Amniotic Membrane Transplantation

Amniotic membrane transplantation (AMT) has been successfully applied to treat various kinds of ocular surface disease. Its application is expanding in many ophthalmologic fields.

The following articles were reviewed for the summary of the application of AMT in the treatment of ocular surface diseases:

The amniotic membrane is the innermost layer of placental membrane. It was first used in 1910 in skin transplantation. Since then, the use of amniotic membrane has expanded in many surgical fields, including brain and genito-urinary tract surgery. The first ophthalmic application to treat ocular surface disorders was reported in the 1940s. The application of AMT in the management of ocular surface disorders is ever increasing. In this review, we will discuss its biologic properties, mechanism of action, and applications in ophthalmology, as well as define existing problems in its application.

Biologic Property

Amniotic membrane, which is derived from fetal ectoderm, is a translucent membrane consisting of five layers starting from the innermost layer: (1) epithelium; (2) basement membrane; (3) compact layer; (4) fibroblast layer; and (5) spongy layer. Its thickness varies from 0.02 to 0.50 mm. It lacks blood vessels or a direct blood supply.

Amniotic membrane produces a large number of cytokines, of which Interleukins 6 and 8 are predominant. Expression of these cytokines increases in the presence of IL-1ß, TNF-alpha, and bacterial lipopolysaccharide. Studies reveal that human amniotic membrane preserved at -80°C for 1 month retains the presence of EGF, TGF-alpha, KGF, HGF, bFGF, TGF-ß1, TGF-ß2, endothelin-1, leukotrienes, and carbonic anhydrase isoenzymes CA-1 and CA-2. These proteins are hypothesized to contribute to immune-mediated defense mechanisms during pregnancy.

According to the literature, amniotic membrane does not express HLA-A, B, or DR antigens, so immunological rejection after transplantation is rare. Additionally, amniotic membrane is also believed to have antimicrobial and antifibroblastic activity properties and cell migration/growth-promoting activity.

The Functions of AMT

Positive Effects

Amniotic membrane executes its functions via multiple mechanisms. Many experimental and clinical studies have demonstrated that AMT can promote corneal re-epithelialization, which is its most important function. Two other important effects include anti-inflammatory properties and fibrosis prohibition.

Promoter of Re-epithelialization

The presence of a normal substrate is essential for normal proliferation, differentiation, and migration of epithelial cells. Lee and Tseng reported successful re-epithelialization of 10 out of 11 cases of persistent epithelial defect by AMT. They postulated that amniotic basement membrane plays an important role in epithelial differentiation, the migration of epithelial cells, and the adhesion of basal epithelial cells.
Inhibitor of Inflammation and Scarring
Amniotic membrane executes anti-inflammatory and antifibrotic effects. Studies show that amniotic membrane induces a downward regulation of transforming growth factor β, which is an important fibroblastic activator in wound healing. Amniotic membrane may also act as an anatomical barrier because its stromal layer is avascular, and blocks new vessels from growing.

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Additionally, antiangiogenic and antimicrobial properties of amniotic membrane are reported in the literature. Kim and Tseng demonstrated that rabbit corneas with limbal stem cell deficiency and total keratectomy were less likely to become revascularized if covered with amniotic membrane.

THE USE OF AMNIOTIC MEMBRANE IN OPHTHALMOLOGY

Ocular Surface Reconstruction in Stem Cell Deficiency
The Kim and Tseng study has led to successful applications in various ocular surface diseases. Cicatrizing diseases of the ocular surface associated with acute or chronic stem cell deficiency constitute an indication for AMT. These ocular surface disorders include chemical or thermal burns, Stevens-Johnson syndrome, and cicatricial pemphigoid. Shimazaki et al reported the first clinical applications of the membrane in patients with the aforementioned conditions in 1997.

Tseng et al applied the membrane in the treatment of 31 eyes of 26 patients with partial and total stem cell deficiency. The majority of these patients had chemical burns or Stevens-Johnson syndrome. Other patients presented with contact lens-induced keratopathy, aniridia, atopy, and iatrogenic stem cell disease.

Application in Persistent Epithelial Defects
AMT was reported to be successful in patients with persistent epithelial defects. Heiligenhaus et al reported that AMT was applied to promote the healing of acute ulcerative and necrotizing herpetic keratitis. In these studies, AMT shows great promise in acute ulcerative and necrotizing ocular surface diseases.

Conjunctival Reconstruction
The conjunctiva is an integral part of the ocular surface.
Most procedures employing amniotic membrane in reconstruction of the ocular surface involve both the cornea and conjunctiva. Amniotic membrane has been used as an alternative to a conjunctival autograft in the treatment of pterygia. Ma et al\(^1\) compared amniotic membrane grafts with conjunctival autografts and topical mitomycin C in 80 eyes of 71 patients with primary pterygia. They found no differences in recurrence rates in the three groups. Because conjunctival autografts have limited success, and administration of mitomycin C increases risk of complications, AMT was suggested as the preferred procedure.

**Other Ophthalmic Applications of AMT**

Pires et al\(^1\) reported that AMT was used effectively for the treatment of symptomatic bullous keratopathy. During the follow-up period of 33.8 weeks after AMT, 90% of the 50 patients studied with intolerable pain preoperatively became pain-free postoperatively. Anderson et al\(^1\) used amniotic membrane in 16 eyes after surgically removing the calcified deposits in band keratopathy. Rodriguez-Ares et al\(^1\) reported on AMT application in the repair of a large scleral perforation in a patient with Marfan's syndrome. Wang et al\(^1\) and Dua et al\(^1\) used amniotic membrane after PRK. Wang et al found that the corneal haze score in the amniotic-membrane-covered group was significantly less than in the control group 7 to 12 weeks postoperatively. Amniotic membrane is applied as a substrate and a stem cell niche for cultivating autologous corneal epithelial cells for ocular surface reconstruction.\(^2\)\(^,\)\(^3\) Results in these instances demonstrated that the sterilized, freeze-dried amniotic membrane retained most of the physical, biological, and morphologic characteristics of cryopreserved amniotic membrane. Consequently, it is a useful biomaterial for ocular surface reconstruction.

**Complications with AMT**

As the use of amniotic membrane in ophthalmic surgery has become widespread, complications have rarely been reported in published studies. Most of the reported complications, such as persistent inflammation and suture granuloma, are not specific to the membrane.\(^2\)\(^,\)\(^3\) Failure to achieve the intended effect with amniotic membrane is perhaps the most significant drawback. Another, less significant undesirable effect is the residual subepithelial membrane that persists in some cases.\(^2\)\(^,\)\(^3\) The incidence of this complication should decrease as ophthalmologists’ experience increases, thereby enhancing appropriate patient selection.

The potential danger of the spread of viruses and bacteria should not be overlooked. Because amniotic membrane from a single donor is often used in several patients, the risk of single donor infections to multiple recipients is real. Adequate donor screening, handling, and storage, as well as frequent microbiological tests should be performed in order to avoid or minimize this risk.

**BOTTOM LINE**

Amniotic membrane has many unique properties that can aid the treatment of different ocular surface disorders. AMT can promote normal epithelialization of the cornea and conjunctiva and prevent excessive fibrosis during ocular surface reconstruction. It is an effective alternative in the treatment of many challenging ocular surface disorders. Although AMT holds great promise and its application is expanding in many ophthalmologic fields, it is not the panacea. Surgical failures and potential risks with its applications are inevitable. A comprehensive understanding of amniotic membrane’s biologic properties, action mechanisms, and associated risks is helpful for appropriate patient selection.

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