Abstract

OBJECTIVE: China is the only country where nerve growth factor is approved for large-scale use as a clinical medicine. More than 10 years ago, in 2003, nerve growth factor injection was listed as a national drug. The goal of this article is to evaluate comprehensively the efficacy and safety of nerve growth factor for the treatment of neurological diseases.

DATA RETRIEVAL: A computer-based retrieval was performed from six databases, including the Cochrane Library, PubMed, EMBASE, Sino Med, CNKI, and the VIP database, searching from the clinical establishment of nerve growth factor for treatment until December 31, 2013. The key words for the searches were “nerve growth factor, randomized controlled trials” in Chinese and in English.

DATA SELECTION: Inclusion criteria: any study published in English or Chinese referring to randomized controlled trials of nerve growth factor; patients with neurological diseases such as peripheral nerve injury, central nerve injury, cranial neuropathy, and nervous system infections; patients older than 7 years; similar research methods and outcomes assessing symptoms; and measurement of nerve conduction velocities. The meta-analysis was conducted using Review Manager 5.2.3 software.

MAIN OUTCOME MEASURES: The total effective rate, the incidence of adverse effects, and the nerve conduction velocity were recorded for each study.

RESULTS: Sixty-four studies involving 6,297 patients with neurological diseases were included. The total effective rate in the group treated with nerve growth factor was significantly higher than that in the control group ($P < 0.0001$, RR: 1.35, 95% CI: 1.30–1.40). The average nerve conduction velocity in the nerve growth factor group was significantly higher than that in the control group ($P < 0.00001$, MD: 4.59 m/s, 95% CI: 4.12–5.06). The incidence of pain or sclerosis at the injection site in the nerve growth factor group was also higher than that in the control group ($P < 0.00001$, RR: 6.30, 95% CI: 3.53–11.27), but such adverse effects were mild.

CONCLUSION: Nerve growth factor can significantly improve nerve function in patients with nervous system disease and is safe and effective.

Key Words: nerve regeneration; neurological diseases; nerve growth factor; randomized controlled trials; meta-analysis; adverse effects; nerve conduction velocity; neural regeneration

Funding: This study was financially supported by the National Science and Technology Major Projects for “Major New Drugs Innovation and Development”, No. 2012ZX09201-301-005.

Zhao M, Li XY, Xu CY, Zou LP (2015) Efficacy and safety of nerve growth factor for the treatment of neurological diseases: a meta-analysis of 64 randomized controlled trials involving 6,297 patients. Neural Regen Res 10(5):819-828.

Introduction

Nerve growth factor is the first neurotrophic factor that was discovered and demonstrates the functions of maintaining the survival of central and peripheral neurons and facilitating their growth, differentiation, and regeneration (Ebenhald, 1989). Nerve growth factor has generated strong interest as a potential target for the treatment of Alzheimer’s disease. The dysfunction of basal forebrain cholinergic neurons is a basic feature of Alzheimer’s disease. Nerve growth factor is synthesized and secreted by cells in the cortex and hippocampus, and high-affinity (TrkA) and low-affinity (p75NTR) neurotrophin receptors are produced within the basal forebrain cholinergic neurons (Eriksdotter Jonhagen et al., 1998). Nerve growth factor released from target cells activates TrkA on axon terminals and triggers the activation of the PI3K/Akt, MEK/ERK, and phospholipase Cγ signaling pathways. The signal then retrogradely travels along axons to the cell body and promotes neuronal survival. The dysfunction of nerve growth factor and its receptors can induce selective degeneration of the basal forebrain cholinergic neurons during end-stage Alzheimer’s disease. The potential benefits treating neurological diseases with nerve growth factor has greatly motivated both clinicians and investigators (Olson et al., 1992; Eriksdotter Jonhagen et al., 1998). Nerve
growth factor clearly promotes the regeneration of damaged nerves (Aloe et al., 2008; Chiaretti et al., 2008; Lambiase et al., 2009), and shows a large potential for other applications. However, the worldwide application of nerve growth factor has only recently started, and the appropriate combination nerve growth factor therapy, the best administration route and dosage, the efficacy, and the potential side effects all require further investigation. Careful basic and clinical research should be performed to support the wider application of nerve growth factor for the treatment of cerebrovascular disease and neurodegenerative diseases and for the repair of damaged nerves.

China is the first country to apply nerve growth factor as a clinical therapy and has accumulated a large amount of research data since nerve growth factor was listed as a national drug (Xia et al., 2009; Hu et al., 2010). Although hundreds of articles on nerve growth factor have been published in China, those results have not been widely appreciated throughout the world because of language restrictions. The present review is a meta-analysis of randomized controlled trials of nerve growth factor during the past ten years with the goal of comprehensively evaluating the efficacy and safety of nerve growth factor for the treatment of neurological diseases.

Data and Methods

Literature retrieval

Six databases were searched, including the Cochrane Library, PubMed, EMBASE, Sino Med, CNKI, and VIP databases, starting from the clinical establishment of nerve growth factor treatment until December 31, 2013. The subject headings and text of the articles were searched for the key words “nerve growth factor” or “NGF” and “randomized controlled trials” or “RCTs.”

Inclusion and exclusion criteria

Inclusion criteria

Any study published in English or Chinese referring to the randomized controlled trials of nerve growth factor; patients with neurological diseases; patients older than 7 years; similar research methods and outcomes assessing symptoms; and measurement of nerve conduction velocities.

Exclusion criteria

Duplicated articles, reviews, those involving animal experiments, those not published in English or Chinese, and those where the full text was unavailable were excluded.

Study selection and data extraction

Eligible studies were selected in two stages: first by screening the title and abstracts for relevance, and then by reviewing the full-text. The following data were extracted from each selected study: basic information, including the title, author, date of publication, and funding; participant information, including age, gender, diagnosis, number of participants in each group, and baseline comparisons; intervention measures information, including drugs, dosages, routes of administration, courses of treatment, and follow-up times in the treatment and control groups; and results information, including the results reported and criteria applied for measuring efficacy and safety. Two of the authors reviewed each citation at both stages. Conflicts were resolved between reviewers or by group consensus.

Quality assessment

The quality of all randomized controlled trials was assessed based on five categories: statistical analysis, outcomes, exposure, study population, and the specific domain of randomization for randomized controlled trial studies. The key elements of these categories for assessing the quality of citations were adapted from the Jadad scale (Jadad et al., 1996) for randomized controlled trial studies. Each quality item was rated as met (yes), unmet (no), or unsure.

Main outcome measurements

The main outcome measures were the total effective rate and the incidence of adverse effects. The secondary outcome measure was the nerve conduction velocity.

Statistical analysis

To reduce the heterogeneity of the studies, the nervous system diseases were divided into four groups: peripheral nerve injury, central nerve injury, cranial neuropathy, and nervous system infections. Each group was further divided into several subgroups, and meta-analyses were conducted within the subgroups. When the heterogeneity in the subgroups could not be explained, a sensitivity analysis was used to determine the impact of excluding specific studies on the overall estimate of the effect.

From each primary study, the effect estimates were extracted for the relationship between nerve growth factor treatment and the neurological disease. The heterogeneity was assessed using a test based on the deviations of the individual study estimates from the summary estimate of the effect and quantified with $I^2$, which describes the proportion of the variance due to heterogeneity among studies rather than due to sampling error. An $I^2 > 50\%$ represents substantial heterogeneity. The random effects meta-analyses were conducted with RevMan 5.2.3 software (The Cochrane Collaboration, Australia) to determine the effect estimates, and the origin of the heterogeneity was discussed. For values of $I^2 < 50\%$, fixed effect models were used to perform the meta-analysis.

Results

Data retrieval

The selection of studies is described in Figure 1. A total of 644 articles were retrieved, and 64 randomized controlled trial studies were finally selected, including two in English using recombinant human nerve growth factor (Apfel et al., 1998; Apfel et al., 2000) and 62 in Chinese using mouse nerve growth factor. Of these 64 articles, 22 (Apfel et al., 1998, 2000; Liu et al., 2007; Peng et al., 2009; Xia et al., 2009; Huang et al., 2010; Li et al., 2010a; Meng et al., 2010; Wang et al., 2009) were suitable for the meta-analysis. In these studies, 48 were randomized controlled trials, and 16 were controlled clinical trials. The remaining 16 were case reports or case series. Exclusion criteria were used to ensure the validity of the analysis. The data were analyzed using RevMan 5.2.3 software (The Cochrane Collaboration, Australia). The random effects model was used to analyze the effect estimates.
et al., 2010a, 2011a; Guo and Liu, 2011; Zhang et al., 2011b; Zhao, 2011; Fang et al., 2012a, b; Jiang et al., 2012; Ye et al., 2012; Chen, 2013; Chi and Zhao, 2013; Feng et al., 2013; Shen, 2013; Shu et al., 2013) examined peripheral nerve injury, 16 (Chen et al., 2004; Yuan and Lei, 2005; Li, 2006; Tang et al., 2008; Zhang et al., 2008, 2009, 2011a, 2012; Li and Yang, 2009; Wang and Liu, 2010; Wang et al., 2010b, c; Hou et al., 2012; Qi et al., 2012; Yan et al., 2012; Zheng et al., 2013) examined central nerve injury, 23 (Yang et al., 2006; Wang et al., 2007, 2012b; Peng et al., 2008; Tang and Wang, 2008; Huang and Li, 2010; Sun, 2010; Wang and Zhang, 2010; Zhang, 2010; Zhang et al., 2010; Chen et al., 2011; Li and Yuan, 2011; Mo et al., 2011; Xia and Pan, 2011; Lin et al., 2012; Ma et al., 2012; Shen, 2012; Zhao and Li, 2012; Li et al., 2013; Lu et al., 2013; Tang et al., 2013; Tian and Dong, 2013; Yu, 2013) examined cranial neuropathy, and three (Xia et al., 2010; Li et al., 2012; Shan et al., 2013) examined nervous system infections (Table 1). There were 6,297 patients in those 64 studies, including 3,346 patients in the experimental groups and 2,951 patients in the control groups. The case numbers in the studies ranged from a maximum of 948 (Apfel et al., 2000) to a minimum of 15 (Jiang et al., 2012). The ages of the patients ranged from 7 to 87 years old. The Chinese patients were from 25 provinces and 59 hospitals, which included 45 provincial or municipal tertiary hospitals and 14 district or county secondary hospitals. The patients distributed in those hospitals represented the general case population, to a certain extent.

The Chinese patients were from 25 provinces and 59 hospitals, which included 45 provincial or municipal tertiary hospitals and 14 district or county secondary hospitals. The patients distributed in those hospitals represented the general case population, to a certain extent.

The Chinese patients were from 25 provinces and 59 hospitals, which included 45 provincial or municipal tertiary hospitals and 14 district or county secondary hospitals. The patients distributed in those hospitals represented the general case population, to a certain extent.

The Chinese patients were from 25 provinces and 59 hospitals, which included 45 provincial or municipal tertiary hospitals and 14 district or county secondary hospitals. The patients distributed in those hospitals represented the general case population, to a certain extent.

The Chinese patients were from 25 provinces and 59 hospitals, which included 45 provincial or municipal tertiary hospitals and 14 district or county secondary hospitals. The patients distributed in those hospitals represented the general case population, to a certain extent.

The Chinese patients were from 25 provinces and 59 hospitals, which included 45 provincial or municipal tertiary hospitals and 14 district or county secondary hospitals. The patients distributed in those hospitals represented the general case population, to a certain extent.

The Chinese patients were from 25 provinces and 59 hospitals, which included 45 provincial or municipal tertiary hospitals and 14 district or county secondary hospitals. The patients distributed in those hospitals represented the general case population, to a certain extent.

The Chinese patients were from 25 provinces and 59 hospitals, which included 45 provincial or municipal tertiary hospitals and 14 district or county secondary hospitals. The patients distributed in those hospitals represented the general case population, to a certain extent.

The Chinese patients were from 25 provinces and 59 hospitals, which included 45 provincial or municipal tertiary hospitals and 14 district or county secondary hospitals. The patients distributed in those hospitals represented the general case population, to a certain extent.

The Chinese patients were from 25 provinces and 59 hospitals, which included 45 provincial or municipal tertiary hospitals and 14 district or county secondary hospitals. The patients distributed in those hospitals represented the general case population, to a certain extent.

The Chinese patients were from 25 provinces and 59 hospitals, which included 45 provincial or municipal tertiary hospitals and 14 district or county secondary hospitals. The patients distributed in those hospitals represented the general case population, to a certain extent.

The Chinese patients were from 25 provinces and 59 hospitals, which included 45 provincial or municipal tertiary hospitals and 14 district or county secondary hospitals. The patients distributed in those hospitals represented the general case population, to a certain extent.

The Chinese patients were from 25 provinces and 59 hospitals, which included 45 provincial or municipal tertiary hospitals and 14 district or county secondary hospitals. The patients distributed in those hospitals represented the general case population, to a certain extent.

The Chinese patients were from 25 provinces and 59 hospitals, which included 45 provincial or municipal tertiary hospitals and 14 district or county secondary hospitals. The patients distributed in those hospitals represented the general case population, to a certain extent.

The Chinese patients were from 25 provinces and 59 hospitals, which included 45 provincial or municipal tertiary hospitals and 14 district or county secondary hospitals. The patients distributed in those hospitals represented the general case population, to a certain extent.

The Chinese patients were from 25 provinces and 59 hospitals, which included 45 provincial or municipal tertiary hospitals and 14 district or county secondary hospitals. The patients distributed in those hospitals represented the general case population, to a certain extent.

The Chinese patients were from 25 provinces and 59 hospitals, which included 45 provincial or municipal tertiary hospitals and 14 district or county secondary hospitals. The patients distributed in those hospitals represented the general case population, to a certain extent.

The Chinese patients were from 25 provinces and 59 hospitals, which included 45 provincial or municipal tertiary hospitals and 14 district or county secondary hospitals. The patients distributed in those hospitals represented the general case population, to a certain extent.

The Chinese patients were from 25 provinces and 59 hospitals, which included 45 provincial or municipal tertiary hospitals and 14 district or county secondary hospitals. The patients distributed in those hospitals represented the general case population, to a certain extent.

The Chinese patients were from 25 provinces and 59 hospitals, which included 45 provincial or municipal tertiary hospitals and 14 district or county secondary hospitals. The patients distributed in those hospitals represented the general case population, to a certain extent.
| Type of neurological diseases | Studies | NGF dose (μg, once daily) | Duration (day) | Control regimen | Number of patients | Age (year) |
|-------------------------------|---------|---------------------------|----------------|----------------|-------------------|-----------|
| Peripheral nerve injury      |         |                           |                |                |                   |           |
| DPN                           | Xia et al., 2009; Huang et al., 2010; Li et al., 2010a; Meng et al., 2010b; Wang et al., 2010a; Guo and Liu, 2011; Zhang et al., 2011b; Zhao, 2011; Fang et al., 2012a; b; Ye et al., 2012; Chen, 2013; Shen, 2013 | 4–30 | 14–60 | Mecobalamin, Tanshinone II A, HOT, lipoic acid, VitB12, VitB12 | 506 | 408 | 42–75 |
| Polyneuropathy                | Wang et al., 2011a; Jiang et al., 2012; Chi and Zhai, 2013; Feng et al., 2013; Shu et al., 2013 | 18–20 | 14–60 | Acupuncture | 167 | 136 | 15–84 |
| GBS                           | Liu et al., 2007; Peng et al., 2009 | 4–20 | 60 | IVIG, citicoline | 134 | 129 | 7–65 |
| Central nerve injury          |         |                           |                |                |                   |           |
| AD                            | Li and Yang, 2009 | 30 | 112 | Donepezil | 31 | 33 | 45–80 |
| Cerebral infarction           | Chen et al., 2004; Li, 2006; Zhang, 2009; Wang and Liu, 2010; Zhang et al., 2011b | 9–20 | 10–30 | Nimodipine, Shuxuetong | 307 | 288 | 38–87 |
| Spinal cord injury            | Yuan and Lei, 2005; Tang et al., 2008; Zhang et al., 2008, 2012; Qi et al., 2012; Yan et al., 2012; Zheng et al., 2013 | 18–30 | 14–60 | Acupuncture | 177 | 168 | 14–74 |
| Traumatic brain injury        | Yuan and Lei, 2005; Wang and Liu, 2010 | 4–20 | 20–30 | Mecobalamin | 74 | 74 | 13–72 |
| CO poisoning                  | Wang et al., 2010a; Hou et al., 2012 | 30 | 28–56 | MP, HOT | 66 | 67 | 18–74 |
| Cranial neuropathy            |         |                           |                |                |                   |           |
| Optic neuropathy              | Wang et al., 2007; Huang et al., 2010; Sun, 2010; Wang and Liu, 2010; Zhang, 2010; Chen et al., 2011; Li and Yuan, 2011; Xia and Pan, 2011; Ma et al., 2012; Shen, 2012; Li et al., 2013; Lu et al., 2013; Yu, 2013 | 18–30 | 14–60 | Dexamethasone, adenosine triphosphate, anisodine MP | 794 | 560 | 7–80 |
| Facial paralysis              | Peng et al., 2008; Tang and Wang, 2008; Zhang, 2010; Tian and Dong, 2013 | 4–30 | 7–30 | Dexamethasone, mecobalamin | 263 | 255 | 14–77 |
| Deafness                      | Yang et al., 2006; Wang et al., 2012b; Zhao and Li, 2012; Tang et al., 2013 | 18 | 28–30 | Oxiracetam | 127 | 117 | 18–80 |
| Nervous system infections     |         |                           |                |                |                   |           |
| Postherpetic neuralgia        | Xia et al., 2010; Shan et al., 2013 | 30 | 44 | Cobamamide | 56 | 56 | 50–87 |
| Meningitis in HIV             | Li et al., 2012 | 18 | 15 | Amphotericin B, 5-fluorocytosine | 16 | 10 | 20–38 |

*Two studies in English using recombinant human NGF (Apfel et al., 1998, 2000) are not included in Table 1. The nervous system diseases were divided into four groups: peripheral nerve injury, central nerve injury, cranial neuropathy, and nervous system infections. The experimental group included patients treated with NGF and the control group included those who received conventional treatments. NGF: Nerve growth factor; DPN: diabetic peripheral neuropathy; GBS: Guillain-Barre syndrome; AD: Alzheimer’s disease; IVIG: intravenous immunoglobulin; MP: methylprednisolone; HOT: hyperbaric oxygen therapy; Shuxuetong: injection of Shuxuetong Chinese medicine; CO: carbon monoxide; HIV: human immunodeficiency virus.
Table 2 Meta-analysis of adverse drug reactions (ADR) related to nerve growth factor treatment

| Adverse reactions | Studies                                                                 | Cases of ADR/total treatment cases | Cases of ADR/total control cases | Heterogeneity | RR (95%CI) | P   |
|-------------------|-------------------------------------------------------------------------|------------------------------------|----------------------------------|---------------|------------|-----|
| Pain or scleroma at the injection site | Chen et al., 2004, 2013; Yuan and Lei, 2005, 2006, 2013; Wang et al., 2007, 2010b, c; Peng et al., 2008; Tang and Wang, 2008; Xia et al., 2009, 2010; Wang and Zhang, 2010; Zhang et al., 2010, 2012; Guo and Liu, 2011; Zhao, 2011; Fang et al., 2012a, b; Ma et al., 2012; Qi et al., 2012; Ye et al., 2012; Zhao and Li, 2012; Chi and Zhai, 2013; Feng et al., 2013; Shan et al., 2013; Tian and Dong, 2013; Zheng et al., 2013 | 89/1,727 | 7/1,486 | P = 0.06, I² = 41% | 6.30 (3.33–12.7), P < 0.00001 |
| Rash | Xia et al., 2009, 2010; Shan et al., 2013 | 4/76 | 0/76 | P = 0.96, I² = 0% | 3.67 (0.62–1.69), 0.15 |
| Gastrointestinal discomfort, diarrhea | Chen et al., 2004; Tang and Wang, 2008; Li and Yang, 2009; Li et al., 2010a; Zhang, 2010; Tian and Dong, 2013 | 4/76 | 0/76 | P = 0.03, I² = 59% | 3.03 (0.39–6.0), 0.0003 |
| Headache or dizziness | Li and Yang, 2009; Li et al., 2010a; Tian and Dong, 2013 | 3/130 | 0/130 | P = 0.35, I² = 6% | 1.01 (0.25–4.03), 0.99 |

Incidence of pain or scleroma was significantly higher in the nerve growth factor group than in the control group.

Figure 4 A RevMan forest plot of the mean difference estimates after treatment of peripheral nerve injury with mouse nerve growth factor. MNCV: Motor nerve conduction velocity; SNCV: sensory nerve conduction velocity.

2009; Huang and Li, 2010; Li et al., 2010b; Meng et al., 2010; Wang and Liu, 2010; Guo and Liu, 2011; Wang et al., 2011a; Zhang et al., 2011b; Zhao, 2011; Fang et al., 2012a, b; Jiang et al., 2013; Ye et al., 2012; Chen, 2013; Chi and Zhai, 2013; Feng et al., 2013; Shen, 2013; Shu et al., 2013) reported the effect of peripheral nerve growth factor for the treatment of peripheral nerve injury. The peripheral nerve injuries were divided into three subgroups: diabetic peripheral neuropathy, polynuropathy, and Guillain-Barre Syndrome. A RevMan forest plot detailing the effects of nerve growth factor on peripheral nerve injury is shown in Figure 3. The test of heterogeneity showed significant differences among the studies (χ² = 98.57, df: 21, P < 0.00001, I² = 79% > 50%). Therefore, a random effect model was applied to determine the effect sizes. The total effective rate of treatment on peripheral nerve injury was significantly higher in the nerve growth factor group than in the control group (P < 0.00001, RR: 1.38, 95%CI: 1.26–1.62; Figure 3).

The heterogeneity in subgroup diabetic peripheral neuropathy (I² = 66%, P = 0.0004) was explained by the combined treatments used. The heterogeneity among the 8 studies (Xia et al., 2009; Li et al., 2010a; Meng et al., 2010; Wang, 2009; Guo and Liu, 2011; Wang et al., 2011a; Zhang et al., 2011b; Zhao, 2011; Fang et al., 2012a, b; Ye et al., 2012; Chen, 2013) that combined nerve growth factor with other therapies (I² = 36%, P = 0.14) was lower than the heterogeneity among the 5 studies (Huang et al., 2010; Guo and Liu, 2011; Fang et al., 2012b; Chen, 2013) that used only nerve growth factor treatments (I² = 57%, P = 0.05). The effect of the combined use of nerve growth factor and other therapies (RR: 1.37, 95%CI: 1.38–1.78) was higher than that of those using only nerve growth factor treatments (RR: 1.32, 95%CI: 1.11–1.57). Twelve studies (Xia et al., 2009; Huang et al., 2010; Li et al., 2009b; Meng et al., 2010; Wang and Liu, 2010; Guo and Liu, 2011; Fang et al., 2012a, b; Ye et al., 2012; Chen, 2013; Feng et al., 2013; Shen, 2013) reported the nerve conduction velocities...
of 994 patients with peripheral nerve injury (Figure 4). The nerve conduction velocities included the median nerve motor conduction velocity, the median nerve sensory conduction velocity, the peroneal nerve motor conduction velocity, and the sural sensory conduction velocity. Because the test of heterogeneity showed significant differences among the studies ($\chi^2 = 224.91, df = 39, I^2 = 83% > 50%, P < 0.00001$), a random effect model was used to determine the effect sizes. The nerve conduction velocity was significantly higher in the nerve growth factor group than in the control group ($P < 0.00001, \text{MD} = 4.59 \text{ m/s}, 95\%CI: 4.12–5.06$; Figure 4).

The subgroup analyses could not eliminate the heterogeneity in motor nerve conduction velocity among the studies ($I^2 = 99\%, P < 0.00001$). A statistically significant heterogeneity ($I^2 = 99\%, P < 0.00001$) remained when the analysis was restricted to studies of the combined use of nerve growth factor and other therapies. Similarly, when the studies were divided into those published before 2011 (Li et al., 2010a; Meng et al., 2010; Wang et al., 2010a; Zhao, 2011) and after 2012 (Fang et al., 2012a, b; Ye et al., 2012; Shen, 2013), the heterogeneities of each group were still statistically significant ($I^2 = 99\%, P < 0.00001; I^2 = 100\%, P < 0.0001$). In addition, the analysis of dosing for 30 µg doses (Meng et al., 2010; Wang et al., 2010a; Fang et al., 2012a; Ye et al., 2012; Shen, 2013) and 4–20 µg doses (Li et al., 2010a; Zhao, 2011; Fang et al., 2012b), showed that the heterogeneities were still statistically significant ($I^2 = 99\%, P < 0.00001; I^2 = 100\%, P < 0.0001$). Finally, the analysis of treatment course of 4 weeks (Li et al., 2010a; Zhao, 2011; Fang et al., 2012a; Ye et al., 2012) and 2–3 weeks (Meng et al., 2010; Wang et al., 2010a; Fang et al., 2012b; Shen, 2013) also showed that the heterogeneities were still statistically significant ($I^2 = 100\%, P < 0.00001; I^2 = 99\%, P < 0.0001$). There was no difference in the age of patients with peripheral nerve injury among the studies, and the age of the patients ranged from 40 to 87 years old. Therefore, age was not a major factor contributing to the heterogeneity. The origin of the heterogeneities may be from the different measurement methods used, the measurement error from the instruments or user, and the different sites where the electrodes were inserted into the muscles when conducting the electromyography testing.

The sensitivity analysis showed that the positive effect was persistent. The overall mean difference in nerve conduction velocity between the nerve growth factor group and the control group was 4.59 m/s ($95\%CI: 4.12–5.06, P < 0.00001$; Figure 4). After removing a low-weight study (Ye et al., 2012), the overall mean difference became 4.41 m/s ($95\%CI: 3.93–4.89, P < 0.00001$).

**Nerve growth factor and cranial nerve injury**

Sixteen studies (Chen et al., 2004; Yuan and Lei, 2005; Li, 2006; Tang et al., 2008; Zhang et al., 2008, 2009, 2011a, 2012; Li and Yang, 2009; Wang and Liu, 2010; Wang et al., 2010b, c; Hou et al., 2012; Qi et al., 2012; Yan et al., 2012; Zheng et al., 2013) reported the effect of nerve growth factor on cranial nerve injury. To reduce the clinical heterogeneity, the studies were divided into five groups by affliction: Alzheimer's disease, cerebral infarction, spinal cord injury, traumatic brain injury, and CO poisoning. The test of heterogeneity showed significant differences among the studies ($\chi^2 = 34.78, df = 15, I^2 = 57% > 50\%$), and thus a random effect model was applied to determine the effect size. The total effective rate of treatment on central nerve injury was significantly higher in the nerve growth factor group than in the control group (RR: 1.22, 95%CI: 1.12–1.32, $P < 0.00001$). Because there was only one study in the Alzheimer's disease subgroup, a sensitivity analysis was conducted. After removing the Alzheimer's disease subgroup (Li and Yang, 2009), the heterogeneity remained ($I^2 = 53% > 50\%, P = 0.009$) and the positive effect of nerve growth factor was unchanged (RR: 1.24, 95%CI: 1.14–1.34, $P < 0.00001$).

**Nerve growth factor and cranial neuropathy**

Twenty-three studies (Yang et al., 2006; Wang et al., 2007, 2010c, 2012b; Peng et al., 2008; Tang and Wang, 2008; Huang and Li, 2010; Sun, 2010; Zhang, 2010, 2011a; Chen et al., 2011, Mo et al., 2011; Xia and Pan, 2011; Ma et al., 2012; Shen, 2012; Zhao and Li, 2012; Li et al., 2013; Lu et al., 2013; Tang et al., 2013; Tian and Dong, 2013; Yu, 2013) reported the effect of nerve growth factor for the treatment of cranial neuropathy, including 14 for optic neuropathy, seven for facial paralysis, and two for hearing loss. The test of heterogeneity showed significant differences among the studies ($\chi^2 = 65.47, df = 22, I^2 = 66% > 50\%, P = 0.003$), and therefore a random effect model was applied to determine the effect size. The total effective rate of treatment on cranial neuropathy was significantly higher in the nerve growth factor group than in the control group (RR: 1.31, 95%CI: 1.21–1.42, $P < 0.00001$). There were significant differences between the nerve growth factor group and control group in the treatment of optic neuropathy (RR: 1.38, 95%CI: 1.24–1.53, $P < 0.00001$), facial paralysis (RR: 1.19, 95%CI: 1.07–1.33, $P = 0.002$), and hearing loss (RR: 1.31, 95%CI: 1.00–1.70, $P = 0.05$).

**Nerve growth factor and nervous system infection**

Three studies reported the effect of nerve growth factor treatment on nervous system infections, including two studies of postherpetic neuralgia (Xia et al., 2010; Shan et al., 2013) and one study of meningitis in HIV (Li et al., 2012). The test of heterogeneity in the postherpetic subgroup showed no significant differences between the two studies ($\chi^2 = 0.12, df = 2, I^2 = 0 < 50\%, P = 0.94$). Therefore, a fixed effect model was applied to determine the effect size. The total effective rate of treatment on nervous system infections was significantly higher in the nerve growth factor group than in the control group (RR: 1.28, 95%CI: 1.10–1.49, $P < 0.00001$).

**Nerve growth factor safety analysis**

Of the 64 studies included, 38 studies reported the adverse effects of the nerve growth factor therapy (Table 2). The test of heterogeneity showed no significant differences in adverse effects among the studies ($\chi^2 = 46.54, df = 25, I^2 = 46% < 50\%$, $P < 0.00001$).
P = 0.006), and thus a fixed effect model was applied to determine the effect size. The most common side effect was pain or sclerosis at the injection site. The incidence of pain or sclerosis was significantly higher in the nerve growth factor group (5.23%, 89/1,727) than in the control group (0.54%, 7/1,486) (RR: 6.30, 95% CI: 3.53–11.27, P < 0.00001). However, the adverse effects were mild and could be relieved without specific treatment or with symptomatic treatment. The incidence of gastrointestinal discomfort or diarrhea was significantly lower in the nerve growth factor group (4.61%, 11/236) than in the control group (15.74%, 37/238) (RR: 0.33, 95% CI: 0.19–0.60, P = 0.0003). There were no significant differences between the nerve growth factor and control groups in the incidences of rash or headache (P = 0.15, P = 0.99).

Analysis of publication bias
The symmetry of the funnel plot (Figure 5) showed that there was no evidence of publication bias among the studies using mouse nerve growth factor and reporting adverse reactions.

Discussion
This systematic review summarized studies to determine the efficacy and safety of nerve growth factor for the treatment of neurological diseases. The meta-analyses showed that the nerve growth factor therapy was effective and safe in patients with neurological diseases. Treatment with nerve growth factor clearly improved the nerve conduction velocity of patients. The average nerve conduction velocity increased by 4.59 m/s in the nerve growth factor group compared with the control group, which met the effectiveness criteria according to the American Diabetes Association standard (2006). The most common side effect was pain or sclerosis at the injection site, but such adverse effects were mild and could be relieved without specific treatment.

Nerve growth factor was also used effectively to treat peripheral nerve injury. The combined use of nerve growth factor and other therapies, such as methylcobalamin, tanshinone II A, lipoic acid, and hyperbaric oxygen therapy, was even more effective than nerve growth factor alone. The effect of injecting Danhong Chinese medicine was better than that of nerve growth factor treatment for diabetic peripheral neuropathy. Diabetic peripheral neuropathy is a common chronic complication of diabetes with a prevalence rate of 32.7% among diabetes patients over 40 years old in the United States (Candrilli et al., 2007). There are no effective treatment methods for diabetic peripheral neuropathy (Brownlee, 2005), and the pathophysiology of diabetic peripheral neuropathy remains unclear. One hypothesis suggested was that diabetic peripheral neuropathy may be associated with a deficiency of nerve growth factor (Palacka et al., 2010). The level of nerve growth factor in the tissue and blood from both animal models of diabetes and patients with diabetic neuropathy is very low. This may be caused by disorders of glucose metabolism that occur with an increased generation of intracellular reactive oxygen species, increased production of oxygen free radicals, and increased NADH oxidase activity. All of these factors together may deplete the amount of neurotrophic factor in the tissue and blood (Chyun et al., 2006). If this hypothesis is true, exogenous nerve growth factor may be able to help relieve peripheral neuropathy.

Several case reports have suggested that the administration of nerve growth factor may cause certain potentially beneficial effects. The results reported by Olson et al. (1992) indicated that nerve growth factor may counteract the cholinergic deficits in Alzheimer’s disease. Nerve growth factor treatment can result in a marked transient increase in the uptake and binding of 11C-nicotine in frontal and temporal cortex, improving verbal episodic memory. Eriksdotter Jonhagen et al. (1998) concluded that the long-term intracerebroventricular administration of nerve growth factor may induce potentially beneficial effects, and lower doses of nerve growth factor can decrease shooting pain. Considerable accumulated evidence has shown that nerve growth factor is a peripheral pain mediator, particularly in states of inflammatory pain (Pezet and McMahon, 2006). Nerve growth factor is upregulated in various inflammatory conditions, and, in many persistent pain models, nerve growth factor neutralizing molecule is an effective analgesic agent.

Treatment with recombinant human nerve growth factor for patients with diabetic peripheral neuropathy had been thought to herald a new type of treatment approach to such hitherto largely untreatable disorders (Zochodne and Said, 1998; Riggs, 1999). Unfortunately, further clinical trials failed to demonstrate significant beneficial effects (Apfel et al., 2000). The author concluded that side effects and lower doses (0.1 μg/kg) may explain why the trials were unsuccessful (Apfel, 2002).

The results presented here are consistent with another systematic review of nerve growth factor treatment for peripheral nerve injury (Liu and Liu, 2012). That review also suggested that nerve growth factor therapy was effective and safe for peripheral nerve injury. However, the authors of that review used the OR instead of the RR as an effect indicator, which resulted in I² = 0, and therefore obscured the heterogeneity among the studies.

Finding effective drugs that can effectively penetrate the blood-brain barrier is one of the most difficult challenges in the treatment of central nerve diseases. One published study determined the permeability of 125I-labeled β-nerve growth factor (13 kDa) extracted from aborted fetuses across the blood-brain barrier in rats. β-nerve growth factor with 4% 125I-β-nerve growth factor was able to cross the blood-brain barrier 30 minutes after injection (Zhu et al., 2002). The molecular weight of nerve growth factor is 13.5 kDa, which is similar to that of β-nerve growth factor. Both in vitro and in vivo studies have shown that nerve growth factor encapsulated in liposomes can also penetrate the blood-brain barrier (Xie et al., 2005).

One case report that was not included in the present review reported the successful application of mouse nerve growth factor (Enjingfu, Xiamen Beida Road Bioengineering, Xiamen, Fujian Province, China) for the treatment of a Chinese patient with radiation-induced temporal lobe necrosis (Wang et al., 2011b). Late temporal lobe necrosis is
We acknowledged Yan-yan Ma from Chinese PLA General Hospital for the assistance in writing the manuscript, Xiuyu Shi from Chinese PLA General Hospital for searching literature, and Lin-yan Hu from Chinese PLA General Hospital for providing supply of materials.

Acknowledgments: We acknowledged Yan-yan Ma from Chinese PLA General Hospital for the assistance in writing the manuscript, Xiuyu Shi from Chinese PLA General Hospital for searching literature, and Lin-yan Hu from Chinese PLA General Hospital for providing supply of materials.

Author contributions: All authors contributed to the protocol proposal, the literature screening (includes developing a search strategy), and drafting the manuscript. MZ extracted data. MZ and CYX evaluated and summarized data. LPZ interpreted data. All authors approved the final version of the manuscript.

Conflicts of interest: None declared.

References
Aloe L, Tirassa P, Lambiase A (2008) The topical application of nerve growth factor as a pharmacological tool for human corneal and skin ulcers. Pharmocol Res 57:253–258.
American Diabetes Association standard (2006) Standards of medical care in diabetes-2006. Diabetes Care 29 Suppl 1:S4–42.
Apfel SC (2002) Nerve growth factor for the treatment of diabetic neuropathy: what went wrong, what went right, and what does the future hold? Int Rev Neurobiol 50:393–413.
Apfel SC, Kessler JA, Adornato BT, Litchy WJ, Sanders C, Rask CA (1998) Recombinant human nerve growth factor in the treatment of diabetic polyneuropathy. NGE Study Group. Neurology 51:695–702.
Apfel SC, Schwartz S, Adornato BT, Freeman R, Biton V, Rendell M, Vinik A, Giuliani M, Stevens JC, Barbano R, Dyck PJ (2000) Efficacy and safety of recombinant human nerve growth factor in patients with diabetic polyneuropathy: a randomized controlled trial. rhNGF Clinical Investigator Group. JAMA 284:2215–2221.
Brownlee M (2005) The pathobiology of diabetic complications: a unifying mechanism. Diabetes 54:1615–1625.
Candrilli SD, Davis KL, Kan HJ, Lucero MA, Rouscup MD (2007) Prevalence and the associated burden of illness of symptoms of diabetic peripheral neuropathy and diabetic retinopathy. J Diabetes Complications 21:306–314.
Chen J (2013) Clinical observation of mouse nerve growth factor for injection for treatment of diabetic peripheral neuropathy. Zhongguo Yiya Zhao Zhanian 11:571–572.
Chen YW, Zi XH, Tu QY, Song Z, Li XB (2004) Role of mouse nerve growth factor in the treatment of cerebrovascular disease with diabetes mellitus. Zhongguo Linchuang Yisheng 6:1573–1574.
Tang XM, Wang Y (2008) Outcome of treatment with nerve growth factor in patients with Bell's palsy. Linchuang Yixue Zazhi 28:23-24.
Tian JW, Dong C (2013) Clinical observation of mouse nerve growth factor for idiopathic facial paralysis. Jiankang Dashiyi 1:46-47.
Wang D, Liu N (2010) Nerve growth factor in the treatment of cerebral contusion and laceration. Zhonghua Shenjing Yixue Zazhi 9:416-418.
Wang DS, Huang LT, Yang XT, Lan GH (2011a) Clinical observation of local injection treatment with mouse nerve growth factor for peripheral nerve injury. Qi qihar Xiyue yuan Xuebao 32:369-370.
Wang LB, Wang Y, Guo L (2010a) Combined treatment with mouse nerve growth factor and hyperbaric oxygen for diabetic peripheral neuropathy. L inchuang Huicui 25:1813-1815.
Wang X, Ying H, Zhou Z, Hu C, Eisenbruch A (2011b) Successful treatment of radiation-induced temporal lobe necrosis with mouse nerve growth factor. J Clin Oncol 29:e166-168.
Wang XS, Zhang X, Zhou RL, Chen MF, Chen XY (2011b) Clinical observation of mouse nerve growth factor for treatment of 26 cases with facial nerve injury. Hua Bei Guofang Yiyao 22:227-229.
Wang Z, Ma MJ, Han Q (2012) Analysis of the efficacy of nerve growth factor in the treatment of facial paralysis. Shenjing Sunshang yu Huabei Guofang Yiyao 22:227-229.
Xia YH, Liu D, Li SJ, Guo JM, Li M, Fu DD, Li ZG, Tian ZW (2010) Efficacy of mouse nerve growth factor for treatment of radiation-induced cerebral infarction. Zhongguo Shiyong Shenjing Zazhi 10:147-151.
Xia YG, Wei GQ, Chen J (2010c) Mouse nerve growth factor in the treatment of delayed encephalopathy after carbon mono xide poisoning. Hua Bei Guofang Yiyao 22:227-229.
Yuan P, Lei TT (2005) Efficacy of nerve growth factor in patients with diffuse axonal injury. Zhongg Jing Xiyue 34:1877-1878.
Ye WC, Fang XM, Wang YR, Gao L (2012) Clinical observation of mouse nerve growth factor combining with a lipoic acid for treatment of diabetic peripheral neuropathy. Sichuan Xiyue 33:2098-2100.
Yu F (2013) Clinical observation of mouse nerve growth factor for optic atrophy. Q u i y i W enyao 11:80-81.
Yuan P, Lei TT (2005) Efficacy of nerve growth factor in patients with diabetic polyneuropathy. Neimenggu Yixueyuan Xuebao 33:37-46.
Zhang KF, Guo ZW, Song HJ (2012) Effect of mouse nerve growth factor on neural function of patients after operation for protrusion of the lumbar intervertebral disc. Zhongguo Kangfu Lilun yu Shijian 18:84-86.
Zhang PL, Wang Y, Du ZY, Zhu YQ, Gu YF, Wu CG (2008) Combined treatment with mouse nerve growth factor and interventional procedures for lumbar intervertebral disc. Zhongguo Kangfu Lilun yu Shijian 7:740-741.
Zhao M, et al. / Neural Regeneration Research. 2015;10(5):819-828.