Acta Ophthalmologica

CO_2 laser-assisted sclerectomy surgery compared with trabeculectomy in primary open-angle glaucoma and exfoliative glaucoma. A 1-year follow-up

Judyta Jankowska-Szmul, Dariusz Dobrowolski and Edward Wylegala

Department of Ophthalmology, School of Medicine with the Division of Dentistry in Zabrze, Medical University of Silesia, Katowice, Poland

ABSTRACT.
Purpose: **To report on the efficacy and safety of CO_2 laser-assisted sclerectomy surgery (CLASS) compared with trabeculectomy in primary open-angle glaucoma and exfoliative glaucoma.**
Methods: **One hundred and thirty-one patients underwent CLASS (66 patients) or trabeculectomy (65 patients) and were followed up for 12 months. 'Complete success' was defined as intraocular pressure (IOP) between 10 and 18 mmHg and reduced by at least 30% from the baseline without medications, while 'qualified success' was compliant with the above criteria with or without the medications.**
Results: **Comparing CLASS with trabeculectomy at 1 year, the mean IOP reduction rate was 32.6 ± 10.8% versus 40.6 ± 15.9% ($p < 0.001$) and the average use of medications was 1.4 ± 1.4 versus 0.7 ± 1.1 ($p < 0.05$). At 12 months, the complete success rate was 35% for CLASS versus 60% for trabeculectomy ($p < 0.01$), while the qualified success rate was 74% versus 75%, respectively, with no significant difference in qualified success rate between the groups at any time-point ($p > 0.05$). Compared with CLASS, patients after trabeculectomy developed a higher rate of early complications (9.1% versus 29.2%, p = 0.004), higher endothelial cell density (ECD) loss (1.4 ± 1.4% versus 6.5 ± 4.8%, $p < 0.001$), higher astigmatism (0.0 ± 0.1 versus 0.1 ± 0.2, $p < 0.001$) and significant visual acuity deterioration (0.1 ± 0.1; range 0–2 lines versus 0.4 ± 0.6; range 0–3 lines, p = 0.016).**
Conclusion: **Although CLASS shows a less potent hypotensive effect, it is similar to trabeculectomy in the qualified success rate and offers the reduction in medications up to 12 months. With a more attractive complications profile, CLASS may be an alternative to trabeculectomy, especially at the earlier glaucoma stage and in patients with a low ECD.**

Key words: CO_2 laser – exfoliative glaucoma – glaucoma surgery – nonpenetrating deep sclerectomy – primary open-angle glaucoma – trabeculectomy

Acta Ophthalmol.

doi: 10.1111/aos.13718

Introduction

The spectrum of surgical options for Open-angle glaucoma (OAG) includes several techniques, but trabeculectomy has remained the gold standard procedure (Mermoud & Schnyder 2000; Landers et al. 2012) for almost half a century, since it was first proposed by Cairns (1968) and modified by Watson (1970). Over the decades, the conventional trabeculectomy has embraced a range of advancements, driven by the need to minimize the risk of complications and surgical failure. In the traditional model, there was a tendency to develop a sudden intraocular pressure (IOP) fall in the first days following the surgery, which may result in early hypotony and a considerable rate of early vision-threatening complications, with hyphema, anterior chamber (AC) shallowing and choroidal effusion. One year after trabeculectomy, a loss of more than one Snellen line of preoperative visual acuity has been reported in 15–18.8% of patients (Edmunds et al. 2002; Gedde et al. 2007; Landers et al. 2012). Modern strategies called the 'Moorfields Safer Surgery System' (Khaw et al. 2012), including the use of perioperative antimetabolites, AC maintainer, adjustable and releasable sutures together with secure conjunctival closure technique, have been proven to result in gradual IOP decrease, reduced risk of complications and improved long-term surgical outcomes (Kirwan et al. 2013). Nowadays, trabeculectomy is widely adopted at an early stage of glaucoma surgery training and is reported to be performed at a similar rate of success and complications by trainees and experienced surgeons (Chan et al. 2007; Sun & Lee 2013; Kwong et al. 2014). Nonetheless, the invasive nature of trabeculectomy carries the risk of late corneal sequelae of surgical trauma, with surgically induced astigmatism

(Rosen et al. 1992; Egrilmez et al. 2004; Alvani et al. 2016; Willekens et al. 2016) and corneal decompensation due to endothelial cells loss (Mietz et al. 2005; Hau & Barton 2009).

Nonpenetrating filtration surgery is an alternative approach for OAG (Sarodia et al. 2007; EGS 2014). In the nonpenetrating deep sclerectomy (NPDS), manual removal of the sclerocorneal tissue and unroofing of the Schlemm's canal aim to relieve local tissue resistance, providing efficient percolation of aqueous humour (Fyodorov 1989; Mermoud & Schnyder 2000). Progressive filtration of the aqueous humour from the AC to the surgically created intrascleral space through an intact trabeculo-Descemet's membrane (TDM) carries a low risk of hyperfiltration. However, compared to trabeculectomy, the dissection of TDM thin enough to provide the efficient fluid filtration in NPDS is perceived as laborious, demanding a high level of surgical experience and, therefore, limiting widespread use of NPDS (Mermoud 2000; Greifner et al. 2016). The risk of intraoperative TDM perforation, which requires conversion to trabeculectomy, decreases with the surgeon's experience (Mermoud & Schnyder 2000). Nevertheless, when contributed to anatomic variations of the iridocorneal angle (Dietlein et al. 2000), it has been reported at a rate of 3–15% even for experienced specialists (Shaarawy et al. 2004; Anand & Atherley 2005). Although the uneventful NPDS does not affect anterior segment integrity, complications including hyphema (2.6–17.6%) and shallow AC (5.9%) have been reported as associated with this procedure (El Sayyad et al. 2000; Cillino et al. 2004). Despite the lower rates of complications when compared to trabeculectomy (Sarodia et al. 2007), the lower IOP-reducing potential has been the main factor limiting the popularity of NPDS (Eldaly et al. 2014). As the continuous search for safe glaucoma surgery motivates surgeons to revise nonpenetrating procedures, a number of adjunctive techniques improving the efficacy of NPDS have been proposed, including laser goniopuncture (GPT), use of implants and use of mitomycin C (MMC) (Sarodia et al. 2007). There has been also a keen interest in a range of, so-called, 'less invasive' ab interno and ab externo procedures for open-angle glaucoma. These potential trabeculectomy alternatives address the trabecular meshwork (Tanito et al. 2017) or the Schlemm's canal (Grieshaber et al. 2017), offering independence of intraoperative antimetabolites, bleb formation and postoperative bleb evolution.

CO_2 laser-assisted sclerectomy surgery (CLASS) is a recent modification of NPDS and has been implemented to overcome the technical difficulty of the manual technique (Assia et al. 2007; Ton et al. 2012). CO_2 laser energy has been found useful in sclerectomy as it provides accurate ablation of dry tissues and is absorbed by fluid, which means that the aqueous humour percolating through the intact TDM intrinsically prevents excessive ablation. Subsequently, the risk of intraoperative TDM perforation is reduced, and the whole procedure is less dependent on the surgeon's skills (Assia et al. 2007; Klink et al. 2008). CO_2 laser-assisted sclerectomy surgery (CLASS) outcomes, in terms of IOP-lowering potential, have already been reported as comparable to classic NPDS over a period of up to 2-year follow-up (Geffen et al. 2012; Skaat et al. 2014; Greifner et al. 2016). Potentially, combining the surgical precision and short learning curve, CLASS may enable patients to benefit from the safety and effectiveness of nonpenetrating surgery.

The following study aims to report on the safety and efficacy profile of CLASS compared with trabeculectomy in primary open-angle glaucoma (POAG) and exfoliative glaucoma (XFG).

Materials and Methods

Study design

This was a prospective cohort comparative study, approved by the local ethics committee (KNW/0022/KB1/132/16) and conducted according to the tenets of the Declaration of Helsinki. Informed written consent was obtained from all patients. Inclusion criteria were as follows: adult patients (aged $\geq$ 18), medically uncontrolled POAG or XFG, open angles confirmed in gonioscopy (grade 3 or 4 in four quadrants, according to Shaffer classification), pseudophakia and a history of uneventful cataract surgery performed >6 months prior to listing for the glaucoma surgery. Patients with a history of any other eye surgery were not included in the study. Medically uncontrolled glaucoma was defined as a progression of glaucomatous optic neuropathy despite the use of maximal topical treatment, or one in which the topical medications were contraindicated or not tolerated by the patient. One hundred and thirty-one white patients (131 eyes) were enrolled in the study and randomly divided into two groups that underwent filtration surgery either by CLASS (group 1: CLASS) or by conventional trabeculectomy (group 2: TRAB). The patients underwent a baseline examination within 2 days before the surgery and were followed up at 1 week, 1, 3, 6 and 12 months postoperatively. At each visit, we recorded best-corrected Snellen visual acuity, IOP as an average of three consecutive measurements with a calibrated Goldmann applanation tonometer (Haag-Streit AG, Koeniz, Switzerland), number of antiglaucoma medications (if topical combinations were used, these were counted according to the number of active drugs) and slit lamp findings of anterior segment and fundus. Preoperatively, and at the last follow-up visit, we took the records of corneal endothelial cell density (ECD) as an average of three consecutive central cornea measurements using specular microscope (SP-3000P; TOPCON, Tokyo, Japan) and corneal astigmatism as mean total corneal refractive power astigmatism in a 3-mm zone (TCRPA3) (Tonn et al. 2014) calculated from three consecutive automatic scans using a rotating Scheimpflug tomography (Pentacam, OCULUS GmbH, Wetzlar, Germany). Comparing the preoperative and the final measurements of ECD and TCRPA3, respectively, we calculated mean ECD loss and mean surgically induced corneal astigmatism. The main outcomes were: IOP reduction, use of adjuvant glaucoma medications, ECD loss, the magnitude of surgically induced corneal astigmatism, change in the best-corrected Snellen visual acuity and rates of complications recorded in both groups. 'Complete success' was defined as IOP values measured at each follow-up visit ranging between 10 and 18 mmHg and reduced by at least 30% from

the baseline without glaucoma medications and 'qualified success' as IOP measurements within the above criteria with or without glaucoma medications. Intraocular pressure (IOP) <10 mmHg or >18 mmHg despite medications, reduction of <30% from the baseline, reoperation for glaucoma within 12 months or loss of light perception were classified as failure.

Surgical procedures

All the procedures were performed under peribulbar anaesthesia (3:1 of bupivacaine 0.5% and lidocaine 2%) and by the same experienced surgeon (EW). There was no application of perioperative antimetabolites.

CO_2 laser-assisted sclerectomy surgery (CLASS) was performed in the superior quadrant, following the technique described by Geffen et al. (2012), using a commercially available OT-135 CO_2 laser system (IOPtiMate; IOPtima Ltd, Ramat Gan, Israel). The procedure involved a corneal traction suture, conjunctival peritomy, opening and dissection of the Tenon's capsule, cauterization of bleeding vessels within the area of exposed sclera and dissection of 50% lamellar scleral flap of dimensions 4 mm × 4 mm at the 12-o'clock position using a feather blade (initial horizontal incision) and a crescent blade (flap dissection). The laser dissection of the deep sclera and Schlemm's canal towards the TDM was performed to achieve aqueous humour percolation. The scleral flap edges were approximated with two fixed 8.0 nylon intrascleral sutures, applied at the corners of the flap, and conventional conjunctival closure was done with two–four 9.0 nylon interrupted sutures. There was no use of intrascleral space-maintaining materials. Trabeculectomy (TRAB) was performed in the superior quadrant, constructing a fornix-based bleb. The procedure involved a corneal traction suture, conjunctival peritomy, opening and dissection of the Tenon's capsule, cauterization of bleeding within the area of exposed sclera, dissection of 50% lamellar scleral flap of dimensions 4 mm × 4 mm at the 12-o' position using a feather blade (initial horizontal incision) and a crescent blade (flap dissection), paracentesis, sclerostomy and peripheral iridectomy. The scleral flap edges were approximated with two fixed 8.0 nylon intrascleral sutures applied at the corners of the flap, and conventional conjunctival closure was done with four 9.0 nylon interrupted sutures. Postoperative management in both groups included routine overnight patching, topical levofloxacin 5 mg/ml, which continued for 4 weeks, and dexamethasone 1 mg/ml, which tapered down over 8 weeks.

Statistical analysis

Descriptive statistical results were presented as mean ± standard deviation (SD) or median with range. Normality of the data was tested with the Shapiro–Wilk test, and parametric or nonparametric tests have been applied accordingly. Comparisons of quantitative variables between the groups were conducted with the chi-squared test (with Yates' correction), for normally distributed variables in both groups, or via the Wilcoxon two-sample test, a.k.a. Mann–Whitney test, in other cases. Repeated measurements of quantitative variables were compared with paired *t*-test (for normally distributed differences in both groups) or paired Wilcoxon tests (otherwise). The cumulative probability of success was illustrated using Kaplan–Meier survival curves. A p value of <0.05 was considered significant. Analysis was performed in R package, version 3.4.1 (R Core Team 2017).

Results

Baseline

One hundred and thirty-one patients were enrolled in the study, 66 patients underwent CLASS (group 1) and 65 patients underwent TRAB (group 2). There was no significant difference in age, sex, glaucoma type, baseline IOP and number of drugs between the groups ($p > 0.05$; Table 1).

IOP

Patients in both groups achieved a significant IOP decrease from baseline ($p < 0.001$), with a higher IOP reduction in the TRAB group through the whole follow-up period of the study ($p < 0.001$). The mean IOP reduction rate at 1 year was 32.6 ± 10.8% in group 1 compared to 40.6 ± 15.9% in group 2, excluding the patients who underwent surgical revision after 6 months. The mean IOP reduction following both procedures over time is illustrated in Table 2 and Fig. 1.

Medications

Table 3 and Fig. 2 present the average numbers of IOP-lowering medications which were used up to 12 months postoperatively, in both study groups. The reduction in number of medications was significant in both groups up to 12 months ($p < 0.001$), but group 1 required significantly more drugs than group 2 after 3, 6 and 12 months following the surgery ($p < 0.05$). Initially, glaucoma medications were routinely withdrawn after the surgery in all patients. Twelve months after the surgery, the average use of hypotensive drops by patients in CLASS and TRAB groups was 1.4 ± 1.4 versus 0.7 ± 1.1 ($p < 0.05$), respectively.

In both groups, there were no significant differences in rates of patients who stopped using at least one drug after the surgery ($p > 0.05$; Table 4).

Success

Complete success

After a week, CLASS procedure was successful in 55 patients (83%) and TRAB in 60 (92%), $p > 0.05$. Significant differences in complete success rates between groups were found after a month from baseline and later, with more TRAB patients meeting complete success criteria. A year after the surgery, the complete success rate dropped to 23 patients (35%) for CLASS versus 39 patients (60%) for TRAB ($p < 0.01$). Table 5 shows the complete success rates over time in both groups.

Qualified success

There was no significant difference in qualified success rate between the groups at any time over the follow-up period of the study ($p > 0.05$). After a year, the qualified success rate was 74% in CLASS group and 75% in TRAB. Table 6 shows the complete success rates over time in both groups.

Early complications

The total number of early complications following TRAB was significantly higher than following CLASS (19 patients (29.2%) versus 6 patients (9.1%) $p = 0.004$).

Choroidal detachment occurred in one patient (1.5%) in the CLASS and in 12 patients (18.5%) in the TRAB

Table 1. Baseline demographic characteristics of study groups.

	CO_2 laser-assisted sclerectomy surgery (*N* = 66) *n* (%)	Trabeculectomy (*N* = 65) *n* (%)	p
Sex			
Male	30 (45%)	35 (54%)	0.413*
Female	36 (55%)	30 (46%)	
Glaucoma type			
Primary open-angle glaucoma	34 (52%)	34 (52%)	1*
Exfoliative glaucoma	32 (48%)	31 (48%)	

	CO_2 laser-assisted sclerectomy surgery (*N* = 66)		Trabeculectomy (*N* = 65)		
	Mean (SD)	Median (quartiles)	Mean (SD)	Median (quartiles)	p†
Age	70 (10.6)	71 (64–77)	68.1 (9.7)	68 (60–75)	0.315†
IOP (mmHg)	23.5 (2)	23 (22–25)	24.1 (4.5)	24 (22–27)	0.213‡
Medications	3.1 (0.7)	3 (3–4)	3.3 (0.6)	3 (3–4)	0.239‡

* Chi-squared test.
† *t*-test (age normally distributed in both groups).
‡ Wilcoxon two-sample test [intraocular pressure (IOP) and drugs non-normally distributed in both groups].

(p = 0.001) group. The list of early complications in both groups is shown in Table 7.

Kaplan–Meier cumulative survival curves

Figure 3A,B shows Kaplan–Meier plots of the cumulative probability of complete success and qualified success in both groups up to 12 months, defining failure as IOP >18 mmHg or not reduced by 30% below baseline at any time-point. There were 17 patients (26%) in the CLASS group and 16 patient (25%) in the TRAB group for whom the surgery was considered failed at the end of the follow-up. Among these, seven patients (11%) in CLASS and four (6%) in TRAB groups, respectively, underwent reoperation for IOP reduction within 6–12 months after the initial surgery. Two patients (3.1%) required urgent revision of trabeculectomy after a week due to iris incarceration with IOP spike. In the CLASS group, three patients required the enhancement procedure of Nd:YAG laser GPT due to iris incarceration with peripheral anterior synechia, which developed within the filtration site of the sclerectomy. The procedures were performed between 1 and 3 months postoperatively and did not result in achievement of the target IOP level despite adjuvant medications.

Endothelial cell density, surgically induced astigmatism and vision loss

Trabeculectomy (TRAB) group developed significantly higher average ECD loss 12 months after the surgery compared to CLASS group (6.5 ± 4.8% versus 1.4 ± 1.4%, respectively, p < 0.001; Table 8).

The magnitude of mean surgically induced astigmatism (change in TCRPA3) 12 months after trabeculectomy was significantly lower in the CLASS than in the TRAB group (0.0 ± 0.1 versus 0.1 ± 0.2, respectively, p < 0.001). Only the astigmatism changes in the TRAB group were statistically significant (p < 0.001). Changes in mean TCRPA3 1 year after the surgery are presented in Table 9 and Fig. 4.

The mean Snellen lines loss 12 months after TRAB was higher than after CLASS (0.4 ± 0.6; range 0–3 lines versus 0.1 ± 0.1; range 0–2 lines, respectively, p = 0.016). Mean best-corrected visual acuity (BCVA) deterioration was statistically significant only in TRAB group (p < 0.001). Table 10 and Fig. 5 illustrate Snellen lines loss at the end of the follow-up period of the study. The loss of at least one line was more common in the TRAB group (29% versus 8%, p = 0.017; Table 11).

Discussion

To the best of our knowledge, we are the first to have conducted a comparison between CLASS and trabeculectomy, which remains a gold standard technique in OAG.

The results of CLASS have already been reported as comparable to classic NPDS in terms of lowered IOP and

Table 2. Mean intraocular pressure (IOP) reduction over time for CO_2 laser-assisted sclerectomy surgery (CLASS) and trabeculectomy (TRAB).

			IOP (% reduction from baseline)								
Time	Group	*N*	Mean	SD	Median	Min	Max	Q1	Q3	p*	p†
After a week	CLASS	66	32.7	13.5	33.3	8.3	65	23.8	45.5	<0.001	<0.001
	TRAB	65	49.3	21.1	53.6	−11.1	78.1	39.1	65.2	<0.001	
After a month	CLASS	66	23.9	19.8	27.3	−36.4	50	15	39.1	<0.001	<0.001
	TRAB	65	42.9	16.1	44.4	−19.4	67.7	36.8	53.9	<0.001	
After 3 months	CLASS	66	26.9	15.9	30	−25	47.8	18.5	39.1	<0.001	<0.001
	TRAB	65	38.4	17.9	41.1	−40	64.3	33.3	50	<0.001	
After 6 months	CLASS	66	24.2	20.3	30	−40	50	18.2	39.1	<0.001	<0.001
	TRAB	65	37.8	16.6	40	−15	62.5	23.5	50	<0.001	
After 12 months	CLASS	59	32.6	10.8	32.6	9.1	54.6	25.3	40.9	<0.001	<0.001
	TRAB	61	40.6	15.9	44.2	−5.6	68.8	30	52.2	<0.001	

* Intragroups analysis: Wilcoxon paired test (reductions non-normally distributed).
† Intergroups analysis: Wilcoxon two-sample test (reductions non-normally distributed in both groups).

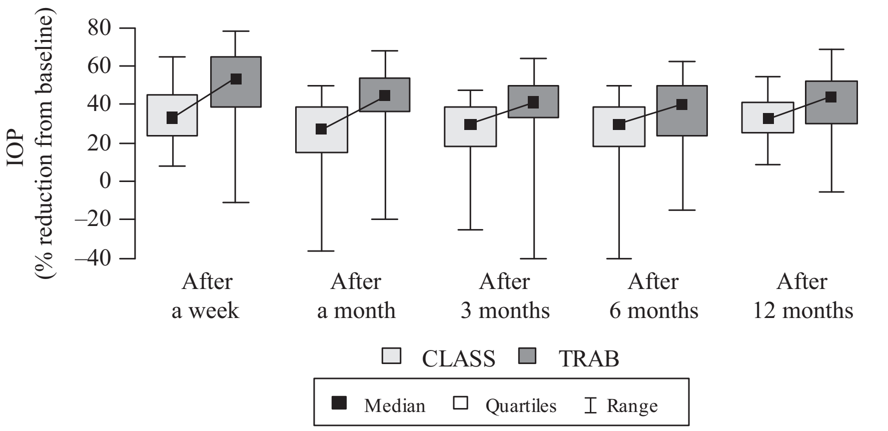

Fig. 1. Mean intraocular pressure reduction over time for CO_2 laser-assisted sclerectomy surgery and trabeculectomy. Boxes indicate quartiles; bars indicate range.

reduced number of medications over the 1-year (Geffen et al. 2012) and the 2-year follow-up period (Greifner et al. 2016). However, as CLASS is a relatively recent procedure, the scientific base on this subject still includes only a small number of research articles. A review of the literature comparing NPDS to trabeculectomy reveals contradictory findings in terms of IOP reduction on a medium-term and long-term basis, with suggestions that NPDS is similar (El Sayyad et al. 2000; Eldaly et al. 2014) or inferior (Chiselita 2001; Hondur et al. 2008) to trabeculectomy. There is a trend to report lower rates of complications following NPDS (Chiselita 2001; Sarodia et al. 2007). The recent paper by Harju et al. (2017) demonstrated that both MMC-augmented and nonaugmented deep sclerectomy can produce a long-term significant IOP reduction in normal tension glaucoma, with a low incidence of sight-threatening complications (Harju et al. 2017).

Through the whole follow-up period of our study, both procedures brought a significant IOP decrease from baseline ($p < 0.001$), but with a lower mean IOP reduction rate 1 year after CLASS compared with trabeculectomy (32.6 ± 10.8% versus 40.6 ± 15.9%, $p < 0.001$). In terms of drug reduction, the number of medications has remained significantly lower in both groups up to 12 months ($p < 0.001$) and CLASS patients, compared with trabeculectomy, required more drugs to maintain the target IOP 3, 6 and 12 months following the surgery ($p < 0.05$). A month after the baseline and later, complete success was maintained by a higher number of patients in the trabeculectomy group. A year after the surgery, the complete success rate dropped to 35% for CLASS versus 60% for trabeculectomy ($p < 0.01$). There was no significant difference, however, in the qualified success rate between the groups at any time through the follow-up period of the study (74% versus 75%, $p > 0.05$). As glaucoma surgery for OAG is still frequently performed in patients with moderate to advanced disease, we

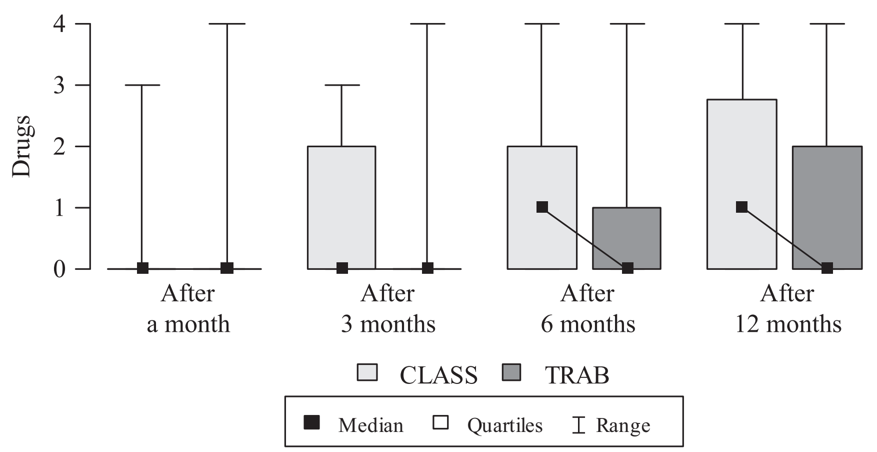

Fig. 2. Average number of intraocular pressure-lowering medications postoperatively in CO_2 laser-assisted sclerectomy surgery and trabeculectomy. Boxes indicate quartiles; bars indicate range.

Table 3. Average number of intraocular pressure-lowering medications postoperatively in CO_2 laser-assisted sclerectomy surgery (CLASS) and trabeculectomy (TRAB).

			Number of medications								
Time	Group	*N*	Mean	SD	Median	Min	Max	Q1	Q3	p*	p†
After a month	CLASS	66	0.3	0.8	0	0	3	0	0	<0.001	0.596
	TRAB	65	0.2	0.8	0	0	4	0	0	<0.001	
After 3 months	CLASS	66	0.9	1.1	0	0	3	0	2	<0.001	0.017
	TRAB	65	0.5	1.1	0	0	4	0	0	<0.001	
After 6 months	CLASS	66	1.3	1.3	1	0	4	0	2	<0.001	0.004
	TRAB	65	0.7	1.2	0	0	4	0	1	<0.001	
After 12 months	CLASS	59	1.4	1.4	1	0	4	0	3	<0.001	0.006
	TRAB	61	0.7	1.1	0	0	4	0	2	<0.001	

* Intragroups analysis: Wilcoxon paired test (change in number of drugs from baseline non-normally distributed).
† Intergroups analysis: Wilcoxon two-sample test (number of drugs non-normally distributed in both groups).

Table 4. Rates of any postoperative reduction in intraocular pressure-lowering medications over time in both groups.

Time	Any reduction in number of drugs: CO_2 laser-assisted sclerectomy surgery (N = 66) *n* (%)	Trabeculectomy (N = 65) *n* (%)	p*
After a month	66 (100)	63 (97)	0.244 F
After 3 months	65 (99)	62 (95)	0.365 F
After 6 months	57 (86)	62 (95)	0.216
After 12 months	51 (77)	59 (91)	0.094

* Chi-squared test, F = Fisher's exact test (due to low expected values).

Table 5. Complete success rates over time in both groups.

Time	Complete success: CO_2 laser-assisted sclerectomy surgery (N = 66) *n* (%)	Trabeculectomy (N = 65) *n* (%)	p*
After a week	55 (83)	60 (92)	0.285
After a month	48 (73)	57 (88)	0.045
After 3 months	33 (50)	49 (75)	0.01
After 6 months	24 (36)	43 (66)	0.001
After 12 months	23 (35)	39 (60)	0.008

* Chi-squared test.

Table 6. Qualified success rates over time in both groups.

Time	Qualified success: CO_2 laser-assisted sclerectomy surgery (N = 66) *n* (%)	Trabeculectomy (N = 65) *n* (%)	p*
After a week	56 (85)	60 (92)	0.285
After a month	51 (77)	58 (89)	0.162
After 3 months	51 (77)	54 (83)	0.523
After 6 months	49 (74)	51 (78)	0.874
After 12 months	49 (74)	49 (75)	1

* Chi-squared test.

decided to set ambitious target IOP (≤18 mmHg with a reduction by 30%), following the European Glaucoma Society guidelines (2014). Skaat et al. (2014) reported a complete and qualified success rate for CLASS after 12 months at 45.5% and 90.9%, respectively. However, they used MMC in 76.9% of the subjects and defined their criteria as the IOP between 5 and 21 mmHg with a 20% reduction from baseline. Other authors (Geffen et al. 2012; Greifner et al. 2016) set the target IOP between 5 and 18 mmHg. Greifner et al. (2016) performed CLASS combined with intrascleral space-occupying implants and MMC, achieving complete success rate in 73% and qualified success in 96% of the patients after the mean follow-up of 20.7 ± 6.8 months. Geffen et al. (2012), using MMC in 83.3% of patients, reported a complete success rate for CLASS with and without MMC after 12 months of 68.2% and 42.9%, respectively. Interestingly, the difference between the MMC and non-MMC groups did not show statistical significance. In our group, CLASS without MMC presented a less potent long-term hypotensive effect; however, it was not inferior to trabeculectomy in the qualified success rate at the end of the follow-up period.

Even though the efficacy of glaucoma surgery is mainly reflected by its potential to lower the IOP, the reduction in the number of medications and the lack of visual acuity deterioration following the procedure contribute to the overall success of the surgery (EGS 2014). Among our subjects, five patients lost at least one line following CLASS, which was significantly less frequent than in the trabeculectomy group (8%, versus 29%, $p < 0.05$), and the mean BCVA change following CLASS was not statistically significant. The main advantages of the nonpenetrating glaucoma surgery compared with trabeculectomy, consistent with our findings, are lower rate of complications (Eldaly et al. 2014) including lower inflammatory response (Chiou et al. 1998), quicker and full visual recovery (Karlen et al. 1999) and lack of significant changes in astigmatism (Corcostegui et al. 2004; Egrilmez et al. 2004). In our study, total rates of early complications and the incidence of choroidal detachment following CLASS were significantly lower compared to trabeculectomy (9.1% versus 29.2% and 1.5% versus 18.5%, respectively). We note, however, that the rate of choroidal detachment in our trabeculectomy group seems to be high compared with the modern literature. Trabeculectomy (TRAB) technique has embraced a range of refinements; therefore, there was a noticeable decrease in the rate of early postoperative complications reported in the major multicenter trabeculectomy surveys carried out in the UK over the last two decades (Edmunds et al. 2002; Gedde et al. 2007; Kirwan et al. 2013). Kirwan et al. (2013) reported lower incidence of shallow AC (0.9%) and choroidal detachment (5%) than those published earlier in the National Survey of Trabeculectomy by Edmunds et al. (2002) (shallow AC 23.9%, choroidal detachment 14.1%) or the TVT study by Gedde et al. (2007) (shallow AC 10%, choroidal detachment 19% in the trabeculectomy group). It has been established that the Moorfields Safer Surgery System results in a reduced rate of hypotony-related early

Table 7. List of early complications in CO_2 laser-assisted sclerectomy surgery (CLASS) versus trabeculectomy (TRAB) groups.

Complications	CO_2 laser-assisted sclerectomy surgery (N = 66) n (%)	Trabeculectomy (N = 65) n (%)	p*
Early complications	6 (9.1)	19 (29.2)	0.004
Shallow AC	1 (1.5)	4 (6.2)	0.208 F
Hyphema	1 (1.5)	4 (6.2)	0.208 F
Bleb leakage	1 (1.5)	6 (9.2)	0.062 F
Choroidal detachment	1 (1.5)	12 (18.5)	0.001
Anterior uveitis	1 (1.5)	1 (1.5)	1 F
Iris incarceration	3 (4.5)	2 (3.1)	1 F

One patient may have more than one complication.
* Chi-squared test, F = Fisher's exact test (due to low expected values).

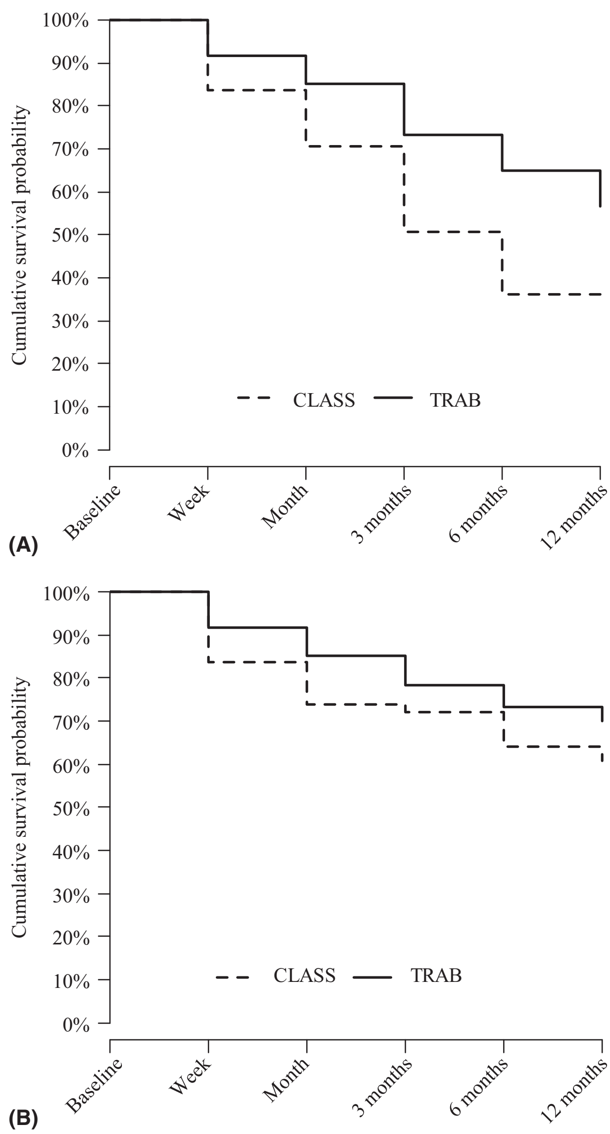

Fig. 3. (A) Kaplan–Meier plots of the cumulative probability of complete success for CO_2 laser-assisted sclerectomy surgery (CLASS) and trabeculectomy (TRAB) groups. (B) Kaplan–Meier plots of the cumulative probability of qualified success for CLASS and TRAB groups

complications and the outflow control may be improved, especially with the use of releasable and adjustable sutures. Therefore, we conclude that our trabeculectomy technique requires revision.

The list of early complications in the CLASS group included hyphema (one patient), bleb leakage with shallow AC and choroidal detachment requiring bleb suturing (one patient) and post-operative anterior uveitis (one patient). Other authors have reported a similar rate of complications following CLASS, including sporadic cases of microhyphema, choroidal detachment, wound dehiscence and leaks (Geffen et al. 2012; Skaat et al. 2014; Greifner et al. 2016). Microperforations of TDM were suspected in three of our patients who developed peripheral anterior synechia and iris incarceration within the filtration site of the sclerectomy. These patients underwent the enhancement procedure of Nd:YAG laser GPT between one and 3 months postoperatively, and they finally failed to achieve the target IOP despite adjuvant medications. CO_2 laser ablation was introduced to replace and simplify the manual dissection of the deep sclerectomy. Indeed, it has been shown to achieve good percolation and low IOP but still at the risk of perforation of the TDM. Geffen et al. (2012) and Greifner et al. (2016) have reported intraoperative macroperforations requiring conversion to trabeculectomy and postoperative iris incarceration occurring spontaneously or following GPT. We did not notice the intraoperative macroperforation in our study group; however, we had observed this complication in our department twice while performing CLASS prior to this study (unpublished data). We agree that the ablation in the CLASS procedure needs standardization, which was already postulated by the other authors (Greifner et al. 2016). We also strongly support the suggestion that using the laser applications of low energy increases the safety of deep ablation, while high energy applications result in creating deeper 'bites' in dry tissue and potentially result in perforation prior to achieving the percolation of fluid.

It has been established that glaucoma surgery can adversely affect the cornea in terms of postoperative astigmatism and accelerated ECD loss. Our

Table 8. Endothelial cell density (ECD) loss 1 year after the surgery in both groups.

			ECD (% reduction from baseline)								
Time	Group	*N*	Mean	SD	Median	Min	Max	Q1	Q3	p*	p†
After 12 months	CO_2 laser-assisted sclerectomy surgery	66	1.4	1.4	1.0	−0.4	5.4	0.5	1.8	<0.001	<0.001
	Trabeculectomy	65	6.5	4.8	5.0	−0.5	18.3	3.2	9.1	<0.001	

* Intragroups analysis: Wilcoxon paired test (reductions non-normally distributed).
† Intergroups analysis: Wilcoxon two-sample test (reductions non-normally distributed in both groups).

Table 9. Change in mean 3-mm-zone total corneal refractive power astigmatism (TCRPA3) 1 year after the surgery in both groups.

		Astigmatism (TCRPA3, Pentacam; change in D from baseline)								
Time	Group	Mean	SD	Median	Min	Max	Q1	Q3	p*	p†
After 12 months	CO_2 laser-assisted sclerectomy surgery	0.0	0.1	0	−0.1	0.2	0	0	0.075	<0.001
	Trabeculectomy	0.1	0.2	0.1	−0.1	0.6	0	0.2	<0.001	

* Intragroups analysis: Wilcoxon paired test (changes non-normally distributed).
† Intergroups analysis: Wilcoxon two-sample test (changes non-normally distributed in both groups).

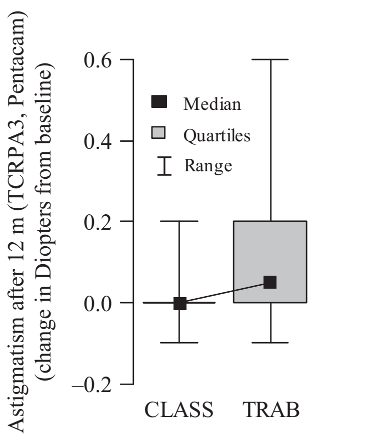

Fig. 4. Change in mean 3-mm-zone total corneal refractive power astigmatism (TCRPA3) 12 months (12 m) after the surgery in both groups. Boxes indicate quartiles; bars indicate range.

results indicated that CLASS remains astigmatically neutral and is followed by low ECD loss. While ECD loss in the normal cornea is linear and estimated between 0.5% and 0.6% per year during adulthood (Bourne et al. 1997; Moller-Pedersen 1997), glaucoma itself predisposes it to faster endothelial cells loss (Gagnon et al. 1997) and surgical trauma may accelerate this process, resulting in mild ECD loss observed in specular microscopy or even in corneal decompensation due to endothelial failure (Aldave et al. 2000; Hau & Barton 2009; Stewart et al. 2011). A wide range of average central ECD loss after glaucoma surgery was reported, between 1.6% and 54.8%, which was correlated with intraoperative and postoperative AC depth (Smith et al. 1991). The recent study by Tan et al. (2017) reported central ECD loss rates of 4.1% and 6.2%, depending on the tube–cornea distance, 1 year after the Baerveldt tube insertion. Storr-Paulsen et al. (2008) studied the central ECD loss after MMC-augmented trabeculectomy and found an ECD loss of 10% after 12 months. Arnavielle et al. (2007) compared ECD loss after trabeculectomy with deep sclerectomy and found a significant difference (9.6% versus 4.5%) after 1 year. Similarly, our study revealed higher ECD loss 12 months after the surgery in the trabeculectomy group (6.5 ± 4.8% versus 1.4 ± 1.4%, $p < 0.001$).

Considering the nature of penetrating and nonpenetrating filtration surgery, it seems unlikely that CLASS can be more potent in IOP lowering than trabeculectomy. In contrast to the results published by Yick et al. (2016), we believe that CLASS is not a viable therapeutic option for any patient with angle closure glaucoma, uveitic glaucoma or for patients in whom trabeculectomy had already failed due to fibrosis. It seems unlikely that CLASS, as a nonpenetrating procedure, could be effective in conditions affecting the anatomy of the iridocorneal angle, for example the primary narrow and occludable angles or secondary glaucoma with the presence of peripheral anterior synechia. This technique, however, offers potential gains for the patients in terms of quality of life. In our study, CLASS provided the

Table 10. Snellen lines loss 12 months after the surgery in both groups.

		Snellen lines loss (lines)								
Group	*N*	Mean	SD	Median	Min	Max	Q1	Q3	p*	p†
CO_2 laser-assisted sclerectomy surgery	66	0.1	0.1	0	0	2	0	0	0.126	0.016
Trabeculectomy	65	0.4	0.6	0	0	3	0	1	<0.001	

* Intragroup analysis: Wilcoxon paired test (changes non-normally distributed).
† Intergroup analysis: Wilcoxon two-sample test (changes non-normally distributed in both groups.

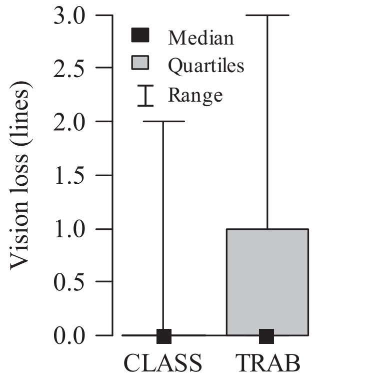

Fig. 5. Snellen lines loss 12 months after the surgery in both groups. Boxes indicate quartiles, bars indicate range.

patients with a significant reduction in medications up to 12 months. Moreover, compared to trabeculectomy, it produced a small number of early complications and a low ECD loss. Additionally, CLASS did not induce significant postsurgical astigmatism and vision loss.

In the light of the above results, as surgery in POAG is still frequently reserved for advanced disease when low IOP is required, trabeculectomy will continue to remain the surgery of choice. CO_2 laser-assisted sclerectomy surgery (CLASS) may be an appealing therapeutic option for certain groups of patients, such as a population of elderly patients with moderate glaucoma, in whom a low target pressure is not necessary and for whom a slightly higher target IOP with a potentially lower risk of complications, compared to trabeculectomy, may be justifiable. As safety concerns are a barrier, CLASS may have a role at an earlier stage of disease, especially in patients with a compromised baseline ECD.

The main limitation of our work was a lack of access to MMC, as at the time of the study the use of MMC in ophthalmology remained uncompliant with Polish state regulations. On the other hand, our study reports on the efficacy of CLASS without antimetabolites, as proposed by Skaat et al. (2014). We conducted our analysis for homogenous groups of patients with POAG and XFG; however, we did not achieve a normal distribution of all the analysed variables, which might have affected the statistical analysis. Nevertheless, as there is still a scarce scientific base in the subject of CLASS, we find our results contributory in terms of providing a comparison between CLASS and trabeculectomy. We believe that the evaluation of the impact of CLASS on corneal astigmatism and ECD is also important.

To conclude, the results of the following study, along with the modern literature on trabeculectomy, indicate that CLASS is certainly a safe surgical procedure; however, it is remarkably less effective than trabeculectomy. Since the complication rates in our trabeculectomy group are high, we note that it may cast a relatively favourable light onto the CLASS results. Surgical precision and safety of CLASS seem to have improved with modifications in the laser operating system (Geffen et al. 2012; Skaat et al. 2014). What remains uncertain is the degree and longevity of IOP control following CLASS compared with modern trabeculectomy. Therefore, we emphasize that the revision of our present trabeculectomy technique is necessary. We suggest that a randomized prospective study with a higher number of participants and a longer follow-up period is required to monitor the safety and the long-term efficacy of MMC-augmented CLASS compared with trabeculectomy technique adherent to the Moorfields Safer Surgery System. Moreover, a cost–benefit analysis evaluating CLASS, microinvasive glaucoma surgery (MIGS) techniques and medical treatment in early to moderate glaucoma could be useful to clarify the economic position of CLASS in the armamentarium of current nonpenetrating procedures for glaucoma.

Table 11. Rates of best-corrected Snellen visual acuity change, 1 year after the surgery in both groups.

Best-corrected Snellen visual acuity change	CO_2 laser-assisted sclerectomy surgery (N = 66) *n* (%)	Trabeculectomy (N = 65) *n* (%)	p*
No change	61 (92)	46 (71)	0.017
At least one line lost	5 (8)	19 (29)	

* Chi-squared test.

References

Aldave AJ, Rudd JC, Cohen EJ, Rapuano CJ & Laibson PR (2000): The role of glaucoma therapy in the need for repeat penetrating keratoplasty. Cornea **19**: 772–776.

Alvani A, Pakravan M, Esfandiari H, Safi S, Yaseri M & Pakravan P (2016): Ocular biometric changes after trabeculectomy. J Ophthalmic Vis Res **11**: 296–303.

Anand N & Atherley C (2005): Deep sclerectomy augmented with mitomycin C. Eye **19**: 442–450.

Arnavielle S, Lafontaine PO, Bidot S, Creuzot-Garcher C, D'athis P & Bron AM (2007): Corneal endothelial cell changes after trabeculectomy and deep sclerectomy. J Glaucoma **16**: 324–328.

Assia EI, Rotenstreich Y, Barequet IS, Apple DJ, Rosner M & Belkin M (2007): Experimental studies on nonpenetrating filtration surgery using the CO_2 laser. Graefes Arch Clin Exp Ophthalmol **245**: 847–854.

Bourne WM, Nelson LR & Hodge DO (1997): Central corneal endothelial cell changes over a ten-year period. Invest Ophthalmol Vis Sci **38**: 779–782.

Cairns JE (1968): Trabeculectomy: preliminary report of a new method. Am J Ophthalmol **66**: 673–679.

Chan CK, Lee S, Sangani P, Lin LW, Lin MS & Lin SC (2007): Primary trabeculectomy surgery performed by residents at a county hospital. J Glaucoma **16**: 52–56.

Chiou AGY, Mermoud A & Jewelewicz DA (1998): Postoperative inflammation following deep sclerectomy with collagen implant versus standard trabeculectomy. Graefes Arch Clin Exp Ophthalmol **236**: 593–596.

Chiselita D (2001): Non-penetrating deep sclerectomy versus trabeculectomy in primary open-angle glaucoma surgery. Eye **15**: 197–201.

Cillino S, Di Pace F, Casuccio A, Calvaruso L, Morreale D, Vadalà M & Lodato G (2004): Deep sclerectomy versus punch trabeculectomy with and without phacoemulsification: a randomised clinical trial. J Glaucoma **13**: 500–506.

Corcostegui J, Rebolleda G & Munoz-Negrete FJ (2004): Refractive changes after phacoemulsification combined with deep sclerectomy assisted by corneal topography. J Cataract Refract Surg **30**: 2391–2396.

Dietlein TS, Jacobi PC, Luke C & Krieglstein G (2000): Morphological variability of the trabecular meshwork in glaucoma patients: implications for non- perforating glaucoma surgery. Br J Ophthalmol **84**: 1354–1359.

Edmunds B, Thompson JR, Salmon JF & Wormald RP (2002): The national survey of trabeculectomy III. Early and late complications.. Eye **16**: 297–303.

Egrilmez S, Ates H, Nalcaci S, Andac K & Yagci A (2004): Surgically induced corneal refractive change following glaucoma surgery: nonpenetrating trabecular surgeries versus trabeculectomy. J Cataract Refract Surg **30**: 1232–1239.

EGS (2014): European glaucoma society terminology and guidelines for glaucoma, 4th edition - chapter 3: treatment principles and options. Supported by the EGS Foundation. Br J Ophthalmol **101**: 130–195.

El Sayyad F, Helal M, El-Kholify H & El-Maghraby A (2000): Nonpenetrating deep sclerectomy versus trabeculectomy in bilateral primary open-angle glaucoma. Ophthalmology **107**: 1671–1674.

Eldaly MA, Bunce C, Elsheikha OZ & Wormald R (2014): Non-penetrating filtration surgery versus trabeculectomy for open-angle glaucoma. Cochrane Database Syst Rev: CD007059.

Fyodorov SN (1989): Non penetrating deep sclerectomy in open angle glaucoma. Eye Microsurg **3**: 52–55.

Gagnon MM, Boisjoly HM, Brunette I, Charest M & Amyot M (1997): Corneal endothelial cell density in glaucoma. Cornea **16**: 314–318.

Gedde SJ, Herndon LW, Brandt JD, Budenz DL, Feuer WJ & Schiffman JC (2007): Surgical complications in the tube versus trabeculectomy study during the first year of follow-up. Am J Ophthalmol **143**: 23–31.

Geffen N, Ton Y, Degani J & Assia EI (2012): CO_2 laser-assisted sclerectomy surgery, Part II. J Glaucoma **21**: 193–198.

Greifner G, Roy S & Mermoud A (2016): Results of CO_2 laser-assisted deep sclerectomy as compared with conventional deep sclerectomy. J Glaucoma **25**: 630–638.

Grieshaber MC, Schoetzau A, Grieshaber HR & Stegmann R (2017): Canaloplasty with Stegmann Canal Expander for primary open-angle glaucoma: two-year clinical results. Acta Ophthalmol **95**: 503–508.

Harju M, Suominen S, Allinen P & Vesti E (2017): Long-term results of deep sclerectomy in normal-tension glaucoma. Acta Ophthalmol [Epub ahead of print].

Hau S & Barton K (2009): Corneal complications of glaucoma surgery. Curr Opin Ophthalmol **20**: 131–136.

Hondur A, Onol M & Hasanreisoglu B (2008): Nonpenetrating glaucoma surgery: meta-analysis of recent results. J Glaucoma **17**: 139–146.

Karlen M, Sanchez E, Schnyder CC, Sickenberg M & Mermoud A (1999): Deep sclerectomy with collagen implant: medium term results. Br J Ophthalmol **83**: 6–11.

Khaw PT, Chiang M, Shah P, Sii F, Lockwood A & Khalili A (2012): Enhanced trabeculectomy: the Moorfields safer surgery system. Dev Ophthalmol **50**: 1–28.

Kirwan JF, Lockwood AJ, Shah P et al. (2013): Trabeculectomy outcomes Group Audit Study Group. Trabeculectomy in the 21st century: a multicenter analysis. Ophthalmology **120**: 2532–2539.

Klink T, Schlunck G, Lieb W, Klink J & Grehn F (2008): CO_2 excimer and erbium: YAG laser in deep sclerectomy. Ophthalmologica **222**: 74–80.

Kwong A, Law SK, Kule RR, Nouri-Mahdavi K, Coleman AL, Caprioli J & Giaconi JA (2014): Long-term outcomes of resident- versus attending-performed primary trabeculectomy with mitomycin C in a United States residency program. Am J Ophthalmol **157**: 1190–1201.

Landers J, Martin K, Sarkies N, Bourne R & Watson P (2012): A twenty-year follow-up study of trabeculectomy: risk factors and outcomes. Ophthalmology **119**: 694–702.

Mermoud A (2000): Sinusotomy and deep sclerectomy. Eye **14**: 531–535.

Mermoud A & Schnyder CC (2000): Nonpenetrating filtering surgery in glaucoma. Curr Opin Ophthalmol **11**: 151–157.

Mietz H, Roters S & Krieglstein GK (2005): Bullous keratopathy as a complication of trabeculectomy with mitomycin C. Graefes Arch Clin Exp Ophthalmol **243**: 1284–1287.

Moller-Pedersen T (1997): A comparative study of human corneal keratocyte and endothelial cell density during aging. Cornea **16**: 333–338.

R Core Team (2017): R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing. Available at: https://www.R-project.org/. (Accessed on 19 Jul 2017).

Rosen WJ, Mannis MJ & Brandt JD (1992): The effect of trabeculectomy on corneal topography. Ophthalmic Surg **23**: 395–398.

Sarodia U, Shaarawy T & Barton K (2007): Nonpenetrating glaucoma surgery: a critical evaluation. Curr Opin Ophthalmol **18**: 152–158.

Shaarawy T, Mansouri K, Schnyder C, Ravinet E, Achache F & Mermoud A (2004): Long-term results of deep sclerectomy with collagen implant. J Cataract Refract Surg **30**: 1225–1231.

Skaat A, Goldenfeld M, Cotlear D & Melamed S (2014): CO_2 laser-assisted deep sclerectomy in glaucoma patients. J Glaucoma **23**: 179–184.

Smith DL, Skuta GL, Lindenmuth KA, Musch DC & Bergstrom TJ (1991): The effect of glaucoma filtering surgery on corneal endothelial cell density. Ophthalmic Surg **22**: 251–255.

Stewart RM, Jones MN, Batterbury M et al. (2011): Effect of glaucoma on corneal graft survival according to indication for penetrating keratoplasty. Am J Ophthalmol **151**: 257–262.

Storr-Paulsen T, Norregaard JC, Ahmed S & Storr-Paulsen A (2008): Corneal endothelial cell loss after mitomycin C-augmented trabeculectomy. J Glaucoma **17**: 654–657.

Sun LL & Lee GA (2013): Trabeculectomy: the limitations for registrar training. Clin Exp Ophthalmol **41**: 135–139.

Tan AN, Webers CA, Berendschot TT et al. (2017): Corneal endothelial cell loss after Baerveldt glaucoma drainage device implantation in the anterior chamber. Acta Ophthalmol **95**: 91–96.

Tanito M, Sano I, Ikeda Y & Fujihara E (2017): Short-term results of microhook ab interno trabeculotomy, a novel minimally invasive glaucoma surgery in Japanese eyes: initial case series. Acta Ophthalmol **95**: e354–e360.

Ton Y, Geffen N, Kidron D, Degani J & Assia EI (2012): CO_2 laser-assisted sclerectomy surgery. Part I: concept and experimental models. J Glaucoma **21**: 135–140.

Tonn B, Klaproth OK & Kohnen T (2014): Anterior surface-based keratometry compared with Scheimpflug tomography-based total corneal astigmatism. Invest Ophthalmol Vis Sci **56**: 291–298.

Watson P (1970): Trabeculectomy: a modified ab externo technique. Ann Ophthalmol **2**: 199–205.

Willekens K, Pinto LA, Delbeke H, Vandewalle E & Stalmans I (2016): Trabeculectomy with moorfields conjunctival closure technique offers safety without astigmatism induction. J Glaucoma **25**: 531–535.

Yick DWF, Lee JWY, Tsang S, Yeung BYM & Yuen CYF (2016): Preliminary results of CO2 laser-assisted sclerectomy surgery (CLASS) in the treatment of advanced glaucoma in a Chinese population. Medicine **95**: 5294.

Received on September 20th, 2017.
Accepted on January 14th, 2018.

Correspondence:
Judyta Jankowska-Szmul
Department of Ophthalmology
School of Medicine with the Division of Dentistry in Zabrze
Medical University of Silesia
Panewnicka 65
40-760 Katowice
Poland
Tel: +48 32 6053592
Fax: +48 32 6053593
Email: jankowskajudyta@wp.pl