PhD theses

SURGICAL TREATMENT OF CORNEAL DISEASES

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A. INTRODUCTION

The development of corneal surgery – similarly to that of most scientific fields – is triggered by the emergence of new challenges and the determination to improve the solutions. Indeed, in the past few years we encountered several problems that urged us to modify our current techniques and to reconsider and reassess our results.

One of the difficulties we had to face was pterygium, since pterygium surgery is by no means a solved problem. It deserves attention partly for its significant prevalence and tendency for recurrence, partly for the possibility that both of these may increase due to the increasing UV radiation, the most important risk factor for its development. Recent developments concerning its etiology and pathogenesis determined new directions in searching more effective surgical methods.

Cases in which tectonic penetrating keratoplasty (PKP) is needed in order to treat peripheral corneal disorders avoiding the central cornea represent a great challenge and cause serious problems. Despite the critical situation, baseline visual functions are often reasonable in these cases of mostly unfavourable prognosis, thus it is not easy to find the most suitable solution. Furthermore, these patients often suffer from serious underlying systemic diseases. It is very important to find solutions achieving reasonable structural and functional results.

The effort to reduce postkeratoplasty corneal astigmatism is comprehensible, as it is the most frequent cause of poor visual functions after PKP with clear grafts. Patients may benefit from the assessment of the advantages of different suture techniques during PKP.

Corneal grafting is the most successful procedure among human alloplasties. However, rejection is the most frequent cause of its failure. Immunological reactions caused by PKP, the possible role of the complement system is not yet understood. Each step that brings us closer may bear importance, as revealing the immunological events may have therapeutical consequences later on.
Facing the above-mentioned questions and problems and the intention of improvement made us strive to search for better solutions and answers.

B. PURPOSES
The questions we tried to answer in this work are as follows:
1. We aimed to perform surgical procedures reducing the chance of recurrence in cases of pterygia requiring surgery. Three types of procedures combined with the removal of pterygia were evaluated:
   a. autologous conjunctival-limbal transplantation,
   b. single intraoperative mitomycin-C (MMC) application, and
   c. amniotic membrane transplantation.
   Besides comparing the results and complications of the methods, their applicability in some special cases was also considered.
2. Is it possible to successfully perform penetrating peripheral mini-keratoplasty that spares the optical axis of the cornea in cases in which PKP is needed in the treatment of peripheral corneal disorders – most frequently peripheral ulcerative keratitis - avoiding the central cornea?
3. How does biconvex penetrating peripheral mini-keratoplasty influence the anterior corneal surface? Does the eccentric, biconvex graft sparing the central cornea necessarily induce visually debilitating central corneal irregularity?
4. Is double running suture technique during PKP reliable? Compared to the simple running suture technique, is it more advantageous, concerning postoperative astigmatism?
5. Is it possible to detect the possible activation of the complement system in the early postkeratoplasty period by examining tear samples?

C. PATIENTS AND METHODS
C.1. Pterygium surgery
    Pterygium surgery was performed in cases of active primary or recurrent pterygia.
    C.1.a. The surgery was combined with autologous conjunctival-limbal transplantation in 35 consecutive pterygium cases
in 33 patients. The interventions were performed by the same surgeon between 1991 and 1997.

**C.1.b.** The surgery was combined with single intraoperative MMC application (0.02% MMC, for 2-3 min., 5 min. in 2 cases) in 29 consecutive pterygium cases in 28 patients. The interventions were performed by the same surgeon between 1997 and 2000.

**C.1.a-b.** The demographic data of the two groups were compared by unpaired parametric t test and the Mann-Whitney test. Kaplan-Meier survival analysis was used to compare time until recurrence, and the logrank test to compare the incidence of recurrence-free cases between the two groups. P values smaller than 0.05 were accepted revealing significant differences.

**C1.c.** The surgery was combined with amniotic membrane transplantation in 12 consecutive pterygium cases in 12 patients. The interventions were performed between 2000 and 2001. In cases of recurrent pterygia MMC application preceded amniotic membrane transplantation during the same procedure.

**C.2. Peripheral penetrating mini-PKP**

In cases of peripheral corneal disorders avoiding the central cornea requiring PKP an eccentric keratoplasty technique was used, in which neither the graft nor the wound involved the central cornea, and the size of the grafts was smaller compared to the usually used central grafts. Out of the peripheral penetrating mini-keratoplasties with a minimum follow-up of 6 months (13 patients/13 eyes/14 operations) 8 were performed for perforated and one for predescemetal peripheral ulcerative keratitis (PUK); in one of the former a repeated mini-PKP was performed later due to a new PUK on a different site. Traumatic wound dehiscence was the cause of the intervention in 3 cases, and the remaining case had a traumatic background, too. Six of the grafts were round, 8 were biconvex in order to avoid the central cornea. In cases with systemic disorders in the background, the local treatment was combined with a systemic one.
C.3. Corneal topography after peripheral, biconvex keratoplasty

Computer-assisted corneal topography was performed postoperatively using a TMS-1 (Computed Anatomy, Inc., New York, N.Y.) in 5 of the above cases, in which the transplants were biconvex. Topographic images were taken in the 12-15. postoperative month, after suture removal except for one case. (Here the sutures were still in place as the patient died 9 months postoperatively before suture removal.)

C.4. Double diagonal running suture during PKP

Double diagonal running suture was used during PKP between June 1995 and May 1996 in 31 unselected cases (31 patients) where the conditions allowed the use of running sutures.

Of the above cases topographic readings of 23 eyes with clear grafts were available 2-4 months after suture removal (group 1.). These data were compared to topographic readings of 23 selected postPKP cases (23 patients, group 2.), which were operated on between June 1994 and Oct. 1996 and were similar in some respects to the cases of group 1., but simple radial running suture was used during PKP.

All operations were performed by the same surgeon. Except for the suturing techniques, the operations were performed similarly.

The condition of the grafts and the ability of the sutures for wound apposition were assessed by slit lamp examination. Group 1. and 2 were compared on the basis of corneal topographic readings taken in the 14-15. postoperative month (2-4 months after suture removal). The TMS-1 corneal topograph (Computed Anatomy, New York, N.Y.) was used for the evaluation. Statistical comparison was performed using unpaired, non parametric t test. P values smaller than 0.05 were accepted revealing significant differences.

C.5. Evaluation of tear samples in order to detect the possible activation of the complement system in the early postkeratoplasty period

Tear samples from both eyes of 19 prekeratoplasty patients were tested. From 15 of them, samples were taken also one week after
PKP. From 10 of them, further sampling was performed three weeks after PKP.

Tear concentrations of two complement activation products, Clrs-C1inh (an activation product of the classical pathway) and C3bBbP (an activation product of the alternative pathway of the complement cascade) were determined by enzyme-linked immunosorbent assay.

We used the Mann-Whitney test, the Wilcoxon matched paired test and the one-way ANOVA test (Friedman) to analyse the data. P values smaller than 0.05 were accepted revealing significant differences.

D. RESULTS
D.1. Pterygium operations

We evaluated the results of patients and eyes with a follow-up period of minimum 7 months. One eye of each patient (the first eye to undergo surgery) was selected for statistical analysis.

D.1.a. Among patients operated on by autologous limbal-conjunctival transplantation 19 were male and 10 female aged between 25-70 years (51.3 +/- 11.9 years). Twelve of the pterygia were primary, 17 were recurrent ones. The follow-up period ranged between 7-135 (66.1 +/- 56.5) months. No intra- or early postoperative complication occurred. Asymptomatic pseudopterygium developed in two cases at the source of the limbal graft. Three pterygia recurred (10.3 %), all of them within the first four postoperative months; 1 recurrency developed in the case of a primary, 2 in the cases of recurrent pterygia. Two of the recurrences were only partial, involving only the lower edge of the operated limbal section (6.9 %).

D.1.b. Fifteen males and eleven females belonged to the group of pterygium operations combined with intraoperative MMC application. Their age ranged between 37-79 (52.7 +/- 9.8) years. Twelve of the pterygia were primary, 14 recurrent. No intraoperative complication occurred. In the early postoperative period wound dehiscence (3 cases) and transient Dellen formation occurred (3 cases). No complications were observed later on (follow-up period: 7-69 months). Three pterygia recurred (11.5%), all of them within the first
two postoperative months. Two of the recurrences were partial, involving only the lower edge of the operated limbal section (7.7%). Two recurrences (one partial) developed in cases of recurrent, one (partial) in the case of a primary pterygium.

**D.1.a-b.** Statistical analysis of the corresponding pre- and postoperative data of patients and eyes operated on by the two different methods (i.e. limbal-conjunctival autograft vs. MMC application) did not reveal any significant difference between the two groups.

**D.1.c.** Seven of the patients in cases of whom pterygium operation was combined with amniotic membrane transplantation were male, 5 female, between 45-67 (53.3 +/- 7.1) years of age. Eight of the pterygia were primary, 4 recurrent. No intra- or postoperative complications occurred. During the follow-up period of 12-23 (18.3 +/- 3.2) months, 3 out of 4 recurrent pterygia and 1 out of 8 primary pterygia recurred. In the cases of recurrences the final condition is far better compared to the preoperative one concerning both the condition of the conjunctiva and the corneal invasion.

**D.2. Peripheral mini-PKP**

No intraoperative complication occurred. Seven eyes healed without complications – four of them were traumatic cases. Transient or repeated local, eventually systemic adjunctive therapy was needed in 6 eyes, in cases of which transient or repeated inflammatory signs in or around the graft were caused by the recurrence of the original process, mechanical factors, the progression of the underlying process or unknown mechanism.

The two most important results concerning the condition achieved by the end of the follow-up period of 6-65 months are the following:

1. long-lasting tectonic results were achieved in 11 eyes without additional intervention.
2. functional results – 0.1 or better visual acuity in 10 eyes, with 0.5 or better visual acuity in 7 of them.
**D.3. Corneal topography after peripheral biconvex PKP**

Postoperative corneal topography showed normal Surface Regularity Index (SRI) values – although various (normal, suspect, abnormal) Surface Asymmetry (SAI) values – in four cases, indicating the regularity of the anterior surface of the central cornea despite the variable central symmetry. The corrected visual acuity of these eyes was at least 0.8, indicating the correlation between the SRI and the corrected visual acuity. Both the SRI and the SAI were abnormal in the remaining case, the corrected visual acuity of which was poorer (0.25).

**D.4. Double diagonal running suture in PKP**

No suture-related complication was found.

Postkeratoplasty astigmatism and mean keratometric value after suture removal were 4.3 +/- 2.9 D and 46.0 +/- 2.5 D in group 1. (23 cases with double diagonal running suture), and 4.4 +/- 3.2 D and 45.7 +/- 3.3 D in group 2. (23 cases with single running suture).

Statistical analysis showed no significant difference between the two groups concerning postoperative astigmatism and mean keratometric value.

**D.5. Evaluation of tear samples in order to detect the possible activation of the complement system in the early postkeratoplasty period**

There was no difference (p=0.339) between baseline samples of the eyes waiting for operation (0.93±0.51 AU/ml, mean ± SEM) and the fellow eyes (0.33±0.33 AU/ml) in respect of mean C1rs-C1inh complex concentration. The one-week-samples of the operated eyes revealed significantly (p=0.006) elevated levels of C1rs-C1inh complexes (18.8±6.37 AU/ml), compared to their baseline samples (1.18 ± 0.64 AU/ml), whereas the one-week values of the fellow eyes did not differ from the baseline values. When baseline, one-week and three-week samples of the 10 operated eyes in cases of which all samples were available were compared by one-way ANOVA, significant (p=0.031) difference was found. Compared to the increased one-week values (21.00 ± 9.76 AU/ml), the 3-week-values (0.48 ± 0.48 AU/ml) decreased to the baseline values (0.58 ± 0.58 AU/ml) in the operated eyes. C3bBbP could
be detected in 3/68 tear samples, in two samples high C3bBbP-levels were coincident with detectable C1rs-C1inh-level.

E. CONCLUSIONS

E.1. Pterygium surgery

Pterygium surgery combined with both autologous limbal-conjunctival transplantation and with intraoperative MMC application seem to be efficient and safe methods in the treatment of pterygia. Limbal-conjunctival transplantation is rather time consuming, demands significant surgical skill, and needs the pre-existence of extended normal limbal-conjunctival areas, where grafts can safely be harvested. Pterygium surgery combined with intraoperative MMC application is easy to perform, is a quick procedure, but – to avoid possible postoperative complications – certain pre-, intra- and postoperative measures must be respected. A long-term follow-up after this type of operation seems to be reasonable.

The main advantage of amniotic membrane transplantation in pterygium surgery is not in the lower recurrence rate compared to the two previous methods, but in the possibility of avoiding normal conjunctival areas and of the risk of antimetabolite therapy. Therefore it can be useful in certain cases in which - due to the extent of the excised conjunctiva - conjunctival autografting is not possible (e.g. in cases of double-head or large advanced pterygia), or in cases of which it seems to be important to reserve the normal conjunctival tissue (e.g. in glaucoma patients with the possibility of a future filtration surgery), or in cases in which the use of antimetabolites has high risks (e.g. in patients with autoimmune diseases).

E.2. Peripheral mini-PKP

Peripheral mini-PKP, sparing the central cornea, may be considered in cases of some special peripheral corneal diseases – most often in the closure of peripheral corneal defects – for its good tectonic effect and the good morphological and functional results. The special advantage of this method is that the eyes may keep their functions even after vascularisation or failure of the graft. In some cases, when the extent and shape of the peripheral lesion is such, that a biconvex graft
rather than a round one can avoid the optical centre, a biconvex peripheral PKP may achieve similarly good tectonic and functional results.

**E.3. Corneal topography after peripheral, biconvex PKP**

The anterior surface of the central cornea may be regular after a peripheral, biconvex PKP sparing the central cornea, and – independent of the central symmetry of the cornea – may allow good corrected visual acuity.

**E.4. Double diagonal running suture during keratoplasty**

Double diagonal running suture is a reliable suture technique in penetrating keratoplasty. Concerning the postoperative astigmatism and mean keratometric value no difference was found between the double diagonal running suture and single radial running suture group.

**E.5. Evaluation of tear samples in order to detect the possible activation of the complement system in the early postkeratoplasty period**

In our study we demonstrated the increased concentration of C1rs-C1inh complex in several tear samples taken early after human penetrating keratoplasty. These findings provide direct evidence that the classical pathway of complement may be activated in the early postoperative period after penetrating keratoplasty.
F. PUBLICATIONS CLOSELY RELATED WITH THE TOPIC OF THIS WORK: