SAS Journal of Surgery
Abbreviated Key Title: SAS J Surg
ISSN 2454-5104
Journal homepage: https://www.saspublishers.com

OPEN ACCESS

Medicine

Ocular Surface Changes in Glaucomatous Patients Undergoing Cataract Surgery Combined with Micro Invasive Glaucoma Surgery (2nd Generation Trabecular Stents Istent Inject ®): A Study about 69 Eyes

Omar Bengebara[1], [2*], Malek Slim[2], Ahmed Bennis[1], Fouad Chraibi[1], Meriem Abdelloui[1], Idriss Benatiya Andaloussi[1]

[1]Service d'ophtalmologie, Centre Hospitalo-universitaire Hassan II, Fès, Maroc
[2]Service d'ophtalmologie, Centre Hospitalier Jacques Cœur, Bourges, France

DOI: 10.36347/sasjs.2024.v10i06.003 | **Received:** 23.09.2023 | **Accepted:** 28.10.2023 | **Published:** 04.06.2024

***Corresponding author:** Omar Bengebara
Service d'ophtalmologie, Centre Hospitalo-universitaire Hassan II, Fès, Maroc

Abstract **Original Research Article**

Introduction: The purpose of this study was to evaluate ocular surface changes and dry eyes symptoms in patients undergoingcataract surgery by phacoemulsification combined with implantation of two trabecular stents (Istent Inject®). ***Methods***: This single-arm prospective interventional clinical trial enrolled 69 patients with mild-to-moderate open-angle glaucomataking 1 to 4 glaucoma medications that underwent phacoemulsification combined with implantation of two trabecular stents (Istent). We explored several key data about ocular surface and glaucoma evolution throughout the follow-up, including the Ocular Surface Disease Index score, the Oxford score, the Efron conjunctival score, and the Fluorescein Tear Break-up Time (FTBUT). ***Results***: Mean OSDI scores improved from 40.1 ± 21.6 (severe dry eye) preoperatively to 17.5 ± 15.3 (mild dry eye) at 3 months. While 73% of eyes had moderate or severe OSDI scores preoperatively, only 29% had such scores at 3 months. The mean FTBUTincreased from 4.3 ±2.4 seconds preoperatively to 6.4 ±2.5 seconds at 3 months; the average Oxfordstaining score decreased from 1.4 ± 1.0 preoperatively to 0.4 ± 0.6 at 3 months. There was a reduction in the number of glaucoma medications from 1.5 to 0.6 medications. Mean IOP decreased from 17.4 ± 4.2mmHg to 14.5 ± 3.2mmHg at the 3 months follow-up. The safety profile of the surgery was excellent. ***Conclusion***: The implantation of two trabecular stents (Istent inject®) combined with cataract surgery resulted in clinical and functional improvements in ocular surface health, as well as significant reductions in IOP and medications in patientswith open-angle glaucoma.

Keywords: Dry eye; Ocular surface, Quality of life, Trabecular stent, micro invasive glaucoma surgery.

INTRODUCTION

Dry eye is one of the main reasons for consultation in ophthalmology [1- 3]. It corresponds to either insufficient tear production or unstable tear film often associated with ocular surface damage, as well as irritative symptoms such as eye stinging, photophobia and blurred vision [1- 3]. Many recent studies estimate the prevalence of dry eye to be around 25% in people over 65 years [4, 5]. This percentage rises to 78% in case of associated glaucoma, among which 69% of patients suffer from a moderate or severe dry eye syndrome [6, 7]. This epidemic prevalence is often linked to the use of preservative-containing hypotonizing eye drops, which are known to promote the development and worsening of dry eye syndrome [7- 9].

More than deteriorating the quality of life (QOL) in glaucoma patients [1- 12], dry eye syndrome also contributes to poor therapeutic compliance [13, 14]. Moreover, it increases the risk of failure of an eventual glaucoma filtration surgery [15, 16]. Therefore, ocular surface is an essential parameter to consider in the management of glaucomatous patients.

To date, the main modifiable risk factor for glaucoma progression is high intraocular pressure (IOP), and only lowering IOP can delay the onset of glaucoma or slow its progression [2]. The conventional therapeutic arsenal to reduce intraocular pressure includes laser procedures as well as filtering surgery, but the first-line treatment of glaucoma consists of the instillation of ocular hypotonizing eye drops [2].

In addition to these treatments, a new promising therapeutic option is the Micro Invasive Glaucoma Surgery (MIGS) with the placement of trabecular stents by an ab-interno approach. Among these devices, the

Istent Inject® trabecular micro-bypass stent (Glaukos Corp., San Clemente, CA) has been the most widely used and studied. A more recent second-generation device, (approved by the FDA in 2018 and widely used in Europe and worldwide) is the Istent Inject G2W ®: The surgeon inserts two micro stents through the failing trabecular meshwork to Schlemm's canal, which allows an increased drainage of aqueous humor from the anterior chamber and a sustainable decrease in intraocular pressure [16- 19].

Istent Inject® indications' include various subtypes of glaucoma such as pseudo exfoliative, pigmentary and normal tension glaucoma, as well as in primary open angle glaucoma (POAG) [16- 19]. Several studies demonstrated the effectiveness of trabecular stents in lowering IOP [34- 46]. This effect persists even long after the implantation, with a proven sustainability up to five years according to recent publications [20]. Numerous studies also evaluated the safety profile of these implants, with very encouraging results, especially when compared to traditional filtering surgery [20- 33]. Despite these findings, no real-life studies -to our knowledge- have investigated the effect of Istent Inject® use on the ocular surface of glaucoma patients.

Thus, given the high prevalence of dry eye in glaucoma patients and the increasing use of MIGS devices worldwide, we felt it is important to address this topic.

METHODS

Study Parameters

This prospective interventional study conducted at the ophthalmology department of Bourges Hospital included 69 eyes of 52 patients with uncomplicated senile cataract and treated for open-angle glaucoma (primary, pseudo exfoliative, or pigmentary) treated by hypotonizing eye drops. The glaucoma cases included in our study were all early or moderate. All our patients underwent cataract surgery by phacoemulsification with placement of a hydrophobic monofocal implant in the capsular bag followed by the implantation of two Istent Inject® 2nd generation trabecular stents (Istent Inject W®, Glaukos Corporation, Laguna Hills, CA, USA) at the end of the procedure. We excluded from our study all glaucoma patients who had undergone another treatment for glaucoma (laser procedure or filtering surgery).

We assessed the following dry eye syndrome markers: the Ocular Surface Disease Index OSDI questionnaire score [21], the Oxford score for corneal/conjunctival staining [22], the Efron score for conjunctival hyperemia [23], and the Fluorescein Tear Break up Time (FTBUT). These four parameters are widely used and set as references in the evaluation of the ocular surface.

The OSDI *(Questionnaire in the Appendix)* is a reference questionnaire used to assess dry eye symptoms, severity and impact on visual function in patients [21]. The OSDI score ranges from 0 to 100, its grading is defined as follows: normal for a score between 0 and 12, mild dry eye for a score between 13 and 22, moderate for a score between 23 and 32 and dry eye is classified as severe for scores above 32. The OSDI score is widely referenced in the literature [1- 21], it is established as the gold standard for the diagnosis of dry eye syndrome because of its reliability and versatility [21]. To fulfill the purposes of our study, all our patients answered this questionnaire at all the clinical examination (preoperatively as well as at the postoperative controls: 7th day, 1st month, 3rd month and 6th month).

We assessed the rest of the scores at the clinical examinations with a slit lamp. The Oxford score *(diagram in appendix*) is based on the observation of the cornea and conjunctiva after instillation of fluorescein on an unanesthetized ocular surface [22]. The FTBUT test is performed by instilling 2% sodium fluorescein in the inferior conjunctival fornix, asking the patient to blink normally, and finally measuring tear breakup time under unanesthetized conditions. FTBUT is defined as normal if longer than 10s, dry eye is diagnosed as mild to moderate for a FTBUT between 5 and 9s, and dry eye classifies as severe for a FTBUT less than 5s [6].

The Efron scale for conjunctival hyperemia is the last score we evaluated *(see diagram in appendix)*, it is based on the slit lamp examination compared to standardized images. The hyperemia score goes from 0 (absent) to 4 (severe) [23].

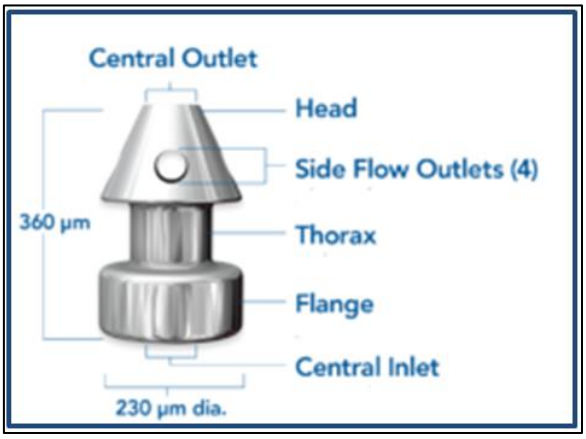
In addition to the above-mentioned parameters, we also assessed the adverse effects of ocular hypotonizing eye drops. We evaluated the different symptoms expressed by the patients, as well as their severity.

The results of the glaucoma follow-up (duration of follow-up, IOP and glaucoma medications) were also collected. We assessed all these information preoperatively as well as during the postoperative follow up that lasted 6 months and included four consultations (at the 7th day, the 1st month, the 3rd month and the 6th month). We measured categorical variables in terms of proportions and continuous variables as means ± standard deviations.

Istent Inject® Devices, Implantation Technique, and Postoperative Treatment

The Istent Inject® device is a biocompatible titanium stent designed to provide controlled shunting through the trabecular meshwork to Schlemm's canal, thereby facilitating aqueous humor drainage from the anterior chamber and decreasing IOP [16-19].

It is a heparin-coated non-ferrous titanium micro-stent intended for ab interno placement. Concerning its measurements, the Istent Inject® has a length of 1 mm and a width of 360 µm. Its internal lumen forms a 230 µm long tube with a diameter of 120 microns (central inlet). The total weight of the stent is 60 µg [16-19, 24].



After successful phacoemulsification and implantation of the intraocular lens in the capsular bag, we proceed a rotation of the operating microscope and a flexion of the patient's neck. We accomplish further exposure of the irido- corneal angle by injection of viscoelastic substance. The operator introduces the preloaded Istent Inject® in the anterior chamber through the existing main phacoemulsification incision after good visualization of the trabeculum with a Gonio-prism [16-19]. Finally, the surgeon implants the two preloaded stents into the inferior nasal trabeculum.

All our patients received the same postoperative cataract surgery treatment, which consisted of topical antibiotic therapy for 1 week, as well as non-steroidal anti-inflammatory (NSAID) and corticosteroid eye drops for 1 month (the corticosteroid therapy stopped after a gradual decrease in the number of instillations spread over 3 weeks).

RESULTS

Study Participants

All eyes (69) underwent uncomplicated phacoemulsification cataract surgery with concomitant implantation of two 2nd- generation Istent Inject® trabecular stents. The mean age was 75.5 +/- 7.6 years, approximately 57% of the patients were female, and all of our patients were diagnosed at the time of surgery with glaucoma classified as early to moderate under hypotonizing eye drops (1 to 3 molecules). Our study included 59% of cases with primary open-angle glaucoma, 22% of cases with pseudo exfoliative glaucoma and the last 19% with pigmentary glaucoma. The average glaucoma evolution of the glaucoma was 6.2+/- 3 years.

Concerning the dry eye syndrome grading, all stages were found preoperatively with a clear predominance of moderate and severe dry eye, as shown by the OSDI score which exceeded 23 in 73% of our patients (moderate or severe dry eye syndrome). The mean OSDI score was 40.1+/-25. The mean Oxford and Efron scores were 1.4 and 1.37, and the average Fluorescein Tear Break up Time value (4.3s +/-2.3) was less than half the normal 10s value.

Efficacy: IOP and Hypotonizing Medications

The average preoperative intraocular pressure of our patients was 19.4 +/- 4.5mmHg. It decreased to 14.5 +/-3.2 mmHg at 3 months (25% decrease in IOP). This effect sustains over time with an average IOP of 14.2+/-2.1 mmHg at 6 months. All our patients were on hypotonizing eye drops with 1.5 +/- 0.9 medications. The majority of them (53%) complained of various adverse effects related to these treatments. The average number of hypotonizing molecules decreased by 0.8+/- 0.6 at 6 months (47% decrease) with 43% of patients no longer requiring anti-glaucoma eye drops at the 6th month postoperative check-up.

	Mean IOP	**Mean number of hypotonizing molecules**	**Percentage of patient under hypotonizing drops**
Preoperatively	19.4 +/- 4.5mmHg	1.5 +/- 0.9 medication	100%
3 months post-operative	14.5 +/-3.2 mmHg	0.9 +/- 0.8 medication	55%
At 6 months post-operative	14.2+/-2.1 mmHg	0.7+/-0.6 medication	43%

Effectiveness: Dry Eye

We noted several changes in dry eye markers between the preoperative examination and the 6-month postoperative checkup. The mean preoperative OSDI score was 40.1 ± 25.6. It decreased to 20.5 ± 19.3 at the 6-month postoperative check-up. Thus, 73% of the eyes had OSDI scores corresponding to moderate or severe dry eye syndrome preoperatively compared to only 32% at 6 months.

At the 6th month postoperative check-up, 54% of the eyes had an OSDI score in the normal range (versus 9% preoperatively). The mean FTBUT increased to 6.4 ± 2.5s from 4.3 ± 2.3s preoperatively, which corresponds to an increase of 48%.

The mean Oxford and Efron scores also decreased significantly from 1.4 and 1.37 preoperatively to 0.4 and 0.6 at 6 months, respectively.

	OSDI	FTBUT	Oxford Score	Efron score
Preoperatively	40.1 +/-25	4.3 +/-2.3 seconds	1.4+/-0.6	1.37+/-0.7
At 6 months post operatively	20.5 ± 19.3	6.4 ± 2.5seconds	0.4 +/- 0.3	0.6 +/- 0.35

Safety

Safety parameters in our study were very favorable. We implanted all of our patients with two trabecular stents. We noted four cases of minimal intraoperative hyphema (5.7%), all of which resolved with adequate postoperative corticosteroid treatment. No postoperative complications occurred during the 6-month follow-up, including no persistent inflammation, no peripheral anterior synechiae (PAS), no ocular hypotony and no corneal decompensation. No patient required additional anti-glaucoma eye drops or filtration surgery during follow-up.

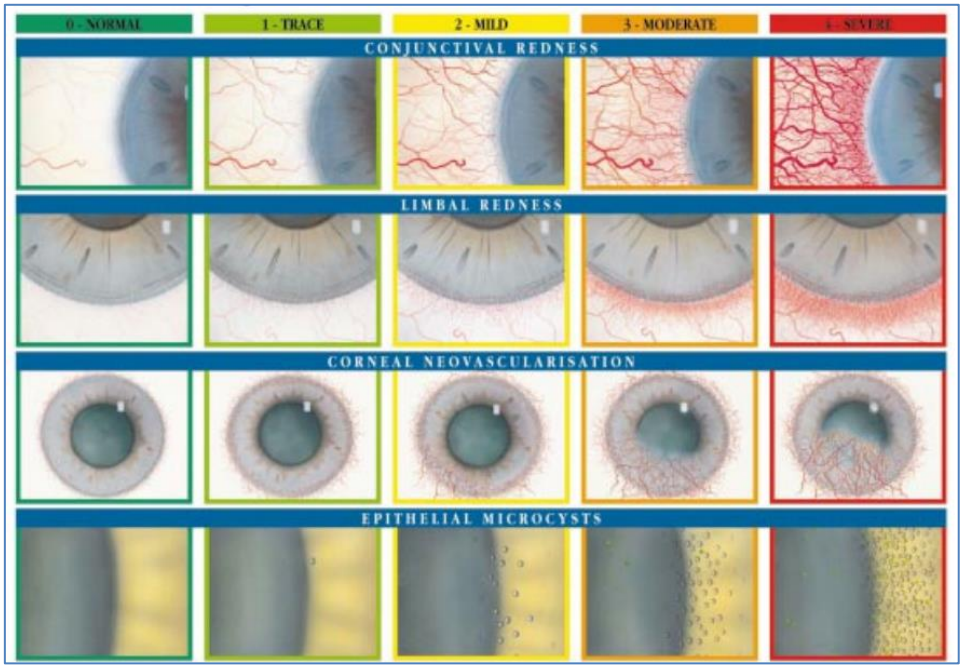


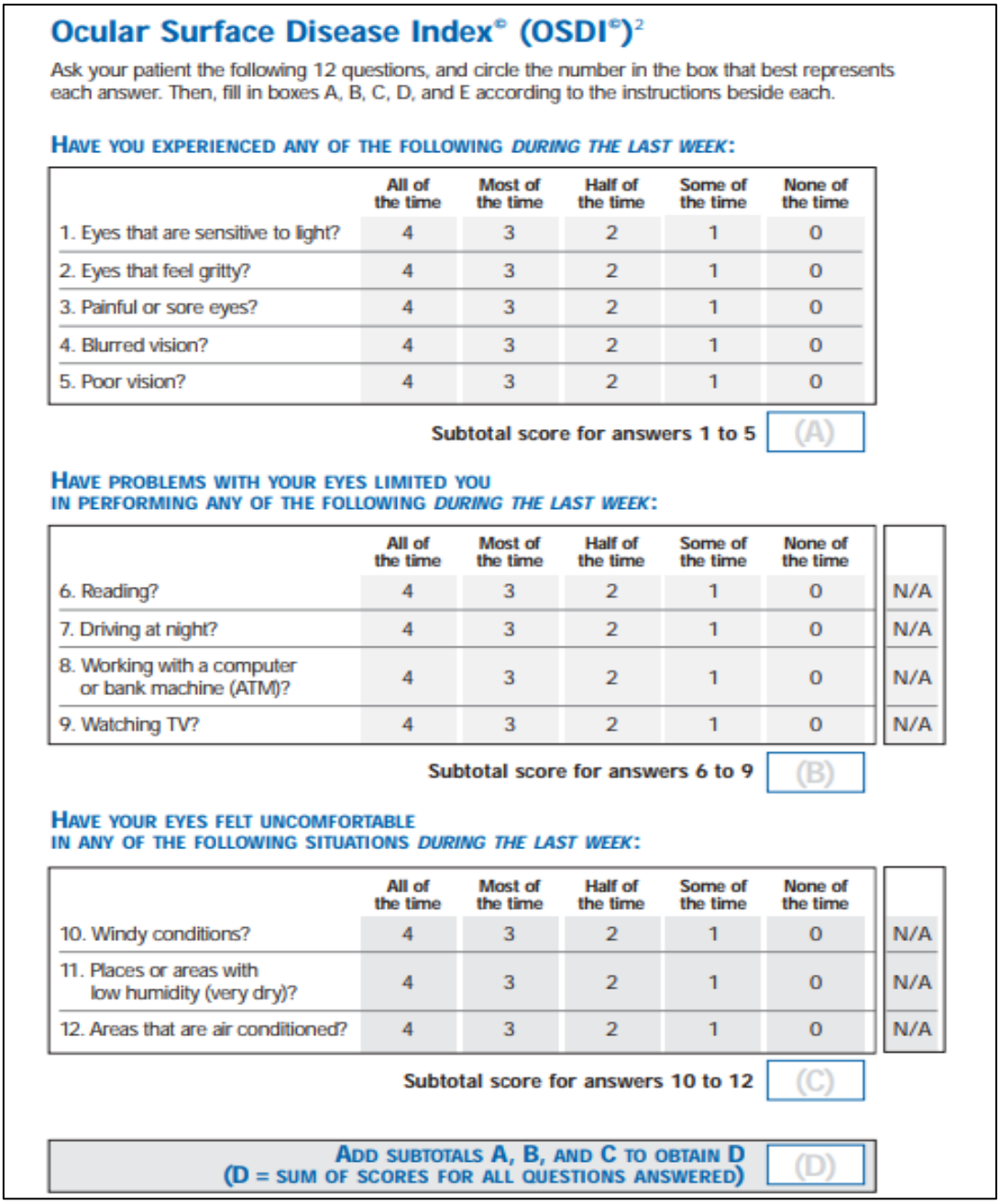
Figure 1 : Score d'hyperhemie conjonctivale Efron.

Grading Schema:

Staining is represented by punctate dots on a series of panels (A-E). Staining ranges from 0-5 for each panel and 0-15 for the total exposed inter-palpebral conjunctiva and cornea. The dots are ordered on a log scale

PANEL	GRADE	CRITERIA
A	0	Equal to or less than panel A
B	I	Equal to or less than panel B, greater than A
C	II	Equal to or less than panel C, greater than B
D	III	Equal to or less than panel D, greater than C
E	IV	Equal to or less than panel E, greater than D
>E	V	Greater than panel E

Figure 2 : Score d'Oxford.



Ocular Surface Disease Index® (OSDI®)[2]

Ask your patient the following 12 questions, and circle the number in the box that best represents each answer. Then, fill in boxes A, B, C, D, and E according to the instructions beside each.

HAVE YOU EXPERIENCED ANY OF THE FOLLOWING *DURING THE LAST WEEK*:

	All of the time	Most of the time	Half of the time	Some of the time	None of the time
1. Eyes that are sensitive to light?	4	3	2	1	0
2. Eyes that feel gritty?	4	3	2	1	0
3. Painful or sore eyes?	4	3	2	1	0
4. Blurred vision?	4	3	2	1	0
5. Poor vision?	4	3	2	1	0

Subtotal score for answers 1 to 5 (A)

HAVE PROBLEMS WITH YOUR EYES LIMITED YOU IN PERFORMING ANY OF THE FOLLOWING *DURING THE LAST WEEK*:

	All of the time	Most of the time	Half of the time	Some of the time	None of the time	
6. Reading?	4	3	2	1	0	N/A
7. Driving at night?	4	3	2	1	0	N/A
8. Working with a computer or bank machine (ATM)?	4	3	2	1	0	N/A
9. Watching TV?	4	3	2	1	0	N/A

Subtotal score for answers 6 to 9 (B)

HAVE YOUR EYES FELT UNCOMFORTABLE IN ANY OF THE FOLLOWING SITUATIONS *DURING THE LAST WEEK*:

	All of the time	Most of the time	Half of the time	Some of the time	None of the time	
10. Windy conditions?	4	3	2	1	0	N/A
11. Places or areas with low humidity (very dry)?	4	3	2	1	0	N/A
12. Areas that are air conditioned?	4	3	2	1	0	N/A

Subtotal score for answers 10 to 12 (C)

ADD SUBTOTALS A, B, AND C TO OBTAIN D (D = SUM OF SCORES FOR ALL QUESTIONS ANSWERED) (D)

Figure 3 : Questionnaire OLSDI détaillé.

DISCUSSION

The results of this prospective interventional study provide several answers about the effect of 2nd generation Istent Inject® micro-invasive glaucoma surgery (MIGS) devices on the ocular surface in glaucoma patients. Six months after a double implantation of these stents combined with cataract surgery, clinically and statistically significant improvements were observed in almost all aspects of ocular surface including OSDI score, corneal/conjunctival staining represented by Oxford and Efron scores and Fluorescein Tear Break up time measurements (FTBUT).

Indeed, the average dry eye syndrome severity of our patients went from severe (Mean OSDI score of 40.1) to mild (20.5), the average corneal staining scores decreased by half and tear breakup time was increased and with a tear film that remained stable about 50% longer at the 6-month postoperative control compared to the preoperative measurement.

Usually, the main challenge in the study of dry syndrome is that subjective symptoms expressed by patients (as measured by the OSDI) do not necessarily correspond proportionally to the clinical signs (as measured by the Oxford, Efron and FTBUT scores) [21]. However, the association of concomitant improvements in functional and clinical criteria for a given patient is

significant even if the correlation between the different parameters is imperfect. These measures are of crucial importance -especially when combined with the assessment of glaucoma parameters (IOP and drug load...) - as the majority of studies converge towards the fact that the final prognosis of glaucoma is closely related to the ocular surface [13, 14].

This study about the effects of Istent Inject® devices on the ocular surface is all the more important when compared to other surgical procedures for the treatment of glaucoma, which are often more invasive and therefore likely to cause inflammatory cascades that counteract ocular surface homeostasis [21- 25]. MIGS devices also offer a more attractive safety profile than traditional filtration glaucoma surgery [16- 24].

Among the different dry eye parameters measured in our study, the most promising improvement is the one observed in patients' OSDI scores. Indeed, this test assesses especially the functional aspect of dry eye syndrome. It is the most widely used test in clinical studies of dry eye syndrome [21- 27]. It is also worth mentioning that at the 6-month postoperative follow-up, significant improvements were not only seen in subjective signs (OSDI score), but also in objective clinical signs (FTBUT measurement, Efron and Oxford score). *In other words, improvements in dry eye syndrome parameters were both detectable by the ophthalmologist and felt by the patients.*

Our hypothesis is that the main factor contributing to these improvements in ocular surface area after the double Istent Inject® implantation is the significant reduction in anti-glaucoma drug load, which is in fact incriminated in initiation and worsening of the dry eye syndrome [8-12].

The deleterious effects of hypotonizing eye drops on the ocular surface have been widely documented over years [13, 14]. Indeed, Baudouin *et al*., have demonstrated that longer exposure to one or more glaucoma medications leads to significant increases in ocular surface inflammatory markers such as immunoglobulins (especially IgE) and HLA-DR leukocyte markers [28]. This same study found a greater increase in inflammatory markers in patients undergoing dual and triple ocular hypotonizing therapy compared to those under a single monotherapy [28]. In another French study conducted by Pisella *et al*., including 4107 patients, 75% of glaucoma patients had a dry syndrome classified as moderate or severe, and in patients diagnosed and put on hypotonizing eye drops, dry eye symptoms increased fivefold after one year of treatment [29].

Similarly, Rossi *et al*., and Fechtner *et al*., demonstrated a clear relationship between dry eye and the number of antiglaucoma medications, with moderate to severe dry eye syndrome found in 11% of eyes on monotherapy, compared to 39% and 43% of eyes receiving bi- and triple-therapy hypotonizing eye drops, respectively [11, 12].

The quality of the ocular surface is even more important in glaucoma patients because it intertwines closely with the therapeutic possibilities and their results. Thus, according to a multicenter study conducted by Jaenen *et al*., in four European countries and including 9658 patients, 40% of patients changed their glaucoma treatment because of ocular surface problems and 35% expressed compliance failures directly related to the adverse effects of hypotonizing eye drops [30]. Many studies have also stated that compliance drops dramatically when more than one hypotonizing molecule is prescribed [13- 31].

Thus, in addition to the considerable improvements on dry eye syndrome previously stated, reducing the drug load may also have a positive impact on the glaucoma patient's adherence to the therapeutic process.

These therapeutic implications also extend to the surgical arsenal of glaucoma treatment; Boimer *et al*., in their study "The Peso Study" including 128 eyes specifically addressed this aspect and stated that the outcome of trabeculectomy relies tremendously on the condition of the ocular surface (especially the conjunctiva). The failure rates of glaucoma filtration surgery increases proportionally with the duration of administration of hypotonizing eye drops that contain preservatives, thus testifying to a cumulative effect of these treatments' toxicity [32- 47].

In parallel to these studies correlating glaucoma eye drops with poor ocular surface, reductions drug load observed after MIGS device implantation are also widely documented [34- 46]. The relationship of trabecular stent implantation and ocular surface improvement seems indeed obvious.

This conclusion is essential to underline because several studies are interested in non-pharmacological alternatives for glaucoma such as selective laser trabeculoplasty (SLT) to reduce dry eye [48]. However, -to our knowledge- data on the effects of MIGS devices on the ocular surface are paradoxically a lot less documented.

Although our study focuses primarily on the impact of Istent Inject® use on ocular surface parameters and anti-glaucoma drug load, the significant reductions in IOP obtained are also worth mentioning. Thus, even with a reduced drug load, the average IOP of our patients reduced by 4.9 mmHg. This significant decrease is obtained in many series of the literature, and starts as early as in the control of the seventh day postoperatively according to most studies [39, 40]. The reduction in the

drug load is established in the majority of series having used MIGS devices [33-46].

At the end of this discussion, however, we want to note a few limitations of our study. As in most single-arm clinical studies, the patients' preoperative measurements were used as the reference, although this does not replace a true control group. The sample size was modest, as this is a pilot study in our department, future series could include a larger number of patients.

It should also be noted that the study was not masked, leaving open the possibility of bias in the patients' perception of their symptoms and to a lesser degree in the ophthalmologist's observation of clinical signs.

Because our follow-up extended to 6 months, longer-term data is still required for a long-term evaluation of the effects of Istent Inject® on the ocular surface. The data available to date on the effect of these devices on IOP and drug load show satisfactory results with an efficacy that extends to 5 years according to the latest data in the literature [20- 33].

Despite its limitations, this study provides useful evidence on a topic that is currently lacking in the literature of MIGS; especially given that the ocular surface -in addition to playing a central role in the therapeutic compliance and quality of life of glaucoma patients- is closely involved in the therapeutic outcomes of a possible later filtration surgery.

Conclusion

Our study concludes that implantation of the 2nd generation Istent Inject® combined with cataract surgery results in significant improvements in dry eye syndrome in glaucoma patients, along with significant reductions in intraocular pressure and drug load with excellent safety and very few adverse effects.

This effect on the ocular surface is an important factor for ophthalmologists and patients to consider when evaluating treatment options for glaucoma. Given the high prevalence of dry eye syndrome in glaucomatous patients and the increasing use and availability of MIGS devices worldwide, these data may be particularly useful to the ophthalmology community.

References

1. Nelson, P., Aspinall, P., Papasouliotis, O., Worton, B., & O'Brien, C. (2003). Quality of life in glaucoma and its relationship with visual function. *Journal of glaucoma*, *12*(2), 139-150.
2. Jampel, H. D., Schwartz, A., Pollack, I., Abrams, D., Weiss, H., & Miller, R. (2002). Glaucoma patients' assessment of their visual function and quality of life. *Journal of glaucoma*, *11*(2), 154-163.
3. Skaliky, S., Mc Cluskey, P. (2012). Ocular surface disease and quality of life in patients with glaucoma. *American Journal of Ophthalmology*, 153.
4. Stapleton, F., Alves, M., Bunya, V. Y., Jalbert, I., Lekhanont, K., Malet, F., ... & Jones, L. (2017). Tfos dews ii epidemiology report. *The ocular surface*, *15*(3), 334-365.
5. Moss, S., Klein, B. (2000). Prevalence of and risk factors for dry eye syndrome. *Archives of Ophthalmology*, 118–119.
6. Leung, E. W., Medeiros, F. A., & Weinreb, R. N. (2008). Prevalence of ocular surface disease in glaucoma patients. *Journal of glaucoma*, *17*(5), 350-355.
7. Mylla Boso, A. L., Gasperi, E., Fernandes, L., Costa, V. P., & Alves, M. (2020). Impact of ocular surface disease treatment in patients with glaucoma. *Clinical Ophthalmology*, 103-111.
8. Baudouin, C., Garcher, C., Haouat, N., Bron, A., & Gastaud, P. (1994). Expression of inflammatory membrane markers by conjunctival cells in chronically treated patients with glaucoma. *Ophthalmology*, *101*(3), 454-460.
9. Baudouin, C., Liang, H., Hamard, P., Riancho, L., Creuzot-Garcher, C., Warnet, J. M., & Brignole-Baudouin, F. (2008). The ocular surface of glaucoma patients treated over the long term expresses inflammatory markers related to both T-helper 1 and T-helper 2 pathways. *Ophthalmology*, *115*(1), 109-115.
10. Nordmann, J. P., Auzanneau, N., Ricard, S., & Berdeaux, G. (2003). Vision related quality of life and topical glaucoma treatment side effects. *Health and quality of life outcomes*, *1*(1), 1-9.
11. Rossi, G. C. M., Tinelli, C., Pasinetti, G. M., Milano, G., & Bianchi, P. E. (2009). Dry eye syndrome-related quality of life in glaucoma patients. *European journal of ophthalmology*, *19*(4), 572-579.
12. Fechtner, R., Godffrey, D. G. (2010). Prevalence of ocular surface complaints in patients with glaucoma using topical intraocular pressure-lowering medications. *Cornea*, 618–621.
13. Robin, A. L., & Covert, D. (2005). Does adjunctive glaucoma therapy affect adherence to the initial primary therapy?. *Ophthalmology*, *112*(5), 863-868.
14. Sianni, S., Schoenfeld, P., Kaulback, K. (2009). Effect of dosing frequency on adherence in chronic diseases. *The American Journal of Managed Care*, 15-22.
15. Broadway, D., Hitchings, R., & Grierson, I. (1995). Topical antiglaucomatous therapy: adverse effects on the conjunctiva and implications for filtration surgery. *Journal of glaucoma*, *4*(2), 136.
16. National Institute for Health and Clinical Excellence. Interventional procedure overview of trabecular stent bypass microsurgery for open-angle glaucoma. London: NICE. 2011: www.nice.org.uk/nicemedia/live/13157/52560/52560.pdf
17. Food and Drug Administration. Summary of safety

and effectiveness data. Glaukos iStent Trabecular Micro-Bypass Stent (Models: GTS-100R, GTS-100L) and Inserter (GTS-100i) - P080030. 2012.
18. National Institute for Health and Clinical Excellence. Trabecular stent bypass microsurgery for open angle glaucoma. London: NICE. 2011: www.nice.org.uk/nicemedia/live/13157/54571/54571.pdf
19. Food and Drug Administration. Approval Letter. Glaukos iStent Trabecular Micro-Bypass Stent (Models: GTS-100R, GTS100L) and Inserter (GTS-100i) - P080030. 2012.
20. Neuhann, T. H., Hornbeak, D. M., Neuhann, R. T., & Giamporcaro, J. E. (2019). Long-term effectiveness and safety of trabecular microbypass stent implantation with cataract surgery in patients with glaucoma or ocular hypertension: five-year outcomes. *Journal of Cataract & Refractive Surgery*, *45*(3), 312-320.
21. Schiffman, R. M., Christianson, M. D., Jacobsen, G., Hirsch, J. D., & Reis, B. L. (2000). Reliability and validity of the ocular surface disease index. *Archives of ophthalmology*, *118*(5), 615-621.
22. Bron, A. J., Evans, V. E., & Smith, J. A. (2003). Grading of corneal and conjunctival staining in the context of other dry eye tests. *Cornea*, *22*(7), 640-650.
23. Efron, N., Morgan, P. B., & Katsara, S. S. (2001). Validation of grading scales for contact lens complications. *Ophthalmic and Physiological Optics*, *21*(1), 17-29.
24. Samuelson, T. W., Katz, L. J., Wells, J. M., Duh, Y. J., Giamporcaro, J. E., & US iStent Study Group. (2011). Randomized evaluation of the trabecular micro-bypass stent with phacoemulsification in patients with glaucoma and cataract. *Ophthalmology*, *118*(3), 459-467.
25. Wolffsohn, J. S., Arita, R., Chalmers, R., Djalilian, A., Dogru, M., Dumbleton, K., ... & Craig, J. P. (2017). TFOS DEWS II diagnostic methodology report. *The ocular surface*, *15*(3), 539-574.
26. Agnifili, L., Brescia, L., Scatena, B., Oddone, F., Figus, M., Perna, F., ... & Mastropasqua, L. (2020). Tear meniscus imaging by anterior segment-optical coherence tomography in medically controlled glaucoma. *Journal of Glaucoma*, *29*(5), 374-380. DOI: 0000000000001469.
27. Begley, C. G., Chalmers, R. L., Abetz, L., Venkataraman, K., Mertzanis, P., Caffery, B. A., ... & Simpson, T. (2003). The relationship between habitual patient-reported symptoms and clinical signs among patients with dry eye of varying severity. *Investigative ophthalmology & visual science*, *44*(11), 4753-4761.
28. Baudouin, C. (2008). Detrimental effect of preservatives in eyedrops: implications for the treatment of glaucoma. *Acta ophthalmologica*, *86*(7), 716-726.
29. Pisella, P. J., Pouliquen, P., & Baudouin, C. (2002). Prevalence of ocular symptoms and signs with preserved and preservative free glaucoma medication. *British Journal of Ophthalmology*, *86*(4), 418-423.
30. Jaenen, N., Baudouin, C., Pouliquen, P., Manni, G., Figueiredo, A., & Zeyen, T. (2007). Ocular symptoms and signs with preserved and preservative-free glaucoma medications. *European journal of ophthalmology*, *17*(3), 341-349.
31. Brown, M. T., & Bussell, J. K. (2011, April). Medication adherence: WHO cares?. In *Mayo clinic proceedings* (Vol. 86, No. 4, pp. 304-314). Elsevier.
32. Boimer, C., & Birt, C. M. (2013). Preservative exposure and surgical outcomes in glaucoma patients: the PESO study. *Journal of Glaucoma*, *22*(9), 730-735.
33. Fechtner, R. D., Voskanyan, L., Vold, S. D., Tetz, M., Auffarth, G., Masood, I., ... & Saheb, H. (2019). Five-year, prospective, randomized, multi-surgeon trial of two trabecular bypass stents versus prostaglandin for newly diagnosed open-angle glaucoma. *Ophthalmology Glaucoma*, *2*(3), 156-166.
34. Ferguson, T., Schweitzer, J. (2016). Clinical evaluation of a trabecular micro-bypass stent with phacoemulsification in patients with open angle glaucoma and cataract. *Clinical ophthalmology Journal*, 767–773.
35. Ferguson, T. J., Swan, R., Ibach, M., Schweitzer, J., Sudhagoni, R., & Berdahl, J. P. (2017). Trabecular microbypass stent implantation with cataract extraction in pseudoexfoliation glaucoma. *Journal of Cataract & Refractive Surgery*, *43*(5), 622-626.
36. Ferguson, T., Swan, R., Ibach, M., Schweitzer, J., Sudhagoni, R., & Berdahl, J. P. (2018). Evaluation of a trabecular microbypass stent with cataract extraction in severe primary open-angle glaucoma. *Journal of Glaucoma*, *27*(1), 71-76.
37. Ferguson, T., Ibach, M., Schweitzer, J. (2019). Trabecular micro bypass stent implantation with cataract extraction in pigmentary glaucoma. *Clinical and experimental ophthalmology Journal*.
38. Gallardo, M. J., & Supnet, R. A. (2019). Three-year outcomes of combined trabecular micro-bypass and phacoemulsification in a predominantly Hispanic population with primary open-angle glaucoma. *Clinical Ophthalmology*, 869-879.
39. Samuelson, T. W., Sarkisian Jr, S. R., Lubeck, D. M., Stiles, M. C., Duh, Y. J., Romo, E. A., ... & Cotter, F. (2019). Prospective, randomized, controlled pivotal trial of an ab interno implanted trabecular micro-bypass in primary open-angle glaucoma and cataract: two-year results. *Ophthalmology*, *126*(6), 811-821.
40. Manning, D. (2019). Real-world case series of iStent or iStent inject trabecular micro-bypass stents combined with cataract surgery. *Ophthalmology and Therapy*, *8*, 549-561.
41. Neuhann, R., & Neuhann, T. (2020). Second-generation trabecular micro-bypass stent implantation: retrospective analysis after 12-and 24-

month follow-up. *Eye and Vision*, *7*(1), 1-10.
42. Hengerer, F. H., Auffarth, G. U., Riffel, C., & Conrad-Hengerer, I. (2019). Second-generation trabecular micro-bypass stents as standalone treatment for glaucoma: a 36-month prospective study. *Advances in therapy*, *36*, 1606-1617.
43. Guedes, R. A. P., Gravina, D. M., Lake, J. C., Guedes, V. M. P., & Chaoubah, A. (2019). One-year comparative evaluation of iStent or iStent inject implantation combined with cataract surgery in a single center. *Advances in Therapy*, *36*, 2797-2810.
44. Baudouin, C. (2012). Ocular surface and external filtration surgery: mutual relationships. *Developments in Ophthalmology Journal*, 64-78.
45. De Keyser, M., De Belder, M., & De Groot, V. (2017). Quality of life in glaucoma patients after selective laser trabeculoplasty. *International journal of ophthalmology*, *10*(5), 742.