TIMING OF RECURRENCE OF PTERYGIA USING POST-OPERATIVE INJECTION OF SUBCONJUNCTIVAL 5-FLUOROURACIL AND CORTICOSTEROID

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ABSTRACT

Purpose: To investigate the efficacy, safety and timing of recurrence of pterygia treated with subconjunctival injections of either 5-Fluorouracil (5-FU) or Dexamethasone post-operatively.

Methods: 44 patients with primary or secondary pterygium underwent conjunctival autografting for pterygium removal. They were treated 1 month post-operatively with 3 subconjunctival injections of 5-FU (19 patients) or Dexamethasone (25 patients). Recurrence was defined as any fibrovascular tissue invading the cornea.

Results: After a mean follow-up of 68 weeks, overall recurrence rate was 13.6%: 4.5% for the 5-FU group and 9% for the Dexamethasone group. Mean timing of recurrence was 17.7 weeks. Regression of recurrence was not observed after any subconjunctival injections. High intraocular pressure (IOP) was the most common complication that occurred in 4 out of 6 patients in the Dexamethasone group. One patient experienced punctuate keratitis and another one developed corneal thinning (both in the 5-FU group). All complications were managed successfully with topical medications.

RIASSUNTO

Scopo: indagare l’efficacia, la sicurezza e i tempi di recidiva dello pterigio associati al trattamento con iniezioni sottocongiuntivali di 5-fluorouracile (5-FU) o desametasone nel post-operatorio.

Metodi: 44 pazienti con pterigio primario o secondario sono stati sottoposti a intervento di asportazione di pterigio con tecnica di autotrasferimento di congiuntiva e sono stati successivamente trattati per 1 mese post-intervento con 3 iniezioni sottocongiuntivali di 5-FU (19 pazienti) o desametasone (25 pazienti). La recidiva era definita come l’invasione della cornea da parte di tessuto fibrovascolare.

Risultati: dopo un follow-up medio di 68 settimane, il tasso di recidiva globale era del 13,6% - 4,5% per il gruppo del 5-FU e 9% per il gruppo del desametasone. I tempi medi di recidiva erano pari a 17,7 settimane. Una regressione della recidiva non è stata osservata dopo nessuna delle iniezioni sottocongiuntivali. Una pressione intraoculare (Intraocular Pressure, IOP) elevata era la complicanza più comune osservata in 4 pazienti su 6 del gruppo del desametasone. Un paziente ha sperimentato cératite puntata, mentre un altro ha sviluppato un assottigliamento della cornea (entrambi nel gruppo del 5-FU). Tutte le complicanze
Conclusions: Subconjunctival injections of antifibrotic agents could be useful to reduce the recurrence rate after pterygium surgery: 5-FU is safer and more effective than steroids and delays recurrences which mostly occur within the first 3 months after surgery.

INTRODUCTION
The main challenge of the management of pterygium is recurrence, and many surgical techniques have been proposed over the years to reduce it. Conjunctival autografting is considered the most effective technique associated with lower recurrence rates (2-9%)\(^1,2\). Several factors other than surgical technique may affect recurrence rate including morphology (flesiness of pterygium)\(^4\), young age\(^5\), Hispanic race\(^5\), demodicosis\(^6\), male gender and high sun exposure\(^7\).

In the attempt to reduce recurrence rate adjunctive treatments such as Beta radiation\(^8\), mitomycin C\(^9\), 5-Fluorouracil (5-FU)\(^10\) and corticosteroid injections have been studied in association to surgery (pre\(^9\), intra\(^10,11,12\) and post-operative\(^13\)). Few literature is available on the comparison between adjuvant therapies and timing of recurrence\(^14\).

Pterygium re-growth may be attributed to fibroblast proliferation and persistent conjunctival inflammation\(^15,16\). 5-FU inhibits fibroblast proliferation\(^16\) and corticosteroids are widely used as anti-inflammatory agents in ophthalmology practice. All adjuvant treatments may induce severe collateral effects to the ocular surface, especially mitomycin C\(^16\) and Beta radiation. Little is also known about timing of recurrence in relation to the different adjunctive treatments\(^17,18\).

Only few papers were focused on timing of recurrence after pterygium surgery. In general recurrences occurred during sono state gestite efficacemente con medicinali topici.

Conclusioni: le iniezioni sottocongiuntivali di agenti antifibrotici potrebbero essere utili per ridurre il tasso di recidiva successivo ad asportazione chirurgica di pterygio: il 5-FU è più sicuro e più efficace e ritarda le recidive, che si sviluppano perlopiù entro i primi 3 mesi post-intervento.
the first postoperative year. We therefore performed study
on patients receiving pterygium surgery treated with post-operative
subconjunctival injections of 5-FU or Dexamethasone in the first
postoperative month. Aim of this study was to evaluate timing of recurrence
and eventual differences due to post-operative management; safety and
efficacy of adjuvant treatments were also assessed.

METHODS
The study was performed on 44 eyes of 44 patients with primary or secondary
pterygium enrolled at San Paolo Hospital Milan from September 2011
to June 2013. Informed consent was signed by all patients.
Inclusion criteria: patients >18 years old
with primary pterygium or patients with
a secondary pterygium arising after a
previous pterygium excision.
Exclusion criteria: glaucoma, ocular hypertension, corneal preexisting
problems, previous ocular surgery (other than pterygium surgery), ocular trauma,
history of allergies to medications used in the study, pregnant or lactating
women.
Patients were examined before surgery
and after it at 1, 2, 4, 6, 8, 14, 24, 32, 48
weeks; after the first year patients were
examined at intervals of 6 months.
Before surgery a complete medical and ocular history was obtained,
including Snellen visual acuity, fundus examination, Goldmann tonometry,
slit-lamp examination, ocular surface disease index (OSDI) questionnaire19
and pterygium size measurement.
At each post-operative visit visual
acuity, slit-lamp examination, tonometry
and other symptoms were recorded.
Ptterygium recurrence was evaluated
at each visit and defined as any

Le conoscenze relative ai tempi di recidiva
correlati ai diversi trattamenti aggiuntivi
sono tuttora limitate17,18.
Solo pochi articoli si sono focalizzati sui
tempi di recidiva successivi alla chirurgia
dello pterigio. In generale, le recidive si
sono verificate nel corso del primo anno
post-operatorio.
Pertanto, abbiamo condotto uno studio
su pazienti sottoposti a intervento
chirurgico trattati con iniezioni
sottocongiuntivali post-operatorie di
5-FU o desametasone nel primo mese
post-intervento. Obiettivo di questo
studio era valutare i tempi di recidiva e le
eventuali differenze dovute alla gestione
post-operatoria; sono state valutate
anche la sicurezza e l’efficacia dei
trattamenti adiuvanti.

METODI
Lo studio è stato eseguito su 44 occhi
di 44 pazienti con pterigio primario o
secondario, arruolati presso l’Ospedale
San Paolo di Milano da settembre 2011 a
giugno 2013. Tutti i pazienti hanno firmato
il consenso informato.
Criteri di inclusione: pazienti di età >18
anni con pterigio primario o con pterigio
secondario sviluppatosi in seguito a una
precedente escissione.
Criteri di esclusione: glaucoma, ipertensione oculare, problemi
preesistenti alla cornea, pregressa
chirurgia oculare (diversa da chirurgia per
pterigio), trauma oculare, anamnesi di
allergie ai medicinali utilizzati nello studio,
gravidanza o allattamento per le donne.
I pazienti sono stati esaminati prima
dell’intervento e dopo 1, 2, 4, 6, 8, 14, 24,
32 e 48 settimane; dopo il primo anno i
pazienti sono stati valutati a intervalli di 6
mesi.
Prima dell’intervento chirurgico, è stata
raccolta un’anamnesi medica e oculare
completa, incluse acuità visiva con test
di Snellen, esame del fondo oculare,
fibrovascular tissue invading the cornea\textsuperscript{20,21}. Initial recurrences such as fibrovascular tissue reaching the limbus but not invading the cornea were not classified as a true recurrence\textsuperscript{20,21}. A single surgeon performed each surgical procedure (PF) on peribulbar anesthesia. The pterygium was dissected and then its head and neck were excised. The hypertrophic Tenon capsule was separated from the overlying conjunctiva and then excised. Corneal surface was smoothed with Alger brush. The remaining area of the conjunctival defect and the conjunctival donor graft site were measured. Donor conjunctiva was therefore excised carefully to separate it from the underlining Tenon capsule. The graft was placed on the bare sclera in a correct orientation and then attached to the adjacent conjunctiva with interrupted Nylon 10/0 sutures at intervals of 1 mm.

Postoperatively all eyes were treated with topical Tobramycin 0.3% eye drops (Angelini, Rome, Italy) 3 times daily for 7 days. Then topical Dexamethasone 0.1\% was started 3 times daily for 15 days; tear film lubricants were given at least 3 times daily.

After surgery, patients were allocated randomly to adjunctive subconjunctival treatments: 5-FU (Group 1) and Dexamethasone (Group 2); adjunctive injections were performed 2, 3, 4 weeks after surgery, and consisted in 0.5-1 ml of either 5-FU (50 mg/ml) or Dexamethasone (4 mg/ml) administered under the nasal conjunctiva after topical anesthesia.

Any complication arising from the adjunctive treatments was recorded and medically managed.

The end points of the study were the rate and the timing of recurrence in the two groups.

tonometria di Goldmann, valutazione mediante lampada a fessura, questionario OSDI (Ocular Surface Disease Index\textsuperscript{19} e misurazione delle dimensioni dello pterigio.

In occasione di ciascuna visita post-operatoria, venivano registrati acuità visiva, esame con lampada a fessura, tonometria e altri sintomi. La recidiva di pterigio è stata valutata nel corso di ogni visita e definita come un’invasione della cornea da parte del tessuto fibrovascolare\textsuperscript{20,21}. Le recidive allo stadio iniziale, con tessuto fibrovascolare presente nel limbo ma senza invasione della cornea, non sono state classificate come vere e proprie recidive\textsuperscript{20,21}.

Un solo chirurgo ha eseguito ogni procedura chirurgica (PF) in anestesia peribulbare. Lo pterigio veniva disseccato per poi procedere all’escissione di testa e collo. La capsula di Tenone ipertrofica veniva separata dalla conjunctiva sovrastante e poi escissa. La superficie della cornea veniva levigata con una fresa corneale AlgerBrush. Venivano poi misurati l’area residua del difetto conjuntivale e il sito di innesto della conjuntiva del donatore. La conjuntiva del donatore veniva quindi attentamente escissa per separarla dalla capsula di Tenone sottostante. L’innesto, correttamente orientato, veniva posizionato sulla sclera nuda e fissato alla conjuntiva adiacente con suture interrotte in nylon 10/0 a intervalli di 1 mm.

Nel post-operatorio, tutti gli occhi sono stati trattati con instillazione topica di gotec oculari di tobramicina 0,3\% (Angelini, Roma, Italia) 3 volte al giorno per 7 giorni. Dopodiché è stato avviato il trattamento topico con desametasone 0,1\% 3 volte al giorno per 15 giorni; i lubrificanti del film lacrimale venivano somministrati almeno 3 volte al giorno.

Dopo la chirurgia, i pazienti sono stati assegnati casualmente ai trattamenti...
RESULTS
Forty-four eyes of 44 patients were included in this study (24 females and 20 males); mean age was 48.1 (15.7) years. Thirty-four patients had a primary pterygium and 10 patients had a secondary one. After surgery, 19 patients were allocated to group 1 (5-FU), and 25 patients to group 2 (Dexamethasone). Three patients refused to receive subconjunctival injections although they had previously accepted the study design and agreed to be enrolled; they were therefore excluded from the study (n=41). Observation period was 65.9 weeks (range 12-124 weeks), with no differences between groups. Overall recurrence rate after surgery was 13.6% (6 patients out of 41): 4.5% in group 1 and 9% in group 2. The timing of recurrence was 17.7 weeks (range 6-48 weeks) for the overall population: 30 (range 12-48 weeks) and 12.7 weeks (range 6-24 weeks) for group 1 and 2, respectively. Two patients out of 6 experienced a recurrence at week 8; the other 4 experienced a recurrence at week 6, 12, 24 and 48, respectively. No complications were experienced during surgery. Post-operatively the most common complication was an IOP increase in 6 patients, 2 treated with 5-FU and 4 with Dexamethasone. IOP increase was managed successfully with topical eye drop medication and topical dexamethasone was tapered to 1 time/day. Among group 1, one patient developed corneal thinning at week 24 and another one developed punctuate keratitis at week 14.

RISULTATI
Nello studio sono stati inclusi 44 occhi di 44 pazienti (24 donne e 20 uomini); l’età media era di 48,1 (15,7) anni. Trentaquattro pazienti avevano uno pterigio primario, mentre 10 pazienti uno pterigio secondario. Dopo l’intervento chirurgico, 19 pazienti sono stati assegnati al gruppo 1 (5-FU) e 25 al gruppo 2 (Dexamethasone). Tre pazienti si sono rifiutati di ricevere le iniezioni sottocongiuntivali, nonostante avessero inizialmente accettato il disegno dello studio e fornito il proprio consenso a essere arruolati; sono stati pertanto esclusi dallo studio (n=41). Il periodo di osservazione era di 65,9 settimane (range 12-124 settimane), senza differenze tra i gruppi. Il tasso di recidiva globale successivo a chirurgia è stato del 13,6% (6 pazienti su 41): 4,5% nel gruppo 1 e 9% nel gruppo 2. I tempi di recidiva sono stati di 17,7 settimane (range: 6-48 settimane) per la popolazione complessiva: 30 (range: 12-48 settimane) e 12,7 settimane (range: 6-24 settimane) per i gruppi 1 e 2, rispettivamente. Due dei 6 pazienti hanno sperimentato una recidiva alla settimana 8; gli altri 4 alla settimana 6, 12, 24 e 48, rispettivamente. Durante l’intervento non si sono verificate complicanze. Nel post-operatorio, la
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conjunctival autografting\(^1\,^2\). Adjunctive treatments have been suggested to reduce recurrence. The intralesional approach used in this study has been shown to be preferable to the topical one to guarantee a higher concentration of the drug in the fibrovascular area\(^20\,^24\,^26\) and to reduce 5-FU side effects to ocular surface epithelia. In this study we compared the efficacy of subconjunctival 5-FU and Dexamethasone after conjunctival autografting technique. Other adjunctive treatments (such as mitomycin C and Beta radiations) have not been considered in our study for the high rate of complications associated with their use\(^27\,^35\). In our study, recurrences occurred in 4.9% of patients treated with 5-FU and 9% with Dexamethasone. Also Prabhasawat et al suggested the superiority of 5-FU in comparison to Triamcinolone on recurrences (7.7% and 14.3%, respectively)\(^20\), although there was no statistically significant difference between the treatment groups. Akarsu et al used the conjunctival autografting technique associated to post-operative injections of 5-FU and found 25% of recurrences\(^36\). None of these studies considered the ethnic origin of these patients\(^5\).

In our study we found an overall recurrence rate of 13.6% (4.5% for the 5-FU group and 9% for the Dexamethasone one), the difference of results in comparison to the study conducted by Prabhasawat et al\(^20\) may be attributed to the different surgical technique used (bare sclera technique, conjunctival autografting, amniotic membrane graft). Timing of recurrence for the overall population in our study was 17.7 weeks (30 weeks for 5-FU and 12.7 weeks for the steroid). Hirst et al in 1994\(^17\) demonstrated a 97% chance

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for a recurrence within 12 months of the removal, suggesting that a follow-up period of 12 months was enough to evaluate this aspect. Other studies demonstrated that the timing of recurrence was relatively coherent to our study: Said et al.\(^{37}\) established that the mean time of recurrence from the preceding surgical excision was 18 weeks; Akarsu et al.\(^{36}\) showed a mean recurrence time of 22 weeks. The difference in the mean recurrence time in our study between 5-FU and Dexamethasone could be due to the fact that 5-FU had an overall lower recurrence rate and may be considered more successful in preventing recurrences.

The limits of our study were the few number of patients included and the fact that the study was not randomized. Mean follow-up may be judged as short being 66 weeks but it should be noted that only one case had a recurrence at week 48, therefore follow-up is adequate. Also, the number of cases with recurrence is low, and this does not allow strong statistical analyses.

Nevertheless, this study confirmed the utility of some of the mainstreams on pterygium surgery: conjunctival autograft is a safe and effective technique; surgical efficacy can be augmented postoperatively by means of subconjunctival antifibrotic agents; of those, 5-FU is safer and more effective than steroid; when using 5-FU, recurrences occur later than steroid.

Finally, we highlighted the importance of evaluate and aggressively treat patients during the first 3 months after surgery, as most of the recurrences occur within this time frame.
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REFERENCES


11. Mastropasqua L, Carpineto P, Ciancaglini M, Lobefalo L, Gallenga PE. Effectiveness of intraoperative...


