Effects of Methylcobalamin on Diabetic Peripheral Neuropathy: A Systematic Review

JIA Hai-yan[1], TIAN Hao-ming[1]*, WEI Dong[2]

1. Division of Endocrinology, Department of Internal Medicine, West China Hospital, Sichuan University, Chengdu 610041, China;

2. Division of Endocrinology, The Second People's Hospital of Chengdu, Chengdu 610017, China

【**Abstract**】 **Objective** To review systematically whether there is enough existing evidence that methylcobalamin is effective and safe in the treatment of the patients with diabetic peripheral neuropathy. **Methods** A Cochrane systematic review of all relevant randomized or quasi-randomized controlled trials of methycobalamin for diabetic peripheral neuropathy was performed. Clinical trials were searched from Cochrane Controlled Trials Register (Issue 4, 2003), MEDLINE (January 1966 to January 2004), EMBASE (January 1980 to January 2004), the Chinese Biological Medicine Database (1978 to January 2004), the Chinese Science and Technology Journal Full-text Database (1989 to January 2004) and references of all included trials. The selection of studies, data extraction and assessment of methodological quality were performed independently by two reviewers. The following outcomes were assessed: effectiveness of clinical signs and symptoms, sensory nerve and motor nerve conduction velocities and serious adverse events of methylcobalamin. **Results** Thirty randomized clinical trials including 1 949 patients met the inclusion criteria. The quality of the most included trials was of low level. The "funnel plot" of the comparison of thirteen studies of methylcobalamin with other B Vitamins studies showed symmetry, which indicated less possible publication bias and the result was partly reliable, but it could not indicate the whole publication biases. The results of meta-analysis indicated that methylcobalamin showed significantly positive effects on the improvement of the signs and symptoms of peripheral neuropathy, and the effects were better than the other vitamin B agents. The increase of some nerves conduction velocities by methylcobalamin was better than by the other vitamin B. No serious adverse events were observed during the treatment period. **Conclusions** Methylcobalamin appears to be a safe and effective treatment on diabetic peripheral neuropathy. However, the evidence is not strong because of the low quality of most trials. Rigorously designed, randomized, double-blinded, placebo-controlled trials of methylcobalamin for diabetic peripheral neuropathy are needed to further assess the effect.

【**Key words**】 Methylcobalamin; Diabetic peripheral neuropathy; Randomized controlled trials; Quasi-randomized controlled trials; Systematic review

【CLC number】R587.205.3;R745.053;R977.22 【Document code】A 【Article ID】1672-2531(2005)08-0609-10

Background

Diabetic peripheral neuropathy is one of the most common complications of diabetes mellitus, the incidence of which is up to about 60% - 90%. About 40% - 80% patients whose duration is over 10 years suffer from diabetic neuropathy[1]. Its typical clinical manifestations include numbness, tingling, absent knee tendon reflex, loss of deep sensibility, development of ulcer and infection in the feet and eventually gangrene often resulting in amputations[2]. This has a serious influence on the quality of life of patients. However, the pathogenesis of diabetic neuropathy has still not been very clear. Now lots of studies have demonstrated that long-standing serious hyperglycemia was the predominant cause which would result in metabolic disorder, microcirculation abnormality and autoimmune disorder[1]. Therefore, intensive control of blood glucose has been regarded as the fundamental treatment of diabetic neuropathy. But it has been noted that the nerve function has not been completely improved in some patients and there are more chances of hypoglycemia. So other treatments must be combined with the intensive control of blood glucose.

Recently some randomized clinical trials have reported on the effect of methylcobalamin on diabetic peripheral neuropathy. Methylcobalamin has been linked to claims to be effective in the relief of clinical symptoms and signs of diabetic peripheral neuropathy, the increase of the nerve conduction velocity and improvement of quality of life. These clinical trials were characterized by small-sample size, however, and it was not clear whether the evidence of effect on treating diabetic neuropathy was sufficient. This review aims to analyze systematically all the randomized controlled trials of methylcobalamin for treating diabetic peripheral neuropathy to provide the best available evidence for clinical practice and to guide future research.

Methods

Criteria for considering studies for this review

Types of studies

Truly or quasi-randomized controlled clinical trials comparing methylcobalamin with placebo or routine treat-

Date received: 2005-05-16 Date revised: 2005-07-15

Biography: JIA Hai-yan, female (1977-), doctoral graduate student, resident doctor, research interest: the treatment of diabetes mellitus.

* Correspondence author

ment or other vitamin B in patients with diabetic peripheral neuropathy were eligible for inclusion. Quasi-randomization refers to allocation using methods which are intended to be random but may not be such as alternation, sequence of admission, case record numbers, dates of birth or day of the week.

Types of participants

Trials which included participants of any age or sex with diabetes mellitus and diabetic peripheral neuropathy were included. The patients must conform to the following criteria:

① The definition of diabetes mellitus must conform to the diagnostic criteria of the World Health Organization;

② With neuropathic symptoms and signs such as: loss of sensation, numbness, tingling, extremity pain, absent or reduced tendon reflex etc;

③ Damaged motor or sensory nerve conduction velocity;

Types of interventions

① Treatment group using methylcobalamin (any types, dose, usage and period) plus routine treatment/some medicine vs. control group using only routine treatment/the same medicine or placebo;

② Treatment group using methylcobalamin vs. an other B vitamin;

Notes: the routine treatment refers to blood glucose control by administering oral hypoglycemic agents and/or insulin and not the specific medicine to treat peripheral neuropathy. Some medicine means other drug but not methylcobalamin such as other B vitamin or Chinese medical herbs.

Types of outcome measures

① The total effect rate of therapy that means the rate of improvement of the clinical symptoms and signs after treatment;

② Peripheral nerve conduction velocity (motor or sensory nerve);

③ Serious adverse events during treatment period.

Search strategy for identification of studies

We searched the following electronic databases: ① Cochrane Central Register of Controlled Trials (Cochrane Library, Issue 4, 2003); ② MEDLINE (January 1966 to January 2004); ③ EMBASE (January 1980 to January 2004); ④ CBM (Chinese Biomedical database, 1978 to January 2004); ⑤ Chinese Science and Technology Journal Full-text Database (1989 to January 2004).

We searched the following Chinese journal by hand: *Chinese Journal of Neurology and Psychiatry*, *Chinese Journal of Endocrinology and Metabolism*, *Chinese Journal of Internal Medicine*, *Chinese Journal of Integrated Traditional and Western Medicine*, *Chinese Journal of Diabetes*, *Chinese Journal of Practical Internal Medicine*, *Journal of Clinical Neuropathy*, *Journal of Clinical Internal Medicine*, *Shanghai Journal of Traditional Chinese Medicine*, *China Journal of Chinese Material Medicine*, *Journal of Traditional Chinese Medicine*, *New Journal of Traditional Chinese Medicine*, *Chinese Journal of the Chinese with Modern Medicine*, *and Progress in Japanese Medicine*, *Japan-China Medical Communication*. All of the journals were searched from the first issue to January 2004.

The search terms used were diabetes, neuropathy, peripheral neuropathy, methycobal, methylcobalamin, CH_3-B_{12}, methylvitamin B_{12}.

Methods of the review

Study selection

Titles, abstracts and full texts identified from the register were examined independently by two reviewers. Studies for inclusion were selected by two reviewers and any disagreements were reported and resolved by discussion or with reference to a third party.

Quality assessment

The methodological quality of trials was evaluated according to the following criteria: allocation concealment, secure method of randomization, patient and observer blinding, losses to follow-up and intention-to-treat analysis. We graded these A: adequate, B: unclear, C: inadequate, D: not done. We also considered adequacy of maintaining and reporting metabolic control in both groups and reliability of outcome measures. Quality assessment was performed by two reviewers independently and disagreements were reported and resolved by a third reviewer.

Data extraction

Data on patients, methods, interventions, outcomes and results were extracted by two reviewers independently using a data extraction form. Missing data were obtained from the authors whenever possible.

Data synthesis

RevMan 4.2 was employed for meta-analysis. The results were reported using odds ration for dichotomous data and weighted mean differences for continuous outcomes. Both were reported using 95 percent confidence intervals (CI). Heterogeneity between trials was tested using a standard Chi-squared test. If there was no heterogeneity, a fixed effects model was used. If heterogeneity was found, a random effects model was used. For dichotomous data intention-to-treat analysis was performed if there was withdrawal or dropout. Sensitivity analysis was applied to explore the influence of the following factors on effect size: 1. Repeat the analysis excluding the high quality studies; 2. Repeat the analysis excluding the studies not using blinded assessment of outcomes and analyses of withdrawal/dropout. Publication bias was examined using a funnel plot.

Results

Description of the included studies

Thirty randomized clinical trials including 1 949 patients met the inclusion criteria. Among these trials there were two studies[3,4] carried out respectively in Singapore and Saudi Arabia. Other trials were carried out in China. Details of authors, year of publication, the number of patients, age, intervention and comparators, duration, methodological quality and allocation concealment are given in Table 1 by types of intervention.

Table 1 Characteristics of included studies

Study	Number (T/C)	Age (years)	Intervention	Control	Duration (day)	Method quality	Allocation concealment
Pang M[6]	58(28/30)	T: 48 C: 46	M	$VitB_1$ + $VitB_{12}$	30	C	B
Pang JH[7]	50(30/20)	T: 55 C: 54	M	$VitB_1$ + $VitB_{12}$	60	C	B
Wu DH[8]	270(170/100)	T: 48.5 C:46.8	M	$VitB_1$, B_{12}, B_6	30	C	B
Jiang YQ1[9]	55(30/25)	40 - 73	M	$VitB_1$, B_6	60	B	B
Jiang YQ2[9]	57(32/25)	40 - 73	M	$VitB_1$, B_6	60	B	B
Meng LQ[10]	58(30/28)	32 - 73	M	$VitB_1$	10 - 30	C	B
Ma SP[11]	64(34/30)	24 - 70	M	$VitB_1$	28	C	B
Du QP[12]	46(23/23)	43 - 67	M	$VitB_{12}$	90	C	B
Kang SQ[13]	54(36/18)	24 - 78	M	$VitB_{12}$	75	C	B
Gan HX[14]	52(26/26)	30 - 83	M	$VitB_{12}$	21	C	B
Yang RL[15]	69(36/33)	>60	M	$VitB_{12}$	56	C	B
Shi KX1[16]	50(30/20)	42 - 74	M	$VitB_1$, B_2	28	C	B
Shi KX2[16]	53(33/20)	42 - 74	M	$VitB_1$, B_2	28	C	B
Li XF[17]	40(20/20)	/	M	$VitB_{12}$	28	C	B
Xu J[18]	56(30/26)	49.2	M	$VitB_1$, B_{12}, B_6	28	C	B
Si XJ[19]	64(32/32)	29 - 73	M	$VitB_1$	28	C	B
Zhang SP[20]	24(12/12)	48 - 67	M	$VitB_{12}$	60	B	B
Xu Z[21]	22(11/11)	40 - 67	M	$VitB_1$	21	B	C
Li GW[22]	108(62/46)	/	M	$VitB_{12}$	60	B	B
Feng LH[23]	78(38/40)	T:57 C:55	PGE1 + M	PGE1	56	C	B
Cen HY[24]	78(37/41)	T:55.7 C:54.9	Fushekangshuangmei + M	Fushekangshuangmei	60	C	B
Shen YF[25]	84(42/42)	44 - 78	PGE1 + M	PGE1	14	C	
Zhu XP[26]	52(32/20)	37 - 70	PGE1 + M	PGE1	28	C	B
Xu XX[27]	60(29/31)	57	Puerarin + M	Puerarin	15	C	B
Zhang XJ[28]	51(35/16)	13 - 79	Xueshuangtong + M	Xueshuangtong	14	C	B
Li FS[29]	58(30/28)	T:61.2 C:64.6	Erigeron + M	Erigeron	28	C	B
Zhong SM[30]	43(35/8)	T:58 C:59	Xueshuangtong + M	Xueshuangtong	14	B	B
Yu FL[5]	60(30/30)	27 - 78	M	R	42	C	B
Devathasan[3]	42(21/21)	/	M	Placebo	84	C	B
Yaqub-BA[4]	50(21/22)	/	M	Placebo	120	C	B

T = treatment group; C = control group; M = methylcobalamin; R = routine treatment

Methylcobalamin was compared with placebo in two studies[3,4]; compared with only routine treatment in one study[5]; compared with other B vitamins in nineteen studies[6-22]; and methylcobalamin plus some other medicinal agent was compared with the same medicinal agent in eight studies[23-30]; Because both of the two groups used the same medicine, the effect of treatment was attributed to methylcobalamin. All the included studies administered diet therapy and oral antihyperglycemic drugs and/or insulin to achieve better control of blood glucose. Baseline characteristics were reported statistically in fourteen studies[8,10-11,14-15,18-20,23-26,28,30]. Among the included studies, twelve studies[3,8-12,14-16,18,20,25] only mentioned that no obvious adverse events were observed; four studies[8,19,22,24] described the adverse events in detail and eleven studies[6-7,13,17,20-21,23,27-30] didn't report the adverse events. Only one study[30] followed up patients after the end of the trials.

Quality of the included studies

Among the thirty studies, no study reported the method of randomization. We contacted with all the authors but no further information was provided. The allocation concealment of all the included studies was unclear. Three studies[4,9,20] were double-blinded and one single-blind study[22]. But none of the studies described the method of blinding in detail. Four studies[3,4,8,19] reported the withdrawals or dropouts during trials and it was not clear whether the author undertook an intention-to-treat analysis.

Description of the results of Meta-analysis

Methylcobalamin vs routine treatment

Effects on the total effect rate of therapy

Seven studies[5,23-24,26-28,30] provided this related data. Among these studies, one study[5] compared methylcobalamin plus routine treatment with only routine treatment; another six studies[23-24,26-28,30] compared methylcobalamin plus some medicine with the same medicine. Heterogeneity was found among the seven trials ($P=0.02$). Because heterogeneity existed, a random effects model was performed. There was significantly statistical difference in effects on the clinical symptoms and signs between two groups. Methylcobalamin significantly improved the clinical signs and symptoms (OR = 11.47, 95% CI 4.05 to 32.54, $P<0.000\,01$) (Fig. 1). At the same time we made a sub-analysis of the six trials. No heterogeneity was found among these six trials ($P=0.06$). There was significantly statistical difference ($P<0.000\,01$), Peto OR = 6.35, 95% CI 3.50 to 11.54, suggested methylcobalamin could obviously improve the clinical symptoms and signs.

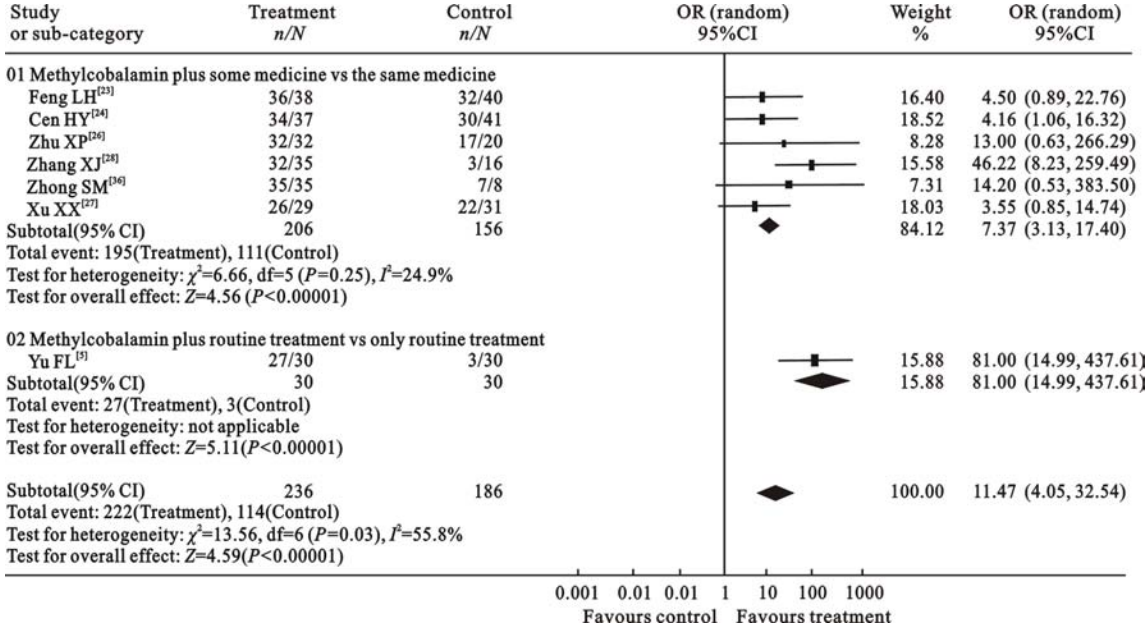

Fig 1 Comparison of effects of methylcobalamin with that of routine treatment or placebo on the total effect rate of therapy for diabetic peripheral neuropathy

Effects on sensory nerve conduction velocity (SNCV)

We performed subgroup meta-analysis according to different sensory nerves because different sensory nerves had different conduction velocity.

① Effects on peroneal sensory nerve conduction velocity

Two studies[5,26] provided this outcome. Because heterogeneity was found between these two studies ($P=0.001$), we performed a random effects model. Meta-analysis results showed that WMD = 5.15, 95% CI −1.03 to 11.30, $P=0.10$, no significantly statistical difference. Therefore, there was no sufficient evidence

of the effects on improving peroneal sensory nerve conduction velocity.

② Effects on median sensory nerve conduction velocity

Two studies[3,26] provided this outcome. Withdrawals or dropouts occurred in one study[3]. No heterogeneity was found between two studies ($P = 0.18$), WMD = 1.65, 95% CI −0.25 to 3.55, $P = 0.09$, no significantly statistical difference was found. Therefore, there was no sufficient evident to verify the effects of improving median sensory nerve conduction velocity.

Effects on motor nerve conduction velocity (MNCV)

① Effects on median motor nerve conduction velocity

Two studies[3,26] provided this outcome. Withdrawals or dropouts occurred in one study[3]. Heterogeneity was found between two studies ($P = 0.01$). So we performed a random effects model analysis. The results showed that WMD = 0.35, 95% CI −4.15 to 4.86, $P = 0.88$, no significantly statistical difference was found and there was no sufficient evidence to verify the effect of improving median motor nerve conduction velocity.

② Effects on peroneal motor nerve conduction velocity

Two studies[3,26] provided this outcome. Withdrawals or dropouts occurred in one study[3]. Heterogeneity was found between two studies ($P = 0.03$). So we performed a random effects model. The results showed that WMD = 1.31, 95% CI −2.89 to 5.51, $P = 0.54$, no significantly statistical difference was found and there was no sufficient evidence to verify the effect of improving peroneal motor nerve conduction velocity.

③ Effects on tibial motor nerve conduction velocity

Two studies[3,5] provided this outcome. No heterogeneity was found between two studies ($P = 0.26$). The results showed: WMD = −1.48, 95% CI 3.16 to 0.20, $P = 0.08$, no significantly statistical difference. So there was no sufficient evidence to verify the effect of improving tibial motor nerve conduction velocity.

Methylcobalamin vs other B vitamins

Effects on the total effect rate of therapy

Thirteen studies[6-10,12-13,16,18-19,21] provided this outcome. One study[19] reported the withdrawals or dropouts. We performed intention-to-treat analysis. No heterogeneity was found among these studies ($P = 0.79$). The results showed that Peto OR = 12.19, 95% CI 9.20 to 16.14, $P < 0.000\,01$. So methylcobalamin was superior to other B vitamins in improving the clinical symptoms and signs (Fig 2).

Effects on sensory nerve conduction velocity

① Effects on median sensory nerve conduction velocity

Five studies[16,16-19] provided this outcome. Because heterogeneity was found among these five studies ($P < 0.000\,01$), we performed a random effects model analysis. The results showed: WMD = 4.53, 95% CI 1.99 to 7.07, $P = 0.000\,5$. It was verified that methylcobalamin was superior to other B vitamins in improving median sensory nerve conduction velocity (Fig 3).

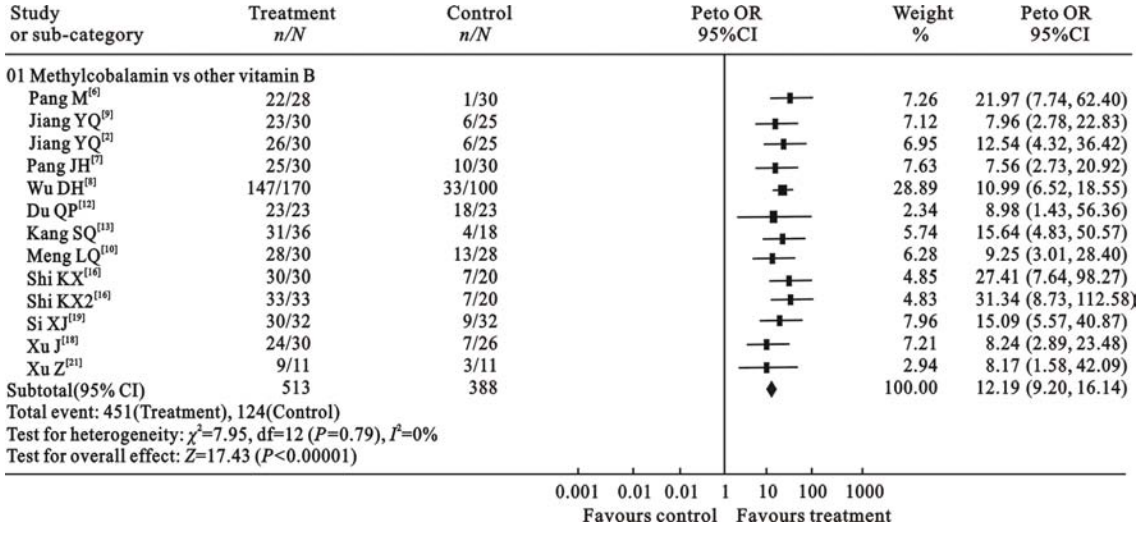

Fig 2 Comparison of effects of methylcobalamin with that of other B vitamin on the total effect rate of therapy for diabetic peripheral neuropathy

② Effects on peroneal sensory nerve conduction velocity

Three studies[18-20] provided this outcome. No heterogeneity was found among these three studies ($P = 0.60$). The results showed: WMD = 4.19, 95% CI 2.53 to 5.84, $P < 0.000\,01$. So methylcobalamin was superior to other B vitamin in improving peroneal sensory nerve conduction velocity (Fig 4).

③ Effects on common peroneal sensory nerve conduction velocity

Two studies[16,16] provided this outcome. No heterogeneity was found between the two studies ($P =$

0.66). The results of meta-analysis showed that WMD = 6.49, 95% CI 2.46 to 10.52. The difference was statistically significant ($P = 0.002$) and methylcobalamin was superior to other B vitamin in improving common peroneal sensory nerve conduction velocity.

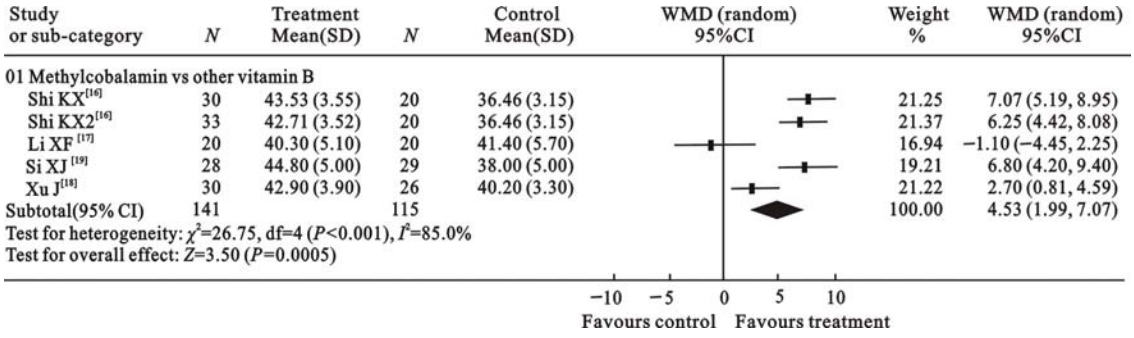

Fig 3 Comparison of effects of methylcobalamin with that of other B vitamin on median sensory nerve conduction velocity

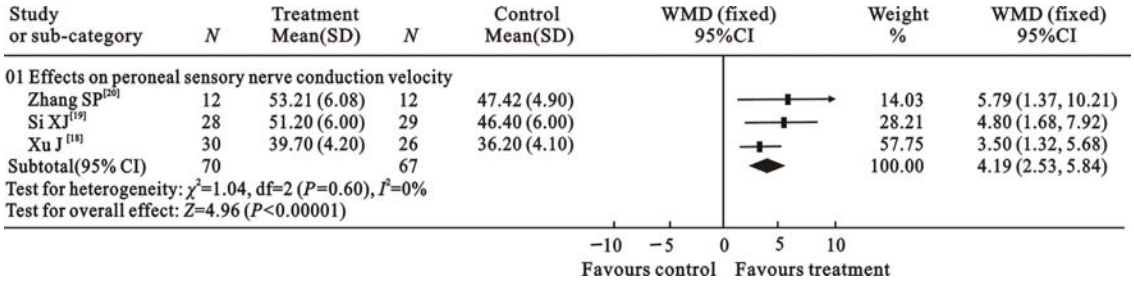

Fig 4 Comparison of effects of methylcobalamin with that of other B vitamin on peroneal sensory nerve conduction velocity

Effects on motor nerve conduction velocity

① Effects on median motor nerve conduction velocity

Seven studies[12,12,16,16-19] provided the concrete data. Because heterogeneity was found among these studies ($P < 0.000\ 01$), we performed a random effects model analysis. The results showed: WMD = 3.63, 95% CI 1.48 to 5.78. There was significantly statistical difference between the two groups ($P = 0.000\ 9$) and it was verified that methylcobalamin was superior to other B vitamin in improving median motor nerve conduction velocity (Fig 5).

② Effects on tibial motor nerve conduction velocity

Three studies[12,12,17] provided the concrete data. Because heterogeneity was found among these three studies ($P = 0.01$), we performed a random effects model analysis. The results showed: WMD = 5.35, 95% CI 2.18 to 8.52. Difference between the two groups was significantly statistical ($P = 0.000\ 9$) and methylcobalamin was superior to other B vitamin in improving tibial motor nerve conduction velocity (Fig 6).

③ Effects on common peroneal motor nerve conduction velocity

Four studies[16,16,19,20] provided the concrete data. No heterogeneity was found among the four studies ($P = 0.76$). The results showed that WMD = 0.98, 95% CI −0.12 to 2.07. Difference between the two groups was no statistical significance ($P = 0.08$). Methylcobalamin was similar to other B vitamins in improving common peroneal motor conduction velocity (Fig 7).

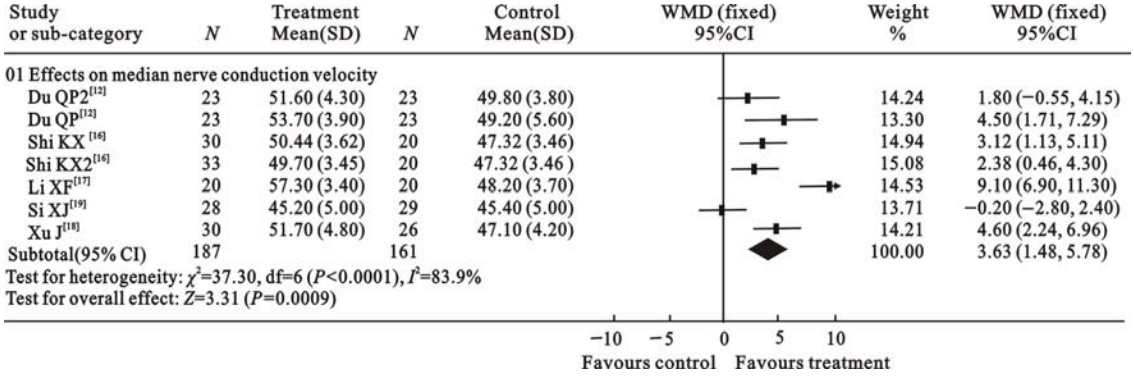

Fig 5 Comparison of effects of methylcobalamin with that of other B vitamin on median motor nerve conduction velocity

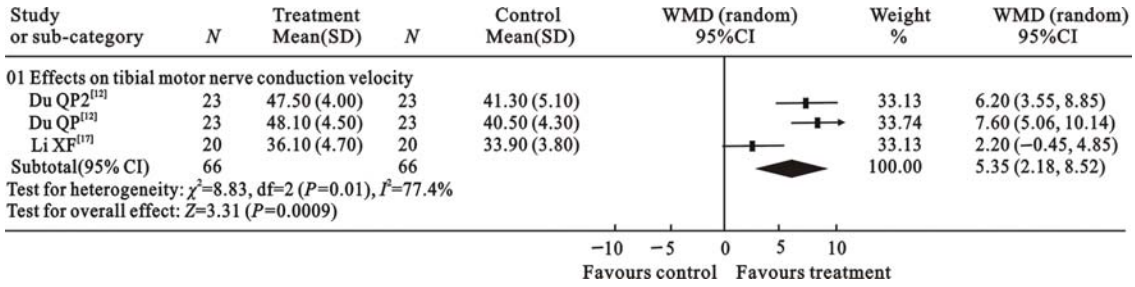

Fig 6 Comparison of effects of methylcobalamin with that of other B vitamin on tibial motor nerve conduction velocity

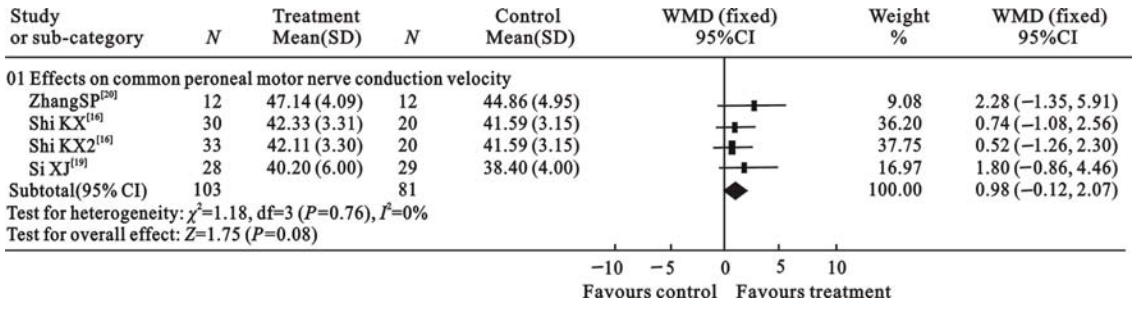

Fig 7 Comparison of effects of methylcobalamin with that of other B vitamins on common peroneal motor nerve conduction velocity

Serious adverse events during treatment period

There are no data for this comparison because all studies did not report serious adverse events in detail. So in this review we didn't compare the rate of serious adverse events.

Sensitivity analysis

Because all included studies were of poor methodological quality, the sensitivity analysis in which the studies with high methodological quality and blind method were excluded could not be carried out in this review.

Publication biases

In this review the comparison of methylcobalamin with other B vitamins showed that methylcobalamin was superior to other B vitamins and the "funnel plot" showed symmetry indicating less possible publication bias (Fig 8).

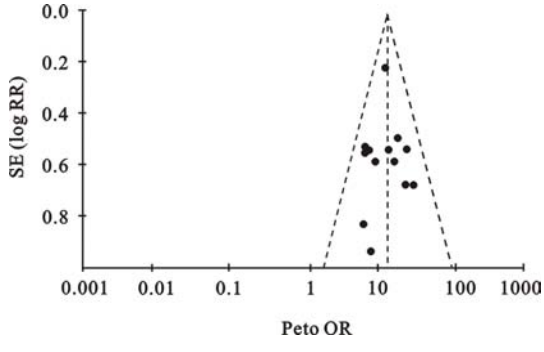

Fig 8 The "funnel plot" of the comparison of effects of methylcobalamin with that of other B vitamin on the total effect rate

Discussion

In an animal study Watanable T *et al.* [31] found that the transport velocity of axoplasm of STZ diabetic rats was lowered by 50%. Methylcobalamin could promote the protein synthesis, normalize the transport of structure protein of the axis and recover the axoplasm transportation. Zhang *et al.* [32] found that the threshold of heat-pain in the treated diabetic rats was significantly lower than that of the untreated diabetic group ($P<0.01$). The number and density of myelinated nerve fibers, the myelin sheath size and the axon size were significantly higher in the methylcobalamin treated diabetic rats than in the untreated rats ($P<0.001$). These findings suggested that methylcobalamin had some effects in the prevention and treatment of peripheral neuropathy in diabetic rats.

This systematic review identified thirty studies (1 949 patients) all of which met the inclusion criteria and were truly or quasi-randomized controlled clinical trials. All the patients participating in the studies were suffering from diabetic peripheral neuropathy. This systematic review did not include autonomic neuropathy. So the outcome analysis only applies to diabetic peripheral neuropathy.

The results of meta-analysis show that methylcobalamin can improve the clinical symptoms and signs of diabetic peripheral neuropathy. But at present no compelling evidence shows that methylcobalamin can accelerate the peroneal SNCV, median SNCV, median MNCV and tibial MNCV. Methylcobalmin is superior to other B vitamins in improving clinical symptoms and signs and in accelerating median SNCV, peroneal SNCV, common peroneal SNCV, median MNCV, tibial MNCV. But methylcobalamin is similar to other B vitamins in improving the common peroneal motor nerve conduction velocity.

Because not all the thirty studies reported serious adverse events, this systematic review did not analyze the rate of the serious adverse events of methylcobalamin.

Most of the studies included in this review had poor methodological quality. These studies didn't report the design, the randomization and the conceal of randomized allocation but only mentioned randomized allocation. There was not enough information to judge whether the studies were randomised appropriately. Most studies were of small sample size and didn't describe withdrawals or dropouts. Even if the study refered to the withdrawal or dropout it didn't explain whether they performed the intention-to-treat analysis.

The treatment of diabetic peripheral neuropathy aims to improve the quality of life of the patients, to prevent the nerve from being damaged further and to prevent the corresponding complications such as diabetic foot. Now the main outcome measures observed by most clinical studies are laboratory measurements-intermediate endpoints such as nerve conduction velocity, the incidence of clinical symptoms and signs. Few studies take the endpoints to evaluate the effects. The endpoints include the incidence of diabetic foot and amputation. Recently some clinical trials evaluate the clinical symptoms and signs by quantitative tables such as NSS (neuropathy symptom score)[33], TSS (total symptom score)[34]. Some trials use the relatively objective outcomes such as NCV (nerve conduction velocity) and QST (quantitative sensory testing)[35]. But these outcome measurements are still intermediate endpoints. In this systematic review the treatment effects was estimated by using the intermediate endpoints.

This systematic review cannot reach firm conclusions about the safety of methylcobalamin because all the included studies are short-duration, lack follow-up data and do not report the adverse event sufficiently. Some trials reported the adverse events of methylcobalamin: dizziness, malaise of stomach and allergy etc.

The "funnel plot" of the six studies of comparison of methylcobalamin plus some other medicines with the same medicine is asymmetrical. The reasons may be publication bias and the lower quality of methodology. It also suggested that some negative studies were not published. Moreover, the asymmetrical distribution may be related to the difference of the treatment methods, duration, small-sample and so on.

When we compared the effects of methylcobalamin with that of routine treatment and the effects of methylcobalamin with that of other B vitamins, heterogeneities were found among some studies. The possible causes were attributed to interference, evaluation criteria, treatment duration, degree of the disease, duration of the disease and so on.

This systematic review suggests that methylcobalamin can improve the clinical symptoms and signs of diabetic peripheral neuropathy and is superior to other B vitamins; methylcobalamin is superior or similar to other B vitamins in accelerating conduction velocity of some nerves. Due to the questions mentioned above, the existed evidence cannot sufficiently verify the effects of methylcobalamin on diabetic peripheral neuropathy. Methylcobalamin may be a potential therapy. Rigorously designed, randomized, double-blinded, placebo-controlled trials of methylcobalamin for diabetic peripheral neuropathy are needed to further assess the effect.

References

1 Greene DA, Sima AAF, Stevens MJ, Feldman EL, Lattimer SA. Complication: neuropathy, pathogenetic consideration[J]. *Diabetes Care*, 1992; 15 (12): 1902-1925.

2 Wang RB, Liu XZ. Pathogenesis of diabetic neuropathy[J]. *Journal of China-Japan Friendship Hospital*, 1998; 12 (1): 87.
汪仁斌, 刘兴洲. 糖尿病神经病的发病机制[J]. 中日友好医院学报, 1998; 12(1): 87.

3 Devathasan G, Teo WL, Mylvaganam A, Thai AC, Chin JH. Methylcobalamin in chronic diabetic neuropathy. A double-blind clinical and electrophysiological study[J]. *Clin Trials J*, 1986; 23(2): 130-140.

4 Yaqub BA, Siddique A, Sulimani R. Effects of methylcobalamin on diabetic neuropathy[J]. *Clin Neurol Neurosurg*, 1992; 94(2): 105-111.

5 Yu FL, Xu FJ, Yu FQ, Wang YZ. Effects of methylcobalamin on diabetic peripheral neuropathy: analysis of 32 cases[J]. *Herald of Medicine*, 2001; 20(9): 577.
于凤玲, 徐方江, 于凤泉, 王艳芝. 甲钴胺治疗糖尿病周围神经病变 30 例[J]. 医药导报, 2001; 20(9): 577.

6 Pang M. Effects of methylcobalamin on diabetic peripheral neuropathy [J]. *Strait Medicine*, 1997; 9(3): 32.
庞明. 弥可保对糖尿病周围神经病变疗效观察[J]. 海峡药学, 1997; 9(3): 32.

7 Pang JH, Kang SQ, Wang Y. Clinical observation of effects of methylcobalamin on diabetic peripheral neuropathy[J]. *Hebei Medicine*, 1998; 4(1): 87.
庞建华, 康胜群, 王燕. 弥可保治疗糖尿病周围神经病变临床观察[J]. 河北医学, 1998; 4(1): 87.

8 Wu DH, Zhao HY, Liu YH, Shi XQ. Clinical observation of effects of methylcobalamin on diabetic peripheral neuropathy[J]. *Harbing Medical Journal*, 1998; 18(3): 13-14.
吴东红, 赵环宇, 刘岳鸿, 史秀琴. 弥可保治疗糖尿病周围神经病变的临床观察[J]. 哈尔滨医药, 1998; 18(3): 13~14.

9 Jiang YQ, Liu GL, Wang QY, Wang YZ. Effects of methylcobalamin on diabetic peripheral neuropathy[J]. *Liaoning Medical Journal*, 1998; 12(2): 100-101.
姜雅秋, 刘国良, 王秋月, 王玉珍. 弥可保治疗糖尿病周围神经病变的疗效观察[J]. 辽宁医学杂志, 1998; 12(2): 100~101.

10 Meng LQ. Effects of methylcobalamin on diabetic peripheral neuropathy[J]. *Journal of ZhenJiang Medical College*, 1999; 9(1): 97-98.
孟丽琴. 弥可保对糖尿病周围神经病变的疗效. 镇江医学院学报, 1999; 9(1): 97~98.

11 Ma SP, Zhao ZG, Liu WH, Wen SL, Lu P. Effects of mecobalamin on latent period of somatosensory evked potential of diabetic peripheral neuropathy[J]. *Chinese Journal of practical internal medicine*, 1999; 19(7): 425-426.
马书平, 赵志刚, 刘卫红, 文世林, 鲁平. 甲钴胺对糖尿病周围神经病变体感诱发电位潜时的影响[J]. 中国实用内科杂志, 1999; 19(7): 425~426.

12 Du QP, Zhang FH, Wang XG, Zhao J. Clinical observation of effects of methylcobalamin on diabetic peripheral neuropathy[J]. *Qinghai Medical Journal*, 1999; 29(3): 23-24.
杜庆萍, 张福华, 王旭光, 赵颉. 弥可保治疗糖尿病周围神经病

变临床观[J]. 青海医药杂志, 1999; 29(3): 23～24.

13 Kang SQ, Zhi ZJ. Clinical observation of effects of methylcobalamin on diabetic peripheral neuropathy[J]. *Modern Journal of Integrated Traditional Chinese and Western Medicine*, 1999; 8(12): 2067.
康胜群, 支忠继. 弥可保治疗糖尿病周围神经病变疗效观察[J]. 现代中西医结合杂志, 1999; 8(12): 2067.

14 Gan HX, Chang YL, Chen HX, Li WX. Clinical observation of effects of methylcobalamin on diabetic peripheral neuropathy[J]. *Acta Academiae Medicinae Jiangxi*, 2000; 40(4): 102, 104.
甘华侠, 昌玉兰, 陈惠贤, 李雯霞. 弥可保治疗糖尿病周围神经病变的疗效观察. 江西医学院学报, 2000; 40(4): 102, 104.

15 Yang RL, Li L, Lv LL, Xiangjie, Zhaoxiangdong. Clinical observation of effects of mecobalamin on older diabetic patients with peripheral neuropathy[J]. *Acta Academiae Medicinae Xuzhou*, 2000; 20(6): 468－469.
杨荣礼, 李励, 吕丽丽, 项洁, 赵向东. 甲钴胺治疗老年糖尿病周围神经病变的临床观察[J]. 徐州医学院学报, 2000; 20(6): 468～469.

16 Shi KX. Effects of methylcobalamin on diabetic peripheral neuropathy: analysis of 63 cases[J]. *Acta Academiae Medicinae Jinzhou*, 2000; 21(1): 39－40.
施克新. 弥可保治疗糖尿病周围神经病变 63 例. 锦州医学院学报, 2000;21(1):39～40.

17 Li XF, Hu Q, Zhu DJ. Clinical trial of mecobalamin in diabetic peripheral neuropathies[J]. *Chinese Journal of Primary Medicine and Pharmacy*, 2001; 8(5): 452－453.
李雪锋, 胡清, 朱大菊. 甲钴胺治疗糖尿病周围神经病变的临床评价[J]. 中国基层医药, 2001; 8(5): 452～453.

18 Xu J, Sun YB. Effects of methylcobalamin on diabetic peripheral neuropathy: analysis of 56 cases[J]. *Chinese Journal of Clinical Rehabilitation*, 2002; 6(7): 1031.
徐静, 孙艳波. 弥可保治疗糖尿病周围神经病 56 例疗效观察[J]. 中国临床康复, 2002; 6(7): 1031.

19 Si XJ. Effects of mecobalamin on diabetic peripheral neuropathy: analysis of 28 cases[J]. *Henan Journal of Practical Nervous Disease*, 2002; 5(3): 55－56.
司献军. 甲钴胺治疗糖尿病周围神经病变 28 例观察[J]. 河南实用神经疾病杂志, 2002; 5(3): 55～56.

20 Zhang SP, Lu JM, Pan CY. Effects of methylcobalamin on diabetic peripheral neuropathy[J]. *TianJing Medical Journal*, 1997; 25(6): 337－340.
张蜀平, 陆菊明, 潘长玉. 弥可保治疗糖尿病周围神经病变疗效观察[J]. 天津医药, 1997; 25(6): 337～340.

21 Xu Z. Effects of methylcobalamin on diabetic peripheral neuropathy: analysis of 11 cases[J]. *JiaXing Medicine*, 2000; 16(2): 121－122.
徐震. 弥可保治疗糖尿病神经病变 11 例疗效观察[J]. 嘉兴医学, 2000; 16(2): 121～122.

22 Li GW, Beijing methycobal clinical trial collaborative group. Effects of mecobalamin on diabetic neuropathies[J]. *Chinese Journal of Internal Medicine*, 1999; 38(1): 14－17.
李光伟, 北京弥可保临床观察协作组. 甲钴胺治疗糖尿病神经病变的临床观察[J]. 中华内科杂志, 1999; 38(1): 14～17.

23 Feng LH, Feng YS, Li CX, Yang HW, Shi GW. Clinical observation of combined therapeutic effect of mecobalamin and prostaglandin E1 on diabetic peripheral neuropathy[J]. *Henan Journal of Practical Nervous Disease*, 1999: 2(4): 25.
冯来会, 冯元森, 李彩霞, 杨洪文, 史广巍. 甲钴胺与前列腺素 E1 联合应用治疗周围神经病变疗效观察[J]. 河南实用神经疾病杂志, 1999; 2(4): 25.

24 Cen HY, Shi WY. Effects of mecobalamin on diabetic neuropathies [J]. *Acta Academiae Medicinae Nantong*, 2000; 20(4): 396－397.
岑海燕, 施文瑜. 弥可保治疗糖尿病周围神经病变疗效观察[J]. 南通医学院学报, 2000; 20(4): 396～397.

25 Shen YF, Zhou WH, Lai XY. Clinical observation of combined therapeutic effect of prostaglandin E1 and methylcobalamin on diabetic peripheral neuropathy[J]. *Acta Academiae Medicinae Jiangxi*, 2001; 41(5): 113－114.
沈云峰, 邹文华, 赖晓阳. 弥可保联用前列腺素 E1 治疗糖尿病神经病变的疗效观察[J]. 江西医学院学报, 2001; 41(5): 113～114.

26 Zhu XP, Zhou ZG. Combined therapeutic effect of prostaglandin E1 and mecobalamin on diabetic peripheral neuropathy[J]. *Bull Hunan Medical University*, 2001; 26(4): 343－344.
朱旭萍, 周智广. PGE1 加甲钴胺治疗糖尿病周围神经病变[J]. 湖南医科大学学报, 2001; 26(4): 343～344.

27 Xu XX, Gu F. Mecobalamin treats the diabetic distal polyneuropathy [J]. *Clinical Medical Journal of China*, 2003;10(1): 64－65.
徐锡祥, 顾峰. 弥可保治疗糖尿病多发性末梢神经病变[J]. 中国临床医学, 2003; 10(1): 64～65.

28 Zhang XJ, Zhang XF. Effects of methylcobalamin on diabetic peripheral neuropathy: analysis of 51 cases[J]. *Chinese Journal of Research of Clinical Medicine and Pharmacy*, 2002; (68): 5655.
张秀菊, 张秀芬. 弥可保治疗糖尿病周围神经病变 51 例疗效观察[J]. 中国临床医药研究杂志, 2002; (68): 5655.

29 Li FS, Guo XH, Pan HF, Liu W. Effects of combined therapy of methylcobalamin and erigeron on diabetic peripheral neuropathy[J]. *Jilin Medicine*, 2002; 23(4): 232－233.
李逢时, 郭兴华, 潘焕峰, 刘巍. 弥可保与灯盏花联合治疗糖尿病周围神经病变[J]. 吉林医学, 2002; 23(4): 232～233.

30 Zhong SM, Liu ZH, Wang JX, Li SJ. Short-term effects of combined therapy of methylcobalamin and XueShuangTong on diabetic peripheral neuropathy[J]. *Chinese Journal of Clinical Rehabilitation*, 2002; 6(23): 3582.
钟树妹, 刘泽洪, 王健雄, 李韶今. 弥可保联用血栓通治疗糖尿病周围神经病变短期疗效[J]. 中国临床康复, 2002; 6(23): 3582.

31 Watanabe T, Kaji R, Oka N, Bara W, Kimura J. Ultra-high dose methyl-cobalamin promotes nerve regeneration in experimental acrylamide neuropathy[J]. *J neurol Sci*, 1994; 122(2): 140－143.

32 Zhang SP, Lu JM, Pan CY, Yin L, Dou JT. Experimental study of effects of methylcobalamin on diabetic peripheral neuropathy[J]. *Chinese Journal of Endocrinology and Metabolism*, 1998; 14(2): 130－132.
张蜀平, 陆菊明, 潘长玉, 尹岭, 窦京涛. 弥可保对糖尿病周围神经病变治疗作用的实验研究[J]. 中华内分泌代谢杂志, 1998; 14(2): 130～132.

33 Dyck PJ, Obrien PC. Meaningful degrees of prevention or improvement of nerve conduction in controlled clinical trials of diabetic neuropathy[J]. *Diabetes Care*, 1989; 12(9): 649－652.

34 Ziegler D, Hanefeld M, Ruhnau KJ, Hasche H, Lobish M, Schutte K, Kerum G, Malessa R. Treatment of symptomatic diabetic polyneuropathy with the antioxidantα-lipoic acid[J]. *Diabetes Care*, 1999; 22(8): 1296－1301.

35 Hotta N, Toyta T, Matsuoka K, Shigeta Y, Kikkawa R, Kaneko T, Takahashi A, Sugimura K, Koike Y, Ishii J, Sakamoto N. Clinical efficacy of fidarestat, a novel aldose reductade inhibitor, for diabetic peripheral neuropathy[J]. *Diabetes Care*, 2001; 24(10): 1776－1782.

(Edited by DU Liang)
(English proofread by Phil Wiffen)

甲基维生素 B_{12} 治疗糖尿病周围神经病变的系统评价

贾海燕[1] 田浩明[1] 魏 东[2]

1. 四川大学华西医院内分泌科（成都 610041）； 2. 成都市第二人民医院内分泌科（成都 610017）

【摘要】 目的 了解甲基维生素 B_{12} 治疗糖尿病周围神经病变的疗效和安全性。方法 按照国际 Cochrane 协作网的系统评价方法，检索全世界关于甲基维生素 B_{12} 治疗糖尿病周围神经病变的随机或半随机对照试验，包括 Cochrane 图书馆 2003 年第 4 期、临床对照试验资料库、MEDLINE、EMBASE、中国生物医学文献光盘数据库、中文科技期刊全文数据库以及所有纳入研究的参考文献。由两位评价者独立地对符合纳入标准的试验进行质量评价和资料提取。采用下列指标对甲基维生素 B_{12} 治疗糖尿病周围神经病变的疗效和安全性进行评价：临床症状体征的总有效率、感觉及运动神经传导速度以及严重不良反应的发生率。结果 30 个试验共纳入1 949例糖尿病周围神经病变患者。大部分试验的方法学质量较低。甲基维生素 B_{12} 与其他 B 族维生素比较的 13 个试验的“漏斗图”图分析显示基本对称，提示发表偏倚的可能性较小，结果比较可靠，但是不一定能代表整体发表偏倚情况。Meta 分析结果显示：甲基维生素 B_{12} 可明显改善糖尿病周围神经病变的临床症状和体征，且疗效优于其他 B 族维生素；甲基维生素 B_{12} 改善某些周围神经传导速度的疗效优于其他 B 族维生素；在治疗期间，试验未发现严重不良反应。结论 甲基维生素 B_{12} 可能是一种相对安全和有效的治疗糖尿病周围神经病变的药物。但由于纳入试验的方法学质量低下和可能存在发表偏倚，证据强度不足，尚有待大样本、高质量的多中心随机双盲对照试验加以证实。

【关键词】 甲基维生素 B_{12}；糖尿病周围神经病变；随机对照试验；半随机对照试验；系统评价

（本文编辑：杜亮）

（英文审校：Phil Wiffen）

消息

News

《中国循证医学杂志》第三届编委会成员名单

Members of the Third Editorial Board of Chinese Journal of Evidence-Based Medicine