ISSN: 2754-4990

Journal of Ophthalmology Research Reviews & Reports

SCIENTIFIC Research and Community

Research Article

Open Access

Amniotic Membrane Transplantation-A Surgical Alternative in Peripheral Ulcerative Keratitis

Shreya Thatte*, Ishita Batra and Himanshi Nandal

Sri Aurobindo Medical College and PG Institute, Indore

ABSTRACT

Introduction: Peripheral Ulcerative Keratitis (PUK) is a group of inflammatory corneal ulcers with stromal thinning and peripheral localization. It begins with immune cellular infiltrates in the juxtalimbal cornea, followed by a crescent-shaped ulcer that appears parallel to the limbus. Medical management includes intense lubrication, antibiotics, along with topical and systemic steroids and immunosuppressants. Definitive surgical management is lamellar patch or penetrating corneal graft. Amniotic membrane has wide array of biological properties, including anti-inflammatory, anti-bacterial, anti-angiogenic, antifibrotic, healing properties hence can be used as an alternative to keratoplasty.

Material and Methods: This mono institutional observational retrospective study was conducted on 15 eyes of 15 patients having PUK in a tertiary health care centre. Patients underwent single-layered Amniotic Membrane Transplantation (AMT) in case of corneal thinning involving <1/2 corneal stroma, multi-layered or rolled AMT in cases of corneal thinning involving >1/2 corneal stroma or with moderate to large perforations along with systemic steroids and immunosuppression.

Results: All 15 Patients (100%) initially had symptomatic relief, 2 patients (13.33%) underwent repeat AMT (86%success rate), 2 failures were noted, out of which 1 patient (6.67%) underwent corneal patch graft while 1 patient (6.67%) underwent large penetrating keratoplasty which failed and landed in Phthisis.

Conclusion: AMT is a safe and effective alternative for the surgical management of PUK in combination with local and systemic immunosuppressive therapy. A close collaboration between the ophthalmologist and the physician is mandatory to prevent corneal perforation and decrease patient morbidity and risk of mortality.

***Corresponding author**

Shreya Thatte, Sri Aurobindo Medical College and PG Institute, Indore, Chaitanya, 17 Yashwant Colony, Indore, Madhya Pradesh, India.

Received: November 11, 2023; **Accepted:** November 20, 2023; **Published:** December 02, 2023

Keywords: Amniotic Membrane, Amniotic Membrane Transplantation, Peripheral Ulcerative Keratitis, Corneal Patch Graft, Immunosuppression

Introduction

Peripheral Ulcerative Keratitis (PUK) is a group of inflammatory corneal ulcers with stromal thinning and peripheral localization. It begins with immune cellular infiltrates in the juxtalimbal cornea, followed by a crescent-shaped ulcer that appears parallel to the limbus. PUK is often contiguous with adjacent conjunctival, episcleral, and scleral inflammation [1-3]. In 10 to 30% of cases, it is associated with scleritis, and in 40% of cases, both eyes are affected [1]. PUK is often associated with an autoimmune disease, rheumatoid arthritis being the most common. It should be noted that the appearance of PUK should be considered a sign of progression of the autoimmune disease. Hence, systemic immunosuppressors are often required not only to control ocular involvement but also to reduce mortality [4]. The risk of perforation increases in case of associated scleritis and decreases with the introduction of an immunosuppressant [5].

Medical management of PUK includes intense lubrication and antibiotics, along with topical and systemic steroids and immunosuppressants to control the underlying inflammatory process. In advanced stages of thinning and perforation, surgical procedures are necessary to preserve globe integrity [6]. Amniotic Membrane (AM) is the innermost layer of the placenta, which consists of a single layer of metabolically active epithelium, a thick basement membrane, and an avascular stromal matrix [7]. It has been shown to exhibit a wide array of biological properties, including anti-inflammatory, anti-bacterial, anti-angiogenic, prevents apoptosis, antifibrotic, healing and analgesic properties, partly because they contain growth factors, cytokines, and metalloproteinases inhibitors [8-10]. AM may be used as a single or multilayered graft for the management of corneal ulcers and perforations [11]. It enhances epithelialisation by facilitating migration and differentiation of epithelial cells, reinforcing adhesion of basal epithelial cells, and regulating proliferation of normal corneal, conjunctival, and limbal fibroblasts [7]. In addition, the wide availability of AM donor tissues, lack of graft rejection and improvement in the storage methods have rendered Amniotic Membrane Transplantation (AMT) a popular choice of treatment for ocular surface diseases. However, there is a paucity of research analysing the efficacy of AMT in treatment of PUK. In advent of same the present study was designed to assess the efficiency of AMT in management of PUK and to evaluate its

success outcome.

Material & Methods

After approval from the institutional ethical committee, this mono institutional observational retrospective study was conducted on 15 eyes of 15 patients having peripheral ulcerative keratitis and who visited department of ophthalmology, in a tertiary health care centre. A written informed consent was taken from all patients who qualified the inclusion and exclusion criteria.

Inclusion Criteria

- Patients with PUK of any age group and sex.
- Patients who gave consent for treatment.
- Patients agreeing for regular follow up.
- Patients with failure for medical treatment.

Exclusion Criteria

- Patients with gross posterior segment abnormalities.
- Patients with severe involvement of eye affecting visual axis.
- Patients with poor compliance.
- Patients not willing for investigations.
- Patients not giving consent for management

Methodology

At the time of presentation, a careful history was taken and thorough systemic and ocular examination was carried out. Slit lamp examination was done and pre operatively posterior segment examination was carried out with an indirect ophthalmoscope and a +20-diopter lens. When the optical medium was not clear, B-scan ultrasonography was performed to evaluate the posterior segment. Routine blood investigations were done. Electrocardiography was done to rule out any associated heart disease. A rheumatologist was consulted and investigations were performed to rule out any associated systemic illness such as Rheumatoid arthritis, Wegener' granulomatosis, Polyarteritis nodosa. Systemic lupus erythematosus, Sarcoidosis, Hepatitis B and C. All patients, who were refractory to medical management (topical prednisolone (0.1%), lubricating, cycloplegics and antibiotics eye drops with systemic steroids and immunomodulators) for PUK with progression of disease in the form of increase in corneal thinning and even perforation was included in the study.

Surgical Indications for Management of PUK Included

- Failure to response to medical treatment
- Patients with involvement more than two quadrants of cornea with thinning of stroma
- Thinning of stroma with corneal perforation

Patients underwent single-layered AMT in case of corneal thinning involving <1/2 corneal stroma, multi-layered or rolled amniotic membrane transplantation in cases of corneal thinning involving >1/2 corneal stroma or with moderate to large perforations along with systemic steroids and immunosuppression. Suturing was done with 10-0 nylon interrupted or running sutures, iris was reposited in case of perforation and AC was reformed with air. Regular follow ups ranged from 6months to 6 years during which amniotic membrane was examined for graft position, rejection, melt, infection and recurrence of disease. Anterior chamber was evaluated for its depth and formation.

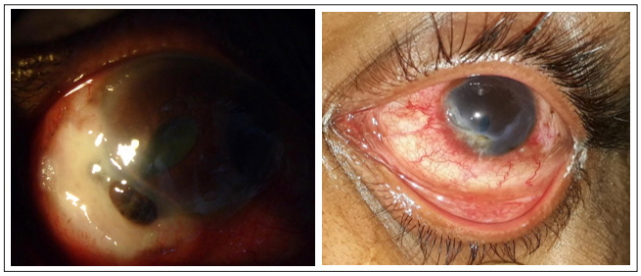

Figure 1A: Medium Sized Perforation B. Healing after AMT

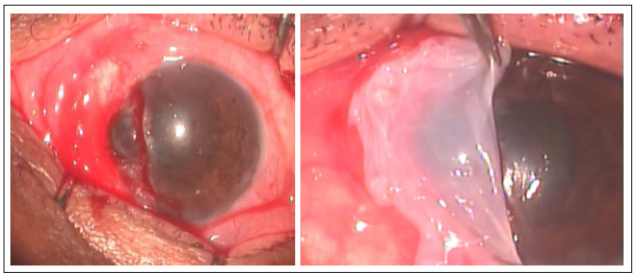

Figure 2A: Large Sized Perforation B. Multi Layered AMT in Place

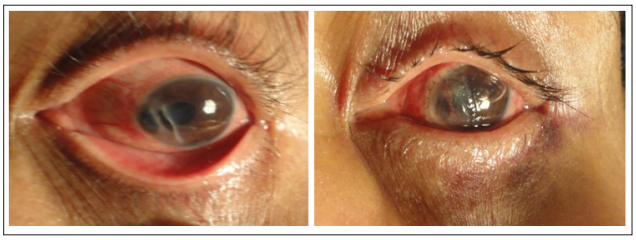

Figure 3A: Recurrence after AMT B. Lamellar Patch Graft in Place

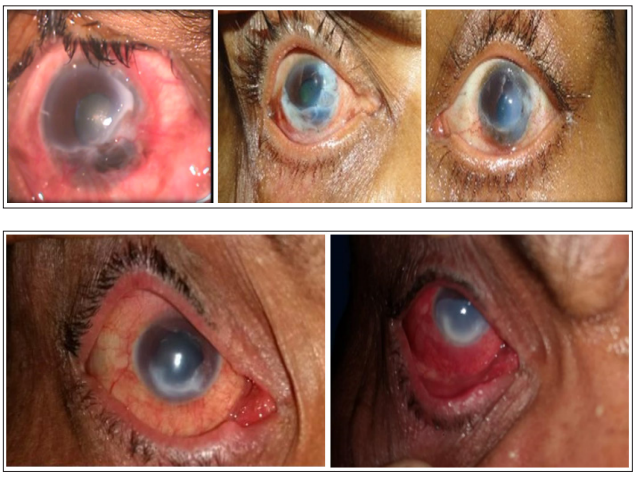

Figure 5A: Corneal Thinning B. Single Layered AMT in Place

Results

Table 1 shows age and gender distribution in our study, in which male preponderance was seen (66.67%) while only minority (33.33%) females were seen. Majority patients belonged in the age group of 60-80 years (53.33%), 33.34% were seen in 40-60 years, minority belonged in the age group of 20-40 years (13.33%).

Table 1: Age and Gender Predilection in Peripheral Ulcerative Keratitis

	No of cases		Total (%)
Age group	**Males**	**Females**	
20-40	0	2	2 (13.33%)
40-60	4	1	5 (33.34%)
60-80	6	2	8 (53.33%)
Total	10 (66.67%)	5 (33.33%)	15 (100%)

The aetiology in peripheral ulcerative keratitis observed was idiopathic in 66.66% while the remaining (33.3%) had rheumatoid arthritis as the causative factor, which is presented in table 2.

Table 2: Aetiology in Peripheral Ulcerative Keratitis

	No of cases		Total (%)
Aetiology	**Males**	**Females**	
RA	3	2	5 (33.33%)
Idiopathic	10	0	10 (66.67%)
Total	10 (66.67%)	5 (33.33%)	15 (100%)

Techniques of AMT used were single layered (20%) in corneal thinning involving superficial 1/3 corneal stroma, multi layered (53.3%) in corneal thinning involving >1/2 corneal stroma and in small sized perforations (13.33%) 3mm x1mm involving temporal quadrant (2-4'o clock) and 2.5x1mm involving superior quadrant (11'o clock-1'o clock) while rolled AMT's (13.33%) were used in larger perforations 5x1.5 mm involving the inferior quadrant (4-8'o clock) and (1-5'o clock) as shown in table 3.

Table 3: AMT Technique in Corneal Thinning and Various Type of Perforation

	Males		**Females**		**Total**	**AMT Technique**
With perforation	3		1		4 (26.67%)	
Perforation type	No. of cases	Properties	No. of cases	Properties		
Big 5mm x 1.5 mm	1	4-8 o clock 6'o clock perforation	1	1-5 o clock	2 (13.33%)	Rolled AMT
Small 3mm x 1mm	1	2-4'o clock involving temporal quadrant			1	Multi layered AMT
Small 2.5mm*1mm	1	11-1o' clock 12o' clock perforation+			1	Multi layered AMT
Without perforation	**Males**		**Females**		**Total**	
	7		4		11 (73.33%)	
	No of cases	Properties	No of cases	Properties		
	2	Superficial Involving 1/3 of stroma	1	Superficial Shallow Sup 1/3 stroma (1 Quad)	3 (20%)	Single layered AMT
	5	> half stroma involved without perforation Size: 3-4 o'clock (1-2 Quad)	3	> half stroma involved without perforation Size: 3-4 o'clock (1-2 Quad)	8 (53.33%)	Multi layered AMT

Post operative outcome in peripheral ulcerative keratitis is shown in table 4 in which initial success outcome (73.33%) was seen, with (26.66%) needing repeat surgery out of which 2 patients (13.33%) underwent repeat AMT changing the success rate from 73.33% to 86.66% ,1 patient (6.67%) had to undergo corneal patch graft due to recurrence of the disease while in 1 patient (6.67%) failure was seen in the form of phthisis even with large penetrating keratoplasty.

Table 4: Post Operative Outcome in Peripheral Ulcerative Keratitis

Post op outcomes	No. of cases	Total (%)
Immediate Symptomatic relief	15	100%
Initial success rate	11	73.33%
Repeat AMT	2	13.33%
Overall success rate after Repeat AMT	13	86.66%
Secondary Corneal Patch Graft	1	6.67%
Large Penetrating Keratoplasty	1	6.67%

Discussion

Peripheral ulcerative keratitis (PUK) is a rare but serious clinical entity due to its ophthalmic and systemic implications. There is a complex interplay between host autoimmunity, anatomy, physiology of the peripheral cornea and the environment. The underlying cause could be local or systemic, infectious or non-infectious [6]. Progressive stromal lysis can cause corneal perforation, and in patients with an underlying autoimmune disease indicates significant morbidity and mortality [12]. In the early stages, PUK is usually managed with intense lubrication to promote healing, topical antibiotics to prevent secondary infections and topical steroids and immunomodulators to control the underlying condition. In more advanced stages with impending perforation, a surgical approach is often needed to preserve globe integrity [13]. In our study, a preponderance of male patients was observed with male to female ratio of 2:1. Maximum patients belonged to elderly age group i.e., 60-80 years. Similar results were shown by Hoffman, Stephan and Berthald-et-al14 where majority population of PUK were elderly with male predominance. Among our patients, aetiology was idiopathic in 11(73.33%) whereas only 4(26.67%) presented with Rheumatoid Arthritis. Similar findings were reported by Hoffman and Berdhald where majority were idiopathic with few cases of rheumatoid arthritis and erythema multiforme were seen [14]. 11(73.33%) patients had no perforations while 4 patients (26.67%) had perforations. 2 big perforations sized around 5mm x 1.5mm and 3 small sized with 1 being 3mm x 1mm involving the temporal quadrant and rest 2 being 2.5mm x 1mm were seen. Conjunctival resection is used in areas of corneal thinning, it also removes the tissue supplying inflammatory mediators to the cornea [26]. Cyanoacrylate glue with a bandage contact lens is used for small perforations and those less than 3mm in diameter [12]. Bernauer used cyanoacrylate glue in rheumatoid arthritis related corneal perforations up to 3mm diameter without concurrent use of immunosuppressives in which temporary closure of perforations occurred in all 6 eyes, PUK continued due to aggressive disease, proving that systemic management of such conditions is of paramount importance. Similar reports were published by Weiss and Messmer in which temporary closure of perforated PUK with a 2mm size surgical drape and cyanoacrylate glue were done until a penetrating keratoplasty could be done later. However, Yin J et al [15-29]. showed no difference in success of managing perforations with glue depending on the aetiology. Larger size of the perforation and single glue application were correlated with higher failure rate. Sharma (2013) reported a series of 16 eyes where PUK-related corneal perforation between 3.5 to 4.5 mm were sealed with scleral patch graft using cyanoacrylate glue [24]. 14 eyes healed in 5–9 weeks, with 2 eyes needing repeat surgery due to loosening of the glue. 5 grafts needed suturing with10–0 nylon sutures. Once the graft fused with the host cornea, the glue was removed. A similar technique of managing PUK-related perforation was reported by Hinduik et al [25]. Progressive corneal thinning or perforations more than 3mm can be managed by use of single layered, multi layered or rolled AMT's. Out of 15 patients with PUK, 12(66.6%) underwent multilayered AMT, 3(13%) underwent rolled AMT while 3(20%) underwent single layered AMT. Solomon used multiple layers of AMT for corneal perforations less than 0.5mm size with poor results in PUK due to progressive autoimmune diseases. Motowa used a double layered AMT sandwich technique for a single case of Mooren's ulcer [15]. In both cases, immunosuppressive drugs were used. There has been mixed response to the use of AMT with fibrin glue for sealing corneal perforations in PUK [17-20]. Hicks reported good outcome (80% success rate) in perforations less than 3mm in diameter. Lamellar patch grafts used along with AMT reduce graft rejection risk compared with a full-thickness patch or tectonic grafts Similarly, a tenon patch taken from the patient's own inflamed eye seems less appropriate than an amniotic membrane. However, tenon grafts could be a solution in emergency situations [30,31].

Recurrence

The primary success rate of AMT was 73.33% and the outcome was excellent. There were 4 recurrences (26.67%), 2 were treated successfully by repeat AMT (Overall 86.66% success rate) and one by secondary corneal patch graft. Remaining one patient failed to respond even with large penetrating keratoplasty due to progressive rheumatoid disease with uncontrolled diabetes and landed up in phthisis. Hoffman et al [14]. in their study reported five recurrences (41%) successfully treated in 4 by repeat AMT (sandwich) and one by emergency penetrating keratoplasty. Hoffman et al [14]. reported a primary success rate of 11/12(92%) as compared to 11/15(73.33%) in the present study Similar results were shown by Eslami M et al [33]. who reported successful use of multilayered amniotic membrane transplantation for the treatment of corneal ulceration and perforation. However, Chen et al18 noted recurrence in a multilayered AMT with conjunctival autografting for Mooren's ulcer. Schallenberg et al reported relapse of aggressive Mooren's ulcer in 6 of 7 eyes which underwent AMT transplantation with conjunctival resection, even on oral immunosuppression [19,20]. However, Hanada had success with multilayered AMT in a Mooren's ulcer, but recurrence in two cases with rheumatoid arthritis [16-21]. Similarly, Rodrigues-Ares et al reported success in 2 cases of rheumatoid with failure in an erythema multiforme major case [22]. In a series of 45 eyes with perforation less than 3mm, Fan et al reported healing with good visual outcome in 6 cases with marginal ulcers. They filled the perforation with rolled-up AMT, covered by 3 layers of larger sized AMT and anterior chamber formation by injection of 0.3mL of 20% perfluoropropane. However, 3 cases had anterior iris synechiae postoperatively. Fan J et al [23]. in their retrospective study included 46 cornea perforations ≤ 3 mm in diameter treated with AMT with a 100% success rate was reported after a single operation. Therefore, Amniotic membrane transplantation is an effective surgical modality in the treatment of corneal ulcers and small to large sized perforation from peripheral ulcerative keratitis before elective penetrating keratoplasty due to its unique structure, biocompatible composition, easy availability and technical simplicity in use. It also preserves and supports stem cells whilst inhibiting neoplastic, inflammatory, angiogenic and fibroblastic cells [13]. Emergency keratoplasties for inflamed eyes due to peripheral ulcerative keratitis are considered to have a worse prognosis because of immunologic graft rejection [32]. Better symptomatic and visual outcomes can be obtained after adequate control of inflammation which can be achieved by use of AMT.

Conclusion

A tailored approach is best, aiming to restore epithelial integrity, halt further stromal lysis, and prevent super-infections of peripheral ulcerative keratitis. AM transplantation is a safe and effective alternative for the surgical management of PUK in combination with local and systemic immunosuppressive therapy. A close collaboration between the ophthalmologist and the physician is mandatory to prevent corneal perforation and decrease patient morbidity and risk of mortality.

References

1. Galor A, Thorne JE (2007) Scleritis and Peripheral Ulcerative Keratitis. Rheum Dis Clin N Am nov 33: 835-854.
2. Odorcic S, Keystone EC, Ma JJ (2009) Infliximab for the treatment of refractory progressive sterile peripheral ulcerative keratitis associated with late corneal perforation: 3-year follow-up. Cornea 28: 89-92.
3. Bartly J, Mondino BJ (1988) Inflammatory diseases of the peripheral cornea. Ophthalmology 95: 463-472.
4. Timlin, Hannah Mary, Hildegard Nikki Hall, Barny Foot, Peter Koay (2018) "Corneal Perforation from Peripheral Ulcerative Keratopathy in Patients with Rheumatoid Arthritis: Epidemiological Findings of the British Ophthalmological Surveillance Unit." British Journal of Ophthalmology 102: 1298-1302.
5. De la Sainz M (2002) Ocular characteristics and Disease Associations in Scleritis-Associated Peripheral Keratopathy. Arch Ophthalmol 1 janv 120: 15.
6. Bertret C, Leveziel L, Knoeri J (2023) Freeze-dried amniotic membrane graft with a spongy layer in bilateral peripheral ulcerative keratitis: a case report. BMC Ophthalmol 23: 387.
7. Van Herendael B J, Oberti C, Brosens I (1978) Microanatomy of the human amniotic membranes. A light microscopic, transmission, and scanning electron microscopic study. Am. J. Obstet. Gynecol 131: 872-880.
8. Dua H S, Gomes J A P, King A J, Maharajan V S (2004) The amniotic membrane in ophthalmology. Surv. Ophthalmol 49: 51-77.
9. Krysik K, Dobrowolski D, Wylegala E, Lyssek-Boron A (2020) Amniotic membrane as a main component in treatments supporting healing and patch grafts in corneal melting and perforations. J Ophthalmol 4238917-42389199.
10. Malhotra C, Jain AK (2014) Human amniotic membrane transplantation: different modalities of its use in ophthalmology. World J Transplant 4: 111-121.
11. Meller D, Pauklin M, Thomasen H, Westekemper H, Steuhl KP (2011) Amniotic membrane transplantation in the human eye. DtschArztebl Int 108: 243-248.
12. Fu L, Jones S (2023) Peripheral Ulcerative Keratitis. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing 14: 140-146.
13. Walkden A (2020) Amniotic Membrane Transplantation in Ophthalmology: An Updated Perspective. Clin Ophthalmol 14: 2057-2072.
14. Hoffmann, Stephan MD PhD, Szentmáry Norá MD PhD, Seitz Berthold MD (2013) Amniotic Membrane Transplantation for the Treatment of Infectious Ulcerative Keratitis Before Elective Penetrating Keratoplasty. Cornea 32: 1321-1325.
15. Solomon A, Meller D, Prabhasawat P (2002) Amniotic membrane grafts for nontraumatic corneal perforations, descemetoceles, and deep ulcers. Ophthalmology. 109: 694-703.
16. Ngan ND, Chau HT (2011) Amniotic membrane transplantation for Mooren's ulcer. Clin Experiment Ophthalmol 13: 386-392.
17. Motowa SA, Zobidi MA (2015) Amniotic membrane transplant with a special technique (Motowa's Sandwich Technique) in Mooren's ulcer. Middle East Afr J Ophthalmol 22: 386-388.
18. Chen KH, Hsu WM, Liang CK (2004) Relapsing Mooren's ulcer after amniotic membrane transplantation combined with conjunctival autografting. Ophthalmology. 111: 792-795.
19. Schallenberg M, Westekemper H, Steuhl KP, Meller D (2013) Amniotic membrane transplantation ineffective as additional therapy in patients with aggressive Mooren's ulcer. BMC Ophthalmol 13: 81.
20. Hick S, Demers PE, Brunette I (2005) Amniotic membrane transplantation and fibrin glue in the management of corneal ulcers and perforations: a review of 33 cases. Cornea 24: 369-377.
21. Hanada K, Shimazaki J, Shimmura S (2001) Multilayered amniotic membrane transplantation for severe ulceration of the cornea and sclera. Am J Ophthalmol. 131: 324-331.
22. Rodríguez-Ares MT, Touriño R, López-Valladares MJ, Gude F (2004) Multilayer amniotic membrane transplantation in the treatment of corneal perforations. Cornea. 23: 577-583.
23. Fan J, Wang M, Zhong F (2016) Improvement of amniotic membrane method for the treatment of corneal perforation. Biomed Res Int 1693815.
24. Sharma A, Mohan K, Sharma R, Nirankari VS (2013) Scleral patch graft augmented cyanoacrylate tissue adhesive for treatment of moderate-sized noninfectious corneal perforations (3.5–4.5 mm). Cornea 32: 1326-1330.
25. Hyndiuk RA, Hull DS, Kinyoun JL (1974) Free tissue patch and cyanoacrylate in corneal perforations. Ophthalmic Surg 5: 50-55.
26. Bernauer W, Ficker LA, Watson PG, Dart JKG (1995) The management of corneal perforations associated with rheumatoid arthritis: an analysis of 32 eyes. Ophthalmology 102: 1325-1337.
27. Weiss JL, Williams P, Lindstrom RL (1983) The use of tissue adhesive in corneal perforations. Ophthalmology 90: 610-615.
28. Messmer EM, Foster CS (1995) Destructive corneal and scleral disease associated with rheumatoid arthritis. Medical and surgical management. Cornea 14: 408-417.
29. Yin J, Singh RB, Karmi RA, Yung A, Yu M, et al. (2019) Outcomes of cyanoacrylate tissue adhesive application in corneal thinning and perforation. Cornea juin 38: 668-673.
30. Sharma N, Singhal D, Maharana PK, Vajpayee RB (2019) Tuck-In Tenon Patch Graft in corneal perforation. Cornea août 38: 951-954.
31. Anitha V, Ghorpade A, Ravindran M (2022) A modified tenons sling annular graft for advanced peripheral ulcerative keratitis with an hourglass cornea. Indian J Ophthalmolfévr 70: 655-657.
32. Kamra D, Chappadi K, Dudam R, Murthy SI (2022) Management of simultaneous bilateral immune-mediated peripheral ulcerative keratitis. Eur J Ophthalmol 11206721221149066.
33. Eslami M, Benito-Pascual B, Goolam S, Trinh T, Moloney G (2022) Case Report: Use of Amniotic Membrane for Tectonic Repair of Peripheral Ulcerative Keratitis with Corneal Perforation. Front Med (Lausanne) 9: 836873.