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Symptomatic Management of Postoperative Bullous Keratopathy With Nonpreserved Human Amniotic Membrane

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Purpose. To report the results of the management of painfully symptomatic postoperative bullous keratopathy (PBK) by performing a nonpreserved human amniotic membrane (NP-AMT) transplantation in nine eyes with poor visual potential. **Methods.** A prospective, comparative, nonrandomized management of symptomatic PBK was done by performing a complete corneal de-epithelialization followed by a NP-AMT transplantation (NP-AMT group) or no NP-AMT transplantation (control group). We evaluated time for re-epithelialization, patient's symptoms, and appearance of new bullae. **Results.** In the NP-AMT group, mean follow-up time was 40 weeks. Mean re-epithelialization time was 11.2 days. Symptoms of PBK resolved completely in eight patients (88%), who were asymptomatic and showing very quiet eyes from postoperative day 1, and resolved partially in one patient in whom we observed barely symptomatic bullae at the peripheral NP-AMT border (sixth postoperative week) and an asymptomatic one at the corneal center under the NP-AMT (seventh postoperative week). In the control group, mean follow-up time was 18 weeks; there were recurrences of symptomatic bullae in four of five patients at a mean time of 6.3 days. **Conclusions.** NP-AMT is a good alternative for the management of painful PBK in eyes with poor visual potential; NP-AMT is widely available, the technique is easy to perform, and it has good results from both the symptomatic and esthetic standpoint.

Key Words: Nonpreserved amniotic membrane—Bullous keratopathy—Anterior stromal puncture—Sallera's Procedure—Therapeutic SCL.

With the increase in the number of cataract extractions performed in recent decades,[1] postoperative bullous keratopathy (PBK) has become one of the main indications for penetrating keratoplasty.[2–4] For the management of painful PBK, several treatment modalities have been proposed, either medical (topical hypertonic solutions, reduction of intraocular pressure, therapeutic soft contact lenses)[5,6,7,8,9,10] or surgical (anterior stromal cauterization [Salleras' procedure],[11] manual[12,13] or YAG-aided[14] anterior stromal puncture, excimer laser phototherapeutic keratectomy[15] and conjunctival flaps[16]).

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De Rötth reported the first transplantation of an amniotic membrane in ophthalmology in 1940, in symblepharon surgery with partial success.[17] Later, Sorsby and Symons used it in the management of severe alkali cornea burns.[18] It then was almost forgotten until 1995, when Tseng et al. began publishing their laboratory and clinical experience using preserved human amniotic membrane (P-AMT).[6] It has been used since then for persistent corneal epithelial defects,[19,20] leaking filtering blebs,[21] pterygium surgery,[22] symblepharon correction,[23] as a conjunctival flap substitute, and for the reconstruction of the diffusely compromised ocular surface with or without limbal conjunctival grafts,[24,25] with good results in most cases. The amniotic membrane has an avascular stromal matrix and a thick and continuous basement membrane with a full complement of collagen type IV and V and laminin and an epithelial monolayer.[26,27] It is avascular and antiangiogenic,[28] does not express histocompatibility antigens,[29] and has antibacterial[30] and antiadhesivness[31] properties; it favors epithelial cell migration,[32] reinforces adhesion of basal epithelial cells,[33] diminishes their apoptosis,[34] and promotes their differentiation.[35,36]

We have been using non-preserved human amniotic membrane (NP-AMT) for more than a year, with similar results to those published by other authors who are using P-AMT. However, P-AMT is not available in all countries; it is expensive, and therefore poses special difficulties for developing countries. Even more, controversy exists regarding the biochemical vitality of the epithelial monolayer after the chemical process it undergoes and the freezing and unfreezing cycles.[37]

The objective of this article is to propose the use of NP-AMT transplantation as a therapeutic alternative for patients with painful PBK in eyes with poor visual potential.

PATIENTS AND METHODS

NP-AMP is obtained by elective cesarean section, from a woman who previously has signed an informed consent form agreeing to the procedure and who has tested seronegative for Hepatitis B and C virus, syphilis, and human immunodeficiency virus (HIV).

Under strict aseptic conditions, the placenta and its membranes are profusely irrigated with normal saline solution, and a section of aminos is then procured by blunt dissection from the chorion. Taking care to keep the epithelial side properly identified at all times, it is stored submerged in normal saline in a Petri dish and

refrigerated (not frozen) for no longer than 24 hours. Antibiotics or preservatives are not used.

Nine patients with diagnosis of PBK (Fig. 1A) were selected to receive the NP-AMT graft. These patients had severe pain secondary to recurrent bullae, photophobia, or foreign body sensation, their eyes had poor visual potential, a penetrating keratoplasty was not viable for any of them, and their symptoms had not improved with medical management. They received a complete explanation about the procedure, and signed an informed consent form.

A nonrandomized control group of five patients with a diagnosis of PBK was observed, in whom a simple de-epithelialization was performed with a blunt spatula under topical anesthesia. The control group had the same postoperative management as the NP-AMT group except that the control group did not receive a contact lens.

For the NP-AMT group, we performed the same surgical technique in all patients. Under topical anesthesia, a complete corneal de-epithelialization was performed with a blunt spatula, and a 9 mm diameter disc of NP-AMT was placed with its epithelial side down, leaving approximately 1.5 mm of peripheral cornea uncovered. It was sutured (10–0 Nylon) with 8 radial interrupted sutures and one continuous, burying the knots in corneal stroma. At the end of the procedure, patients were given one atropine 1% drop, and tobramycin and dexamethasone ointment (TobraDex, Alcon Laboratories, Fort Worth, Texas, U.S.A.). Postoperatively, (Figs. 1B and 1C) they received tears supplement (Tears Naturale, Alcon Laboratories, Fort Worth, Texas, U.S.A.) every hour, and tobramycin and dexamethasone drops three times a day (TobraDex, Alcon Laboratories, Fort Worth, Texas, U.S.A.) during the day, which were tapered down in 2 weeks. A high water content soft contact lens was left in place until re-epithelialization was complete. Sutures were removed at an average of 2 weeks post operation (Fig. 1D)

RESULTS

In the NP-AMT group, there were six men and three women, mean age 65.5 years (51–98 years), all of whom lived in rural areas; seven had pseudophakic bullous keratopathy and two had aphakic bullous keratopathy. There were no cases of infection, necrosis, or NP-AMT rejection; in no case did the patient's epi-

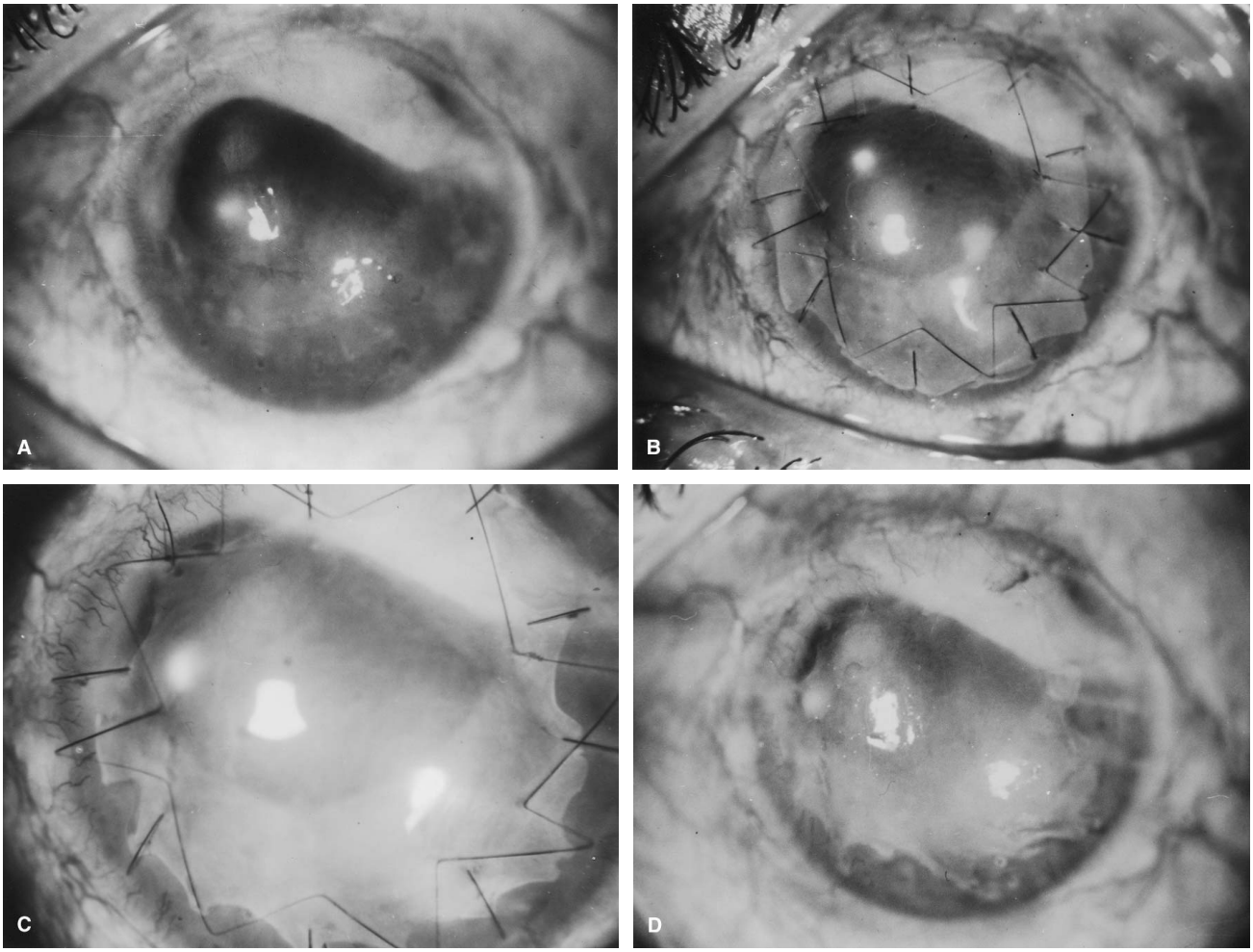

FIG. 1. A: Preoperative view. Note diffuse corneal edema and bullae. **B:** First postoperative day. Note the well defined borders of the NP-AMT, not reaching the limbus. **C:** Two weeks postoperative, before suture removal. There is some nonsignificant shrinking of the NP-AMT. **D:** Four weeks postoperative. No bullae are present. Note NP-AMT thinning.

thelium grow under the NP-AMT dissecting it. Mean re-epithelialization time was 11.2 days (6–20 days). From the symptomatic standpoint, pain, photophobia, and foreign body sensation disappeared in all patients with one exception, and the cosmetic result was fairly acceptable, remaining so until the last control. Mean follow-up time was 40 weeks (4–62 weeks). During the postoperative period, the appearance of the NP-AMT changed form a thick, whitish, ropy membrane with well-defined borders during the first week to a very thin– sometimes almost imperceptible– membrane with diffuse borders at 3 weeks; thereafter it progressively thinned and its borders became indistinctly fused with the peripheral cornea, but it never completely disappeared; even at 6-months follow-up, the NP-AMT-covered area could be easily identified at the slit lamp. The only complication was a patient who rubbed his eye and tore the NP-AMT at postoperative day 11, creating a large central epithelial defect; we reoperated on him using the same technique, and 6 weeks after the second surgery he returned, complaining of a slight foreign body sensation. Upon examination we found three bullae, located at the NP-AMT/peripheral cornea interface: a large one, located inferiorly (Fig. 2), and two small ones, located superiorly, that spontaneously ruptured and produced moderate pain, then re-epithelialized completely. The patient returned for control 1 week later, and we observed a completely asymptomatic small bulla located under the NP-AMT at the corneal mid-periphery that was not present when we re-examined him 1 week later. He denied any symptoms during that week.

In the control group, there were three women and two men with a mean age of 70 years (range 60–88 years), three of whom lived in urban areas and two who lived in rural areas. Four of the patients had pseudophakic bullous keratopathy and one had aphakic bullous keratopathy. Four of these five patients (80%) had multiple and symptomatic recurrent bullae at a mean time of 6.3 days (4–8 days), requiring the use of a permanent therapeutic contact lens in two patients and a NP-AMT graft in the other two, which adequately controlled their symptoms. Mean follow-up was 18 weeks (10–45 weeks).

DISCUSSION

PBK is a grave complication of cataract surgery and has became a frequent indication for penetrating keratoplasty (PK) (26–50%).[38,39] The main preoperative factor predisposing to PBK is the presence of endothelial dysfunction. The main intraoperative factors are toxicity from the irrigating solutions,[40] ultrasound-induced endothelial damage,[41] and excessive intraocular instrumentation, particularly when there is vitreous loss.[42] Postoperatively, some factors are endothelial touch by the intraocular lens[38,43] or the vitreous,[42] excessive inflammation, and the presence of peripheral anterior synechiae.[44]

Some patients with PBK have a poor visual potential, usually because of preexisting or iatrogenic retinal diseases, which makes them ineligible for PK. For these patients, there are a number of treatments targeted purely on symptom control. Among the clinical options are the hyperosmotic solutions, which reduce corneal epithelial edema; unfortunately these solutions have no effect on the stromal edema. The use of therapeutic contact lenses alleviates foreign body sensation and prevents pain from ruptured bullae; however, it has to be used permanently and usually indefinitely, with the concurrent risk of a bacterial, mycotic, or acanthamebic infection.[45–48]

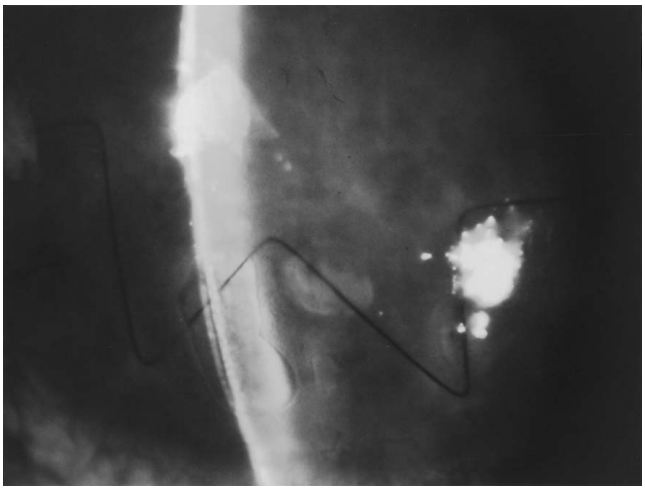

FIG. 2. Note the large bulla located inferiorly at the NP-AMT/peripheral cornea junction.

Among the surgical alternatives, the conjunctival flap is most frequently used. It was initially described by Gundersen[49] in 1958, with multiple variations thereafter; it has the disadvantage of the risk of superior eyelid ptosis, the compromise of the superior conjunctiva for future surgeries, a less-than-subtle postoperative appearance, and a more prolonged and uncomfortable postoperative course than that of NP-AMT. Another alternative is the anterior stromal cauterization proposed by Salleras[11]; it is an effective and easily performed procedure, but it has the inherent risk of diffuse corneal stromal necrosis. The anterior stromal puncture (ASP) also has been used in these patients,[12,13] with good results, but with a moderate rate of recurrence, making it a repetitive procedure.

As an alternative to the chronic management of these patients, we propose the transplantation of NP-AMT, which will provide a new basal membrane more resistant to bullae formation and a good substrate for the growth of the corneal epithelium. In cases of PBK, we have reserved the NP-AMT for those with poor visual potential, in whom a PK is not planned for the near future, and in whom the use of a therapeutic soft contact lens is precluded because of poor handling and hygiene. It is simpler, easier to perform, and more aesthetically acceptable than a conjunctival flap.

The epithelial side is placed down, to offer a denuded basal membrane for the limbal epithelium to grow; it must be sutured tightly to avoid its dissection by the patient's tears and to warrant the growth of the limbal epithelium over and not under it. This is why we use a mixed suturing technique as in a PK.

Regarding the case with the regrowth of bullae at the NP-AMT/host peripheral interface, we now recommend covering as much of the cornea as possible, but always leaving the limbal zone out, so that re-epithelialization takes place over and not under the NP-AMT. We are intrigued by the complete lack of symptoms with the bulla that grew under the NP-AMT, both during its presence as when it ruptured (perhaps because of the contact lens effect).

The NP-AMT has some advantages over the P-AMT, such as its low cost of procurement and enormous availability; it is easily obtainable in university hospitals by ophthalmologists, fellows, or residents with the help of obstetricians. Its ease of procurement

from the logistic as well as legal standpoint varies among countries. From the physiological point of view, it is more consistent to use the nonpreserved amniotic membrane because the epithelial cell monolayer– responsible for the production of some cytokines and growth factors– vitality is not compromised; on the other hand, the vitality of these cells is compromised to a greater or lesser extent with the different preservation protocols.[37]

The use of NP-AMT transplantation for the management of painfully symptomatic PBK is a safe option. As with any new technique, it should be used rationally and critically, as to properly evaluate its results in the future.

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