Influence of Selective Laser Trabeculoplasty (SLT) on the iStent inject® outcomes

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Abstract

Background: To evaluate the influence of Selective Laser Trabeculoplasty (SLT) on iStent inject® outcomes in open-angle glaucoma (OAG).

Methods: In this retrospective comparative cohort outcome study, 66 patients who were treated with two iStent inject® devices were included. Patients were divided into two subgroups consisting of patients without SLT treatment prior to surgery and patients who had been treated previously with 360° SLT but without sufficient response. Outcome measures included intraocular pressure (IOP) and number of antiglaucoma medications after 6 weeks with three, six, 12, and 24 month follow-ups.

Results: Mean preoperative IOP decreased from 20.4 ± 5.3 mmHg to 14.8 ± 3.0 mmHg for patients without SLT treatment prior to surgery (p = 0.001) and from 19.2 ± 4.5 mmHg to 14.0 ± 1.6 mmHg for patients with insufficient response to 360° SLT treatment (p = 0.027) at 12 months after iStent inject® implantation. No significant difference was found between the two groups (p > 0.05). The number of antiglaucoma medications did not change in both groups (p > 0.05) and showed no significant difference between the two groups (p > 0.05).

Conclusion: Prior SLT treatment seems to have no negative influence on the IOP lowering-effect of iStent inject® implantation in patients with OAG. It is therefore an appropriate incremental procedure with no exclusion criterion for an iStent inject® implantation.

Keywords: SLT, iStent inject

Background

The treatment of Primary Open Angle Glaucoma (POAG) and secondary Glaucoma like Pseudoexfoliation Glaucoma (XFG) or Pigment dispersion Glaucoma remains a challenge despite several treatment methods. The primary focus of these methods is treating the elevated intraocular pressure (IOP), because an elevated IOP is a major risk factor for the development and progression of glaucoma. Medical treatment, laser treatment and surgery are the available methods to reduce IOP.

Selective Laser Trabeculoplasty (SLT) is one possibility of laser treatment. The method uses a 532 nm Nd:YAG laser to target the pigmented cells of the trabecular meshwork [1]. Several studies demonstrated that SLT is an efficient and safe method to reduce sustainably the IOP in glaucoma patients [1-13], although the mechanism remains uncertain. Three possible involved mechanisms are discussed: dislodging of trabecular cells, mechanical distension of Schlemm’s canal, stimulation of cellular production, and turnover of extracellular matrix [14]. In contrast to the argon laser trabeculoplasty (ALT), histologic and ultrastructural studies found less extensive damage and no coagulative effects on the trabecular meshwork after SLT [12, 15, 16]. Nonetheless,
mechanical damages can still be observed because SLT produces disruption of trabecular beams, accumulation of cellular debris, fragmentation and sloughing of endothelial cells [15] and results in an increased trabecular meshwork monocyte recruitment as a result of increased chemokine production [12, 17]. Additionally, in-vitro experiments showed an increase in pro-inflammatory cytokine expression [12, 18].

Micro-invasive glaucoma surgery (MIGS) is used more and more often and can easily be combined with microincision cataract surgery. The iStent inject® (Glaukos Corporation, Laguna Hills, CA, USA) is one of the available MIGS and fulfills the criteria of MIGS: ab interno microincision, minimal trauma, efficacy, high safety profile and rapid recovery [19]. The target structure of performing this procedure is also the trabecular meshwork. As the trabecular meshwork is considered as the primary source of resistance to aqueous drainage in many glaucoma forms, the aim of the iStent inject® is lowering the IOP by bypassing the trabecular meshwork and using the natural physiological pathways behind it [20–23]. Trabectome is an alternative MIGS with the same intent as the iStent inject®. Prior SLT treatment seems to have no negative influence on combined clear cornea phacemulsification and Trabectome outcomes in glaucoma patients [24], although it leads to an alteration of the trabecular meshwork. But Wimmer et al. showed, that ALT appears to increase the risk of bleb scarring in XFG patients after trabeculectomy because of increased levels of activated TGF-beta 2. In addition, Khalili et al. demonstrated a significant lower success rate in terms of normalization of IOP after trabeculectomy in patients with prior argon laser trabeculoplasty [25, 26]. Since SLT may lead to mechanical damage and results in chemokine production, SLT may affect a subsequent glaucoma surgery and its success.

The impact of SLT treatment and the associated alteration of the trabecular meshwork previously performed to iStent inject® implantations remains unclear. Our hypothesis is that the prior SLT could decrease the treatment effect of iStent inject® implantations. Therefore, this study examined the influence of SLT treatment on iStent inject® outcomes in open-angle glaucoma (OAG).

Methods

In this retrospective, comparative, cohort, outcome study between June 2014 and February 2016, we included eyes from patients that underwent MIGS with implantation of two iStent inject® devices at the Department of Ophthalmology, Charité – Universitätsmedizin Berlin. All patients diagnosed with moderate OAG (including primary and pseudoexfoliative glaucoma) who underwent MIGS with implantation of two iStent inject® devices were included into this study. Cases with missing follow-up data, with previous incisional procedures (trabeculectomy, tube shunts, Trabectome, cyclophotocoagulation) and implantations combined with cataract surgery were excluded. Only data of the right eye were included in patients who underwent implantation of iStent inject® devices on both eyes. If a secondary glaucomatous surgery during the follow-up time was necessary data were not analysed anymore after the time point of secondary glaucomatous surgery. Ethic approval had been given by the Ethikkommission, Charité – Universitätsmedizin Berlin, EA4/047/20. For this type of study formal consent is not required because it is a retrospective, single-center study and the Ethikkommission, Charité – Universitätsmedizin Berlin approved the waiver of consent. This study adhered to the ethical standards of the Declaration of Helsinki. An informed written consent was provided for surgery. The following was performed for each patient: a complete ophthalmological examination – including a medical history review – best corrected visual acuity (BCVA) measurement tested with a Snellen chart, slit-lamp examination, IOP measurement using Goldmann’s applanation tonometry, gonioscopy, dilated fundus examination, stereoscopic photographs of the optic disc, a baseline bilateral standard automated perimetry threshold visual test using the 30–2 Tendency-Oriented Perimetry (TOP) programme (Octopus, Haag-Streit), and a baseline peripapillary retinal nerve fibre layer (RNFL) thickness measurement by Spectralis optical coherence tomography (OCT) (Spectralis OCT, Heidelberg Engineering GmbH, Heidelberg, Germany).

Mild- or early stage open angle glaucoma and moderate open angle glaucoma were defined as described by Gonnermann et al. [23]. Two independent observers categorised the visual field status of all patients before surgery as mild, moderate or advanced based on the 30–2 Tendency-Oriented Perimetry programme. In cases of disagreement, the visual field status was judged by a third senior glaucoma specialist (MK). In this study we included only patients with mild and moderate visual field defects. Average RNFL thickness was documented for mild and moderate stage, defining the open angle glaucoma.

Drawing from routine questionnaires given to all patients prior to examination, it is to the author’s best knowledge that all patients were free from other oculic diseases apart from glaucoma and cataract.

MIGS with implantation of two iStent inject® devices was performed in patients with OAG because of two reasons. The first reason was an insufficient IOP despite well tolerated local antiglaucomatous therapy and the preference for a minimally invasive procedure. The second reason was an insufficient IOP without local therapy. In these patients the minimally procedure was chosen to avoid a local antiglaucomatous therapy. In all
other cases, where the local therapy was not well toler- 
ated or a low target pressure was needed because of an 
advanced glaucoma, an alternative procedure (trabecu-
lectomy or glaucoma drainage device) was performed 
and patients were not included. All included patients 
were divided into two subgroups. These included pa-

tients without previous SLT treatment (group A) and 
patients who had insufficient or no longer sufficient IOP 
reduction after 360° SLT treatment with a minimum of 
3 months prior to surgery (group B) – the Trabeculas 
SLT (A.R.C. Laser, Nuernberg, Germany) using 95–105 
spots applied to the trabecular meshwork. The evalu-
ation of success rates (IOP < 18 mmHg) after SLT pro-

dure could be shown to be 74.5% after 3 years (data 
submitted for publication). The main reasons for initially 
performed SLT before following iStent inject™ implant-
amination was a barely not achieved target pressure (2–4 
mmHg above target pressure) with or without local anti-
glaucomatous therapy or patients preference to avoid 
initially a surgery. Insufficient or no longer sufficient IOP 
reduction after SLT treatment was defined as an 
IOP above the target pressure, needing an increase of 
the antiglaucoma medication in routine examination 
with a minimum of 3 months after SLT in the study eye. 
The target pressure was individualized based on the fac-
tors recommended by the European Glaucoma Society 
including stage of glaucoma, IOP before treatment, age 
and life expectancy, rate of progression and presence of 
risk factors for progression.

Goldmann applation tonometry was performed 
measuring IOP and the topical antiglaucoma medica-
tions applied were noted 1 day preoperatively, and then 
on a 1 day, six-week, three-, six-, 12-, 24- month fre-
quency postoperatively.

Surgical technique
All procedures were performed by three experienced 
surgeons (MK, JG, NT) using the same surgical protocol 
under topical anaesthesia.

The implantation of two iStent inject™ devices was per-
fomed as published before after an ophthalmic viscosur-
gical substance was injected into the anterior chamber 
for stability [22, 23]. Per protocol, the iStents were 
inserted nasally under gonioscopic control through the 
trabecular meshwork into Schlemm’s canal, separated by 
approximately two clock hours.

Standard postoperative treatment included a topical 
combination of steroids and antibiotics. Following the sur-
gery, therapy was reduced over a period of 4 weeks. Anti-
glaucoma medication was used by patients as needed.

Statistical methods
Statistical analysis was performed using IBM SPSS statis-
tics 19 (SPSS Software, Munich, Germany). A sample 
size calculation was based on the assumption of a mean 
postoperative IOP 11.83 ± 2.21 mmHg based on the 
available data in the literature and a distribution of 4:1 
[24]. At a power of 80% and an alpha level of 5%, we es-

timated that a group size of 60 patients would allow to 
detect a difference of 2 mmHg. A post-hoc power ana-
ysis revealed that we could find a difference of 3 mmHg 
at an alpha of 5% and a power of 80%.

Descriptive statistics were expressed as mean ± stand-
ard deviation (SD) and minimum and maximum. Nor-
mality was tested for all outcome measures and the 
appropriate statistical test was used. We used nonpara-
metric tests (Wilcoxon signed-rank test, Mann-Whitney-
U test). Kaplan-Meier survival analysis and the log-rank 
test were used to analyze the second surgery free sur-

vival incidence. To explore independent risk factors for 
IOP, we entered preoperative parameters (patient’s age, 
status of lens, POAG versus XFG, SLT treatment prior 
to surgery or not) into a linear regress model. Differences 
were considered statistically significant when p-values were less than 0.05.

Results
Between June 2014 and February 2016, 193 eyes of 170 
patients diagnosed with moderate OAG (including pri-
mary and pseudoexfoliative glaucoma) who underwent 
MIGS with implantation of two iStent inject™ devices were 
screened for the study. Fifteen eyes with missing follow-

up data, 23 eyes because of the second eye of a patient, 74 
eyes with implantations combined with cataract surgery 
and 15 eyes with previous incisional procedures (trabecu-
lectomy, tube shunts, Trabectome, cyclophotocoagulation) 
were excluded. In total, sixty-six eyes of 66 Caucasian pa-
tients (35 females, 31 males; mean age 73.1 ± 11.7 years) 
with moderate OAG (POAG n = 45 and XFG n = 21) were 
included in the study. In all cases, two iStent inject™ de-

vices were implanted. The average follow-up time was 
539 ± 285 days.

Table 1 presents the preoperative characteristics. Fig-

ure 1 shows the IOP measurements and Fig. 2 the 
change in number of antiglaucoma medication over time 
for both groups.

A significant decrease was present in postoperative 
IOP compared to preoperative IOP at any time point 
(p < 0.001 after 12 months, p = 0.001 after 24 months). 
At 12 months, the average decrease in group A was 
19.0% ± 20.7% (p = 0.001) and in group B 19.8% ± 11.8% 
without significant differences between the two groups 
(p = 0.981). Similarly, when considering absolute IOP 
values, no significant differences were noted during the 
entire follow-up period (preoperative p = 0.538, n = 66, 
after 1 day p = 0.720, n = 63, after 6 weeks p = 0.329, n = 
55, after 3 months p = 0.364, n = 32, after 6 months p =
0.448, n = 32, after 12 months p = 0.633, n = 31 and after 24 months p = 0.171, n = 19).

The number of antiglaucoma medications did not change in both groups (p > 0.05) from 2.56 ± 1.04 in group A and 2.57 ± 1.16 in group B preoperatively to 2.46 ± 1.18 (p = 0.917) and 2.57 ± 1.27 (p = 0.317) at 12 months after surgery, respectively. Only 6 weeks after surgery the amount of topical medications was significantly decreased (p < 0.001). There was no significant difference in both groups during the entire follow-up period (preoperative p = 0.915, n = 66, after 1 day p = 0.160, n = 66, after 6 weeks p = 0.529, n = 56, after 3 months p = 0.532, n = 32, after 6 months p = 0.381, n = 32, after 12 months p = 0.825, n = 31 and after 24 months p = 0.712, n = 19).

Linear regression showed no association between preoperative parameters (patient’s age, status of lens, POAG versus XFG, SLT treatment prior to surgery or not) and postoperative IOP values after 12 and 24 months postoperatively (Tables 2 and 3).

Best-corrected visual acuity did not change significantly at any point in time. Additionally, there was no significant difference in BCVA between the two groups at any point in time during the entire follow-up (p > 0.05).

Apart from a reflux bleeding that occurred in 100% of patients, there were no severe intraoperative and postoperative complications including choroidal effusion, sustained hypotony, choroidal hemorrhage, or infection. The reflux bleeding resolved spontaneously itself. Secondary glaucomatous surgery had to be performed in 21.2% in group A and in 21.4% in group B due to insufficient IOP lowering-effect after MIGS (p = 0.788) (Fig. 3).
Discussion

The study investigated the influence of previous SLT treatment on the outcomes of iStent inject® implantation in OAG. SLT and other glaucoma surgeries like trabecurome, trabeculotomy and iStent inject® implantation have the same target: the trabecular meshwork. These procedures improve the outflow of aqueous humor. However, literary information about the influence of SLT on further glaucoma surgeries with the same target is sparse.

The Trabectome Study Group showed data that previous laser trabeculoplasty did not affect the following Trabec- tome surgery negatively [27], however no differentiation between ALT, SLT, and micropulse diode laser trabecu- loplasty modalities was made in the data collection. Furthermore, Klamann et al. demonstrated data that previous SLT treatment did not influence negatively combined clear cornea phacoemulsification and Trabec- tome outcomes in glaucoma patients [24]. Additionally,
the effect of prior laser treatment (ALT, SLT) on the IOP lowering effect of trabectulectomy is not clear [25, 26, 28, 29].

According to the mean postoperative IOP, the mean number of antiglaucoma medications, and the number of eyes needing a secondary surgery to control IOP, we found no significant difference between patients without SLT treatment prior to iStent inject® implantation and patients who had insufficient or no longer sufficient response to 360° SLT treatment previous to surgery. Additionally, we found no correlation between the preoperative parameters, patient’s age, status of lens, POAG versus XFG, and especially SLT treatment prior to surgery or not, and postoperative IOP after 12 and 24 months postoperatively (p > 0.05). The iStent inject® implantation as a single procedure has shown to be effective in lowering IOP with minimal side effects as seen in our study [20–23]. Additionally, the effect in a lower IOP seems not to be influenced by a prior SLT treatment as hypothetically thought. The 360° SLT treatment alone is effective in lowering the IOP by improvement the outflow pathways of the whole trabecular meshwork in patients with XFG and PG [1–13]. In our study, if SLT treatment was insufficient or no longer sufficient to reduce IOP, a following iStent inject® implantation would lead to an IOP reduction by bypassing the trabecular meshwork – which is the major source of outflow resistance in open angle glaucoma. The previous treated pigmented cells and the associated alterations of the trabecular meshwork by SLT did not influence the IOP lowering-effect. Additionally, the number of eyes needing a secondary surgery to control IOP did not differ between SLT treated and non-treated groups. However, due to the study design, which included patients with an insufficient or no longer sufficient SLT, it has to be taken into account that the alterations of the trabecular meshwork by SLT in these patients might be less and this could be a reason for the missing influence. Based on our data, there was no significant group difference between patients with or without previous SLT. Further detailed studies that analyze inflammatory factors in the anterior segment and the alterations of the trabecular meshwork after SLT are necessary.

Nevertheless, an insufficient or a no longer sufficient SLT treatment should not be considered as an exclusion criterion for successful treatment by using iStent inject® implantation. Additionally, both interventions have the main advantage over standard filtering procedures like trabeculectomy to increase an outflow facility along the natural pathway [20–23]. Although in some cases, an IOP lowering is not sufficient and other surgical procedures like filtering or cyclodestructive procedures become necessary during follow-up sessions.

The main limitations of this study are the retrospective nature of the study design and the limited number of patients. Moreover, the follow-up time period of only 2 years is relatively short for glaucoma. Additionally, we included only patients with implantations of iStent inject® as single procedure and only patients with no other glaucoma surgery before. These might be selection bias. Therefore we cannot discuss the IOP lowering effect of iStent inject® implantations after SLT in more complicated cases and these factors may limit the generalizability of our findings to the entire population of patients with OAG. Additionally, the iStent inject® implanations were performed by 3 different surgeons in our study. Therefore, it is possible that surgeon depending differences influenced the results. To confirm the results of the present study, further prospective studies with a larger number of patients and a longer follow-up period are necessary.

| Table 2 | Data of linear regression for postoperative IOP values after 12 months |
|---|---|---|---|---|
| IOP after 12 months | Regression coefficient | 95% confidence interval lower bound | 95% confidence interval upper bound | p-value |
| Patient’s age | −0.101 | −0.231 | 0.028 | 0.119 |
| POAG versus XFG | 0.931 | −1.688 | 3.550 | 0.471 |
| SLT treatment prior to surgery or not | −0.791 | −3.258 | 1.676 | 0.516 |
| Status of lens | −0.015 | −3.511 | 3.481 | 0.993 |

| Table 3 | Data of linear regression for postoperative IOP values after 24 months |
|---|---|---|---|---|
| IOP after 24 months | Regression coefficient | 95% confidence interval lower bound | 95% confidence interval upper bound | p-value |
| Patient’s age | −0.005 | −0.151 | 0.140 | 0.942 |
| POAG versus XFG | −1.149 | −4.861 | 2.562 | 0.517 |
| SLT treatment prior to surgery or not | −2.142 | −5.575 | 1.290 | 0.202 |
| Status of lens | 0.740 | −3.364 | 4.845 | 0.705 |
Conclusion
In conclusion, SLT is effective in lowering the IOP safely in a high number of glaucoma patients including POAG and XFG [1–13]. In this study, we did not find strong evidence for a negative effect of insufficient or no longer sufficient SLT prior to iStent inject® implantations. Nevertheless, SLT could have a negative effect on iStent inject® implantations but given our findings, we believe that such effect would be very small and possibly of no clinical importance. Therefore, SLT is an appropriate procedure prior to iStent inject® implantations with no exclusion criterion for an additional intervention on the trabecular meshwork.

Abbreviations
ALT: Argon Laser Trabeculoplasty; IOP: intraocular pressure; SLT: Selective Laser Trabeculoplasty; MIGS: Micro-invasive glaucoma surgery; OAG: open angle glaucoma; POAG: Primary Open Angle Glaucoma; XFG: Pseudoexfoliation Glaucoma

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Authors’ contributions
AKM, PA, MP, AMD and DP collected, analyzed and interpreted the patient data. AKM, MKJK and SW were major contributors in writing the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
Ethic approval has been obtained by the Ethikkommission, Charité – Universitätsmedizin Berlin, EAA/047/20. For this type of study formal consent is not required because it is a retrospective, single-center study and the Ethikkommission, Charité – Universitätsmedizin Berlin approved the waiver of consent. The study adhered to the ethical standards of the Declaration of Helsinki. An informed written consent was provided for surgery. No administrative permission was required to access the raw data from the Charité – Universitätsmedizin Berlin.

Consent for publication
Not Applicable.

Competing interests
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. SW has served as consultant for: Allergan, Novartis, Beyer, Heidelberg engineering.

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