Review Article
Tongxinluo-mecobalamin combination treatment is superior to mecobalamin alone for diabetic peripheral neuropathy: a meta-analysis

Fanghua Zhang[1*], Xia Wang[2*], Minxiu Yao[1], Qian Xu[1], Aimei Xu[1], Huiling Wang[1], Shan Gao[1], Shengli Yan[3]

[1]Department of Endocrinology, The Affiliated Central Hospital of Qingdao University, Qingdao 266042, Shandong Province, China; [2]Department of Healthcare, Qingdao Economic & Technological Development Area First People's Hospital, Qingdao 266555, Shandong Province, China; [3]Department of Endocrinology, The Affiliated Hospital of Qingdao University, Qingdao 266042, Shandong Province, China. *Equal contributors.

Abstract: The purpose of this study was to evaluate whether the efficacy of Tongxinluo-mecobalamin combination treatment on diabetic peripheral neuropathy (DPN) is superior to that of treatment with mecobalamin alone. Literature search on PubMed, Excerpta Medica database, Cochrane Central Register of Controlled Clinical Trials database, China National Knowledge Infrastructure, Chinese Biomedical Literature Database, Chinese Wanfang database, and Weipu database was performed up to July 2016. Risk ratio (RR) and its 95% confidence interval (CI) were calculated to assess the dichotomous data, whereas the weighted mean difference (WMD) and its 95% CI were used to assess the continuous data. A total of 13 studies including 1087 participants (546 received the combination treatment, 541 received the mecobalamin treatment) were included for meta-analysis. The overall effect size (RR = 1.52, 95% CI: 1.38-1.67, P < 0.00001) revealed that the effective rate of Tongxinluo-mecobalamin combination treatment was significantly higher than that of mecobalamin treatment in treating DPN. Furthermore, the effects of Tongxinluo-mecobalamin combination treatment on the improvement of median nerve motor conduction velocity (MCV) (WMD = 7.16, 95% CI: 3.72-10.60, P < 0.00001), median nerve sensory conduction velocity (SCV) (WMD = 9.07, 95% CI: 5.24-12.89, P < 0.00001), peroneal nerve MCV (WMD = 6.63, 95% CI: 2.27-11.00, P = 0.003), and peroneal nerve SCV (WMD = 4.59, 95% CI: 1.60-7.59, P = 0.003) were superior to those of mecobalamin treatment. These results suggest that Tongxinluo-mecobalamin combination treatment is more efficacious for DPN than mecobalamin treatment alone.

Keywords: Meta-analysis, Tongxinluo, mecobalamin, combination treatment, diabetic peripheral neuropathy

Introduction

Diabetic peripheral neuropathy (DPN), characterized by pain, paresthesia, and sensory loss, is one of the most common complications of diabetes [1]. In patients with diabetes, 30%-50% will develop diabetic peripheral neuropathy (DPN) and up to 20% will experience peripheral neuropathic pain [2]. In absolute numbers, the estimated global prevalence of diabetes will increase to 472 million by 2030 as predicted by the International Diabetes Federation (http://www.idf.org/diabetesatlas/diabetes-and-impaired-glucose-tolerance). Thus, there is an urgent need to improve the therapeutic schemes for DPN.

Chinese herbal medicine is frequently used for treating DPN in China. Tongxinluo is a compound Chinese medicine capsule, which includes ginseng, leeches, scorpion, *Eupolyphaga*, centipedes, cicada, chishao, borneol, and sandalwood, among others [3]. Tongxinluo displays the functions of anti-platelet aggregation, fibrinogen reduction, clot-protein dissolution, blood and plasma viscosity reduction, small arteries expansion, microcirculation improvement, and blood circulation promotion [4, 5]. For blood circulation disease induced peripheral neuropathy, Tongxinluo is able to restore the blood supply, raise the level of aerobic metabolism of nerve tissue, and help nerve function recovery [3]. Multiple studies have reported that

Tongxinluo capsules are effective for improving the nerve conduction velocity in DPN [6-8]. Mecobalamin is a coenzyme form of vitamin B12, and it is also referred to as MeCBl or MeB12 [9]. It can improve the metabolism of DNA, protein, and adipose tissue; repair injured nerve myelin; and improve nerve conduction velocity [9]. It is widely used as monotherapy or in combined therapy for the treatment of DPN [10, 11]. Furthermore, the efficacy of mecobalamin in combination with Tongxinluo on DPN has been reported, and most studies have shown that Tongxinluo in combination with mecobalamin is more effective on the nerve conduction velocity in DPN than mecobalamin alone [12-15]. However, small sample sizes were used in those studies, and no meta-analysis has been performed to comprehensively evaluate the clinical efficacy of Tongxinluo and mecobalamin combination treatment on DPN.

Meta-analysis is an important technique in clinical trials research, and is a method of reviewing and combining the evidence from clinical trials [16]. In this study, we conducted a meta-analysis to obtain an integrative understanding of the clinical efficacy of Tongxinluo- mecobalamin combination treatment on DPN.

Material and methods

Search strategy

We performed a literature search based on pre-established search strategies using the following databases: PubMed, Excerpta Medica database (EMBASE), Cochrane Central Register of controlled clinical trials database (CCTR), China National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database (CBM), Chinese Wanfang database, and Weipu (VIP) database up to July 2016. The key words included "diabetic peripheral neuropathy", "Tongxinluo", "methycobal", "methylcobalamin", "mecobalamin", "randomized controlled trial", and "clinical controlled trial". References from the retrieved articles were also checked to obtain additional studies.

### Inclusion and exclusion criteria for studies

To be included in the present meta-analysis, studies had to meet the following criteria: 1) study type was randomized controlled trial (RCT) or clinical controlled trial (CCT); 2) participants were patients with diabetic peripheral neuropathy; 3) the experimental group was administered Tongxinluo combined with mecobalamin therapy, and the control group was administered mecobalamin treatment alone; and 4) at least one of the following outcomes was assessed: effective rate and changes of median and peroneal nerve motor conduction velocity (MCV) or sensory conduction velocity (SCV). Furthermore, the effective rate was calculated as the percentage of patients who met the following criteria: (1) the clinical symptoms were relieved or disappeared; (2) deep and superficial sensation as well as the tendon reflex was improved or recovered; and (3) nerve conduction velocity in electromyogram was increased or restored to normal.

Additionally, studies with the following conditions were excluded: 1) the studies did not provide the source of cases and controls; 2) patients showed other complications of diabetes; 3) patients were treated by other drugs; 4) participants were pregnant; 5) participants were patients with serious heart, liver, or renal insufficiency diseases; 6) studies were non-therapeutic clinical research, animal experiments, or retrospective studies; and 7) articles were non-original literature, such as reviews, letters, and comments. In addition, duplicated publications were excluded, except for the version with the most complete data.

Data abstraction and quality evaluation

Articles were reviewed and screened independently by two investigators according to the inclusion and exclusion criteria. Subsequently, the data in each included study were extracted independently by the two investigators using a standardized form. The extracted data included first author's name, year of publication, study region, sample size, study design, the details of the participants in case and control groups (age, gender, duration of diabetes, and duration of peripheral neuropathy), and the outcomes. Following the data extraction, literature quality assessment was conducted to evaluate the risk of bias according to Cochrane Collaboration recommendations [17]. Discrepancies were resolved by discussion with a third assessor during the course of data extraction and quality evaluation.

Figure 1. Flow chart of literature search and study selection.
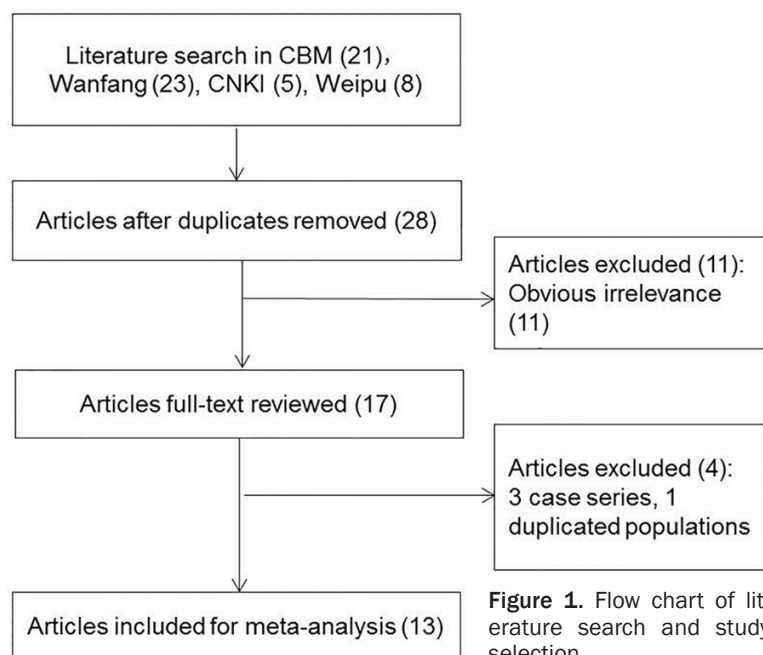
Results

Literature search

A flow chart of the literature search is shown in **Figure 1**. In accordance with the pre-established search strategies, a total of 57 papers were selected (CBM, 21; Wanfang, 23; CNKI, 5; and VIP, 8). Among these, 17 papers were retained after removing duplicates and those on irrelevant studies. Subsequently, 3 case series and 1 duplicated population were excluded. Thus, 13 articles were finally included in the meta-analysis [3, 12-15, 23-30].

Characteristics of eligible studies

The characteristics of the 13 included studies are shown in **Table 1**. The papers on these studies were published from 2004 to 2013. A total of 1087 participants (experimental group, n = 546; control group, n = 541) with a mean age between 50 and 62 years were reanalyzed in this meta-analysis. The duration of diabetes for the participants ranged from 1 to 28 years, and the duration of peripheral neuropathy ranged from 0.4 to 10 years. There was no significant difference in the duration of diabetes and peripheral neuropathy between the experimental group and the control group. All of the included studies were RCTs, and none of them reported details of the numbers lost to follow-up and level of blindness of the study.

Quality assessment of the included studies

Based on the Cochrane Collaboration recommendations, seven types of publication bias, namely, selection bias (random sequence generation and allocation concealment), performance bias, detection bias, attribution bias, reporting bias, and other bias, were assessed. The results of the quality assessment showed that only three studies had a low risk of random sequence generation (14, 24, 30), whereas one had a high risk (12), and four studies had a high risk of other bias (3, 14, 15, 28). Thus, the quality of the included studies was low because the studies were all from China and most of the

Statistical analysis

The pooled estimates of risk ratio (RR) and its 95% confidence interval (CI) were calculated to assess the dichotomous data, whereas the weighted mean difference (WMD) and its 95% CI were used to assess the continuous data. The overall estimates of RR and WMD were obtained by using the Mantel-Haenszel method in the fixed effect model [18] or by using the inverse variance method in the random effect model [19]. The heterogeneity was evaluated by Q-statistic chi-square test [20] and I^2 parameter [21], with $P < 0.05$ or $I^2 > 50\%$ indicating significant heterogeneity among studies, and the random effect model was used for meta-analysis. Otherwise, the fixed effect model was applied for pooling data. The significance for the overall effect was evaluated using z-test with $P < 0.05$ being considered to represent a statistically significant result. Analyses were performed using the software Review Manager 5.0 (Cochrane Collaboration, http://ims.cochrane.org/revman).

To test the stability of our meta-analysis, we performed a sensitivity analysis by removing each study one at a time. In addition, publication bias was evaluated by using Egger's linear regression test [22] with meta package (version 3.8-0, https://cran.r-project.org/web/packages/meta/) in R (version 3.1.0).

Table 1. The general characteristics of the included articles

Study	Observation Time	Male/Female		Average age (year)		Duration of diabetes (year)		Duration of peripheral neuropathy (year)	
		Experimental group	Control group	Experimental group	Control group	Experimental group	Control group	Experimental group	Control group
Dong 2005 [23]	NA	68/52		56.7 ± 8.9		9.6 ± 6.5		3.7 ± 2.0	
Fan 2010 [13]	2007-2009	55/17		55		NA	NA	0.5~4	
Jiao 2007 [14]	NA	12/18	13/17	58.1	56.9	11.2 ± 4.5	10.5 ± 3.4	3.2 ± 2.19	3.15 ± 2.88
Li 2008 [24]	2005.08-2007.12	17/7	15/6	55.0 ± 3.6	54.0 ± 4.8	11.4	12.3	5.8	5.9
Li 2010 [15]	2003.01-2008.12	21/19	22/18	62.1 ± 5.2	61.5 ± 4.9	3 ~ 28	2 ~ 27	0.4 ~ 9	0.5~10
Ming 2004 [25]	2001.7-2003.5	80 (total)	80 (total)	NA	NA	NA	NA	NA	NA
Peng 2007 [26]	NA	10/14	11/13	54.6 ± 8.8	56.8 ± 9.6	7.5 ± 3.6	6.5 ± 2.5	4.4 ± 2.6	4.0 ± 2.2
Wang 2009 [27]	2007.1-2008.12	18/12	17/13	52 ± 6	54 ± 6	NA	NA	NA	NA
Wang 2011 [28]	2006.1-2010.12	26/24	24/22	58.6 ± 6.3	58.8 ± 5.6	12.5 ± 6.2	13.0 ± 5.8	3.6 ± 0.6	3.4 ± 0.8
Xiong 2010 [29]	2007.5-2008.7	18/13	20/11	57.3 ± 5.7	56.8 ± 5.3	10.8 ± 4.2	11.2 ± 4.7	2.8 ± 4.2	3.1 ± 0.9
Yu 2009 [3]	NA	20/14	18/16	56.6 ± 4.5	53.3 ± 5.7	8.3 ± 3.9	10.3 ± 4.5	4.6 ± 1.3	4.8 ± 1.4
Zang 2009 [30]	NA	42/38		50 ± 5.25		1~12		NA	NA
Li 2013 [12]	2011.1-2013.1	25/24	26/23	69.24 ± 6.47	69.41 ± 6.16	NA	NA	NA	NA

Note: NA, not mentioned. In the paper by Ming (2004), detailed information is not provided, but as described in this paper, there are no significant differences in age, gender, and disease duration between the experiment and control groups.
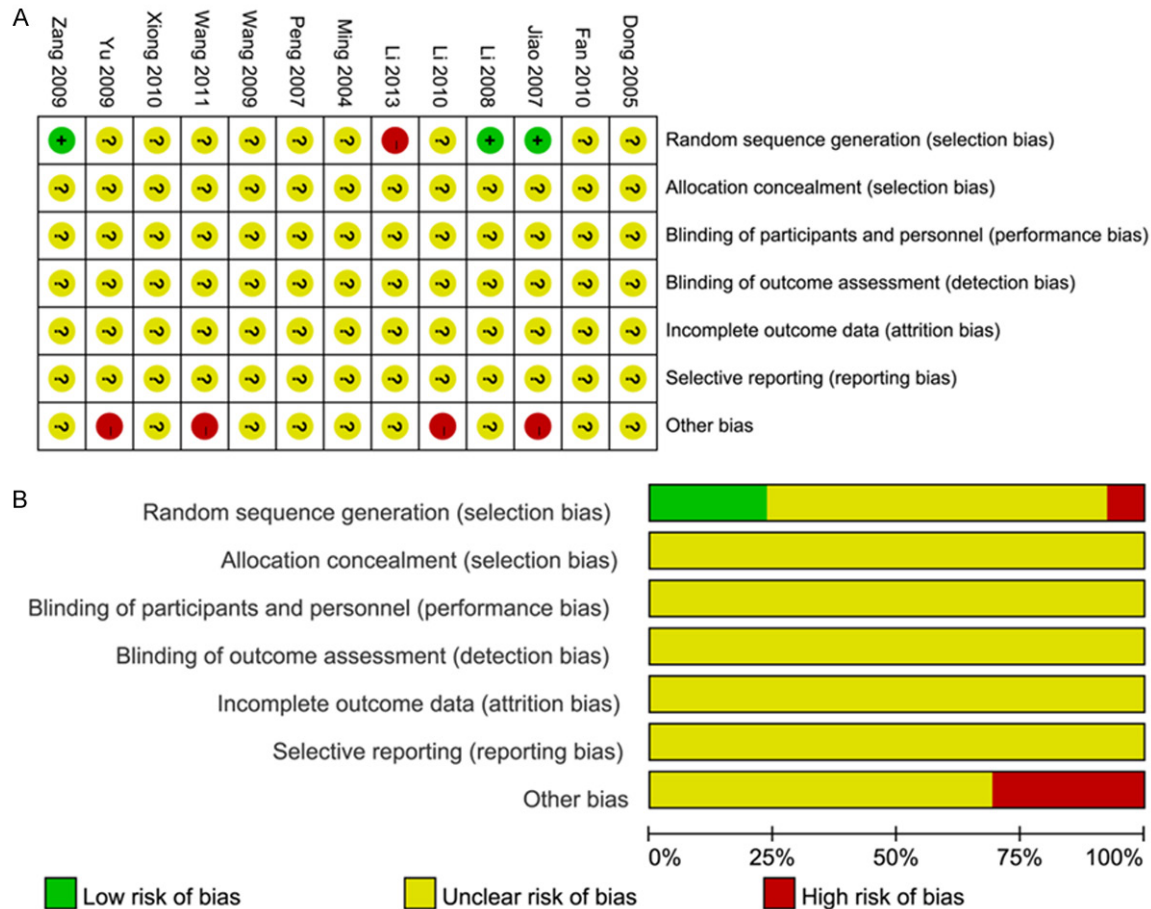
Figure 2. Quality assessments of the included studies. A. Sensitivity and specificity of the 13 included studies. B. Bias risk of the identified studies. "+" indicates low risk of bias; "?" indicates unclear risk of bias; "-" indicates high risk of bias.

information about bias was unclear or not presented (**Figure 2**). Owing to the description of the bias in each part being insufficient, high-quality articles will be needed for future studies.

Meta-analysis for effective rate

Among the included papers, 11 studies reported the effective rate of Tongxinluo-mecobalamin combination treatment on DPN [3, 13-15, 23, 24, 26-30]. The test for heterogeneity showed that there was no significant heterogeneity among these 11 studies (P = 0.59, I^2 = 0%); therefore, the fixed effect model was used for pooling estimates of effect size. The overall effect size (RR = 1.52, 95% CI: 1.38-1.67, P < 0.00001) revealed that there were significant differences in the effective rate between the experimental group and the control group

(**Figure 3**). The results indicated that the clinical efficacy of Tongxinluo-mecobalamin combination treatment was significantly higher than that of mecobalamin treatment alone for DPN.

Meta-analysis for the change of median nerve MCV and SCV

Among the included studies, 6 studies assessed the change of median nerve MCV [3, 12, 24, 27, 28, 30]. There were significant heterogeneities among the six studies (P < 0.00001, I^2 = 94%); therefore, the random effect model was used for pooling estimates of effect size. The overall effect size (MD = 7.16, 95% CI: 3.72-10.60, P < 0.00001) revealed that there were significant differences in the median nerve MCV change between the experimental group and the control group (**Figure 4A**), which suggested that the effect of Tongxinluo-
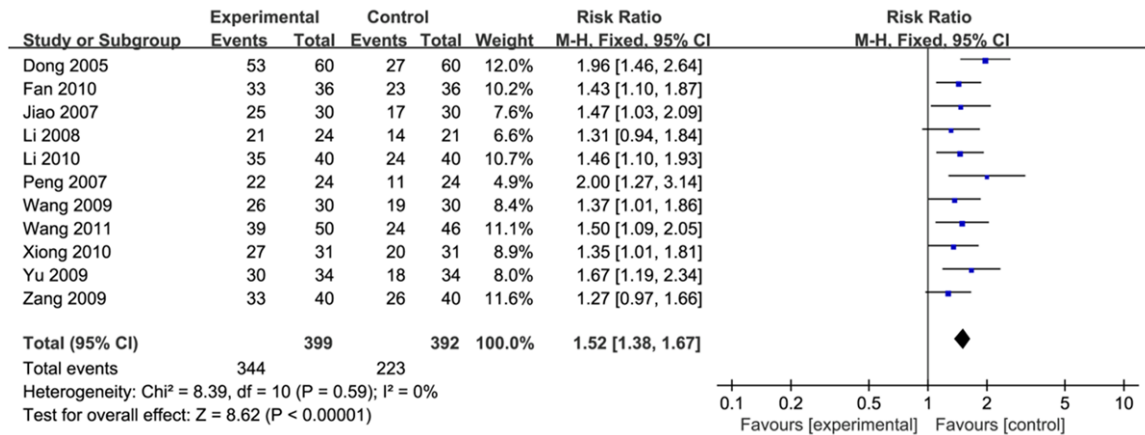
Figure 3. Forest plot for risk ratio of clinical efficacy between Tongxinluo-mecobalamin combination treatment and mecobalamin treatment alone on diabetic peripheral neuropathy. Squares represent the effect size for the risk ratio, and the size of the squares is proportional to the size of the cohorts. Error bars represent 95% CI. The diamond shape represents the pooled estimates within each analysis. CI, confidence interval.
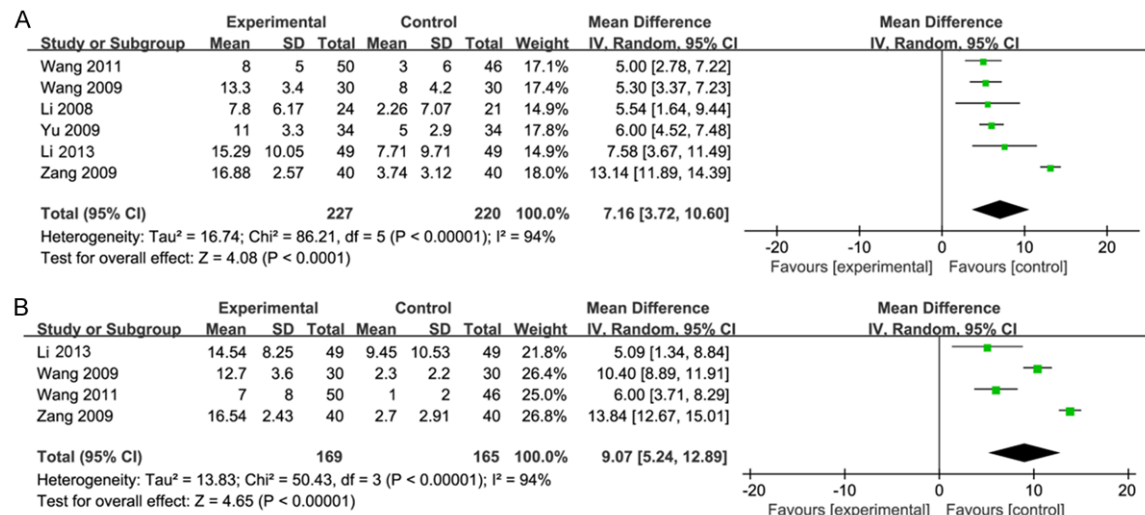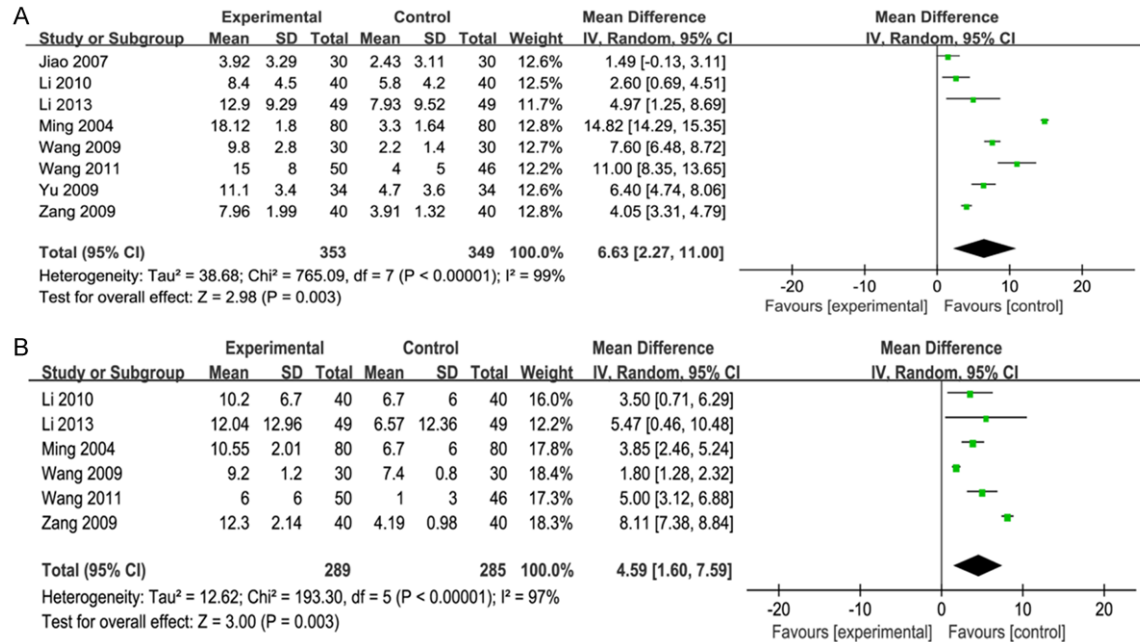

Figure 4. Forest plots for mean difference of median nerve conduction velocity change between Tongxinluo-mecobalamin combination treatment and mecobalamin treatment alone on diabetic peripheral neuropathy. A. Forest plot for mean difference of median nerve motor conduction velocity change between Tongxinluo-mecobalamin combination treatment and mecobalamin treatment alone on diabetic peripheral neuropathy. B. Forest plot for mean difference of median nerve sensory conduction velocity change between Tongxinluo-mecobalamin combination treatment and mecobalamin treatment alone on diabetic peripheral neuropathy. Squares represent the effect size for the risk ratio, and the size of the squares is proportional to the size of the cohorts. Error bars represent 95% CI. The diamond shape represents the pooled estimates within each analysis. CI, confidence interval.

mecobalamin combination treatment on the improvement of median nerve MCV was superior to that of the mecobalamin treatment alone.

Among the included papers, 4 studies assessed the change of median nerve SCV [12, 27, 28, 30]. There were significant heterogeneities among the 4 studies ($P < 0.00001$, $I^2 = 94$%);

therefore, the random effect model was chosen for pooling estimates of effect size. The overall effect size (MD = 9.07, 95% *CI*: 5.24-12.89, $P < 0.00001$) revealed that there were significant differences in the median nerve SCV change between the experimental group and the control group (**Figure 4B**). These results suggested that the effect of Tongxinluo-mecobalamin combination treatment on the

Figure 5. Forest plots for mean difference of peroneal nerve conduction velocity change between Tongxinluo-mecobalamin combination treatment and mecobalamin treatment alone on diabetic peripheral neuropathy. A. Forest plot for mean difference of peroneal nerve motor conduction velocity change between Tongxinluo-mecobalamin combination treatment and mecobalamin treatment alone on diabetic peripheral neuropathy. B. Forest plot for mean difference of peroneal nerve sensory conduction velocity change between Tongxinluo-mecobalamin combination treatment and mecobalamin treatment alone on diabetic peripheral neuropathy. Squares represent the effect size for the risk ratio, and the size of the squares is proportional to the size of the cohorts. Error bars represent 95% CI. The diamond shape represents the pooled estimates within each analysis. CI, confidence interval.

improvement of median nerve SCV was superior to that of the mecobalamin treatment alone.

Meta-analysis for the change of peroneal nerve MCV and SCV

Among the included studies, 8 assessed the change of peroneal nerve MCV [3, 12, 14, 15, 25, 27, 28, 30]. There were significant heterogeneities among these 8 studies ($P < 0.00001$, $I^2 = 99\%$); therefore, the random effect model was chosen for pooling estimates of effect size. The overall effect size (MD = 6.63, 95% *CI*: 2.27-11.00, *P* = 0.003) showed that there were significant differences in the peroneal nerve MCV change between the experimental group and the control group (**Figure 5A**), indicating that the effect of Tongxinluo-mecobalamin combination treatment on the improvement of peroneal nerve MCV was superior to that of the mecobalamin treatment alone.

Among the included studies, 6 studies assessed the change of peroneal nerve SCV [12, 15, 25, 27, 28, 30]. The test for heterogeneity showed that there were significant heterogeneities among these 6 studies (*P* < 0.00001, $I^2 = 97\%$); therefore, the random effect model was used for pooling estimates of effect size. The overall effect size (MD = 4.59, 95% *CI*: 1.60-7.59, *P* = 0.003) showed that there were significant differences in the peroneal nerve SCV change between the experiment and control groups (**Figure 5B**), indicating that the effect of Tongxinluo-mecobalamin combination treatment on the improvement of peroneal nerve SCV was superior to that of the mecobalamin treatment alone.

Publication bias and sensitivity analysis

Egger's linear regression test showed that there was no publication bias in this study (t = 1.5241, P = 0.1618). After removing any of the included studies, the merged RR could not cause a reverse result of the comparison between the two therapies in the sensitivity analysis, indicating the result was stable.

Discussion

DPN is one of the most common complications of diabetes [1]. Tongxinluo in combination with mecobalamin has been widely used in the treatment of DPN in China. In the present study, based on data from 13 RCT studies including 1087 participants, the meta-analysis revealed that Tongxinluo-mecobalamin combination treatment was superior to the treatment with mecobalamin alone in terms of the effective rate and improvement of median nerve and peroneal nerve MCV/SCV in DPN patients.

Tongxinluo, a Chinese herbal medicine, is frequently used for treating DPN in China. Its components (ginseng, leeches, scorpion, *Eupolyphaga*, centipedes, and others) can maintain vascular endothelial function, improve blood supply to the surrounding tissue, and relieve nerve ischemia oxygen deficit, which contribute to the recovery of nerve injury [3]. In a clinical study of 65 DPN cases, Ge et al. found that the sensory nerve conduction velocity of bilateral sural nerve and the physical signs of patients treated with Tongxinluo capsules clearly improved [6]. Moreover, it was reported that Tongxinluo capsules were effective for improving nerve conduction velocity in DPN patients [8]. Furthermore, the symptoms of peripheral neuropathic pain and abnormal sensation in DPN patients were significantly relieved after treatment with Tongxinluo capsules [7]. Tongxinluo was also reported to cause significant reductions in the levels of intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) in blood, as well as ICAM-1, VCAM-1, and nuclear factor kappa B in ischiadic nerve in DPN patients [31], which may be among the molecular mechanisms by which Tongxinluo results in the treatment of DPN.

In China, Tongxinluo is widely used in combination with mecobalamin to treat DPN, and this combination treatment shows better clinical efficacy on DPN patients than mecobalamin alone. A study reported that Tongxinluo improved blood and oxygen supply to the peripheral nerves, which synergistically enhanced the effect of mecobalamin on hemocyte aggregation, thus collaboratively promoting the recovery of nerve injury and increasing nerve conduction velocity [32]. Additionally, the combination treatment of Tongxinluo and mecobala-

min has no toxic or side effects in patients and no influence on glycometabolism [13]. However, the molecular mechanisms of Tongxinluo-mecobalamin combination treatment for DPN are still unknown, requiring further investigation.

This study is the first to evaluate the clinical efficacy of Tongxinluo-mecobalamin combination treatment for DPN by using a meta-analysis. However, the number of included studies was small and all of them did not report the details of loss to follow-up and blind method, suggesting that the quality of the papers was low. Moreover, other indexes, such as change of blood glucose level, were not assessed in this meta-analysis due to the lack of sufficient data. Thus, more high-quality RCTs with a larger sample size are necessary to confirm the efficacy of Tongxinluo-mecobalamin combination treatment on DPN. In conclusion, our meta-analysis suggests that Tongxinluo-mecobalamin combination treatment has better efficacy in DPN than mecobalamin treatment alone.

Disclosure of conflict of interest

None.

Address correspondence to: Shengli Yan, Department of Endocrinology, The Affiliated Hospital of Qingdao University, No. 16 Jiangsu Road, Qingdao 266042, Shandong Province, China. Tel: +86-0532-84882721; Fax: +86-0532-84882721; E-mail: shengliyan2016vip@163.com

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