GAVIN PUBLISHERS

OPEN ACCESS

Journal of Surgery

Msika LC and Bourges JL. J Surg 6: 1431

Research Article

DOI: 10.29011/2575-9760.001431

Amniotic Membrane Transplantation after Phototherapeutic Keratectomy: Postoperative Pain, Epithelial Healing and Visual Recovery Outcomes

Laetitia-Claire Msika[1], Jean-Louis Bourges[1,2*]

[1]Department of Ophthalmology, Cochin Hospital, Assistance Publique-Hôpitaux de Paris, France

[2]INSERM 1138E17, Centre de Recherche des Cordeliers, University of Paris, Paris, France

[*]**Corresponding author:** Jean-Louis Bourges, Department of Ophthalmology, University of Paris, Paris, France.

Citation: Msika LC, Bourges JL (2021) Amniotic Membrane Transplantation after Phototherapeutic Keratectomy: Postoperative Pain, Epithelial Healing and Visual Recovery Outcomes. J Surg 6: 1431 DOI: 10.29011/2575-9760.001431

Received Date: 17 September, 2021; **Accepted Date:** 01 October, 2021; **Published Date:** 05 October, 2021

Abstract

Purpose: We aimed to evaluate postoperative pain, epithelial healing features, visual recovery, and refractive outcome after Phototherapeutic Keratectomy (PTK) with and without sutureless Lyophilized Amniotic Membrane Transplantation (AMT).

Design: Retrospective, non-randomized monocentric, comparative case series.

Setting: Department of Ophthalmology, Ophtalmopole APHP, Cochin hospital, Paris, France.

Methods: This study reviewed the consecutive files of 47 eyes which received PTK over a 9-month period. Two groups were analyzed: after PTK, one group, the AMT group, received sutureless lyophilized AMT with Bandage Contact Lens (BCL) whereas a Control group, did not. The primary outcome measurement was the patients' postoperative pain. The secondary outcome measurements were the corneal epithelial thickness from AS-OCT, the delay to recover best-corrected visual acuity, and the refractive outcome, all measured before surgery, 1 and 4 weeks after surgery.

Results: We analyzed 47 eyes, with 25 in the AMT group and 22 in the Control group. No statistically significant difference in pain alleviation was observed on the 1st postoperative day (4.9± 3.1 vs. 6.7± 1.7; p=0.2) or on the following postoperative days between the AMT and Control groups. The change in epithelial thickness was moderately but statistically significantly smaller in the AMT group between pre- and 1week post-operatively in the paracentral (-5.8µm± 9.7 vs -10.7± 7.7; p=0.045), midperipheral (-3.6µm± 10.3 vs -8.3± 6.9; p=0.03) and peripheral (-3µm± 7.0 vs -7.1± 5.1; p=0.028) annular zones. The visual acuity recovery was not different between the groups AMT vs Control, as measured between preoperative and 1st week after surgery (-0.06 ± 0.27 vs -0.06± 0.25; p=0.9) and between 1st and 4th week after surgery (0.17± 0.17 vs 0.20± 0.18; p=0.7). No statistical difference in refractive shift was observed (spherical equivalent: 0.03± 2.33 vs -0.12± 2.16; p=0.9). The two groups differed in multiple ways: AMT patients were older (63 years± 17 vs 50± 23; p=0.044), had more anterior stromal pathologies (60% vs 28%; p=0.033), lower visual acuity (0.45± 0.36 vs 0.22± 0.18; p=0.04) and higher refractive cylinder (-1.76D± -1.06 vs -1.13± -0.81; p=0.047) compared to Control group. Stromal ablation was also deeper (37µm± 36 vs 14± 5; p=0.001) in the AMT group. No surgical perioperative complication or infection was noticed. Less haze was observed 4th week after surgery in AMT group (0% vs 23%; p=0.017).

Conclusion: The use of AMT after PTK does not offer clinically relevant pain alleviation in our study but it seems to provide faster epithelial healing and clearer cornea. After PTK, AMT and BCL do not influence visual recovery time course in patients.

Introduction

Phototherapeutic Keratectomy (PTK) is a routine procedure. It is effective and accessible [1] to treat corneas with either Recurrent Corneal Erosions (RCE) or stromal opacities localized in the 5-20% anterior corneal thickness [2,3]. In the context of RCE treatment, PTK aims to remove abnormal epithelium and the Bowman's layer. PTK also promotes efficient bonds between the corneal epithelium basal membrane and the anterior stroma, as observed with electron microscopy [4], and creates favorable conditions for the formation of a new, smoother, and more adherent epithelium. In the context of anterior stromal pathology treatment, PTK's goal is to withdraw opacities.

While the PTK procedure is itself painless, all patients report pain for several days, with a peak 24 to 72h after surgery. Such postoperative pain may be caused by inflammation, ocular surface irregularities, or damages to nerve endings. To reduce the pain induced by PTK, several strategies have been employed. Oral analgesics, potentially including opioids and corneal cooling are often used to relieve pain [5]. Bandage Contact Lenses (BCLs) are also commonly applied to manage postoperative pain and discomfort. However, patients still experience substantial corneal pain after PTK even when a BCL is applied. A prospective randomized clinical [6] trial failed to demonstrate any effect of a BCL on pain score or epithelialization time course after corneal transplantation. The authors posited that this lack of antalgic effect is due to the fact that the pain is mainly caused by damaged nerve endings rather than ocular surface disorders. Yet, while BCL does not appear to provide relief to patients after corneal nerves section, it still isolates corneal surface from eyelid blinks. It also favors both corneal hydration and topical medications biodisponibility. However, BCL can increase the risk of infectious keratitis, which is a real concern [7-11]. Studies reported that the rate of infectious keratitis is about five times higher after photorefractive keratectomy than after LASIK, mainly because of the application of BCLs [11-13]. For this reason, the use of BCLs after PTK is disputable.

An alternative to BCL is an Amniotic Membrane Transplantation (AMT), a procedure commonly performed to enhance epithelial healing [14], which is important as shorter times of re-epithelialization result in less refractive errors and less corneal haze [15]. Indeed AMT provides anti-inflammatory, antifibrotic, and antiangiogenic effects [16], maintains epithelial stem cell niches [15], and acts as a mechanical barrier to the proinflammatory cytokines contained in tears. AMT also optimally blocks sub-epithelial fibrosis during the initial step of the wound healing process [15]. As a result, AMT is now common in the treatment of corneal diseases [17-20]. Indeed, it is used, among other indications, in infectious keratitis to preserve visual outcomes [21] and to relieve patients with painful bullous keratopathy [22], in combination or not with PTK [23]. Finally, a study shows that following PTK treatment for various conditions, AMT performs similarly to BCL [24], as measured by postoperative pain, visual outcome, and manifest refraction at 12 months, despite the fact that the AMT used was ring-shaped, which might have hindered its efficacy. After PTK, visual acuity fluctuates because of both epithelial layer ingrowths and the wound healing process of the anterior stroma. Refraction also changes throughout midterm outcomes. Indeed, some degree of hyperopic shift is expected after deep photoablations, proportional to central stroma photoablation which flattens corneal curvature [25].

Aiming to reduce postoperative pain, enhance visual recovery, and prevent infectious keratitis resulting from BCL, some surgeons are now considering AMT in association with BCLs, positioning the AMT between the cornea and the BCL after PTK. In this case, the PTK procedure ends by applying a sutureless AMT and a BCL is used to secure the AMT in place. As we failed to find any results regarding the outcome of such a procedure in the literature, we aimed here to report pain after PTK performed with or without AMT and BCL (AMT+BCL). We also investigated the effects of this combined use on the epithelial thickness, time course of visual recovery, and refractive outcome.

Methods

Patients

We conducted a retrospective study based on the records of patients treated in our ophthalmology department from November 2020 to April 2021. We selected all consecutives files from patients operated with excimer laser Phototherapeutic Keratectomy (PTK). We excluded patients with neurotrophic keratopathy or severe dry eye, at risk of delayed healing. For each selected file, we obtained from the patient an informed consent and the authorization to proceed retrospectively with their data for anonymous analysis and publication. Patient demographics included gender, patient's age, laterality, indication for PTK, underlying ocular or systemic disease. Based on each patient's files, we attributed them to either to the Control or to the AMT group.

Data Collection

To collect clinical data, we reviewed consecutive files from patients who underwent PTK in our ophthalmology department, using our institutional database (ORBIS ®, Dedalus). We analyzed data from 3 specific visits systematically planned within the schedule of our standard care protocol: the preoperative visit and the 1st and 4th week postoperative visits. The preoperative examination provided the following data: Corrected Distant Visual Acuity (CDVA), manifest refraction, slit-lamp examination results, Anterior Segment Optical Coherence Tomography (AS-OCT), and corneal Scheimpflug tomography (Pentacam, Oculus). The postoperative examinations provided the following data: CDVA,

manifest refraction, Visual Analogue Pain Scale (VAPS) follow-up, slit-lamp examination results, and AS-OCT.

Endpoints

Our primary endpoint was the subjective pain reported by patients following their PTK procedure with or without associated AMT+BCL. Our secondary endpoints were the estimation of corneal epithelial wound healing, the time course of visual acuity recovery, and the refractive outcome after PTK with or without associated AMT+BCL.

Outcome Measurements

The main outcome measurement was a pain score provided by the patients in the days following surgery. The PTK standard protocol included a standard form assessing pain at 4 consecutive time points daily over the first postoperative week, using a VAPS, labeled from zero to ten, zero being an example of someone with no pain and ten the worst pain possible. Patients filled the VAPS each day postoperatively until complete analgesia. The patients brought back the filled pain form at the first postoperative visit, which was then added to the patient's medical records. We assessed epithelial healing using notes from slit-lamp examinations and measurements of the Epithelial Thickness (ET) performed at each visit. ET was measured with a AS-OCT (RTVue XR OCT, Optovue) with a corneal adaptor module. The AS-OCT system works at 840 nm wavelengths, has a scan speed of 70,000 axial scans per second, and depth resolution of 5 µm in tissue. We obtained thickness maps at each visit using the "PachymetryWide" mode by covering the 9-mm diameter area of the cornea in a pupil-centered fashion. We split. maps in 25 sectors: the 2 mm central zone and 8 equally distributed octants in the paracentral (2 to 5 mm), midperipheral (5 to 7 mm), and peripheral (7 to 9 mm) annular zones. AS-OCT provided the average ET for the corresponding area. We collected both the thinnest (min) and thickest (max) ET as well as the thinnest pachymetry. The current study analyzed data acquired at the visits of interest (preoperatively, after removal of the amniotic membrane at the 1st week postoperatively, and at the 4th week postoperatively).

We defined the Change of Epithelial Thickness (CET) 1 and CET 4 of the central zone, paracentral, midperipheral, and peripheral annular zones for each patient as the ET difference between preoperative and 1st week and between 1st and 4th week after surgery respectively. Experienced and qualified technicians, supervised by an experienced corneal specialist, performed all OCT measurements. We assessed CDVA at each visit using the Monoyer decimal visual chart. We converted all data into a logarithmic scale. We defined the Variation of Corrected Distant Visual Acuity (VCDVA) 1 and VCDVA 4 for each patient as the CDVA difference between preoperative and 1st week and between 1st and 4th week after surgery respectively. We obtained the manifest refraction, with refractive sphere and cylinder at each visit. We calculated for each patient at each visit the Manifest Refractive Spherical Equivalent (MRSE). We defined the Spherical Equivalent Refractive Shift (SERS) as the MRSE difference between preoperative and 4th week after surgery.

We followed a single blind protocol to analyze all patients' data.

Surgical Techniques

According to our institutional standard of care protocol, the PTK procedure briefly consists of:

Topical anesthesia.

For the treatment of RCE: mechanical removal of epithelium over a 9 mm central corneal area and PTK laser treatment centered on the pupil, with pupil tracker engaged and with an optical zone of 6.5 mm diameter. The thickness of the bowman's layer being estimated at 12 µm, the laser is programmed at 15 µm thickness.

For the treatment of stromal opacities: Transepithelial Phototherapeutic Keratectomy (TE-PTK) centered on the pupil, with pupil tracker engaged and with an optical zone of 6.5 mm diameter. The programmed treatment depth depends on the depth of the anterior opacity to be treated. We programmed 50 µm for initial delivery then we proceeded to stromal ablation in 10 µm steps until the opacity reduces. Stromal ablation depth in TE-PTK is determined by subtracting from the total ablation depth the central ET measured preoperatively when available, or, when not available, the mean measurement of central ET over all patients (here, 52 µm).

PTK is performed using Excimer laser (VisX SI6, AMO). From selected files, we calculated an average energy density of 160 mJ/cm2 and a pulse repetition rate of 10 Hz.

Regardless of the procedures performed, adjuvant treatments could be used: EDTA applied for 3 min on calcified deposits further debrided with a curved blade; Mitomycin C 0,02 % (MMC 0,2 mg/mL) applied for 30 seconds then abundantly rinsed with BSS on cornea displaying stromal opacities to improve recurrence rate.

At the end of the procedure, and independently from the previous surgical steps, some patients received lyophilized AMT (spongious layer, VisioAmtrix) following a standard protocol. Lyophilized AMT can be kept at room temperature and stored for several months, unlike cryopreserved amniotic membrane. Thus, for ease of use, we used lyophilized AMT. The protocol of AMT+BCL consisted of a 9 mm diameter AMT trephination. AMT is then applied on the dried cornea and left sutureless. A BCL (Bausch & Lomb, Pure Vision 2) is positioned on top of the AMT. Both AMT and BCL are removed after one week, at the first postoperative visit. The choice to use AMT+BCL or not was left to the discretion of surgeons.

. **Postoperative Regimen**

The postoperative treatment was identical for all patients, without any relation to the surgical technique performed. One drop of topical antibiotic -ciprofloxacine- was instilled at the end of the procedure and further administrated TID for 3 weeks systematically. Oral pain relievers were proposed at will/QID maximum (Tramadol chlorhydrate + paracetamol; 37.5 mg/325 mg) for 2 days, topical lubricants (Vismed) were prescribed TID for 1 month, and topical Dexamethasone + Neomycine starting 2 days after surgery, as not to interfere with epithelial healing, TID for 3 weeks.

Complications

All complications observed preoperatively and at each postoperative visit were collected. We evaluated haze through the Hanna's grading scale at the 4th week visit.

Data Analysis

All analyses were performed using RStudio statistical software (Version 1.4.869 X Rstudio, Inc). P values less than 0,05 were considered statistically significant. Multiple imputation was used to handle missing data.

Results

Demographic, surgical techniques, Visual Analogue Pain Scale (VAPS), Epithelial Thickness (ET), visual acuity, refractive and complications outcomes are displayed in Table 1. The ET profile data are displayed in Figure 1 for AMT group and in Figure 2 for PTK group.

Demographic	Group AMT[1]	Group Control[1]	p-value[2]
Number of eyes	25	22	
Number of patients	24	20	
Sex (% women)	48%	45%	0.09
Mean age (year)	63 (+/- 17)	50 (+/- 23)	0.044*
Right eye	56%	36%	0.2
Indications for PTK			
Recurrent corneal erosions	12%	27%	0.3
Cogan dystrophy	28%	45%	0.2
Anterior stromal pathologies	60%	28%	0.033*
Stromal dystrophy	32%	18%	0.3
Band keratopathy	24%	9%	0.3
Salzmann degeneration	4%	0%	0.9
Previous PTK	24%	14%	0.5
Minimal pachymetry (µm)	530 (+/- 49)	524 (+/- 68)	0.7
Underlying ocular disease	48%	23%	0.07
Cataract	32%	18%	0.3
Corneal graft	16%	0%	0.1
Glaucoma	20%	0%	0.05
Retinal disease	12%	4.50%	0.6
Underlying systemic disease	32%	32%	0.9
Diabetes	12%	4.50%	0.6

Hypertension	20%	18%	0.9
Others	24%	23%	0.9
Surgical Techniques			
PTK	56%	73%	0.2
TE-PTK	44%	27%	
Optical zone (mm)	6.4 (+/- 0.19)	6.3 (+/- 0.28)	0.6
Transition zone (mm)	0.01 (+/- 0.03)	0.04 (+/- 0.08)	0.3
Stromal ablation depth (µm)	37 (+/- 36)	14 (+/- 5)	0.001*
MMC	24%	5%	0.1
EDTA	16%	5%	0.3
Visual Analogue Pain Scale, VAPS			
Day 1	4.9 (+/- 3.1)	6.7 (+/- 1.7)	0.2
Day 2	3.6 (+/- 2.8)	4.4 (+/- 1.7)	0.4
Day 3	2.2 (+/- 2.1)	2.8 (+/- 1.7)	0.3
Day 4	1.2 (+/- 1.5)	1.4 (+/- 1.8)	0.8
Day 5	0.4 (+/- 0.8)	0.4 (+/- 0.8)	0.9
Day 6	0.2 (+/- 0.4)	0.1 (+/- 0.3)	0.3
Day 7	0	0	
Epithelial Thickness, ET (µm)			
CET 1			
Central zone	-6.3 (+/- 10.7)	-9.6 (+/- 10.4)	0.3
Paracentral annular zone	-5.8 (+/- 9.7)	-10.7 (+/- 7.7)	0.045*
Midperipheral annular zone	-3.6 (+/- 10.3)	-8.3 (+/- 6.9)	0.03*
Peripheral annular zone	-3 (+/- 7.0)	-7.1 (+/- 5.1)	0.028*
Minimal epithelium	-12.4 (+/- 11.4)	-19.8 (+/- 12.3)	0.069
Maximal epithelium	0.2 (+/- 9.2)	-3.1 (+/- 11.1)	0.4
CET 4			
Central zone	1.25 (+/- 12.3)	1.74 (+/- 12.3)	0.9
Paracentral annular zone	2.56 (+/- 9.2)	5.1 (+/- 8.6)	0.4
Midperipheral annular zone	1.9 (+/- 9.3)	2.7 (+/- 7.3)	0.9
Peripheral annular zone	-0.34 (+/- 9.4)	0.95 (+/- 7.8)	0.7
Minimal epithelium	6.1 (+/- 13.7)	10.1 (+/- 13.5)	0.6
Maximal epithelium	1.33 (+/- 8.9)	-0.35 (+/- 12.6)	0.4
Visual Acuity (logMAR)			

CDVA			
Preoperative	0.45 (+/- 0.36)	0.22 (+/- 0.18)	0.04*
1st week	0.65 (+/- 0.54)	0.25 (+/- 0.24)	0.005*
4th week	0.35 (+/- 0.27)	0.1 (+/- 0.14)	0.001*
VCDVA			
VCDVA 1	-0.06 (+/- 0.32)	-0.06 (+/- 0.25)	0.9
VCDVA 4	0.17 (+/- 0.17)	0.20 (+/- 0.18)	0.7
Refractive (Diopter)			
Preoperative			
Refractive sphere	-0.3 (+/- 2.88)	-0.32 (+/-2.24)	0.9
Refractive cylinder	-1.76 (+/- 1.06)	-1.13 (+/- 0.81)	0.047 *
MRSE	-1.11 (+/- 2.72)	-0.89 (+/- 2.22)	0.8
1st week			
Refractive sphere	-0.08 (+/- 3.94)	0.58 (+/-1.96)	0.6
Refractive cylinder	-2.18 (+/- 1.68)	-1.61 (+/-1.05)	0.5
MRSE	-1.18 (+/- 3.69)	-0.26 (+/- 1.83)	0.7
4th week			
Refractive sphere	-0.4 (+/- 3.7)	-0.1 (+/- 2.7)	0.7
Refractive cylinder	-2.00 (+/- 1.23)	-1.72 (+/- 1.32)	0.4
MRSE	-1.4 (+/- 3.7)	-1 (+/- 2.8)	0.8
SERS	0.03 (+/-2.33)	-0.12 (+/-2.16)	0.9
SERS Myopic > 0.5D	40%	36%	0.8
	1.8 (+/- 0.9)	1.4 (+/- 1.5)	0.1
SERS Hyperopic > 0.5D	20%	18%	0.9
	3.1 (+/- 2.4)	2.7 (+/- 1)	0.9
SERS </= 0.5D	24%	14%	0.5
Complications			
Surgical complication	0	0	
AMT + BCL spontaneous extrusion	3		
Delayed healing	0	0	
AMT adhesion to the cornea	3		
Epithelium tear on AMT removal	2		
AMT Integration	0	0	
Haze	0%	23%	0.017 *

0.5+	0%	14%	0.09
1+	0%	9%	0.2
Infection	0	0	

[1]Mean (+/- Standard deviation).

[2]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test. $^{*}p < 0.05$.

PTK: Phototherapeutic Keratectomy.

AMT: Amniotic Membrane Transplantation.

BCL: Bandage Contact Lens.

TE-PTK: Transepithelial Phototherapeutic Keratectomy.

EDTA: Ethylenediaminetetraacetic Acid.

MMC: Mitomycin C.

VAPS: Visual Analogue Pain Scale.

ET: Epithelial Thickness.

CET: Change of Epithelial Thickness.

CDVA: Corrected Distance Visual Acuity.

VCDVA: Variation of Corrected Distance Visual Acuity.

MRSE: Manifest Refractive Spherical Equivalent.

SERS: Spherical Equivalent Refractive Shift.

Table 1: Demographic, surgical techniques, visual analogue pain scale, epithelial thickness, visual acuity, refractive, and complications outcomes.

Figure 1 : Epithelium thickness for AMT group

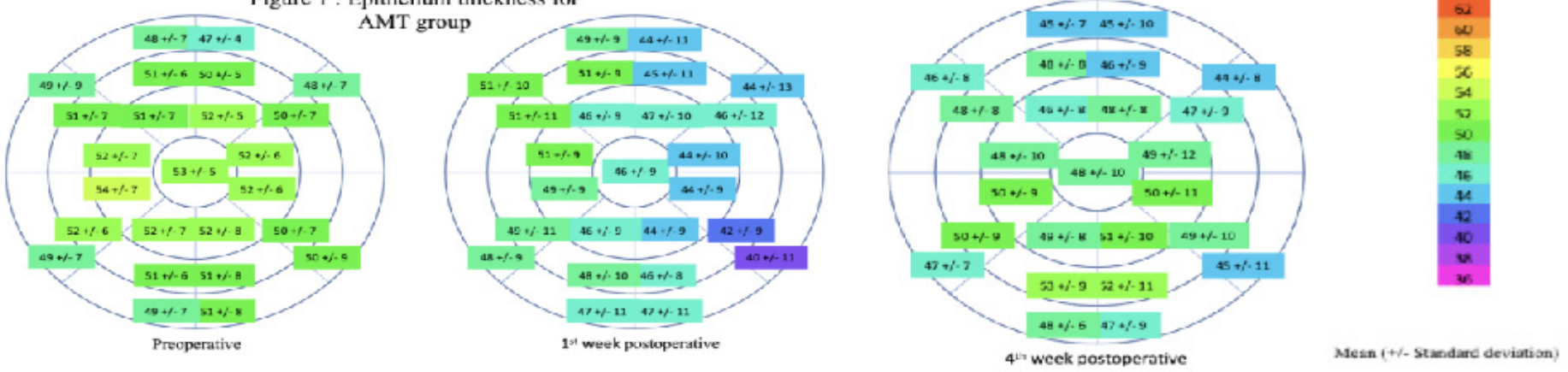
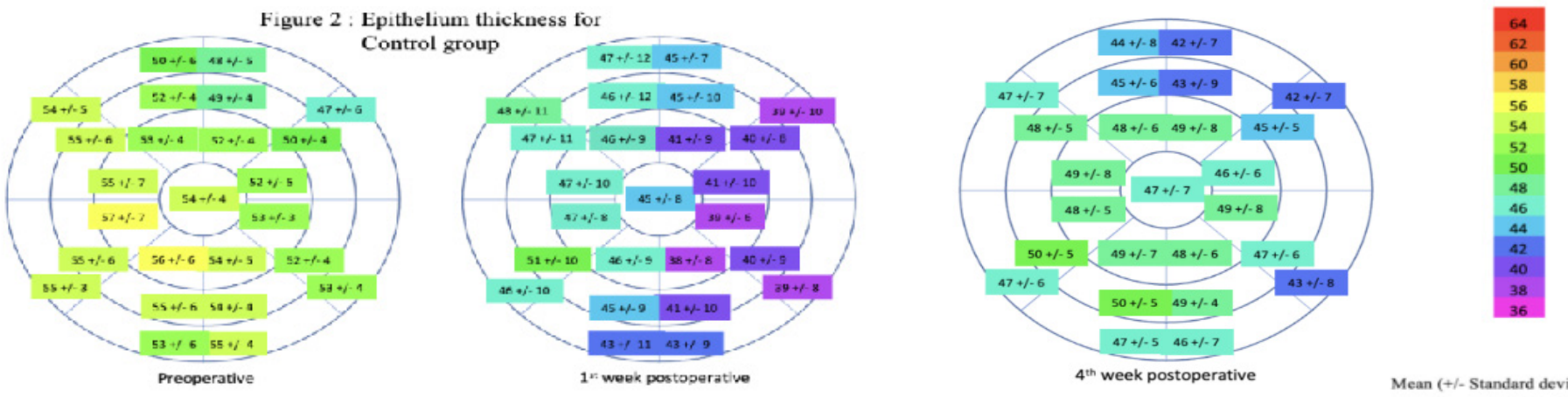


Figure 2 : Epithelium thickness for Control group



Discussion

We did not observe any significant difference between groups for postoperative pain. Would an increased number of patients have empowered our statistical tests to obtain a statistically significant difference between pain scores, the reduction in pain would not have been relevant for patients in real life. Indeed, the mean pain score in the AMT group still remains high. AMT does not relieve patients enough for them to live differently their surgical experience. Yet, our results might have been confounded by the variability of surgical techniques in each group. First, stromal ablation depths are statistically different between the 2 groups. Deeper ablation, up to 25% of stromal thickness, generates less pain compared to superficial ablation within 25 µm [26]. Indeed, the ablation of nerve plexuses is more complete with deep PTK than with superficial PTK and might explain this observation. While TE-PTK has been shown to be less painful [27] than the conventional PTK with mechanical debridement as it exposes a smaller area of the central stroma (6.5 mm vs. 9 mm with conventional PTK), each group contained similar proportions of TE-PTK and PTK.

We regarded ET progression as a marker of the corneal surface wound healing time course. Non-confluent corneal epithelial cells migrate centripetally to form a confluent monolayer of basal cells [28]. Then, epithelial layers accumulate to reach 5 to 7 superimposed layers. ET preoperative, 1st and 4th week after surgery were comparable in both groups. However, there is a smaller change in ET in the paracentral, midperipheral, and peripheral annular zones 1 week after surgery with AMT. This suggests a faster healing with early restoration of ET under the AMT+BCL protocol. It is worth mentioning that, although we used different surgical techniques, both groups received TE-PTK equally. As mentioned, the epithelium defect is smaller with TE-PTK (6,5mm) compared with conventional PTK (9mm). Thus, epithelial confluence delay is facilitated after TE-PTK as well as epithelial layer regeneration, especially by the 1st postoperative week. We did not find any report of the ET within the 1st week after PTK.

We observed a difference in CDVA preoperatively and after surgery between the 2 groups. This is most probably explained, preoperatively, by the higher proportion of anterior stromal pathologies in the AMT group and, postoperatively, by its foreseen impact on vision. There was no statistical difference regarding VCDVA 1 and 4 between groups. Indeed, only some patients had a decrease in vision, and some partially recovered because of underlying ocular disease. Patients treated for RCE, some with Cogan dystrophies, who demonstrated preserved visual acuity but recurrent pain, were equally represented in both groups. Similarly, patients with poor visual prognosis, with underlying ocular diseases such as cataract or retinal disease, had limited improvements after PTK, and were equally represented in both groups too. Patients with concurrent cataract received PTK before cataract surgery to include possible modifications of corneal shape in biometry and intraocular lens power estimation [29]. PTK also aimed at improving corneal clarity to optimize intraoperative vision field.

The MRSE preoperatively, at 1st and 4th week after surgery were relatively comparable in both groups despite a more important refractive cylinder in the AMT group. We attribute this difference to the higher proportion of anterior corneal pathologies in this group. Besides, SERS did not differ between groups. In contrast to induced hyperopia or myopia observed in other studies [30,31], the refractive shift of our patients was similar in both groups, with no specific trend. We considered a refractive shift when the PTK induced a SERS of | 0,5 | diopters or more.

Haze was less present in the AMT group which is in agreement with the literature. Indeed, AMT has an additive anti-scarring effect preventing corneal haze formation [32,33], due to its antiapoptotic effects on keratocytes [34] and to the growth factors provided by the AMT matrix to the ocular surface. However, anterior stromal pathologies are overrepresented in the AMT group, which may have jeopardized our final haze evaluation. Firstly, some degree of postoperative residual and untreated opacity is possible, overestimating the part of haze related to the wound healing process. Secondly, stromal opacities need deeper PTK stromal ablation which favors postoperative haze as cases with deeper ablations are at an increased risk of postoperative haze [35]. Some patients received prophylactic MMC application to prevent haze after PTK [36,37]. PTK indication and outcomes vary depending upon the underlying disease. For instance, deposits cleared with PTK in corneal dystrophies linked to keratoepithelin accumulate all over again systematically within 5 years [38]. There, adjuvant therapy like MMC intraoperatively applied on photoablation area has been proposed [39-45], as well as deep stromal ablation [25] and PTK repetition [46,47]. In our patients, both groups had MMC equally. Given the fact that the VCDVA was similar across the two groups, we do not think that the haze, preferentially noticed in the Control group, has impacted our patients' visual recovery.

The time course of epithelial healing is masked by AMT, as long as it remains on the corneal surface. AMT tolerance is excellent, but a postoperative visit is mandatory to remove it. There, the AMT itself can adhere to the corneal surface. AMT removal can thus be at risk of tearing the freshly rebuild epithelium, and thus at risk of iatrogenic ulcer.

While the postoperative strategy can vary significantly among eye care centers and procedures, the PTK procedure was followed by 2 postoperative visits for all our patients. The 1st and 4th week visits aimed both at controlling corneal healing and visual recovery. The second visit was scheduled 4 weeks after surgery to evaluate a maximized visual recovery with a minimized corneal remodeling and probability of dystrophy recurrence. At this time point, we obtained a better analysis of the patients' PTK outcomes. For further follow-up, the patients were invited to visit their referring ophthalmologist. It is likely that visual acuity, refractive and corneal clarity further evolved at a later follow-up. To balance surgical indications, AS-OCT offers high-resolution preoperative pictures and discriminate epithelium over stromal layers. It localizes stromal opacities in position and depth with high accuracy [25]. As a routine examination, standard care protocols more and more frequently include AS-OCT as a systematic exploration for anterior stromal pathologies. The shape of the anterior stroma observed with AS-OCT underneath the flattening effect of epithelium guides the choice of TE-PTK over PTK [25,48-50].

Both the cryopreserved and lyophilized membranes have comparable immunohistochemical properties [51]. It is important to remember that, regardless of the AMT's preservation technique, the biological properties of lyophilized and cryopreserved amniotic membranes are both altered versions of the "fresh" amniotic membranes [52]. Thus, it does not appear likely that the use of cryopreserved AMT instead would have changed our results. Our postoperative approach combining AMT with BCL was more expensive than PTK alone. After pterygium surgery, AMT reduces the risk of pathology recurrence and thus prevents additional costs and procedures [18, 53-56]. It would certainly be interesting to know whether the use of PTK combined with AMT in patients with corneal dystrophy or opacity also reduces the need for a secondary procedure to treat recurrences after a long-term follow-up. Until this is demonstrated, the additional cost caused by AMT cannot be easily supported.

It is important to note that this study has limitations. First, it is retrospective in nature and the data was provided by a single care center. Second, our patients sample size is small which hinders the statistical power of the study and could result in failing to report real differences between groups. Still, we believe that the statistical power of our study makes clinical sense as our sample size is relevant to evaluate differences with real life outcomes. Third, the choice to perform PTK combined with AMT was left to the discretion of the surgeons. Subsequently, we observed a statistically significant difference in age, anterior stromal pathologies, preoperative CDVA, and refractive cylinder between the 2 groups. The PKT+AMT combined procedure still being uncommon, it remains difficult to obtain homogeneous groups of patients retrospectively. Fourth, different surgical techniques have been performed depending on the patients' pathologies, leading to statistically significant differences in stromal ablation depth. This prevented us from performing further sub-group analysis and thus from fully answering our initial questions. Last, the evaluation of postoperative haze was unmasked which might have limited the reliability of haze scores.

Conclusion

The use of AMT postoperatively does not provide clinically significant pain relief in our patients but promotes epithelial thickness recovery and corneal transparency. Because it fails to improve pain and visual recovery when combined with PTK in patients with RCE or corneal opacity, the use of AMT does not seem to be indicated in our opinion.

References

1. Sharma N, Prakash G, Sinha R, Tandon R, Titiyal JS, et al. (2008) Indications and Outcomes of Phototherapeutic Keratectomy in the Developing World. Cornea 27: 44-49.
2. Ayres BD, Rapuano CJ (2006) Excimer Laser Phototherapeutic Keratectomy. Ocul Surf 4: 196-206.
3. Rapuano CJ (2010) Phototherapeutic keratectomy: who are the best candidates and how do you treat them? Curr Opin Ophthalmol 21: 280-282.
4. Szentmáry N, Seitz B, Langenbucher A, Schlötzer-Schrehardt U, Hofmann-Rummelt C, et al. (2006) Histologic and Ultrastructural Changes in Corneas With Granular and Macular Dystrophy After Excimer Laser Phototherapeutic Keratectomy. Cornea 25: 257-263.
5. Fay J, Juthani V (2015) Current trends in pain management after photorefractive and phototherapeutic keratectomy. Refract Surg 26: 5.
6. Shimazaki J (2016) Effectiveness of bandage contact lens application in corneal epithelialization and pain alleviation following corneal transplantation; prospective, randomized clinical trial 2016: 6.
7. Donnenfeld ED, O'Brien TP, Solomon R, Perry HD, Speaker MG, et al. (2003) Infectious keratitis after photorefractive keratectomy. Ophthalmology 110: 743-747.
8. Fleiszig SMJ, Kroken AR, Nieto V, Grosser MR, Wan SJ, et al. (2020) Contact lens-related corneal infection: Intrinsic resistance and its compromise. Prog Retin Eye Res 76: 100804.
9. Ting DSJ, Ho CS, Deshmukh R, Said DG, Dua HS (2021) Infectious keratitis: an update on epidemiology, causative microorganisms, risk factors, and antimicrobial resistance. Eye 35: 1084-1101.
10. Haq Z, Farooq AV, Huang AJW (2016) Infections after refractive surgery. Curr Opin. Ophthalmol 27: 367-372.
11. Das S, Garg P, Mullick R, Annavajjhala S (2020) Keratitis following laser refractive surgery: Clinical spectrum, prevention and management. Indian J Ophthalmol 68: 2813-2818.
12. de Rojas V, Llovet F, Martínez M, Cobo-Soriano R, Ortega-Usobiaga J, et al. (2011) Infectious keratitis in 18 651 laser surface ablation procedures. J Cataract Refract Surg 37: 1822-1831.
13. Ortega-Usobiaga J, Llovet-Osuna F, Djodeyre MR, Llovet-Rausell A, Beltran J, et al. (2015) Incidence of corneal infections after laser in situ keratomileusis and surface ablation when moxifloxacin and tobramycin are used as postoperative treatment. J Cataract Refract Surg 41: 1210-1216.
14. Azuara-Blanco A, Pillai CT, Dua HS (1999) Amniotic membrane transplantation for ocular surface reconstruction. Br J Ophthalmol 1999: 4.
15. Lee HK, Kim JK, Kim SS, Kim EK, Kim KO, et al. (2004) Effect of amniotic membrane after laser-assisted subepithelial keratectomy on epithelial healing: Clinical and refractive outcomes. J Cataract Refract Surg 30: 334-340.
16. Nakamura T, Inatomi T, Sekiyama E, Ang LPK, Yokoi N, et al. (2006) Novel clinical application of sterilized, freeze-dried amniotic membrane to treat patients with pterygium. Acta Ophthalmol Scand 2006: 5.
17. Anderson DF, Prabhasawat P, Alfonso E, Tseng SCG (2001) Amniotic Membrane Transplantation After the Primary Surgical Management of Band Keratopathy: Cornea. Mai 20: 354-361.
18. Kwon YS, Song YS, Kim JC (2004) New Treatment for Band Keratopathy: Superficial Lamellar Keratectomy, EDTA Chelation and Amniotic Membrane Transplantation. J Korean Med Sci 19: 611.
19. Hick S, Demers PE, Brunette I, La C, Mabon M, et al. (2005) Amniotic Membrane Transplantation and Fibrin Glue in the Management of Corneal Ulcers and Perforations: A Review of 33 Cases. Cornea 24: 369-377.
20. Im S-K, Lee K-H, Yoon K-C (2010) Combined Ethylenediaminetetraacetic Acid Chelation, Phototherapeutic Keratectomy and Amniotic Membrane Transplantation for Treatment of Band Keratopathy. Korean J Ophthalmol 24: 73.
21. Ting DSJ, Henein C, Said DG, Dua HS (2021) Amniotic membrane transplantation for infectious keratitis: a systematic review and meta-analysis. Sci Rep 11: 13007.
22. Srinivas S, Mavrikakis E, Jenkins C (2007) Amniotic Membrane Transplantation for Painful Bullous Keratopathy. Eur J Ophthalmol 17: 7-10.
23. Vyas S, Rathi V (2009) Combined Phototherapeutic Keratectomy and Amniotic Membrane Grafts for Symptomatic Bullous Keratopathy 28: 4.
24. Vlasov A, Sia RK, Ryan DS, Mines MJ, Stutzman RD, et al. (2016) Sutureless cryopreserved amniotic membrane graft and wound healing after photorefractive keratectomy. J Cataract Refract Surg 42: 435-443.
25. Rapuano CJ (2003) Excimer laser phototherapeutic keratectomy in eyes with anterior corneal dystrophies: Preoperative and postoperative ultrasound biomicroscopic examination and short-term clinical outcomes with and without an antihyperopia treatment. Trans Am Ophthalmol Soc 2003: 29.
26. Maini R, Sullivan L, Snibson GR, Taylor HR, Loughnan MS (2001) A comparison of different depth ablations in the treatment of painful bullous keratopathy with phototherapeutic keratectomy. Br J Ophthalmol 2001: 4.
27. Celik U, Bozkurt E, Celik B, Demirok A, Yilmaz OF (2014) Pain, wound healing and refractive comparison of mechanical and transepithelial debridement in photorefractive keratectomy for myopia: Results of 1 year follow-up. Contact Lens Anterior Eye 37: 420-426.
28. Dua HS, Gomes JA, Singh A (1994) Corneal epithelial wound healing. Br J Ophthalmol 78: 401-408.
29. Salah T, El Maghraby A, Waring GO (1996) Excimer Laser Phototherapeutic Keratectomy Before Cataract Extraction and Intraocular Lens Implantation. Am J Ophthalmol 122: 340-438.
30. Dogru M, Katakami C, Yamanaka A (2001) Refractive changes after excimer laser phototherapeutic keratectomy. J Cataract Refract Surg 27: 686-692.

31. Tobalem S, Panthier C, Moran S, Debellemaniere G, Gatinel D (2021) Myopic outcomes after excimer laser phototherapeutic keratectomy (PTK). J Fr Ophtalmol 44: 35-40.

32. Woo H-M, Kim MS, Kweon O-K, Kim D-Y, Nam T-C, et al. (2001) Effects of amniotic membrane on epithelial wound healing and stromal remodelling after excimer laser keratectomy in rabbit cornea. Br J Ophthalmol 2001: 5.

33. Choi YS, Kim JY, Wee WR, Lee JH (1998) Effect of the application of human amniotic membrane on rabbit corneal wound healing after excimer laser photorefractive keratectomy. Cornea 17: 389-395.

34. Lee H-K, Kim J-K, Kim EK, Kim G-O, Lee I-S (2003) Phototherapeutic keratectomy with amniotic membrane for severe subepithelial fibrosis following excimer laser refractive surgery. J Cataract Refract Surg 29: 1430-1435.

35. Rathi V, Sangwan V, Vyas S (2012) Phototherapeutic keratectomy. Indian J Ophthalmol 60: 5.

36. Hashemi H, Taheri SMR, Fotouhi A, Kheiltash A (2004) Evaluation of the prophylactic use of mitomycin-C to inhibit haze formation after photorefractive keratectomy in high myopia: a prospective clinical study. BMC Ophthalmol 4: 12.

37. McCarty CA, Aldred GF, Taylor HR (1996) Comparison of results of excimer laser correction of all degrees of myopia at 12 months postoperatively. The Melbourne Excimer. Laser Group. Am J Ophthalmol 121: 372-383.

38. Hafner A, Langenbucher A, Seitz B (2005) Long-term Results of Phototherapeutic Keratectomy With 193-nm Excimer Laser for Macular Corneal Dystrophy. Am J Ophthalmol 140: 392.e1-392.e.

39. Ayres BD, Hammersmith KM, Laibson PR, Rapuano CJ (2006) Phototherapeutic Keratectomy With Intraoperative Mitomycin C to Prevent Recurrent Anterior Corneal Pathology. Am J Ophthalmol 142: 490-492.

40. Bowers PJ, Price MO, Zeldes SS, Price FW (2003) Superficial keratectomy with mitomycin- C for the treatment of Salzmann's nodules. J Cataract Refract Surg 29: 1302-1306.

41. Khaireddin R, Katz T, Baile RB, Richard G, Linke SJ (2011) Superficial keratectomy, PTK, and mitomycin C as a combined treatment option for Salzmann's nodular degeneration: a follow-up of eight eyes. Graefes Arch Clin Exp Ophthalmol 249: 1211-1215.

42. Reddy JC, Rapuano CJ, Felipe AF, Nagra PK, Hammersmith KM (2014) Quality of Vision After Excimer Laser Phototherapeutic Keratectomy With Intraoperative Mitomycin-C for Salzmann Nodular Degeneration. Eye Contact Lens Sci Clin Pract 40: 213-219.

43. Miller A, Solomon R, Bloom A, Palmer C, Perry HD, et al. (2004) Prevention of Recurrent Reis-Bücklers Dystrophy Following Excimer Laser Phototherapeutic Keratectomy With Topical Mitomycin C 23: 4.

44. Marcon AS, Rapuano CJ (2002) Excimer Laser Phototherapeutic Keratectomy Retreatment of Anterior Basement Membrane Dystrophy and Salzmann's Nodular Degeneration with Topical Mitomycin C: Cornea 21: 828-830.

45. Kim T, Pak JH, Chae J, Kim EK, Tchah H (2006) Mitomycin C Inhibits Recurrent Avellino Dystrophy After Phototherapeutic Keratectomy. Cornea 25: 220-223.

46. Hieda O, Sotozono C, Nakamura Y, Wakimasu K, Kinoshita S (2021) Surgical outcomes of re-excimer laser phototherapeutic keratectomy (re-PTK). Sci Rep 11: 11503.

47. Dedes W, Faes L, Schipper I, Bachmann LM, Thiel MA (2015) Phototherapeutic keratectomy (PTK) for treatment of recurrent corneal erosion: Correlation between etiology and prognosis – prospective longitudinal study. Graefes Arch Clin Exp Ophthalmol 253: 1745-1749.

48. Reinstein DZ, Archer TJ, Dickeson ZI, Gobbe M (2014) Transepithelial Phototherapeutic Keratectomy Protocol for Treating Irregular Astigmatism Based on Population Epithelial Thickness Measurements by Artemis Very High-Frequency Digital Ultrasound. J Refract Surg 30: 380-387.

49. Pogorelov P, Langenbucher A, Kruse F, Seitz B (2006) Long-Term Results of Phototherapeutic Keratectomy for Corneal Map-Dot-Fingerprint Dystrophy (Cogan-Guerry) 25: 4.

50. Cavanaugh TB, Lind DM, Cutarelli PE, Mack RJS, Durrie DS, et al. (1999) Phototherapeutic Keratectomy for Recurrent Erosion Syndrome in Anterior Basement Membrane Dystrophy 106: 6.

51. Rodríguez-Ares MT, López-Valladares MJ, Touriño R, Vieites B, Gude F, et al. (2009) Effects of lyophilization on human amniotic membrane. Acta Ophthalmol (Copenh) 87: 396-403.

52. Niknejad H, Deihim T, Solati-Hashjin M, Peirovi H (2011) The effects of preservation procedures on amniotic membrane's ability to serve as a substrate for cultivation of endothelial cells. Cryobiology 63: 145-51.

53. Rosen R (2018) Amniotic Membrane Grafts to Reduce Pterygium Recurrence. Cornea 37: 189-193.

54. Clearfield E, Hawkins BS, Kuo IC (2017) Conjunctival Autograft Versus Amniotic Membrane Transplantation for Treatment of Pterygium: Findings From a Cochrane Systematic Review. Am J Ophthalmol 182: 8-17.

55. Fonseca EC, Rocha EM, Arruda GV (2018) Comparison among adjuvant treatments for primary pterygium: a network meta-analysis. Br J Ophthalmol 102: 748-756.

56. Röck T, Bramkamp M, Bartz-Schmidt KU, Röck D (2019) A Retrospective Study to Compare the Recurrence Rate After Treatment of Pterygium by Conjunctival Autograft, Primary Closure, and Amniotic Membrane Transplantation. Med Sci Monit 25: 7976-7981.