Anterior Stromal Puncture vs. Annular Keratotomy in the Treatment of Painful Bullous Keratopathy: Randomized Clinical Trial

Abstract

Purpose: Determine if anterior stromal puncture (ASP) has a more effective decrease in symptomatology (pain, photophobia, and foreign body sensation) than annular keratotomy (AK) in patients with painful bullous keratopathy (PBK) and poor visual prognosis.

Methods: Patients with PBK, refractory to combined medical treatment and poor visual prognosis were randomly assigned to one of two surgical procedures. Symptomatology, central corneal thickness (CCT), visual acuity (VA), and best corrected (BCVA) were evaluated with a 12-month follow up.

Results: From 78 patients with PBK, 13 met inclusion criteria; ASP was performed to 7 and AK to 6 of them. There was improvement in the magnitude of symptoms in both groups; however, there was no difference when groups were compared. CCT showed in the 7-month follow-up a significant reduction of 10.4% in the ASP group compared with a 9.6% increase in the AQ group (p=0.05). Twelve-month-follow up CCT presented a non-significant reduction of 9.3% in the ASP group compared with a 3.3% increase in the AQ group. VA and BCVA in both groups were not modified. None of the groups presented complications related to the surgical procedures.

Conclusion: In this clinical trial, we documented that ASP and AQ produce a similar improvement in the symptomatology of patients with PBK refractory to combined medical treatment and poor VA potential. The ASP group additionally presented a significant decrease in CCT at 7 months of follow up, which loses statistical significance at 12 months of follow up, but maintains a clinical reduction of 9.3%. A longer follow-up period would be required to evaluate if this CCT reduction is able to modify the frequency of bullae development and symptoms relapse. Furthermore, the material used for ASP has a lower cost than the one used for AQ, which could represent an economic advantage for patients that attend our Hospital.

Keywords: Anterior stromal puncture; Annular keratotomy; Painful bullous keratopathy

INTRODUCTION

Painful bullous keratopathy (PBK) is a clinical disorder that presents with corneal edema, epithelial and sub-epithelial bullae. The abnormal corneal hydration with the subsequent bullae formation is due to the endothelial cell loss and the consequent reduced homeostatic functions. The decrease of corneal transparency produces a reduction in visual acuity (VA), which is occasionally accompanied by foreign body sensation, tearing, intense pain, and photophobia. In severe cases the corneal edema can cause thickening greater than 650m, generally stroma dependent. The list of possible etiologies for PBK is extensive; the most frequent cause is the loss of corneal endothelial cells secondary to surgical trauma.

Histochemical and immunohistochemical studies have shown that PBK is characterized by altered extracellular matrix with fibrinogen deposition, Tenascin-C, fibrillin-1, and loss of glycosaminoglycans (which causes the Bowman’s ruptures and the separation of the corneal epithelium from the stroma). There are several options for medical (topical) treatment of PBK, such as hypertonic solutions, anti-inflammatories, anti-hypertensive, corticosteroids, aggressive lubricant eye drop therapy, as well
as therapeutic contact lenses. However, there are some patients that do not report any reduction of their symptoms and surgical treatment needs to be considered, especially for individuals with limited VA potential. Surgical treatments available for patients with poor visual potential are amniotic membrane, lamellar keratectomy, conjunctival flaps, thermal cauterezation, anterior stromal puncture (ASP), and annular keratotomy (AK). In this paper we focus on ASP and AK in patients with PBK in patients with poor VA potential.

AK produces a corneal nervous plexus injury with the consequent decrease in sensibility, thus reducing pain and foreign body sensation. On the other hand, ASP creates epithelial anchorage projections to the anterior stroma documented through immunohistochemical reports that have shown the increased expression of extracellular matrix proteins involved in basal epithelial cells adhesion. The presence of other components of the basal membrane augments the epithelial adhesion to the subjacent stroma, which is associated with the sub-epithelial fibrosis formation that impedes fluid entrance, thereby avoiding corneal hydration and new bullae formation.

Currently, there are only nine clinical trials (CT) related to these two surgical techniques. ASP was analyzed in seven and AK was evaluated in two. Additionally, one report is a review about PBK management. All the ASP CTs have shown reduction of symptoms, without changes in VA and complications attributed to the procedure, but with controversial results regarding corneal thickness. On the other hand, AK CTs have reported similar reduction of symptoms and VA stability, but with an increase in corneal thickness.

The aim of this study was to evaluate if ASP reduces the symptoms (pain, photophobia, and foreign body sensation) of PBK compared to AK in the treatment of patients with poor VA potential. Additionally, we measured central corneal thickness (CCT) by ultrasonic pachymetry as an indicator of corneal edema.

METHODS

We conducted a randomized, open clinical trial, approved by the Research and Ethics Committees of the Hospital General Dr. Manuel Gea González. During two years we evaluated and treated 78 individuals aged 18 years and older with PBK, low VA potential (<20/400 with ocular comorbidities), no deep corneal vascularization, and no history of surgical treatment for the PBK. We included individuals who had previously signed the informed consent who did not respond to therapeutic contact lenses and systematized combined topical medical treatment with at least two of the following: hypertonic solutions, and/or anti-inflammatory, and/or hypotensive medication, and/or corticosteroids eye drops. Thirteen patients were assigned randomly, seven to the ASP group and six to the AK group. The same surgeon with a subspecialty in cornea and refractive surgery performed both procedures under topical anesthesia, with an ophthalmic microscope. ASP was done with a 20g needle. Twenty punctures were performed with 50% of the bevel indicating the anterior stroma, punctures were made perpendicular to the corneal surface in every “corneal time zone” at 1.00 mm from the limbus (12 punctures) and 8 punctures in the middle of the cornea guided by the pupillary center. Topical tobramycin was indicated every 4 hours for 2 weeks. The AK was performed by an anterior-stromal-depth circular perforation (measured to 50%-bevel boundary) in the center of the cornea with a 7.00 mm trephine, with clock and counter-clockwise movements to avoid corneal folding. The same antibiotic regime was prescribed for both groups. Pain, photophobia, and foreign body sensation were evaluated previous to the procedure and during every follow up visit with a visual analog scale ranging from 0 (no pain) to 10 (severe pain). CCT in the studied eye was obtained by an average result of a three-time-ultrasonic pachymetry measurement previous to the procedure and on each follow-up consult; in the fellow eye only one measurement was obtained. VA and the best-corrected visual acuity (BCVA) were also evaluated. No patients were lost to follow-up.

Statistical Analysis: Variables are expressed as means and standard deviations (SD) for continuous data, frequencies and percentages for categorical data. To compare the symptomatology scores between surgical groups and CCTs, we used the Mann Whitney U test. We used ANOVA to compare the five intra-group measurements (pain, photophobia, foreign body sensation, CCT, and BCVA). Statistical significance was defined as p ≤0.05. The analyses were performed with the statistical package for PC, SPSS V 22.

RESULTS

A total of 78 patients with PBK were followed during 2 years, from which 13 patients were included in the study, 7 in the ASP group and 6 in the AK group. All of the subjects were followed a total of 12 months and none were excluded. There were no significant differences between both surgical procedures with the exception of an intra-group difference between the baseline and 12-month follow-up pain values for the ASP group (p=0.002) and for the AK group (p=0.001). Nonetheless, during the 7-and 12-month follow-ups, the subjects surgically treated with ASP showed a tendency in pain increase. In contrast, subjects in the AK group continued with lower pain results (Graphic 1). This outcome was expected because of the latter’s mechanism of action.
In contrast with pain, subjects with ASP reported an early and noteworthy decrease regarding photophobia at the first postoperative week, with further decrease and sustained values throughout the study. There were no significant differences when comparing both procedures (Graphic 2).

Foreign body sensation also presented an early and similar improvement in both groups, and was maintained throughout the entire study (Graphic 3).

During the 12 months of follow-up, the ASP subjects showed a reduction in CCT, while subjects in the AK group presented an increase of CCT. Graphic 4 shows the average values of the ultrasonic pachymetry.

When we calculated the differences obtained in the basal pachymetry values and the ones from the 7 and 12-month follow-up evaluation, we observed in the 7-month follow-up a significant reduction in the ASP group of 10.4% from the basal CCT, compared to an increase of 9.6% (p=0.05) in the AK group (Graphic 5). Interestingly, the 12-month follow-up showed that statistical significance was not reached maintaining, nonetheless clinical significance in the ASP group with a CCT reduction of 9.3% and 3.3% increase in the AK group (Graphic 6).

This study only included patients with poor VA potential; nevertheless, their VA was not significantly modified with either of the procedures; there were no changes in 11 subjects and a two-line reduction in two patients. Table 1 shows the comparative VA before the procedures and at the 12-month follow-up.

No complications such as perforation, infection, or problems with wound re-epithelization was observed in the study.

**DISCUSSION**

The initial PBK treatment is topical. In some patients with intense pain, that are not candidates for any kind of corneal transplant, therapeutic contact lenses are a good option.7-9,11-13 Contact lenses should be considered provisional because of the high risk of infection. Patients with PBK refractory to medical treatment should be offered surgical options such as amniotic membrane, phototherapeutic keratectomy, thermal cautery, conjunctival flap, ASP, and AK.

ASP and AK have proven their temporal effectiveness for reducing PBK symptomatology for an average of 6 months.1,2,5,11-13,16,17 All the reported studies to date have an observational, descriptive design, or are CTs with small number of cases that evaluate only one procedure. It has been reported that AK reduces pain and foreign body sensation; however, it has been observed that in the late postoperative period there is an increase in stromal edema.3,12 Alternatively, ASP has shown improvement of the symptomatology but controversial results regarding CCT.2,4,6

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**Graphic 2.** Visual analogue scale showing photophobia evolution in patients with PBK treated with ASP and AK during 7 months of follow up. There were no significant differences among groups at each evaluation (U de Mann Whitney), but intragroup there was a significant reduction of photophobia in the ASP group and AK group (p = 0.001, and p = 0.014, respectively, with Friedman test).

**Graphic 3.** Visual analogue scale showing foreign body sensation evolution in patients with PBK treated with ASP and AK during 7 months of follow up. There were no significant differences among groups at each evaluation (U de Mann Whitney), but intragroup there was a significant reduction of foreign body sensation in the ASP group and AK group (p = 0.001, and p = 0.006, respectively, with Friedman test).
This is the first longitudinal, randomized CT with a systematic evaluation of symptomatology, CCT, VA, and BCVA after ASP and AK during 12 months of follow-up, in patients refractory to topical medical treatment and poor VA potential. With both procedures, as mentioned in the literature, a reduction of symptoms was observed during the time of the study. It has been reported that the AK’s effect on pain is probably due to the trepanation of the nervous plexus of the cornea, which decreases the cornea sensitivity. Nonetheless, the pain lessened until the second postoperative week, similar to the subjects managed with ASP. An important difference in photophobia evolution was observed, showing an important reduction from the first postoperative week in the ASP group compared to the AK group. The evolution of foreign body sensation was similar in both groups. This could be due to the abovementioned mechanism of action for both treatments, the corneal nervous plexus laceration with a sensitivity reduction with AK and the anchorage projections that compress the anterior cornea, decreasing the amount of bullae present in the cornea with ASP. The pain tendency to increase observed in both ASP and AK the 7 and 12-month follow-ups could be attributed to the known 6-8 months temporal effectiveness of the procedures.

Corneal thickness is a main concern for PBK patients because the chronic presence of stromal edema represents a risk factor for bullae recurrence. CCT presented a tendency to decrease in the ASP group during the entire study without significance when compared with the AK results. However, when we compared the measures obtained in the 7-month evaluation with the basal, a statistically significant 10.4% reduction in corneal thickness in the ASP group was noted. In contrast, the AK group showed a 9.6% increase. Notably, in the 12-month evaluation statistical significance was not reached but a clinical significant reduction of 9.3% in the ASP group was maintained and a 3.3% increase in the AK group was observed. This could be explained because of the anchorage projections that compress the anterior cornea in the ASP (a phenomenon that does not happen in AK), as mentioned, its therapeutic effect has been described to have a temporal effectiveness between 6 to 8 months. It would be interesting to evaluate if with repeated ASP every 7 to 12 months a longer lasting effect could be obtainable.

VA and BCVA remained stable. Even though it is not the aim of ASP and AK to improve VA or BVCA, it has been described a decrease of VA in patients treated with ASP.

ASP can be performed by an ophthalmologist without subspecialty training; in contrast, AK performed by inexperienced hands could present complications such as anterior chamber perforation.
Table 1. Basal visual acuity and VA at 7 months of follow up. ETDRS = early treatment diabetic retinopathy study eye charts, VA = visual acuity, ASP = anterior stromal puncture, AK = annular keratotomy, NLP = no light perception, LP CD = light perception color discrimination, HM = hand movement, CF = counting fingers.

<table>
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<tr>
<th>ETDRS VA</th>
<th>Pre procedure ASP</th>
<th>Pre procedure AK</th>
<th>7th month ASP</th>
<th>7th month AK</th>
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<tbody>
<tr>
<td>VA</td>
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<td>VA</td>
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<td>VA</td>
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<tr>
<td>NLP</td>
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<tr>
<td>LP CD</td>
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<td>1 (7.7)</td>
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<tr>
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<tr>
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<td>0</td>
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<td>0</td>
</tr>
<tr>
<td>CF 40 cm</td>
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<td>0</td>
<td>1 (7.7)</td>
</tr>
<tr>
<td>CF 20 cm</td>
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<td>6 (46.2)</td>
<td>7 (53.8)</td>
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</tr>
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</table>

All the procedures in our study were performed by a cornea and refractive surgery subspecialist, possibly explaining the absence of complications.

Because of the results obtained, we believe that the original technique for ASP by McLean is an option that helps reduce costs in comparison with AK, which requires the 7.00 mm trephine. Both procedures, ASP and AK, need for their realization the same resources, with exception of the 7.00 mm trephine for the AK (average cost of 50USD) and the 20 g needle for the ASP (average cost of 1USD). This difference in cost is substantial for the patients at the Hospital General Dr. Manuel Gea González.

This study has the limitation that the results reported for the comparison between both groups for symptomatology did not reach statistical significance probably due to sample size, however clear tendencies were observed for each group. Larger sample numbers with a longer follow-up time would render useful information.

This CT documents for the same time symptom reduction, CCT, and VA in subjects with PBK refractory to combined medical treatment and poor VA potential treated with ASP and AK. In summary, subjects in the AK group presented further pain reduction and the subjects in the ASP group reported lower photophobia scores, and both groups showed a similar reduction in foreign body sensation. Patients treated with ASP showed a significant decrease in corneal thickness, which can possibly translate in fewer relapse events. To document whether the reduction of corneal thickness is able to modify the frequency of symptom relapse, a longer follow-up period would be required. Furthermore, ASP utilizes for its realization materials with a lower cost than AK, which could represent a greater economic advantage for the patients who attend the Ophthalmology Division of the Hospital General Manuel Gea González.