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Inflammatory and intraocular pressure outcomes after trabeculectomy in active uveitic glaucoma in Chinese

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活动期葡萄膜炎性青光眼患者接受小梁切除术后的炎症反应及眼压情况

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摘要

目标:分析活动期葡萄膜炎患者在小梁切除术后的炎症反应及眼压情况。

方法:我们回顾了2006-10/2011-03期间,接受了小梁切除术的活动期葡萄膜炎性青光眼患者纪录。手术前后的炎症反应、复发频率、类固醇依赖度及眼压均以配对t检验作比较。

结果:在29例29眼患者中,90%的患眼在手术时正在接受局部类固醇治疗。患者平均年龄为58.3±14.0a,术前眼压为35.7±8.9mmHg。患者平均复诊时期为35.2±18.7mo。术后3mo前房炎症反应分级平均减少了0.4±0.6(P<0.01)。复发频率在复诊期内每年减少了2.3±2.1次(P<0.01)。术后1a的平均眼压为13.1±4.5mmHg,而其中44.8%患者的眼压无需用药亦能维持在21mmHg或以下。

结论:小梁切除术后的葡萄膜炎性青光眼患者在炎症反应及眼压方面均有改善,但成功率较原发性青光眼患者低。小梁切除术可以作为活动期葡萄膜炎性青光眼患者早期控制眼压和炎症反应治疗的一个选择。

关键词:葡萄膜炎;小梁切除术;青光眼;眼压

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Abstract

• AIM: To analyze the outcomes in uveitic activity and intraocular pressure (IOP) control after trabeculectomy for uveitis with uncontrolled IOP.

• METHODS: The medical records of consecutive uveitic glaucoma patients undergoing trabeculectomy between October 2006 to March 2011 were retrospectively reviewed. Uveitic activity, frequency of recurrence, steroid dependence, and intraocular pressure control were compared with paired t-test before and after trabeculectomy.

• RESULTS: In 29 eyes from 29 patients, 90% of eyes were on topical steroids at the time of trabeculectomy. The mean age was 58.3±14.0 years old with a pre-operative IOP of 35.7±8.9mmHg. The mean follow up time was 35.2±18.7mo. There was a reduction of anterior chamber activity grading of 0.4±0.6 (P<0.01) at 3mo post-operatively. The uveitis recurrence rate was significantly reduced by 2.3±2.1 episodes/year (P<0.01) during the follow-up period. The mean 1y post-trabeculectomy IOP was 13.1±4.5mmHg with 44.8% of eyes with IOP ≤ 21mmHg without medication.

• CONCLUSION: Uveitic activity and IOP control improved after trabeculectomy with a lower success rate to primary glaucomas. Trabeculectomy may be considered as a possible early intervention of active uveitis with high IOP for pressure and uveitic activity control.

• KEYWORDS: uveitis; trabeculectomy; glaucoma; intraocular pressure

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INTRODUCTION

Uveitis and glaucoma are two closely related disease entities. Uveitis is a well documented cause of secondary glaucoma. Mechanisms include increase in aqueous viscosity, obstruction of trabecular meshwork by cellular debris and

protein, angleclosure from peripheral anterior synechiae, pupillary block from posterior synechiae, decrease in conventional outflow, angle neovascularization and use of steroids for treatment[1-3]. However, glaucoma is more prevalent in patients with uveitic activities not responsive to corticosteroids as the intraocular pressure (IOP) rise was more likely to return to normal if the uveitis can be controlled by steroids[4]. Adequate uveitis control is essential for the management of secondary glaucoma as the risk of blindness is 10% in uveitis[5].

Trabeculectomy is often required for patients with secondary uveitic glaucoma if the IOP is not controlled by topical anti-glaucoma medication alone. It has been postulated that trabeculectomy complications are more likely to occur in uveitic patients then patients with primary glaucoma. Based on experience from cataract operations, it has been suggested that the success of trabeculectomy relies on an adequate quiescent period of uveitic activity preoperatively[6]. However, Kaburaki *et al*[7] reported that pre-existing uveitis was not, in itself, a risk factor for trabeculectomy failure.

In management of these uveitic glaucoma patients, there are 2 important clinical dilemmas. Firstly, according to the conventional teachings, the eye should be quiet for a certain period of time before operation is to be contemplated. However some of these eyes will never be totally quiet. Secondly, in order to achieve stable disease activity, steroids are often used and steroid response often aggravates the IOP rise.

Therefore it would be essential to know the disease course of uveitis after trabeculectomy so that the management timeframe can be optimized. The purpose of this study is to analyze the effects of trabeculectomy on uveitic activity and IOP in patients with active uveitic glaucoma with uncontrolled IOP.

SUBJECTS AND METHODS

This study was approved by the Institutional Review Board of the Hospital Authority of Hong Kong and adhered to the principles outlined in the Declaration of Helsinki. Written informed patient consent was obtained prior to all surgical interventions. This was a non-funded study. The authors declare no competing or proprietary interests.

The medical records of all consecutive patients with active uveitis and glaucoma with trabeculectomies performed were retrospectively reviewed in a district hospital in Hong Kong, China during the period of October 2006 to March 2011. For subjects with bilateral uveitic glaucoma receiving trabeculectomies, only 1 eye was randomized (by card shuffling) for inclusion in the study to prevent the double counting of outcome effects from using 2 eyes from the same patient.

Uveitic glaucoma was defined as having a history of uveitis withan open angle on gonioscopy, IOP ≥ 21mmHg on 2 or more episodes, and characteristic glaucomatous field changes on the Humphrey Visual Field Analyzer (Carl Zeiss AG, Carl-Zeiss-Strasse 22, 73447 Oberkochen, Germany) as defined by the Hoddap-Parrish-Anderson criteria[8]: 1) three non-edge adjacement scotomas in pattern deviation probability plot with 2 points probability <5% and 1 point <1%; 2) pattern standard deviation probability less than 5% or 3) abnormal glaucoma hemifield test. Uveitis was controlled using topical steroids and where indicated, oral steroids or systemic immunosuppressants were used, after liaison with physicians, in those with uncontrolled uveitic activity despite topical steroids. Trabeculectomy was indicated for IOP control where IOP was persistently ≥21mmHg despite maximally tolerated topical anti-glaucoma medication. Oral acetazolamide was used as a temporary measure to control the IOP whilst waiting for trabeculetectomy if there were no systemic contraindications. All of the trabeculectomies were performed by a single glaucoma specialist (Yick DW) or under the direct supervision of that surgeon (2 surgeons in total). All cases received a fornix-based conjunctival flap operation with application of intra-operative Mitomycin-C (MMC) (0.4mg/mL) for 3min. Post-operatively, they were all given topical steroids (prednisolone acetate 1%) every 1-2h immediately after the operation and titrated according to clinical response. The exclusion criteria include trabeculectomies performed with combined cataract operation to avoid the combined effect of cataract operation on uveitis and IOP. Patients with less than 1y follow-up postoperatively were excluded as the long term effect of the operation may not be revealed with insufficient time. Baseline pre-operative anterior chamber activity, IOP, and uveitis recurrence frequency were documented for comparison with the following primary outcome measures: 1) Uveitic activity as determined by anterior chamber activity at 3mo post-operatively. The anterior chamber activity was graded on a 1×1mm slit on slit lamp examination according to the Standardization of Uveitis Nomenclature workshop as follows: a) <1 cell=grade 0; b) 1-5 cells=grade 0.5; c) 6-15 cells=grade 1; d) 16-25 cells=grade 2; e) 26-50 cells=grade 3; f) >50 cells=grade 4[9]. The 3mo post-operative period was chosen to reduce the effect of peri-operative fluctuation of the disease activity from the operations or from the concomitant use of peri-operative topical steroids. 2) Success of trabeculectomy as quantified by post-operative IOP control at 1y. Absolute success rate was defined as IOP≤21mmHg without topical anti-glaucoma agents. Partial success rate was defined as IOP≤21mmHg with the use of topical anti-glaucoma agents.

Secondary outcome measures included: 1) uveitis recurrence rate as defined by repeated episodes of uveitis separated by

periods of inactivity of at least 3mo' duration; 2) percentage of eyes dependent on topical steroids for uveitis control.

Statistical Analysis The D'Agostino & Pearson omnibus normality test was performed to confirm a Gaussian distribution of the sample. A paired *t*-tests was performed on: 1) anterior chamber activity pre-operatively and 3mo post-operatively; 2) recurrence rates of uveitis pre-operatively and post-operatively; 3) IOP pre-operatively and at 1y post-operatively. Snellen visual acuity pre-operatively, 1y post-operatively, and on last follow-up were compared using the Repeated Measures ANOVA with Bonferroni's Multiple Comparison Test. A P-value of <0.05 was taken to be significant. All the data have been analyzed using SPSS version 13.0. The results have been expressed in terms of mean±standard deviation.

RESULTS

A total of 29 eyes from 29 patients were included in the study. Ninety percent of cases (26/29) were on topicalprednisolone acetate 1% and 31% (9/29) were on oral prednisolone (0.5mg/kg) at the time of operation without the specific addition of steroids empirically. All patients were on maximally tolerated topical anti-glaucoma pre-operatively, with average of 3.79 topical medications used pre-operatively. The mean age of subjects was 58.3±14.0y. There were 23 male patients and 6 female patients. The majority of subjects were diagnosed as idiopathic uveitis. The mean time from presentation to operation was 20.0±31.1mo. The pre-operative mean deviation and pattern standard deviation were −14.5±11.3dB and 4.5±2.7dB respectively. The vertical cup-disc ratio was 0.7±0.2. The mean post-operative follow up time was 35.2±18.7mo (range: 12-61mo; Table 1). All patients had recurrent active anterior uveitis at the time of trabeculectomy.

The pre-operative anterior chamber activity grading was 0.7±0.5 and the 3mo post-operative grading was 0.3±0.4. There was a mean reduction of anterior chamber activity grading of 0.4±0.6 ($P<0.01$; Table 2).

The mean pre-op IOP was 35.7±8.9mmHg. Post-operatively, the mean IOP was 13.1±4.5mmHg, signifying a 63.3% reduction in IOP at 35.2±18.7mo post-operatively ($P<0.01$). At 1y post-trabeculectomy, the absolute success rate (IOP≤21mmHg without topical anti-glaucoma agents) was 44.8%. The partial success rate (IOP≤21mmHg with the use of topical anti-glaucoma agents) was 55.2%.

The pre-operative uveitis recurrence rate was 3.1±2.1 episodes/year and the uveitis recurrence rate post-operatively was 0.9±1.2 episodes/year signifying areduction of 2.3±2.1 episodes/year ($P<0.01$) during the 35.2±18.7mo follow-up period. Moreover, only 20.7% of eyes still required topical steroids by 1y compared with 89.7% pre-operatively (Table 2).

Table 1 Patient background information

Parameters	n(%)
Mean age (a)	58.3±14.0
Sex (n=29)	
M	23(82.4)
F	6(17.6)
Type of uveitic glaucoma (n=29)	
Idiopathic	16(55.2)
Post-operative	3(10.3)
Posner Schlossman	5(17.2)
Herpetic	2(6.9)
Fuch's heterchromic iridocyclitis	1(3.4)
Behcet disease	1(3.4)
Psoriasis	1(3.4)
Laterality	
R	14(48.3)
L	15(51.7)
Time from presentation to trabeculectomy (mo)	20.0±31.1
Mean follow-up time (mo)	35.2±18.7

Regarding complications, there were 2 cases of choroidal detachment from post-operative hypotony with 1 case requiring drainage procedure and 1 case required re-suturing due to over-filtration. There were no significant differences among the Snellen visual acuity measured pre-operatively (0.29±0.25), at 1y post-operatively (0.32±0.27), and on last follow-up at 35.2±18.7mo post-operatively (0.36±0.25; $P=0.5$).

DISCUSSION

There was a significant reduction in inflammatory activities as evidenced by the reduction of anterior chamber activity by 3mo ($P<0.01$) and also the reduction in uveitis recurrence episodes ($P<0.01$). This cannot be totally attributed by the use of intense post-operative steroids since the effect was likely to have worn off by 3mo post-operatively. Secondly, the IOP was significantly reduced post-operatively to a mean of 13mmHg. Hence, trabeculectomy on active uveitis and uncontrolled IOP has yielded modification to both aspects of uveitic glaucoma: a reduction in uveitic activity and a better control of IOP. There are no exact proven mechanisms to explain the findings but we postulate that the trabeculectomy will improve aqueous outflow, which may allow the egression of inflammatory mediators from the anterior chamber and the clearing of cellular debris. Our findings were consistent with a study by Heinz *et al*[10] that that reported a significant reduction of laser flare after trabeculectomy in uveitic glaucoma patients following trabeculectomy while in those receiving transscleral diode cyclophotocoagulation, the laser flare remained unchanged. However, there is always the possibility of the uveitis coincidentally progressing into a chronic smoldering stage which may confound the beneficial effects of the trabeculectomy on uveitic control.

Table 2 Inflammatory activity and IOP outcomes before and after trabeculectomy

Parameters	Pre-trabeculectomy	Post-trabeculectomy	*P*
[a]IOP(mmHg)	35.7±8.9	13.1±4.5	<[1]0.01
Percentage of steroid eye drops requirement (%)	89.7	20.7	n/a
Uveitis recurrence (episodes/a)	3.1±2.1	0.9±1.2	<[1]0.01
[b]Anterior chamber activity grading	0.7±0.5	0.3±0.4	<[1]0.01

[a]At 35.2±18.7mo post-operatively; [b]At 3mo post-operatively. [1]Statistically significant.

The IOP reduction in our study was 63.3% at 35.2±18.7mo of follow-up. In a study by Carreño *et al*[11], the mean IOP reduction in uveitic glaucoma was 46.2% at 69.6±54.9mo. Since the duration of follow-up was different, it was difficult to directly compare the amount of IOP reduction between our studies.

Pertaining to the success of the trabeculectomy, the absolute success rate of 45% and partial success rate of 55% was expectedly lower than non-uveitic glaucoma cases. Our success rate was comparable to Carreño *et al*[11] that reported a complete success rate of 48.2%, which was defined as IOP≤16mmHg without medication. With concomitant anti-glaucoma medications, Chawla *et al*[9] reported that the success rate (IOP≤21mmHg) of trabeculectomy in uveitic glaucoma can be increased to 76.5% at 5y. The use of intra-operative MMC modulates the accelerated wound healing in uveitic glaucoma[12,13]. The use of post-operative 5-Fluoruracil (5-FU) injections was also found to be beneficial in maintaining the IOP ≤21mmHg in 79% of uveitic glaucoma patients at 2y[14]. The median survival of trabeculectomy in uveitic glaucoma increased from 42mo to 60mo after daily subconjunctival injections of 5mg 5-FU over 7d post-operatively[15]. The use of subconjunctival bevacizumab injection has also been reported to control the IOP 6mo following trabeculectomy with MMC in a small case series of 6 patients with uveitic glaucoma[16].

Contrary to conventional teachings, we have demonstrated that the success of the trabeculectomy will not be affected by active uveitic activity at the time of operation. The findings of this study have 2 significant implications. First, trabeculectomies may be performed successfully on patients with active uveitis. Secondly, trabeculectomies may become one of the possible treatment options for the control of resistant uveitis, though larger scale randomized control trials should be warranted.

This study had its limitations. Firstly, the population was not totally homogenous in the etiology of uveitis, this may have influenced the duration, progression, response to the treatments and uveitis recurrence rates.

Secondly, it would have been ideal to randomize the trabeculectomy as an early and late intervention for those with active uveitic glaucoma. However, ethical concerns would arise in withholding surgical intervention for those with persistent IOP elevations despite maximal topical anti-glaucoma medications. Thirdly, none of the patients received post-operative 5-FU injections in our centre as this was not routine practice at the time the operations were performed; future addition of this modification may further increase the success rate. Fourthly, our study did not investigate the difference in outcome between those receiving trabeculectomy alone versus combined with phacoemulsification as previous studies have suggested that non-combined operation may be preferred due to less post-operative inflammation and flare[10,17], although some have reported no difference in a uveitic population[18]. Fifthly, the retrospective nature of the study subjected it inevitable inconsistencies in clinical data including the absence of central corneal thickness measurement in the majority of patients, which is essential in the interpretation of IOP. Sixthly, as it is the common practice of most glaucoma surgeons to follow-up their own post-operative cases, we do recognize that another limitation of this clinical study is that the surgeon may also be one of the primary examiners post-operatively, leading to a potential bias. Seventhly, a number of subjects were inevitably on prostaglandin analogues for maximal control of IOP, which may have influenced the degree of inflammation but the influence of prostaglandin on uveitic activity is still at large controversial and are useful if other topical anti-glaucoma mediations fail to control the IOP; Markomichelakis *et al*[19] confirmed the safe and effective use of latanoprost in uvetic glaucoma[20].

Lastly, it was beyond the scope of this study to explore and compare the outcomes of other glaucoma surgeries in uveitic glaucoma including glaucoma drainage device[21] and non-penetrating trabeculectomy in the control of uveitis post-operatively[22].

Uveitic activity and IOP control improved after trabeculectomy for active uveitis with uncontrolled IOP. Trabeculectomy may be considered as a possible early intervention to optimize both the uveitic activity and IOP control.

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