Comparison of the Efficacy of Topical 0.2% Loteprednol Etabonate and Topical 0.1% Dexamethasone in Impending Recurrent Pterygium.

Wannisa Suphachearabhan[1], Wimolwan Tangpagasit[2], Thanapat Rakpanichmanee[1]

[1]Panyananthaphikkhu Chonprathan Medical Center Srinakharinwirot University, Thailand.
[2] Department of Ophthalmology, Faculty of Medicine,Thammasat University, Thailand

Background: Recurrence is a common complication of pterygium excision. The objective of this study was to evaluate the efficacy of topical 0.2% loteprednol etabonate, a 'soft steroid', compared to topical 0.1% dexamethasone widely used in postoperative pterygium excision to prevent the recurrence of pterygium.

Methods: A Randomized control trial study, patients undergoing pterygium excision with amniotic membrane transplantation who developed impending recurrent pterygium stage 3 were randomized into 2 groups. Group 1 received 0.2% loteprednol etabonate and group 2 received 0.1% dexamethasone. The rate of true recurrence of pterygium, impending recurrent pterygium scores, and intraocular pressure were compared between the groups.

Results: Fifty-four eyes of 54 patients in each group were included. The true recurrence of pterygium in between groups was not significantly different (15 patients [27.8%] in group 1 vs. 17 patients [31.5%] in group 2, $p = 0.67$). However, the time to recurrence ± SD was longer in group 2 than in group 1 (3.35 ± 1.7 vs. 1.47 ± 0.8 months, respectively, $p = 0.0002$). No ocular hypertension was found in group 1, but found 6 patients (11.1%) in group 2.

Conclusions: This study found the efficacy of 0.2% loteprednol etabonate was non-inferior to 0.1% dexamethasone in preventing the recurrence of pterygium and controlling inflammation after pterygium excision with better safety in avoiding steroid-induced ocular hypertension.

Conflicts of Interest: No conflicts of interest in this study.

Keywords: Loteprednol etabonate, dexamethasone, impending recurrent pterygium
EyeSEA 2020;15(2):67-76
DOI: https://doi.org/10.36281/2020020205

Correspondence to:
Wannisa Suphachearabhan, *Department of Ophthalmology, Panyananthaphikkhu Chonprathan Medical Center Srinakharinwirot University, Nonthaburi, Thailand*
Email: wannisas@g.swu.ac.th
Received :July 21,2020
Accepted : August 19,2020
Published : December 31,2020

Introduction

Pterygium is a triangular fibrovascular tissue expanding from conjunctiva into limbus and cornea, commonly found at the nasal side. It can cause irritation, itching, dryness, red eye, and blurred vision from corneal astigmatism or obscuring central

vision. The major cause of pterygium is prolonged exposure to solar ultraviolet radiation.[1-2] The mainstay of treatment is pterygium excision.

A common complication of pterygium excision is the recurrence of pterygium. The results after pterygium excision are classified into 4 stages: stage 1 is the normal appearance of the conjunctiva after pterygium excision, stage 2 is the appearance of small conjunctival vessels in the area of excision reaching the limbus without fibrovascular occurrence, stage 3 is fibrovascular growth into the area of excision without invasion into the cornea, and stage 4 is fibrovascular growth into the cornea, which is defined as the true recurrence of pterygium (Table 1).[3] The recurrence rate after pterygium excision with bare sclera is as high as 80%.[4] Pterygium excision with conjunctival autograft or with amniotic membrane transplantation (AMT) can reduce the rate of recurrence to 2-35%.[5] The use of other adjunctive treatments such as beta radiation, mitomycin C (MMC) or 5-fluorouracil (5-FU) intraoperatively or postoperatively can also further reduce the recurrence rate.[6] In highly inflamed eyes or impending recurrent pterygium, the use of 5-FU, MMC, or dexamethasone subconjunctival injection can be added to reduce the recurrence rate. 5-FU is commonly used because it has low complication rates and does not effect intraocular pressure (IOP) to the extent as that of dexamethasone.

An important aspect of care in pterygium excision is controlling the conjunctival inflammation in both the preoperative and postoperative period.[7] Currently, there is no standard guideline for reducing inflammation postoperatively by topical steroids. Therefore, it depends on the individual ophthalmologist's judgement for the selection of type, concentration, and frequency of steroid used. Frequently, topical steroid is prescribed every 2-4 hours in the early postoperative period and then gradually reduced depending on the severity of the conjunctival inflammation for 1-3 months. Complications of topical steroid include ocular hypertension or secondary glaucoma, cataract, infectious keratitis, ptosis, scleral thinning and macular edema.[8] Certain types of 'soft steroids' have lower rates of steroid-induced ocular hypertension although with a lower efficacy in reducing inflammation compared with other steroids. One of these is loteprednol etabonate 0.5% and 0.2%. The 0.2% loteprednol etabonate is a new and very low potency soft steroid that was selected for comparison with 0.1% dexamethasone in this study.

The objective of this study was to evaluate the efficacy of topical 0.2% loteprednol etabonate, a 'soft steroid', compared with topical 0.1% dexamethasone, which is widely used in postoperative pterygium excision to prevent the recurrence of pterygium. If 0.2% loteprednol etabonate is non-inferior in efficacy compared with 0.1% dexamethasone, it may be used postoperatively in pterygium excision patients with the benefit of a low incidence of ocular hypertension or secondary glaucoma.

Materials and Methods

A prospective randomized control trial was performed from October 2015 to April 2019 at the Department of Ophthalmology, Thammasat Hospital, Thailand and Panyananthaphikkhu Chonprathan Medical Center, Thailand.

Subjects

Patients who had pterygium excision with AMT and impending recurrent pterygium stage 3 defined as fibrovascular tissue not invading the cornea (Table 1 and Figure 1) were included.

Patients were excluded if they had 1) recurrent pterygium, 2) received adjunctive treatment with beta radiation, MMC or 5-FU, 3) glaucoma or IOP > 21 mmHg, or 4) history of 5-FU or chloramphenicol allergy.

The included patients were randomized into 2 groups. Group 1 were treated with subconjunctival 5-FU injection and topical 0.2% loteprednol etabonate while group 2 were treated with subconjunctival 5-FU injection and topical 0.1% dexamethasone (CD-oph: dexamethasone sodium phosphate 1 mg/mL, chloramphenicol 5 mg/mL, tetrahydrozaline hydrochloride 0.25 mg/mL).

Methods

Patient data were collected before treatment including age, sex, effected eye, IOP, and severity score of impending recurrent pterygium (Table 2 and Figure 1).

The patients who developed impeding recurrent pterygium stage 3 included in this study were randomized into 2 groups. Both groups received subconjunctival 5-FU injection 5mg/0.1 mL with 27-gauge needle in the area of fibrovascular tissue, and then the eyes were irrigated with 30 mL of normal saline. 0.2% loteprednol etabonate was prescribed in group 1, and 0.1% dexamethasone (CD-oph) was prescribed in group 2 every 4-6 hours for 4 weeks. After that, the regimen was gradually decreased until cessation at 3 months. 5-FU was repeatedly injected monthly in the presence of marked inflammation and not more than 3 times to prevent complications.

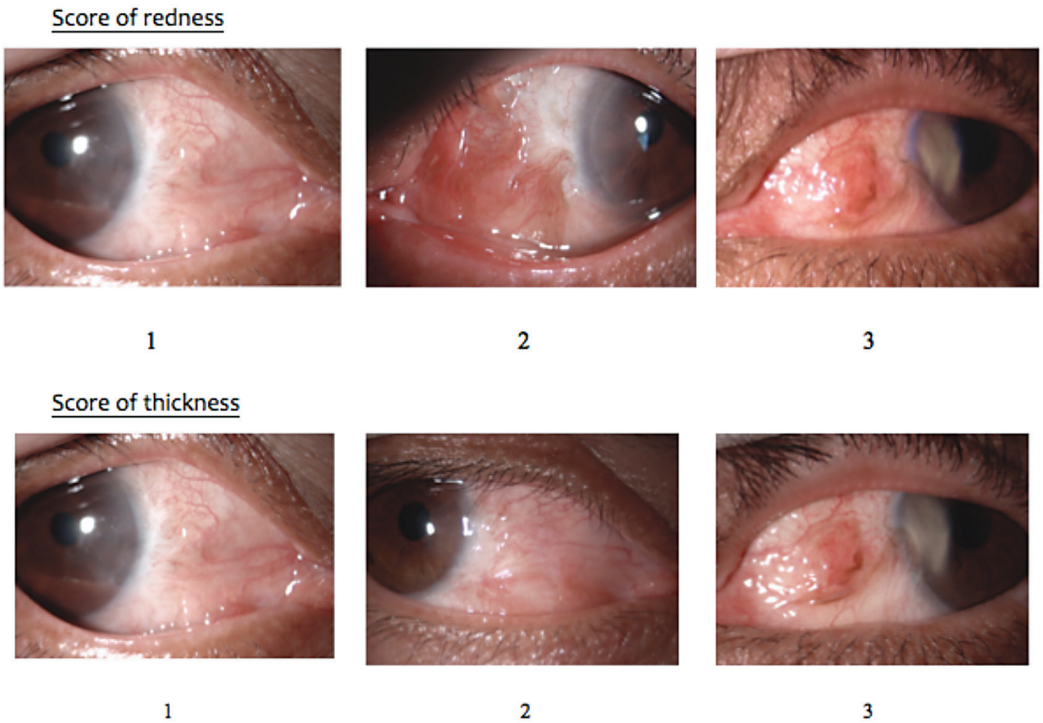

Figure 1. Severity score of impending recurrent pterygium (redness and thickness)

Table 1. 4 stages of postoperative pterygium excision.

4 stages of postoperative pterygium excision	
Stage 1	Normal appearance of conjunctiva after pterygium excision
Stage 2	Appearance of small conjunctival vessels in the area of excision reaching limbus without fibrovascular occurrence
Stage 3[a]	Fibrovascular growth into the area of excision without invasion into the cornea
Stage 4	Fibrovascular growth into the cornea (true recurrence of pterygium)

[a]Defined as impending recurrent pterygium in the present study

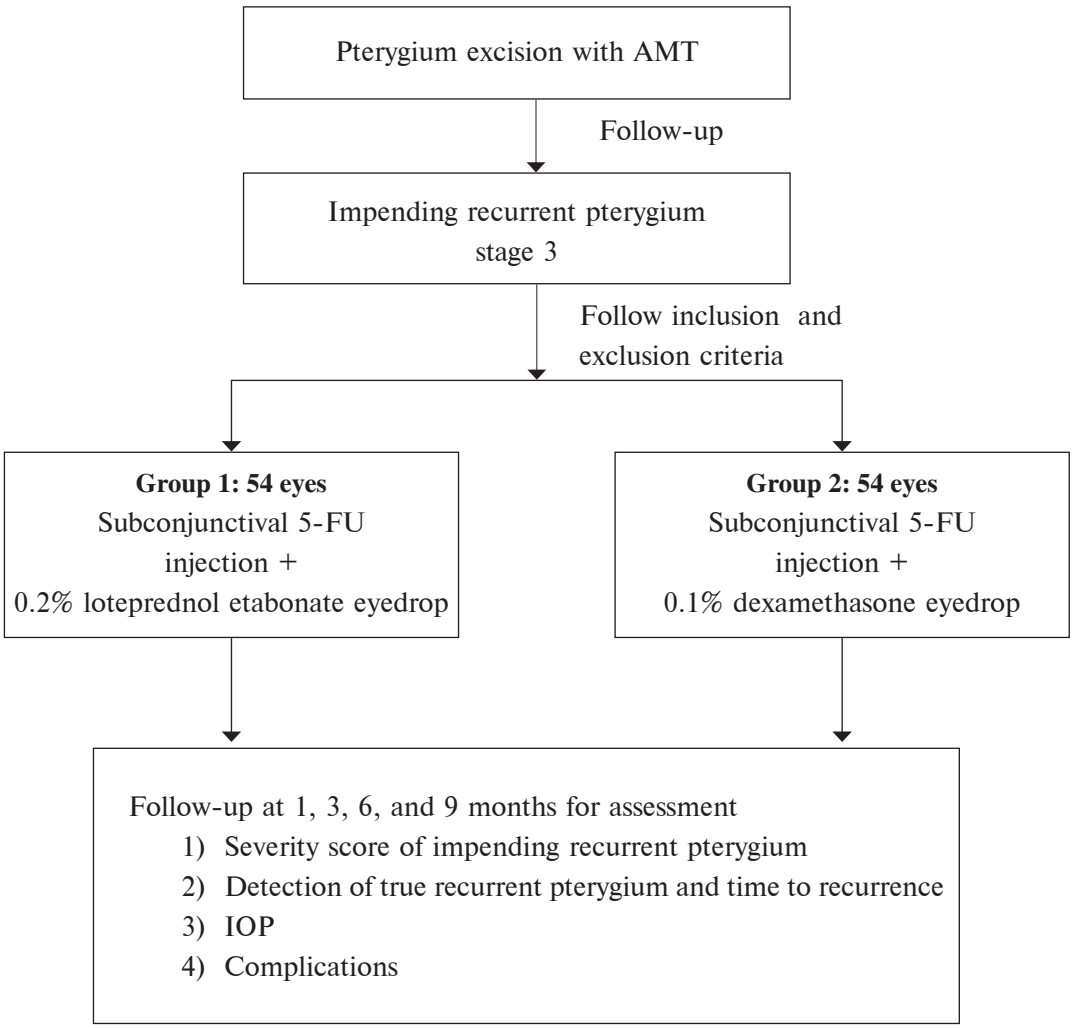

Figure 2. Flow chart of the progress through the randomized control trial. Abbreviations: AMT, amniotic membrane transplantation; 5-FU, 5-fluorouracil; IOP, intraocular pressure.

Table 2. Severity score of impending recurrent pterygium

Factors	Severity score		
	1	2	3
Redness	Mild injection	Moderate injection	Marked injection
Thickness	Thin fibrovascular tissue that dose not obscure underlying vessels	Thick fibrovascular tissue that obscures underlying vessels	Marked elevated fibrovascular tissue
Size (vertical plane at 3 mm from limbus)	<3 mm	3-6 mm	>6 mm
Score 2-4 = mild, Score 5-6 = moderate, Score 7-9 = severe			

All patients were followed-up at 1, 3, 6, and 9 months to assess the impending recurrent pterygium severity score, IOP, complications, detection of true recurrent pterygium, and time to recurrence.

Statistical Analysis

Baseline characteristics of patients were analyzed as mean ± SD for continuous data such as age, preoperative IOP, and score of impending recurrent pterygium. Sex and affected eye were analyzed using frequencies and percentages.

The chi-squared test was used to determine a significant difference of recurrent rate between groups. The significant difference of score of impending recurrent pterygium were analyzed using Mann-Whitney U test for ordinal data while continuous data, such as size of impending recurrent pterygium, IOP, and time to recurrence were analyzed by the independent t-test.

Correlation between the true recurrence of pterygium and factors such as age, sex, and pretreatment score of impending recurrent pterygium were analyzed by point biserial correlation coefficient and chi-square test.

Ethics

Informed written consent was obtained from all participants before inclusion in this study at department of ophthalmology. The present study was approved by the institutional review board and human research ethics committee of Faculty of Medicine, Thammasat University, and Panyananthaphikkhu Chonprathan Medical Center, Thailand. The study was performed in accordance with the Declaration of Helsinki. And this study has no conflict of interest.

Results

Fifty-four eyes of 54 patients in each group were included in the study. In the 0.2% loteprednol etabonate group (group 1), the mean of age ± SD was 61.39 ± 10.3 years with 16 (29.5%) males and 38 (70.4%) females. In the 0.1% dexamethasone group (group 2), the mean of age ± SD was 57.2 ± 10.9 years with 15 (27.8%) males and 39 (72.2%) females. All baseline characteristics including age, sex, affected eye, preoperative IOP, and score of impending recurrent pterygium did not show significant differences between both groups (Table 3).

The true recurrence of pterygium

in group 1 and 2 were seen in 15 patients (27.8%) and 17 patients (31.5%) respectively, and there was no significant difference (p = 0.67). The mean time to recurrence ± SD was 1.47 ± 0.8 months in group 1 and 3.35 ± 1.7 months in group 2, and there was a significantly longer time to recurrence in group 2 compared with group 1 (p = 0.0002). The mean score of impending recurrent pterygium at 1 month and 6 months after treatment were not significantly different between both groups (p =0.26 at 1 month and p = 0.1 at 6 months). However, the score was significantly higher in group 2 compared with group 1 at 3 months (p = 0.015). The mean number of 5-FU injection ± SD was not significantly different between the groups (1.5 ± 0.6 in group 1 vs. 1.37 ± 0.6 in group 2, p = 0.13) (Table 4).

Regarding complications, the study found ocular hypertension, defined as IOP > 21 mmHg, in 6 patients (11.1%), all of which were in the 0.1 % dexamethasone group. The mean rise in IOP ± SD, defined as the maximum IOP minus the baseline preoperative IOP, was 1.43 ± 1.3 mmHg and 2.94 ± 2.8 mmHg in group 1 and group 2, respectively.

Table 3. Baseline characteristics

Characteristics	**Group 1** 0.2% Loteprednol etabonate (n = 54)	**Group 2** 0.1% Dexamethasone (n = 54)	*P-value*
Age, mean ± SD, yr.	61.39 ± 10.3	57.2 ± 10.9	0.23
Sex, n (%)			
Male	16 (29.5)	15 (27.8)	0.83
Female	38 (70.4)	39 (72.2)	
Affected eye, n (%)			
Right eye	24 (44.4)	17 (31.5)	0.17
Left eye	30 (55.6)	37 (68.5)	
Preoperative IOP, mean ± SD, mmHg	14.0 ± 3.6	14.4 ± 3.1	0.28
Score of impending recurrent pterygium, mean ± SD	5.63 ± 1.4	5.98 ± 1.5	0.1
Injection	1.65 ± 0.7	1.87 ± 0.7	0.06
Thickness	2.06 ± 0.5	2.06 ± 0.7	0.48
Size	4.30 ± 1.5	4.34 ± 1.4	0.44

Abbreviations: IOP, intraocular pressure

Table 4. Comparison of recurrence rate, score of impending recurrent pterygium, and complications between the 0.2% loteprednol etabonate and 0.1% dexamethasone groups

Characteristics	**Group 1** 0.2% Loteprednol etabonate (n = 54)	**Group 2** 0.1% Dexamethasone (n = 54)	*P-value*
True recurrent pterygium, n (%)	15 (27.8)	17 (31.5)	0.67
Time to recurrence, mean ± SD, mo.	1.47 ± 0.8	3.35 ± 1.7	<0.001
Score of impending recurrent pterygium, mean ± SD	4.81 ± 0.9	5.12 ± 1.3	0.26
Score at 1 month	1.23 ± 0.6	1.31 ± 0.5	0.32
Injection	1.65 ± 0.6	1.78 ± 0.8	0.29
Thickness	4.40 ± 1.3	4.56 ± 1.1	0.27
Size	3.69 ± 0.9	4.44 ± 1.4	0.015
Score at 3 months	0.74 ± 0.5	0.85 ± 0.6	0.25
Injection	1.28 ± 0.5	1.58 ± 0.7	0.06
Thickness	3.69 ± 1.4	4.42 ± 1.2	0.06
Size	3.31 ± 0.9	3.62 ± 1.0	0.10
Score at 6 months	0.36 ± 0.5	0.43 ± 0.5	0.29
Injection	1.26 ± 0.4	1.32 ± 0.6	0.42
Thickness	3.90 ± 1.4	4.07 ± 0.9	0.27
Size			
5-FU injection, mean ± SD, n	1.5 ± 0.6	1.37 ± 0.6	0.13
1 injection, n (%)	29 (53.7)	36 (66.7)	
2 injections, n (%)	23 (42.6)	16 (29.6)	
3 injections, n (%)	2 (3.7)	2 (3.7)	
IOP rising, mean ± SD, mmHg (maximum IOP− pre-op IOP)	1.43 ± 1.3	2.94 ± 2.8	<0.001
Complications, n (%) Ocular hypertension	0	6 (11.1)	

Abbreviations: 5-FU, 5-fluorouracil; IOP, intraocular pressure

There was a significantly higher IOP elevation in the 0.1% dexamethasone group (p= 0.0002) (Table 4).

Correlations between true recurrence of pterygium and pretreatment factors were analyzed. The age of patients had a significantly negative correlation with the recurrence of pterygium (r = -0.28, p =0.002). Male sex had a significant association with recurrence rate (p = 0.02). However, initial score of impending recurrent pterygium, including score of injection, thickness, and size, were not significantly correlated with the recurrence of pterygium.

Discussion

Previous studies have found many factors associated with higher recurrence rate of pterygium, including some patient characteristics, such as younger age, area or size of pterygium, current active growth, family history, and concurrent ocular surface inflammation.[9-16] The present study also found association between younger age and male sex with higher recurrence rate.

Controlling ocular surface inflammation is the key to reducing recurrence of pterygium, and topical steroids of various types and regimen are the most common form of medication to control this inflammation.[17] Yaisawang found a high recurrence rate of pterygium in patients who received inadequate post-operative topical steroid.[3] Prabhasawat, et al. reported subconjunctival injection of triamcinolone or 5-FU added to topical steroid was more effective in halting the progression of impending recurrent pterygium.[18]

Unfortunately, topical steroids can cause many ocular side effects. An important one is steroid-induced ocular hypertension, which may progress to secondary glaucoma. Amaly found one-third of the normal population and 90% of primary open angle glaucoma developed ocular hypertension after 4 weeks of using topical 0.1% dexamethasone.[19] Makornwattana reported the incidence of steroid responders to be 9.68% in postoperative pterygium excision when 0.1% dexamethasone eye drops were used.[20] To avoid this unwanted side effect, 'soft steroids', including loteprednol etabonate 0.5% and 0.2% were developed by retrometabolic engineering that replaces the C-20 ketone with a C-20 ester, producing a compound designed to induce rapid metabolism to inactive metabolites.[21-22] Preclinical and clinical studies have confirmed the safety and efficacy of loteprednol etabonate for the treatment of many ocular inflammatory conditions, including giant papillary conjunctivitis, seasonal allergic conjunctivitis, anterior uveitis, blepharokeratoconjunctivitis, keratoconjunctivitis sicca along with the control of postoperative inflammation following PRK, LASIK, and cataract surgery.[22] John, et al. suggested loteprednol etabonate QID drops or BID ointment were sufficient for controlling inflammation in postoperative pterygium excision patients in a retrospective case series.[22] However, there are currently no prospective studies to evaluate the efficacy of loteprednol etabonate in postoperative pterygium excision.

This study demonstrated the non-inferior in efficacy of 0.2% loteprednol etabonate to 0.1% dexamethasone Although recurrence rates of pterygium were not significantly different between the 2 treatment groups, longer time to recurrence in the 0.1% dexamethasone

group was demonstrated. Moreover, no ocular hypertension (IOP > 21 mmHg) was found in the loteprednol etabonate group, compared to 6 patients (11.1%) in the 0.1% dexamethasone group. Rise in mean IOP ± SD was also significantly lower in 0.2% loteprednol etabonate group compare with the 0.1% dexamethasone group (1.43 ± 1.3 vs. 2.94 ± 2.8 mmHg, respectively, p = 0.0002). Our results concord with previous studies that demonstrated a low propensity for loteprednol etabonate to cause significant elevation of IOP ≥ 10 mmHg in both short-term (< 28 days, 0.8%) and long-term use (≥ 28 days, 1.5%) when compared to prednisolone acetate and dexamethasone.[23]

Experience of the surgeon is one factor that affects the recurrence rate of pterygium, the limitation of this study is the lack of control of this confounding factor. I recommend further studies of the use of several topical steroids, especially soft steroid, to compare pterygium recurrence rate after surgery and if other interfering factors such as surgeon can controlled, the results may be more reliable.

Conclusion

The efficacy of 0.2% loteprednol etabonate was non-inferior to 0.1% dexamethasone in preventing the recurrence of pterygium and controlling inflammation after pterygium excision. 0.2% loteprednol etabonate was also safer with regards to avoiding steroid-induced ocular hypertension.

Acknowledgement

This study was funded by the Panyananthaphikkhu Chonprathan Medical Center Srinakharinwirot University Research Fund.

Pontential Conflicts of Interest

Researchers have no financial interest in any products or instruments mentioned in this study.

Reference

1. Mahar PS, Manzar N. Pterygium recurrence related to its size and corneal involvement JCPSP. J Coll Physicians Surg 2013;23(2): 120-3.
2. Sherwin JC, Hewitt AW, Kearns LS, Griffiths LR, Mackey DA, Coroneo MT. The association between pterygium and conjunctival ultraviolet autofluorescence: The Norfolk Island Eye Study. Acta Ophthalmologica 2013;91(4):363-70.
3. Yaisawang S, Piyapattanakorn P. Role of post-operative topical corticosteroids in recurrence rate after pterygium excision with conjunctival autograft. J Med Assoc Thai 2003;86 (Supp 2):S215-223.
4. Hirst LW. The treatment of pterygium. Surv Ophthalmol 2003;48:145-180. 2.
5. Kucukerdonmez C, Akova YA, Altinors DD. Comparison of conjunctival autograft with amniotic membrane transplantation for pterygium surgery:surgical and cosmetic outcome. Cornea 2007;26:407-413.
6. Pikkel J, Porges Y, Ophir A. Halting pterygium recurrence by postoperative 5-fluorouracil. Cornea 2001;20(2):168-171.
7. Sheha H, Liu J, Tseng SCG. Inflammation and the recurrence of pterygium. Advance ocular care 2010;49-51.
8. Basic and clinical science course. Fundamentals and principles of ophthalmology. Section 2. American

academy of ophthalmology 2014-2015:329-334.
9. Anguria P, Ntuli S, Carmichael T. Young patient's age determines ptetrygium recurrence after surgery. Afr Health Sci 2014 Mar; 14(1):72-76.
10. Han SB, Jeon HS, Kim M, Lee SJ. Risk factors for recurrence after pterygium surgery: an image analysis study. Cornea 2016 Aug;35(8):1097-103.
11. Sang WH, Joon HP, Hong KK. Clinical analysis of risk factors contribution to recurrence of pterygium after excision and graft surgery. Int J Ophthalmol 2015;8(3):522-527.
12. Olusany BA, Ogun OA, Bekibele CO, Ashaye AO. Risk factors for pterygium recurrence after surgical excision with combined conjunctival autograft (CAG) and intraoperative antimetabolite use. Afr J Med Sci 2014 Mar;43(1):35-40.
13. Pi SM, Nabeel M. Pterygium recurrence related to its size and corneal involvement. JCPSP 2013;23(2):120-123.
14. Dan Y, Olivia LL. Risk factors for pterygium recurrence after primary excision. IOVS 2011 Apr;52(14).
15. Raffaele N, Federico T. How to minimize pterygium recurrence rates: clinical perspectives. Clin Ophthalmol 2018;12:2347-2362.
16. Kim KW, Kim JC. Current approaches and future directions in the management of pterygium. Int J Ophthalmol 2018;11(5):709-711.
17. Hosam S, Jingbo L, Scheffer T. Inflammation and the recurrence of pterygium. Advance Ocular Care.2010 Jan.
18. Prabhasawat P, Tesavibul N, Leelapatranura K, Phonjan T. Efficacy of subconjunctival 5-fluorouracil and triamcinolone injection in impending recurrent pterygium. Ophthalmology 2006;113:1102-1109.
19. Armaly MF. Effect of corticosteroid on intraocular pressure and fluid dynamics (II). The effect of dexamethasone in the glaucomatous eye. Arch Ophthalmol 1963;70:492.
20. Makornwattana M, Suphachearaphan W. Incidence of steroid induced-ocular hypertension in postoperative ptergum excision. J Med Assoc Thai 2015;98(Suppl 2):S151-S157.
21. Bodor N, Buchwald P. Soft drug design: general principles and recent applications. Med Res Rev 2000;20(1):58−101.
22. Timothy LC, John DS. Loteprednol etabonate for inflammatory conditions of the anterior segment of the eye: twenty years of clinical experience with a retrometabolically designed corticosteroid. Expert Opin Pharmacother 2018;19(4):337-353.
23. John DS, Timothy LC, Megan EC. Impact of the topical ophthalmic corticosteroid loteprednol etabonate on intraocular pressure. Adv Ther 2016;33:532-552.