Aus dem Department für Augenheilkunde Tübingen

Universitäts-Augenklinik

Outcomes of Ab-externo Trabeculotomy in the Treatment of Primary Open Angle and Uveitic Glaucoma and outcomes of Primary Transconjunctival 23-Gauge Vitrectomy in the Diagnosis and Treatment of Presumed Endogenous Fungal Endophthalmitis.

Inaugural-Dissertation

zur Erlangung des Doktorgrades

der Medizin

der Medizinischen Fakultät

der Eberhard-Karls Universität zu Tübingen

vorgelegt von

William, Antony

2022

Dekan: **Professor Dr. B. Pichler**

1. **Berichterstatter:** **Privatdozent Dr. B. Voykov**
2. **Berichterstatter:** **Professor Dr. K. Januschowski**

Tag der Disputation: **13.10.2022**

Table of Contents

Pages

Abbreviations

POAG	Primary open Angle glaucoma
UG	Uveitic glaucoma
ISGEO	International Society of Geographical and Epidemiological Ophthalmology
IOP	Intraocular pressure
TM	Trabecular meshwork
JCT	Juxtacanalicular tissue
SC	Schlemm´s canal
SS	Scleral spur
CPC	Cyclophotocoagulation
GDD	Glaucoma drainage device
NPGS	Non–penetrating glaucoma surgery
EFE	Endogenous fungal endophthalmitis

1. Introduction and aim of work

1.1 Primary Open Angle Glaucoma and Uveitic Glaucoma

1.1.1 Definitions, Physiology of Aqueous Humor Formation and Dynamics

It is generally known that the term ``*glaucoma"* implies to a large number of diseases that are associated with distinctive characteristic progressive optic neuropathy with specific visual field changes that can lead to total and irreversible blindness if the disorder is not diagnosed and treated properly. Primary open angle glaucoma*" (POAG)* is defined as chronic progressive optic neuropathies, that have in common characteristic morphological changes at the optic nerve head and the retinal nerve fiber layer in the absence of either ocular disease or congenital anomalies. On the other hand, the term "uveitic glaucoma" *(UG)* is defined according to the recent definition of the ISGEO as different forms of inflammatory diseases that lead to elevated intraocular pressure (IOP) above the normal range that leads to glaucomatous optic neuropathy and visual fields defects (BJO 2016).

Aqueous humor production occurs in the posterior chamber by the ciliary processes and flows through the pupil into the anterior chamber. It is a structurally supportive medium, providing nutrients to the lens and the cornea. Aqueous humor exits the eye via two pathways: the trabecular meshwork and the uveoscleral pathway. The trabecular meshwork *(TM)* is considered the *conventional, pressure-dependent pathway,* while the uveoscleral pathway is known as the *unconventional, pressure-independent pathway*.

1.1.2 Pathophysiology of Aqueous Outflow in Primary Open Angle Glaucoma and Uveitic Glaucoma

The pathogenesis of the primary open angle glaucoma (POAG) and uveitic glaucoma (UG) are different. In POAG the pathogenesis is mainly due to the increased outflow resistance

that is caused by the increased extracellular material and modulation of TM cell tone by the action of the cells' actomyosin system in the juxtacanalicular tissue. (Johnson et al., 2002, Lutjen-Drecoll, 1999, Tamm, 2009). The pathogenesis of the uveitic glaucoma (UG) is complex and several factors play a role in its development such as the site, type, duration and frequency of inflammation. Corticosteroids have proven to be effective in reducing inflammation, however, as a side effect elevated IOP can occur along the treatment course and may lead to increase in the IOP in up to one-third of the patients. Secondary ocular hypertension from corticosteroid administration is dependent on the dose, the chemical structure of the corticosteroid compound, the frequency and route of delivery, the duration of treatment, and the patient's susceptibility to steroid response ("steroid responders") (Becker, 1965, Siddique et al., 2013).

1.1.3 Current Concepts of Treatment of Primary Open Angle Glaucoma and Uveitic Glaucoma

The main goal in the treatment of glaucoma is to preserve the visual field and to avoid any further retinal ganglion cells loss (EGSG, 2017). Till now, lowering of the IOP is the only scientifically proven strategy that results in stabilization of the disease and stops its progression (Hitchings and Tan, 2001). There are three known modalities of treatment for both POAG and UG including medical treatment, cyclodestructive and surgical procedures.

Medical treatment is the first line of treatment. Currently, five classes of IOP lowering medication are used: beta-adrenergic antagonists, carbonic anhydrase inhibitors, alpha-agonists, prostaglandine analogues, and cholinergic substance. Recently, a new class of medication, Rho-kinase inhibitors, has been introduced (Inoue and Tanihara, 2017). Topical antiglaucoma medications are considered as first-line treatment in both POAG and UG (EGSG, 2017). In the case of insufficient effect of lowering the IOP under medical treatment, cyclodestractive procedures or surgical treatment can be considered to decrease the IOP and to avoid any further deterioration of the visual field**.**

Cyclodestructive procedures reduce the IOP through decreasing the aqueous production by destructing some of the non-pigmented ciliary epithelium of the ciliary body.

There are two types of cyclodectractive procedures; transscleral diode laser cyclophotocoagulation (TSCPC) and the cyclocryocoagulation. Several studies have demonstrated that TSCPC is efficient in the treatment of POAG and UG glaucoma, however repetitive treatment were needed to control the IOP (Schlote et al., 2000, Voykov et al., 2014).

Surgical treatment in the treatment of primary open glaucoma and uveitic glaucoma involves different forms of surgery and glaucoma drainage devices. Surgical treatment should be considered in case of failure of medical or cyclodestructive treatment in regulating the IOP.

There are different forms of surgical treatment; such as trabeculectomy, non-pentrating glaucoma surgery, ab externo trabeculotomy, microinvasive glaucoma surgery (MIGS) and glaucoma drainage devices (GDD). However, the success rate in terms of controlling the IOP in POAG in all types of surgery are more favorable than in UG (Ceballos et al., 2002b, Dupas et al., 2010, Gil-Carrasco et al., 1998, Iwao et al., 2014, Rachmiel et al., 2008, William et al., 2016).

1.2 Outcomes of primary Transconjunctival 23-Gauge Vitrectomy in the diagnosis and treatment of presumed Endogenous Fungal Endophthalmitis

1.2.1 Definition and Causative Organisms

Endogenous fungal endophthalmitis (EFE) is an urgent sight-threatening intraocular infection associated with potentially devastating ocular complications leading to visual loss. Ocular seeding occurs through hematogenous spread and may involve both the anterior and posterior segments of the eye (Lingappan et al., 2012). EFE usually occurs in severely immunocompromised individuals. Predisposing associated risk factors for EFE include: recent hospitalization, recent abdominal surgery, systemic malignancy, chronic illness, immunosuppression, chemotherapy, and intravenous drug abuse (Feman et al., 2002).

The most common species causing EFE are candida and Aspergillus infection (Essman et al., 1997). EFE due to candida spp. occurs mainly in patients with a history of gastrointestinal surgery and hyperlimentation whereas aspergillosis is seen mainly in individuals who receive immunospressive agents or those who undergo organ transplants or valvular cardiac surgery (Rao and Hidayat, 2001).

1.2.2 Management of Endogenous Fungal Endophthalmitis.

The clinical manifestations of endophthalmitis involve the development of inflammation of the anterior and posterior segment of the eye with a decreased visual acuity. Although both Candida and Aspergillus are associated with inflammatory involvement of the anterior and the posterior segment of the eye, however, candida spp. are associated with primarily vitritis and the development of yellow/white circumscribed lesions (String of pearls/ Paff ball like lesions). However, Aspergillus spp. are associated with deep retinal or chorioretinitis with progressive horizontal enlargement of the lesion. Preretinal or subretinal exudation may be

accompanied by a hypopyn as result of layering of inflammatory cells (Rao and Hidayat, 2001).

The diagnosis of EFE is confirmed through microbiological, laboratory and histolopathological examination of the vitreous humor after obtaining an adequate and undiluted vitreous sample through vitrectomy firstly. (Birnbaum and Gupta, 2016, Celiker and Kazokoglu, 2020, Christmas and Smiddy, 1996, William et al., 2017).

The primary treatment of EFE involves vitrectomy followed directly by intravitreal injection of antifungal agent (Amphotericin B or Variconazole) and by systemic antimycotic treatment depending on the drug sensitivity, pharmacokinetics and efficacy of the drug (Riddell et al., 2011). Intravitreal injections of Amphotericin B at a dose of 5-10mg is the treatment of choice in fungal endophthalmitis with vitreous involvement. The decision of the period of treatment, the frequency of intravitreal antifungal injections and the systemic antifungal treatment depends on several factors such as the causative organism, clinical findings during and after vitrectomy and the associated ocular findings and the general systemic condition of the case.

1.3 Aim of Work

There is little evidence about the long-term safety and efficacy of ab externo trabeculotomy in the treatment of POAG. Even less is known about the role of ab externo trabeculotomy in the treatment of UG. Therefore, our goal was to study the efficacy and safety of ab externo trabeculotomy in POAG and UG and to compare the results of UG with POAG. *"Long-term Results of ab externo Trabeculotomy for Glaucoma Secondary to Chronic Uveitis"was* the first published study on this topic (Voykov et al., 2016). Further, our second study "*Comparison of ab externo Trabeculotomy in Primary Open-Angle Glaucoma and Uveitic Glaucoma: long-term outcomes*" was also the first published study comparing and determining the long term results of ab externo trabeculectomy in POAG and UG (William et al., 2016). Furthermore, our third study "*Outcomes of Primary Transconjunctival 23 Gauge Vitrectomy in the diagnosis and treatment of presumed Endogenous Fungal Endophthalmitis*" was also the first published study regarding this topic in determining the diagnostic a´nd therapeutic value of 23 gauge vitrectomy in the diagnosis of presumed endogenous fungal endophthalmitis.

1.3.1. Long-term Results of ab externo Trabeculotomy for Glaucoma Secondary to Chronic Uveitis (Bogomil Voykov, Spyridon Dimopoulos, Martin Alexander Leitritz, Deshka Doycheva, Antony William.published in Graefes Arch Clin Exp Ophthalmol. 2016).

In this study we investigated the efficacy and the safety of ab externo Trabeculotomy in the management of UG.

1.3.2. Comparison of ab externo Trabeculotomy in Primary Open-Angle Glaucoma and Uveitic Glaucoma: long-term outcomes (Antony William, Martin S Spitzer, Deshka Doycheva, Spyridon Dimopoulos Martin Alexander Leitritz, Bogomil Voykov, published in Clin Ophthalmol. 2016).

In this study we investigated and compared the long-term efficacy and the safety of ab externo trabeculotomy in POAG and UG. We also investigated if inflammation is a risk factor for failure of surgical procedure even it was controlled preoperatively?

1.3.3. Outcomes of Primary Transconjunctival 23 Gauge Vitrectomy in the diagnosis and treatment of presumed Endogenous Fungal Endophthalmitis. (Antony William, Martin S Spitzer, Christoph Deuter, Michael Partsch, Bogomil Voykov, Focke Ziemssen, Karl Ulrich Bartz-Schmidt, Deshka Doycheva. Published in Ocular Immunology and Inflamation 2017).

In this study we evaluated the role of 23 gauge vitrectomy in the diagnosis of presumed endogenous fungal Endophthalmitis and in its treatment, with the consideration of the clinical findings.

2. Results and Discussion

2.1. Long-term results of ab externo trabeculotomy for glaucoma secondary to chronic uveitis

Graefes Arch Clin Exp Ophthalmol (2016) 254:355–360 DOI 10.1007/s00417-015-3204-y

INFLAMMATORY DISORDERS

Long-term results of *ab externo* trabeculotomy for glaucoma secondary to chronic uveitis

Bogomil Voykov[1] · Spyridon Dimopoulos[1] · Martin Alexander Leitritz[1] · Deshka Doycheva[1] · Antony William[1]

Received: 27 August 2015 / Revised: 8 October 2015 / Accepted: 20 October 2015 / Published online: 31 October 2015

Abstract
Purpose To present the long-term results of *ab externo* trabeculotomy in the management of glaucoma secondary to chronic uveitis.
Methods In this retrospective single-centre case series, medical records of patients with glaucoma secondary to chronic uveitis, who underwent *ab externo* trabeculotomy, were evaluated. Two definitions of success were used: intraocular pressure (IOP) 6≤IOP≤21 mmHg (success 1) or 6≤IOP≤21 mmHg and at least 25 % reduction from baseline (success 2). Success was complete when no additional medication was required or qualified when additional medication or cycloablative procedures were required to achieve the specific IOP definition.
Results Twenty-two eyes of 18 patients were included. After 3 years, median IOP decreased from 27 mmHg [range 17–43 mmHg, mean 27.5 mmHg, 95 % confidence interval of the mean (CI) 24.5–30.5 mmHg] to 15 mmHg (range 9–19 mmHg, mean 14.5 mmHg, CI 13–16.1 mmHg). Complete and qualified success 1 was 23 and 45 % after 3 years, respectively. For success 2, the rates were 23 and 32 %, respectively. Hyphema was the most common complication, which resolved completely within 1 month after surgery without further intervention.
Conclusion Trabeculotomy *ab externo* was moderately successful in glaucoma secondary to chronic uveitis after 3 years. No sight-threatening complications were observed during the follow-up period.

Keywords Glaucoma · Glaucoma surgery · Trabeculotomy *ab externo* · Uveitic glaucoma

✉ Bogomil Voykov
bogomil.voykov@med.uni-tuebingen.de

[1] Centre for Ophthalmology, University of Tuebingen, Schleichstr. 12-16, 72076 Tuebingen, Germany

Introduction

Secondary glaucoma is a common and potentially devastating complication in chronic forms of uveitis [1–3]. In uveitis, a breakdown of the blood-ocular barrier leads to influx of proteins as well as inflammatory and immunocompetent cells, cytokines and chemokines, leading to alteration in the aqueous humor composition [4, 5]. Several mechanisms are involved in the pathogenesis of uveitic glaucoma (UG), including obstruction of the trabecular meshwork (TM) by inflammatory cells and proteins, direct TM tissue damage, formation of anterior synechia, steroid-induced alteration of the TM function, and neovascularization [6]. Management of UG is challenging. Considering the limitations of the medical antiglaucoma therapy, surgery is often required to achieve a significant and sustained lowering of the intraocular pressure (IOP) [7]. Different approaches have been proposed in the surgical treatment of refractory UG, such as transscleral diode laser cyclophotocoagulation (TDLC), trabeculectomy with and without antimetabolites, deep sclerectomy and glaucoma drainage devices [8–22]. To our knowledge, the role of trabeculotomy *ab externo* in UG has not yet been described. A major advantage of the procedure is that it improves outflow facility without the need of external fistulation with its bleb-related complications. In the present study, the efficacy and safety of *ab externo* trabeculotomy in the treatment of glaucoma secondary to chronic uveitis were investigated.

Patients and methods

In this study, all medical records of consecutive patients with UG who underwent *ab externo* trabeculotomy between June 2004 and May 2011 in the Centre for Ophthalmology at the University Hospital Tübingen, were reviewed. Glaucoma was defined as the presence of either glaucomatous optic disc damage and/or glaucomatous visual field defect according to the guidelines of the European Glaucoma Society. In all patients, surgery was required because of uncontrolled IOP on maximal tolerated glaucoma medications. If cycloablative procedures had been performed first, trabeculotomy was performed after at least 4 weeks. We documented age at surgery, gender, preoperative and postoperative best corrected visual acuity (BCVA), IOP, number of glaucoma medications and postoperative complications for each patient. Two definitions of success were used: 6 mmHg≤IOP≤21 mmHg (success 1) and 6 mmHg≤IOP≤21 mmHg and at least 25 % reduction from baseline (success 2). If after glaucoma surgery further glaucoma medication was required, the outcome was described as a qualified success, and when the patient was free of glaucoma medication after the surgery, the outcome was considered a complete success. If cycloablative procedures were needed to control the IOP postoperatively, this was considered as qualified success. Failure of the procedure was defined as IOP>21 mmHg at 2 consecutive visits despite reintroduction of glaucoma medications, which required further surgical interventions such as filtering surgery or the implantation of an Ahmed glaucoma valve. In these eyes, the examination before the reoperation was considered as the final follow-up examination for the patient.

This work adhered to the tenets of the Declaration of Helsinki. According to German legislation and the requirements of the local institutional review board (IRB), completely anonymized data was used for this study.

Operative technique

Uveitis was inactive for at least 3 months in all eyes before surgery. All patients received systemic body weight-adjusted oral steroid therapy starting with 1 mg per kg 5 days prior to surgery. Steroids were tapered over 10–12 weeks after surgery.

The surgical procedure followed the technique described previously [23]. Briefly, after conjunctival incision, a 4×4-mm scleral flap at four-fifths thickness was created at the corneal limbus. The Schlemm's canal was identified and deroofed. U-shaped probes were then inserted into both ends of the opened canal and rotated 90 degrees against the trabecular meshwork. Rotation of the probes achieved at least a 120-degree opening of the trabecular meshwork. The scleral flap was then closed watertight. Postoperative treatment comprised topical administration of combined antibiotic corticosteroid medication for 2 weeks. Pilocarpine 1 % was given postoperatively for 4 weeks to avoid formation of peripheral anterior synechia.

Statistical analysis

For statistical analysis, chi-squared tests, Fisher's exact test, and rank-sum tests were performed using JMP software (version 11.0, SAS Institute Inc., Cary, NC, USA). Values of p less than 0.05 were considered to reflect statistically significant differences.

Table 1 Patients' demographics and characteristics

Demographic	
General	
Eyes, n (%)	22
Right	11
Left	11
Female, n (%)	4 (18)
Male, n (%)	18 (82)
Age (years)	
Mean±standard deviation	38±20.7
Range	11–74
Type of uveitis, n (%)	
Herpetic	2 (9)
Granulomatous	2 (9)
Idiopathic anterior	8 (36)
Idiopathic intermedia	4 (18)
Idiopathic posterior	1 (5)
Fuchs uveitis syndrome	5 (23)
Baseline IOP, mmHg	
Median	27
Range	17–43
95 % confidence interval	24.5–30.5
Baseline glaucoma medications	
Median	5
Range	3–5
95 % confidence interval	4.2–5
Previous glaucoma surgery, n (%)	16 (73)
Cyclophotocoagulation, n (%)	11 (69)
Cyclocryocoagulation, n (%)	5 (31)
Lens status, n (%)	
Phakic	8 (36)
Pseudophakic	8 (36)
Aphakic	6 (27)
Systemic immunosuppressive therapy, n (%)	
None	8 (44)
1 medication	4 (22)
2 medications	6 (33)

Results

Demographics

Twenty-two eyes of 18 patients were included in the study. Demographic characteristics of the patients are summarized in Table 1. Systemic immunosuppressive medication included prednisolone, methotrexate, mycophenolate mofetil and mycophenolate sodium, adalimumab, and azathioprine.

Ocular pressure and antiglaucoma medications

Median IOP decreased significantly from 27 mmHg (range 17–43 mmHg, mean 27.5 mmHg, 95%CI 24.5–30.5 mmHg) at baseline to 15.0 mmHg (range 9–19 mmHg, mean 14.5 mmHg, CI 13–16.1 mmHg) after 3 years ($p<0.001$, Fig. 1). Figure 2 shows the median IOP at different time points.

The median number of antiglaucoma medications decreased from 5 (range 3–5, CI 4.2–5.0) at baseline to 1 (range 0–3, CI 0.5–1.7) after 3 years ($p<0.001$). Combination glaucoma medications were enumerated as individual medications. Thirteen patients (13 eyes) received systemic acetazolamide prior to surgery. In these cases, acetazolamide was enumerated as an individual medication. No patient received acetazolamide after surgery.

Success

Table 2 shows the success results. Interestingly, if complete success was achieved, it fulfilled the stricter criteria (success 2) in all cases. Three eyes required one cycloablative procedure within 6 months after surgery. One eye required two cycloablative procedures after 6 and 12 months. IOP was controlled in all of these eyes. They were considered as qualified successes.

Seven eyes were considered as failures. Failure occurred within the first 3 months in six eyes and after 7 months in one eye. In all these eyes, an Ahmed glaucoma valve was implanted. The uveitis remained inactive and the immunosuppressive therapy did not need to be intensified during the study period in all patients.

Complications

Complications are presented in Table 3. We did not observe any sight-threatening complications after 3 years of follow-up.

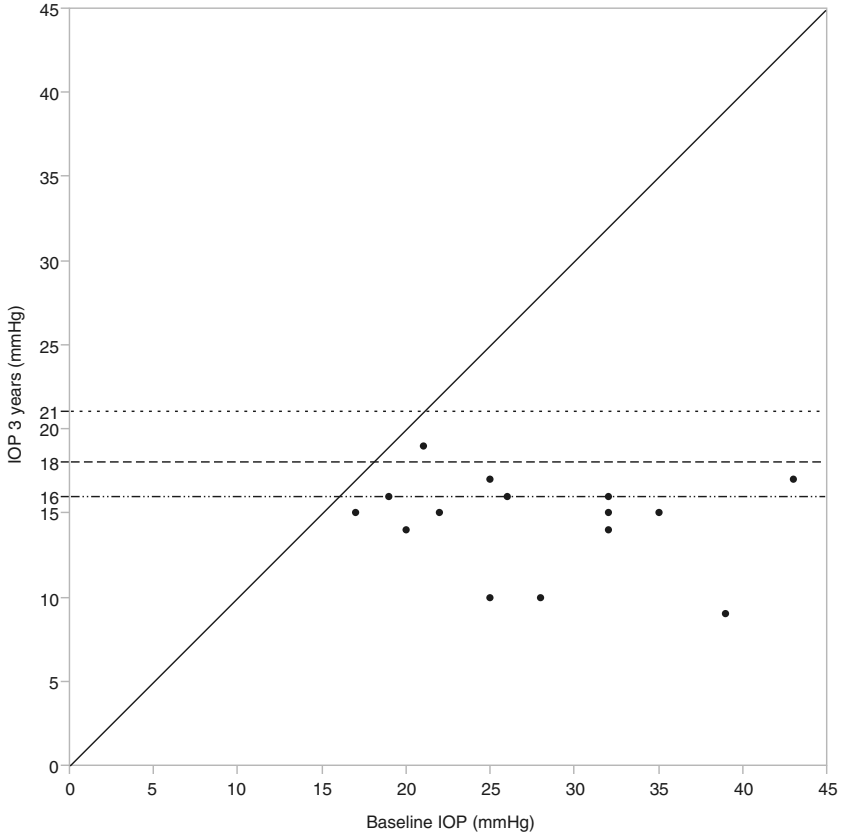

Fig. 1 Scatterplot diagram of IOP at baseline and at 3 years. Eyes with failure were not included

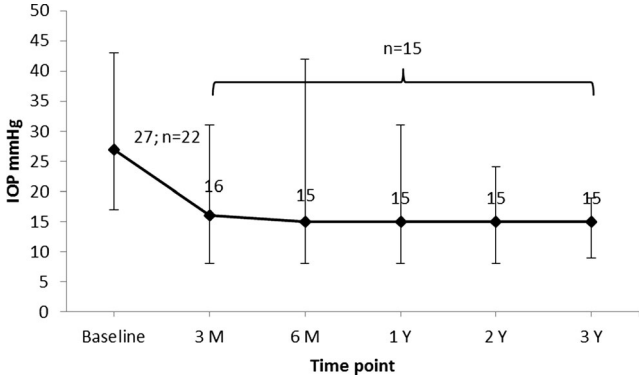

Fig. 2 Median IOP at different time points. The decrease in median IOP was statistically significant for all time points compared to the baseline value. The whiskers represent the range of IOP. One eye with an IOP of 31 mmHg at one visit at the 1-year follow up was treated with a cycloablative procedure, which was able to control IOP during further follow up. Similarly, one eye had an IOP of 24 mmHg at one visit at the 2-year follow up. The IOP could be controlled with additional anti-glaucoma medication. Eyes with failure were not included

Discussion

Glaucoma is a common, potentially sight-threatening complication of chronic uveitis. The reported incidence of UG is between 6.5 and 46 % [1, 2, 24, 25]. It increases in the course of chronic uveitis from 6.5 % after 1 year to 22.3 % after 10 years [25]. Surgical treatment is often required to control IOP in UG. Transscleral diode cyclophotocoagulation, deep sclerectomy, trabeculectomy with and without antimetabolites, and glaucoma drainage devices have been used with variable success.

Schlote et al. reported a success rate of 77.2 % after 1 year for TDLC in the treatment of UG. Similar results were reported for patients with Fuchs uveitis syndrome (FUS) [20, 22]. However, more than one TDLC treatment was necessary to achieve success in the majority of eyes. Also, the efficacy of TDLC seems to depend on the type of uveitis. Heinz et al. reported a failure rate of 68 % for TDLC in a series of 21 eyes with glaucoma secondary to juvenile idiopathic arthritis. Interestingly, in the present study, failure was more common in patients with FUS (four of five eyes) and granulomatous uveitis (two of two eyes). However, while different treatment approaches might produce different results depending on the type of uveitis, the small number of eyes in the various uveitis subgroups in our study does not allow for further statistical analysis.

Non-penetrating deep sclerectomy (NPDS) is another option in the treatment of UG. It has been introduced to avoid bleb-related postoperative complications of filtration surgery. Dupas et al. reported in a prospective comparative study similar success rates for NPDS and trabeculectomy in UG after 1 year. However, deep sclerectomy patients required significantly more postoperative adjustments in the form of goniopuncture or needling to achieve success compared to the trabeculectomy group [12]. Similar results were reported by others as well [8, 26]. However, there are no sufficient long-term data of deep sclerectomy in the treatment of UG. One study reported a success rate of 18.9 % after 30 months, which is lower than the success rates for trabeculotomy *ab externo* in the current study [27].

Trabeculectomy with or without antimetabolites has also been studied in patients with UG. Promising results with success rates of 90 and 79 % after 1 and 2 years, respectively, have been reported for trabeculectomy with mitomycin C [9, 18]. Stavrou et al. reported a qualified success rate of 78 % (IOP≤21 mmHg) in a case series of 32 eyes with UG after 5 years [21]. However, patients with UG more often develop a cystic bleb and require significantly more postoperative procedures compared to patients with primary open-angle glaucoma [18]. Also, the incidence of potentially sight-threatening complications like persistent postoperative hypotony and hypotony maculopathy is considerably higher in uveitic patients [16].

Glaucoma drainage devices (GDDs) are an alternative approach in the treatment of uncontrolled UG. Ceballos et al. reported a success rate of 91.7 % with the Baerveldt glaucoma drainage device after 2 years [10]. Very promising results have been reported for the Molteno implant with a success rate of 75 % after 10 years [17]. Papadaki et al. showed good results

Table 2 Success rates

	Success rate n (%)		
	1 year *n*=22	2 years *n*=22	3 years *n*=22
Complete success			
≤21 mmHg	4 (18)	3 (14)	5 (23)
≤21 mmHg and ≥25 % IOP reduction from baseline	4 (18)	3 (14)	5 (23)
Qualified success			
≤21 mmHg	11 (50)	12 (55)	10 (45)
≤21 mmHg and ≥25 % IOP reduction from baseline	8 (36)	9 (41)	7 (32)
Failure	7 (32)	7 (32)	7 (32)

Table 3 Postoperative complications

Complication	N (%)	Management
Hyphema	7 (32)	Self-limited
Hypotony	1 (5)	Injection of sodium hyaluronate in the anterior chamber
External filtration	1 (5)	Observation
Vitreous prolapse in anterior chamber	1 (5)	Anterior vitrectomy

for the Ahmed glaucoma valve in UG with success rates of 77 and 50 % after 1 and 4 years, respectively [19]. However, high success rates of GDD go along with possible serious postoperative complications like postoperative hypotony, hypotony maculopathy, choroidal effusion and corneal endothelium dysfunction [10, 17, 28]. Also, the postoperative Tenon cyst formation is considered a rate-limiting step in the success of glaucoma implant surgery [29–32]. The reported incidence of the encapsulated bleb formation ranges between 23 and 42.8 % [30, 32]. Gil-Carrasco et al. reported that encapsulated blebs tend to occur in young patients (range 22–44 years), which corresponds to the typical age of patients with UG [30].

In a recent study, Anton et al. showed that trabeculectomy *ab interno* with the Trabectome® can be used in patients with UG. The short-term results showed an IOP reduction of approximately 40 % and a medication reduction from 2 to 0.67. These results are similar to the efficacy of the current study. However, comparison is difficult because of heterogenic study populations and somewhat different success criteria [33].

Compared to the above surgical techniques, trabeculotomy *ab externo* was moderately successful as a stand-alone procedure in our case series. However, the use of glaucoma medications or cycloablative procedures improved the success rates considerably. The majority of treatment failures in the current study occurred within the first 3 months after surgery. Most of these patients were under the age of 30 years (4/7, range 15–43 years), and had either FUS (four eyes) or granulomatous uveitis (two eyes). A possible explanation for early failure in these cases might be secondary structural abnormalities in the Schlemm's canal and the collecting channels associated with longstanding uveitis. Younger age is also a possible reason for failure, considering that an age below 30 years is a well-known risk factor for failure in glaucoma surgery [34, 35]. It should also be considered that FUS differs from other uveitic forms in its unilaterality, absence of acute symptoms and the mild anterior chamber inflammation which is irresponsive to steroids [36]. It is, therefore, possible that the specific features of FUS lead to different results of glaucoma treatment in these patients compared to glaucoma secondary to other uveitis entities.

The high safety profile of trabeculotomy *ab externo* is a major advantage of the procedure compared to filtration surgery. The most common complication in our study was the postoperative hyphema, which resolved completely within 1 month without any further intervention in all cases. Actually, one could argue if hyphema is a complication of the procedure at all since it could be interpreted as a sign of patency of the Schlemm's canal and the collector channels. Postoperative hypotony is a feared complication of filtration surgery. In the current study, one eye (5 %) developed early postoperative hypotony which was controlled and resolved after a single injection of sodium hyaluronate in the anterior chamber.

A drawback of the current study is its retrospective design. The decision for a surgical intervention was purely at the individual surgeon's discretion. Additionally, a variety of UG types and a broad spectrum of disease severity were treated. This precluded determination of prognostic indicators for success and failure. Also, both eyes were treated in four patients, which can be a confounder of results. Further, prospective studies are warranted to better evaluate the role of the procedure in the treatment paradigm for UG.

In conclusion, this study demonstrated a moderate success rate and a high safety profile of *ab externo* trabeculotomy in patients with UG after 3 years. A major advantage of *ab externo* trabeculotomy in the treatment of UG is that it improves outflow facility and restores the physiological pathway of the aqueous humor outflow without the need of external fistulation with its bleb-related complications. Success rates can be improved using glaucoma medication or cycloablative procedures.

Compliance of ethical standards

Funding No funding was received for this research.

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

Informed consent Informed consent was obtained from all individual participants included in the study.

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Comparison of ab externo trabeculotomy in primary open-angle glaucoma and uveitic glaucoma: long-term outcomes

a ntony William
Martin s spitzer
Deshka Doycheva
spyridon Dimopoulos
Martin a lexander l eitritz
Bogomil Voykov

Centre for Ophthalmology, University h ospital Tübingen, Tübingen, g ermany

Background: The aim of this study was to compare the long-term outcomes of ab externo trabeculotomy in primary open-angle glaucoma (POAG) and uveitic glaucoma (UG).

Design: This was a retrospective single-center case series study.

Participants: Twenty eyes of 17 patients with POAG and 22 eyes of 18 patients with UG were included in this study.

Patients and methods: The medical records of all consecutive patients with POAG and UG who underwent ab externo trabeculotomy since 2004 were reviewed.

Main outcome measure: The main outcome measure was change in median intraocular pressure (IOP). Success was defined as IOP ≤21 mmHg (success 1) and IOP ≤21 mmHg and at least 25% reduction from baseline (success 2).

Results: In the POAG group, the median IOP decreased significantly from 22 mmHg (95% CI 21–25 mmHg; n=20) at baseline to 14 mmHg (95% CI 12–16; n=13) after 4 years, $P<0.001$. In the UG group, the median IOP decreased significantly from 27 mmHg (95% CI 24.5–30.5 mmHg; n=22) at baseline to 12 mmHg (95% CI 9–15 mmHg; n=15) after 4 years, $P<0.001$. Seven eyes in the UG group failed within the first year after surgery compared to none in the POAG group. Of these, four eyes had Fuchs' uveitis syndrome and two had granulomatous uveitis. No sight-threatening complications occurred in both POAG and UG groups.

Conclusion: Ab externo trabeculotomy effectively reduced IOP in both UG and POAG groups. However, the success rates in the UG group were significantly lower due to the high failure rate in patients with Fuchs' uveitis syndrome and granulomatous uveitis. The procedure demonstrated a high safety profile in both UG and POAG patients.

Keywords: ab externo trabeculotomy, primary open-angle glaucoma, uveitic glaucoma

Introduction

Increased outflow resistance plays a major role in the elevation of intraocular pressure (IOP) in glaucoma.[1] In primary open-angle glaucoma (POAG), increased outflow resistance is caused by increased extracellular material and modulation of trabecular meshwork (TM) cell tone by the action of the cells' actomyosin system in the juxtacanalicular tissue.[2–4] In contrast, the elevation of IOP in uveitic glaucoma (UG) is caused by breakdown of the blood–ocular barrier followed by influx of proteins, immunocompetent cells, cytokines, and chemokines, which leads to obstruction of the TM, direct tissue damage, and alteration in the function of the TM.[5–7] Recently, we have reported that ab externo trabeculotomy was moderately successful in UG after 3 years.[8] However, the different mechanisms of IOP elevation in POAG and UG raise several questions. First, is there a difference in the efficacy of surgical procedures in POAG

Correspondence: Bogomil Voykov
Centre for Ophthalmology, University h ospital Tübingen, schleichstraße 12-16, 72076 Tübingen, g ermany
Tel +49 7071 298 3721
Fax +49 7071 29 5455
email bogomil.voykov@med.uni-tuebingen.de

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http://dx.doi.org/10.2147/OPTH.S102414

and UG? Second, if so, should we follow different surgical strategies in POAG and UG? Third, is chronic inflammation a risk factor for failure even if it was controlled preoperatively? There is only a limited number of studies that have compared a surgical procedure in both POAG and UG.[9–12] None of them has reported on trabeculotomy. The purpose of our study was to compare the long-term results of ab externo trabeculotomy in patients with POAG and UG.

Patients and methods

We reviewed the medical records of all consecutive patients with POAG and UG who underwent ab externo trabeculotomy at the Centre for Ophthalmology at the University Hospital Tübingen since 2004. In both POAG and UG groups, the indication for surgery was insufficiently controlled IOP despite maximal tolerated medical treatment. Preoperatively, a target range IOP in the mid- to high-teens was considered sufficient based on age, glaucoma stage, visual field impairment, and tolerability for glaucoma medications in both POAG and UG groups. Ab externo trabeculotomy was performed in patients who were considered to have a high risk of bleb failure or bleb-related complications due to chronic conjunctival inflammation or young age. We documented age at surgery, sex, best-corrected visual acuity, IOP, number of glaucoma medications, and postoperative complications for each patient. Success was defined as IOP ≤21 mmHg (success 1) and IOP ≤21 mmHg and at least 25% reduction from baseline (success 2). The success was complete if after glaucoma surgery no further glaucoma medication was required and qualified if glaucoma medication or a cycloablative procedure was necessary to control IOP. If the IOP was >21 mmHg at two consecutive visits despite reintroduction of glaucoma medications and further surgical treatment such as filtering surgery or the implantation of Ahmed glaucoma valve necessary to control IOP, then these eyes were considered as failure. The examination before the reoperation was then the final follow-up, and IOP data were displaced forward. A minimum follow-up of 3 years was required for inclusion.

This work adhered to the tenets of the Declaration of Helsinki. According to the requirements of the institutional review board of Eberhard Karls University of Tuebingen, as completely anonymized data were used for this study institutional review board approval was not required. Patients signed an informed consent prior to surgery, but the use of anonymized retrospective data does not require additional consent of the patient according to the requirements of the IRB.

Operative technique

The surgical procedure has been described previously.[13] Briefly, after conjunctival incision, a 4 mm ×4 mm scleral flap was created at the corneal limbus. The Schlemm's canal was identified and deroofed. U-shaped probes were then inserted into both ends of the opened canal and rotated 90° against the TM. Rotation of the probes achieved at least 120° opening of the TM. The scleral flap was then closed watertight. Postoperative treatment comprised topical administration of combined antibiotic and steroid medication for 2 weeks. Pilocarpine 1% was given postoperatively for 4 weeks to avoid formation of peripheral anterior synechia. In the UG group, uveitis was inactive in all eyes before surgery for at least 3 months and all patients preoperatively received systemic body weight-adjusted oral steroid therapy (1 mg/kg) starting 5 days prior to surgery. Steroids were then tapered over 10–12 weeks after surgery.

statistical analysis

For statistical analysis, chi-squared test, one-way analysis of variance, and Fisher's exact test were performed using JMP software (version 11.0; SAS Institute Inc., Cary, NC, USA). *P*-values <0.05 were considered to reflect significant differences.

Results

Twenty eyes of 17 patients with POAG and 22 eyes of 18 patients with UG were included in this study. The demographic characteristics of the patients are summarized in Table 1. Uveitic etiology included idiopathic anterior uveitis (six eyes), idiopathic intermediate uveitis (four eyes), posterior uveitis (two eyes), Fuchs' uveitis syndrome (FUS; five eyes), herpetic uveitis (one eye), Posner–Schlossman syndrome (two eyes), and granulomatous uveitis (two eyes).

Table 1 Patients' demographics

Demographic	POAG	UG	*P*-value
eyes, n	20	22	0.6
sex			
Female, n (%)	17 (85)	4 (18)	
Male, n (%)	3 (15)	18 (82)	
a ge (years)			
Mean ± sD	62.5±9.7	38±20.7	**<0.001**
r ange	40–76	11–74	
Baseline iOP (mmh g)			
Median	22	27	**0.02**
95% Ci	21.4–25.2	24.5–30.5	
Baseline medications			
Median	4	5	**<0.001**
95% Ci	3.2–4.0	4.2–5	
Baseline BCVa (logMar)			
Median	0.2	0.5	**<0.001**
95% Ci	0.05–0.5	0.4–0.8	

Note: Statistically significant changes are shown in bold in the *P*-value column.
Abbreviations: POag , primary open-angle glaucoma; Ug , uveitic glaucoma; iOP, intraocular pressure; BCVa , best-corrected visual acuity; logMar , logarithm of the minimum angle of resolution; CI, confidence interval.

Uveitis was inactive for at least 3 months in all the patients preoperatively.

In four eyes with anterior uveitis, uveitis was controlled with methotrexate and in two eyes with adalimumab and mycophenolate mofetil. In the eyes with intermediate uveitis, inflammation was controlled with mycophenolate sodium in two eyes, mycophenolate mofetil in one eye, and low-dose systemic steroid in another eye. Patients with posterior uveitis received low-dose systemic steroids. All five patients with FUS received only nonsteroid anti-inflammatory eyedrops. Herpetic uveitis was controlled with systemic acyclovir. In the two eyes with Posner–Schlossman syndrome, uveitis was controlled with valganciclovir. Granulomatous uveitis was controlled with methotrexate.

Postoperative reactivation of the uveitis was not seen in any patient during the follow-up.

iOP and glaucoma medications

The median IOP in the POAG group decreased significantly from 22 mmHg (95% CI 21–25 mmHg; n=20) at baseline to 14 mmHg (95% CI 12–15 mmHg; n=20, $P<0.001$) after 3 years and remained 14 mmHg (95% CI 12–16 mmHg; n=13, $P<0.001$) after 4 years. Similarly, the median IOP in the UG group decreased from 27 mmHg (95% CI 24.5–30.5 mmHg; n=22) at baseline to 15 mmHg (95% CI 13–16 mmHg; n=22, $P<0.001$) after 3 years and to 12 mmHg (95% CI 9–15 mmHg; n=15, $P<0.001$) after 4 years. The median IOP was statistically significantly different between the UG group and POAG group at baseline ($P=0.03$) on the first postoperative day ($P<0.01$) and at the 1-year follow-up ($P=0.01$). Figure 1 shows the median IOP at different time points in both groups.

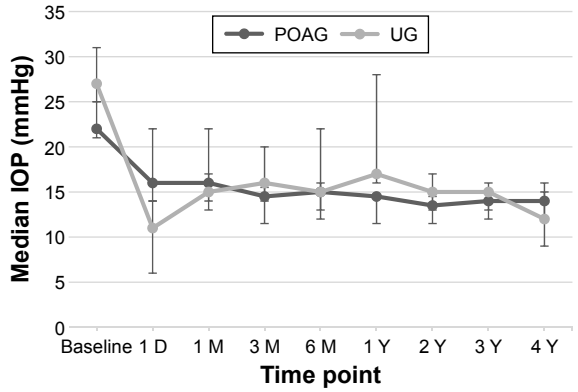

Figure 1 Median iOP at different time points.
Notes: Decrease in median IOP was statistically significant for all time points compared to baseline value in both groups. The whiskers represent the 95% Ci. The median IOP was statistically significantly different between the UG group and POag group at baseline ($P=0.03$), on the first postoperative day ($P<0.01$), and at the 1-year follow-up ($P=0.01$).
Abbreviations: iOP, intraocular pressure; Ug , uveitic glaucoma; POag , primary open-angle glaucoma; D, day; M, month; Y, year.

In the POAG group, the median number of glaucoma medications decreased significantly from 4 (95% CI 3.2–4; n=20) at baseline to 2 (95% CI 1.4–2.6; n=20, $P<0.001$) after 3 years and remained 2 (95% CI 1.0–2.4; n=13, $P<0.001$) after 4 years. The median number of glaucoma medications in the UG group decreased significantly from 5 (95% CI 4.2–5.0; n=22) at baseline to 1 (95% CI 0.5–1.7; n=22, $P<0.001$) after 3 years and remained 1 (95% CI 0.3–2.3; n=15, $P<0.001$) after 4 years. The median number of glaucoma medications showed no statistically significant differences between both groups at the different time points.

Cycloablative treatment was performed once within the first 6 months in three eyes and repeated in a single eye within the first year postoperatively in the UG group. Only one eye received cycloablative treatment 1 week postoperatively in the POAG group.

Seven eyes failed in the UG group compared to none in the POAG group. Failure in the UG group occurred within the first 3 months in six eyes and after 7 months in one eye. In all these eyes, Ahmed glaucoma valve was needed to control the IOP. Success results are shown in Table 2.

Complications

Hyphema was the most common postoperative complication in both groups. It resolved completely within 4 weeks postoperatively without any interventions. We did not observe any sight-threatening complications during the 4 years of follow-up. Complications are presented in Table 3.

Discussion

There is only a limited number of studies that have compared the outcomes of a surgical procedure between patients with POAG and patients with UG.[9–12] However, since the pathomechanisms of increased IOP differ between UG and POAG, it is important to know if a surgical procedure can achieve similar results in both conditions.

Ab externo trabeculotomy is usually a first-choice surgical treatment in congenital and juvenile glaucoma. However, a study by Tanihara et al[13] has demonstrated that the procedure is an effective treatment for POAG, as well, even in adults. In this study, the success rate of the procedure was 58% after 5 years. The authors also reported that the success was significantly higher in patients with lower preoperative IOP (<30 mmHg). In these patients, the final success probability after 5 years was 66.9%. On the other hand, age did not significantly influence the success of surgery. Although direct comparison is difficult because of different study populations and success criteria, our results in the POAG group are similar (qualified success). However, the success

Table 2 success rates at different time points

Success	1 year		2 years		3 years		4 years	
	POAG (n=20)	UG (n=22)	POAG (n=20)	UG (n=22)	POAG (n=20)	UG (n=22)	POAG (n=13)	UG (n=15)
Complete success								
≤21 mmh g, n (%)	4 (20)	4 (18)	5 (25)	3 (14)	4 (20)	5 (23)	2 (15)	2 (13)
P-value	1.0		0.44		1.0		1.0	
≤21 mmh g and ≥25% iOP reduction from baseline, n (%)	4 (20)	4 (18)	2 (10)	3 (14)	2 (10)	5 (23)	1 (8)	3 (20)
P-value	1.0		1.0		0.44		0.6	
Qualified success								
≤21 mmh g, n (%)	16 (80)	11 (50)	15 (75)	12 (55)	16 (80)	10 (45)	11 (85)	6 (40)
P-value	**0.02**		0.12		**0.03**		**0.03**	
≤21 mmh g and ≥25% iOP reduction from baseline, n (%)	12 (60)	8 (36)	15 (75)	9 (41)	14 (70)	7 (32)	8 (62)	4 (27)
P-value	0.2		**0.03**		**0.03**		0.12	
Failure								
n (%)	n one	7 (32)	n one	7 (32)	n one	7 (32)	n one	7 (47)

Notes: Success was defined as IOP ≤21 mmh g (success 1) and iOP ≤21 mmh g and at least 25% reduction from baseline (success 2). Complete success was achieved when no further glaucoma medication was required after glaucoma surgery. If glaucoma medication or a cycloablative procedure was necessary to control IOP, then success was qualified. if the iOP was >21 mmHg at two consecutive visits despite reintroduction of glaucoma medications and further surgical treatment such as filtering surgery or the implantation of Ahmed glaucoma valve was necessary to control IOP, then these eyes were considered as failure. Statistically significant changes are shown in bold.
Abbreviations: POag , primary open-angle glaucoma; Ug , uveitic glaucoma; iOP, intraocular pressure.

rate in the UG group was significantly lower. The different pathomechanisms of IOP elevation in POAG and UG groups are a possible explanation for this difference. This is demonstrated by the fact that the majority of failures in the UG group occurred in patients with FUS (four eyes) and granulomatous uveitis (two eyes). Typically, the inflammation is of low grade, but more difficult to control and irresponsive to steroids in patients with FUS compared to other uveitis forms.[14] A recent study described the intraoperative observation of a perilimbal and/or episcleral vessel fluid wave seen during trabectome surgery and termed it episcleral venous fluid wave.[15] The episcleral venous fluid wave correlated well with the outcomes of trabectome surgery in patients with various types of open-angle glaucomas. The authors demonstrated that if a wave was not seen or barely present, there was likely obstruction in the collector channel opening or intrascleral channels preventing flow to the episcleral veins.[16] Unfortunately, the authors did not report on different subtypes of glaucomas. However, it is possible that the persistent low-grade inflammation in FUS leads to obstruction in the collector channel opening or the intrascleral channels, which could explain the high failure rate in FUS eyes in our study. Similarly, Hamanaka et al[17] showed that eyes with granulomatous uveitis are associated with infiltration of lymphocytes, monocytes, and macrophages around the inner wall, posterior outer wall of the Schlemm's canal, and the collector channels, leading to narrowing and occlusion of the Schlemm's canal. Interestingly, a recent histological study suggested that the enhancement of conventional routes may not, however, be important for the IOP-lowering effect of trabeculotomy. The authors hypothesized that four different types of histological changes in the TM may reduce enhancement of the newly created unconventional routes by trabeculotomy.[18] In this case, it is possible that in UG, the breakdown of the blood–ocular barrier followed by influx of proteins, immunocompetent cells, cytokines, and chemokines leads more often to the aforementioned histological changes in the TM compared to POAG. Again, active inflammation in FUS probably accelerates these changes even more. Consequently, pre- and postoperative care is crucial for improving the success rate of trabeculotomy in uveitis patients. In our experience, surgery should be performed in eyes that have been calm for at least 3 months prior to surgery. Preoperatively, we treat the patients with systemic body weight-adjusted steroid therapy, which is started 5 days before surgery (1 mg/kg). We then taper the steroids slowly during a period of 10–12 weeks postoperatively to avoid recurrence of inflammation.

Table 3 Postoperative complications

Complication	POAG, n (%)	UG, n (%)
h yphema	11 (55)	7 (32)
h ypotony	1 (5)	1 (5)
Filtering bleb	1 (5)	1 (5)
Vitreous prolapse	0	1 (5)

Abbreviations: POag , primary open-angle glaucoma; Ug , uveitic glaucoma.

Notably, the outcomes of filtration surgery are also worse in UG compared to POAG. Kaburaki et al[10] reported similar success rates after 5 years of follow-up in a retrospective study in patients with inactive uveitis in comparison to

patients with POAG. However, postoperative complications such as long-standing ocular hypotony, hypotonic maculopathy, and cataract formation were more common in the UG group. In contrast, Noble et al[11] reported that results of trabeculectomy with MMC were significantly worse in patients with UG compared to patients with POAG. UG patients required also more postoperative procedures and developed more often cystic blebs. Additionally, a study by Iwao et al[9] demonstrated that trabeculectomy with MMC was less effective in maintaining the IOP reduction in UG patients than in POAG patients. One study compared the results of Ahmed glaucoma valve implantation between patients with UG and patients with POAG. The success rates were similar in both groups after 30 months. However, failure in terms of tube removal occurred significantly more often in patients with UG.[12]

The role of the higher preoperative IOP as a prognostic factor associated with poor prognosis after ab externo trabeculotomy remains a matter of debate. Tanihara et al[13] reported that higher preoperative IOP was a negative prognostic factor in POAG. In contrast, Iwao et al[19] demonstrated that higher preoperative IOP was not a prognostic factor for surgical failure of trabeculotomy in the treatment of steroid-induced glaucoma. Likewise, in our study, the preoperative IOP in the eyes with failure was not statistically significant different compared to the eyes without failure. However, due to the small number of eyes, we could not determine the role of preoperative IOP level conclusively.

The influence of age on the outcomes of ab externo trabeculotomy has been controversially discussed in the literature. Some authors have reported better results in patients with congenital and juvenile glaucoma compared to those with adult-onset glaucoma.[20,21] However, Tanihara et al[13] showed that there was no significant difference in the outcomes between a younger (<60 years) and an elderly (≥60 years) group having eyes with POAG. In our study, patients with UG were much younger than those with POAG. However, in our opinion, the worse results in the aforementioned studies by Schwartz and Anderson, Lunt and Livingston, and ours for the non-POAG eyes compared to the eyes with POAG are caused by structural changes of the outflow system that differ among various glaucoma types and are only indirectly correlated to age.

There was a statistically significant difference in sex between both groups in our study. However, the failure rates were not statistically significantly different in both sexes, and sex was not a prognostic factor for success or failure. The strength of this analysis is limited by the small number of patients. Surprisingly, the influence of sex on the outcomes of glaucoma surgery has not yet been specifically addressed in the published literature. This makes it impossible for us to compare our results to others.

A major advantage of ab externo trabeculotomy is that it avoids the potentially sight-threatening complications of filtration surgery. In our study, complication rates were similar and low in both UG and POAG groups, although postoperative hyphema was slightly more common in the POAG group. Interestingly, Grieshaber et al[22] demonstrated that postoperative hyphema was a positive prognostic indicator in uneventful canaloplasty in regard to IOP reduction, possibly representing a restored and patent physiologic aqueous outflow system.

The limitations of our study include its retrospective design as well as the variety of UG types treated. Notably, the outcomes in eyes with FUS and granulomatous uveitis were worse compared to both the remaining eyes in the UG group and the POAG group. However, the small number of eyes precluded from further analyses of these differences.

Conclusion

Our results showed that ab externo trabeculotomy effectively reduced IOP in both UG and POAG groups. However, the long-term success rates in the UG group were significantly lower due to the high failure rate in patients with FUS and granulomatous uveitis. The procedure demonstrated a high safety profile in both UG and POAG patients.

Disclosure

The authors report no conflicts of interest in this work.

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Ocular Immunology & Inflammation, 2016; 00(00): 1–7

ISSN: 0927-3948 print / 1744-5078 online
DOI: 10.3109/09273948.2015.1115080

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ORIGINAL ARTICLE

Outcomes of Primary Transconjunctival 23-Gauge Vitrectomy in the Diagnosis and Treatment of Presumed Endogenous Fungal Endophthalmitis

Antony William[1], Martin S. Spitzer[1], Christoph Deuter[1], Gunnar Blumenstock[2], Michael Partsch[1], Bogomil Voykov[1], Focke Ziemssen[1], Karl Ulrich Bartz-Schmidt[1], and Deshka Doycheva[1]

[1]*Centre for Ophthalmology, University of Tuebingen, Tuebingen, Germany and* [2]*Department of Clinical Epidemiology and Applied Biometry, University of Tuebingen, Tuebingen, Germany*

ABSTRACT

Purpose: To report the outcomes of primary transconjunctival 23-gauge (23-G) vitrectomy in the diagnosis and treatment of presumed endogenous fungal endophthalmitis (EFE).

Methods: Retrospective analysis of patients with EFE who underwent diagnostic transconjunctival 23-G vitrectomy at a tertiary referral center.

Results: Nineteen eyes of 15 patients with EFE were included in the study. Four patients had bilateral and 11 patients unilateral disease. Sixteen eyes of 15 patients underwent 23-G vitrectomy to confirm the diagnosis using vitreous culture, polymerase chain reaction, and histopathologic examinations. All affected eyes were treated with intravitreal amphotericin B 5 µg/0.1 mL. Fourteen patients received additional systemic antifungal therapy. Diagnostic 23-G vitrectomy confirmed the diagnosis of EFE in 75% of the eyes (12/16). *Candida* was found to be a causative agent in 62.5% and *Aspergillus* in 12.5% of the eyes. Retinal detachment was the most common complication (42% of eyes).

Conclusions: EFE can be easily confirmed using primary 23-G vitrectomy.

Keywords: Amphotericin B, diagnosis, endogenous fungal endophthalmitis, transconjunctival 23-gauge vitrectomy, treatment

Endogenous fungal endophthalmitis (EFE) is an urgent sight-threatening intraocular infection associated with potentially devastating ocular complications leading to visual loss.[1,2] Ocular seeding occurs through hematogenous spread of causative agents in patients with fungemia.[3] Usually, severely immunocompromised individuals are affected. Predisposing associated risk factors for EFE include: recent hospitalization; recent abdominal surgery; systemic malignancy; chronic illness; immunosuppression; chemotherapy; and intravenous drug abuse.[1,2,4–6] *Candida albicans* has been reported to be the most common causative organism for EFE.[2,7]

The usefulness of pars plana vitrectomy in the diagnosis of fungal endophthalmitis has been shown in several studies,[7–10] however, to date, the diagnostic and treatment outcomes of primary transconjunctival sutureless 23-G vitrectomy in patients with presumed EFE have not been investigated. The 23-G vitrectomy technique, introduced by Eckardt in 2005, has demonstrated advantages over conventional 20-G vitrectomy, such as decreased operation time due to sutureless self-sealing, increased patient comfort, less postoperative inflammation, faster conjunctival and scleral surgical wound healing, and faster visual recovery due to the reduced onset of corneal astigmatism.[11–13] In a recent study analyzing the fluidics of different vitreous probe gauge sizes, it has been shown that the 23-G probe has a smaller sphere of influence on surrounding tissues than the 20-G probe, and would produce better safety and efficiency.[14] It

Received 14 July 2015; revised 20 October 2015; accepted 27 October 2015; published online 28 January 2016

Correspondence: Deshka Doycheva, Centre for Ophthalmology, University of Tuebingen, Schleichstr. 12–16, Tuebingen 72076, Germany. E-mail: deshka.doycheva@med.uni-tuebingen.de

seems that the 23-G vitrectomy could be used to target specific tissues while minimizing the effects on adjacent structures. However, in the literature no data exist showing if this technique is suitable as a diagnostic procedure in patients with fungal endophthalmitis. We do not know the quality of vitreous samples and the rate of successful identification of causative agents after 23-G vitrectomy in patients with presumed EFE. Therefore, in the present study, we investigated the role of primary transconjunctival sutureless 23-G vitrectomy in the diagnosis and management of EFE.

PATIENTS AND METHODS

Patients

In this study, the medical records of all consecutive patients who underwent primary diagnostic transconjunctival 23-g vitrectomy at our clinic for strongly suspected endogenous fungal endophthalmitis between December 2006 and December 2014, were reviewed. Strong suspicion of endogenous fungal endophthalmitis was defined as a presence of typical ocular findings (severe anterior chamber cell reaction with/without hypopyon, severe vitreous cell reaction with intravitreal puff ball-like lesions, and/or fluffy creamy white chorioretinal infiltrates) and associated predisposing risk factors. To eliminate cases of exogenous endophthalmitis, patients with a history of recent ocular surgery, ocular trauma, or extraocular infection were excluded from the study. Best-corrected visual acuity (BCVA) was measured at the first visit (baseline), 1 week after vitrectomy, and at the last follow-up visit in decimals, and converted to a logarithm of minimum angle of resolution (logMAR) for statistical analysis. In all patients, an extensive uveitis work-up was performed. Anterior chamber (AC) cells and vitreous cells were graded according to the recommendations of the International Uveitis Study Group and the Standardization of Uveitis Nomenclature (SUN) Working Group.[15,16] Data collected from patients' medical records included: age; sex; medical history; predisposing risk factors; patient complaints and their duration; laterality; BCVA; ocular findings; ocular complications; diagnostic work-up; date and type of vitrectomy; microbiologic and histopathologic findings; intravitreal and systemic treatment; duration of follow-up.

This work adhered to the tenets of the Declaration of Helsinki. In accordance with German legislation and the requirements of the local institutional review board, completely anonymized data was used for this study.

Operative Technique

To determine the causative organisms and to exclude other differential diagnoses such as bacterial endophthalmitis, viral retinitis and intraocular B-cell lymphoma, primary diagnostic transconjunctival sutureless 23-G vitrectomy for vitreous culture, polymerase chain reaction (PCR) and histopathological examinations were performed in all patients. In patients with bilateral affection, the more severe affected eye was operated on, with an exception of a single patient, on whom both eyes were operated. The transconjunctival sutureless 23-G vitrectomy was performed according to the technique described previously by Claus Eckardt.[11] Three self-sealing 23-G pars plana tunnel incisions were made in the inferotemporal, superotemporal, and superonasal quadrants. The vitreous cutter was used during the first few minutes of vitrectomy to collect undiluted vitreous into a 10 mL syringe directly connected to the suction pipe of the vitreous cutter, using manual suction, and a cutting rate of ~1.500 cuts/min. During vitreous sampling, the infusion line was connected to sterile air at a pressure of 40 mmHg in order to ensure that undiluted vitreous was collected. After an adequate volume of vitreous (of at least 1.5 mL) was obtained, the infusion fluid was turned on and vitrectomy continued. All eyes underwent central and peripheral vitrectomy, however thorough cleaning of the vitreous base was not performed due to an increased risk of iatrogenic breaks in eyes with endophthalmitis. In one pseudophakic eye, the intraocular lens was removed. In two eyes with retinal detachment detected during vitrectomy, silicon oil tamponade was done. All other eyes were filled with balanced salt solution. At the end of surgery, all eyes received an intravitreal injection of amphotericin B 5 µg/0.1 mL. Vitreous specimens were submitted for microbiologic, virologic and histopathologic examinations.

In six eyes that developed retinal detachment during follow-up, standard three-port 20-G pars plana vitrectomy with silicon oil filling was performed as a secondary operation. In six eyes with cataract, phacoemulsification with intraocular lens implantation was performed; in two eyes the phacoemulsification was done simultaneously during the 20-G vitrectomy as a one-step procedure and in another four eyes the cataract surgery was performed as a separate procedure.

Statistical Analysis

For statistical analysis, the Wilcoxon signed-rank test, Mann–Whitney *U*-test and multiple logistic regression analysis were performed using JMP software (version 11.0, SAS Institute Inc., Cary, NC, USA). Values of $p<0.05$ were considered to reflect significant differences.

RESULTS

Demographic Data

In total, 19 eyes of 15 patients (10 male and 5 female) were included in the study. Four patients had bilateral

TABLE 1. Demographic data.

Demographic data	Number of patients/eyes or period of time	
	n/*N*	(%)
Total number of patients	15	
Gender		
Female	5/15	33
Male	10/15	67
Laterality		
Unilateral	11/15	73
Bilateral	4/15	27
Affected eyes, total	19	
Right eyes	10	
Left eyes	9	
Pseudophakic eyes	2/19	11
Age at presentation (years) (median, range)	66 (28–81)	
Duration of symptoms till presentation (days) (median, range)	28 (3–180)	
Referring diagnosis		
Uveitis	9/15	60
Endogenous fungal endophthalmitis	2/15	13
Endogenous bacterial endophthalmitis	2/15	13
Exudative retinal detachment	1/15	7
No diagnosis	1/15	7
Pretreatment		
None	5/15	33
Local corticosteroids	5/15	33
Local and systemic corticosteroids	4/15	27
Systemic antifungal agents	1/15	7

n, number of affected patients/eyes; *N*, total number of patients/eyes.

and 11 patients had unilateral disease. Age at first presentation (baseline) ranged between 28 and 81 years (median: 66 years). Median period of follow-up was 6 months (range: 1–50 months). Baseline patient characteristics are summarized in Table 1.

All patients had at least one associated predisposing risk factor for endogenous fungal endophthalmitis. In 13 patients (87%), more than one risk factor was found. The most common risk factors were recent hospitalization and history of malignancy (nine patients each, 60%). Only one patient had a history of systemic candidiasis. Associated risk factors are shown in detail in Table 2.

TABLE 2. Associated risk factors.

Associated risk factors	Number of patients	
	n/*N*	(%)
Recent hospitalization	9/15	60
Malignancy	9/15	60
Systemic surgery	6/15	40
Chronic illness	6/15	40
Chemotherapy	5/15	33
Intravenous drug abuse	4/15	27
Perforating sigmoid diverticulitis	1/15	7
Systemic candidiasis	1/15	7

n, number of affected patients; *N*, total number of patients.

The time from onset of ocular symptoms to presentation ranged from 3 to 180 days (median: 28 days). Eleven patients (73%) were referred to our department with an initial diagnosis different from endogenous endophthalmitis. The most common referring diagnosis was uveitis (nine patients, 60%). The referring suspected diagnoses and the pretreatment are presented in Table 1.

Clinical Features

The most common ocular symptoms were decreased vision (11 patients, 73%) and floaters (four patients, 27%). Ocular pain was reported in two patients (13%).

The most common anterior segment findings were 2+ or 3+ anterior chamber cells (13 eyes, 68%), small hypopyon (<1 mm) (nine eyes, 47%) and keratic precipitates (eight eyes, 42%). Mild ciliary injection was observed in four eyes (21%).

Vitreous cells were found in all affected eyes. Vitreous inflammation was very marked and precluded viewing the posterior pole in the majority of eyes (14 eyes, 74%). Puff ball-like intravitreal lesions were seen in 13 eyes (68%). The puff ball-like lesions were whitish and located mainly in the posterior vitreous. Fluffy creamy white chorioretinal infiltrates were observed in nine eyes (47%). Clinical features are summarized in Table 3.

TABLE 3. Clinical features.

Clinical features	Number of eyes *n/N*	(%)
Ciliary injection	4/19	21
Keratic precipitates	8/19	42
Anterior chamber (AC) cells	15/19	79
1+ AC cells	2/19	11
2+ AC cells	3/19	16
3+ AC cells	10/19	52
Hypopyon	9/19	47
Posterior synechia	2/19	11
Vitreous cells	19/19	100
1+ vitreous cells	3/19	16
2+ vitreous cells	9/19	47
3+ vitreous cells	7/19	37
Intravitreal puff ball-like lesions	13/19	68
Chorioretinal infiltrates	9/19	47
Intraretinal hemorrhages	2/19	11

n, number of affected eyes; *N*, total number of eyes; AC, anterior chamber.

TABLE 4. Diagnostic and treatment procedures.

Diagnostic and treatment procedures	Number of patients/eyes (*n/N*)	(%)
Primary 23-G vitrectomy	16/19	84
Diagnostic outcomes of 23-G vitrectomy		
Positive for *Candida*	10/16	62.5
Positive for *Aspergillus*	2/16	12.5
Negative for fungi	4/16	25
Blood culture	8/15	53
Positive blood culture	0/8	0
Intravitreal injections of amphotericin B	19/19	100
1 intravitreal injection	13/19	68
2 intravitreal injections	4/19	21
3 intravitreal injections	2/19	11

n, number of affected patients/eyes; *N*, total number of patients/eyes; 23-G, 23-gauge.

Diagnostic Procedures and Their Results

Sixteen eyes of 15 patients underwent primary diagnostic transconjunctival 23-G vitrectomy to clarify the diagnosis and to determine the causative agent of a potential endophthalmitis. In one of 4 patients with bilateral involvement, both eyes were operated; in the other 3 patients with bilateral involvement, the more severe affected eye was operated only. Diagnostic procedures and their results are shown in Table 4.

Positive vitreous culture for fungi was found in 10 of 16 eyes. Yeasts were detected in eight eyes, in which *Candida albicans* was the causative agent in seven eyes and *Candida dubliniensis* in one eye. Molds (*Aspergillus flavus*) were detected in the vitreous culture in two eyes (12.5%).

Histopathologic examination had confirmed *Candida* in two eyes, in which the vitreous culture was negative, suggesting at the end, that fungi were found in 12 of 16 eyes (75%) of 12 patients (80%), and *Candida* was detected as the most common causative organism (10 of 16 eyes, 62.5%).

Negative culture, PCR and histopathologic examinations were found in four eyes (25%) of four patients. In one of these patients, *Candida albicans* was determined in the partner eye. In another patient, *Candida* was strongly suspected because systemic candidiasis had been previously proven and treated with fluconazole, however blood cultures during the hospital admission for endophthalmitis were negative for *Candida*. In the other two patients, fungal infection was strongly suspected due to typical ocular findings and associated risk factors.

In three fellow eyes, in which a vitrectomy was not performed, *Candida* was confirmed by diagnostic vitrectomy in the partner eye.

Blood cultures for fungal infection were performed for eight patients, and revealed no positive results. All vitreous specimens were negative for herpes simplex virus, varicella-zoster virus and cytomegalovirus PCR. Vitreous culture and histopathologic examinations ruled out bacterial endophthalmitis and intraocular B-cell lymphoma.

TREATMENT AND RESULTS

All eyes that had undergone vitrectomy received intravitreal injection of amphotericin B 5 μg/0.1 mL at the end of surgery. Amphotericin B 5 μg/0.1 mL was also given intravitreally in the fellow eye of patients with bilateral involvement. Intravitreal injections of amphotericin B were repeated if needed according to the clinical course up to three times, within a mean period of 2.5 weeks (range 1–6 weeks) between each injection. Intravitreal amphotericin B was given in four eyes twice and in two eyes three times.

Fourteen patients received additional systemic antifungal therapy. Twelve patients were treated with fluconazole 400 mg twice daily for 3 days and then 200 mg twice daily. Both patients with *Aspergillus* endophthalmitis received voriconazole 200 mg twice daily. Systemic treatment was usually started after vitrectomy and was ended depending on clinical course. One patient with negative microbiologic and histopathologic results did not receive systemic treatment.

In the four eyes in which no causative agent was detected, a significant improvement in clinical findings and visual acuity during antimycotic therapy was observed.

At baseline, the BCVA of ≤20/400 was measured in 14 eyes (74%) of 13 patients. At the end of follow-up, BCVA of ≤20/400 was found in five eyes (26%) of five patients. BCVA at the end of follow-up was obtained in five eyes filled with silicon oil. If we exclude these

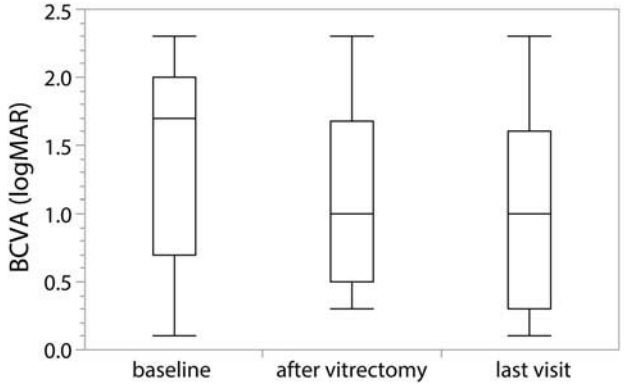

FIGURE 1. Boxplot diagram showing best-corrected visual acuity (BCVA) in logMAR at baseline, 1 week after vitrectomy and at the last visit. The whiskers indicate minimum and maximum values, the length of boxes represents the interquartile range, and the horizontal line in the boxes shows the median BCVA. Median BCVA increased significantly at the different time points compared with the baseline, p value = 0.036 and <0.001, respectively.

eyes from the analysis, BCVA of ≤20/400 was found only in two eyes (11%) of two patients.

A significant increase of median BCVA 1 week after vitrectomy and at the end of follow-up in comparison with the median baseline BCVA was observed (p = 0.036 and p<0.001, Figure 1). BCVA at the end of follow-up was significantly better in the eyes in which retinal detachment did not occur than in the eyes that developed retinal detachment (p = 0.013).

Ocular Complications

The most common ocular complication was retinal detachment (eight eyes, 42%). In two eyes (10%) retinal detachment was found during the diagnostic 23-G vitrectomy and these eyes received silicon oil tamponade. In six eyes (32%) retinal detachment occurred after vitrectomy: two eyes developed retinal detachment 5 days after vitrectomy and in four eyes, retinal detachment occurred after a mean period of 5 weeks after vitrectomy. In these eyes, the retinal detachment was surgically repaired by 20-G vitrectomy and silicon oil tamponade. At the end of follow-up, five eyes were filled with silicon oil. No association between a longer duration of symptoms and development of retinal detachment was found (OR = 0.77; 95% CI: 0.32–1.72; p = 0.53). However, poor baseline BCVA was associated with an increased risk of retinal detachment (OR = 5.86; 95% CI: 1.13–82.02; p = 0.034).

Secondary cataract was the second most common complication (six eyes, 32%) that occurred during a median follow-up of 6 months. In all eyes that developed cataract, cataract surgery was performed. Transient postoperative hypotony was observed in one eye. Secondary choroidal neovascularization occurred in one eye with *Candida albicans* and was treated with intravitreal anti-VEGF (vascular endothelial growth factor) therapy. Foveal chorioretinal atrophy occurred in one eye with *Aspergillus flavus*.

TABLE 5. Ocular complications.

Ocular complications	Number of eyes (n/N)	(%)
Retinal detachment	8/19	42
Secondary cataract	6/19	32
Postoperative hypotony	1/19	5
Secondary choroidal neovascularization	1/19	5
Foveal chorioretinal atrophy	1/19	5

n, number of affected eyes; N, total number of eyes.

No severe complications related to vitrectomy were observed. No patient underwent enucleation. Ocular complications are summarized in Table 5.

DISCUSSION

Endogenous fungal endophthalmitis is a rare but potentially blinding disease and frequently presents a diagnostic and therapeutic challenge. Previous reports have shown that vitreous samples obtained during vitrectomy may be more sensitive to a diagnosis of EFE than samples obtained by vitreous tap.[5,17] However, in most published studies, only culture-proven EFE cases are considered, and very limited data exists about the yield of positive cultures in all patients with presumed EFE who underwent diagnostic vitrectomy.[8,17,18] In a large case series, Lingappan et al. confirmed by vitrectomy, the diagnosis of EFE in 81% of eyes, but the authors did not specify what type of vitrectomy was performed on their patients.[7] To the best of our knowledge, no studies exist to date explicitly assessing the role of primary 23-G vitrectomy in the diagnosis and treatment of EFE. Due to its improved wound construction and fluidics, 23-G vitrectomy is thought to be more efficient and safer than 20-G vitrectomy.[11,14] The reduced sphere of influence of 23-G vitrectomy on adjacent tissues seems to be an important advantage in eyes with endophthalmitis, which are highly susceptible to iatrogenic damages. Therefore, we used primary transconjunctival 23-G vitrectomy in the diagnosis of presumed EFE and could determine the causative agent in 75% of investigated eyes. Our data show that 23-G vitrectomy is an effective diagnostic procedure in patients with presumed fungal endophthalmitis. Obviously, an adequate undiluted vitreous sample, enough for microbiologic and histopathologic examinations, can be obtained by transconjunctival 23-G vitrectomy. Moreover, a significant increase in BCVA after vitrectomy was observed compared with the baseline BCVA. This suggests that 23-G vitrectomy is not only useful

for making a diagnosis of EFE, but it is also an effective therapeutic modality in patients with endophthalmitis. Vitrectomy removes vitreous opacities, decreases the overall burden of organisms and leads to visual improvement.[6,19]

In the present study, no severe complications related to vitrectomy were observed. However, after vitrectomy, retinal detachment occurred in 32% of eyes. In the literature, few data exist regarding the incidence of retinal detachment after vitrectomy for endogenous fungal endophthalmitis. Analyzing patients with EFE treated at the Bascom Palmer Eye Institute between 1990 and 2009, Lingappan et al. observed retinal detachment in 29% of vitrectomized eyes without providing data on the type of vitrectomy.[7] Because 23-G vitrectomy has been used in ophthalmologic practice since 2005, it can be assumed that in the case series from the Bascom Palmer Eye Institute, a significant number of patients underwent 20-G vitrectomy. Due to the similar rate of postoperative retinal detachment in our study and in the study by Lingappan et al. one can speculate that the risk of retinal detachment in patients with EFE does not increase after 23-G vitrectomy compared with 20-G vitrectomy. Searching for factors predictive of retinal detachment, we found that poor baseline BCVA is associated with an increased risk of retinal detachment in EFE. Similar observations were reported in the Endophthalmitis Vitrectomy Study for patients with acute exogenous endophthalmitis.[20] Since the visual acuity in patients with endophthalmitis is limited by the severity of vitreous infiltration and macular involvement, our observation that poor baseline BCVA is associated with the likelihood of developing retinal detachment gives an indirect hint that eyes with more severe inflammation are at risk of retinal detachment.

In two of our patients, the causative organism could be confirmed by histopathologic examination, in spite of negative fungal cultures. Recently, the reliability of vitreous histologic detection of pathogenic fungi in the diagnosis of fungal endophthalmitis was assessed by Liu et al.[21] The authors reported that the sensitivity of the histologic detection of fungi was greater than that of the conventional smear and culture. It seems that complementary diagnostic techniques should be applied to increase the rate of confirmed diagnosis after diagnostic vitrectomy. In cases of suspected EFE, not only microbiologic but also histopathologic examinations of vitreous samples should be performed.

In this study, we could not detect the causative agent in four eyes that were clinically suspected of having fungal endophthalmitis and were successfully treated with antimycotic therapy. The diagnosis of fungal infection remains difficult because of the limited sensitivity of non-molecular diagnostic techniques. The use of molecular methods increases the possibility of rapidly identifying pathogens; however, the reported sensitivity ranges considerably from 43% to 100%.[22] False-negative PCR results have been observed in patients with fungal endophthalmitis.[23] Fungal organisms have strong cell walls that are difficult to lyse, thus requiring complex methods for DNA isolation.[22] The entry of fungal antigens contributing to intraocular inflammation, but not living organisms in the eyes of patients with systemic fungal infection, might be another explanation for the negative microbiologic results. An additional point of consideration is the time of sampling and the effect of pretreatment given prior to vitrectomy. One of our patients with negative results had been pretreated with antifungal agents due to systemic candidiasis. Antimycotic treatment may negatively affect the sensitivity of diagnostic tests. In patients with presumed EFE who had received antifungal therapy prior to diagnostic vitrectomy, negative microbiologic and histopathologic results should be interpreted very cautiously. Due to a significant risk of visual loss in untreated eyes with EFE, in such cases, further antifungal treatment should be considered, in spite of negative diagnostic tests.

In the present series, 73% of the patients were referred to our department with an incorrect diagnosis. In clinical practice, many patients with endogenous fungal endophthalmitis are misdiagnosed.[7,8,10] The consequences of unrecognized fungal endophthalmitis are severe and despite improved diagnostic and treatment options, EFE remains a sight-threatening disease due to delayed diagnosis. In the majority of our patients, no signs of systemic fungal infection or fungemia were observed. Thus, the ophthalmologist may be the first clinician to confirm the diagnosis of fungal infection. Therefore, it is important to be aware of EFE, especially in patients with a severe intraocular inflammation and a history of risk factors such as recent hospitalization, abdominal surgery, an immunocompromised state, or intravenous drug abuse. Clinical findings with a high index of suspicion for EFE are: a severe anterior chamber cell reaction or hypopyon associated with mild or no ciliary injection and mild or no ocular pain, severe vitreous inflammation with intravitreal puff ball-like lesions, and/or fluffy creamy white chorioretinal infiltrates. In such cases, we recommend a prompt diagnostic pars plana vitrectomy to establish the correct diagnosis.

The limitations of this study arise from its retrospective nature, the small patient number, the lack of standardized treatment regimen, and the variable periods of follow-up. However, we can show for the first time that primary transconjunctival sutureless 23-G vitrectomy is a reliable and safe procedure in the diagnosis and treatment of EFE. Clinicians should be aware of EFE, particularly in patients with associated risk factors.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

ORCID

Focke Ziemssen http://orcid.org/0000-0002-3873-0581

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3. Discussion

3.1. Ab externo Trabeculotomy in primary open angle glaucoma and uveitic glaucoma.

Glaucoma is a common, potentially sight-threatening complication of chronic uveitis. The reported incidence of UG is between 6.5% and 46% (Heinz et al., 2009, Merayo-Lloves et al., 1999, Neri et al., 2004, Panek et al., 1990). It increases in the course of the chronic uveitis from 6.5% after one year to 22.3% after 10 years (Neri et al., 2004). Surgical treatment is often required to control the IOP in UG. Transscleral diode cyclophotocoagulation, deep sclerectomy, trabeculectomy with and without antimetabolites, and glaucoma drainage devices have been used with variable success (Auer et al., 2004, Ceballos et al., 2002a, Ceballos et al., 2002b, Chawla et al., 2013, Dupas et al., 2010, Heinz et al., 2006, Hill et al., 1993, Iwao et al., 2014, Kaburaki et al., 2009, Molteno et al., 2001, Noble et al., 2007, Papadaki et al., 2007, Schlote et al., 2000, Stavrou and Murray, 1999, Voykov et al., 2014).

Schlote et al. reported a success rate of 77.2% after one year for TDLC in the treatment of UG. Similar results were reported for patients with Fuchs uveitis syndrome (FUS) (Schlote et al., 2000, Voykov et al., 2014). However, more than one TDLC treatment was necessary to achieve success in the majority of eyes. Also, the efficacy of TDLC seems to depend on the type of uveitis. Heinz et al. reported a failure rate of TDLC of 68% in a series of 21 eyes with glaucoma secondary to juvenile idiopathic arthritis.

Non-penetrating deep sclerectomy (NPDS) is another option in the treatment of UG. It has been introduced to avoid bleb-related postoperative complications of filtration surgery. Dupas et al. reported in a prospective comparative study similar success rates for NPDS and trabeculectomy in UG after one year. However, deep sclerectomy patients required significantly more postoperative adjustments in form of goniopuncture or needling to achieve success compared to the trabeculectomy group (Dupas et al., 2010). Similar results were reported by others as well (Auer et al., 2004, Souissi et al., 2006). However, there are no sufficient long-term data of deep sclerectomy in the treatment of UG. One study reported a success rate of 18.9% after 30 months,

which is lower than the success rates for trabeculotomy ab externo in the current study (Khairy et al., 2006).

Glaucoma drainage devices (GDD) are an alternative approach in the treatment of uncontrolled UG. Ceballos et al. reported a success rate of 91.7% with the Baerveldt glaucoma drainage device after two years (Ceballos et al., 2002b). Very promising results have been reported for the Molteno implant with a success rate of 75% after 10 years (Molteno et al., 2001). Papadaki et al showed good results for the Ahmed glaucoma valve in UG with success rates of 77% and 50% after one and four years, respectively (Papadaki et al., 2007). However, high success rates of GDD go along with serious postoperative complications like postoperative hypotony, hypotony maculopathy, choroidal effusion and corneal endothelium dysfunction (Ceballos et al., 2002b, Gedde et al., 2012, Molteno et al., 2001). Also, the postoperative Tenon cyst formation is considered as a rate limiting step in the success of glaucoma implants surgery (Eibschitz-Tsimhoni et al., 2005, Gil-Carrasco et al., 1998, Lai et al., 2000, Ozdal et al., 2006). The reported incidence of the encapsulated bleb formation ranges between 23% and 42.8% (Gil-Carrasco et al., 1998, Ozdal et al., 2006). Gil-Carrasco et al. reported that encapsulated blebs tend to occur in young patients (range 22-44 years), which corresponds to the typical age of patients with UG (Gil-Carrasco et al., 1998).

Compared to the above surgical techniques, trabeculotomy ab externo was moderately successful as a stand-alone procedure in our case series. However, the use of glaucoma medications or cycloablative procedures improved the success rates considerably. The majority of treatment failures in the current study occurred within the first three months after surgery. Most of these patients were under the age of 30 years (4/7, range 15-43 years), and had either FUS (four eyes) or granulomatous uveitis (two eyes). A possible explanation for early failure in these cases might be secondary structural abnormalities in the Schlemm's canal and the collecting channels associated with longstanding uveitis. Younger age is also a possible reason for failure, considering that age below 30 years is a well-known risk factor for failure in glaucoma surgery (Costa et al., 1993, Investigators, 2002). It should also be considered, that FUS differs from other uveitic forms in its unilaterality, absence of acute symptoms and the mild anterior chamber inflammation which is irresponsive to steroids (Bonfioli et al., 2005).

It is therefore possible that the specific features of FUS lead to different results of glaucoma treatment in these patients compared to glaucoma secondary to other uveitis entities. The

treatment failures that have occurred in UG raised up several questions; firstly whether surgical efficacy of ab externo trabeculotomy differs between UG and POAG? Secondly, if so, should we follow different surgical strategies in POAG and UG? And thirdly, is chronic inflammation a risk factor for failure even it was controlled preoperatively? To answer the above mentioned questions we had to investigate the efficacy of ab externo Trabeculeculotomy in POAG to compare them with UG.

Ab externo trabeculotomy is usually a first choice surgical treatment in congenital and juvenile glaucoma. However, a study by Tanihara et al. has demonstrated that the procedure is an effective treatment for POAG, as well, even in adults. In this study, the success rate of the procedure was 58% after five years. The authors also reported that the success was significantly higher in patients with lower preoperative IOP (< 30 mmHg). In these patients, the final success probability after five years was 66.9%. On the other hand, age did not significantly influence the success of surgery (Tanihara et al., 1993).

Although direct comparison is difficult because of the different study populations and success criteria, our results in the POAG group are similar (qualified success) to those mentioned in the above study. However, the success rate in the UG group was significantly lower. The different pathomechanisms of IOP elevation in POAG and UG might be a possible explanation for this difference. Another point that might explain the lower success in the uveitis group is the type of uveitis forms. It's heir important to mention that the cornerstone in the proper management of uveitis is based on the proper diagnosis of the form of uveitis and the proper adjustment of its therapy according to its activity status and recurrence. In our study the uveitic aetiologies were idiopathic anterior uveitis (six eyes), idiopathic uveitis intermedia (four eyes), posterior uveitis (two eyes), Fuchs uveitis syndrome (FUS) (five eyes), herpetic uveitis (one eye), Posner-Schlossmann syndrome (two eyes) and granulomatous uveitis (two eyes). In four eyes with anterior uveitis, uveitis was controlled with MTX and low dose of systemic steroid and in two eyes with Humira and Cellcept. Granulomatous uveitis was controlled with MTX and low dose of systemic steroid. Two of the four eyes with uveitis intermedia, were controlled with Myfortic, in a single eye with Cellcept and in another single eye with only low doses of systemic steroid. Herpetic uveitis was controlled with systemic Aciclovir. The two eyes with Posner-Schlossmann syndrome, were controlled with systemic Valcyte. All five eyes with FUS were under non steroid anti-inflammatory eye drops. Active uveitis was absent in all patients preoperatively for

at least a period of three months. The majority of failures in the UG group occurred in patients with FUS (four eyes) and granulomatous uveitis (two eyes). Typically, FUS

associated with mild anterior chamber inflammation which is difficult to control and irresponsive to steroids compared to other uveitis forms (Mohamed and Zamir, 2005). It is possible that the persistent low-grade inflammation in FUS leads to obstruction in the collector channel opening (CCO) or the intrascleral channels, which could explain the high failure rate in FUS eyes in our study. A recent study described the intraoperative observation of a perilimbal and/or episcleral vessel fluid wave seen during trabectome surgery and termed it episcleral venous fluid wave (EVFW) (Fellman and Grover, 2014). The EVFW correlated well with the outcomes of trabectome surgery in patients with various types of open-angle glaucomas. The authors demonstrated that if a wave was not seen or barely present, there was likely obstruction CCO or intrascleral channels preventing flow to the episcleral veins (Fellman et al., 2015).

Unfortunately, the authors did not report on different subtypes of glaucomas. Similarly, Hamanaka et al. showed that eyes with granulomatous uveitis are associated with infiltration of lymphocytes, monocytes and macrophages around the inner wall, posterior outer wall of the Schlemm's canal and the collector channels leading to narrowing and occlusion of the Schlemm's canal (Hamanaka et al., 2002). Interestingly, a recent histological study suggested that the enhancement of conventional routes may not, however, be important for the IOP-lowering effect of trabeculotomy. The authors hypothesized that four different types of histological changes in the TM may reduce enhancement of the newly created unconventional routes by trabeculotomy (Amari et al., 2015). In this case, it is possible that in UG the breakdown of the blood-ocular barrier followed by influx of proteins, immunocompetent cells, cytokines and chemokines leads more often to the above histological changes in the TM compared to POAG. Again, active inflammation in FUS probably accelerates these changes even more. Although, there are only limited number of studies which have compared the outcomes of a surgical procedure between patients with POAG and patients with UG, yet however most of these studies have determined that the success rate in POAG is higher than that seen in UG (Iwao et al., 2014, Kaburaki et al., 2009, Noble et al., 2007, Rachmiel et al., 2008).

The outcomes of filtration surgery are also worse in UG compared to POAG. Noble et al. reported that results of trabeculectomy with MMC were significantly worse in patients with UG compared to patients POAG. UG patients required also more postoperative procedures and

developed more often cystic blebs.(Noble et al., 2007). In contrast, Kaburaki et al. reported similar success rates after five years of follow-up in a retrospective study in patients with inactive uveitis in comparison to patients with POAG. However, postoperative complications such as longstanding ocular hypotony, hypotonic maculopathy and cataract formation were more common in the UG group (Kaburaki et al., 2009). Additionally, a study by Iwao et al. demonstrated that trabeculectomy with MMC was less effective in maintaining the IOP reduction in UG patients than in POAG patients (Iwao et al., 2014). One study compared the results of Ahmed glaucoma valve implantation between patients with UG and patients with POAG. The success rates were similar in both groups after 30 months. However, failure in terms of tube removal occurred significantly more often in patients with UG (Rachmiel et al., 2008).
The role of the higher preoperative IOP as a prognostic factor associated with poor prognosis after ab externo trabeculotomy remains a matter of debate. Tanihara et al. reported that higher preoperative IOP was a negative prognostic factor in POAG (Tanihara et al., 1993).
In contrast, Iwao et al. demonstrated that higher preoperative IOP was not a prognostic factor for surgical failure of trabeculotomy in the treatment of steroid induced glaucoma (Iwao et al., 2011).
Likewise, in our study the preoperative IOP in the eyes with failure was not statistically significant different in comparison to the eyes without failure. However, due to the small number of eyes we could not determine the role of preoperative IOP level conclusively.
The influence of age on the outcomes of ab externo trabeculotomy has been controversially discussed in the literature. Some authors have reported better results in patients with congenital and juvenile glaucoma compared to adult-onset glaucoma (Luntz and Livingston, 1977, Schwartz and Anderson, 1974). However, Tanihara et al. showed that there was no significant difference in the outcomes between a younger (<60 years) and an elderly (≥60 years) groups in eyes with POAG (Tanihara et al., 1993). In our study, patients with UG were much younger than those with POAG. However, in our opinion, the worse results in the above studies by Schwartz and Anderson, Lunt and Livingston, and ours for the non-POAG eyes compared to the eyes with POAG are caused by structural changes of the outflow system that differ among various glaucoma types and are only indirectly correlated to age.
Gender was also statistically significant different in both groups, however, failure was similar in both gender without any statistically significant different. To reveal and compare this point in our results with the previous studies and to evaluate its significance in the different types of

glaucoma surgery through what was written in literature, it was very surprising for us to find out that this in particular point was never been discussed or interpreted before in correlation with the outcomes of glaucoma surgery. Hence, we can't compare our results with any, yet we can tell from our data that gender is not a potential risk factor for the failure of trabeculotomy.

A major advantage of ab externo trabeculotomy is that it avoids the potentially sight-threatening complications of filtration surgery. In our study, complication rates were similar and low in both UG and POAG groups, although postoperative hyphema was slightly more common in the POAG group. Interestingly, Grieshaber et al. demonstrated that postoperative hyphema was a positive prognostic indicator in uneventful canaloplasty in regard to IOP reduction, possibly representing a restored and patent physiologic aqueous outflow system (Grieshaber et al., 2013).

In our own experience we have found out that a better success rate can be achieved through proper preoperative and postoperative care. Preoperatively, special attention and consideration should be given for the patients with UG. Activity of Uveitis should be controlled at least three months preoperatively. Systemic adjusted body weight steroid therapy should be given to all patients and should be started at least 5 days preoperatively and be tapered slowly postoperatively to control any inflammatory responses that might occur. Pilocarpine eyes drops should be started directly postoperatively and given for at least 4 weeks to avoid any peripheral anterior synechie formation and to maintain the patency of the newly created outflow route.

In the case of lack of proper adjustment of the IOP postoperatively, we have found out that both re-introduction of glaucoma medications or cyclodestructive procedures can be helpful and effective in adjusting the IOP postoperatively. The limitations of our two above studies include their retrospective design as wells as the variety of uveitic glaucoma types treated. Notably, the outcomes in eyes with FUS and granulomatous uveitis were worse compared to the remaining eyes in the UG group as well as to POAG group. However, the small number of eyes precluded from further analyses of these differences.

3.2. Primary Transconjunctival 23gauge vitrectomy in the diagnosis and treatment of presumed fungal endophthalmitis

Endogenous fungal endophthalmitis is a rare but potentially blinding disease and frequently presents a diagnostic and therapeutic challenge. Previous reports have shown that vitreous samples obtained during vitrectomy may be more sensitive to a diagnosis of EFE than samples obtained by vitreous tap (Tanaka et al., 2001, Weishaar et al., 1998). However, in most published studies, only culture proven EFE cases are considered, and very limited data exists about the yield of positive cultures in all patients with presumed EFE who underwent diagnostic vitrectomy (Essman et al., 1997, Sridhar et al., 2013, Weishaar et al., 1998). In a large case series, Lingappan et al. confirmed by vitrectomy, the diagnosis of EFE in 81% of eyes, but the authors did not specify what type of vitrectomy was performed on their patients (Lingappan et al., 2012). To the best of our knowledge, no studies exist to date explicitly assessing the role of primary 23-G vitrectomy in the diagnosis and treatment of EFE. Due to its improved wound construction and fluidics, 23-G vitrectomy is thought to be more efficient and safer than 20-G vitrectomy (Dugel et al., 2012, Eckardt, 2005). The reduced sphere of influence of 23-G vitrectomy on adjacent tissues seems to be an important advantage in eyes with endophthalmitis, which are highly susceptible to iatrogenic damages. Therefore, we used primary transconjunctival 23-G vitrectomy in the diagnosis of presumed EFE and could determine the causative agent in 75% of investigated eyes. Our data show that 23-G vitrectomy is an effective diagnostic procedure in patients with presumed fungal endophthalmitis. Obviously, an adequate undiluted vitreous sample, enough for microbiologic and histopathologic examinations, can be obtained by transconjunctival 23-G vitrectomy. Moreover, a significant increase in BCVA after vitrectomy was observed compared with the baseline BCVA. This suggests that 23-G vitrectomy is not only useful for making a diagnosis of EFE, but it is also an effective therapeutic modality in patients with endophthalmitis. Vitrectomy removes vitreous opacities, decreases the overall burden of organisms and leads to visual improvement (Pappas et al., 2009, Sallam et al., 2006). In the present study, no severe complications related to vitrectomy were observed. However, after vitrectomy, retinal detachment occurred in 32% of eyes. In the literature, few data exist regarding the incidence of retinal detachment after vitrectomy for endogenous fungal endophthalmitis. Analyzing patients with EFE treated at the Bascom Palmer Eye Institute

between 1990 and 2009, Lingappan et al. observed retinal detachment in 29% of vitrectomized eyes without providing data on the type of vitrectomy (Lingappan et al., 2012). Because 23-G vitrectomy has been used in ophthalmologic practice since 2005, it can be assumed that in the case series from the Bascom Palmer Eye Institute, a significant number of patients underwent 20-G vitrectomy. Due to the similar rate of postoperative retinal detachment in our study and in the study by Lingappan et al. one can speculate that the risk of retinal detachment in patients with EFE does not increase after 23-G vitrectomy compared with 20-G vitrectomy. Searching for factors predictive of retinal detachment, we found that poor baseline BCVA is associated with an increased risk of retinal detachment in EFE. Similar observations were reported in the Endophthalmitis Vitrectomy Study for patients with acute exogenous endophthalmitis.20 Since the visual acuity in patients with endophthalmitis is limited by the severity of vitreous infiltration and macular involvement, our observation that poor baseline BCVA is associated with the likelihood of developing retinal detachment gives an indirect hint that eyes with more severe inflammation are at risk of retinal detachment. In two of our patients, the causative organism could be confirmed by histopathologic examination, in spite of negative fungal cultures. Recently, the reliability of vitreous histologic detection of pathogenic fungi in the diagnosis of fungal endophthalmitis was assessed by Liu et al.(Liu et al., 2015). The authors reported that the sensitivity of the histologic detection of fungi was greater than that of the conventional smear and culture. It seems that complementary diagnostic techniques should be applied to increase the rate of confirmed diagnosis after diagnostic vitrectomy. In cases of suspected EFE, not only microbiologic but also histopathologic examinations of vitreous samples should be performed. In this study, we could not detect the causative agent in four eyes that were clinically suspected of having fungal endophthalmitis and were successfully treated with antimycotic therapy. The diagnosis of fungal infection remains difficult because of the limited sensitivity of non-molecular diagnostic techniques. The use of molecular methods increases the possibility of rapidly identifying pathogens; however, the reported sensitivity ranges considerably from 43% to 100%(Arvanitis et al., 2014). False-negative PCR results have been observed in patients with fungal endophthalmitis (Ogawa et al., 2012). Fungal organisms have strong cell walls that are difficult to lyse, thus requiring complex methods for DNA isolation (Arvanitis et al., 2014). The entry of fungal antigens contributing to intraocular inflammation, but not living organisms in the eyes of patients with systemic fungal infection, might be another explanation for the negative microbiologic results. An additional point of consideration is the time of sampling and the effect

of pretreatment given prior to vitrectomy. One of our patients with negative results had been pretreated with antifungal agents due to systemic candidiasis. Antimycotic treatment may negatively affect the sensitivity of diagnostic tests. In patients with presumed EFE who had received antifungal therapy prior to diagnostic vitrectomy, negative microbiologic and histopathologic results should be interpreted very cautiously. Due to a significant risk of visual loss in untreated eyes with EFE, in such cases, further antifungal treatment should be considered, in spite of negative diagnostic tests. In the present series, 73% of the patients were referred to our department with an incorrect diagnosis. In clinical practice, many patients with endogenous fungal endophthalmitis are misdiagnosed (Essman et al., 1997, Lingappan et al., 2012, Shen and Xu, 2009, Zhang and Wang, 2005). The consequences of unrecognized fungal endophthalmitis are severe and despite improved diagnostic and treatment options, EFE remains a sight-threatening disease due to delayed diagnosis. In the majority of our patients, no signs of systemic fungal infection or fungemia were observed. Thus, the ophthalmologist may be the first clinician to confirm the diagnosis of fungal infection. Therefore, it is important to be aware of EFE, especially in patients with a severe intraocular inflammation and a history of risk factors such as recent hospitalization, abdominal surgery, an immunocompromised state, or intravenous drug abuse. Clinical findings with a high index of suspicion for EFE are: a severe anterior chamber cell reaction or hypopyon associated with mild or no ciliary injection and mild or no ocular pain, severe vitreous inflammation with intravitreal puff ball-like lesions, and/or fluffy creamy white chorioretinal infiltrates. In such cases, we recommend a prompt diagnostic pars plana vitrectomy to establish the correct diagnosis. The limitations of this study arise from its retrospective nature, the small patient number, the lack of standardized treatment regimen, and the variable periods of follow-up. However, we can show for the first time that primary transconjunctival sutureless 23-G vitrectomy is a reliable and safe procedure in the diagnosis and treatment of EFE. Clinicians should be aware of EFE, particularly in patients with associated risk factors.

4. Summary

A major advantage of ab externo trabeculotomy is that it improves the outflow facility and restores the physiological pathway of the aqueous humor outflow without the need of external fistulation and hence avoiding the bleb-related complications. In our two studies we were able to demonstrate that ab externo trabeculotomy was moderately successful as a stand-alone procedure in the management of POAG and UG.

However, the success rate in the UG group was significantly lower in comparison to the higher success rate in POAG. The majority of treatment failures that occurred in the current study in the UG group occurred within the first three months after surgery. Most of these patients were young patients that had either FUS or granulomatous uveitis.

Therefore special attention should be given to the form of Uveitis and treatment, nevertheless; the age of the patients, young patients are associated with a higher risk of failure.

Nevertheless, our study showed that trabekulotomy in combination with antiglaucoma medications or cyclodestructive procedures is helpful in increasing its success rate. The procedure demonstrated a high safety profile in both UG and POAG.

If endogenous fungal endophthalmitis is suspected, a diagnostic 23G vitrectomy can detect the pathogen in the majority of the effected patients. As expected, Candida species are the most frequently detected pathogens for the endogenous fungal endophthalmitis.

5. Zusammenfassung

Ein Hauptvorteil der ab externo Trabekulotomie ist, dass sie den Abfluss erleichtert und den physiologischen Pfad des Kammerwassers wiederherstellt, ohne die Notwendigkeit einer externen Fistulation. Somit können die mit einem Filterkisssen assoziierten Risiken vermieden werden. In unseren zwei Studien konnten wir zeigen, dass die ab externo Tabekulotomie einen mäßigen Erfolg in der Behandlung des POAG und des UG erzielen kann.

Insbesondere in der UG Gruppe war die Erfolgsrate deutlich geringer als im der POAG Gruppe. Die ersten drei Monate nach der Operation waren entscheidend über den Behandlungserfolg. Die jungen Patienten mit FUS oder granulomatöser Uveitis profitierten am wenigsten von dem Eingriff. Deshalb ist die ab externo Trabekulotomie für diese Patientengruppen eher ungeeignet.

Unsere Studie konnte außerdem zeigen, dass die Trabekulotomie in Kombination mit drucksenkender Medikation oder mit einem zyklodestruktiven Verfahren die Erfolgsraten erhöhen kann. Das Verfahren zeigte ein hohes Sicherheitsprofil, sowohl in der UG als auch in der POAG.

Bei Verdacht auf endogene Pilz Endophthalmitiden kann durch eine diagnostische 23G Vitrektomie der Erreger bei der Mehrheit der betroffenen Patienten nachgewiesen werden. Candida Species waren erwartungsgemäß die am häufigsten nachgewiesenen Erreger für die endogenen Pilz Endophthalmitiden.

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7. Erklärung zum Eigenanteil

Die Arbeit wurde in der Universitäts-Augenklinik Tübingen unter der Betreuung von PD Dr. med. Bogomil Voykov durchgeführt. Die Konzeption die drei Studien erfolgte in Zusammenarbeit mit PD Dr. med. Bogomil Voykov (Betreuer). Die Datensammlung, die statistische Auswertung und die Verfassung des Manuskripts die drei Studien wurden von mir eigenständig durchgeführt (nach Anleitung und unter der Aufsicht von PD Dr.med Bogomil Voykov). Ich versichere, das Manuskript selbständig (nach Anleitung durch PD Dr. med. Bogomil Voykov) verfasst worden und keine weiteren als die von mir angegebenen Quellen verwendet zu haben.

Den 13.10.2021

8. Acknowledgment

I would like to thank my parents and wife who supported me and encouraged me through my medical carrier and who are still supporting me.

I also like to express my sincere gratitude to my advisor PD Dr. med. Bogomil Voykov for his continuous support, encouragement, patience, motivation and immense knowledge in the various researches that we did together during my residency period in the Ophthalmology Center of the University of Tübingen.

My sincerest appreciation goes to Prof. Dr. med. Bartz-Schmidt who gave me the great opportunity to join his team and learn from him and from his team and I am very grateful for his great support during my residency period in his Department.