Research Proposal

1. **Title:** *Determining Distal Outflow Tract Function in Open Angle Glaucoma as a Predictive Test for the Success of Ab Interno Trabeculectomy*

Protocol: Version 1.0 / 07.04.2021

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4. Rationale

4.1.1. Narrative / Project Narrative

Post-trabecular outflow resistance in glaucoma was described only recently and remains poorly understood. The outcome of two commonly performed microincisional glaucoma surgeries, ab interno trabeculectomy (AIT) and trabecular bypass stent implantation (TBS) depends on a patent distal outflow system with a normal post-trabecular outflow resistance. The failure rate of AIT is between 10 to 35% and that of TBS is even higher [1,2].

The proposed research will determine the post-trabecular outflow resistance by comparing the drop of intraocular pressure (IOP) after a noninvasive trabeculopuncture (TP) to the IOP achieved after the subsequent AIT. Predicting surgical success by assessing the distal

outflow resistance will avoid unnecessary AIT by triaging patients with a negative test directly to the group of higher risk epibulbar glaucoma surgeries.

4.2. Studienziele / Major Goals of the Project

To create a non-invasive predictive test (TP) for distal outflow tract function after AIT in individuals with open angle glaucoma (OAG). We hypothesize that the IOP drop by a presurgical TP predicts the success of trabecular ablation in AIT. The results of this study will allow surgeons to use TP to select the proper procedure for a given glaucoma patient.

4.3. Hintergrund / Background and Significance

Open angle glaucoma is a leading cause of irreversible blindness. 42% of patients eventually become blind in one eye [3]. The annual costs of glaucoma in the US are $2.5 B. Most OAG is treated with eye drops, but even the latest prostaglandin analogs offer continuous-treatment success rates of 10% at one year [4]. 59% of patients continue to lose vision during initial medical treatment [5], and 32% [6] need surgery within one year.

One of the microincisional glaucoma surgeries, ab interno trabeculectomy with the trabectome, has a low risk and effectively lowers IOP but only in approximately 65% [7]-85% [8] of patients after 12 months. The six-month success rate of AIT is about 90% [8]. In this process, the nasal 180 degrees circumference of the trabecular meshwork is ablated. After AIT, the aqueous humor can directly enter the drainage system [9,10]. We perform close to 600 AITs per year in our center. Similarly, the insertion of trabecular bypass stents (TBS, iStent, Glaukos Corp, San Clemente, California, USA) creates a direct connection between the anterior chamber and Schlemm's canal using a nitinol implant.

Failure of AIT or TBS to lower the IOP indicates a non-functioning distal drainage system located downstream of the trabecular meshwork. Despite systematic outcome analyses, no clinical features have been identified to predict failure nor is there a preoperative test that assesses the distal drainage system. Having a predictive test of surgical success for AIT or TBS would dramatically reduce unnecessary treatments and avoid vision loss that continues in patients with failed procedures until a secondary, more invasive surgery is chosen.

TP could be such a test. It uses a common ophthalmic neodymium-YAG laser to create a small, temporary opening in the trabecular meshwork thereby increasing conventional outflow and lowering IOP for up to a few weeks [11]. The IOP drop caused by TP has to be related to the IOP drop caused by permanent surgical removal of the trabecular meshwork in AIT or by implantation of a TBS.

4.4. Vorstudien / Preliminary Studies

Many studies were performed on trabeculopuncture at the dawn of laser eye surgery in the mid-1970s. We provide a summary of key studies and list laser type, settings, and results **(Table 1)**.

Table 1: Summary of trabeculopuncture studies with laser type, settings, and results.

Laser	Paper	Technique	Time to trough	IOP drop	pre-TP	post- TP	comment
Q-Switched ruby	Krasnov 1973 [11]	Spots: not described Spot size: 0.25 - 0.5 mm Energy: 0.2 J	1 week - 6 months	8.6	32.4	23.8	-in vivo human eyes
Argon	Ticho 1978 [12]	Spots: 50 Spot size: 100 µm Duration: 0.1s Energy: 1-3 W Wave: continuous	< 30 days				- in vivo primate eyes
Argon	Wickham & Worthen 1979 [13]	Spots: 150 / 100 Spot size: 50 µm Duration: 0.01 s / 0.02 s Energy: 2 - 3 W Wave: continuous Spots: 150 Spot size: 50 µm Duration: 0.1 s Energy: 0.1-0.15W Wave: pulsed	4-5 years "The lowest lOPs are seen at four and five years, when the sample size had decreased greatly."	12.0	36.0	24.0	- in vivo human eyes - protocol is more akin to argon laser trabeculoplasty
Excimer	Töteberg-Harms 2011 [14]	Spots: 10 Spot size: 0.5 mm Duration: 60 ns Energy: 1.2 mJ Wavelength: 308 nm	IOP measurement only once after 12 months	8.8	25.3	16.5	- in vivo human eyes - very large TP spots (200-µm)
Table 1 continued: YAG-Laser trials							
Nd:YAG	Epstein 1985 [15]	Spots: 4-6 Energy: 2-6 mJ	24h	5.5	25.5	20.0	- in vivo human eyes - tonography was performed
Nd:YAG	Melamed 1985 [16]	Spots: 4 Spot size: 20 µm Duration: 14 ns Energy: 5-7 mJ	Immediate effect	10.0	20.5	9.8	- in vivo primate eyes

Nd:YAG	Melamed 1987[17]	Spots: 4 (one in each quadrant) Energy: 40 mJ	1h	10.0	25.6	19.1	- in vivo human eyes - tonography was performed
Nd:YAG	Del Priore 1988 [18]	Spots: 10 Energy: 10 mJ	1 month	10.2	28.9	21.7	- in vivo human eyes
			1 year	10.6			
Nd:YAG	Fukuchi 1993 [19]	Spots: 65 Spot size: 20 µm Energy: 1 - 2.5 mJ Single-pulse mode	Differs from 1 to 12 months	16.0	31.0	15.0	- in vivo human eyes - ALT had failed before TP
			averages	**9.0 (33%)**	**27.3±4.9**	**18.9±4.8**	

To this date, there have been no studies comparing TP to AIT but the implantation of a TBS is similar to TP in that it creates a hole-shaped opening in the TM maintained by the implant [20]. Both establish a connection between the anterior chamber and Schlemm's canal. Because of the proliferation of the TM, the opening in TP closes within weeks to months while the trabecular bypass stent can reduce IOP considerably longer [21]. At one week, the mean IOP reduction from baseline is about 8% after AIT and 6% after TBS injection **(Table 2)**. Based on this data, we estimate a reduction of the six-month AIT success rate by at least 40% if TP shows no significant IOP reduction after one week.

Table 2 - Studies comparing trabecular bypass stent (TBS) and ab interno trabeculectomy (AIT)

Paper	pre TBS	1d post TBS	1w post TBS	3m post TBS	pre AIT	1d post AIT	1w post AIT	3m post AIT
[22]	17.6	19.8	16.8	15.5	17.4	17.7	19.0	14.4
[23]	16.7	18.3	16.2	14.5	17.2	14.5	17.2	14.8
[24]	17.8	16.4	16.7	14.4	19.8	16.9	17.8	13.2
[25]	16.7	-	16.0	14.1	18.2	-	15.3	13.4
[2]	18.3	-	15.5	13.2	18.3	-	13.1	14.6
[26]	16.2	14.8	-	14.1*	15.8	12.9	-	13.8*
mean	**17.22**	**17.33**	**16.24**	**14.3**	**17.78**	**15.50**	**16.48**	**14.0**

numbers in mmHg, d = day, w = week, m = month, * = only 6 months data

4.5. Nutzen-Risiko-Abwägung / Risk-Benefit Evaluation

Trabeculopuncture is a low-risk procedure that is usually performed at the nasal trabecular meshwork, the same site that is later to be ablated 180° using a trabectome (AIT). Its side effects are comparable to those of similar laser treatments such as selective laser trabeculoplasty or peripheral laser iridotomy. TP is described by patients to be almost painless [11]. Previous studies have shown only minor complications including blood reflux into the anterior chamber, mild iritis, and temporary visual impairment [18,19]. These events have no impact on the subsequent AIT.

The primary benefit to our patients in participating in this trial is that TP lowers the IOP instantly. However, this effect is not sustained. The main purpose is to develop a test that predicts the success of AIT. This test will reduce both risks and costs by avoiding unnecessary surgery.

The failure of AIT, a minimally invasive procedure, requires a traditional filtering surgery (trabeculectomy) or a glaucoma drainage device, both of which have an approximately 20 times higher risk of serious complications and subsequent surgeries. If the probability of success can be determined beforehand, the surgical risk can be much reduced and unnecessary

procedures can be avoided. The target IOP at which glaucoma stops progressing would be achieved sooner and there would be fewer sick days.

There will be decreased costs from fewer procedures, fewer hospitalizations and fewer patient visits. In Germany, the annual treatment cost per glaucoma patient ranges from 918 € - 1194 €, depending on the severity of the glaucoma [27]. The prevalence of OAG in Germany among adults aged 40 to 80 years old is about 2.51 % [28,29]. This implies that the estimated total cost of glaucoma treatment in Germany is about 875 MM € per year (35 MM Germans between 40 - 80 years of age, prevalence 2.5 %, average cost of 1000 € per patient per year). The average costs for a standard glaucoma procedure in local anesthesia are about 2800 € according to Diagnosis Related Groups (C06Z G-DRG). In 2019, over 10,000 AIT or equivalent procedures were performed [31]. A one-year success rate of 70 % leads to 3000 unsuccessful interventions. Consequently, a simple predictive test like TP could save about 8.5 MM € annually by avoiding 2800 € for 3000 redundant interventions.

5. Objektive & Hypothese / Objective & Hypothesis

We expect an unsatisfactory drop in IOP and post-trabecular outflow resistance after TP to be associated with AIT failure. The primary endpoint will be the final IOP. The post-trabecular outflow resistance (R) will however also be measured. The outflow resistance is defined as reciprocal value of the outflow facility C (µL/(min*mmHg))

Null hypothesis (H0): The amount of IOP reduction after TP (ΔIOP_{TP}) is not correlated to the IOP reduction after AIT (IOP_{AIT}).

Alternative hypothesis (H1): The amount of IOP reduction after TP (ΔIOP_{TP}) is correlated to the IOP reduction after AIT (IOP_{AIT}).

6. Study Design/ Studiendesign

6.1. Studiendesign / Research design

This clinical trial is designed as a monocentric, longitudinal prospective, one-armed, cohort study.

6.2. Untersuchungen und Eingriffe / Examination and Procedures

The protocol is as follows:

1. Patients with an IOP equal to or above 21 mmHg who qualify for AIT will be identified (see inclusion criteria below). A comprehensive eye exam will then be performed followed by an explanation of the risks and benefits of TP. Informed consent forms for both TP and AIT will then be signed.

2. IOP and outflow facility will be then measured with a pneumatonometer (Model 30, Reichert, Buffalo, NY, United States).
3. As is common practice before glaucoma surgeries, glaucoma drops will be stopped two days prior to surgery.
4. On the day before surgery, trabeculopuncture will be performed with a Q-switched Nd:YAG Laser (VISUALS YAGIII, Zeiss, Oberkochen, Germany) by placing four trabeculotomies with a trabeculoplasty lens (Ocular Latina SLT Gonio Laser, Ocular Instruments Inc., Bellevue, USA) 40 degrees apart along the nasal 120 degrees of the trabecular meshwork (energy per shot = 4 mJ, single-shot mode, 4 shots per TP, total energy < 100 mJ). The procedure will be carried out only by physicians experienced with this laser. Because this laser is low risk and easy to use, first-year resident physicians are familiar with this device and use it daily after their first six months of training.
5. IOP and outflow facility will then be measured two hours after TP.
6. AIT will subsequently be performed within two days of admission.
7. At their one week follow-up visit, IOP and outflow facility will be measured with a pneumatonometer. The measurements will also be repeated one and three months after the AIT procedure.

Recruitment is planned for about six months. For each individual the period of participation will be approximately three months with the total course of the study being 12 months.

7. Studienpopulation / Human Subjects

Glaucoma patients with open angle glaucoma (OAG) who qualify for AIT are recruited in our glaucoma clinic at the University Hospital Würzburg.

The **inclusion criteria** are as described previously [1,2,8,32] and consist of:

- worsening glaucoma as evidenced by
    - uncontrolled IOP while using maximally tolerated medical therapy or
    - progressive thinning of retinal nerve fiber layer by Spectral Domain OCT ($p < 0.05$) or
    - visual field progression: new glaucoma-associated peripheral defects or extension of preexisting defects or
- visually significant cataract and indication to reduce IOP or glaucoma medication burden by combining cataract surgery with AIT
- individuals ≥ 18 years of age
- diagnosis of open angle glaucoma including
    - primary open angle glaucoma
    - pigmentary glaucoma
    - pseudoexfoliation glaucoma

The **exclusion criteria** are:

- diagnosis of
    - neovascular glaucoma
    - angle-closure glaucoma
    - uncontrolled uveitis
- prior glaucoma surgery
- preexisting conditions affecting the episcleral venous pressure
    - Grave's ophthalmopathy
    - Sturge-Weber syndrome
    - arteriovenous fistulas (carotid-cavernous fistula)

8. Individueller Studienablauf / Individual Course of Study

Recruitment in glaucoma clinic	day 0	- detailed discussion of study - information leaflet - informed consent - schedule appointment within 14 days
Admission for surgery	within 2 weeks	- additional questions answered - best corrected visual acuity (BCVA) measured - IOP and outflow facility measurements - TP with YAG-Laser - AIT / Phaco-AIT
Follow-up #1 Follow-up #2 Follow-up #3	1 week after AIT 1 month after AIT 3 months after AIT	- BCVA - eye exam - IOP and outflow facility measurements

BCVA: The best corrected visual acuity is assessed using a number chart at 5 meters.
IOP and outflow facility: The IOP measurement is performed using a pneumatonometer. The cornea anesthetized using Oxybuprocain eye drops. Next, the probe is placed on the central cornea and the IOP is measured.

TP: The patient's eye is anaesthetized using Oxybuprocain eye drops. A trabeculoplasty lens is placed on the eye using contact gel and four trabeculopunctures are carried out along the nasal trabecular meshwork with the aid of an Nd:YAG laser.

AIT/Phaco-AIT: The procedure is performed in the operation theatre in either local or general anesthesia. A trabectome is used to excise the trabecular meshwork around 180 degrees nasally. If applicable (Phaco-AIT), the patient will also undergo a lensectomy followed by an intraocular lens insertion.

8.1. Medikation / Medications

Postoperative drops after TP/AIT

- dexamethasone drops four times daily, reduced weekly by one drop
- ofloxacin eye drops four times daily for seven days
- glaucoma drops may be restarted depending on postoperative IOP (but not when IOP < 20 mmHg in the first month)

9. Unerwünschte Ereignisse (AE) und schwerwiegende unerwünschte Ereignisse (SAE) / Adverse Events (AE) and Serious Adverse Events (SAE)

9.1. Definition / Definition of AE and SAE

Adverse events

- after trabeculopuncture
    - persistent IOP elevation by more than 30% above baseline
    - hyphema
    - corneal erosion
- after AIT
    - persistent IOP elevation by more than 30% above baseline
    - cystoid macular edema

Serious adverse events

- after TP
    - uncontrolled IOP elevation by more than 30% above baseline using maximal glaucoma medication
- after AIT
    - uncontrolled IOP elevation by more than 30% above baseline using maximum glaucoma medication
    - persistent hyphema of more than 50% for five days or longer
    - IOL sub-/luxation
    - endophthalmitis

9.2. Medizinische Maßnahmen / Treatment Plan of AEs & SAEs

AE	**Treatment**
IOP elevation by more than 30% above baseline after TP	1x apraclonidine eye drops - IOP check in 1 h if no decrease - additional pressure lowering drops (miotic, beta-blocker, prostaglandin agonist, carbonic anhydrase inhibitor) - IOP check in 1 h if no decrease - oral acetazolamide 1 g, then 500 mg three times per day (if no contraindications) if no decrease - see glaucoma section SOP (“Therapie Glaukomverdacht und Glaukom”)
hyphema	observe and reassure that there is no active bleeding, blood will be removed during AIT
corneal erosion	lubricating eye drops + ointment if large, antibiotic eye drops four times daily for three days
IOP elevation by more than 30% above baseline after AIT	initiate one of prior glaucoma drops if no decrease - additional pressure lowering drops - (miotic, betablocker, prostaglandin agonist, carbonic anhydrase inhibitor) - IOP check in 1 h if no decrease - oral acetazolamide 1 g, then 500 mg three times per day if no decrease - see glaucoma section SOP (“Therapie Glaukomverdacht und Glaukom”) -
SAE	**Treatment**

uncontrolled IOP elevation by more than 30% above baseline using maximal glaucoma medications after TP	see glaucoma section SOP (“Therapie Glaukomverdacht und Glaukom”), perform glaucoma surgery sooner
uncontrolled IOP elevation by more than 30% above baseline using maximal glaucoma medication after AIT	see glaucoma section SOP (“Therapie Glaukomverdacht und Glaukom”), consider additional glaucoma surgery - micro-shunt implant (Preserflo) - filtering surgery (trabeculectomy) - tube shunt (Ahmed, Baerveldt)
persistent hyphema	anterior chamber lavage
IOL sub-/luxation	IOL-reposition or implantation of new IOL
postoperative endophthalmitis	follow “UKW Augenklinik SOP - Endophthalmitis”

10. Biometrische Aspekte / Biometrics and Data Analysis

Surgical success is defined as IOP reduction by at least 20% after AIT, which equals an increase in outflow facility of approximately 25% according to the Goldmann equation. Individuals are assigned retrospectively to one of two groups, responders and non-responders, depending on the surgical success of AIT. This study is a pilot study and we aim to recruit as many patients as possible, within the allotted time frame, to increase the power and validity/generalisability of results. The statistical analysis calculates a sample size of 55 individuals.

Changes in IOP and outflow resistance are to be compared between groups using a Student’s t-Test. A predictive parameter P, defined as $R_{tp}/R_{baseline}$, will be used as a preoperative test to measure the distal outflow resistance of the individual’s eye. Eyes with a P value of 0.75 or greater will be considered to have an increased distal outflow resistance and therefore, potential non-responders to AIT treatment. In this case, mere ablation of TM is predicted to result in an insufficiently decreased postoperative IOP.

For all our statistical analyses, a p-value of 0.05 or less will be considered statistically significant.

11. Datenmanagement / Data Management

Patient data and data analyses are saved in an access-protected, access-logged online UKW drive. Signed paper documents of informed consent are filed and locked.

12. Ethische und Rechtliche Aspekte / Ethical and Legal Aspects

The study conforms to the Declaration of Helsinki and the guidelines of Good Clinical Practice (ICH-GCP 1997). The European General Data Protection Regulation (EU GDPR 2016/679) is likewise respected.

13. Referenzen / References

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