COMPARISON OF RECURRENCE RATE, SURGICAL TIME AND PAIN SCORE IN PRIMARY PTERYGIUM EXCISION WITH AND WITHOUT HYDRO-FLUORESCEIN TENONECTOMY

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DISCLAIMER

I hereby certify that the work in this dissertation is my own except for the quotations andsummaries which have been duly acknowledged.

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Dr. Foo Lee Min

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ABSTRAK

Tujuan

Untuk membandingkan kadar pertumbuhan semula, tempoh pembedahan, dan tahap kesakitan semasa pembedahan selaput luar (pterygium) dengan dan tanpa hidro-fluorescein tenonektomi.

Metodologi

Kajian kohort prospektif telah dijalankan antara Februari 2021 dan Januari 2022 melibatkan 80 pesakit. Kaedah persampelan adalah mengikut kaedah persampelan berstrata, data yang dikumpul adalah berdasarkan teknik pembedahan yang dilakukan oleh doktor mata, iaitu pembedahan selaput luar dengan atau tanpa hidro-fluorescein tenonektomi. Hasil kajian adalah tempoh pembedahan, skor kesakitan intraoperatif dan pterygium berulang. Penilaian klinikal dilakukan pada minggu pertama, bulan ketiga dan bulan keenam selepas pembedahan. Ujian khi kuasa dua Pearson digunakan untuk membandingkan kadar pengulangan dua kumpulan. Regresi logistik binari digunakan untuk menilai hubangkait antara factor-faktor dengan kadar berulang. Purata masa pembedahan dan skor kesakitan intraoperatif dibandingkan antara dua kumpulan menggunakan ujian-t.

Keputusan

Kadar berulang adalah 5.0% (dua kes) dan 22.5% (sembilan kes) dalam kumpulan hidro-fluorescein dan tanpa hidro-fluorescein tenonektomi (p = 0.023). Terdapat perkaitan teknik dengan kadar berulang (OR 0.18, 95% CI 0.036, 0.90, p=0.037). Purata masa pembedahan ialah 29.70 (± 8.35) minit dalam kumpulan hidro-fluorescein dan 33.63 (± 12.16) minit dalam kumpulan tanpa hidro-fluorescein tenonektomi (p = 0.003). Subjek dalam kumpulan hidro-fluorescein tenonektomi mengalami kesakitan intraoperatif yang kurang ketara berbanding kumpulan tanpa hidro-fluorescein tenonektomi, di mana purata skor kesakitan masing-masing adalah 2.05 (± 0.64) dan 3.33 (± 1.83) (p <0.001).

Kesimpulan

Hydro-fluorescein tenonektomi dengan ketara mengurangkan kadar berulang, masa pembedahan, dan tahap kesakitan semasa pembedahan selaput luar. Oleh itu, ia boleh menjadi pilihan teknik untuk dipertimbangkan untuk pembedahan selaput luar.

ABSTRACT

Purpose:

To compare recurrence rate, surgical time, and pain score in primary pterygium excision with and without hydro-fluorescein tenonectomy.

Methods:

A prospective cohort study was conducted between February 2021 and January 2022 involving 80 patients. The sampling method was stratified sampling. The data collected was based on the surgical technique performed by the surgeon, which were primary pterygium excision with or without hydro-fluorescein tenonectomy. Outcome measures were duration of surgery, intraoperative pain score and recurrence of pterygium. Clinical assessment was performed on first week, third month and sixth month post operation. Pearson's chi-square test was used to compare recurrence rate of two groups. Binary logistic regression was used to test the factors associated with recurrence rate. Mean surgical time and intraoperative pain score were compared between two groups using independent t-test.

Results:

The recurrence rates were 5.0% (two cases) and 22.5% (nine cases) in the with and without hydro-fluorescein tenonectomy group respectively ($p = 0.023$). Techniques and recurrence rate were related (OR 0.18, 95% CI 0.036, 0.90, $p=0.037$). Mean surgical times were 29.70 (± 8.35) minutes and 33.63 (± 12.16) minutes in the with and without hydro-fluorescein tenonectomy group respectively ($p = 0.003$). Subjects in hydro-fluorescein tenonectomy group experienced significantly less intraoperative pain compared to without hydro-fluorescein tenonectomy group, where mean pain scores were 2.05 (± 0.64) and 3.33 (± 1.83) respectively ($p < 0.001$).

Conclusions:

Hydro-fluorescein tenonectomy significantly reduces the recurrence rate, surgical time, and intraoperative pain score. Thus, it can be a technique option to take into consideration for pterygium surgery.

Keywords:

pterygium, recurrence rate, hydro-fluorescein, tenonectomy, conjunctival autograft

Chapter 1

Introduction

1.1 Pterygium

Pterygium is defined as a triangular-shaped fibrovascular proliferation of subconjunctival tissue that encroaches on the cornea in the medial and lateral palpebral fissure (Sarkar and Tripathy, 2022). It is divided into three parts, namely apex, neck and body. The body is the conjunctival part with a base that faces the medial or lateral canthus. The communication area between the body and the head, which lies above the limbus, is known as the neck. The head is the invading region that houses the tissue's apex (Shahraki et al., 2021).

Pterygium is one of the common ocular surface disorders, and has highest prevalence in "pterygium belt", which is located in tropical and subtropical regions around the equator between 40º north and 40º south (Sarkar and Tripathy, 2022; Shahraki et al., 2021; Rokohl, & Heindl. 2022). Malaysia and Singapore are situated 1º north of the equator within the pterygium belt, where ultraviolet (UV) radiation is of higher intensity. The overall prevalence of pterygium in Singapore was 10.1%. Malays (15.5%) had a higher prevalence than Chinese (7.0%) or Indians (7.0%) (Ang et al., 2012).

The significant prevalence of pterygium in tropical nations lends weight to the theory that UV light plays a role in the disease's aetiology (Shahraki et al., 2021). Reactive oxygen species are produced by UV radiation, which impair limbal stem cells (LSCs) and stromal fibroblasts by destroying their DNA, resulting in mutation of p53 gene, activating transcription factors that regulate expression of multiple genes involved in extracellular matrix (ECM) changes, and inducing inflammatory reactions and tissue remodeling. Through ECM remodeling and Bowman layer breakdown, upregulated

inflammatory cytokines, growth factor and matrix metalloproteinases (MMPs) production facilitate invasion of highly proliferative fibroblast and altered LSCs (Sarkar and Tripathy, 2022; Shahraki et al., 2021).

1.2 Management of pterygium

Medical care is given to relieve the inflammatory signs and lessen the lingering discomfort. Artificial tear drops, vasoconstrictor drugs, or decongestants are some of the medical treatments available. They reduce redness, offer momentary comfort, and slightly improve cosmetics. Additional relief is provided by topical non-steroidal anti-inflammatory drugs (NSAIDS) or steroids (Sarkar and Tripathy, 2022).

Surgery is indicated by impaired vision brought on by encroachment of the visual axis, chronic pain or inflammation, aberrant astigmatism, constrictive ocular motility, and cosmesis (Malhotra et al., 2015; Sarkar and Tripathy, 2022; Shahraki et al., 2021). However, pterygium excision remains to be the cornerstone of treatment in pterygium.
There have been numerous surgical methods described and used from antiquity to the present such as bare sclera technique, conjunctival autograft, amniotic membrane graft, and conjunctival-limbal graft which may include adjuvant therapy in the form of antimetabolites, antiangiogenic agents, and radiation (Palewski et al., 2022; Sarkar and Tripathy, 2022; Shahraki et al., 2021) but none are universally accepted due to variable recurrence rate. Depending on the technique, reported recurrence rates range from 6.7% to 88% (Palewski et al., 2022).

1.3 The importance of tenonectomy in pterygium excision

A few studies showed that the Tenon layer's fibroblasts may be induced to release hyaluronate, which stimulates cell proliferation and modulates angiogenesis, in response to various growth stimuli (Denk et al., 2000, 2003; Kria et al., 1998). The tenon layer clearance has therefore been stressed as a key element in minimizing recurrences following pterygium excision, for which various strategies have evolved over time, such as conjunctival resection and Tenon extended removal (CRATER), pterygium extended removal followed by extended conjunctival transplantation (P.E.R.F.E.C.T.), and removal of Tenon fortified by conjunctival limbal-autograft (Ciftci et al., 2017; Hirst, 2008; Liu et al., 2017; Malhotra et al., 2015).

Adequate covering of the operation site is also necessary for a successful pterygium procedure (Shahraki et al., 2021). Different techniques such as conjunctival autograft, amniotic membrane graft, and conjunctival-limbal graft had been outlined (Sarkar and Tripathy, 2022; Shahraki et al., 2021). The most efficient way to reduce the likelihood of recurrences and complications is conjunctival autograft (CAG) transplantation (Malhotra et al., 2015). However, Tenon's layer, which is a component of CAG can be challenging to be removed entirely. Incomplete removal of Tenon's layer of the CAG will result in postoperative graft retraction, which can result in high rate of recurrence. A successful autograft should be virtually transparent without any Tenon's layer.

1.4 Hydro-fluorescein tenonectomy

Removal of tenons using hydro-fluorescein technique in pterygium surgery was introduced by Kamal and Khairidzan in year 2019 during American Society of Cataract and Refractive Surgery (ASCRS) and American Society of Ophthalmic Administrators (ASOA) Annual Meeting.

Khaw et al. described tenon hydration technique in Moorfields safer surgery system for enhanced trabeculectomy, where balance salt solution is applied to hydrate and thicken the Tenon's capsule and thus enhance its visualization, for easy handling (Khaw et al., 2012).

Hydro-fluorescein technique improvised the tenon hydration technique by adding fluorescein, thus enhance visualization of the Tenon. In this technique, Tenon layer and fibrous tissue at the recipient bed, and also tenon on the harvested graft would be hydrated with diluted fluorescein sodium 0.1mg/ml (Kamal, & Khairidzan, 2019). All hydrated and stained tissue would be removed.

1.5 Rationale of Study

Complete removal of the Tenon is one of the key elements to a success pterygium surgery. We are describing a new technique, which is the hydro-fluorescein technique to aid in removal of the tenon.

No previous study has been found on hydro-fluorescein tenonectomy in pterygium excision and there is no agreement exists as to which technique is better. This study was designed to directly compare prospectively and report our experience with the outcomes of primary pterygium excision with and without hydro-fluorescein tenonectomy.

If hydro-fluorescein technique is proven to be effective in reducing recurrence rate, it can thus be considered to become a common practice in ophthalmology field. The patients are then able to benefit from a better surgery outcome. With the results of this study, we hope to aid in improving our services and patient's post operative satisfaction, and serve as a comparative baseline for future prospective clinical study.

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Chapter 2

Objective

STUDY OBJECTIVES

2.1 General Objective

To compare recurrence rate, surgical time, and pain score in primary pterygium excision with and without hydro-fluorescein tenonectomy.

2.2 Specific Objective

2.2.1 To compare the recurrence rate of primary pterygium excision with and without hydro-fluorescein tenonectomy at 6 months.

2.2.2 To compare the mean surgical time of primary pterygium excision with and without hydro-fluorescein tenonectomy.

2.2.3 To compare the mean intraoperative pain score during primary pterygium excision with and without hydro-fluorescein tenonectomy.

Chapter 3

Manuscript

TITLE PAGE

Comparison of Recurrence Rate, Surgical Time and Pain Score in Primary Pterygium Excision With and Without Hydro-Fluorescein Tenonectomy

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ABSTRACT

Purpose:

To compare recurrence rate, surgical time and pain score in primary pterygium excision with and without hydro-fluorescein tenonectomy.

Methods:

A prospective cohort study was conducted between February 2021 and January 2022 involving 80 patients. The sampling method was stratified sampling. The data collected was based on the surgical technique performed by the surgeon, which were primary pterygium excision with or without hydro-fluorescein tenonectomy. Outcome measures were duration of surgery, intraoperative pain score and recurrence of pterygium. Clinical assessment was performed on first week, third month and sixth month post operation. Pearson's chi-square test was used to compare recurrence rate of two groups. Binary logistic regression was used to test the factors associated with recurrence rate. Mean surgical time and intraoperative pain score were compared between two groups using independent t-test.

Results:

The recurrence rates were 5.0% (two cases) and 22.5% (nine cases) in the with and without hydro-fluorescein tenonectomy group respectively ($p = 0.023$). Techniques and recurrence rate were related (OR 0.18, 95% CI 0.036, 0.90, $p = 0.037$). Mean surgical times were 29.70 (± 8.35) minutes and 33.63 (± 12.16) minutes in the with and without hydro-fluorescein tenonectomy group respectively ($p = 0.003$). Subjects in hydro-fluorescein tenonectomy group experienced significantly less intraoperative pain compared to without hydro-fluorescein tenonectomy group, where mean pain scores were 2.05 (± 0.64) and 3.33 (± 1.83) respectively ($p < 0.001$).

Conclusions:

Hydro-fluorescein tenonectomy significantly reduces the recurrence rate, surgical time, and intraoperative pain score. Thus, it can be a technique option to take into consideration for pterygium surgery.

Keywords:

pterygium, recurrence rate, hydro-fluorescein, tenonectomy, conjunctival autograft

INTRODUCTION

Pterygium excision remains to be the cornerstone of treatment in pterygium, however recurrence is the main challenge. There have been numerous surgical methods described and used from antiquity to the present such as bare sclera technique, conjunctival autograft, amniotic membrane graft, and conjunctival-limbal graft which may include adjuvant therapy in the form of antimetabolites, antiangiogenic agents, and radiation [1,2] but none are universally accepted due to variable recurrence rate. Depending on the technique, reported recurrence rates range from 6.7% to 88% [2].

The tenon layer clearance has been stressed as a key element in minimizing recurrences following pterygium excision [3–9]. Removal of tenons using hydro-fluorescein technique in pterygium surgery was introduced by Kamal and Khairidzan in year 2019 during American Society of Cataract and Refractive Surgery (ASCRS) and American Society of Ophthalmic Administrators (ASOA) Annual Meeting [10]. Hydro-fluorescein technique improvised the tenon hydration technique described by Khaw et al. in Moorfields safer surgery system for enhanced trabeculectomy[11] by adding fluorescein, thus enhance visualization of the Tenon. In this technique, Tenon layer and fibrous tissue at the recipient bed, and also tenon on the harvested graft is hydrated and stained with diluted fluorescein sodium 0.1mg/ml [10]. All hydrated and stained tissue is removed [10].

The effectiveness of the hydro-fluorescein tenonectomy has not been reported. Herein, this study is designed to evaluate the efficacy of hydro-fluorescein tenonectomy by

comparing the technique to without hydro-fluorescein tenonectomy technique, and to serve as a comparative baseline for future prospective clinical study.

MATERIALS AND METHODS

We conducted a prospective cohort study involving 80 adults who underwent primary nasal pterygium excision in Ophthalmology Clinic in Hospital Sultanah Nur Zahirah, Terengganu, Malaysia from February 2021 to January 2022. This study was conducted in accordance with the Declaration of Helskinki, and the study was approved by the Human Research and Ethical Committee of Universiti Sains Malaysia (Reference: USM/JEPeM/21010047) and the Ministry of Health, Malaysia (Reference: NMRR-20-2643-55613).

The sampling method was stratified according to the level of type of primary pterygium excision (with and without hydro-fluorescein tenonectomy). Then, we randomly selected the patients according to type of surgery performed. The patients fulfilled the inclusion and exclusion criteria. The inclusion criteria was age of above 18 years old with primary nasal pterygium. Exclusion criteria were patients with recurrent pterygium, temporal pterygium, pterygium with symblepharon, history of ocular surgery or trauma, collagen vascular disease and patients who were on prolonged usage of topical steroid or systemic immunosuppressive drugs. All patients underwent a complete ophthalmic examination, including slit-lamp examination and dilated fundus examination.

All surgeries were performed by a single surgeon (N.H). Proparacaine 0.5% eye drops

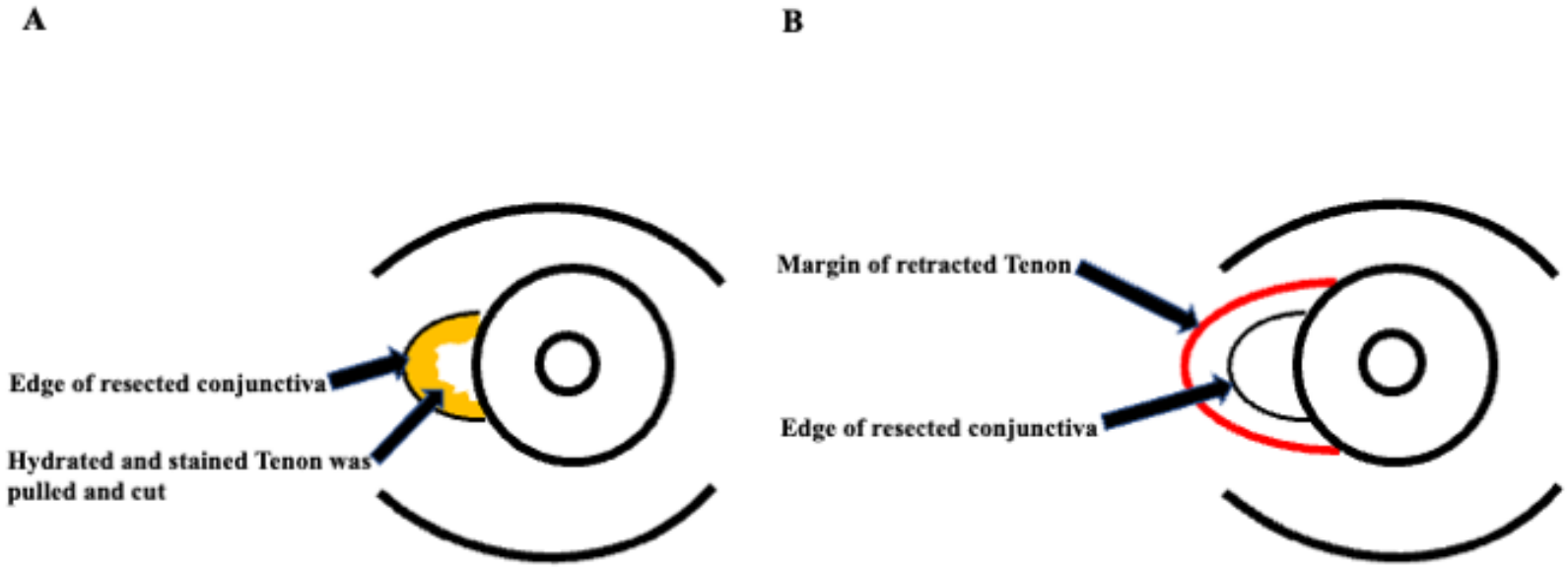
was instilled in the eye twice at an interval of 10 minutes before surgery. After a standard ophthalmologic sterile preparation and draping, a lid speculum was used to expose the surgical field of the involved eye. The size of the pterygium was measured horizontally in millimeters (mm) with a caliper from limbus to the head of pterygium, before 0.5ml of local anesthetic lignocaine HCL 20mg/ml (2%) was injected under the pterygium body with a 25-gauge needle.

A combination of dissection (both blunt and sharp) and stripping was carried out to separate the head of pterygium from the underlying corneal tissue with the aim of releasing the traction on the nasal conjunctiva. The pterygium was then resected from the tip of released pterygium head up to the body of pterygium 4 mm away from limbus. The recipient bed posterior to the pterygium then was prepared meticulously for the subsequent graft. The retracted conjunctiva was raised with non-toothed forceps to expose remnant Tenon at the recipient bed.

Two surgical techniques were applied: in the hydro-fluorescein tenonectomy group, the tenon layer at the recipient bed was hydrated with fluorescein sodium 0.1mg/ml (fluorescein sodium sterile ophthalmic strips which contain 1mg of fluorescein diluted in 10cc of water), the hydrated and stained tissues were removed (Figure 1); while in the without hydro-fluorescein tenonectomy, the immediate adjacent tenon layer measuring about 2mm at the recipient bed, were removed without the aid of fluorescein.

The bare sclera area was measured using caliper. The intended graft in inferotemporal zone was marked with a gentian violet marker pen. Subconjunctival injection of 2% lidocaine was given to balloon the conjunctiva, creating a plane for dissection between

Figure 1: A, Line diagram showing primary nasal pterygium which was excised 4mm from the limbus, Tenon was hydrated and stained with diluted fluorescein (0.1mg/ml). B, Line diagram showing margin of retracted Tenon, after the hydrated and stained Tenon was excised.

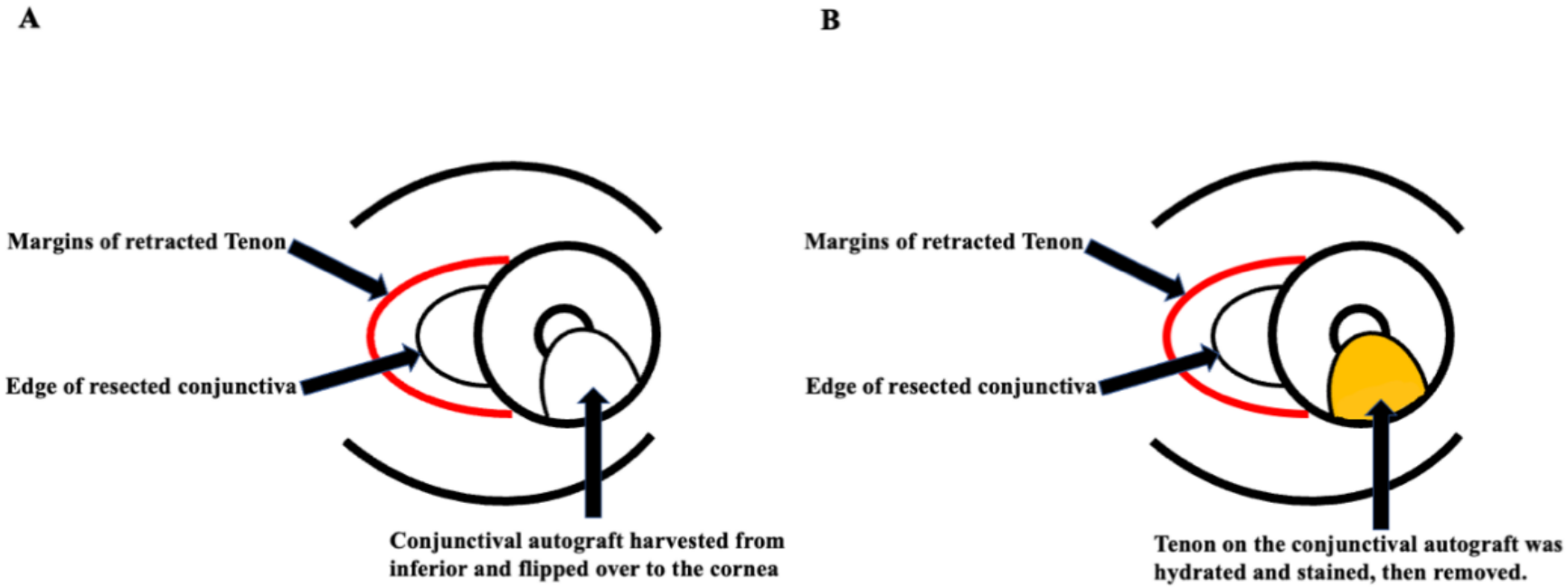


the conjunctiva and Tenon capsule. The graft was cut at the limbus using blunt-tipped Vannas scissors and non-toothed conjunctival forceps. The tenon tissue from harvested graft was also removed using two surgical techniques: in the hydro-fluorescein tenonectomy group, the tenon tissue was identified by hydrating the tenon with fluorescein sodium 0.1mg/ml and was detached from the graft (Figure 2); while in the without hydro-fluorescein tenonectomy group, the tenon tissue was carefully detached from the graft without the aid of fluorescein staining. Care taken to avoid rolling edge and buttonhole of the graft for both groups.

The free graft was placed on the bare sclera, where the limbal end was directed towards the cornea. The bare sclera was ensured to be completely covered by the graft. The graft was sutured to the adjacent conjunctiva using Vicryl 8/o. Two sutures at the limbal site, then other two sutures at the medial canthus region. The lid speculum was then removed, followed by instillation of one drop of chloramphenicol 0.5%.

The duration of surgery was measured from the time anesthetic was administered until the lid speculum was removed was collected. Intraoperative pain score was recorded once the lid speculum was removed. Patient was required to rate the intraoperative pain based on numerical rating scale (NRS), recommended by International Association for the Study of Pain (IASP). Post operatively, all patients were prescribed topical dexamethasone sodium phosphate 0.1% and topical chloramphenicol 0.5% every four hours for one month, then only topical dexamethasone sodium phosphate six hourly for another one month and were follow up at first week, third months and sixth months after surgery. Uncorrected and best corrected visual acuity, intraocular pressure, complication, and recurrence were recorded. Recurrence of pterygium was defined as

Figure 2: A, Line diagram showing conjunctival autograft harvested from inferotemporal region. B, Line diagram showing Tenon on the conjunctival autograft was hydrated and stained with diluted fluorescein (0.1mg/ml), then removed.



any regrowth of fibrovascular tissue across the limbus observed with a slit-lamp.

Data was analyzed using the Statistical Package for the Social Sciences (SPSS) version 27. All continuous variables were described using mean (standard deviation), whereas categorical data as frequency (%). Pearson's chi-square test was used to compare recurrence rate of two groups. Fisher exact test was used to compare timing of recurrence rate of two groups. Binary logistic regression was used to test the factors associated with recurrence rate. Mean surgical time and intraoperative pain score were compared between two groups using independent t-test. A *p*-value less than 0.005 was considered statistically significant.

RESULTS

80 eyes of 80 patients who completed the 6-months follow-up were analysed. The present study showed the mean age of patients for the hydro-fluorescein tenonectomy group was 54.63 (12.63) years and that of the without hydro-fluorescein tenonectomy group was 57.35 (11.93) years. The gender distribution for both groups were almost equal. Mean size of pterygium was 3.79 (1.12) mm and 3.97 (0.88) mm for the with and without hydro-fluorescein tenonectomy group respectively, the difference was not statistically significant. For the hydro-fluorescein tenonectomy group, 52.5% had diabetes mellitus, while 62.5% had diabetes mellitus for the without hydro-fluorescein tenonectomy group. All data are illustrated in Table 1.

Having completed a 6-months follow-up, there were only 5.0% recurrence after primary pterygium excision with hydro-fluorescein tenonectomy, whereas there were 22.5%

recurrence after primary pterygium excision without hydro-fluorescein tenonectomy. This difference was statistically significant, p=0.023. However, at three months and six months postoperatively, there was no significant difference between the two groups. There was significant difference in mean surgical time and pain score in between primary pterygium excision with and without hydro-fluorescein tenonectomy (p = 0.003 and $p < 0.001$, respectively). The above data are presented in Table 2.

The association of techniques with recurrence rate, gender, diabetes mellitus, age, size of pterygium, surgical time and intraoperative pain score are shown in Table 3. It was found that hydro-fluorescein tenonectomy had 82% lower odd for recurrence (p = 0.037). However no association were found between techniques with gender, diabetes mellitus, age, size of pterygium, surgical time and intraoperative pain.

The correlation between size of pterygium, pain score and surgical time is shown in Table 4. The surgical time increase with increasing size of pterygium (p = 0.016). The pain score increase with increasing surgical time, however this was statistically not significant (p = 0.819). There were no graft dislocation, graft infection, graft necrosis, dellen formation, conjunctiva granuloma, inclusion cyst, restricted ocular mobility or steroid induced glaucoma seen.

DISCUSSION

Our study's key finding was that the hydro-fluorescein tenonectomy group had a recurrence rate of 5%, which is comparable to other studies that emphasized on tenon removal. Ciftci et al. [6], Malhotra et al. [5] and Hirst [3,12,13] revealed almost no

recurrence for their pterygium excision method, while Liu et al. reported 7% recurrence in their study [4]. Our result was also consistent with the literatures that used adjuvant therapies such as mitomycin (MMC) and 5-fluorouracil (5-FU) to inhibit pterygium fibroblast which reported recurrence rate of 0- 11.8% [14–16] and 8.7% respectively [15,17]. Although our result was in line with the studies mentioned above, we recommend a large-scale, randomized, controlled study to compare hydro-fluorescein tenonectomy with other techniques, to elucidate the efficacy of the techniques in reducing recurrence rate of pterygium after excision.

Besides reducing the recurrence rate, the use of hydro-fluorescein to remove the tenon shortens the surgical time significantly ($p = 0.03$). The reduction of surgical time is believed to be because of easily identified tenon using hydro-fluorescein technique, thus faster removal, and completion of the surgery. The results are comparable with the study on pterygium excision with conjunctival autograft (CAG) fixed with fibrin adhesive versus suture group. The reported surgical time in fibrin adhesive group was 34.43 (4.94) minutes when compared to 50.93 (4.96) minutes in the suture group [18] suggesting that the hydro-fluorescein tenonectomy is not inferior to the fibrin adhesive technique.

Our results also showed greater intraoperative patient comfort. Subjects in hydro-fluorescein tenonectomy group had less intraoperative pain when compared to without hydro-fluorescein tenonectomy group ($p < 0.001$). Despite the fact that both groups had appropriate anesthetic treatment, less pain in hydro-fluorescein tenonectomy group is thought to be due to precise identification of tenon, thus avoiding unnecessary manipulation and eventually a shorter surgical time.