Systematic Review and Meta-Analysis

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Fasudil combined with methylcobalamin or lipoic acid can improve the nerve conduction velocity in patients with diabetic peripheral neuropathy

A meta-analysis

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Abstract

Background: Fasudil (F) plus methylcobalamin (M) or lipoic acid (L) treatment has been suggested as a therapeutic approach for diabetic peripheral neuropathy (DPN) in numerous studies. However, the effect of the combined use still remains dubious.

Objective: The aim of this report was to evaluate the efficacy of F plus M or L (F + M or F + L) for the treatment of DPN compared with that of M or L monotherapy, respectively, in order to provide the basis and reference for clinical rational drug use.

Methods: Randomized controlled trials (RCTs) of F for DPN published up to September 2017 were searched. Relative risk (RR), mean difference (MD), and 95% confidence interval (CI) were calculated and heterogeneity was assessed with the I^2 test. Sensitivity analyses were also performed. The outcomes measured were as follows: the clinical efficacy, median motor nerve conduction velocities (NCVs) (MNCVs), median sensory NCV (SNCV), peroneal MNCV, peroneal SNCV, and adverse effects.

Results: Thirteen RCTs with 1148 participants were included. Clinical efficacy of F + M combination therapy was significantly better than M monotherapy (8 trials; RR 1.26, 95% CI 1.17–1.35, $P < .00001$, $I^2 = 0\%$), the efficacy of F + L combination therapy was also obviously better than L monotherapy (4 trials; RR 1.27, 95% CI 1.16–1.39, $P < .00001$, $I^2 = 0\%$). Compared with monotherapy, the pooled effects of combination therapy on NCV were (MD 6.69, 95% CI 4.74–8.64, $P < .00001$, $I^2 = 92\%$) for median MNCV, (MD 6.71, 95% CI 1.77–11.65, $P = .008$, $I^2 = 99\%$) for median SNCV, (MD 4.18, 95% CI 2.37–5.99, $P < .00001$, $I^2 = 94\%$) for peroneal MNCV, (MD 5.89, 95% CI 3.57–8.20, $P < .00001$, $I^2 = 95\%$) for peroneal SNCV. Furthermore, there were no serious adverse events associated with drug intervention.

Conclusion: Combination therapy with F plus M or L was superior to M or L monotherapy for improvement of neuropathic symptoms and NCVs in DPN patients, respectively. Moreover, no serious adverse events occur in combination therapy.

Abbreviations: CI = confidence interval, DPN = diabetic peripheral neuropathy, F = fasudil, FE = fixed-effect, L = lipoic acid, M = methylcobalamin, MNCV = motor nerve conduction velocity, RCT = randomized controlled trial, RE = random-effect, RR = risk ratio, SNCV = sensory nerve conduction velocity.

Keywords: diabetic peripheral neuropathy, efficacy, fasudil, lipoic acid, meta-analysis, methylcobalamin, nerve conduction velocity

1. Introduction

Diabetic peripheral neuropathy (DPN) is one of the common chronic complications of diabetes mellitus, and its risk factors include diabetes duration and poor glycemic control.[1,2] Diabetic patients with above 10 years duration frequently have obvious neuropathy symptoms. The pathogenesis of DPN is highly complicated and has not yet been clarified up to now. It is believed that the occurrence of DPN is related with metabolic disorders, oxidative stress, vascular injury, neural ischemic lesion, and autoimmune disorder, resulted from long-term hyperglycemia.[2,3] Currently, there is no specific pharmacologic curative approach for DPN, and drug monotherapy has no ideal clinical curative effects. The patients with DPN mainly accepted comprehensive therapies on the basis of intensive blood glucose control, including vascular dilation, microcirculation improvement, antioxidation, and trophic regulation of nerve cells in the peripheral nervous system.[1,4,5] Fasudil (F) can improve microcirculatory disturbance by dilating blood vessels and inhibiting platelet aggregation.[6,7] Methylcobalamin (M) can promote myelinogenesis and axon regeneration through nucleic acid and protein synthesis, and then repair peripheral nerve injury.[8,9] Lipoic acid (L), a potent antioxidant drug, eliminates oxygen radicals in peripheral nervous system, enhances Na^+/K^+ ATPase activity, reduces hypoxic–ischemic neuronal death by increasing blood flow, and improves nerve conduction velocities (NCVs) finally.[10–12] The 3 drugs can improve clinical outcomes of DPN in practice to a certain extent.[11,13–15]

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The efficacy of F plus M (F + M) combination therapy versus M monotherapy, and F plus L (F + L) combination therapy versus L monotherapy have been explored by many studies in China.[15–18] In order to understand the effect of F used in combination on the NCVs for patients with DPN comprehensively, the present meta-analysis identified the efficacy of F + M or F + L in DPN more precisely by retrieving data published in the randomized controlled trials (RCTs).

2. Methods

2.1. Search strategy

We retrieved the electronic databases of PubMed, Embase, Web of Science, Cochrane Library, Chinese BioMedical Database, Chinese National Knowledge Infrastructure Database, and Wanfang Database (last search date September 2017) without language restrictions. The key terms used in this search were (DPN or diabetic neuropathy or diabetic neuropathies or DPN) and (F or Rho kinase inhibitor) and (M or mecobalamin or vitamin B12) and (L or thioctic acid or alpha-L).

2.2. Study selection criteria

All the following inclusion criteria must be met for this study at the same time: First, study design was RCT. Second, Patients had diabetes mellitus and distal symmetrical sensorimotor polyneuropathy of the limbs, the diagnostic basis included standardized diabetes mellitus criteria of World Health Organization,[19] clinical assessments, and nerve conduction.[20] Third, Patients were treated with combination therapy (F + M or F + L) versus M or L alone. Fourth, Data on symptoms and (or) NCVs could be extracted, and treatment duration of at least 14 days. The exclusion criteria included, First, sensorimotor polyneuropathy caused by other factors. Second, Trials with some deficiencies in data or study design. Third, Published work with only abstracts.

2.3. Data extraction

All potentially relevant data including patient baseline characteristics, trial durations, daily doses of 3 drugs along with outcomes were extracted independently by the investigators from the collected studies. The primary outcomes were clinical therapeutic efficacy, median motor NCV (MNCV), median sensory NCV (SNCV), peroneal MNCV, and peroneal SNCV. Clinical therapeutic efficacy was divided into 3 categories including markedly effective (disappearance of subjective symptoms, recovered tendon reflex, and NCV increased by at least 5 m/s), effective (alleviated subjective symptoms, improved tendon reflex, and NCV increased by at least 3 m/s), and ineffective (no improvement in symptoms, tendon reflex, and NCV).[21] Moreover, adverse events were secondary outcomes.

2.4. Quality assessment

The established Jadad scale (Table 1) was used to evaluate the quality of included RCTs by study authors.[22] Items included randomization, concealment of allocation, double blinding, withdrawals, and dropouts. 0 to 3 points indicated poor or low-quality trials, and 4 to 7 points indicated high-quality trials.[20,23] The inconsistencies with quality assessment were discussed until consensus was reached.

2.5. Ethical approval

All the data in present meta-analysis were extracted from the previous published studies, no ethical approval or patient consent was required.

2.6. Statistical analysis

Dichotomous data (efficacy) were presented as risk ratio (RR) and 95% confidence intervals (CIs), and the weighted mean difference (MD) and 95% CIs were estimated for continuous data (NCVs). The statistical heterogeneity between trials was evaluated by the Q-statistic and I^2-test.[24] The random-effect (RE) model was used to pool the data when heterogeneity was confirmed ($P \leq .10$ or $I^2 \geq 50\%$ suggested significant heterogeneity among studies),[25] otherwise, the fixed-effect (FE) model was employed. Funnel plot was delineated to screen for potential publication bias. Sensitivity analysis was carried out by excluding 1 trial at a time, starting from those with a lower quality score, to further study the effect of a single trial on pooled data. All tests were 2-sided and a value of $P < .05$ was regarded as statistically significant. The data were analyzed using Revman Manager 5.3 software (Cochrane Collaboration, Oxford, UK).

3. Results

3.1. Description of the studies

Figure 1 showed the process of study selection. Thirteen RCTs[15–18,26–34] involving 1148 patients fulfilled the inclusion criteria. Eight trials[16,18,27,29,31–34] compared treatment with F + M combination therapy to M monotherapy, and 5 trials[15,17,26,28,30] compared treatment with F + L combination therapy to L monotherapy, the aim of these trials was to clarify the efficacy and safety of combination treatment approach among patients with DPN. The key characteristics of the 13 RCTs and Jadad scores were presented in Table 2. A total of 378

Table 1

Methodology quality assessment-modified jaded score (7-point).

Items	Score standard		
	0	1	2
Randomization	Not randomized or inappropriate method of randomization	The study was described randomized	The method of randomization was described, and it was appropriate
Concealment of allocation	Not describe the method of allocation concealment	The study was described as using allocation concealment	The method of allocation concealment was described appropriately
Double blinding	No blind or inappropriate method of blinding	The study was described as double blind	The method of double blinding was described and it was appropriate
Withdrawals and dropouts	Not describe the follow-up	A description of withdrawal and dropout	

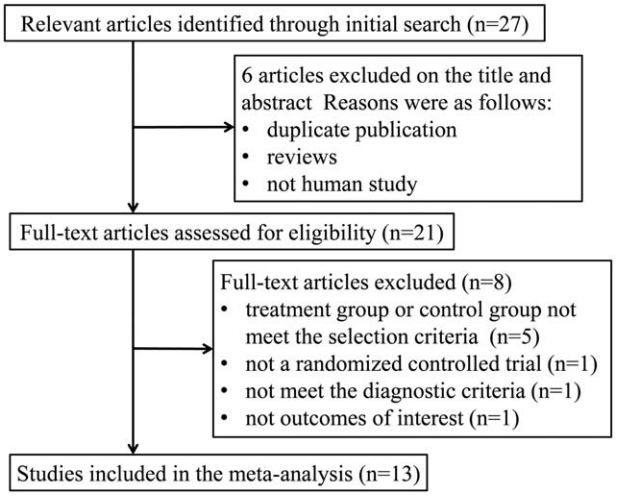

Figure 1. Map of the literature search and selection process.

DPN patients were included in the F+M combination therapy group, and 353 DPN patients were included in the M monotherapy group. A total of 212 DPN patients were included in the F+L combination therapy group and 205 DPN patients were included in the L monotherapy group. The dosages of F administration were 30 or 60 mg/day, dosages of M administration were 0.5 or 1.0 mg/day, dosages of L administration were 160 or 600 mg/day. The modes of 3 drugs administration included intravenous infusion or intravenous; furthermore, intramuscular injection was also used for M administration. The duration of combination therapy was 14 to 28 days in most trials and 30 days in 1 trial. Only 3 trials[18,27,33] with 4 points were of high quality, and the remaining 10 trials with 3 or lower points were all of low quality. Six trials reported the DPN duration. Nine trials reported the diabetes mellitus duration. The type of diabetes was available in only 4 trials.

3.2. Efficacy

Twelve trials involving a total of 1096 patients measured the efficacy of F+M or L combination therapy compared with M (8 trials) or L (4 trials) monotherapy. Although high dosage of L (600 mg daily) was used in Liu YF's trial,[28] both F+L and L groups showed relatively less improved efficacy in this trial compared to the other 4 low-dosage trials (L 160 mg daily), we excluded this trial to eliminate a potential publication bias. As shown in Fig. 2, the FE model was used because insignificant heterogeneity between studies for the 2 groups was observed ($P=.98$, $I^2=0\%$). F+M combination therapy for DPN enhanced the efficacy obviously compared with M treatment (RR 1.26, 95% CI 1.17–1.35, $P<.00001$). Compared with L monotherapy, F+L combination therapy for DPN also increased the efficacy significantly (RR 1.27, 95% CI 1.16–1.39, $P<.00001$). Figure 3 showed the funnel shape was not perfectly symmetrical, indicating a potential publication bias.

3.3. Median MNCV

Six trials[15,18,27,29,31,33] involving a total of 587 patients measured median MNCV. Heterogeneity was significant for the analysis ($P<.00001$, $I^2=92\%$), the RE model was used. Compared with monotherapy group, median MNCV showed significant improvement in the combination group (MD 6.69, 95% CI 4.74–8.64, $P<.00001$) (Fig. 4A). On sensitivity analyses, we found the I^2 value ranged from 90% to 93%, which indicated that the result was robust.

3.4. Median SNCV

Six trials[15,18,27,29,31,33] involving a total of 587 patients measured the median SNCV. As shown in Fig. 4B, the RE model was used because significant heterogeneity between studies for the 2 groups was observed ($P<.00001$, $I^2=99\%$). Compared with monotherapy, combination therapy increased median SNCV significantly (MD 6.71, 95% CI 1.77–11.65, $P=.008$). On sensitivity analyses, after excluding the study reported by Liang et al[27], the I^2 value ranged from 99% to 10% and the overall effect ranged from 2.66 to 14.80, we found that the dosage of F administration in Liang's study was 60 mg daily, while the dosages in other 5 studies were 30 mg daily.

3.5. Peroneal MNCV

Seven trials[15,16,18,27,29,31,33] involving a total of 653 patients measured the peroneal MNCV. As shown in Fig. 5A, the RE model was used because significant heterogeneity between studies for the 2 groups was observed ($P<.00001$, $I^2=94\%$). Compared with monotherapy, combination therapy

Table 2

Characteristics of the studies included in the meta-analysis.

Reference	Number trial/control	Age trial/ control	Gender male/female	Type of diabetes (n)	DM duration (y) trial/control	DPN duration (y) trial/control	Study duration (d)	Treatment drugs sig (d)		Outcomes	Quality
								Trial	Control		
Chang et al[16]	36/30	62.5/59.5	46/20	2	1–15/1.5/16	NR	28	F: 60 mg ivgtt M: 0.5 mg ivgtt	M: 0.5 mg ivgtt	①④⑤	2
Liang et al[27]	83/65	56.2/54.1	74/74	NR	9.3/9.1	4.5/4.1	28	F: 60 mg ivgtt M: 0.5 mg im	M: 0.5 mg im	①②③④⑤	4
Wang and Lu[29]	34/34	NR	46/22	2	NR	NR	14	F: 30 mg ivgtt M: 0.5 mg iv	M: 0.5 mg iv	①②③④⑤	2
Xie and Zhou[18]	48/48	51.3/50.8	55/41	2	11.3/11.2	3.8/3.7	14	F: 30 mg ivgtt M: 0.5 mg iv	M: 0.5 mg iv	①②③④⑤	4
Yuan[31]	58/57	52.3/52.3	63/52	NR	9.26/9.25	NR	21	F: 30 mg ivgtt M: 0.5 mg iv	M: 0.5 mg iv	①②③④⑤	1
Zhang[32]	39/39	57.3/58.1	43/35	NR	7.8/8.2	3.5/3.7	30	F: 60 mg ivgtt M: 0.5 mg im	M: 0.5 mg im	①	2
Zhou[33]	30/30	57/56	36/24	NR	10/10	4.5/3.9	28	F: 30 mg ivgtt M: 1 mg ivgtt	M: 1 mg ivgtt	①②③④⑤	4
Zhou[34]	50/50	57.1/58.5	51/49	NR	8.1/7.9	3.8/3.9	28	F: 60 mg ivgtt M: 0.5 mg im	M: 0.5 mg im	①	3
Dong and Zhang[26]	30/30	NR	40/20	NR	NR	NR	14	F: 60 mg iv L: 160 mg iv	L: 160 mg iv	①	1
Liu[28]	29/23	NR	NR	2	NR	NR	14	F: 30 mg ivgtt L: 600 mg ivgtt	L: 600 mg ivgtt	①	2
Ren et al[17]	61/61	NR	50/72	NR	NR	NR	14	F: 60 mg iv L: 160 mg iv	L: 160 mg iv	①	2
Wen et al[15]	50/50	56.5/55.2	46/54	NR	6.8/6.5	2.3/2.4	14	F: 30 mg ivgtt L: 160 mg ivgtt	L: 160 mg ivgtt	①②③④⑤	3
Yang[30]	42/41	60.3/60.1	48/35	NR	8.7/8.9	NR	14	F: 60 mg iv L: 160 mg iv	L: 160 mg iv	①	3

DM = diabetes mellitus, DPN = diabetic peripheral neuropathy, F = fasudil, ① = efficacy, ② = median MNCV, ③ = median SNCV, ④ = peroneal MNCV, ⑤ = peroneal SNCV, im = intramuscular, iv = intravenous, ivgtt = intravenous infusion, L = lipoic acid, M = methylcobalamin, NR = not report.

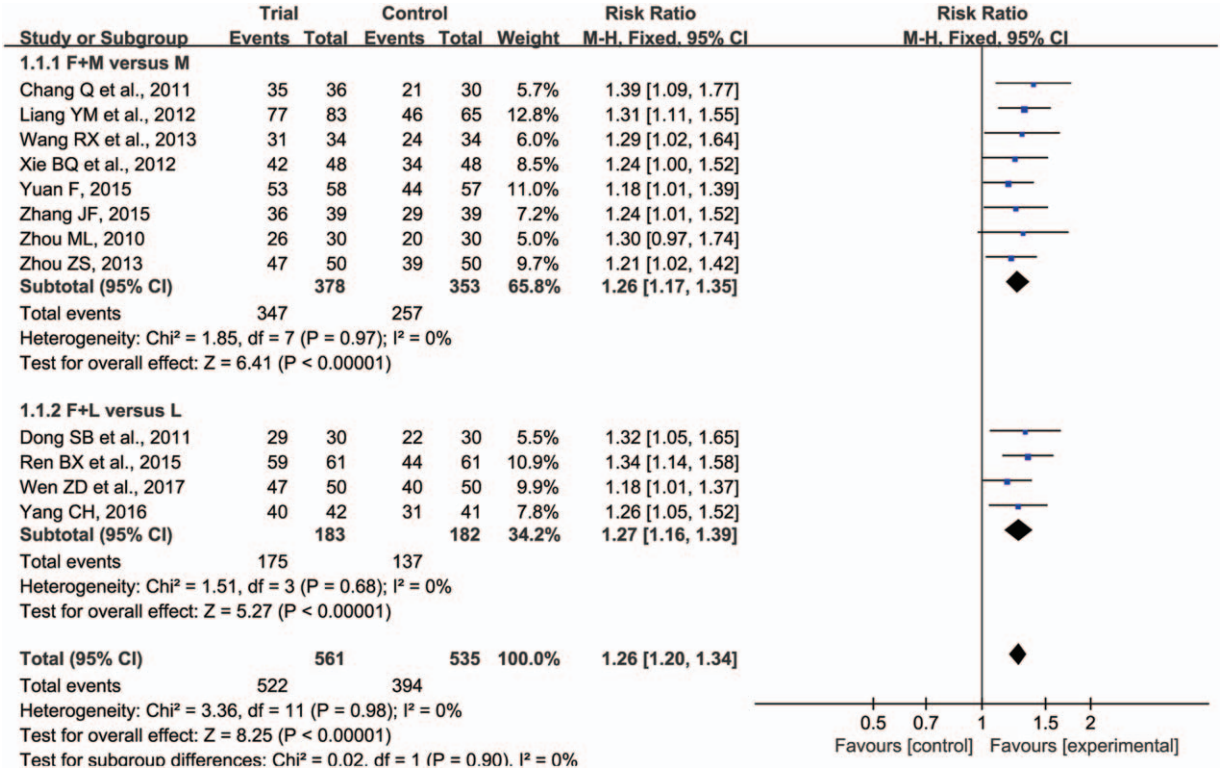

Figure 2. Comparison of F + M or F + L combination therapy and M or L monotherapy in the efficacy for patients with diabetic peripheral neuropathy. F = fasudil, L = lipoic acid, M = methylcobalamin.

accelerated peroneal MNCV significantly (MD 4.18, 95% CI 2.37–5.99, $P < .00001$). The sensitivity analyses showed that the I^2 value ranged from 88% to 95%, which indicated the result was robust.

3.6. Peroneal SNCV

Seven trials[15,16,18,27,29,31,33] involving a total of 653 patients measured the peroneal SNCV. As shown in Fig. 5B, the RE model was used because significant heterogeneity between studies for

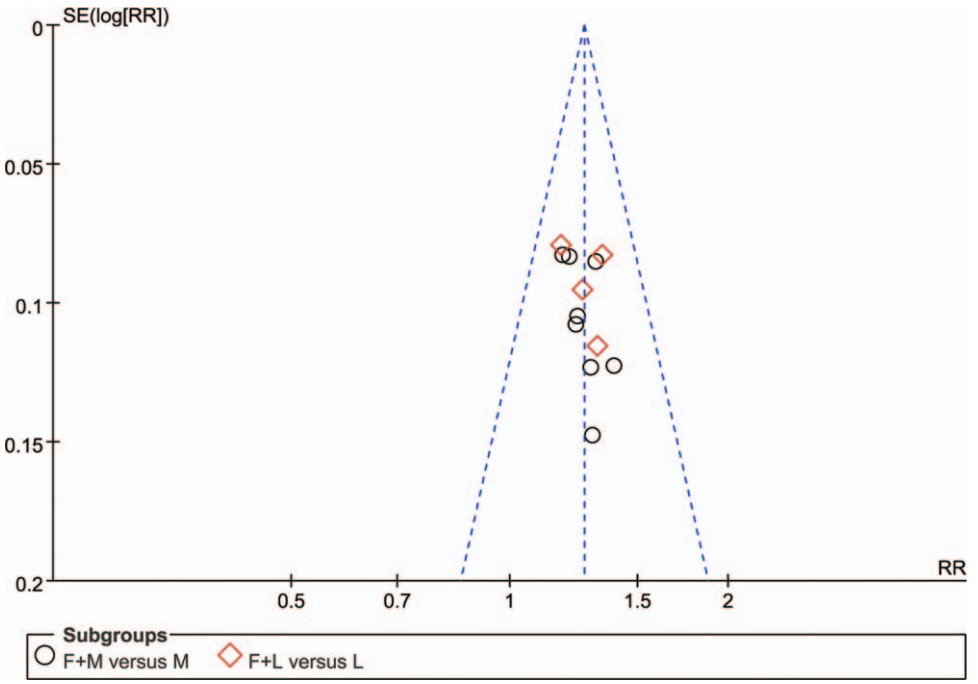

Figure 3. Funnel plot for estimation of heterogeneity. F = fasudil, L = lipoic acid, M = methylcobalamin.

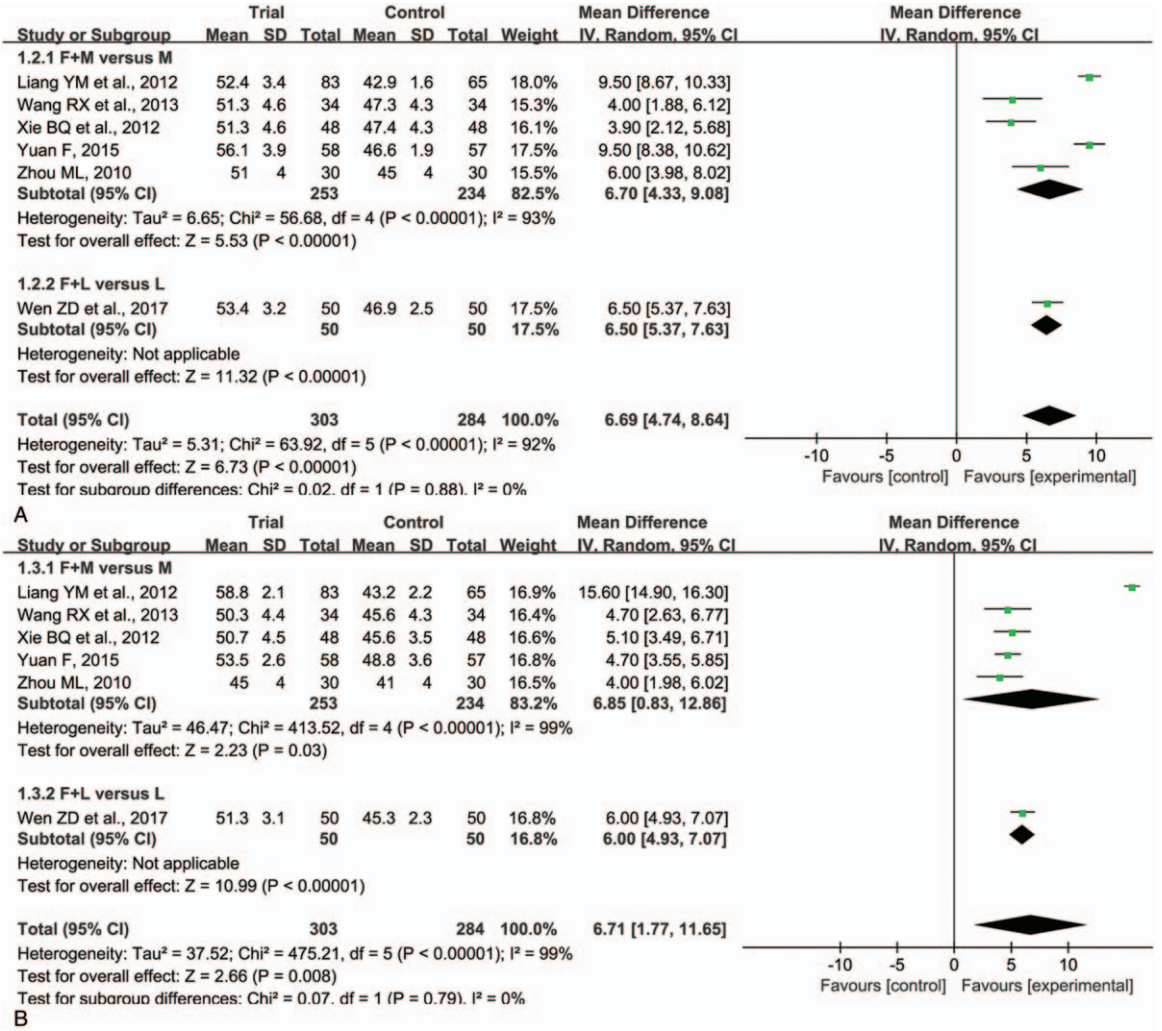

Figure 4. Comparison of F + M or F + L combination therapy and M or L monotherapy in the median motor nerve conduction velocity (A) and median sensory nerve conduction velocity (B) for patients with diabetic peripheral neuropathy. F = fasudil, L = lipoic acid, M = methylcobalamin.

the 2 groups was observed ($P < .00001$, $I^2 = 95\%$). Compared with monotherapy, combination therapy improved peroneal SNCV significantly (MD 5.89, 95% CI 3.57–8.20, $P < .00001$). On sensitivity analyses, we found the I^2 value ranged from 89% to 96%, which indicated that the result was robust.

3.7. Safety

Four of the 13 trials reported the adverse events, 2[18,31] of which demonstrated that there were no side effects, the other 2[15,29] reported that there were no serious treatment-related side effects during treatment period in both combination therapy group and monotherapy group. Only some mild adverse effects including nausea (3 cases),[15] local skin redness (2 cases),[29] pain at the injection site (2 cases),[29] emesis (1 case),[15] fever (1 case),[15] and constipation (1 case)[15] in the combination therapy group, and pain at the injection site (2 cases),[29] nausea (2 cases),[15] emesis (1 case),[15] constipation (1 case)[15] in monotherapy group were reported.

4. Discussion

DPN, accompanied with diabetic microangiopathy in most cases,[2] causes motor and sensory nerve fibers injury. The clinical symptoms include numbness, pain, and scorching hot in hands and/or feet. Severe patients also present with sensory disturbance of distal limbs, skin ulcer, and even lower limbs gangrene.[3,35] The mortality and disability rates of DPN are both high, and the quality of life in DPN patients was lowered significantly. At present, it has been found that polyhydric alcohols and inositol related metabolic disorders induce nerve cell degeneration and dysfunction, then result in slower NCVs, segmental demyelination in peripheral nerves and axonal degeneration/necrosis.[36,37] The neurological injury usually occur in distal sensory nerves. Persistent hyperglycemia causes damage to myelin membrane integrity and neurosecretory system by increasing nonenzymatic glycation of myelin proteins in peripheral nervous system.[4,38] Moreover, reduced expression of neurotrophic factors in diabetic patients might be involved in occurrence and progression of DPN.[2]

The microangiopathy symptoms of diabetic patients include thickened basilar membrane capillaries, vascular endothelial hyperplasia and swelling, glycoprotein deposition, peripheral hypoperfusion of nourishing vessels caused by vascular wall thickening, inadequate peripheral blood flow, which result in subsequent occurrence of necrotic and apototic neurodegeneration.[2,3] In addition, oxidative stress play crucial roles in the

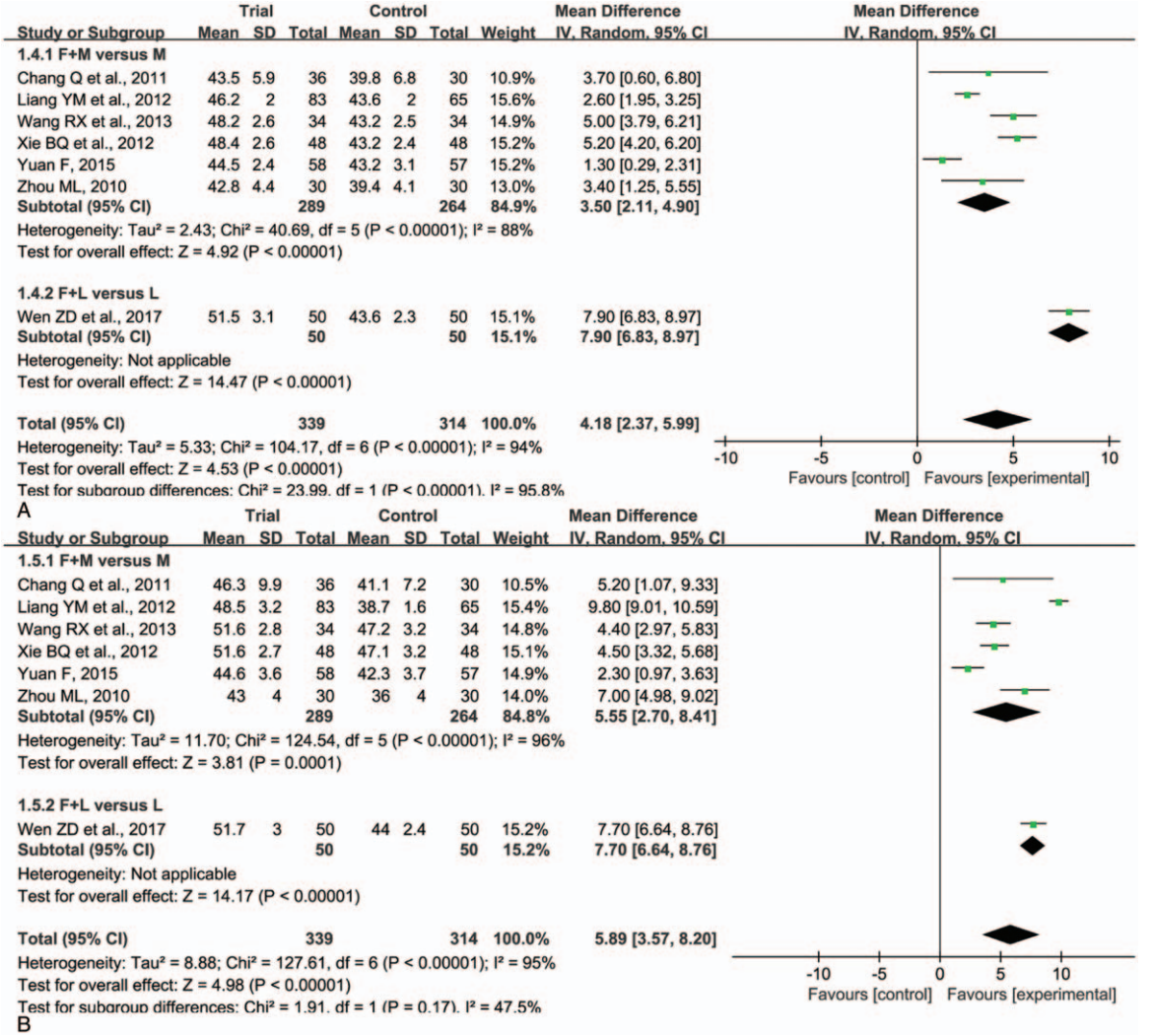

Figure 5. Comparison of F+M or F+L combination therapy and M or L monotherapy in the peroneal motor nerve conduction velocity (A) and peroneal sensory nerve conduction velocity (B) for patients with diabetic peripheral neuropathy. F = fasudil, L = lipoic acid, M = methylcobalamin.

progress of DPN.[39] Compared with the euglycemic condition, body shows greater oxidative stress and more NO and reactive oxygen species in neuron under hyperglycemia condition.[1,40] The imbalance between oxidant production and removal by the antioxidant system induces neural cytotoxicity, which result in DPN occurrence and development.

F, an intracellular calcium ion channel antagonist as well as a Rho-kinase inhibitor, can evoke vasodilatation and relieve vasospasm through relaxing vascular smooth muscle cells, caused by activating myosin light-chain phosphatase.[6] F increases blood flow and oxygen supply to peripheral nervous system and accelerates NCVs by blocking platelet aggregation.[7,41,42] F promotes Schwann cell proliferation and axon regeneration, and facilitates injured peripheral nerve repair.[43–45] In addition, F can inhibit nerve cell apoptosis by reducing inflammatory factors and reactive oxygen species production.[46,47] F can be used to prevent and treat cerebral vasospasm post-subarachnoid hemorrhage,[48,49] dementia,[50] DPN,[15,17] and pulmonary arterial hypertension[51] in clinical practice.[52]

In the present study, we found that compared to the monotherapy (M or L) group, DPN clinical symptom in the combination therapy (F+M or F+L) group was significantly attenuated, and the improvement of NCVs in the combination therapy group were obvious. No severe adverse events occurred in the course of drug treatment. It is indicated that F polytherapy with L or M is an effective, definite, and safe therapy for patients with DPN.

Some limitations of our meta-analysis should be considered. First, the sample size of 3 trials was small.[26,28,33] Second, a reporting bias existed in our meta-analysis, due to only the data from published trials were included and the unpublished statistically nonsignificant results were excluded, but it would be very difficult to gain access to data from the unpublished studies. Third, the adjustment according to patient-level confounders in this study was not observed because the meta-analysis was based on group-level data and not individual patient data. In addition, the asymmetry of funnel plot, indicating the likelihood of publication bias, may be resulted from small-study effect, insufficient number of trials, and significant statistical heterogeneity.

In summary, this meta-analysis suggests that DPN patients with F+M or F+L combination therapy have significant higher-level improvement in clinical symptoms and NCVs compared with M or L monotherapy, respectively. Moreover, the results

also indicate that no serious adverse events occur in combination therapy group. However, the results should be interpreted cautiously since relevant evidence is still limited, and further large-scale, well-designed RCTs are urgently needed. Due to poor methodological quality of the studies included, strong and definitive recommendations cannot be made for patients with DPN.

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Writing – original draft: de-qi jiang.
Writing – review & editing: li-lin jiang, ming-xing Li, yong wang.

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