

## AMNIOTIC MEMBRANE IN THE TREATMENT OF NEUROPARALYTIC KERATOPATHY

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**SUMMARY** – The aim of the study was to determine whether amniotic membrane could be used to treat neuroparalytic keratopathy. Amniotic membrane transplantation was performed in 19 patients with neuroparalytic ulcer. All patients were younger than 61 and all developed corneal problems due to interruption of the sensory afferent fiber innervating the cornea. In all patients, the follow up period was longer than 18 months. Postoperatively, all patients underwent fluorescein test and biomicroscope examination as well as subjective pain evaluation. Postoperatively, the pain was reduced in study patients. In one patient, retransplantation for disease recurrence was performed two months after the first operation. After the second operation, the pain was minimized for more than 18 months. Amniotic membrane transplantation appears to be a good method for pain reduction and better epithelial healing in patients with neuroparalytic keratopathy.

**Key words:** *amniotic membrane, neuroparalytic keratopathy*

### Introduction

In this study, which was a continuation of a similar study conducted in 2002 by Iveković *et al.*<sup>1</sup>, we analyzed clinical experience in the management of neuroparalytic keratopathy. Ocular surface disturbances remain a therapeutic problem despite various conservative and surgical treatments. If there is no normal ocular surface defense and healthy limbal cells are lacking, these disturbances can lead to the loss of vision.

Neuroparalytic keratopathy is a clinical entity that involves all degrees of degenerative corneal and conjunctival changes secondary to the loss of sensory function in the nasociliary branch of the trigeminal nerve with or without decreased tear production. Loss of neural stimulation from the sensory division of trigeminal nerve or from the autonomic nervous system can have devastating consequences on corneal epithelial wound healing and the precorneal tear film. The ophthalmic division of trigeminal nerve supplies sensory innervation to the

cornea, conjunctiva, and upper and lower eyelids. Therefore, trigeminal denervation abolishes reflexes controlling tear secretion and lid blinking and closure. This innervation constitutes the basic neuroanatomical integration of the entire ocular surface defense<sup>2</sup>. The interruption leads to corneal anesthesia with frequent breakdown of corneal epithelial surface, which can cause persistent epithelial defects, ulcer and finally perforation<sup>3</sup>. Trauma, tumors, inflammatory lesions like herpetic infections and surgical procedures can damage the first branch of the trigeminal nerve on its entire course from the brainstem to and within the cornea, and lead to this condition<sup>4,5</sup>.

Timely and appropriate action is required in the management of this condition to prevent serious complications. The corneal epithelium becomes diseased and breakdown occurs even in the absence of desiccation, infection, and trauma. This stage, if not treated aggressively with ocular lubricants, tarsorrhaphy, or a bandage soft contact lens, will result in stromal lysis with or without perforation. Depending on the size and location of corneal perforation, procedures like the application of cyanoacrylate glue, penetrating keratoplasty, or conjunctival flap may be required<sup>6</sup>.

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Lee and Tseng were the first to introduce the use of amniotic membrane in the treatment of persistent epithelial corneal ulcers in 1997. The procedure has been shown to promote epithelial healing, reduce vascularization, yield good cosmetic effect, and is relatively easy to perform<sup>7</sup>. Kruse *et al.* have also reported rapid healing of corneal surface with an increase in stromal thickness after multilayer amniotic membrane transplantation for deep corneal ulcers<sup>8</sup>. The aim of this study was to determine whether amniotic membrane could be used to treat neuroparalytic keratopathy and its effect on this clinical entity.

## Material and Methods

Human amniotic membrane was prepared and preserved as previously described<sup>8</sup>. Amniotic membrane with an attached placenta was obtained shortly after cesarean section. Human immunodeficiency virus (HIV), hepatitis virus type B and C, and syphilis were excluded by serological testing. The placenta was cleaned by washing with BSS containing penicillin (50 µg/mL), streptomycin (50 µg/mL), neomycin (100 µg/mL), and amphotericin B (2.5 µg/mL). The amniotic membrane was separated from the chorion and was flattened over a nitro-cellulose filter paper with epithelial surface up and stromal matrix down in contact with the paper. Thus prepared amnion was placed in a plastic container and stored at -80 °C<sup>1</sup>.

All surgeries were performed by the same surgeon. After anesthesia, parabolbar injection of 2% lidocaine, in the eyes with persistent corneal ulceration the base of the ulcer was debrided and poorly adherent epithelium adjacent to the edge of the ulcer was removed up to the area where the epithelium became adherent. The amniotic membrane was removed from the storage medium and peeled from the filter paper. The membrane was used to cover the defect, placed on the surface of the cornea stromal side down. Excess material was trimmed off and then sutured to the edge of the defect by 10.0 nylon interrupted sutures. If the defect was deep, it was filled with more than one layer of the membrane, excess material was also trimmed off, and the final layer was sutured as previously described, while bottom layers were left unsutured.

After the transplantation, a bandage contact lens was applied. Postoperatively, topical Maxitrol (neomycin sulfate, polymyxin B sulfate and dexamethasone) was

administered 4 times a day until complete epithelialization occurred. Then it was tapered off.

Fluorescein staining was used to detect epithelial defects. All patients were examined on postoperative day one, at the end of the first, second, third and fourth postoperative week, and monthly thereafter. Corneal epithelialization was classified as success or failure, and the results were evaluated by the patients' subjective symptoms (pain, discomfort, irritation), signs of inflammation and healing period.

The preoperative and postoperative data were analyzed by  $\chi^2$ - and t-test; p value lower than 0.05 was considered significant.

## Results

Amniotic membrane transplantation was performed in 19 patients (19 eyes) with neuroparalytic keratopathy, 11 of them male and eight female, mean age  $38.5 \pm 10.8$  (range 12-61) years. In seven patients, the cause of neurotrophic problems with cornea was acoustic neuroma surgery, three had had multiple eye operations, and one patient developed decreased corneal sensitivity after extraction of the right upper molar and neurosurgical treatment for intensive pain afterwards by vascular decompression. One patient aged 12 years developed epithelial defects due to meningitis which he had during varicella infection at the age of 2 years, and seven patients had sustained injury of the ocular surface, four of them by alkali burn of the cornea and three due to herpes zoster ophthalmicus. The neurotrophic state of all patients was established by the lack of corneal sensation, and therefore markedly reduced and infrequent blinking resulting in exposure keratopathy, and all other degrees of persistent epithelial defects. This state was further substantiated by the lack of intensive subjective symptoms. One of the study patients had diabetes mellitus.

All study patients had previously been treated with some or all of the mentioned methods, without much success. The duration of persistent corneal ulcers varied from 11 weeks to up to 4 years, mean  $103.1 \pm 38.1$  weeks, i.e. almost 2 years.

The localization of neurotrophic ulcers was central in nine, inferior corneal periphery in six, and nasal corneal periphery in four patients. Eight patients had monolayer transplantation, 10 had two-layer transplantation, and one patient (with diabetes mellitus) had multilayer transplantation.

Subjective symptoms were reduced in all patients, almost immediately after the operation. The mean preoperative visual acuity was  $0.11 \pm 0.06$ . These figures included only 14 patients because two patients had no light perception and three had only light perception. Postoperative visual acuity improved in five (26.3%) and remained unchanged in 14 (73.7%) patients. None of the patients got worse. The mean postoperative visual acuity was  $0.2 \pm 0.12$  in the same 14 patients, and showed no change in another five patients. We connect these results to the poor preoperative visual acuity; however, it was not a parameter for evaluating operative success.

Signs of inflammation were reduced during the first two weeks of the operation in all study patients.

The mean healing period was  $1.6 \pm 0.6$  weeks. The longest healing period (32 days) was recorded in the patient with diabetes mellitus, despite multilayer amniotic membrane transplantation.

The mean follow up was  $31.2 \pm 13.1$  month (all eyes longer than 18 months). None of the eyes except for one eye showed recurrence during this period. The only exception was the boy with a history of childhood meningitis due to varicella zoster infection, who had recurrence 2 months after the operation. He was reoperated on and showed no new relapse thereafter.

In the end, all eyes achieved anatomical integrity with various opacity of the remaining stroma.

## Discussion and Conclusion

This study showed that amniotic membrane could be taken in consideration when treating neuroparalytic keratopathy. The common characteristic of all study eyes was neuroparalytic state of the cornea of different origin, from direct trauma of the cornea to lesions to the ophthalmic division of trigeminal nerve due to surgery, tumor or trauma (see Results section). The severity of neurotrophic damage to the corneal surface was also illustrated in all these 19 eyes by their persistent epithelial defects despite all conventional therapy attempts.

Amniotic membrane is composed of monolayer epithelial cells, basement membrane and avascular stromal matrix<sup>9</sup>. It permits rapid epithelialization *via* various mechanisms: it facilitates migration of epithelial cells, reinforces adhesion of basal epithelial cells, promotes epithelial differentiation, and prevents epithelial apoptosis<sup>10</sup>. It also produces basic fibroblast growth factor, hepatocyte growth factor and transforming growth factor  $\alpha$ , while stromal matrix excludes inflammatory cells

and contains several forms of protease inhibitors<sup>11</sup>. All these facts are the reasons why stromal inflammation is reduced after amniotic membrane transplantation. All this combined with prevention of mechanical trauma caused by the lids and prevention of exposure and dryness makes amniotic membrane transplantation very useful in the management of neuroparalytic keratopathy<sup>3,7,8</sup>.

This report is in fact an extension of the study by Iveković *et al.* dealing with the same problem<sup>1</sup>. In the present study, we applied amniotic membrane in 19 cases, all previously described. None of the eyes showed fluorescein staining in less than 2 weeks postoperatively, which was described as successful epithelialization. During the mean follow up of more than 18 months in all study eyes, only one eye had a recurrence after 2 months and showed no new symptoms after reoperation. Visual acuity was not the parameter to evaluate operative success; however, postoperative visual acuity improved in five (26.3%) and remained unchanged in 14 (73.7%) patients. None of the patients worsened. These results were ascribed to the poor preoperative visual acuity such as no light perception and light perception only, and could not be used on statistical analysis.

These results are consistent with similar literature reports. For example, Chen *et al.* report that 13 of 16 ulcers healed in a mean period of 16.6 days<sup>3</sup>. Our study is also in agreement with Kruse *et al.* report on successful treatment recorded in 9 of 11 eyes submitted to multilayer amniotic membrane transplantation<sup>8</sup>. Lee and Tseng performed amniotic membrane transplantation with favorable outcome in 10 of 11 eyes<sup>7</sup>.

In comparison with other studies dealing with the treatment of persistent epithelial defects, ulcers and perforations of different origin than neurotrophic state with amniotic membrane transplantation, results are similar. They all point to the method as very beneficial when it comes to ocular surface reconstruction<sup>12-16</sup>. Pain relief after this procedure is associated with restoration of corneal epithelial integrity and can be contributed to the therapeutic effect of the membrane<sup>1</sup>.

All these results indicate that amniotic membrane transplantation is a good method in reducing pain and achieving better epithelial healing in patients with neuroparalytic keratopathy. The use of amniotic membrane as a patch or graft for ocular surface reconstruction has been recognized as an important alternative for the treatment of persistent epithelial defects and sterile ulceration that are refractory to conventional therapy<sup>17</sup>. A ma-

major problem on evaluating the efficacy of amniotic membrane transplantation is the lack of controlled clinical studies. Moreover, for some diseases there is no accepted "standard" therapy, and the incidence of the disease is too low to allow proper randomization<sup>13</sup>, just like in our case. In the light of long-term problems concerning neurotrophic state, in some cases more than one year, we could not, without any doubt, suggest the right timing of the transplantation. This problem was also caused by prior usage of all conventional treatments. Anyway, this study showed the simplicity of the method and no adverse effect on the course of this clinical entity; so, we can recommend it as an important option in the treatment of neuroparalytic keratopathy.

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## Sažetak

## AMNIJSKA MEMBRANA U LIJEČENJU NEUROPARALITIČNE KERATOPATIJE

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Cilj rada bio je utvrditi može li se amnijska membrana rabiti u liječenju neuroparalitične keratopatije. Transplantacija amnijske membrane je učinjena kod 19 bolesnika s neuroparalitičnim ulkusom. Svi bolesnici bili su mlađi od 61 godine i kod svih su se problemi s rožnicom razvili kao rezultat prekida senzornih aferentnih vlakana koja inerviraju rožnicu. Razdoblje praćenja je kod svih bolesnika bio duži od 18 mjeseci. Poslijeoperacijski je kod svih bolesnika učinjen fluoresceinski test i biomikroskopski pregled, kao i subjektivna procjena boli. Nakon operacije bol je bila smanjena kod svih bolesnika. Kod jednog bolesnika učinjena je druga transplantacija, dva mjeseca nakon prve, zbog recidiva. Nakon druge operacije bol je bila smanjena više od 18 mjeseci. Transplantacija amnijske membrane čini se kao dobra metoda smanjenja boli i postizanja boljeg epitelijskog cijeljenja kod bolesnika s neuroparalitičnom keratopatijom.

Ključne riječi: *amnijska membrana, neuroparalitična keratopatija*

