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 I² test. Sensitivity analyses were also performed. The outcomes measured were as follows: the clinical efficacy, median motor nerve conduction velocities (MNCVs) (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, I² = 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, I² = 0%). Compared with monotherapy, the pooled effects of combination therapy on NCV were (MD 6.69, 95% CI 4.74–8.64, P < .00001, I² = 92%) for median MNCV, (MD 6.71, 95% CI 1.77–11.65, P = 0.008, I² = 99%) for median SNCV, (MD 4.18, 95% CI 2.37–5.99, P < .00001, I² = 94%) for peroneal MNCV, (MD 5.89, 95% CI 3.57–8.20, P < .00001, I² = 96%) 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.[1,2,3] 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.[4,5] Fasudil (F) can improve microcirculatory disturbance by dilating blood vessels and inhibiting platelet aggregation.[6,7] Methylcobalamin (M) can promote myelogenesis 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.[1,3,13–15]
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, 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 de 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 5m/s), effective (alleviated subjective symptoms, improved tendon reflex, and NCV increased by at least 3m/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 I²-test.[24] The random-effect (RE) model was used to pool the data when heterogeneity was confirmed (P≤.10 or I²≥50% suggested significant heterogeneity among studies).[23] 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). | Score standard |
|---------------------------------------------------------------|----------------|
| Items                                         | 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 | |
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 were 30 or 60 mg/day, dosages of L administration were 160 or 600 mg/day, dosages of M administration were 1.5 or 3 mg/day, dosages of L administration were 30 or 60 mg/day, dosages of M administration were 1 mg or 0.5 mg/day.

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 study, 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 ($I^2 = 98\%$, $P = 0.0001$). F+M combination therapy for DPN enhanced the efficacy obviously compared with M treatment ($RR = 1.26$, 95% CI 1.17–1.35, $P < 0.0001$). Compared with L monotherapy, F+L combination therapy for DPN also increased the efficacy significantly ($RR = 1.27$, 95% CI 1.16–1.39, $P < 0.0001$). Figure 3 showed the funnel shape was not perfectly symmetrical, indicating a potential publication bias.

3.3. Median MNCV

Six trials involving a total of 587 patients measured median MNCV. Heterogeneity was significant for the analysis ($I^2 = 92\%$), 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, $P < 0.0001$) (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 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 ($I^2 = 99\%$, $P = 0.0008$). Compared with monotherapy, combination therapy increased median SNCV significantly (MD 6.71, 95% CI 1.77–11.65, $P = 0.008$). On sensitivity analyses, after excluding the study reported by Liang et al, 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 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 ($I^2 = 94\%$, $P < 0.0001$). Compared with monotherapy, combination therapy

Table 2

| Reference | Number | 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) |
|-----------|--------|-------------------|--------------------|---------------------|-----------------------------|-----------------------------|---------------------|-------------------------|
| Chang et al[19] | 36/30 | 62.5/59.5 | 46/23 | 2 | 1–15/15.1/16 | NR | 28 | F: 60 mg ivgtt M: 0.5 mg ivgtt M: 0.5 mg ivgtt |
| Liang et al[20] | 83/65 | 56.25/54.1 | 74/74 | NR | 9.3/9.1 | 4/4.4/4.1 | 28 | F: 60 mg ivgtt M: 0.5 mg ivgtt M: 0.5 mg ivgtt |
| Ren et al[21] | 34/24 | 31/26 | 63/62 | NR | 9.0/9.9/25 | NR | 21 | F: 30 mg ivgtt M: 0.5 mg ivgtt M: 0.5 mg ivgtt |
| Zhou[22] | 33/30 | 57.5/58.1 | 43/45 | NR | 7.8/8.3 | 3.5/3.7 | 30 | F: 60 mg ivgtt M: 0.5 mg ivgtt M: 0.5 mg ivgtt |
| Xue and Zhou[23] | 34/24 | 31/26 | 63/62 | NR | 9.0/9.9/25 | NR | 21 | F: 30 mg ivgtt M: 0.5 mg ivgtt M: 0.5 mg ivgtt |
| Dong and Zhang[24] | 30/30 | 60/60 | 36/34 | NR | 10/10 | 4/4.9 | 28 | F: 60 mg ivgtt M: 0.5 mg ivgtt M: 0.5 mg ivgtt |
| Liang et al[25] | 30/30 | 57.5/58.1 | 43/45 | NR | 7.8/8.3 | 3.5/3.7 | 30 | F: 60 mg ivgtt M: 0.5 mg ivgtt M: 0.5 mg ivgtt |
| Ren et al[26] | 34/24 | 31/26 | 63/62 | NR | 9.0/9.9/25 | NR | 21 | F: 30 mg ivgtt M: 0.5 mg ivgtt M: 0.5 mg ivgtt |
| Wang and Lu[27] | 34/24 | 31/26 | 63/62 | NR | 9.0/9.9/25 | NR | 21 | F: 30 mg ivgtt M: 0.5 mg ivgtt M: 0.5 mg ivgtt |
| Jiang et al[28] | 83/65 | 56.25/54.1 | 74/74 | NR | 9.3/9.1 | 4/4.4/4.1 | 28 | F: 60 mg ivgtt M: 0.5 mg ivgtt M: 0.5 mg ivgtt |
| Zhang[29] | 30/30 | 57.5/58.1 | 43/45 | NR | 7.8/8.3 | 3.5/3.7 | 30 | F: 60 mg ivgtt M: 0.5 mg ivgtt M: 0.5 mg ivgtt |
| Yuan[30] | 30/30 | 57.5/58.1 | 43/45 | NR | 7.8/8.3 | 3.5/3.7 | 30 | F: 60 mg ivgtt M: 0.5 mg ivgtt M: 0.5 mg ivgtt |
| Zhou[31] | 55/55 | 57.5/58.1 | 43/45 | NR | 7.8/8.3 | 3.5/3.7 | 30 | F: 60 mg ivgtt M: 0.5 mg ivgtt M: 0.5 mg ivgtt |
| Xue and Zhou[32] | 48/48 | 51.3/50.8 | 55/54 | NR | 11.3/11.2 | 3.8/3.7 | 14 | F: 60 mg ivgtt M: 0.5 mg ivgtt M: 0.5 mg ivgtt |
| Liang et al[33] | 30/30 | 57.5/58.1 | 43/45 | NR | 7.8/8.3 | 3.5/3.7 | 30 | F: 60 mg ivgtt M: 0.5 mg ivgtt M: 0.5 mg ivgtt |

DM = diabetes mellitus, DPN = diabetic peripheral neuropathy, F = fasudil, † = efficacy, ‡ = median MNCV, § = median SNCV, ‡ = peroneal MNCV, § = peroneal SNCV, im = intramuscular, iv = intravenous, ivgtt = intravenous infusion, L = lipic acid, M = methylcobalamin, NR = not report.
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 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
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\cite{18, 31} of which demonstrated that there were no side effects, the other 2\cite{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),\cite{15} local skin redness (2 cases),\cite{29} pain at the injection site (2 cases),\cite{29} emesis (1 case),\cite{11} fever (1 case),\cite{11} and constipation (1 case)\cite{15} in the combination therapy group, and pain at the injection site (2 cases),\cite{29} nausea (2 cases),\cite{11} emesis (1 case),\cite{15} constipation (1 case)\cite{15} in monotherapy group were reported.

4. Discussion

DPN, accompanied with diabetic microangiopathy in most cases,\cite{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.\cite{3, 33} 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.\cite{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.\cite{4, 38} Moreover, reduced expression of neurotrophic factors in diabetic patients might be involved in occurrence and progression of DPN.\cite{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 apoptotic neurodegeneration.\cite{12, 3} In addition, oxidative stress play crucial roles in the
Compared with the euglycemic condition, body shows greater oxidative stress and more NO and reactive oxygen species in neuron under hyperglycemia condition.\cite{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.\cite{6} F increases blood flow and oxygen supply to peripheral nervous system and accelerates NCVs by blocking platelet aggregation.\cite{7,41,42} F promotes Schwann cell proliferation and axon regeneration, and facilitates injured peripheral nerve repair.\cite{43–45} In addition, F can inhibit nerve cell apoptosis by reducing inflammatory factors and reactive oxygen species production.\cite{46,47} F can be used to prevent and treat cerebral vasospasm post-subarachnoid hemorrhage,\cite{48,49} dementia,\cite{50} DPN,\cite{15,17} and pulmonary arterial hypertension\cite{51} in clinical practice.

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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References
[1] Tesfaye S, Stevens LK, Stephenson JM, et al. Prevalence of diabetic peripheral neuropathy and its relation to glycemic control and potential risk factors: the EURODIAB IDDM Complications Study. Diabetologia 1996;39:1377–84.
[2] Valensi P, Giroux C, Seebold-Ghalayini B, et al. Diabetic peripheral neuropathy: effects of age, duration of diabetes, glycemic control and vascular factors. J Diabetes Complications 1997;11:27–34.
[3] Tesfaye S, Selvarajah D. Advances in the epidemiology, pathogenesis and management of diabetic peripheral neuropathy. Diabetes Metab Res Rev 2012;28:8–14.
[4] Cohen K, Shinkazh N, Frank J, et al. Pharmacological treatment of diabetic peripheral neuropathy. P T 2015;40:372–88.
[5] Yorek MA. Vascular impairment of epi neural arterics of the sciotic nerve: implications for diabetic peripheral neuropathy. Rev Diabet Stud 2015;12:13–28.
[6] Chen YC, Yuan TY, Zhang HF, et al. Fasudil evokes vasodilatation of rat mesenteric vascular bed via Ca(2+) channels and RhoROCK pathway. Eur J Pharmacol 2016;788:226–33.
[7] Kosumura A, Hamanaka J, Kawasaki K, et al. Fasudil and oxazole in combination show neuroprotective effects on cerebral infarction after murine middle cerebral artery occlusion. J Pharmacol Exp Ther 2011;338:377–44.
[8] Kuwabara S, Nakazawa R, Azuma N, et al. Intravenous methylcobalam in treatment for uremic and diabetic neuropathy in chronic hemodialysis patients. Intern Med 1999;38:472–5.
[9] Jiang DQ, Li MX, Wang Y, et al. Effects of prostaglandin E1 plus methylcobalamin alone and in combination with lipoic acid on nerve conduction velocity in patients with diabetic peripheral neuropathy: A meta-analysis. Neurosci Lett 2015;594:23–9.
[10] Nagamatsu M, Nickander KK, Schmelzer JD, et al. Lipoic acid improves nerve blood flow, reduces oxidative stress, and improves distal nerve conduction in experimental diabetic neuropathy. Diabetes Care 1995;18:1160–7.
[11] Ziegler D, Hanefeld M, Ruhnau KJ, et al. Treatment of symptomatic diabetic peripheral neuropathy with the anti-oxidant alpha-lipoic acid. A 3-week multicentre randomized controlled trial (ALADIN Study). Diabetologia 1995;38:1425–33.
[12] Bartkoski S, Day M. Alpha-lipoic acid for treatment of diabetic neuropathy. Am Fam Physician 2016;93:786.
[13] Ide H, Fujiya S, Asanuma Y, et al. Clinical usefulness of intrathecal injection of methylcobalamin in patients with diabetic neuropathy. Clin Ther 1987;9:183–92.
[14] Wang XT, Lin HX, Xu SA, et al. Lipoic acid combined with epalrestat versus lipoic acid in treating diabetic peripheral neuropathy: a meta-analysis. Zhongguo Yi Xue Ke Xue Yuan Xue Bao 2017;39:656–64.
[15] Wen ZD, Yang J, Chen ZM. Effects of fasudil therapy on the nerve conduction velocity in patients with diabetic peripheral neuropathy. Chin Prim Health Care 2017;3:81–2.
[16] Chang Q, Dai QX, Xu HN. Clinical efficacy of Rho kinase inhibitor and mecobalamin combination therapy in patients with diabetic peripheral neuropathy. Qinghui J Med 2011;4:17–9.
[17] Ren RX, Tian DZ, Wei XF, et al. Clinical observation of fasudil and lipoic acid combination therapy in the treatment of patients with diabetic peripheral neuropathy. China Prac Med 2015;10:139–40.
[18] Xie BQ, Zhou QM. Therapeutic effect of mecobalamin combined with fasudil in the treatment of patients with diabetic peripheral neuropathy. Chin J Gerontol 2012;32:949–50.
[19] Alberti KG, Zimmer PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part I: Diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 1998;15:539–53.
[20] Deng H, Yin J, Zhang J, et al. Meta-analysis of methylcobalamin alone and in combination with prostaglandin E1 in the treatment of diabetic peripheral neuropathy. Endocrine 2014;46:445–54.
[21] Xu Q, Pan J, Yu J, et al. Meta-analysis of methylcobalamin alone and in combination with lipoic acid in patients with diabetic peripheral neuropathy. Diabetes Res Clin Pract 2013;101:99–105.
[22] Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17:1–2.
[23] Moher D, Pham B, Jones A, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? Lancet 1998;352:609–13.
[24] Cochran WG. The combination of estimates from different experiments. Biometrics 1954;10:101–29.
[25] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–58.
[26] Dong SB, Zhang LX. Effect of combination therapy of fasudil and mecobalamin in the treatment of 83 patients with diabetic peripheral neuropathy, Chin J Med Drug Clin 2012;13:62–3.
[27] Li MY, Zou P, Lu W. Clinical observation of fasudil combined with mecobalamin in the treatment of 83 patients with diabetic peripheral neuropathy. Chin J Mod Drug Appl 2012;6:85–7.
[28] Liu YF. Lipoic acid injection and needle lipoic hydrochloride combination therapy for patients with diabetic peripheral nerve lesions caused by glucotoxic effects. World Latest Med Inform 2014;14:12–3.
[29] Wang RX, Lu YY. Clinical efficacy analysis of mecobalamin combined with fasudil for elderly patients with type 2 diabetes mellitus peripheral neuropathy. Chin J Prim Med Pharmac 2013;20:2692–3.
[30] Yang CH. Drug therapies and therapeutic effect evaluation for diabetic peripheral neuropathy. P T 2015;40:372–88.
[31] Yuan F. Analysis of mecobalamin combined with fasudil and improve nerve conduction velocity in patients with diabetic peripheral nerve effect. China Foreign Med Treat 2015;34:133–6, 9.
[32] Zhang JF. Therapeutic effect of fasudil combined with mecobalamin in treatment of diabetic peripheral neuropathy. China Contin Med Educ 2015;7:150–1.
[33] Zhou ML. Effect of mecobalamin and fasudil for the treatment of diabetic peripheral neuropathy. Chin Med 2010;30:10–1.
[34] Zhou ZN. Combined therapeutic effects of fasudil and mecobalamin in patients with diabetic peripheral neuropathy. Chin J Mod Drug Appl 2013;7:66–7.
[35] Zhang X, Fang C, Li X, et al. Clinical characteristics and risk factors of diabetic peripheral neuropathy of type 1 diabetes mellitus patients. Diabetes Care 2017;39:97–104.
[36] Li QR, Wang Z, Zhou W, et al. Epalrestat prevents against diabetic peripheral neuropathy by alleviating oxidative stress and inhibiting polyol pathway. Neural Regen Res 2016;11:455–51.
[37] Austas PS. Polysol pathway and diabetic peripheral neuropathy. Int Rev Neurobiol 2002;50:325–92.
[38] Jaiswal M, Divers J, Dabelea D, et al. Prevalence of and risk factors for diabetic peripheral neuropathy in youth with type 1 and type 2 diabetes: SEARCH for diabetes in youth study. Diabetes Care 2017;40:1226–32.
[39] Vincent AM, Russell JW, Low P, et al. Oxidative stress in the pathogenesis of diabetic neuropathy. Endocr Rev 2004;25:612–28.
[40] Greene DA, Stevens MJ, Obrosova I, et al. Glucose-induced oxidative stress and programmed cell death in diabetic neuropathy. Eur J Pharmacol 1999;375:217–23.
[41] Kanazawa Y, Takahashi-Fujigasaki J, Ishiwa S, et al. The Rho kinase inhibitor fasudil restores normal motor nerve conduction velocity in diabetic rats by assuring the proper localization of adhesion-related molecules in myelinating Schwann cells. Exp Neurol 2015;247:438–46.
[42] Sugiyama T, Shibata M, Kajiura S, et al. Effects of fasudil, a Rho-associated protein kinase inhibitor, on optic nerve head blood flow in rabbits. Invest Ophthalmol Vis Sci 2011;52:64–9.

[43] Pereira JA, Benninger Y, Baumann R, et al. Integrin-linked kinase is required for radial sorting of axons and Schwann cell remyelination in the peripheral nervous system. J Cell Biol 2009;185:147–61.

[44] Cheng C, Webber CA, Wang J, et al. Activated RHOA and peripheral axon regeneration. Exp Neurol 2008;212:358–69.

[45] Hiraga A, Kuwabara S, Doya H, et al. Rho-kinase inhibition enhances axonal regeneration after peripheral nerve injury. J Peripher Nerv Syst 2006;11:217–24.

[46] Madura T, Kubo T, Tanag M, et al. The Rho-associated kinase fasudil hydrochloride enhances neural regeneration after axotomy in the peripheral nervous system. Plast Reconstr Surg 2007;119:526–35.

[47] He Q, Li YH, Guo SS, et al. Inhibition of Rho-kinase by fasudil protects dopamine neurons and attenuates inflammatory response in an intranasal lipopolysaccharide-mediated Parkinson’s model. Eur J Neurosci 2016;43:41–52.

[48] Mutoh T, Kobayashi S, Tamakawa N, et al. Multichannel near-infrared spectroscopy as a tool for assisting intra-arterial fasudil therapy for diffuse vasospasm after subarachnoid hemorrhage. Surg Neurol Int 2011;2:68.

[49] Wu CT, Wong CS, Yeh CC, et al. Treatment of cerebral vasospasm after subarachnoid hemorrhage—a review. Acta Anaesthesiol Taiwan 2004;42:215–22.

[50] Kamei S, Oishi M, Takasu T. Evaluation of fasudil hydrochloride treatment for wandering symptoms in cerebrovascular dementia with 31P-magnetic resonance spectroscopy and Xe-computed tomography. Clin Neuropharmacol 1996;19:428–38.

[51] Jiang R, Ai ZS, Jiang X, et al. Intravenous fasudil improves in-hospital mortality of patients with right heart failure in severe pulmonary hypertension. Hypertens Res 2015;38:539–44.

[52] Rikizake Y, Kim HH, Huang Z, et al. Inhibition of Rho kinase (ROCK) leads to increased cerebral blood flow and stroke protection. Stroke 2005;36:2251–7.