clinical trials, only in small case series. In December 2009, 3,4-DAP was approved for the first time in Europe and was subsequently recommended as a first-line treatment for LEMS in 2010 [15]. Amifampridine phosphate (salt form of 3,4-DAP) was found to be more stable than the base form, because it can be stored at room temperature [16].

In recent years, the efficacy of 3,4-DAP in the treatment of LEMS has been widely discussed, but the results of these studies are still uncertain. However, no reliable conclusions have been drawn and it is unclear whether the potential advantages outweigh the disadvantages. We therefore performed a meta-analysis of randomized controlled trials (RCTs) to evaluate the efficacy and safety of 3,4-DAP in the treatment of LEMS in adults.

Methods

Literature Search

Various databases including the Cochrane Neuromuscular Disease Group Specialized Register, Cochrane Central Register of Controlled Trials (CENTRAL), Pubmed and EMBASE were retrieved and the retrieval deadline was January 2020. We searched studies with the following terms: 'Lambert-Eaton (myasthenic syndrome)' or 'Eaton-Lambert' or 'LEMS' combined with '3,4-Diaminopyridine' or '3,4-Diaminopyridine' or 'Firdapse' or 'Amifampridine Phosphate' or '3,4-DAP'. We consulted the bibliography of the randomized trial reports and contacted the authors to determine other published or unpublished data. The search and select process was shown in Figure 1.

Inclusion Criteria

All randomized or quasi-randomized controlled trials of adult patients diagnosed with LEMS, with or without SCLC, received 3, 4-DAP treatment. The primary outcome indicator was change in muscle strength score (Quantitative Myasthenia Gravis, QMG), or limb muscle strength measured by myometry. The secondary outcome indicator was change in the average CMAP amplitude at rest.

Data Extraction

Two reviewers independently examined all literature titles and abstracts retrieved from various databases and evaluated the full text of all potential related studies. The reviewers decided which studies meet the inclusion criteria and discussed together when disagreements about inclusion arised. Both authors performed the data extraction. Baseline data were collected using standardized tables, including author, year of publication, number of cases, patient age, gender, presence of cancer, and outcome measures (mean, standard deviation). Whenever possible, insufficient data was obtained from the study authors.

Quality Assessment

The methodological quality of each included article was independently assessed by two authors using the Cochrane collaboration to determine the risk of bias [Figure 2]. The risks of bias process include sequence generation, blinding, allocation concealment, selective reporting, processing of incomplete result data, or any other form of bias[17]. The items were rated on the "Yes", "No" or "Unclear" of the established Cochrane scale, with "Yes" representing a low risk of bias and "No" representing a high risk of bias. 'Unclear' was used when there is inappropriate information to make a judgment, or when the project is not relevant to the research. The review authors reached agreement by consensus.

Statistical Analysis

Mean difference (MD) and 95% CIs were output to perform the test of combined statistics. All the P values were 2-sided, with $P < 0.05$ indicating statistical significance. The heterogeneity of these studies was tested by I^2 statistics. If $I^2 > 50\%$, it indicated the existence of substantial heterogeneity and random effect model was adopted, otherwise, fixed effect model was used for analysis[18]. All the statistical analysis was made with RevMan (version 5.3, The Cochrane Collaboration, London).

Results

Description of studies

By searching, we found 8 RCTs of 3,4-DAP used to treat LEMS. However, in two RCTs, 3TUG was used to evaluate the outcome of treatment without the use of QMG or CMAP, so the two RCTs did not meet the inclusion criteria and were excluded. Finally, only six RCTs were eligible for inclusion in this meta-analysis. The six eligible RCTs included 115 patients with LEMS treated with oral or intrevenous 3,4-DAP or placebo, without any healthy participants. The characteristics of included studies were shown in Table 1.

The first RCT was a cross-sectional trial of 12 patients with LEMS, which compared the efficacy of the maximum oral dose of 3, 4-DAP (100 mg/ day) with the placebo for 6 days, using muscle strength score and CMAP at day 3 and 6[19].

The second RCT, a parallel group design, compared oral dose of 3, 4-DAP(60 mg/day) for 12 participants with placebo for 14 participants. QMG muscle strength score and CMAP were performed on days 5 and 6[20].

The third RCT was a double blind, double dummy, cross-over study of 9 participants. It compared intravenous 3,4-DAP against placebo, intravenous pyridostigmine, and a combination infusion of 3,4-DAP and pyridostigmine. Muscle strength and CMAP between 10 and 170 minutes after infusion were taken as endpoints[14].

The fourth RCT was a double-blind, cross-over study of 6 participants. Three patients in the first group received an initial dose of 15 mg per day, increased to daily dose of 80 mg at the end of the eight-day course. The second group increased their daily intake of 30 mg to 75 mg during the three-day study because of time constraints. QMG muscle strength score and CMAP were recorded as the outcomes[21].

The fifth RCT was a double-blind, parallel study. It compared 3,4-DAP for 16 participants with placebo for 20 participants. QMG muscle strength score and CMAP were performed on day 14[22].

The sixth RCT was a double-blind, parallel study. It compared 3,4-DAP for 13 participants with placebo for 13 participants. QMG muscle strength score were recorded on day 4[23].

Data Synthesis

Primary outcome measure: the score on a muscle strength scale

Six included RCTs used muscle strength or myometric limb measurement as outcome indicators, and reported significant improvements in muscle strength score, or myometric limb measurement after treatment. However, a meta-analysis of all the studies is impossible on account of obvious differences in primary outcome of these studies. QMG score was used to be a primary outcome to assess muscle strength in four RCTs[20–23]. The muscle strength score used by McEvoy et al[19] and isometric muscle strength score used by Wirtz et al[14] were different from QMG score. The muscle strength scoring systems from McEvoy[19] or Wirtz[14] could not be converted into an equivalent QMG score. Therefore, we could compare the overall therapeutic effect by observing the change in QMG score from baseline to 3,4-DAP or placebo treatment. A meta-analysis of the four RCTs showed that QMG scores decreased (improved) by 2.33 points (95% CI, –2.81 to –1.85 points) after treatment with 3,4-DAP [Figure 3].

Secondary outcome measure: improvement in the amplitude of the resting CMAP

Changes in resting CMAP amplitude after 3,4-DAP or placebo treatment were recorded in five trials[14, 19–22]. Moreover, all the five trials showed significant improvements in CMAP after administration of 3, 4-DAP compared to placebo. A meta-analysis of the secondary outcome CMAP showed that the overall CMAP amplitude increased significantly in LEMS patients with 3, 4-DAP treatment, compared with placebo treatment. The overall mean improvement in CMAP on meta-analysis was 1.63 mV (95% CI, 0.85 to 2.41), favouring the 3, 4-DAP treatment [Figure 4]. All trials assessed CMAPs at one specific time point during their trial, with only the study of McEvoy and colleagues [19] providing three month follow up results.

Publication bias

Funnel plots are commonly used in general evaluation of publication bias in systematic reviews and meta-analyses. In this meta-analysis, the funnel plots of two outcomes QMG and CMAP were basically symmetrical, indicating that the risk of publication bias was small. The funnel plots of primary outcome QMG and secondary outcome CMAP were shown in Figure 5 and Figure 6. In addition, in order to further accurately assess publication bias, we also performed Begg's test with the StatsDirect statistical software (Version 14.0, StatsDirect Ltd, Cheshire, England), and the results of QMG ($P = 0.329 > 0.05$) and CMAP ($P = 0.760 > 0.05$) in Begg's test indicated the absence of publication bias.

Heterogeneity analysis and sensitivity analysis

The heterogeneity tests for both QMG and CMAP showed $I^2 < 50\%$ ($I^2 = 30\%$ for QMG and $I^2 = 0\%$ for CMAP). These results indicated a lack of heterogeneity in these groups and could be considered as coming from a homogeneous group. Thus, combined statistics could be used in fixed effects models. Due to low heterogeneity, sensitivity analysis was not carried out in meta-analysis.

Discussion

Efficacy of 3,4-DAP treatment for LEMS

In LEMS, 3,4-DAP blocks VGCCs, prolongs the action potential depolarization of motor nerve endings, and increases the opening time of VGCC[24]. This process leads to an increase in presynaptic calcium influx and an improvement in acetylcholine release, manifested as enhancement in muscle function.

In 1989, McEvoy and colleagues studied the effect of oral 3, 4-DAP on 12 LEMS patients, 7 of whom were cancer participants, in a double-blind RCT[19]. This trial showed distinct improvements in neurological dysfunction scores, isometric muscle strength tests, limb strength measurements, autonomic function, and CMAP amplitude after oral 3,4-DAP of up to 100 mg compared to placebo. Oh and colleagues published a cross-over RCT of oral 3,4-DAP of up to 80 mg daily, which indicated significant effect over the placebo in patients with LEMS[21]. Similarly, another randomized, parallel group trial of 26 patients demonstrated significant enhancement of QMG score and CMAP with the oral 60 mg of 3,4-DAP daily [20]. Similar results of intravenous administration of 3,4-DAP was also reported by Wirtz and colleagues[14].

All primary outcome indicators of isometric muscle strength[14], neurological disability score[19] and QMG score[20–23] had significant improvements after the administration of oral or intravenous 3,4-DAP. We could conduct a meta-analysis of QMG score according to the results provided in the studies by Sanders et al[20], Oh et al[21, 22], and Shieh et al[23]. The QMG rating system, with a score from 0 to 39, is a physician-rated assessment, including assessments of speech, swallowing, external ocular muscles, facial muscle strength, and all limb muscles. The QMG score is a quantitative evaluation, in which the lower score indicates the better muscle function[25]. In this study, meta-analysis showed a significant overall benefit (decreased 2.33 points, 95% CI, –2.81 to –1.85) in QMG for LEMS patients with 3,4-DAP compared to placebo. However, according to the Barohn et al[26], only a QMG change of more than 2.6 indicates a clinically significant improvement on the basis of 5 myasthenia gravis patients and 4 controls. If Barohn's criterion is used, no significantly clinical improvement was obtained in the Sanders study[20] and this meta-analysis. Thus, Sanders' concern is therefore understandable, which may due to the fact that bulbar, ocular, and distal limb items of the QMG score are less common in LEMS than in myasthenia gravis. However, both Oh et al. and Shieh et al. demonstrated that QMG score is an effective method to assess clinical enhancement in muscle strength, provided the QMG score system is followed[21–23].

Keogh M et al[27] and Maddison P et al[28] believed that in future LEMS treatment trials, QMG score should still be the preferred outcome indicator of muscle strength. Using uniform primary outcome measurements and data from further tests will be able to describe more specific effects. The authors also believe that in keeping with previous studies, it is appropriate to continue to evaluate the effect of 3,4-DAP treatment by performing a QMG assessment 3–4 days after the initiation of treatment.

Sanders et al[20] reported 26 participants with LEMS in a RCT and the median resting CMAP amplitude improved by 1.3 mV (+64%) in 12 cases receiving 3, 4-DAP 60mg daily, compared with a decrease of 0.1 mV(–3%) in the placebo group ($P < 0.001$). The meta-analysis also showed an average improvement in secondary outcome measure, with a resting CMAP amplitude of 1.63 mV (95% CI, 0.85 to 2.41). Therefore, the change of mean amplitude of CMAP appears to be a repeatable and objective secondary outcome for LEMS treatment trial. The authors suggest that since the duration of action of 3, 4-DAP is relatively short, the duration of action should be recorded three to six hours after taking 3, 4-DAP, and that future studies should record the CMAP assessment time related to the dose of the drug.

The results of six trials of 3, 4-DAP in the treatment of LEMS showed that the drug had a significant effect on LEMS, which was consistent with the earlier reports of the beneficial effect of

3, 4-DAP on LEMS and reflected the current practice of symptomatic first-line treatment of LEMS patients with the drug.

Adverse events

Adverse events associated with 3,4-DAP treatment reported from the included trials[14, 19–23] included temporary perioral tingling and digital paraesthesiae, back pain, headache, and epigastric discomfort. Besides, Wirtz et al[14] described a participant of cellulitis with 3,4-DAP infusion and McEvoy et al reported a participant suffered from epilepsy while taking 100mg of 3,4-dap daily[19]. In these included trials, there were not other major adverse events.

Limitations

Although these RCTs and pooled results showed significant improvement in the treatment of LEMS with 3,4-DAP, the number of RCTs studied was relatively limited and the total number of cases in this meta-analysis was limited. In addition, not all RCTs used the same primary outcome (QMG) and secondary outcome (CMAP) measures. Finally, the follow-up time for these RCTs was limited. In future, more large sample sizes, consistent outcome measures, and long-term follow-up RCTs are needed to further confirm the therapeutic efficacy and safety of 3,4-DAP on LEMS.

Conclusions

The pooled results demonstrated that 3,4-DAP had a significant effect on LEMS treatment, with improvements in muscle strength score and CMAP amplitude, which are moderate to high evidence from randomized controlled trials.

Abbreviations

Lambert-Eaton myasthenic syndrome (LEMS)

3,4-diaminopyridine (3,4-DAP)

compound muscle action potentials (CMAP)

Quantitative Myasthenia Gravis (QMG)

randomised controlled trials (RCT)

mean difference(MD)

confidence intervals (CI)

small-cell lung cancer(SCLC)

voltage-gated calcium channels (VGCC)

Declarations

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Availability of data and materials: The datasets supporting the conclusions of this article were included within the article.

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Conflict of interest: The authors declared no competing interests.

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Table

Author	Year	Country	Study type	Study design	Number	Age (year)	Female (%)	Cancer (%)	Treatment	QMG	CMAP
McEvoy	1989	USA	RCT	Cross-over	12	34-75	8(66.7%)	7(58.3%)	3,4-DAP	N/A	CMAP
Sanders	2000	USA	RCT	Parallel	26	41-68	15(57.7%)	10(38.5%)	3,4-DAP	QMG	CMAP
Oh	2009	USA	RCT	Cross-over	6	25-75	1(16.7)	2(33.3%)	3,4-DAP	QMG	CMAP
Wirtz	2009	Netherlands	RCT	Cross-over	9	33-73	4(44.4%)	N/A	3,4-DAP	N/A	CMAP
Oh	2016	USA	RCT	Parallel	36	21-88	23(63.9%)	6(16.7%)	3,4-DAP	QMG	CMAP
Shieh	2019	USA	RCT	Parallel	26	31-75	16(61.5%)	6(23.1%)	3,4-DAP	QMG	N/A

Table 1: Characteristics of literatures included in the meta-analysis.

N/A: without data. QMG: Quantitative Myasthenia Gravis. CMAP: compound muscle action potentials

Figures

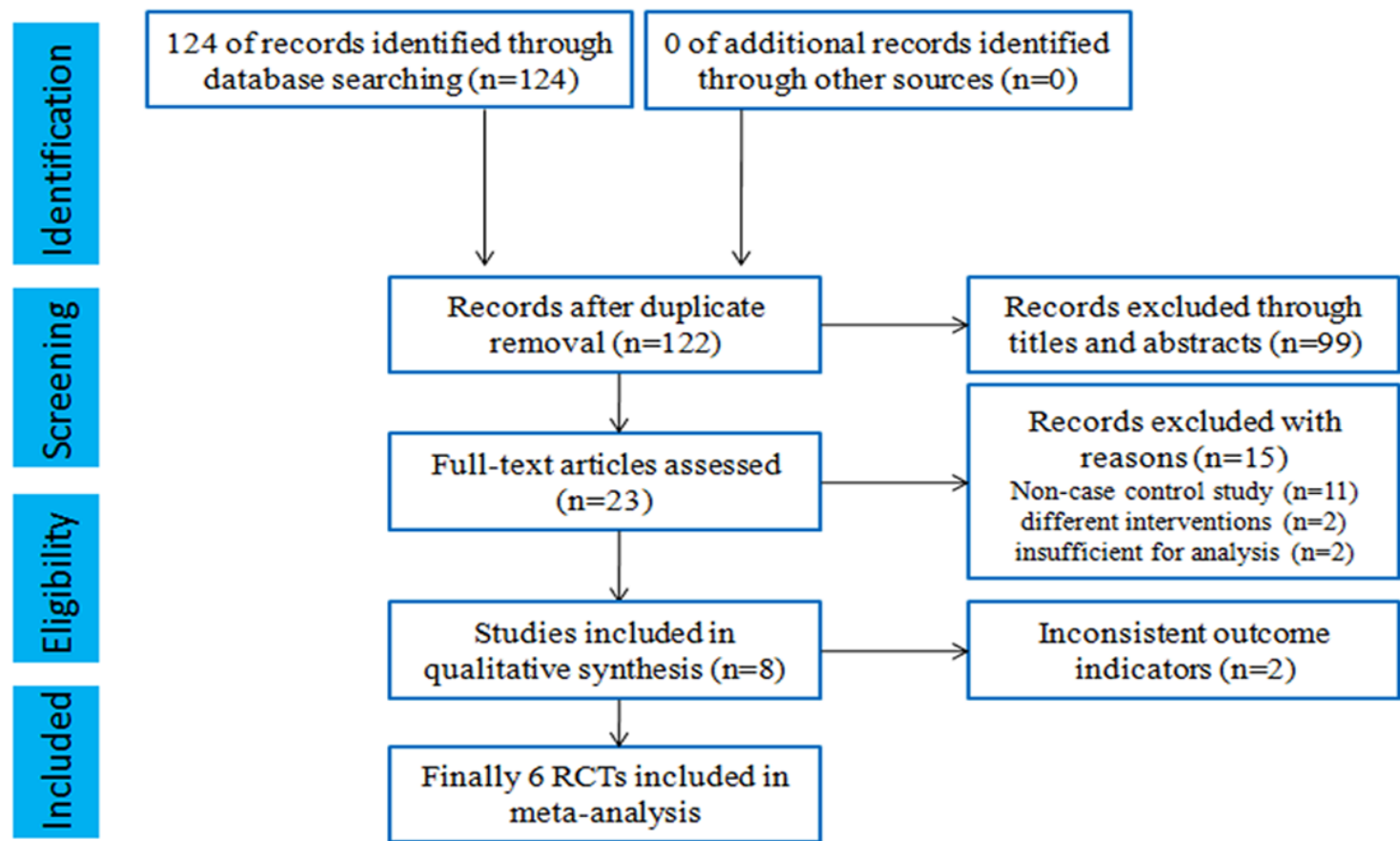


Figure 1
PRISMA flow diagram of search and select process.

	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)	Selective reporting (reporting bias)	Other bias
McEvoy 1989	+	?	+	+	+	+	+
Oh 2009	+	+	+	+	+	+	+
Oh 2016	+	?	+	+	+	+	+
Sanders 2000	+	?	+	+	+	+	+
Shieh 2019	+	?	+	+	+	+	+
Wirtz 2009	+	?	+	+	+	+	+

Figure 2

Risk of bias summary: Methodologic quality graph showing review authors' judgments about each methodologic quality item presented as percentages across all included studies.

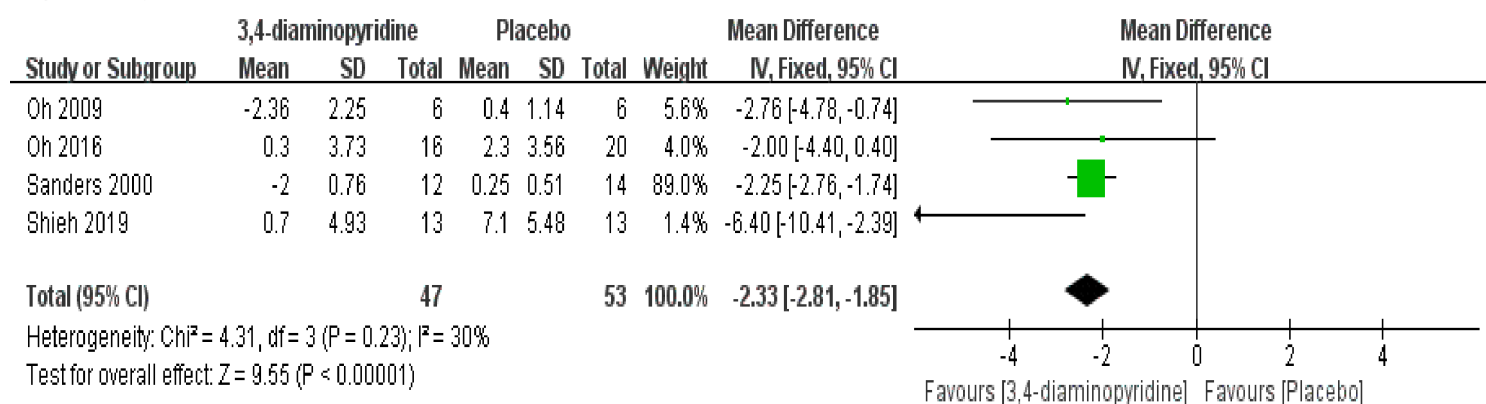


Figure 3

Forest plot for comparison 3,4-diaminopyridine treatment versus placebo, outcome improvement in mean QMG scores(assumed $r = 0.5$ for within-patient treatment effects in cross-over trials).

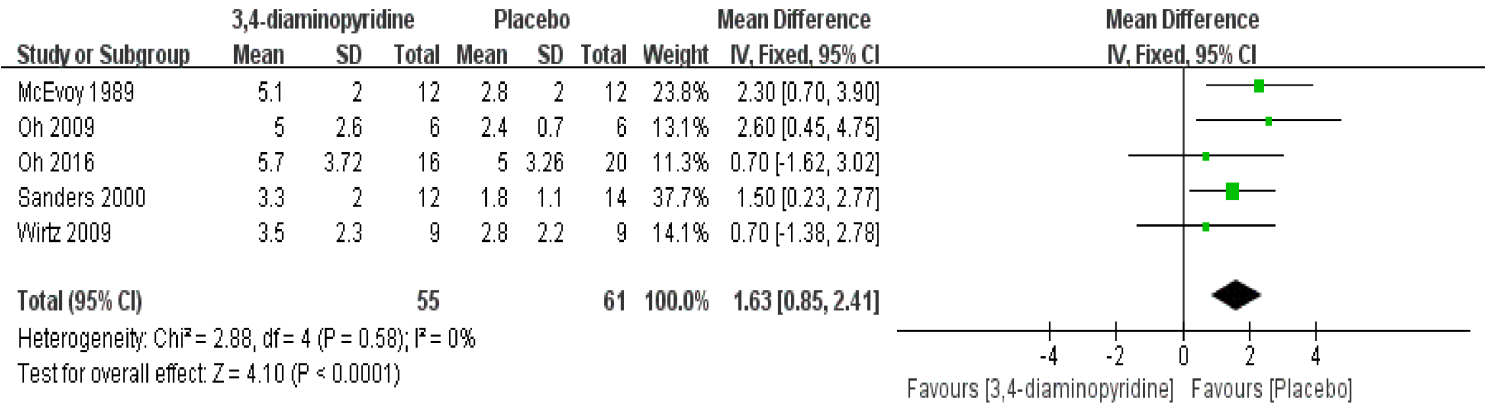


Figure 4

Forest plot for comparison 3,4-diaminopyridine treatment versus placebo, outcome improvement in mean CMAP amplitude(assumed $r = 0.5$ for within-patient treatment effects in cross-over trials).

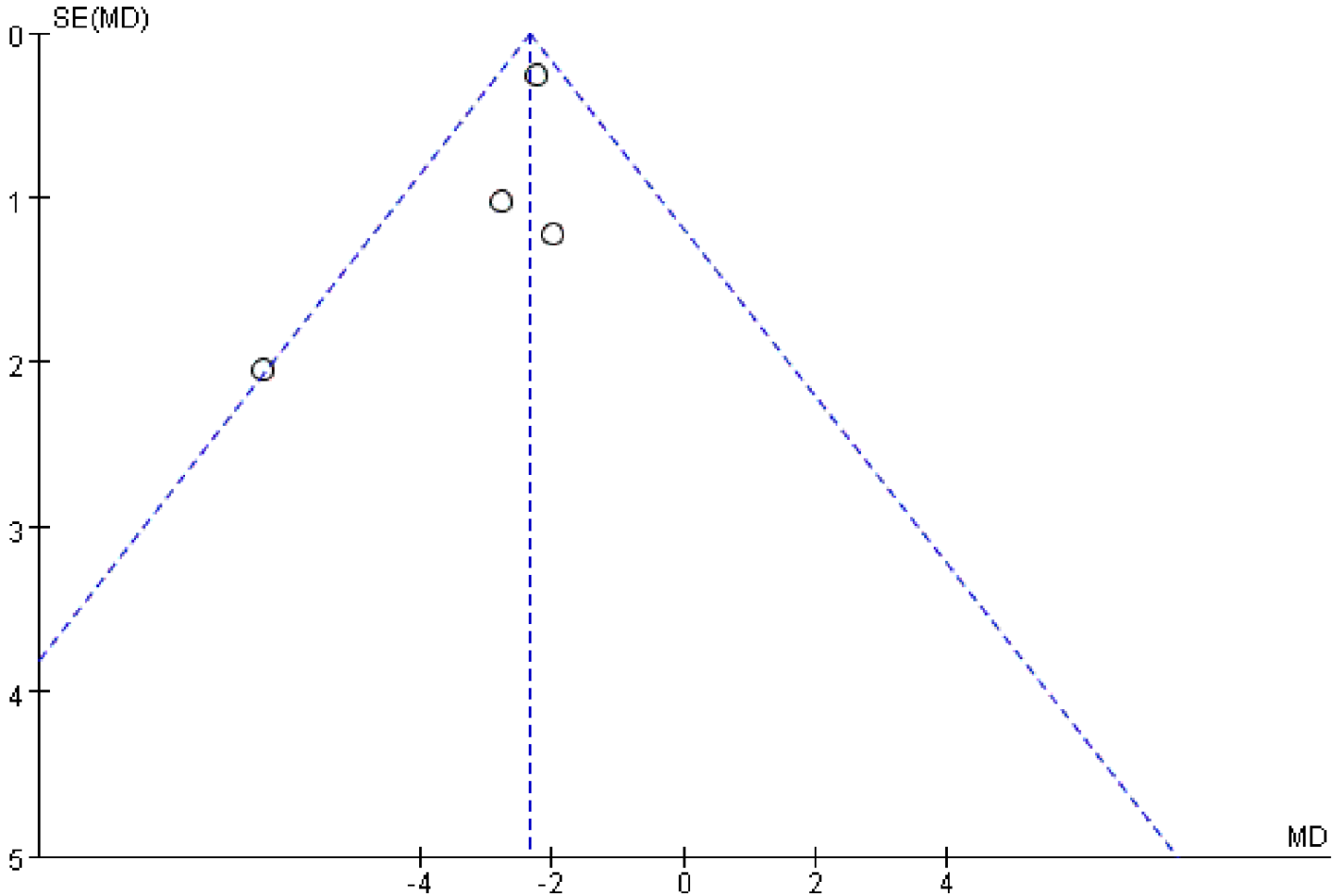


Figure 5

Funnel plot for within study QMG difference between 3,4-diaminopyridine treatment and placebo groups for each trial.

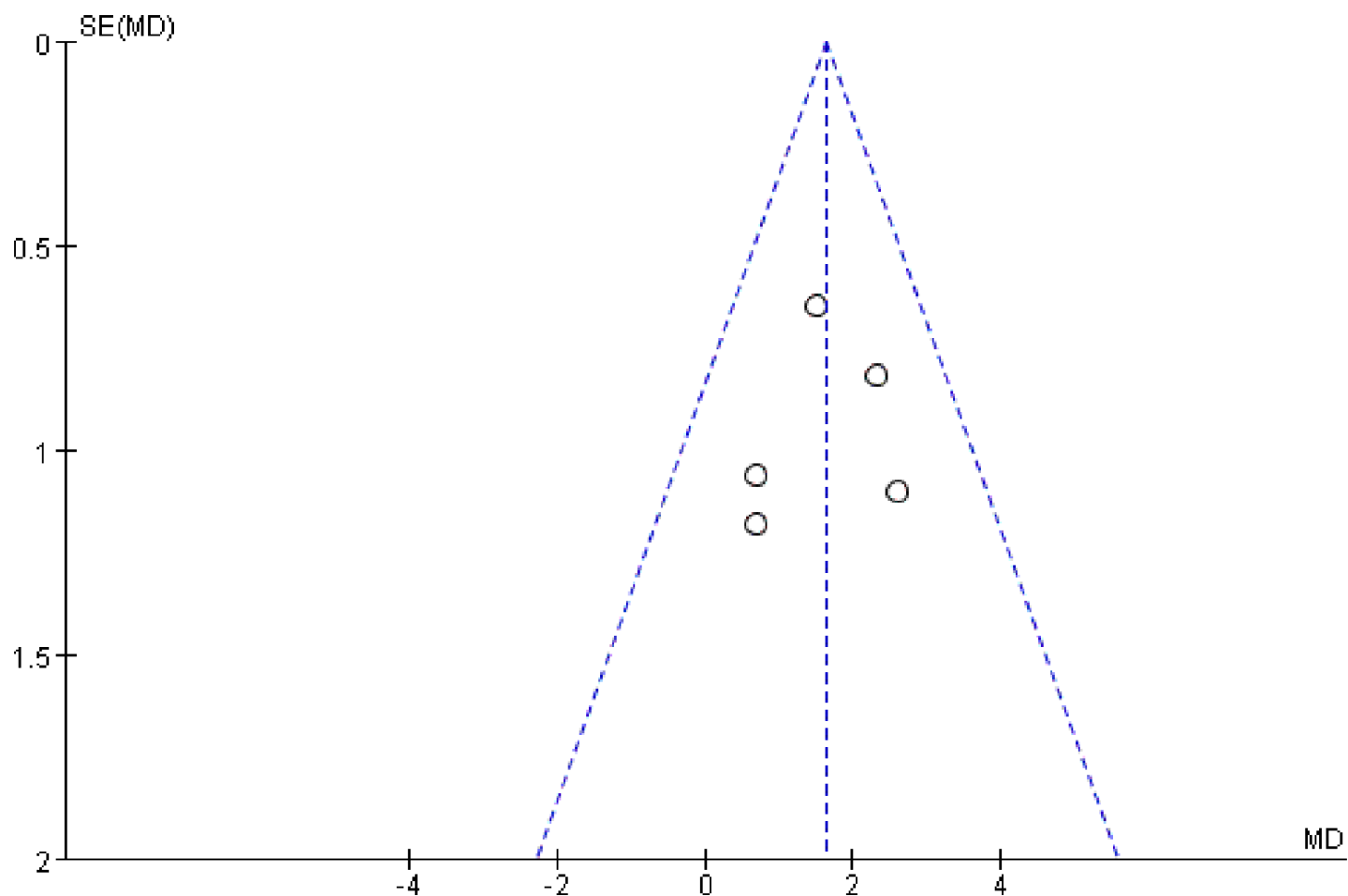


Figure 6

Funnel plot for within study CMAP difference between 3,4-diaminopyridine treatment and placebo groups for each trial.