USE AND EFFICACY OF INSULIN EYE DROPS IN NEUROTROPHIC CORNEAL ULCERS: A SYSTEMATIC LITERATURE REVIEW

ABSTRACT

This research aimed to analyse the use and efficacy of insulin eye drops in the treatment of neurotrophic corneal ulcers by means of a systematic literature review. To this end, relevant studies found in various databases were analysed, including PubMed, Scopus, Science Direct, Scielo, Bireme, Google Scholar and Web of Science. The selected studies were assessed in terms of their objectives, methodology, results and conclusions, with the aim of providing a comprehensive understanding of the current state of evidence on the subject. From the articles by Serrano-Giménez *et al*. (2020), Wang et al. (2017), Jaworski *et al* (2024), Tong et *al*. (2020), Khilji et *al*. (2023), Moreker et al. (2023), Soares *et al. (*2022), CUARTERO-MARTINEZ *et al.* (2022), Lorente-Pascua et *al*. (2022), Erin et *al*. (2022), Diaz-Valle *et al. (*2021), Dana *et al*. (2021) and Ruiz-Lozano *et al*. (2021), trends, knowledge gaps and recommendations for clinical practice and future research were identified. As a result, the studies analysed showed a variety of outcomes in relation to the efficacy and safety of insulin eye drops in the treatment of neurotrophic corneal ulcers. There was also a lack of standardisation in the methods used and the evaluation measures, highlighting the need for a more uniform approach in subsequent studies. The main trends identified indicate that insulin eye drops can be effective in treating corneal neurotrophic ulcers, especially in refractory stages. However, there is a need for further research to define more precise diagnostic criteria and more standardised assessment measures. In conclusion, this systematic review has provided a solid basis for future research into the use of insulin eye drops in the treatment of corneal neurotrophic ulcers. The recommendations resulting from this study have the potential to inform clinical practice and guide future research in this field, with the aim of improving these procedures for patients with this specific ophthalmological condition.

Keywords: Insulin eye drops; Corneal neurotrophic ulcers; Systematic review; Efficacy; Safety.

INTRODUCTION

Neurotrophic corneal ulcers represent a significant challenge in contemporary ophthalmology, especially when associated with conditions such as diabetes mellitus. The complexity of managing these ulcers demands innovative and effective approaches to improve healing and preserve corneal integrity. In this context, this

study aims to explore the potential use of insulin eye drops as a promising therapeutic strategy to optimise the healing process in neurotrophic corneal ulcers (CHANG *et al*., 2020). This pathology represents an important cause of morbidity in patients with chronic diseases. These ulcers are characterised by an imbalance in the healing process, resulting in chronic progression that can lead to serious complications, including corneal perforation and loss of vision. Faced with this challenging scenario, the search for innovative therapeutic interventions becomes imperative (ROSENBLATT *et al.*, 2020)).

Insulin, recognised for its fundamental role in glucose metabolism, has demonstrated properties beyond its traditional functions. Previous studies suggest that insulin may play a crucial role in cell regeneration and the healing process. This perspective raises the hypothesis that insulin eye drops may offer specific benefits in promoting the healing of neurotrophic corneal ulcers (SERRANO-GIMÉNEZ *et al*., 2020).

When reviewing the existing literature, it is possible to observe a significant gap in knowledge about the use of insulin eye drops in this specific context. While some research has investigated the effects of insulin on healing processes in other areas of the body, the direct application and specific results on the cornea still lack a systematic and comprehensive analysis (LEONG *et al*., 2023).

A systematic literature review is an essential methodological approach for consolidating and critically evaluating the available evidence on the topic in question. This study undertakes to carry out a rigorous systematic review, following the guidelines established by ABNT, with the aim of synthesising existing findings and identifying gaps in current knowledge (JAHAN *et al*., 2016).

The clinical relevance of this research lies in the prospect of offering an effective and innovative therapeutic intervention to improve outcomes in patients with neurotrophic corneal ulcers, and a greater understanding of the mechanisms by which insulin eye drops can influence the corneal healing process could open up new therapeutic possibilities and improve the quality of life of these patients (LEONG *et al*., 2023).

Therefore, this monograph aimed to make a significant contribution to the field of ophthalmology by exploring a potentially innovative therapeutic approach to the treatment of neurotrophic corneal ulcers. And this review will provide a critical and

comprehensive analysis of the available evidence, providing a solid basis for future research and clinical interventions in this crucial field of ophthalmological medicine.

MATERIALS AND METHODS

Collecting information

The methodology of this article was a systematic review of an integrative and analytical nature of a set of articles related to the general and specific objectives, which were obtained through a search of the PubMed, Scopus, Science Direct, ScieloBrasil, Bireme, Google Academico and Web of Science databases and Periódicos Capes, which show various publications from a variety of sources. Information was collected from the databases between the fifteenth of August 2023 and the end of January 2024. The search in the databases and the selection of the descriptor words used were guided by the objectives of this article.

Search strategy

After establishing the groups of articles that made up this research, the problem question of this systematic review and its objectives (general and specific) were stipulated. This was followed by a list of descriptors to guide the search in the databases. It was decided to use the same descriptors in the databases mentioned above. Once this had been done, with the articles already filtered, a brief reading of their published abstracts was carried out to decide which would be included or excluded from this work, and using the inclusion and exclusion criteria, 13 publications in the databases analysed were delimited for use.

Inclusion and exclusion criteria

The inclusion criteria were: to use publications available in full, in Portuguese, Spanish and English, published in the last 8 years, produced in Brazil and abroad; focused on the use of insulin eye drops in the treatment of neurotrophic corneal ulcers; and which identified and synthesised the main findings and trends in the field.

On the other hand, the exclusion criteria were as follows: publications that spoke exclusively about other types of ulcers or eye drops, articles that were incomplete or unavailable, publications older than eight (8) years.

Descriptors

The descriptors used to search PubMed, Scopus, Science Direct, ScieloBrasil, Bireme, Google Academic and Web of Science and Periódicos Capes were: insulin eye drops; neurotrophic corneal ulcers; treatment of neurotrophic corneal ulcers. In the search for journals, 35 peer-reviewed articles were found, of which 13 met our inclusion and exclusion criteria, which are listed in the references of this paper and ordered from 1 to 13 in the table of results in the next section.

Benefits

The benefits of this research include the identification of the main findings and trends in the field of treating neurotrophic corneal ulcers using insulin eye drops. And the contribution to organising the state of the art in this field and discussing its effectiveness in treating this pathology.

Limitations

The limitations of this research were the lack of studies from Eastern and African countries; in Cyrillic language; French and German. This may limit the framework for discussion of this research. It does not reflect a global reality regarding the use of these eye drops in different ethnicities and peoples.

RESULTS

We identified 35 studies using the expression "treatment of neurotrophic corneal ulcers with insulin eye drops" on the PubMed portal, as well as on the

ScieloBrasil, Scopus, Science Direct, Bireme, Google Academico, Web of Science and Periódicos Capes databases. Of the 35 studies, 15 were related to ScieloBrasil, 1 to Scopus, 1 to Bireme, 4 to PubMed, 1 to Science Direct, 5 to Google Scholar, 3 to Web of Science and 5 to Periódicos Capes. The criterion of complete reading was established only for articles published between 2017 and 2024, which addressed the use and efficacy of insulin eye drops in neurotrophic corneal ulcers.

After a thorough analysis of these publications and the application of exclusion criteria, 5 articles were selected from Scielo Brazil, 4 from PubMed, 1 from Google Scholar and 3 from Periódicos Capes, totalling 13 titles of interest. As for the type of study of the articles analysed, 4 studies adopted a quantitative approach, 4 adopted a qualitative approach and 5 presented a combination of the two approaches (see Table 1).

Within the scope of this study, there was a significant concentration of research into the treatment of neurotrophic corneal ulcers with insulin eye drops on the American (5), European (6) and Asian (2) continents. Furthermore, of the 13 studies selected, all were scientific articles, and none were master's dissertations or specialisation monographs.

All the studies focused on the binomial that converges to analyse the existing scientific literature on the use of insulin eye drops in the treatment of neurotrophic corneal ulcers, as well as identifying and synthesising the main findings and trends in the field.

It was also noted that the publications related to this topic occurred in 2017 (1); 2020 (2); 2021(3); 2022 (4); 2023 (2) and 2024 (1), with no publications recorded in 2019 and 2018, as shown in Table 1 below:

Table 1. Presentation of scientific publications on the use and efficacy of insulin eye drops in neurotrophic corneal ulcers with authors' names, years of publication, journal names, methodological approaches and main findings.

AUTHOR	YEAR	SOURCE	TYPE OF PUBLICATION	STUDY SITE	RELATIONSHIP WITH THE RESEARCH OBJECTIVES	METHODOLOGICAL APPROACH	MAIN FINDINGS
Jaworski *et al*.	2024	*Pharmaceutics* Magazine	Scientific article	Katowice (Poland)	This article reviewed the efficacy and current understanding of the mechanism of action of topical insulin in the treatment of neurotrophic keratopathy.	Literature review study.	Topical insulin has been shown to be effective in treating neurotrophic keratopathy. Topical insulin improved corneal wound healing.
Khilji *et al*.	2023	Cureus Magazine	Scientific article	Peshawar (Pakistan)	This article reports on the clinical evolution of a patient with neurotrophic keratopathy who was successfully treated with topical insulin.	This research was a case report.	A remarkable improvement in the condition of the treated patient was reported after one month, with a reduction in the size of the ulcer, and after two months the ulcer was completely re-epithelialised. This case report illustrated the use of topical insulin in the initial treatment of neurotrophic keratopathy. And not just its conventional use in refractory neurotrophic corneal ulcers.

Moreker *et al*.	2023	Indian Journal of Ophthalmology	Scientific article	Mumbai (India)	This article reports on the clinical evolution of 2 patients with neurotrophic keratopathy who were successfully treated with topical insulin.	This research was a case report.	Topical insulin drops can be used to treat NK that doesn't respond to conventional treatments. We hope to have more studies from other centres in our country to determine the ideal concentration of insulin drops, identify side effects and further characterise the patients who can benefit from this therapy.
Soares *et al.*	2022	Cornea Magazine	Scientific article	Porto (Portugal)	This study evaluated the clinical evolution of patients with refractory neurotrophic keratopathy (NK) in stages 2 and 3 after treatment with topical insulin.	Retrospective Research.	These results suggest that topical insulin drops may be an effective therapy in refractory NK. This therapy could be extremely useful due to its low cost and high accessibility.
Cuartero-Martinez *et al*.	2022	Hospital Pharmacy Magazine	Scientific article	Santiago de Compostela (Spain)	In this study, the physicochemical and microbiological stability of insulin eye drops over 120 days was	Quantitative and qualitative research.	Insulin eye drops made with saline remain stable for 120 days, whether stored at room temperature, in the fridge or freezer, as long as they are protected from light.

					determined and compared.		
Lorente-Pascua *et al*.	2022	Ibero Latin American Journal of Health System Pharmacy	Scientific article	Seville (Spain)	This study reports on the clinical evolution of a series of cases of patients with persistent corneal epithelial defects (CPED) treated with insulin eye drops.	Retrospective review associated with five case studies.	Insulin formulated as eye drops 1 U/mL and administered four times a day can be an effective and safe option for DPEC.
Erin *et al*.	2022	Magazine Annals of Medicine	Scientific article	Hawaii (USA)	Elucidate the current challenges and future prospects in the approach and treatment options for Neurotrophic Keratopathy (NK).	Literature review study.	Numerous topical treatment modalities can be employed to stabilise the disease. Curing NK with medical and surgical reinnervation has been an innovative therapy for appropriate candidates. New therapies on the horizon may broaden the provider's arsenal in treating patients at various stages of involvement. But more research is needed to continue to expand our knowledge of disease prevention, identification and treatment.

Diaz-Valle *et al*.	2021	Acta Ophthalmologica Magazine	Scientific article	Madrid (Spain)	To investigate the effect of topical insulin on epithelialisation in persistent epithelial defects (PED) refractory to the usual treatment compared to autologous serum.	The methodological approach of the study was retrospective and consecutive case-control.	Topical insulin is an effective treatment and safely promotes healing of DPE. In our series, topical insulin showed better epithelialisation results than autologous serum and could therefore be considered a first-line treatment.
Dana *et al*.	2021	BMC Ophthalmology Magazine	Scientific article	Boston (USA)	To shed more light on the identification, diagnosis and treatment of Neurotrophic Keratopathy (NK) through expert consensus.	Literature review study.	The findings of this article provide guidance for improving the quality of care for NK patients by recommending evidence-based treatments for each stage of the disease. However, further studies are needed to demonstrate whether these recommendations improve health outcomes and whether they will further advance the management of this relatively rare but serious disease.
					To review the diagnostic and therapeutic implications of the molecular		This review has described up-to-date knowledge of the molecular basis of NK pathogenesis and the new target-specific therapeutic

Ruiz-Lozano *et al*.	2021	The Ocular Surface Magazine	Scientific article	Monterrey (Mexico)	basis of neurotrophic keratopathy (NK).	Literature review study.	approaches based on this molecular mechanism.
Tong *et al*.	2020	Journal Of Ophthalmology	Scientific article	Vancouver Alberta (Canada)	This study reports a case of bilateral neurotrophic keratitis (NK) that was successfully treated with topical insulin and reviews the existing literature on the subject. The aim was to explore the usefulness of topical insulin in the armoury for treating NK when conventional methods have failed.	This research was a review study with a case report.	Topical insulin drops (25 IU/mL) can be used to successfully treat neurotrophic corneal ulcers that do not respond to conventional treatments. It could be an effective and affordable therapy for bilateral NK where conventional treatments have failed. However, more studies are needed to determine the ideal concentration of insulin drops, identify side effects and further characterise the patients and underlying etiologies of NK that may benefit. Therefore, insulin eye drops have shown potential to promote the healing of Neurotrophic Keratitis, suggesting their viability as a therapeutic option.
					This study presented a case study of the use of a formulation of		The use of an insulin drop formulation in the treatment of non-diabetic patients with post-calcific corneal ulcers, refractory to conventional therapy, was

Serrano-Giménez *et al*.	2020	Hospital Pharmacy Magazine	Scientific article	Seville (Spain)	insulin drops with efficacy and absence of toxicity in a non-diabetic patient with a post-calculous corneal ulcer.	This research was a case report.	carried out effectively and without toxicity. On the other hand, it is also desirable, in future studies, to create formulations with a longer stability time, especially microbiological, for greater patient convenience. Therefore, the use of insulin eye drops was associated with significant improvements in the healing of corneal ulcers, highlighting its therapeutic potential.
Wang *et al*.	2017	Cornea Magazine	Scientific article	Wisconsin (USA)	This study reported on the clinical evolution of 6 patients with refractory neurotrophic corneal ulcers who were treated with topical insulin drops. To investigate the effects of insulin on corneal healing.	This study was a retrospective review of medical records, concatenating 6 case reports.	Topical insulin may be a simple and effective treatment for refractory neurotrophic corneal ulcers. More studies are needed to determine the clinical efficacy and side effect profile of insulin drops. Therefore, insulin administration was associated with a significant acceleration in corneal wound healing, indicating its therapeutic potential in corneal ulcers.

This table provided an overview of the research framework that makes up the state of the art on the use and efficacy of insulin eye drops in the treatment of neurotrophic corneal ulcers, providing a comprehensive view of the different findings presented by renowned researchers around the world. Among the studies analysed, the work of Jaworski *et al.* (2024) stood out. Through a detailed and comprehensive study, they emphasised the remarkable efficacy of topical insulin in promoting the healing of corneal ulcers. These results are corroborated by the findings of Morekere*t al.* (2023), who also highlighted the usefulness of insulin drops in refractory cases of neurotrophic keratopathy, offering a valuable perspective on the effectiveness of this treatment. Soares *et al.* (2022) contributed to the picture, suggesting that topical insulin drops not only represented an effective therapy, but were also affordable, presenting themselves as an attractive option for refractory neurotrophic keratopathy cases. This retrospective study pointed to the economic viability of this approach, highlighting its potential positive impact on the management of the condition. Meanwhile, the studies by Cuartero-Martinez *et al.* (2022) and Lorente-Pascua *et al.* (2022) made valuable contributions by addressing the physicochemical and microbiological stability of insulin eye drops. By revealing that the formulation remained stable for up to 120 days under different storage conditions, these studies provide crucial information for the practical implementation of the treatment. In addition, the study by Lorente-Pascua *et al.* (2022) highlighted the efficacy of insulin eye drops in promoting the healing of persistent corneal epithelial defects. Khilji *et al.* (2023) and Tong *et al.* (2020) complemented the scenario by presenting cases of successful treatment of corneal ulcers with topical insulin, indicating its effectiveness when conventional methods fail. In addition, the study by Khilji *et al.* (2023) also reinforced the relevance of this approach by reporting a notable improvement in the condition of treated patients, showing a reduction in ulcer size and complete re-epithelialisation after two months.

Wang *et al.* (2017) provided an additional perspective by suggesting that topical insulin drops could be a therapeutic alternative for refractory ulcers, emphasising the importance of exploring new options in the face of persistent clinical challenges. And this innovative approach presented itself as a possible

solution for complex cases of bilateral neurotrophic keratitis, but also recommended the need for further studies to improve these treatment protocols. In parallel, Erin *et al.* (2022) emphasised the importance of advancing knowledge about the use of topical insulin, highlighting the diversity of topical treatment modalities available to stabilise the disease. They also encourage the continuous expansion of knowledge in the prevention, identification and treatment of ophthalmological diseases. Diaz-Valle *et al.* (2021) presented valuable findings when investigating the effect of topical insulin on epithelialisation in persistent epithelial defects refractory to usual treatment, highlighting the efficacy and safety of topical insulin, and reinforcing the position of this approach as a viable alternative to conventional treatment with autologous serum. In addition, Dana *et al.* (2021) addressed the need for consensus in the identification, diagnosis and treatment of Neurotrophic Keratopathy (NK), providing valuable guidelines to improve the quality of patient care. Their findings suggested the importance of evidence-based treatments for each stage of the disease, indicating a promising path for the management of this clinical condition. Ruiz-Lozano *et al.* (2021) carried out a review on the diagnostic and therapeutic implications of neurotrophic keratopathy, highlighting the need to understand the molecular basis and new specific therapeutic approaches. They also emphasised, through their detailed review, the need for a solid basis for future research that could improve understanding of the pathogenesis of NK.

In the same vein, Tong *et al.* (2020) provided evidence, through a review study associated with a case report, which demonstrated that topical insulin drops can be used successfully to treat neurotrophic corneal ulcers that have not responded to conventional treatments, pointing to the potential efficacy of insulin drops as an affordable and effective therapeutic option for refractory cases. Similarly, Serrano-Giménez *et al.* (2020) shared their experience of using insulin drops in a non-diabetic patient with a post-capillary corneal ulcer. Their case report highlighted the efficacy and absence of toxicity associated with the use of insulin eye drops, reinforcing the safety of this approach in specific cases.

That said, these diverse perspectives have revealed a general consensus on the potential efficacy of insulin eye drops in the treatment of

refractory neurotrophic corneal ulcers. However, it is clear that there are still gaps to be filled, and more research is needed to establish standardised protocols, identify possible side effects and optimise the ideal concentrations of the eye drops. The current outlook suggests that this innovative therapeutic approach has the potential to revolutionise the treatment of challenging ophthalmic conditions, offering new hope for patients who face significant difficulties in the conventional management of these conditions. Table 1 therefore provides a summary of the most recent and relevant findings on the use of insulin eye drops in the treatment of neurotrophic corneal ulcers, and the diversity of perspectives and approaches highlighted by the different studies underscore the complexity of this area of research and the ongoing need for investigations to improve the understanding, application and optimisation of this innovative therapy. Insulin eye drops have therefore emerged as a promising option, but their definitive clinical role still requires more extensive validation through randomised controlled clinical trials. However, this amalgam of information offered a solid basis for guiding future research and eventually integrating insulin eye drops as a valuable tool in the therapeutic armoury for refractory neurotrophic corneal ulcers.

DISCUSSION

In this session, the results obtained in this study were discussed in the light of comparisons with similar and contrary findings in the literature, as well as comparisons of the theoretical data that elucidate the phenomena found here with other studies. Firstly, they were compared to the findings of other researchers who have exclusively investigated insulin eye drops in neurotrophic corneal ulcers; secondly, they were compared to the findings of studies with other types of ocular ulcers, methodology and objectives similar to those of this study. Finally, the phenomena found in this research were discussed with studies that elucidate and/or touch on them, in order to explain the data reported in the previous section of this research, but which had not been reported in the articles in this field of study. For this reason, the most accessible and relevant published works were shown below, as well as the most prominent findings in the 2 categories addressed in this research: identifying and

synthesising the main findings and trends in the field and discussing the use and efficacy of insulin eye drops in the treatment of neurotrophic corneal ulcers in the studies shown in Table 1.

STATE-OF-THE-ART RESEARCH INTO THE USE OF INSULIN EYE DROPS IN THE TREATMENT OF NEUROTROPHIC CORNEAL ULCERS

The systematic review carried out, covering a thorough search of various databases (PubMed, Scopus, Science Direct, Scielo, Bireme, Google Scholar and Web of Science), provided an in-depth analysis of the use of insulin eye drops in the treatment of neurotrophic corneal ulcers. Jaworski *et al*. (2024), in their review of the current understanding of the mechanism of action and therapeutic approach, emphasised the importance of understanding corneal insulin receptors, highlighting the need for further studies to fully elucidate this process. It serves as a crucial foundation for understanding the molecular and pharmacological aspects involved in the proposed treatment. In parallel, Khilji *et al*. (2023), through a case study, presented a valuable clinical perspective on the use of insulin eye drops in specific cases of neurotrophic keratopathy. This practical approach corroborated the importance of the systematic review by providing direct clinical evidence to support the applicability of this innovative therapy. And the inclusion of clinical cases reinforced the relevance of insulin eye drops in different clinical situations. Morekere*t al*. (2023) made a significant contribution by reviewing studies that investigated the benefits of insulin eye drops in cases of neurotrophic keratitis. Above all, by synthesising the results of these studies, the study highlighted the clinical usefulness of insulin eye drops, reinforcing their effectiveness in a variety of contexts. This comprehensive analysis has broadened our understanding of the potential benefits of this therapy. In the same vein, Soares *et al*. (2022), by evaluating the usefulness and results of insulin eye drops in stages 2 and 3 of refractory neurotrophic keratopathy, provided a practical and straightforward perspective on the clinical application of this approach. While their results provided valuable data that contributed to the scientific foundation needed to implement insulin eye drops in ophthalmological practice. Furthermore, Cuartero-Martinez *et al*. (2022) addressed the stability of insulin eye drops, a fundamental aspect for their

practical application. By considering the stability of the drug, this study provided crucial information for the development of reliable clinical protocols, emphasising the importance of proper handling of insulin eye drops. Likewise, Lorente-Pascua *et al*. (2022), through a series of cases, enriched the discussion by presenting a deeper understanding of the application of insulin eye drops in refractory corneal epithelial defects. The analysis of clinical cases contributed to the practical contextualisation of the use of insulin eye drops, providing important observational data. Similarly, Erin *et al*. (2022) offered a comprehensive overview of the current challenges and future prospects related to neurotrophic keratopathy. They also highlighted the complexity of the condition and the need for innovation in therapeutic strategies. The inclusion of insulin eye drops in their discussion of treatment emphasises their potential role in future clinical guidelines for this pathology. Ratifying these findings, Diaz-Valle *et al*. (2021) made a significant contribution by comparing the efficacy of insulin eye drops with autologous serum eye drops in persistent epithelial defects. And this comparison provided valuable insight into the relative effectiveness of these approaches, highlighting insulin eye drops as an alternative worthy of consideration. Furthermore, Dana *et al*. (2021), in presenting an expert consensus on the identification, diagnosis and treatment of neurotrophic keratopathy, integrated insulin eye drops into the clinical context. Their contribution is vital for standardising and improving the quality of patient care, recognising insulin eye drops as an integral part of therapeutic approaches. (2021) provided a comprehensive review of the molecular basis of neurotrophic keratopathy, exploring diagnostic and therapeutic implications. And their critical analysis highlighted the potential role of insulin eye drops in molecular intervention, indicating new directions for future research. In addition, Serrano-Giménez *et al*. (2020) presented a successful case using insulin eye drops in a non-diabetic patient with a post-calculous corneal ulcer. This practical contribution reinforced the applicability of insulin eye drops in specific cases, highlighting their potential in challenging clinical situations.

That said, this systematic review was enriched by the diversity of perspectives offered by these studies, providing an in-depth understanding of the use of insulin eye drops in the treatment of neurotrophic corneal ulcers. In addition, the variety of clinical contexts addressed by the studies highlighted the

need for personalised assessments to determine the best application of insulin eye drops in different clinical situations, thus contributing to a complete overview of the current state of the evidence on the subject.

COMPARISON OF STATE-OF-THE-ART EVIDENCE ON THE USE OF INSULIN EYE DROPS IN PATIENTS WITH NEUROTROPHIC CORNEAL ULCERS

The review on the use of insulin eye drops in the treatment of neurotrophic corneal ulcers provided a comprehensive and critical analysis of the available scientific evidence, presenting a detailed overview of the current state of research on the subject. Khilji *et al*. (2023) contributed a study that highlighted the efficacy of topical insulin therapy in patients with neurotrophic keratopathy, providing direct clinical evidence on the applicability of this approach. By presenting tangible results that reinforced the importance of insulin eye drops as an effective therapeutic option in specific clinical situations. Morekeret *al*. (2023) addressed the use of insulin eye drops in cases of neurotrophic keratitis, highlighting the usefulness of insulin eye drops, corroborating the idea that this therapeutic modality can represent a promising intervention for refractory situations. Soares *et al*. (2022) brought a practical perspective by evaluating the usefulness and results of insulin eye drops in stages 2 and 3 of refractory neurotrophic keratopathy, suggesting that insulin eye drops can be effective in different stages of the condition. According to Lorente-Pascua *et al*. (2022) who presented a case series that provided a deeper understanding of the application of insulin eye drops in refractory corneal epithelial defects. To further corroborate the clinical evidence, and broaden the range of situations in which insulin eye drops can be considered as an integral part of treatment. Erin *et al*. (2022) touched on the current challenges, future perspectives, as well as a discussion on the use of insulin eye drops emerging as a promising element for future investigations related to neurotrophic keratopathy. In parallel, Diaz-Valle *et al*. (2021) compared the efficacy of insulin eye drops with autologous serum eye drops in persistent epithelial defects, providing insight into the relative efficacy of these approaches, highlighting insulin eye drops as an alternative worthy of

therapeutic application. In addition, Dana *et al*. (2021) offered an expert consensus on the treatment of neurotrophic keratopathy. And the inclusion of insulin eye drops in treatment discussions emphasised their potential role in future clinical guidelines. In the same vein, Ruiz-Lozano *et al*. (2021) took a critical look at the gaps in the current understanding and treatment of neurotrophic keratopathy and suggested the potential role of insulin eye drops in therapeutic intervention. Ratifying these findings, Serrano-Giménez *et al*. (2020) presented a successful case using insulin eye drops in a non-diabetic patient with a post-capillary corneal ulcer, reinforcing the applicability of insulin eye drops in specific cases and highlighting their potential in challenging clinical situations.

Bringing these perspectives together has highlighted the complexity and richness of research into the use of insulin eye drops in neurotrophic corneal ulcers. And it can be seen that while some studies provided robust evidence of clinical efficacy, others addressed practical issues and drug stability, but all contributed to a comprehensive understanding of this innovative therapeutic approach. The diversity of clinical contexts addressed by the studies highlighted the need for personalised assessments to determine the best application of insulin eye drops in different clinical situations, thus providing a complete overview of the current state of the evidence on the subject.

ANALYSIS OF CLINICAL VARIABLES, OUTCOMES AND SAFETY MEASURES USED WITH INSULIN EYE DROPS IN THE HEALING OF CORNEAL ULCERS

Analysing the results of the selected studies, highlighting clinical variables, outcomes and measures to assess the efficacy and safety of insulin eye drops in healing corneal ulcers, was essential to support discussions on the subject. Researchers have contributed significantly to this analysis, offering diverse and enriching perspectives. Such as Jaworski *et al*. (2024), who emphasised the importance of assessing the response of corneal insulin receptors. They also highlighted clinical variables related to the expression of these receptors, providing insights into possible correlations with the clinical efficacy of the treatment. Khilji *et al*. (2023), on the other hand, presented

clinical data, their measures used, and specific clinical outcomes on the practical application of insulin eye drops. These measures were used to assess the efficacy of the treatment, and in this context, were fundamental to understanding the patient's response. Morekere*t al*. (2023) made a significant contribution by analysing clinical variables, such as the extent of the lesion and healing time, which were discussed in the studies on the use of insulin eye drops in neurotrophic keratitis, thus providing a comprehensive view of the outcomes observed in the different clinical contexts addressed. According to Soares *et al*. (2022), by focussing their research on the usefulness and results in refractory stages of neurotrophic keratopathy, they offered a specific analysis of the efficacy of insulin eye drops in more advanced cases. In addition to the clinical variables related to the severity of the condition, which were fundamental to understanding the applicability of the treatment at different stages of the disease. At the same time, Cuartero-Martinez *et al*. (2022) addressed the stability of insulin eye drops, a crucial variable in guaranteeing the efficacy and safety of the treatment. They also highlighted the measures used to assess this stability, which was essential for establishing reliable clinical protocols to guarantee the efficacy of insulin eye drops. In addition, Lorente-Pascua *et al*. (2022), by presenting a series of cases, enriched the analysis by highlighting specific clinical outcomes for each patient. The individualisation of the response to treatment was also highlighted, underscoring in this study the importance of considering personalised clinical variables to assess the efficacy of insulin eye drops. In the same vein, Diaz-Valle *et al*. (2021) made a significant contribution by comparing the efficacy of insulin eye drops with autologous serum eye drops. In this research, the measures used for this comparison were crucial to understanding the relative efficacy of these approaches, providing important data on the safety and efficacy of insulin eye drops. In addition, Erin *et al*. (2022) offered a comprehensive overview of the current challenges in neurotrophic keratopathy, including clinical variables related to resistance to conventional treatment. Their discussion of the efficacy of insulin eye drops in refractory patients also highlighted the need for personalised measures for assessment. As did Dana *et al*. (2021), who highlighted the need for standardised treatment criteria. They contributed with a clear definition of vital standardised clinical outcomes to assess the efficacy of

insulin eye drops in a uniform manner, contributing to the validation of their clinical use. Similarly, Ruiz-Lozano *et al*. (2021) provided an analysis of molecular and clinical endpoints, which offered an integrated perspective, indicating that measures related to gene expression can complement the clinical evaluation of insulin eye drops' efficacy. Ratifying these findings, Serrano-Giménez *et al*. (2020), in presenting a successful case, highlighted specific clinical variables in this non-diabetic patient. This approach once again reinforced the importance of considering individual characteristics when assessing the efficacy of insulin eye drops in different populations.

Therefore, analysing the results of the selected studies highlighted the complexity of assessing the efficacy and safety of insulin eye drops in healing corneal ulcers. As well as the individualisation of the measures, taking into account the specific clinical variables of each study, it was essential to fully understand the impact of this therapeutic innovation on ophthalmic practice. It should also be emphasised that these integrated approaches, considering both clinical and molecular aspects, contributed to a comprehensive view of the current state of the evidence on the subject.

MAIN TRENDS, KNOWLEDGE GAPS AND RECOMMENDATIONS IN THE FIELD OF TREATING NEUROTROPHIC CORNEAL ULCERS WITH INSULIN EYE DROPS

The concatenation of the findings of the systematic review on the use of insulin eye drops in the treatment of neurotrophic corneal ulcers revealed a range of perspectives, trends and recommendations from the various authors involved in the studies. The following summarises the opinions of each author in this regard: More recently, Jaworski *et al.* (2024) provided an up-to-date understanding from a molecular perspective, which may be a knowledge gap, especially in clinical efficacy, essential to understanding the mechanisms involved in clinical efficacy. According to Khilji *et al*. (2023), the direct clinical approach with the use of insulin eye drops contributed to the creation of practical recommendations in the approach to corneal neurotrophic ulcers, suggesting the real applicability of the treatment. As for Morekere*t al*. (2023), the specific analysis of efficacy, in terms of variables such as the extent of the

lesion and healing time, filled an important knowledge gap in this field. In parallel, Soares *et al*. (2022) also deepened the discussion by highlighting the need to consider the severity of the condition in order to optimise the clinical results related to the use of insulin eye drops in refractory stages. In the same vein, Cuartero-Martinez *et al*. (2022), by focussing on the stability parameters of insulin eye drops as a therapeutic resource, highlighted a practical concern that could have a direct impact on the efficacy and safety of the treatment if left unresearched. Furthermore, Lorente-Pascua *et al*. (2022), by presenting a series of cases, enriched the discussion by considering unique clinical variables, suggesting a more personalised treatment perspective. Likewise, Erin *et al*. (2022) provided valuable recommendations through their broad approach, but also covered not only the immediate clinical efficacy, but also the ongoing challenges and future improvement possibilities against neurotrophic keratopathy. Similarly, Diaz-Valle *et al*. (2021) also contributed to the practical recommendations for treatment with eye drops, especially when considering the choice between alternative treatments with insulin and autologous serum eye drops. Ratifying these findings, Dana *et al*. (2021), by presenting the standardisation of diagnostic criteria, was essential for the standardisation of consistent assessments of the efficacy of insulin eye drops. And the combined analysis of these studies highlighted a general trend towards the efficacy of insulin eye drops in the treatment of neurotrophic corneal ulcers. However, gaps in knowledge, such as the need for more diagnostic criteria and a greater understanding of the molecular basis, suggest directions for future research. The practical recommendations derived from these findings could guide clinical practice and contribute to significant advances in the field of ophthalmology.

CONCLUSION

In view of the extensive analysis and synthesis carried out on the relevant studies on the use of insulin eye drops in the treatment of neurotrophic corneal ulcers, valuable conclusions emerged that have significant implications for clinical practice and future research. Especially when looking at the studies listed, which provided a comprehensive overview of the efficacy and safety of insulin eye drops. And in the context of the systematic search carried out, the

studies identified shed light on the current state of the evidence. However, there was still a lack of standardisation in the methods used by these studies, from diagnostic criteria to evaluation measures, which highlighted a gap that deserves attention in future research. And the diversity in the clinical variables analysed also highlighted the need for a more uniform approach in subsequent studies. In addition, the careful analysis of the results made it possible to identify promising trends. For example, the efficacy of insulin eye drops, especially in refractory stages, was consistently highlighted. However, the lack of consensus on certain aspects, such as the best way to assess treatment success, highlighted the complexity of the subject.

Therefore, in trying to concatenate the findings of this systematic review, interesting guidelines for clinical practice were elucidated and recommendations on more uniform diagnostic criteria, as well as standardised assessment measures, and specific considerations for refractory stages were highlighted. Furthermore, these conclusions had the potential to inform clinical decision-making; optimise treatment efficacy and improve outcomes for patients with neurotrophic corneal ulcers. And, for future medical specialists in Ophthalmology, it is essential to recognise that research in this area is dynamic and ongoing. As well, this review has provided a solid foundation for future research, highlighting specific gaps and areas that need further investigation. That said, a comprehensive understanding of the current state of the evidence, by analysing these studies, will serve as a guide for future discoveries and improvements in the clinical approach to corneal neurotrophic ulcers with the use of insulin eye drops.

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