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SYSTEMATIC REVIEW

Efficacy and Safety of Nerve Growth Factor in Treating Neurotrophic Keratitis Patients: A Meta-Analysis

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Abstract

Aims/Background Nerve growth factor has been approved for treating neurotrophic keratitis in Europe and the United States. However, its clinical efficacy and safety profile in neurotrophic keratitis patients have not been systematically evaluated. Therefore, this study systematically assessed the efficacy and safety of nerve growth factor (NGF) in treating patients with neurotrophic keratitis.

Methods Various databases, including Wanfang, China National Knowledge Internet (CNKI), Embase, PubMed, and Web of Science were systematically searched. This search included all articles published up to January 2024. Moreover, these articles were thoroughly reviewed and carefully screened following predetermined inclusion and exclusion criteria. Furthermore, the quality of the included studies was assessed using the Cochrane Risk of Bias Manual 5.3 (The Cochrane Collaboration, London, UK). Stata26.0 (StataCorp LLC, College Station, TX, USA) was used for meta-analysis. The outcome indicators evaluated in this study included corneal healing efficiency, corneal complete healing rate, best vision correction rate, ailment progression, and the number of adverse events.

Results A total of 4 articles were included in this study, including 293 sufferers. The findings from the meta-analysis revealed that the corneal healing efficiency (odds ratio (OR) = 1.72, 95% confidence interval (CI): 1.20–2.45), the corneal complete healing rate (OR = 2.23, 95% CI: 1.41–3.54), and the best visual acuity correction rate (OR = 1.97, 95% CI: 1.11–3.47) were significantly higher in the experimental group compared to the control group. However, the incidence of ailment progression (OR = 0.44, 95% CI: 0.17–1.13) and adverse events (OR = 0.88, 95% CI: 0.50–1.56) did not show significant differences between these two groups.

Conclusion In summary, for patients with neuropathic keratitis, NGF treatment can promote corneal healing efficiency, effectively improve visual correction, and reduce disease progression and incidence of adverse events to a large extent. The clinical effect and safety are high, and it is worthy of clinical promotion and application.

Key words: nerve growth factor (NGF); neurotrophic keratitis; safety

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Introduction

Neurotrophic keratitis, also known as neuroparalytic keratitis, is a corneal degenerative disease that arises from damage to the trigeminal nerve due to several reasons, such as surgery, trauma, inflammation, tumour, and other factors. This condition reduces corneal sensitivity and disrupts the corneal nutrition supply. Consequently, the cornea becomes more vulnerable to external harmful factors, potentially resulting in dryness and increased susceptibility to mechanical damage (Dua

et al, 2018). Neurotrophic keratitis or keratopathy usually affects the central or paracentral area of the cornea. The primary symptom in affected individuals is typically the presence of epithelial lamellar defects shown by fluorescein staining of the superficial corneal epithelium, ranging from punctate lesions to a larger area without epithelium in severe cases. In the cases where secondary infection occurs, the ailment may progress to a suppurative corneal ulcer, enhancing the risk of perforation (Versura et al, 2018). The therapy for this ailment primarily involves the combination of surgery, physical therapy, and medication (Jabbour et al, 2021). Surgical intervention can be a traumatic procedure that significantly impacts the quality of life for patients (Hao et al, 2023). Surgery is often recommended when drugs and physical therapy yield unsatisfactory outcomes. Research has shown that the optimal strategy for treating neurotrophic keratitis involves restoring corneal nerve nutrient supply or stimulating corneal reinnervation and healing (Lambiase et al, 2012). Nerve growth factor (NGF), an immune regulatory and neurotrophic factor, is crucial in promoting the survival, proliferation, differentiation, and wound healing of sensory nerves (Beykin et al, 2022). Matsuyama et al (2017) conducted *in vivo* and *in vitro* experiments exploring the effects of NGF. Their results indicated that NGF could promote the production of substance P in the central and peripheral nervous system, restoring sensory neurons. Substance P, in turn, promoted the growth and synthesis of corneal epithelial cells. Furthermore, NGF stimulated the proliferation of epithelial cells when combined with acetylcholine.

Additionally, a case report demonstrated that NGF significantly enhanced punctate epithelial erosion, corneal sensation, and overall quality of life in individuals with stage I neurotrophic keratitis. While most cases showed enhancement, only one of the reported cases did not show significant improvement in best-corrected vision. These observations indicate the considerable therapeutic effect of NGF in treating this ailment (Epitropoulos and Weiss, 2022). A study by Mastropasqua et al (2020) showed that NGF promoted corneal healing in patients by increasing the number, density, and diameter of subbasal nerve branches in the cornea. Pflugfelder et al (2020) demonstrated a substantial improvement in the rate of corneal healing among individuals treated with NGF. However, to our knowledge, no meta-analysis has been conducted to assess the efficacy and safety of NGF in treating neurotrophic keratitis. Therefore, we conducted a meta-analysis to evaluate the therapeutic efficacy and safety of NGF in neurotrophic keratitis patients, aiming to provide a clinical basis for treating this condition.

Methods

Literature Search Strategy

A systematic search was conducted across various databases such as Wanfang, China National Knowledge Internet (CNKI), Embase, PubMed, Web of Science, and others. This literature survey included all published articles up to January 2024. The English keywords utilized for literature retrieval included “neurotrophic keratopathy”, “neurotrophic keratitis”, “cenegermin”, “Recombinant human NGF”, and “NGF”. Chinese keywords used were “neurotrophic keratitis”, “neuroparalytic

keratitis", "NGF", "recombinant human NGF", "Senegimine eye drops", and "rat NGF". Additionally, these articles were manually screened following retrieval to ensure the inclusion of all relevant literature meeting the required criteria.

This manuscript was written to comply with PRISMA guidelines (**Supplementary Table 1**). This includes a clear definition of research questions, a comprehensive literature search strategy, strict literature screening criteria, appropriate data extraction and analysis methods, and clear and transparent reporting of results.

Literature Inclusion Criteria

(1) The study subjects included in the literature were diagnosed with neurotrophic keratitis. (2) The middle groups described in the literature were treated with a neurotrophic factor alone or the combination of neurotrophic factor + standard therapy, and the contrast groups were treated with traditional therapy or carrier eye drops or a combination of traditional therapy/carrier eye drops + standard therapy. (3) The type of literature included was limited to randomized controlled trials (RCTs). (4) The study subjects were >18 years old. (5) The outcome indicators assessed in the literature included the therapy response rate (defined as the maximum diameter of fluorescein staining in the lesion area being <0.5 mm), corneal healing rate (defined as absence of fluorescein sodium staining in the lesion area and no other continuous staining), optimal vision correction (defined as an increase of 15 early treatment diabetic retinopathy study (ETDRS) letters or 3 rows on the eye chart), and the number of study subjects experiencing adverse events.

Literature Exclusion Criteria

(1) Individuals who met the cytological and pathological diagnostic criteria for clinical diagnosis, but the diagnostic results were irrelevant to this study. (2) Individuals who had been treated with neurofactors before the study. (3) Summary of the meeting. (4) The literature in which study subjects were considered independent. (5) Review, meta-analyses, and case reports were excluded. (6) Individuals with more severe blood ailments. (7) The follow-up loss rate was greater than 20% due to mid-follow-up withdrawal or interruption.

Literature Screening and Quality Assessment

The retrieved literature was individually screened by two expert reviewers utilizing the predetermined inclusion and exclusion criteria. In case of discrepancies during the screening process, inclusion or exclusion decisions were adopted through consensus between the two qualified reviewers or with the involvement of a third expert if needed. The quality of the included literature was carefully assessed, following the selection method outlined in the Cochrane Systematic Review Manual 5.3 (The Cochrane Collaboration, London, UK) (Sterne et al, 2019). Furthermore, bias within the retrieved manuscripts was described as "overtop or high bias (–)", "low bias (+)", or "unclear (?)" depending on the specific situation.

Data Extraction

During this study, two researchers independently extracted data from the given literature. Any uncertainties or questions in data extraction were resolved through

Table 1. Baseline characteristics of selected literature.

Author	Year	Set	Sufferers	Gender (Male/ Female)	Age	Therapeutic method	Course of therapy	Corneal healing effi- ciency	Corneal complete healing rate	Vision correc- tion rate	Illness progress	Adverse event
(Pflugfelder et al, 2020)	2020	Experimental set	24	10/14	65.9 ± 13.85	20 μg/mL rhNGF	8 weeks	15	14	3	5	10
		Contrast set	24	9/15	64.5 ± 14.15	Vehicle	8 weeks	6	3	4	12	8
(Bonini et al, 2018a)	2018	Experimental set 1	7	4/3	61.7 ± 21.47	10 μg/mL rhNGF	8 weeks	4	-	-	1	1
		Experimental set 2	7	3/4	52.0 ± 17.24	20 μg/mL rhNGF	8 weeks	6	-	-	0	3
		Contrast set	4	2/2	64.3 ± 14.06	Vehicle	8 weeks	1	-	-	0	1
(Bonini et al, 2018b)	2018	Experimental set 1	52	22/30	59.0 ± 17.17	10 μg/mL rhNGF	8 weeks	38	32	24	1	6
		Experimental set 2	52	22/30	62.5 ± 14.01	20 μg/mL rhNGF	8 weeks	37	36	17	0	9
		Contrast set	52	17/35	60.5 ± 16.78	Vehicle	8 weeks	22	17	9	2	10
(Li et al, 2011)	2011	Experimental set	31	-	-	mNGF	21 days	26	-	-	-	-
		Contrast set	40	-	-	Traditional therapy	21 days	25	-	-	-	-

NGF, nerve growth factor; rhNGF, recombinant human nerve growth factor; mNGF, mouse nerve growth factor.

discussion between them or with the involvement of a third expert. The extracted data included details such as the first author's name, publication date and year, number of study subjects in each dataset, participant ages, intervention approaches, duration of therapy, outcome indicators, and other relevant information.

Statistical Methods

The RevMan5.2 statistical software (version 5.2, Cochrane Collaboration, Oxford, UK) was employed to analyze categorical data. Relative risk (RR) with 95% confidence interval (CI) was applied for each effect size. Furthermore, heterogeneity was determined using the Chi-squared test. If heterogeneity analysis yielded a $p < 0.1$ and I^2 statistics $>50\%$, a random effects model was utilized for analysis. Otherwise, a fixed-effect model was used, and statistical significance was determined at a p-value of less than 0.05.

Results

Literature Screening Results and Quality Evaluation

After reviewing the titles and abstracts, 20 manuscripts were selected for subsequent screening. After this, the full text of these 20 literatures was obtained and thoroughly reviewed. Consequently, four randomized controlled trials (RCTs) were included in the final analysis (Fig. 1). The quality of the included literature was evaluated utilizing the Cochrane Systematic Review Manual 5.3 (The Cochrane Collaboration, London, UK). The outcomes of the literature quality assessment are shown in Fig. 2.

Basic Features of the Included Literature

We included 293 affected individuals in this study, with 120 participants in the contrast set and 173 in the experimental set. Among these 4 selected literatures, 3 were published in English, and 1 was in Chinese. The intervention in the observation set of 3 articles was recombinant human NGF, and the intervention in the observation set of 1 article was mouse NGF (Table 1).

Results of Meta-Analysis

Corneal Healing Efficiency

Corneal healing efficiency was evaluated across 4 RCTs. The overall heterogeneity analysis demonstrated no significant heterogeneity across all included studies ($I^2 = 0.0\%$, $p = 0.940$). A meta-analysis using a fixed-effect model indicated that corneal healing efficiency was better in neuroparalytic keratitis patients treated with neurotrophic factors (odds ratio (OR) = 1.72, 95% CI: 1.20–2.45). A summary of corneal efficacy analysis is depicted in Figs. 3,4.

Corneal Complete Healing Rate

A total of 2 literatures reported the rate of complete corneal healing in affected individuals after treatment. The overall effect size heterogeneity analysis revealed no substantial heterogeneity across all included studies ($I^2 = 0.0\%$, $p = 0.506$). Hence, a fixed-effect model was used in subsequent analysis. Meta-analysis re-

sults indicated that the corneal complete healing rate was significantly higher in the experimental set compared to the contrast set (OR = 2.23, 95% CI: 1.41–3.54), suggesting the promoting impact of NGF on corneal healing in patients (Figs. 5,6).

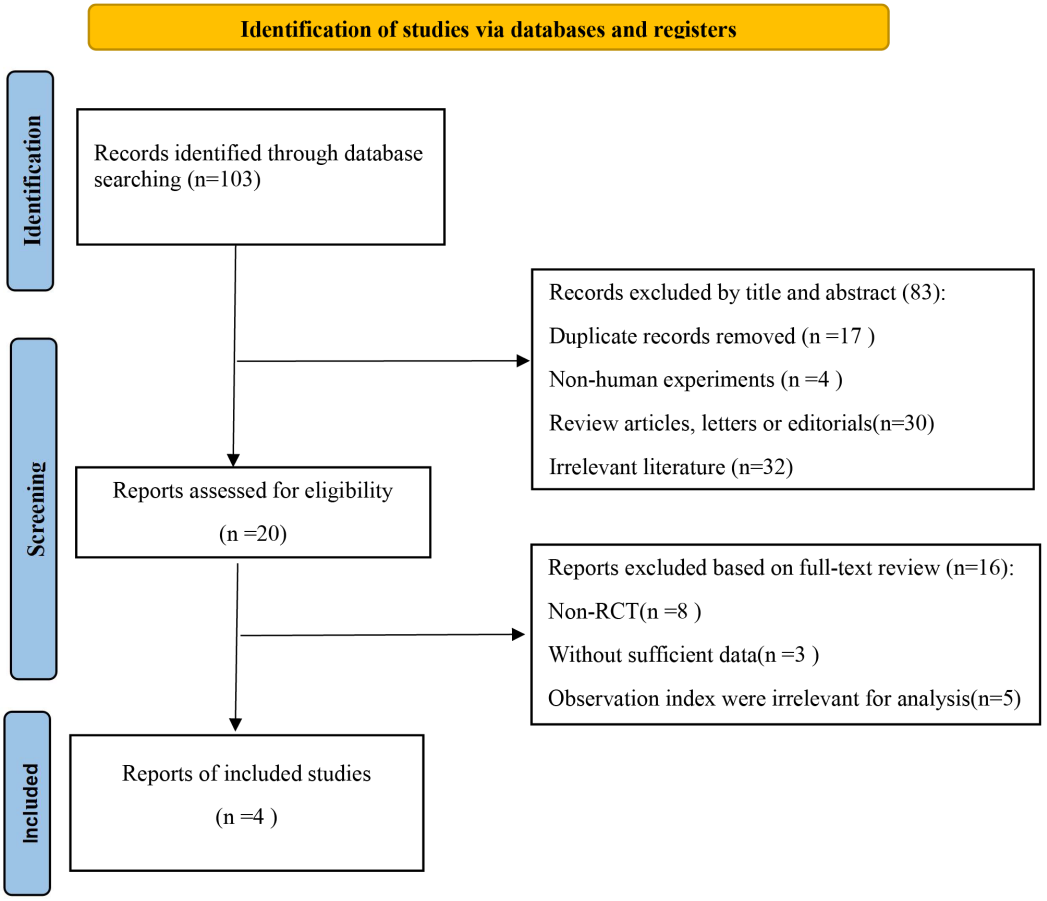

Fig. 1. A flow chart of literature screening. RCT, randomized controlled trial.

Vision Correction Rate

Two articles reported the rate of visual acuity correction in patients after therapy. The overall effect size heterogeneity analysis showed no significant heterogeneity across all included studies (I^2 = 0.0%, p = 0.389). The fixed-effect model was used for meta-analysis, demonstrating that the visual acuity correction rate was significantly elevated in the experimental group treated with NGF compared to the contrast set (OR = 1.97, 95% CI: 1.11–3.47), suggesting better visual acuity recovery in nerve paralytic keratitis patients treated with NGF (Figs. 7,8).

Ailment Progression

Three articles reported disease progression, and the overall effect size heterogeneity tests indicated low heterogeneity (I^2 = 0.0%, p = 0.812). As depicted in Figs. 9,10, analysis using the fixed-effect model revealed no significant difference in disease progression between the experimental group and the control group (OR = 0.44, 95% CI: 0.17–1.13).

Fig. 2. The quality assessment chart of the included literature. +, low risk bias; ?, uncertain risk bias; –, high risk bias.

Adverse Events

Three papers reported the occurrence of adverse events in patients after treatment. The overall effect size heterogeneity test indicated no significant heterogeneity across all included studies ($I^2 = 0.0\%$, $p = 0.875$). Therefore, meta-analysis using the fixed-effect model showed no significant difference in the number of adverse

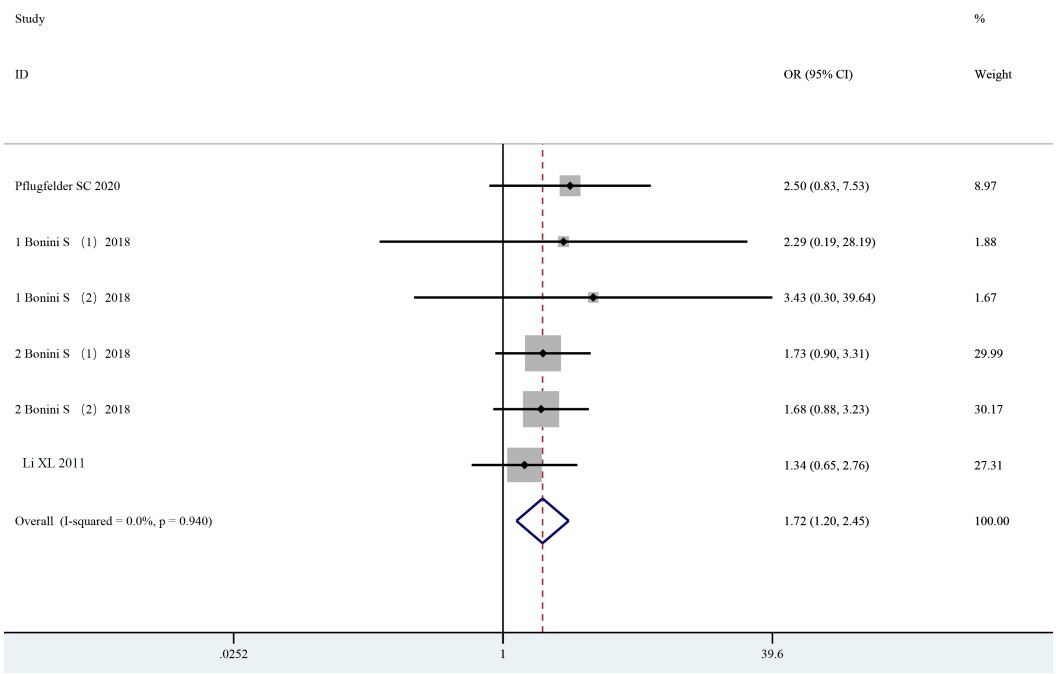

Fig. 3. Summary of corneal healing efficiency analysis within control and experimental groups after therapy. CI, confidence interval; OR, odds ratio.

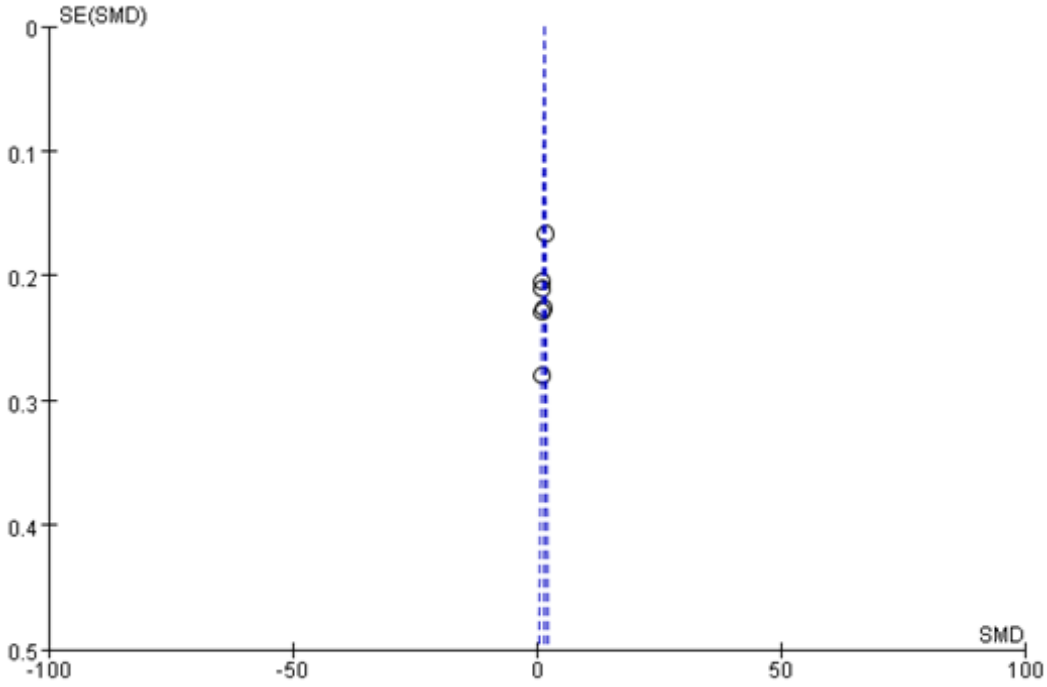

Fig. 4. Funnel diagram of corneal healing efficiency. SMD, Standardized mean difference; SE, Standard error.

events between the NGF treatment group and the control group (OR = 0.88, 95% CI: 0.50–1.56) (Figs. 11,12).

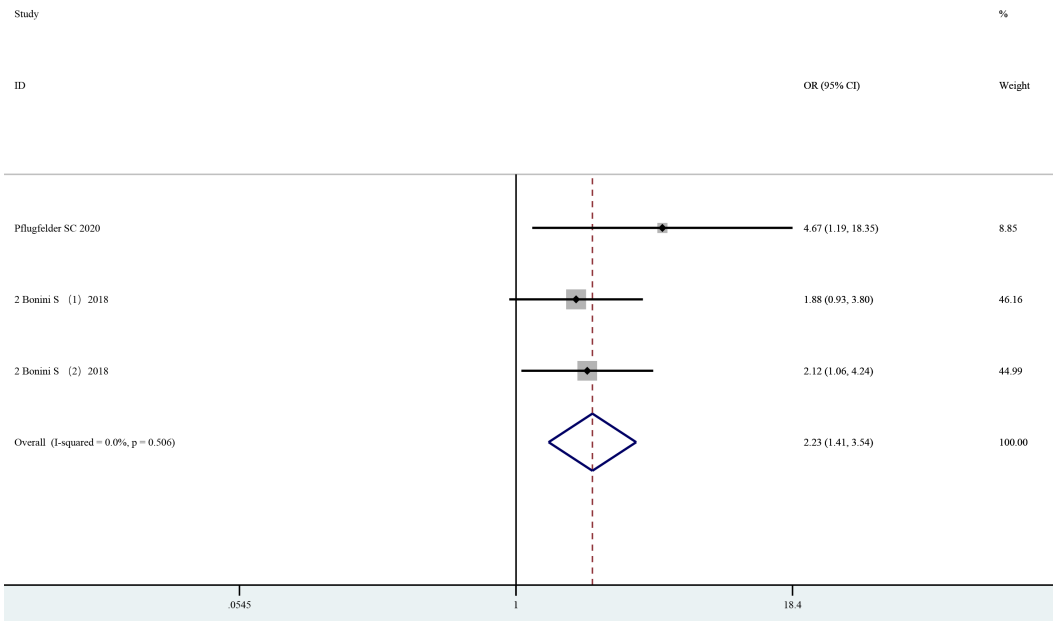

Fig. 5. Summary of corneal complete healing rate between contrast set and experimental set after treatment.

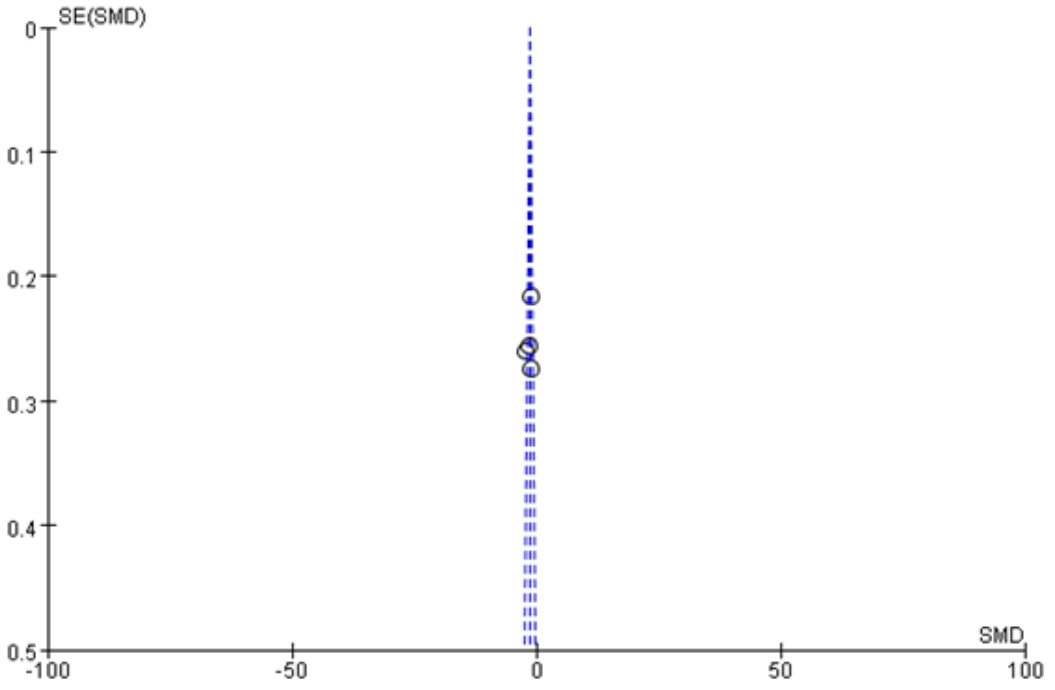

Fig. 6. Funnel diagram of corneal complete healing rate.

Discussion

Neuroparalytic keratitis is a relatively rare degenerative eye ailment primarily associated with eye disorders, neurological diseases, diabetes, and prolonged use of eye drops (Koay and Larkin, 2022). Research has shown that approximately 1.6–4.2 per 10,000 individuals are affected by this ailment (Neurotrophic Keratopathy Study Group, 2023). Despite its low prevalence, treating neuroparalytic keratitis

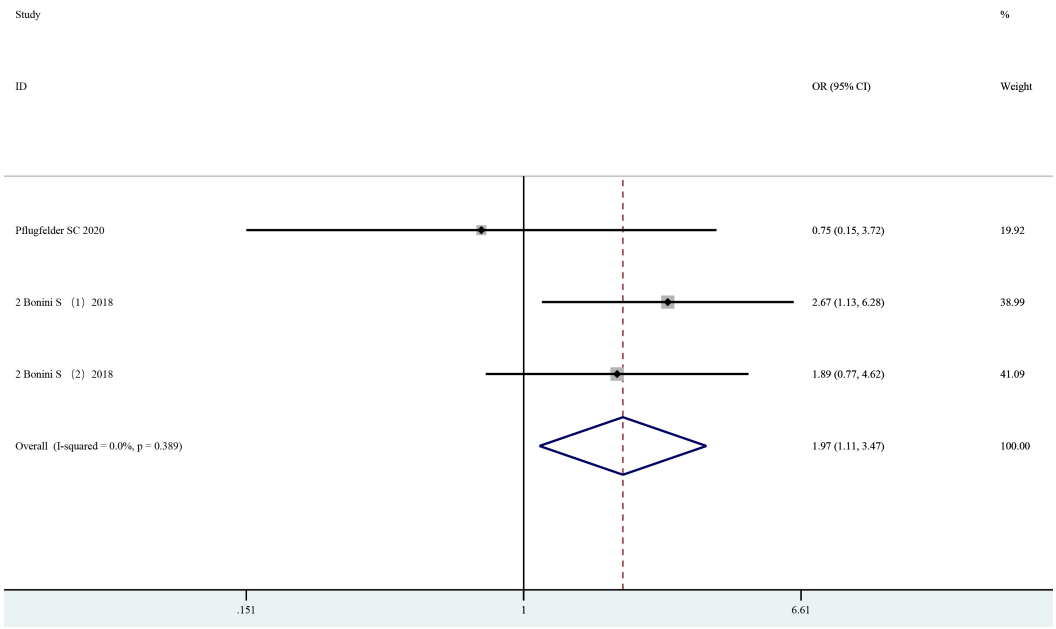

Fig. 7. Summary of visual acuity correction rates after therapy in the contrast set and experimental set.

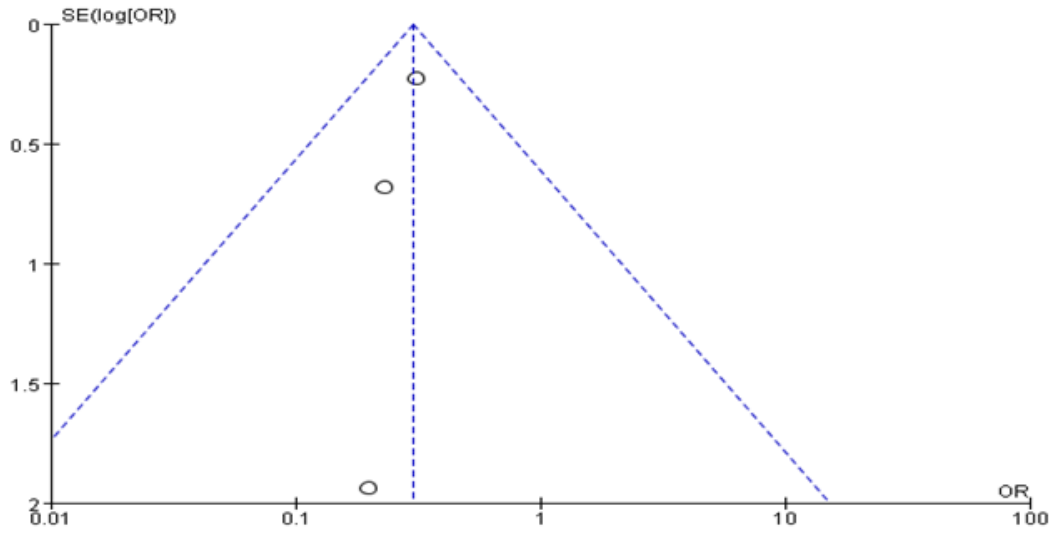

Fig. 8. Vision correction rate funnel diagram.

poses considerable challenges (Roth et al, 2022). Current therapeutic approaches to treat this condition include artificial tears, serum eye drops, amniotic membrane transplantation, and palpebral margin sutures (Weis et al, 2018). However, these treatment methods are often unable to cure this condition completely, and patients undergoing surgical therapy may experience vision loss (Mead et al, 2020). Research on neuroparalytic keratitis has revealed that NGF can be an effective treatment option with minimal side effects. For example, a study conducted by (Li et al, 2011) used rat NGF to treat neuroparalytic keratitis patients and observed a significantly higher therapeutic efficacy rate of 83.87% compared to 62.50% in the control group. However, the high-risk bias in the study by Li et al (2011) may have

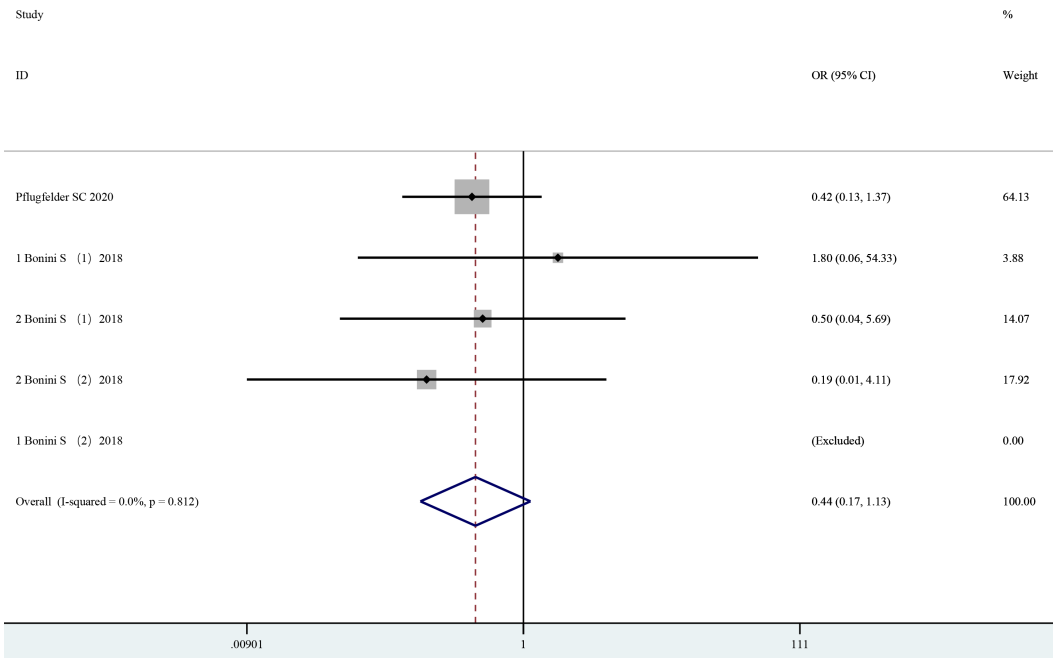

Fig. 9. Summary of ailment progression in the contrast set and experimental set after treatment.

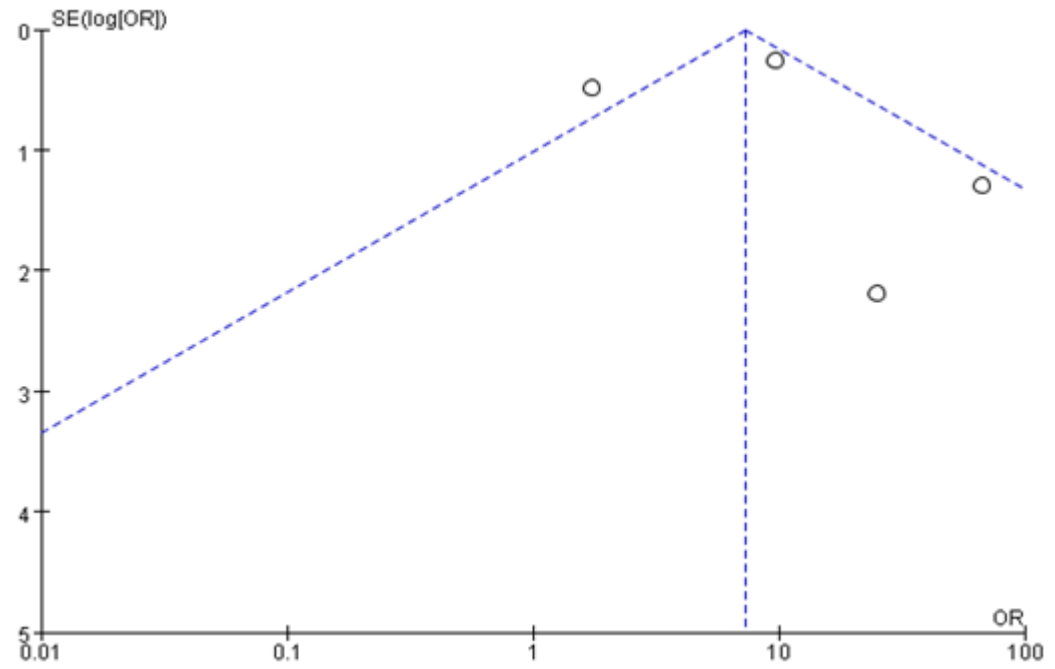

Fig. 10. Funnel diagram of ailment progression.

some impact on the results of this study, such as reducing the credibility of the conclusions and increasing the uncertainty of the results, making the conclusions less clear or limiting. Pocobelli et al (2020) used recombinant human NGF in corneal transplantation for individuals with functional monocular neurotrophic keratitis, indicating that recombinant human NGF could reduce the recurrence of the ailment without complications for the patients. Bonini et al (2018b) conducted a random-

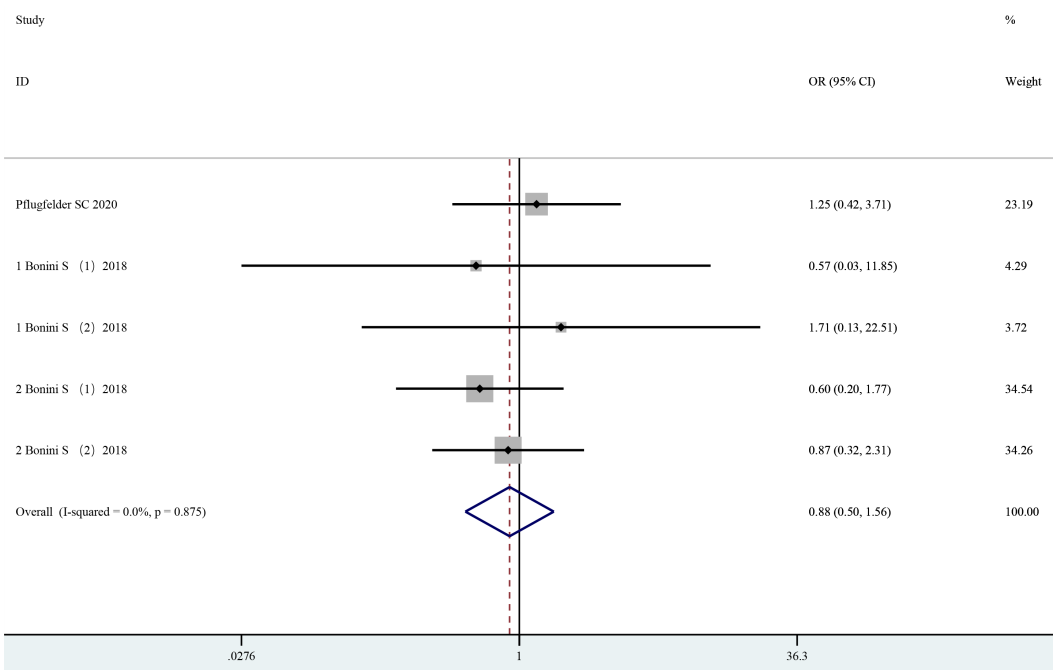

Fig. 11. The number of patients experiencing adverse events after therapy.

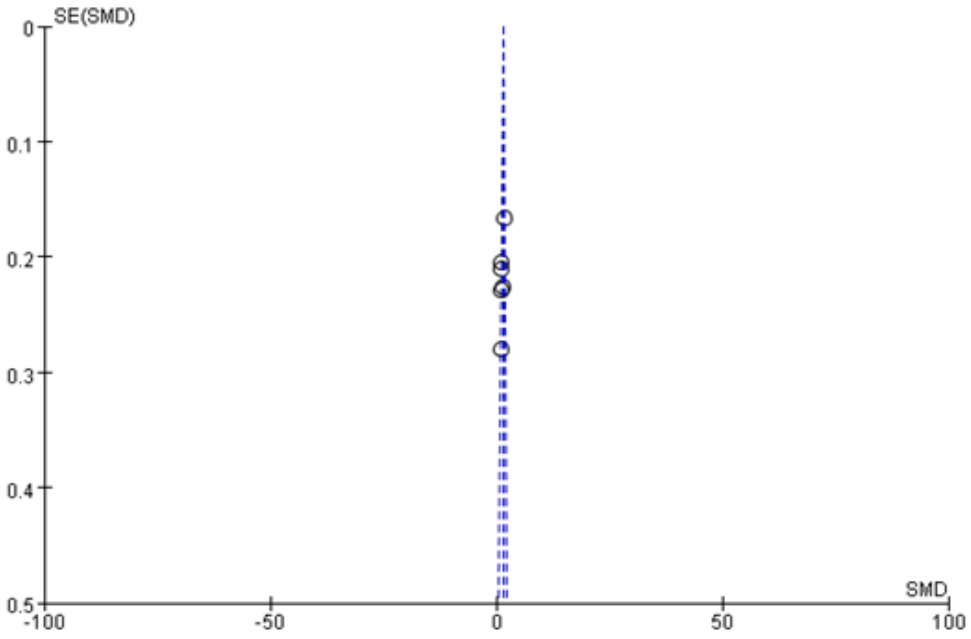

Fig. 12. Funnel diagram of adverse events.

ized, multicentre, double-blind, controlled trial, indicating that recombinant human NGF could promote corneal healing in neuroparalytic keratitis patients, resulting in improved corneal sensitivity. In the same year, recombinant human NGF was approved for treating this ailment in Europe and the United States. However, to our knowledge, the efficacy of NGF in treating neuroparalytic keratitis has not been systematically evaluated. Based on these facts, a meta-analysis was conducted to provide clinical evidence regarding the therapeutic effect of NGF in this ailment.

The findings of our study revealed that corneal healing efficiency (OR = 1.72, 95% CI: 1.20–2.45) and complete corneal healing rate (OR = 2.23, 95% CI: 1.41–3.54) were significantly higher in neuroparalytic keratitis patients treated with NGF compared to those without NGF therapy. Additionally, Hamrah et al (2024) demonstrated that the cornea of sufferers treated with NGF had significant enhancement, suggesting that NGF may continuously promote the healing of corneal epithelial defects in affected individuals. The effect is due to the high affinity of NGF for binding to Tropomyosin receptor kinase A and p75 neurotrophin receptor, which promotes and maintains the survival, proliferation, differentiation, and migration of cells (Marlin and Li, 2015). As a result, the corneal healing rate is significantly improved in NGF-treated patients. Similarly, the results of this study also found that the visual acuity correction rate in patients treated with NGF was substantially higher than in the contrast set (OR = 1.97, 95% CI: 1.11–3.47), aligning with the findings of Pflugfelder et al (2020), suggesting that NGF can enhance visual acuity. It is speculated that the ability of NGF to restore damaged neurons and induce neuron growth contributes to neuron regeneration (Liu et al, 2021), resulting in elevated nerve density and neuron count compared to before therapy, leading to enhanced vision in patients (Li et al, 2020).

Furthermore, the results of this study showed that the ailment progression (OR = 0.44, 95% CI: 0.17–1.13) and the incidence of adverse events (OR = 0.88, 95% CI: 0.50–1.56) in neuroparalytic keratitis patients treated with NGF were not significantly different from those in the contrast set. Recently, Kerstman et al (2013) also assessed adverse events in neuroparalytic keratitis patients treated with recombinant human NGF, indicating fewer adverse events in patients treated with NGF, with most of these adverse events unrelated to NGF therapy. Therefore, NGF therapy may have a significantly safer profile in treating neuroparalytic keratitis (Li et al, 2024).

This study has several limitations that need to be acknowledged: (1) The literature included in this study was relatively small, potentially impacting the research outcomes. (2) The treatment duration and drug dosage among the patients included in the literature were inconsistent, and due to the small number, subset analysis could not be performed, which might impact the results. (3) Some of the included studies have lower quality, elevating the risk of bias and affecting the accuracy of the research findings. Therefore, more RCTs need to be included in future investigations to demonstrate the efficacy of NGF in neuroparalytic keratitis patients.

Although this study has achieved certain research results, there are still some shortcomings. For example, 2 articles are from a unified study, and the included literatures are few, leading to certain biases in the results. Therefore, the number of included literatures should be expanded in future studies to further analyze the positive effect of nerve growth factor on improving neuroparalytic keratitis.

Conclusion

Neurotrophic keratitis is a degenerative disease of the cornea caused by damage to the trigeminal nerve from a variety of causes such as surgery, trauma, inflamma-

tion, and tumours, a condition that reduces the sensitivity of the cornea and disrupts its supply of nutrients. As a result, the cornea is more susceptible to harmful external factors, which can lead to corneal dryness and increased susceptibility to mechanical damage, and treatment for this disease mainly involves a combination of surgery, physical therapy and medication. This study found through meta-analysis that, for patients with neuropathic keratitis, NGF treatment can promote corneal healing efficiency, effectively improve visual correction, and reduce disease progression and incidence of adverse events to a large extent. The clinical effect and safety are high, and it is worthy of clinical promotion and application.

In the current medical field, neuropathic keratitis, as a difficult disease, has garnered attention. In recent years, the treatment of neuropathic keratitis has been explored and innovated. As a powerful research method, meta-analysis provides us with more comprehensive and reliable conclusions through the integration and analysis of a large number of relevant research data. In this study, we reviewed many clinical cases on the treatment of neurokeratitis in detail and adopted rigorous screening criteria and scientific data analysis methods. After in-depth research and systematic evaluation, we found that NGF treatment has shown significant advantages for patients with neurokeratitis. NGF treatment can not only promote the efficiency of corneal healing, effectively improve vision correction, but also reduce the incidence of disease progression and adverse events to a large extent. Its clinical efficacy and safety are high, and it is indeed worthy of clinical promotion and application.

Key Points

- This study aims to fill the gap that the clinical efficacy and safety of nerve growth factors in patients with neurotrophic keratitis have not been systematically evaluated.
- Through systematic retrieval of multiple databases and selection of articles according to strict criteria, comprehensive and accurate data sources are provided for the research.
- Authoritative evaluation tools and professional software were used to conduct an in-depth analysis of the quality and related data included in the study, ensuring the scientific nature of the study.
- The study results clearly showed that nerve growth factor treatment was significantly better than the control group in terms of corneal healing efficiency, complete healing rate and optimal vision correction rate.
- It also showed that there was no significant difference in the incidence of disease progression and adverse events between the experimental group and the control group.
- In general, nerve growth factor in the treatment of neurokeratitis has excellent clinical efficacy and safety, and has broad prospects for clinical promotion.

Availability of Data and Materials

The dataset analyzed during the current study are available request on the corresponding author.

Author Contributions

XL and AT designed the research study. XL and AT performed the research. AT analyzed the data. XL drafted the manuscript. Both authors contributed to important editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgement

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://www.magonlinelibrary.com/doi/suppl/10.12968/hmed.2024.0369.

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