Original article

Effectiveness of topical autologous serum treatment in neurotrophic keratopathy

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ABSTRACT

Objective: To evaluate the effectiveness of 20% autologous serum as a treatment for neurotrophic keratopathy.

Material and methods: A longitudinal, observational and descriptive study was performed on 19 patients (22 eyes) with neurotrophic keratopathy in different stages of Mackie’s classification. The following variables were evaluated on the first visit, and then 4 months later: best corrected visual acuity (BCVA), subjective patient symptomatology (faces scale), Schirmer’s test without anesthesia (mm), tear film break-up time (BUT) (sg) and healing of the epithelial defect (weeks). The Wilcoxon signed-rank test was used for the statistical analysis of the data.

Results: A symptomatic improvement was observed in 100% of the cases, and a 71% improvement in best corrected visual acuity (P < .05). There was also a statistically significant improvement in the Schirmer’s test and BUT (P < .05). Healing of epithelial defect occurred in 71% of the cases within 6 weeks, and in 91% of the cases within 12 weeks of treatment. The remaining 9% of the cases that did not heal had a grade 3 neurotrophic keratopathy.

Conclusions: The use of 20% autologous topical serum represents an effective treatment for grades 1 and 2 neurotrophic keratopathy, but is an insufficient treatment for a grade 3 keratopathy. In cases where there is a significant loss of tissue, the application of a higher concentration of autologous serum, or platelet-rich derivatives, or plasma rich in growth factors, may be more effective than the application of 20% autologous serum, due to their greater effect on cell proliferation.

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Efectividad del tratamiento con suero autólogo tópico en la queratopatía neurotrófica

R E S U M E N

Objetivo: Evaluar la efectividad del colirio de suero autólogo al 20% como tratamiento en la queratopatía neurotrófica.

Material y métodos: Estudio longitudinal, observacional y descriptivo a partir de 19 pacientes (22 ojos) diagnosticados de queratopatía neurotrófica en distintos estadíos según la...
Introduction

Neurotrophic keratopathy involves a corneal degenerative process secondary to diminished sensitivity, giving rise to inadequate surface regeneration and cicatrization.1

The most frequent cause of this anesthesia is infection by herpes simplex and herpes zoster viral infection as well as sequelae of physical, chemical or surgical treatment of the V pair, or neuropathic damages produced by diabetes.2,3 While the clinical diagnostic of neurotrophic keratopathy is not difficult, its therapeutic management is challenging, being one of the most difficult to manage corneal disorders.

Autologous serum has been reported in numerous publications as an efficient treatment for disorders such as persistent epithelial defects4–6 and dry eye.7,10 However, the series of cases published to date on the use of autologous serum for neurotrophic keratopathy are very few and with small samples.11–13 Accordingly, the objective of this study is to assess the efficacy of autologous serum for treating neurotrophic keratopathy.

Material and methods

A descriptive, longitudinal and retrospective study of 22 eyes (19 patients) diagnosed with neurotrophic keratopathy. To this end, in the first visit and throughout the 4 months of treatment we assessed best corrected visual acuity (Snellen optotype), symptomatic subjective impressions of patients according to the faces scale (matching an even number of 0–10, where zero is the highest degree of comfort and 10 intolerance), the stage of neurotrophic keratopathy according to Mackie clinical scale (scale 1–3) (Table 1), Schirmer test without anesthesia (mm), tear breakup time or BUT (s), as well as the epithelial defect healing time (weeks).

The application frequency of 20% autologous serum was of 4–6 times/day depending on the keratopathy severity (in Mackie stage 1 it was applied 4 times/day and 6 times/day in Mackie stages 2 and 3).

The results were compared with the Chi-square test for categorical variables, and the test for ranges of Wilcoxon for numerical variables.

Table 1 – Clinical classification of neurotrophic keratopathy.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Staining (+) Rosa Bengal in palpebral conjunctiva &lt;br&gt; Diminished Tear Breakup Time &lt;br&gt; Increased tear viscosity &lt;br&gt; Neovascularization of superficial cornea &lt;br&gt; Corneal Dellen &lt;br&gt; Superficial keratitis punctata under examination with fluorescein &lt;br&gt; Dehydrated epithelial injuries (Gaule spots)</td>
</tr>
<tr>
<td>2</td>
<td>Corneal epithelium loss &lt;br&gt; Smooth and rolled-up epithelial defect edges &lt;br&gt; Stromal edema &lt;br&gt; Reaction in anterior chamber</td>
</tr>
<tr>
<td>3</td>
<td>Corneal ulcer &lt;br&gt; Stromal lysis &lt;br&gt; Corneal melting &lt;br&gt; Perforation</td>
</tr>
</tbody>
</table>

Of all cases, 86% exhibited concomitant treatment with artificial tears without preservatives and application of night creams, 68% were on topical antibiotic therapy and 45% were on concomitant treatment with oral doxycyclin, 100 mg/24 h.

For the statistical analysis of data the Wilcoxon ranges test was applied and Pearson’s Chi square as well as the Windows NT Excel software (Microsoft Corporation, USA). Patient information was obtained in accordance with the Helsinki declaration.

Results

Of the 19 patients included in the study, gender distribution was 52.6% males and 47.4% females. The mean age was of 60.9 years (range: 29–87) (Table 2).

In our study, the most frequent etiology was neurotrophic keratopathy associated to diabetes mellitus (10 eyes, 45.5%),

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Table 2 - Clinical characteristics of patients.

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age</th>
<th>Main diagnostic</th>
<th>Other diagnostics</th>
<th>Mackie stage</th>
<th>Healing time (wks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>64</td>
<td>DM</td>
<td>RDNP</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>64</td>
<td>DM</td>
<td>RDNP</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>66</td>
<td>DM</td>
<td>DME</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>66</td>
<td>DM</td>
<td>RDNP, dry eye</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>78</td>
<td>DM</td>
<td>RDNP</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>65</td>
<td>DM</td>
<td>RDNP</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>67</td>
<td>DM</td>
<td>RDNP</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>67</td>
<td>DM</td>
<td>RDP, PFC</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>29</td>
<td>DM</td>
<td>VPP, RDP, PFC</td>
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<tr>
<td>10</td>
<td>F</td>
<td>75</td>
<td>DM</td>
<td>RDP, PFC, Bl</td>
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<td>10</td>
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<tr>
<td>11</td>
<td>M</td>
<td>39</td>
<td>Herpetic</td>
<td>Bl</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>54</td>
<td>Herpetic</td>
<td>Uveitis, Bl</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>47</td>
<td>Herpetic</td>
<td></td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>56</td>
<td>Herpetic</td>
<td>Uveitis, dry eye</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>87</td>
<td>Herpetic</td>
<td>Uveitis, dry eye</td>
<td>3</td>
<td>No healing</td>
</tr>
<tr>
<td>16</td>
<td>M</td>
<td>56</td>
<td>Herpetic</td>
<td>Bl</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>17</td>
<td>F</td>
<td>69</td>
<td>Herpetic</td>
<td></td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>18</td>
<td>F</td>
<td>75</td>
<td>Herpetic</td>
<td></td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>19</td>
<td>F</td>
<td>60</td>
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<td>Uveitis</td>
<td>2</td>
<td>8</td>
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<tr>
<td>20</td>
<td>M</td>
<td>31</td>
<td>Tumoral</td>
<td>Bl</td>
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<td>8</td>
</tr>
<tr>
<td>21</td>
<td>F</td>
<td>48</td>
<td>NeuroqX</td>
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</tr>
<tr>
<td>22</td>
<td>M</td>
<td>77</td>
<td>NeuroqX</td>
<td>OAPG</td>
<td>3</td>
<td>No healing</td>
</tr>
</tbody>
</table>


followed by infection with herpes virus (9 eyes, 41%). Two cases (9%) exhibited neurotrophic keratopathy due to lesions in the V cranial pair after neurosurgery and one case (4.5%) as the result of cavum cancer with cavernous sinus involvement.

Following the Mackie classification, 7 eyes corresponded to stage 1 (31.8%), thirteen eyes to stage 2 (68.2%) and two eyes to stage 3 (9%).

In 77.27% of cases (17 eyes) visual acuity improvements equal to or greater than one line with Snellen optotypes was observed (Fig. 1), and a subjective improvement of symptoms in 100% of patients. In both cases these percentages were statistically significant (p<0.05). No local or systemic described adverse reactions were found during treatment. Even though mean improvements were observed in the Schirmer test without anaesthesia (Fig. 2) of 2.72 mm (range: 0–5) and 1.23 s (range: 0–3) in the tear breakup time (BUT) (Fig. 3), these improvements were not statistically significant.

In the experience of the authors, even though this study is not paired with controls, it was observed that epithelial defects closed with this therapy in 91% of cases before 3 months (71.5% before 6 weeks), with low tendency toward recurrence (Figs. 4 and 5). The 9% of patients who did not heal the epithelial defects were the ones exhibiting Mackie stage III keratopathy.

![Fig. 1 – Pre- and post treatment visual acuity.](image1)

![Fig. 2 – Tear breakup time (BUT) pre- and post treatment.](image2)

![Fig. 3 – Pre- and post treatment Schirmer test.](image3)
Fig. 4 – (A) Corneal trophic ulcer with abscess in a patient with V1 PC lesion as a consequence of cavum cancer. (B) Six weeks later. Persistent epithelial defect stained with fluorescein.

Fig. 5 – Image of inferior paracentral corneal leukemia after 8 weeks of treatment with autologous serum.

Discussion

Topical treatment with autologous serum was first used by Fox et al. as a substitute for natural tears with few secondary effects. In addition to having a superficial hydrating effect, this serum has several growth factors (EGF, vitamin A, fibronectin, anticollagenases, NGF, etc.) and antimicrobial factors (lysozyme, Ig G, complement factors, etc.) that promote not only the epithelial regeneration process which is inhibited by the disorder but also in the overinfection thereof.6,14

To date, the study with the largest sample size on the treatment of neurotrophic keratopathy with autologous serum is that performed by Matsumoto et al. with a sample size of 14 eyes.13 Said study describes a statistically significant improvement of visual acuity in 85.8% and of symptoms in 100% of cases. These results are similar to those obtained in this study. The authors believe that the improvement is due not only to increases in corneal regularity due to the healing of the epithelial defect but also to the improvements in lacrimal film quality which provides better optical conditions for the eye.

It is known that the lacrimal functional unit comprises several interrelated subsystems and that the involvement of one of these will also affect the rest. Neurotrophic keratopathy produces an alteration of the reflex secretion of tears due to corneal anaesthesia as shown in lower Schirmer test results. In this study we found improved Schirmer test results without anaesthesia as well as for BUT after 4 months of treatment with autologous serum and we believe these data could be related to corneal anaesthesia improvements as described in the study by Matsumoto et al.13 This produces an increase of the blinking reflex thus improving the lacrimal aqueous system and secondarily the other subsystems as well (>BUT) 7,10,15 It must also be borne in mind that 68% of our patients were in concomitant treatment with oral tetracycline, an antibiotic also used for Meibomium gland dysfunctions, which could contribute to increase the tests.16 Even though it is true that the improvement found herein was not statistically significant and that, due to technical limitations and the absence of clinical record information, we were not able to obtain the changes in the corneal anaesthesia in order to confirm these data with previously published data.

The treatment of neurotrophic keratopathy is a challenge for ophthalmologists. This disorder requires early and aggressive treatment with the aim of not only alleviating symptoms but controlling the progressive corneal ulceration process in order to avoid potentially severe complications.1

In the presence of a neurotrophic keratopathy case, the first stage to take into account to decide treatment is to identify the existence of poor prognosis factors as these enhance the rapid and numbing evolution of this keratopathy. Said factors comprise etiology due to herpes zoster (which usually produces marked numbness), a high degree of corneal hypoesthesia, large size and depth of the lesion, and the association with other corneal surface alteration diseases such as dry eye, exposure keratitis and limbar insufficiency. In our experience we have observed that while in the initial stages of neurotrophic keratopathy (stages 1–2) the application of 20% autologous serum healed the epithelial defect in 100% of cases, whereas in the more advanced stages (stage 3: poor prognosis factor) this effect was not achieved and therefore other treatments were sought. In the 2 cases of this report single layer amniotic membrane18 was applied. This could be due to the fact that
with a significant tissue loss and stromal damage, the regenerative effect this treatment can supply on its own is not enough to reverse the process. Even though it is true that in vitro toxicity studies carried out by Poon et al.\textsuperscript{19} demonstrated that higher concentrations of autologous serum enabled greater cellular growth.

Even though the authors do not have experience in the use of platelet rich plasma (E-PRP) or plasma rich in growth factors (PRGF), these have demonstrated to be efficient for treating numbing corneal ulcers.\textsuperscript{19} Platelets are large reservoir of growth factors and tissue adhesion molecules among others, thus playing a clearly leading role in tissue damage repair. López García et al.\textsuperscript{20} described greater effect of these preparations in cell proliferation activation whereas autologous serum is more effective for migration and differentiation. Perhaps in advanced stages with significant corneal tissue loss, the proliferative property exhibited by said blood products would achieve greater effectiveness in neurotrophic keratopathy stage 3 than the application of 20% autologous serum.

The authors consider it necessary to carry out new controlled and comparative studies between different concentrations and platelet derivatives rich in growth factors in order to obtain more knowledge about the subject.

Conflicts of interest

No conflict of interests has been declared by the authors.

References