Young patient's age determines pterygium recurrence after surgery.

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Abstract

Background. It is not clear whether demographic or pterygium characteristics or limbal stem cell deficiency determine pterygium recurrence after surgery.

Purpose. To determine whether the demographic, pterygium characteristics, or limbal stem cell deficiency determine pterygium recurrence after excision.

Methods. Of 190 patients operated and followed-up for 6 months, 101 and 89 underwent free conjunctival autotransplant (CAT) or limbal conjunctival autotransplant (LCAT) respectively. The age, gender, occupation, grade of pterygium extent and degree of fleshiness, and laterality were compared between recurrent and no recurrent pterygia. Multivariate analysis was performed to determine the predictors of pterygium recurrence. Recurrence rates after surgery were compared between CAT and LCAT.

Results. The age range of the 190 patients was 22-65 years, mean ±SD 46.4 ±10.8 years. Pterygium recurred in 52 (27.4%). Thirty-nine (75%) of 52 patients with pterygia that recurred were aged <50 years (young) vs. 72 (52%) of 138 young patients with no recurrence; odds ratio (OR) = 1.54; 95% confidence interval (95% CI) = 0.70-3.36; p = 0.28. Thirty-one (60%) of 52 participants with post-surgical recurrent pterygia had large pre-operative pterygium (grade ≥3) vs. 130 (94%) of 138 patients with large pterygia that did not recur; OR = 0.11; 95% CI = 0.04-0.28; p <0.001. Of 101 patients undergoing CAT, 29 (28.7%) experienced recurrence vs. 23 (25.8%) of 89 undergoing LCAT; p = 0.66.

Conclusions. Young age seems to be associated with pterygium recurrence after excision followed by conjunctival graft. Large pterygia were protective.

Key words: Young age; pterygium extent; pterygium recurrence.

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Introduction

Young age may be associated with pterygium recurrence after excision,[1,2,3] and recurrence has been observed in young members of one family.[4]

Pterygium fleshiness rather than young age has also been associated with recurrence.[5] However, these results are derived from studies that involved small numbers of the patients with fleshy primary pterygia, treated with free conjunctival graft (CAT).[5] The extent of primary pterygium on the cornea seems to have no relationship with pterygium recurrence after surgery however, due to the small study sample, it is not clear whether pterygium extent is related or not with recurrence.[6] Another study found that recurrence after surgery was associated with a large pterygium extent but, it is possible that some large pterygia in that study were inadequately treated by radiotherapy as an adjunct to excision because the size of the radiation applicator was the same for small and large pterygia.[7]

The effect of excessive exposure to sunlight on pterygium recurrence after surgery also remains controversial. Although exposure was not compared between recurrence and no recurrence, one report blamed excessive sunlight exposure for pterygium recurrence[7] whereas another study concluded otherwise because recurrent pterygia did not show collagen degeneration.[9] Limbal stem cell deficiency may be a possible reason for pterygium,[10] and this prompted a comparison of recurrence rates between CAT and limbal conjunctival autotransplant (LCAT).[11] However, the efficacy of CAT and LCAT in the treatment of primary pterygium has not been compared in a prospective randomised study with a large sample.

This study was aimed to determine whether demographic factors, pterygium characteristics, or limbal stem cell deficiency determine recurrence after excision of primary pterygium followed by conjunctival graft.

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Methods

A prospective randomised study was designed. Clearance was obtained from the 2 institutional research ethics committees and the clinical trials register number NCT 00713180 at nih.gov was obtained before starting the study. The tenets of the Declaration of Helsinki (2000) were followed in obtaining consent.

One hundred seventy six patients (88 per group) were needed to detect a 15% difference in recurrence rates between CAT and LCAT at an alpha value of 5% and a power of 80%, assuming a base recurrence rate of 20% in CAT. This assumption was based on a reported recurrence rate of 21% following CAT in a similar population.[6] Because the present study factored a default rate of 12%, 200 patients were operated-on.

The 200 patients comprised 120 who had participated in an earlier epidemiological study and 80 others who were interviewed and examined in the same way as those in the epidemiological study.[12] The indications for surgery were corneal astigmatism, obstruction or threatened obstruction of vision, disfigurement, or frequent inflammation.[13] No patient had received topical anti-inflammatory treatment before surgery. Participants were recruited and randomised to CAT or LCAT as adjunctive treatment to pterygium excision. Age, sex, occupation, pterygium extent and degree of fleshiness,[5] and laterality were recorded. Pterygium extent was assessed as previously described by Youngson.[14] Grade 1 was a growth that had just crossed the limbus; grade 2 was approaching half of the corneal radius; grade 3 crossed half of the radius; grade 4 extended up to the corneal centre; and according to Carmichael (personal communication August 2007), grade 5 crossed the corneal centre.

Between 2008 September and 2011 July, the patients underwent pterygium excision and treated as reported earlier.[11] Only one eye per patient was enrolled in the study. The pterygia were excised at 4mm from the limbus and at the superior and inferior borders of the growth. The head was dissected off using a crescent knife. The grafts, which were harvested 1mm larger than the host pterygium were sutured-in using 10/0 nylon. Post-operative treatment consisted of topical ciprofloxacin 3mg/ml four times daily for one week, and prednisolone acetate 10mg/ml four times daily for 4 weeks. Sutures were removed at 1 month following surgery.[8] The patients were followed-up for possible recurrence for a minimum duration of 6 months because a prospective study has reported that 94% of recurrences occurred within 6 months.[1] Recurrence was defined as a wing-shaped re-growth of fibrovascular tissue at the site of previous pterygium,[5] which was confirmed by a masked ophthalmologist.

Data analysis

Demographic and pterygium factors were compared in the patients whose pterygia recurred and those in whom pterygia did not recur after excision. The odds ratios (ORs) for recurrence and their 95% confidence intervals (CI) and significances were calculated using Chi-square test. Multivariate analysis was performed that only included factors that significantly determined pterygium recurrence in univariate analyses. Recurrence rates were compared between CAT and LCAT using Chi-square test. Statistical significance was tested by Student t test in continuous variables and Chi-square test in categorical variables. $P \leq 0.05$ was considered to be significant. STATA 9 for widows software (STATA Corporation, College Station, USA) was used for statistical calculations.

Results

All 200 patients had pterygia of fleshiness degree 3 (thick pterygia). After 10 patients were lost to follow-up, data were available for 190 patients who were followed-up for a minimum duration of 6 months. Their age range was 22-65 years with a mean ±SD of 46.4±10.8 years. Pterygium recurred after excision in 52 (27.4%) of the 190 participants. Seven pterygia (13.5%) of 52 recurred within 1 month, 31 (59.6%) between 1 and 3 months, and 14 (26.9%), between 3 and 6 months. Of 38 pterygia that recurred within 3 months, 29 (76.3%) occurred in young patients (<50yrs) Similarly, 10 (71.4%) patients who experienced pterygium recurrence more than 3 months after surgery were young individuals.

Table 1 shows the results of univariate regression analysis of the demographic and pterygium characteristics in participants whose pterygia recurred and those in whom pterygia did not recur after surgery. Recurrence was more frequent than no recurrence in young participants. Recurrence was less frequent than no recurrence after excision of large pterygia.

It also presents the results of multifactorial analysis of factors that were significant predictors of pterygium recurrence in univariate regression analysis.

The OR for developing pterygium recurrence in young patients decreased and was no more significant compared to the OR in univariate regression. In contrast, the OR for grade 3 or larger pterygia recurrence increased and remained significant.

Table 1: Univariate and multivariate analysis of demographic and pterygium characteristics in patients with recurrence and those with no recurrence.

			Crude			Adjusted		
Variable	**Recur (%)**	**Not recur (%)**	**OR**	**95% CI**	**p-value**	**OR**	**(95%)**	**p-value**
Age								
<50yrs	39 (75)	72 (52)	2.75	1.35-5.59	*0.005	1.54	(0.70-3.36)	*0.28
Gender								
Female	42 (81)	113 (82)	0.92	0.41-2.09	*0.86			
Occupation								
Outdoors	28 (54)	83 (60)	0.77	0.40-1.47	*0.43			
Laterality								
Bilateral	40 (77)	97 (70)	1.41	0.67-2.96	*0.36			
Extent								
Grade ≥3	31 (60)	130 (94)	0.09	0.03-0.22	*<0.001	0.11	0.04-0.28	*<0.001

*Chi-square test

One hundred and one (53.2%) of 190 participants underwent CAT whereas 89 (46.8%) underwent LCAT. Each participant was operated in only one eye. Table 2 shows the results of univariate regression analysis of the demographic and pterygium characteristics, as well as surgical outcome in participants who underwent CAT or LCAT. The proportions of the patients were similar in the two groups with regard to demographic and pterygium characteristics.

Table 2: Demographic and pterygium characteristics of patients operated, and surgical outcome

Characteristic	**CAT surgery**	**LCAT surgery**	**p – value**
Age (mean ± SD)	46.6 ±10.2	46.1 ±11.5	+0.72
Gender			
Male	18 (17.8%)	17 (19.1%)	*0.82
Female	83 (82.2%)	72 (80.9%)	
Occupation			
Indoors	43 (42.6%)	36 (40.5%)	*0.77
Outdoors	58 (57.4%)	53 (59.6%)	
Laterality			
Unilateral	29 (28.7%)	24 (27.0%)	*0.79
Bilateral	72 (71.3%)	65 (73.0%)	
Extent grade			
2≥3	15 (14.9%)	14 (15.7%)	*0.87
	86 (85.1%)	75 (84.3%)	
Surgical outcome			
Recur	29 (28.7%)	23 (25.8%)	*0.66
Not recur	72 (71.3%)	66 (74.2%)	

+Student t-test; *Chi-square test

Discussion

Despite recurrence of some large pterygia, large pterygia were protective against recurrence independently of the patients' old ages, which has not been reported before. This result contradicts an earlier study that reported that recurrence after surgery was associated with large pterygium extent.[7] The contradiction is most likely to be due to the application of adjunctive treatment in a proportion larger than the bare sclera after pterygium excision in the present study.

Young age was not confirmed to be associated with recurrence independently of pterygium extent, which is consistent with a previous study that failed to confirm an association between young age and recurrence independently of pterygium fleshiness.[5] However, the present study failed to confirm that fleshiness was associated with recurrence[5] perhaps because all the pterygia in the present study were fleshy. It looks as if thick pterygia that qualified for surgery were common in this study population. And it seems that fleshiness protected old patients from pterygium recurrence after excision followed by conjunctival graft. Yet fleshiness seems to have failed to protect young individuals from pterygium recurrence. It is unlikely that pterygium fleshiness was important for the growth to recur or not to recur after surgery.

The present study did not corroborate previous studies that showed that young age is associated with recurrence independently of other significant factors.[1,2] This is probably because this study excluded most small pterygia in old individuals due to a lack of indication for surgery, hence, the study found that large pterygium size was protective.

Pterygium progression is the reason for recurrence after surgery.[13] Young age implicates growing pterygium in this study. Pterygium progress may be intrinsically controlled because of two possible explanations in the present study thus. Most of the patients had participated in an earlier study that found heredity to be associated with pterygium occurrence.[12] Most of the recurrences occurred within three months after surgery, the majority of which were in young individuals, which is consistent with a previous report that observed that aggressive pterygia recurred within a short period after excision in young members of one family.[4] Pterygium progression may explain the varying recurrence times after surgery. It is possible that pterygia with shorter recurrence times grow faster than those with longer recurrence times, the discrepancy being dependent on the difference in concentration of growth factors.[15]

Although young age may be implicated in pterygium growth pterygia in nearly 65% of young individuals did not recur. It is possible that those pterygia had stopped growing thus; young age is not tantamount to progress. Since MMPs are underexpressed in fibroblasts and stroma of individuals with chronic solar conjunctivitis,[16] suggesting presence of transforming growth factor-beta,[17] we imagine that a decrease in available growth factors to a level that is insufficient to promote fibrovascular proliferation that causes pterygium, yet enough to suppress MMPs may well explain lack of pterygium progress. Fibroblast mitotic rate has been shown to be proportional to the level of growth factors.[15]

It is maybe that pterygia that had stopped growing at a young age would be still small and thick later in life and would not recur after surgery.[1] However, it is clear that most pterygia in the present study had grown larger. Since some large pterygia recurred after excision irrespective of the patients' age, this suggests that growth continued in those large pterygia and that pterygium growth is independent of chronological age. Notwithstanding sunlight exposure in all patients whose pterygia recurred, sunlight is unlikely to determine recurrence. However, sunlight irrespective of its duration of exposure might be just a trigger for recurrence after surgery.

CAT and LCAT procedures appeared to have similar recurrence rates, which has been reported before.[2,11] Because the present study had a large sample, and it was prospective, the similar post-surgical outcome suggests that recurrence after excision of primary pterygium is unlikely to be due to limbal stem cell deficiency. This is consistent with our previous report on the follow-up investigation of pterygium samples from the present study's participants, which showed a lack of association between damaged limbal stem cells and pterygium.[18] As we are finalizing this paper we are not aware of a study that has reported that LCAT was superior than CAT in the treatment of primary pterygia.

Conclusions

Young patient's age determines pterygium recurrence after surgery, and large pterygium extent appears to be protective. Recurrence after excision of primary pterygium seems unlikely to have a relationship with limbal stem cell deficiency. For the sake of simplicity and to avoid potential damage to normal limbal stem cells at the donor area, free conjunctival grafting is to be

preferred over limbal conjunctival grafting for treatment of primary pterygium.

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References

1. Chen PP, Ariyasu RG, Kaza V, Labree LD et al. A Randomized Trial Comparing Mitomycin C and Conjunctival Autograft After Excision of Primary Pterygium. *Am J Ophthalmol* 1995; 120: 151-160. (PMID 7639298)
2. Fernandes M, Sangwan VS, Bansal AK, Gangopadhyay N, Sridhar MS, Garg P, Aasuri MK, Nutheti R, Rao GN. Outcome of pterygium surgery: analysis over 14 years. Eye 2005; 19: 1182-1190.
3. Ramalingam M, Joshi N, Nair J, Ali AM. Outcome of surgical management of pterygium in Brunei Darussalam. Brunei Int Med J. 2011; 7: 8-14.
4. Islam SI, Wagoner MD. Pterygium in young members of one family. Cornea 2001; 20: 708-710. (PMID 11588421).
5. Tan DTH, Chee S-P, Dear KBG, Lim ASM. Effect of Pterygium Morphology on Pterygium Recurrence in a Controlled Trial Comparing Conjunctival Autografting With Bare Sclera Excision. *Arch Ophthalmol* 1997; 115: 1235-1240. (PMID 9338666)
6. Lewallen S. A Randomized Trial of Conjunctival Autografting for Pterygium in the Tropics. Ophthalmology 1989; 96: 1612-1614. (PMID 2694049)
7. Yamada T, Mochizuki H, Ue T, Kiuchi Y, Takahashi Y, Dinaka M. Comparative study of different β-radiation doses for preventing pterygium recurrence. Int J Radiat Oncol Biol Phys 2011; 81: 1394-8. (PMID 20889266)
8. Tananuvat T, Martin T. The results of Amniotic Membrane Transplantation for Primary Pterygium Compared with Conjunctival Autograft. Cornea 2004; 23: 458-463. (PMID 15220729)
9. Cameron ME. Histology of pterygium: an electron microscopic study. Br J Ophthalmol 1983; 67: 604-608. (PMID 5058717)
10. Tseng SCG, Lee S-B and Li D-Q. Limbal stem cell deficiency in the pathogenesis of pterygium. In: PTERYGIUM edited by Hugh R Taylor. 2000 Kugler Publications, The Hague, The Netherlands. ISBN 90 6279 1742.
11. Al Fayez ML. Limbal versus Conjunctival Autograft Transplantation for Advanced and Recurrent Pterygium. *Ophthalmology* 2002; 109: 1752-1755. (PMID 12208727)
12. Anguria P, Ntuli S, Interewicz B, Carmichael T. Traditional eye medication and pterygium occurrence in Limpopo Province. *S Afr Med J*. 2012; 102: 687-690. (PMID 22831948)
13. Herbert E Kaufman, Bruce A Barron, Marguerite B McDonald, Stephen C Kaufman. Pterygium. In: Companion Handbook to the Cornea. Second edition cc2000. Pp 473-498.
14. Youngson RM. Recurrence of pterygium after excision. Br J Ophthalmol 1972; 56: 120-125. (PMID 5010313)
15. Kria L, Ohira A, Amemiya T. Growth factors in cultured pterygium fibroblasts: immunohistochemical and ELISA analysis. Graefs Arch. Clin. Exp. Ophthalmol. 1998; 236: 702-708. (PMID 9782432)
16. Anguria P, Carmichael T, Ntuli S, Kitinya J. Chronic inflammatory cells and damaged limbal cells in pterygia. Afr Health Sci 2013 Sept; 13(4): 725-730.
17. Mitchell RN, Cotran RS. Acute and chronic inflammation; tissue repair: cell regeneration and fibrosis in: ROBBINS BASIC PATHOLOGY 7th edition 2002; 38-78. SAUNDERS. An imprint of ELSEVIER.