

RESEARCH ARTICLE

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ARAŞTIRMA

Evaluation of the Effect of Cryotherapy in Limbal Conjunctival Autograft Technique in Pterygium Surgery

Pterjium Cerrahisinde Limbal Konjonktival Otogreft Tekniğinde Kriyoterapinin Etkinliğinin Değerlendirilmesi

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ABSTRACT

Aim: To compare the complication and recurrence rates in patients undergoing limbal conjunctival autograft with or without adjuvant cryotherapy for primary or recurrent

Methods: All information about the cases operated between January 2014 and January 2019 was scanned from the electronic database. Fifty-three eyes undergoing limbal conjunctival autograft combined with cryotherapy were classified as Group 1, and 47 eyes undergoing only limbal conjunctival autograft were classified as Group 2. Any development of new fibrovascular tissue from the limbus to the cornea after surgery was considered a recurrence. Any complications occurring during and after surgery were noted.

Results: In Group 1, 45 of the 53 patients had primary and eight had recurrent pterygia. In Group 2, 41 of the 47 patients had primary and six had recurrent pterygia. Both groups were similar in terms of age and gender (p=0.880 and p=0.835, respectively). The mean follow-up period was 27.0±8.6 months in Group 1 and 28.7±7.8 months in Group 2 (p=0.287). No recurrences were observed during the follow-up period in Group 1, while the recurrence rate in Group 2 was 10.6% (p=0.02). All relapses occurred within the first year. No complications were observed during surgery in either group. Graft oedema was observed in the early post-operative period in four patients in Group 1 and three patients in Group 2.

Conclusion: Limbal conjunctival graft technique combined with cryotherapy is a successful and reliable method in the treatment of primary and recurrent pterygium.

Keywords: cryotherapy, limbal conjunctival autograft, pterygium

ÖZ

Amaç: Primer veya tekrarlayan pterjiumda adjuvan kriyoterapi ile birlikte veya tek başına limbal konjonktival otogreft uygulanan hastalarda komplikasyon ve nüks oranlarını karşılaştırmak.

Metot: Ocak 2014 ile Ocak 2019 tarihleri arasında ameliyat edilen vakalarla ilgili tüm bilgiler elektronik veri tabanından tarandı. Kriyoterapi ile kombine olarak limbal konjonktival otogreft uygulanan 53 göz Grup 1, sadece limbal konjonktival otogreft uygulanan 47 göz Grup 2 olarak sınıflandırıldı. Ameliyattan sonra limbustan korneaya herhangi bir yeni fibrovasküler doku gelişimi nüks olarak kabul edildi. Ameliyat sırasında ve sonrasında ortaya çıkan herhangi bir komplikasyon not edildi.

Bulgular: Grup 1'de 53 hastanın 45'inde primer ve sekizinde tekrarlayan pterjium vardı. Grup 2'de 47 hastanın 41'inde primer ve altısında tekrarlayan pterjium vardı. Her iki grup yaş ve cinsiyet açısından benzerdi (p=0.880 ve p=0.835; sırasıyla). Ortalama takip süresi Grup 1'de 27.0±8.6 ay, Grup 2'de 28.7±7.8 aydı (p=0.287). Grup 1'de takip döneminde nüks görülmezken, Grup 2'de nüks oranı % 10,6 idi. (p=0.02). Tüm nüksler ilk yıl içinde gerçekleşti. Her iki grupta da ameliyat sırasında herhangi bir komplikasyon görülmedi. Grup 1'de 4, Grup 2'de 3 hastada erken postoperatif dönemde greft ödemi görüldü.

Sonuç: Kriyoterapi ile kombine edilerek yapılan limbal konjonktival greft tekniği primer ve rekürren pterjium tedavisinde başarılı ve güvenilir bir yöntemdir.

Anahtar Kelimeler: kriyoterapi, limbal konjonktival otogreft, pterjiyum

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INTRODUCTION

A pterygium is a conjunctival pathology with an unclear aetiology, manifesting as fibrovascular proliferation of the bulbar conjunctiva towards the cornea. Although it has a good prognosis, surgical removal is recommended if it extends to the visual axis, which may threaten visual acuity and cause astigmatism or frequent inflammation and discomfort [1].

Many surgical techniques, such as bare sclera, conjunctival autograft, limbal conjunctival autograft, amniotic membrane, and conjunctival trans positional flap, have been described in pterygium surgery [1]. The most important problem after surgery is recurrence. Today, conjunctival autograft and limbal conjunctival autograft are considered the most effective techniques [1].

However, even after conjunctival autograft surgery, studies have reported recurrence rates ranging between 3.3% and 14.6% [2-4]. Therefore, various adjuvant therapies, including mitomycin-C, 5-fluorouracil, anti-vascular endothelial growth factor, radiation, and cryotherapy, have been recommended to prevent recurrence [5,6]. In addition, it has been reported that the use of topical cyclosporine before and after surgery reduces the development of recurrence [7].

Cryotherapy as an adjuvant treatment was first described in a case series by Fraunfelder in 2008 [6]. The purpose of cryotherapy is to induce ice crystal formation in intracellular and extracellular areas, thereby causing organelle damage, local vasoconstriction, thrombosis, and cell death by ischemia and immune mechanisms, by freezing living tissue [8,9]. Fraunfelder suggested that cryotherapy could reduce the recurrence rate by preventing abnormal cell proliferation after primary pterygium surgery [6].

The aim of this study, therefore, was to compare the recurrence and complication rates in primary and recurrent pterygium cases undergoing limbal conjunctival autograft with and without adjuvant cryotherapy.

MATERIAL AND METHOD

The study included 100 eyes of 100 patients of the same ethnic origin who underwent surgery for primary or recurrent pterygia between January 2014 and January 2019. Fifty-three patients who undergo limbal conjunctival autograft combined with cryotherapy were classified as Group 1, and 47 patients who underwent only limbal conjunctival autograft were classified as Group 2. Ocular surface diseases, keratoconjunctivitis sicca, dry eye, ocular pemphigoid, limbal stem cell deficiency, previous ocular surgery and systemic diseases and drugs that affect ocular surface were excluded from the study. Patients who had glaucoma or suspected malignancy and findings consistent with malignancy on post-operative histopathological examination and patients with a follow-up period of less than one year were also excluded. Pterygium grading was performed in all patients. All study participants signed informed consent forms prior to surgery. This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethics approval was obtained from the Diyarbakır Gazi Yaşargil Research and Training Hospital ethic committee.

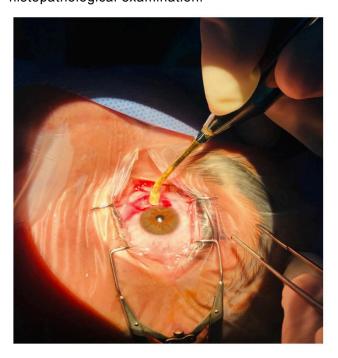
Surgical Method

Before surgery, local anaesthesia was induced with proparacaine hydrochloride drops, and local site cleaning was performed with 10% povidone iodine solution. The ocular surface was washed with 5% povidone iodine. After three minutes, the eye was irrigated with saline solution. Conjunctival local anaesthesia was induced by a subconjunctival injection of lidocaine containing 1 ml of 2% epinephrine in the pterygium area. The pterygium body was separated from the underlying conjunctiva by blunt dissection. The pterygium head was separated from the cornea towards the limbus using a blunt-tip knife. The procedures followed thus far were identical in both groups.

In Group 2, immediately after these procedures, graft tissue of the same size as the conjunctival defect obtained after excision of pterygium tissue was prepared from the superior temporal conjunctiva of the same eye to the limbal area. Care was taken to completely separate the graft from the Tenon tissue. After the limbus part of the graft was placed to coincide with the limbus part of the open sclera, the graft was sutured to the conjunctiva one by one with vicryl 8-0 suture.

In Group 1, cryotherapy was performed using a

Cryo-S Electric II (Metrum Cryoflex, Poland) device after excision of the pterygium tissue. The Cryo-S Electric is a cryosurgery device that uses nitrous oxide (N2O) as a cooling medium. N2O expands in the cryoprobe, producing a temperature as low as -89°C. The cryotherapy procedure was performed by contacting an approximately 3-mm cryoprobe with the corneoscleral limbus for one-two seconds (fig 1). The procedure was applied one or more times using a double freeze-thaw technique depending on the size of the lesion, with intervals of approximately 30 seconds between freeze applications. Cryotherapy was then also applied to the margins of the rest of the conjunctiva (fig 2). After that, using the same technique as in Group 2, a limbal conjunctival autograft taken from the superior temporal conjunctiva was placed in the open sclera and sutured to the conjunctiva one by one with vicryl 8-0 suture. In both groups, the pterygium tissue removed was sent for histopathological examination.



 $Figure\ 1.\ Contacting\ the\ cryoprobe\ to\ the\ corneoscleral\ limbus.$

All eyes were kept closed for 24 hours by applying a tight bandage with an antibiotic ointment. Moxifloxacin 4×1 and topical corticosteroid fluorometholone 3×1 were applied fifteen days after surgery. Preservative-free artificial eye drops, polyvinyl alcohol povidone 6×1, and antibiotic ointment oxytetracycline 2×1 were used for one month after surgery. All cases were followed up for at least one year to monitor

recurrences and complications. Any fibrovascular tissue development from the limbus to the cornea was considered a recurrence.

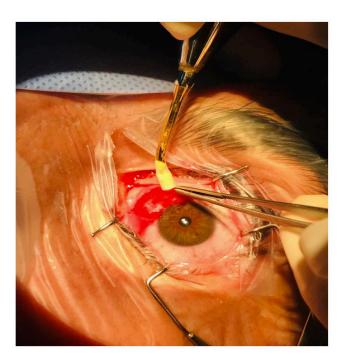


Figure 2. Cryotherapy application to the remaining conjunctival tissue.

Statistical Analysis

Statistical analysis was performed using SPSS 20.0 (Statistical Package for the Social Sciences, IBM, NY, USA). The normality of data distribution was checked with the Kolmogorov-Smirnov test. Comparisons between the two groups were performed with the independent t-test, Pearson's chi-square test, or Fisher's exact test. Descriptive statistics were expressed as means \pm standard deviations (minimum-maximum) for numerical variables and as numbers and percentages for categorical variables. A value of p < 0.05 was considered statistically significant.

RESULTS

The groups were similar in terms of age and gender (p = 0.880 and p = 0.835, respectively; Table 1). In Group 1, 45 of the 53 patients had primary and eight had recurrent pterygia. In Group 2, 41 of the 47 patients had primary and six had recurrent pterygia. There was no statistical difference between groups in pterygium grading (p = 0.879). In all cases, histopathological examination was consistent with pterygium.

Table 1. Distribution of demographic and clinical characteristics in the two groups

Variable	Group 1 (n = 53)	Group 2 (n = 47)	P
Age (years), mean ± SD	47.4 ± 14.8	47.0 ± 13.3	0.880*
Gender (female/male)	17/36	16/31	0.835†
Follow-up period (months), mean ± SD	27.0 ± 8.6	28.7 ± 7.8	0.287*
Recurrences, n (%)	0 (0)	5 (10.6)	0.02‡

 $Group\ 1: limbal\ conjunctival\ autograft\ combined\ with\ cryotherapy$

Group 2: limbal conjunctival autograft only

*Independent t-test; †Pearson's chi-square test; ‡Fisher's exact test SD: standard deviation

The mean follow-up time was 27.0 ± 8.6 months (12–42 months) in Group 1 and 28.7 ± 7.8 months (13–40 months) in Group 2 (p = 0.287). No recurrences were observed during the follow-up period in Group 1. In Group 2, recurrences were observed in five (10.6%) patients (p = 0.02), of whom two had primary and three had recurrent pterygia. The median recurrence time was five months (three–nine months). None of these patients accepted a second surgical procedure.

No complications were observed during surgery in either group. Graft oedema was observed in the early post-operative period in four cases in Group 1 and three cases in Group 2. In all cases, it was relieved by intensive topical steroid therapy.

DISCUSSION

Cryotherapy induces cell death by six therapeutic mechanisms, including cryodestruction, cryoadhesion, cryoextraction, cryostripping, and cryoobliteration [10,11]. Today, it is widely and safely used in many medical fields, such as gynaecology, dermatology, proctology, phlebology, and ophthalmology.

Cryotherapy was first used in ophthalmology by Bietti in 1933 for the treatment of retinal hollows [12]. It was later used for the treatment of many retinal diseases, such as retinal detachment, retinopathy of prematurity, and retinoblastoma, glaucoma, conjunctival diseases, and benign and malignant lesions in the eyelid [13-18].

When cryotherapy is mentioned in the treatment of conjunctival diseases, the first thing that comes to mind is malignant lesions in the conjunctiva. After surgical excision of the conjunctival malignant lesion, small tumour residues at the surgical margins causing recurrence are eliminated by cryotherapy applied to the surgical margins. Although pterygium is considered a degenerative disease of the conjunctiva, pterygium tissue may exhibit tumour-like properties [19].

Based on these tumour-like properties of the pterygium, Fraunfelder suggested that cryotherapy could be used as an adjuvant treatment to prevent recurrence after pterygium surgery, claiming that it can directly induce cytotoxicity and apoptosis in proliferating epithelial stem cells, which are believed to cause recurrences [6]. He also suggested that the elimination of the microvascular structure in pterygium tissue with a rich vascular structure by cryoobliteration may be effective [6]. Fraunfelder first presented a case series of 24 patients, 18 of whom had primary and six had recurrent pterygia, undergoing liquid nitrogen cryotherapy after surgical excision of pterygium tissue [18]. After excision, the author made a 2-mm liquid nitrogen cryoprobe contact with the corneoscleral limbus several times (using a double freeze-thaw technique) for approximately one second. He then sutured the conjunctiva primarily over the limbus. In the primary pterygium group, within a median follow-up of 24.5 months, one case reported a recurrence nine months after surgery (recurrence rate: 5.5%). In the recurrent pterygium group, the median follow-up period was 27 months, and four of six patients reported recurrences after an average of 3.3 months. The author recommended liquid nitrogen cryotherapy as adjuvant to primary pterygium surgery but reported that it was unsuccessful in recurrent pterygium treatment [18]. However, he performed surgical excision and cryotherapy for a second time in a patient in the recurrent pterygium group who developed a recurrence and observed no recurrence after the second procedure [18].

In our study, no recurrence was observed during the follow-up period in any patients with primary or recurrent pterygia undergoing cryotherapy. However, a few differences between our and Fraunfelder's study should be noted. First, Fraunfelder preferred to close the conjunctiva by suturing following primary excision after cryotherapy, whereas in this study, we applied cryotherapy combined with limbal conjunctival

autograft surgery. Primary excision is a simple and fast surgical procedure, but degenerative cells may proliferate and lead to a recurrence as a result of insufficient excision of subconjunctival fibrovascular tissue [20]. In limbal conjunctival graft surgery, it is assumed that limbal stem cells can provide faster healing of the wound site and reconstruct it anatomically [20]. Furthermore, in this study, we compared recurrence rates between patients undergoing limbal conjunctival autograft and cryotherapy and patients undergoing limbal conjunctival autograft only. Although it has been reported that limbal conjunctival graft application decreases the recurrence rates after ptervojum surgery, the literature suggests that it does not eliminate the risk [2-4]. In our study, the recurrence rate was 10.6%. The fact that no recurrences were observed in Group 1 demonstrates the effectiveness of cryotherapy as an adjuvant treatment.

Another difference between our and Fraunfelder's study is that the latter used liquid nitrogen as a cryogen, whereas we used N2O. Various cryogens are used in cryosurgery. In ophthalmology, freon $(-29.8^{\circ}C$ to $-40.8^{\circ}C)$, N2O $(-89^{\circ}C)$, and solid carbon dioxide (-79°C) are preferred [18]. Liquid nitrogen (-196°C) has a very low boiling point and causes cell destruction by inducing very fast freezing. Because of this property, liquid nitrogen cryotherapy is mostly used in the treatment of eye and eyelid tumours [17,21]. N2O cryotherapy is also successfully used for the same purpose [22,23]. However, the biological effects of the various cryogens on ocular tissues are not fully known [18]. Our results show that N2O cryotherapy is as successful as liquid nitrogen cryotherapy as a therapy adjuvant to pterygium surgery.

A third difference between our and Fraunfelder's study is the area where cryotherapy was applied. Based on the assumption that recurrences are caused by epithelial stem cells in the limbal region, Fraunfelder applied cryotherapy only to the corneoscleral limbal region [24]. In our study, in addition to the corneoscleral limbus, cryotherapy was applied to the margins of the remaining conjunctiva after primary excision. Thus, degenerated fibrovascular cells at the conjunctival surgical margin were eliminated. We believe that this technique can be effective in

preventing recurrence even in recurrent pterygium cases.

In terms of complications during and after surgery, the results were similar in the two groups. No complications occurred during surgery in either group, and the only complication in the early post-operative period was graft oedema.

Limitations

The main limitation of our study is that it is a retrospective study and has a short follow-up period. We included cases with a follow-up period of at least one year, as it is known that most recurrences after pterygium surgery are seen within the first year [25]. This is consistent with the fact that the five recurrence cases in our study were seen in the first year and were all cases where only limbal conjunctival grafts had been applied.

CONCLUSION

In conclusion, we believe that cryotherapy can be used as an effective treatment adjuvant to limbal conjunctival graft in both primary and recurrence pterygium cases. Moreover, with the right technique, it appears to be a very reliable method in terms of complications. In future studies, longer follow-up periods to monitor patients for any recurrences are recommended.

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