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Letters to the Editor

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AT A GLANCE

2025 Issue 3 at a Glance:

Esteemed colleagues,

In its third issue of 2025, the Turkish Journal of Ophthalmology features five original studies, two reviews, and two letters to the editor.

The prospective interventional study by Sachan et al. titled "Comparison of 20% Autologous Platelet-Rich Plasma Versus Conventional Treatment in Moderate to Severe Dry Eye Patients" included 40 individuals (80 eyes) with moderate to severe dry eye disease. The patients were randomized to the study and control groups (20 each). Those in the study group received 20% autologous platelet-rich plasma eye drops, while the control group received artificial tears as conventional treatment. At the end of three months, there was a significantly greater decrease in ocular surface disease index score in the study group than in the control group, and tear meniscus height, Schirmer test values, and tear breakup time were significantly improved in the study group. The post-treatment improvements in fluorescein staining and impression cytology scores were also significantly greater in the study group compared to the control group. The authors emphasized that autologous platelet-rich plasma therapy is safer and more effective than conventional treatments for moderate to severe symptomatic dry eye disease (See pages 112-119).

In their study titled "Comparative Analysis of Automated vs. Expert-Designed Machine Learning Models in Age-Related Macular Degeneration Detection and Classification", Durmaz Engin et al. aimed to compare the effectiveness of expert-designed machine learning models and code-free automatic machine learning (AutoML) models in detecting age-related macular degeneration (AMD) and distinguishing dry from wet AMD on optical coherence tomography images. The expert-designed model was developed by an AI expert using EfficientNet V2 architecture, while the AutoML model was created by an ophthalmologist using the LobeAI platform, which utilizes transfer learning with ResNet-50 V2. The study compared performance metrics by calculating sensitivity, specificity, accuracy, and F1 scores. The expert-designed model provided 99.67% overall accuracy in classifying all images, and F1 scores were calculated as 0.99 or higher in all binary classifications. On the other hand, while the AutoML model had 89.00% overall accuracy, its F1 scores ranged from 0.86 to 0.90 in binary classifications. The authors stated that although the AutoML model had acceptable performance in recognizing and classifying AMD cases, the expert-designed model had significantly superior performance, emphasizing the importance of the advanced neural network architectures and optimization processes used in expert-developed models (See pages 120-126).

In a cross-sectional study titled "Pattern of RNFL Damage in Early- and Late-Stage Primary Open-Angle Glaucoma Using the Disc Damage Likelihood Scale and Optical Coherence Tomography", UlAin et al. included 267 eyes of 135 patients aged 18 years and older with suspected or diagnosed glaucoma. After a comprehensive ocular examination, the Disc Damage Likelihood Scale was used for glaucoma staging, with disease severity rated in three zones: green, orange, and red. Retinal nerve fiber layer (RNFL) thickness was measured in the four quadrants using optical coherence tomography, and patterns of RNFL damage were analyzed according to the ISNT rule (inferior>superior>nasal>temporal) and compared between the three groups. The groups differed significantly in terms of mean, inferior, superior, and temporal RNFL thickness, while the difference in nasal RNFL was not significant. While the ISNT rule was found to be the most common pattern among the participants included in the study, progressive loss of this pattern was observed with increased disease severity (See pages 127-131).

In their study titled "Real-Life Effectiveness and Safety of Selective Laser Trabeculoplasty as Primary, Adjunctive, and Substitutive Therapy", Oliver-Gutierrez et al. aimed to evaluate the real-life outcomes of selective laser trabeculoplasty (SLT) in treatment-naïve patients compared to SLT used as adjunctive therapy (AT) and to investigate the potential of SLT to lower intraocular pressure (IOP) and reduce topical medication burden. Patients who had not previously undergone glaucoma surgery or laser treatment received SLT as primary therapy (PT), as AT, or as substitution therapy (ST). Success in the PT and AT groups was defined as ≥20% IOP reduction and IOP ≤21 mmHg in two consecutive follow-ups with the same or fewer drugs without additional glaucoma surgery (including repeat SLT), while success in the ST group was defined as the same or lower IOP with fewer topical medications. The study included a total of 120 eyes of 120 patients with an average follow-up of 32.7 months. The reduction in IOP was greater in the PT group than in the AT group at 24-36 months (22.1% vs.14.5%, p=0.039). Treatment nonresponse was reported in 28.6% of the PT group and 37.0% of the ST group. Success rates were higher in the PT group than in the AT group at 12, 24, and 36 months (47.1% vs. 69.0%, 31.4% vs. 38.8%, and 23.5% vs. 31.1%, respectively). In the ST group, the success rate was 34.2% at 12 months and increased to 38.3% at 24 months (See pages 132-140).

Üçgül et al. conducted a retrospective study titled "Gonioscopy-Assisted Transluminal Trabeculotomy versus Bent Ab Interno Needle Goniectomy in Patients with Open-Angle Glaucoma" comparing the efficacy and safety of gonioscopy-assisted transluminal trabeculotomy (GATT) and bent ab interno needle goniectomy (BANG) in patients with open-angle glaucoma. They evaluated 34 eyes that underwent GATT and 31 eyes that underwent BANG. The preoperative mean IOP was 32.9±6.1 mmHg in the GATT group and 31.8±5.4 mmHg in the BANG group. At the last postoperative follow-up, the mean IOP had decreased to 15.8±4.5 mmHg (51.9% reduction) in the GATT group and 17.9±5.7 mmHg (43.7% reduction) in the BANG group. The rate of complete surgical success was 88.2% for the GATT procedure and 61.3% for the BANG procedure. Early surgical failures were more common

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in the BANG group, while the BANG group had fewer early surgical failures and more late surgical failures. While the authors emphasized that GATT surgery provides a larger and more sustainable IOP reduction compared to BANG surgery and has higher surgical success rates, they stated that GATT is a more reliable option in the management of open-angle glaucoma (See pages 141-147).

In their review titled "Binocular Approaches in Amblyopia Treatment Based on Dichoptic Stimulation", Yabanoğlu and Taylan Şekeroğlu systematically examined the literature on dichoptic stimulation techniques that aim to improve binocular function in the treatment of strabismus. Based on various studies in the literature, they explained the basic principles of these treatment methods with emphasis on their results compared to traditional monocular treatment methods. This excellent review provides a comprehensive assessment of the integration of dichoptic treatment approaches into clinical practice and a guiding perspective on the future use of these methods (See pages 148-158).

The second review of the issue was penned by Aktaş et al. and is titled "Ab Interno Goniotomy/Goniectomy Techniques". Minimally invasive glaucoma surgeries (MIGS), which include techniques such as Kahook Dual Blade, BANG, GATT, OMNI, Trabectom, Streamline, and TrabEx+, have made significant advances in the treatment of glaucoma by reducing IOP and improving aqueous humor outflow. These innovative procedures offer effective alternatives to more invasive filtration surgeries by targeting structures such as the trabecular meshwork and Schlemm's canal. MIGS enhances the natural drainage pathways, leading to marked reductions in IOP and reduced dependence on glaucoma medications. Clinical studies show that these MIGS techniques are safe and effective, resulting in fewer complications than traditional surgeries such as trabeculectomy or tube shunt implantation. In addition to providing an overview of the MIGS techniques, this review successfully summarizes the extensive topic of these techniques' evolution, practical applications, and outcomes (See pages 159-170).

In the first letter to the editor in this issue, titled "A Promising Outcome of the Augmented Modified Hummelsheim Procedure in a Challenging Case of Inferior Rectus Hypoplasia", Priscilia and Bani summarized the treatment approach used for a 25-year-old female patient with inferior rectus hypoplasia, a rare pathology (See pages 171-173).

Kaynak et al. share another letter to the editor titled "Ptosis Repair by "PEANUTS" MMCR: "Pelin's Easy and Needle Up To Stretch" Müller's Muscle Conjunctival Resection Without the Putterman Clamp". The authors describe a surgical method that is based on the original Müller muscle-conjunctiva resection technique but uses a 21-gauge needle instead of the Putterman clamp and evaluate the outcomes of three ptosis patients operated using this technique (See pages 174-176).

Covering diagnostic and therapeutic approaches to various ocular pathologies from glaucoma to AMD, from ptosis to dry eye, we hope this issue will provide both scientific and practical guidance for our valued readers.

We would like to thank all the researchers who contributed to this issue. Through your contributions, we hope that each and every issue will feature even richer content.

Respectfully on behalf of the Editorial Board,

Hakan Özdemir, MD

Original Article

Comparison of 20% Autologous Platelet-Rich Plasma Versus Conventional Treatment in Moderate to Severe Dry Eye Patients

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Abstract

Objectives: To evaluate the effectiveness of conventional therapy and 20% autologous platelet-rich plasma (aPRP) eye drops for moderate to severe dry eye disease (DED).

Materials and Methods: In this prospective interventional study, 40 individuals (80 eyes) with moderate to severe DED were analyzed. Twenty patients each were randomly assigned to the study and control groups. The study group was given 20% aPRP eye drops; the control group was given artificial tears as per conventional treatment. Comprehensive eye examinations including evaluation of best corrected visual acuity (BCVA), tear meniscus height, tear break-up time (TBUT), Schirmer's test, corneal fluorescein staining, conjunctival impression cytology, and Ocular Surface Disease Index (OSDI) were conducted in both groups for 3 months. Pre- and posttreatment results were compared.

Results: The average age of patients in the study group was 51±14 years (range, 37-65 years), whereas that of the control group was 50±17 years (range, 33-67 years). After 3 months, there was a more significant decrease in OSDI score in the study group than in the control group ($p<0.01$). The BCVA data demonstrated no statistically significant difference ($p>0.05$). Measurements of tear meniscus height, Schirmer's value, and TBUT at 3 months showed statistically significant differences ($p<0.01$). The posttreatment improvements in fluorescein staining and impression cytology scores in the study group were markedly superior to those in the control group ($p<0.01$).

Conclusion: aPRP is both safe and more effective than conventional treatments for moderate to severe symptomatic DED.

Keywords: Autologous platelet-rich plasma (aPRP), dry eye disease, OSDI, autologous serum, impression cytology

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Introduction

Dry eye disease (DED) is a prevalent and multifactorial condition of the ocular surface marked by disruption of tear film homeostasis and accompanied by ocular symptoms. The etiology of this disease includes inflammation and damage to the ocular surface, abnormalities in the neurosensory system, and tear film instability and hyperosmolarity.[1] Burning, photophobia, tearing, and foreign body sensation are symptoms of this disorder that can greatly impair a patient's quality of life. The estimated global prevalence of DED varies greatly (4%-50%) depending on the diagnostic criteria used and the population under consideration.[2,3,4] Smoking, contact lens wear, and prolonged use of digital screens are all contributing factors.[5]

The topical use of artificial tears is the primary conventional treatment for dry eye, despite the fact that the outcomes are frequently unsatisfactory. This has prompted the use of other hemoderivative-based treatment approaches. Autologous platelet-rich plasma (aPRP) has been proposed as a more suitable therapy for severe DED than artificial tears without preservatives. aPRP is a hemoderivative that contains a high concentration of platelets and is used to stimulate corneal epithelial cell migration, proliferation, and differentiation. The platelets in aPRP adhere to injured tissues and release growth factors and cytokines that promote healing.[6]

There are several benefits of aPRP over conventional therapies. Being homologous, it lowers the possibility of immunological problems or allergic responses that may occur with other therapies. Research indicates that aPRP is more effective than conventional therapies in improving tear film stability, increasing tear output, and decreasing ocular surface damage. aPRP has great promise, but it also has certain limitations, such as the need for specific handling and preparation, the possibility of infection and contamination, limited availability, and the lack of standard protocols. According to a recent meta-analysis assessing the

effect of PRP on dry eye, only 19 studies were eligible for inclusion. Of these, 10 were comparative (6 randomized and 4 nonrandomized studies).[7] Investigating the efficacy of this treatment approach, especially in comparison to conventional treatment, is important because the frequency of DED is increasing worldwide. This increase is particularly pronounced in younger populations, which may be a result of greater use of digital devices or other unidentified reasons. With its capacity for regeneration and low risk of side effects, aPRP may be a valuable development in the treatment of moderate to severe DED.

Materials and Methods

This prospective interventional comparative research was undertaken at the Regional Institute of Ophthalmology (MD Eye Hospital) in Prayagraj, Uttar Pradesh, over one year, from July 2023 to June 2024. The study was initiated after approval from the ethics council of MLN Medical College, Prayagraj (ECR/922/Inst/UP/RR-22 on 5/7/2023). Patients of either sex between 18 to 70 years of age were included in the study. Based on their Ocular Surface Disease Index (OSDI) score, the patients' symptoms were categorized, and those diagnosed with DED were randomly allocated to the study group (n=20) or control group (n=20). After explaining the procedures, all participants signed an informed consent form.

The study assessed OSDI score, best corrected visual acuity (BCVA), tear meniscus height, tear break-up time (TBUT), Schirmer's test, and corneal fluorescein staining before treatment and after 1 week, 1 month, and 3 months of treatment, as well as conjunctival impression cytology in both groups before and after 3 months of treatment. The study group received 20% aPRP eye drops, while the control group received conventional treatment consisting of Systane Complete lubricant eye drops (active ingredient: propylene glycol 0.6%; Alcon, Nagpur, India). As per the Dry Eye Workshop II recommendation, artificial tears are the first line of management in mild to severe cases of both evaporative and aqueous-deficient dry eye.[4]

Sample size was calculated using the following formula:

$$n = \frac{2(Z\alpha/_2 + Z_{(1-\beta)})^2 \times \sigma^2}{(\mu 1 - \mu 2)^2}$$

Assuming a 0.05 level of significance, n was calculated as 79.8. Therefore, 80 eyes were included in the study.

Inclusion and Exclusion Criteria

Patients aged 18-70 years with ODSI scores above 23 were eligible for the 12-week study. If the patient was already using topical lubricant eye drops, they were stopped 48 hours before starting the study intervention.

Patients meeting any of the following criteria were excluded from the study: being younger than 18 or older than 70 years of age or having advanced cancer, active infection, uncontrolled illness, pregnancy, contraindication for blood donation (e.g., recent anticoagulants or antiplatelets use, surgical interventions, positive HIV, hepatitis B or C, syphilis, or anemia), severe meibomian gland dysfunction, aberrant eyelid function, or ongoing ocular infection or inflammation. Patients with intolerable ocular side effects or allergic reactions to the topical therapies were also excluded during follow-up. Follow-up examinations were performed on day 0 and at 1 week, 1 month, and 3 months.

Method of Autologous Platelet-Rich Plasma Preparation

Ten milliliters of blood was collected from each patient in a blood collection tube coated with sodium citrate. The samples were centrifuged at soft spin (2400 rpm). The upper two-thirds was transferred to a separate tube which was subjected to hard spin (3600 rpm). The upper layer was removed and 3-5 mL of buffy coat/PRP was extracted. This was diluted with balanced salt solution to obtain a 20% concentration of aPRP. The aPRP eye drops were stored in sterile amber glass vials with eye drop applicators. The 20% aPRP drops were dispensed in 5 mL eye drop vials to the patient. The currently used vial was stored at 2-8 °C between instillations, while the remaining vials were stored at -20 °C until needed (Figure 1). Patients were advised to wash their hands before administering eye drops.

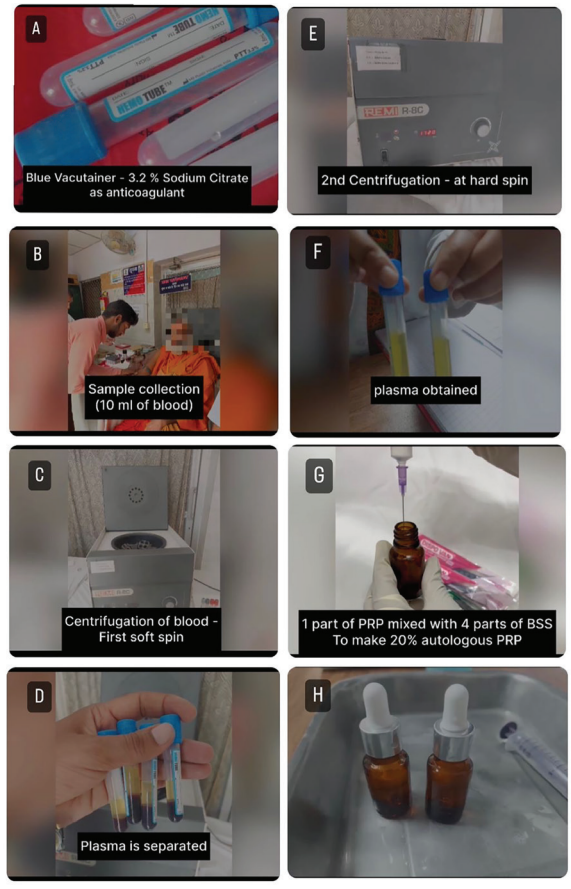

Figure 1. Method of preparing 20% autologous platelet-rich plasma eye drops
BSS: Balanced salt solution, PRP: Platelet-rich plasma

Statistical Analysis

We utilized Microsoft Excel 2016 and IBM SPSS Statistics for Windows version 29.0 (IBM Corp., Armonk, NY) for data analysis. Frequency and percentage were used for categorical variables and mean and standard deviation for continuous variables. Comparisons between the groups were made using independent-samples t-test for continuous variables and chi-square test for qualitative categorical data. The significance threshold was set at 0.05 for all statistical tests.

Results

OSDI scores in the study group ranged from 57 to 88, whereas those in the control group ranged from 54 to 88. There was no statistically significant difference in OSDI between the two groups at day 0 ($p>0.05$). However, there were statistically significant differences at 1 week ($p<0.05$), 1 month ($p<0.01$), and 3 months ($p<0.01$). The study group had lower mean OSDI values at these time points compared to the control group (Table 1).

The differences in BCVA between the study and control groups were not statistically significant at any time interval (Table 2).

Tear meniscus height did not differ significantly between the groups on day 0 or at 1 week ($p>0.05$). However, it was significantly higher in the study group than the control group at 1 month ($p<0.05$) and 3 months ($p<0.001$) (Table 3).

Table 1. Comparison of Ocular Surface Disease Index (OSDI) values between the groups

OSDI	Group	n	Mean	SD	t	p
Day 0	Study	20	71.95	9.10	0.018	0.986
	Control	20	72.00	8.91		
Week 1	Study	20	61.25	10.11	2.304	0.027*
	Control	20	68.35	9.37		
Month 1	Study	20	50.55	11.36	4.415	0.0005**
	Control	20	64.90	9.07		
Month 3	Study	20	38.90	9.00	7.473	0.0005**
	Control	20	61.55	10.14		

Independent-samples t-test, *Statistically significant ($p<0.05$), **Highly statistically significant ($p<0.01$). n: Number of patients, SD: Standard deviation

Table 2. Comparison of best corrected visual acuity (BCVA) between the groups

BCVA (logMAR)	Group	n	Mean	SD	t	p
Day 0	Study	40	0.123	0.11	0.090	0.929
	Control	40	0.120	0.14		
Week 1	Study	40	0.113	0.11	0.267	0.790
	Control	40	0.120	0.14		
Month 1	Study	40	0.108	0.11	0.445	0.658
	Control	40	0.120	0.14		
Month 3	Study	40	0.098	0.11	0.991	0.325
	Control	40	0.128	0.16		

Independent-samples t-test. logMAR: Logarithm of the minimum angle of resolution, n: Number of eyes, SD: Standard deviation

Table 3. Comparison of tear meniscus height between the groups

Tear meniscus height (µm)	Group	n	Mean	SD	t	p
Day 0	Study	40	188.38	56.37	0.861	0.392
	Control	40	199.13	55.31		
Week 1	Study	40	196.85	58.80	0.704	0.484
	Control	40	205.90	56.21		
Month 1	Study	40	234.58	48.65	2.259	0.027*
	Control	40	208.40	54.79		
Month 3	Study	40	262.20	48.74	4.576	0.0005**
	Control	40	208.18	56.57		

Independent-samples t-test, *Statistically significant ($p<0.05$), **Highly statistically significant ($p<0.01$). n: Number of eyes, SD: Standard deviation

TBUT improved with duration of aPRP therapy. There was no statistical difference between the groups on day 0 or at 1 week ($p>0.05$), whereas highly significant differences favoring the study group were observed at 1 month and 3 months ($p<0.01$) (Table 4).

Comparisons of Schirmer's test between the two groups revealed statistically significant differences at the $p<0.01$ level on day 0 and at 1 week, 1 month, and 3 months. At all time points, Schirmer's test values were significantly higher in the study group (Table 5).

Fluorescein staining also showed highly significant differences between the two groups at all time points ($p<0.01$). Staining was more extensive in the control group on day 0 and at 1 week, 1 month, and 3 months (Figure 2, Table 6).

The comparison of impression cytology between the groups showed that there was no statistically significant difference on day 0 ($p>0.05$), whereas at 3 months there was a highly significant difference (Figures 3 and 4, Table 7).

Refer to Table 8 for summarized results and Table 9 for main outcomes.

Table 4. Comparison of tear film break-up time (TBUT) between the groups

TBUT (s)	Group	n	Mean	SD	t	p
Day 0	Study	40	3.63	0.84	0.502	0.617
	Control	40	3.75	1.33		
Week 1	Study	40	4.13	0.91	0.466	0.643
	Control	40	4.00	1.43		
Month 1	Study	40	5.30	0.91	2.873	0.005**
	Control	40	4.55	1.38		
Month 3	Study	40	7.28	1.66	6.823	0.0005**
	Control	40	5.05	1.22		

Independent-samples t-test, **Highly statistically significant ($p<0.01$). n: Number of eyes, SD: Standard deviation

Table 5. Comparison of Schirmer's test results between the groups

Schirmer's test (mm)	Group	n	Mean	SD	t	p
Day 0	Study	40	4.3	2.1	2.867	0.005**
	Control	40	3.2	1.0		
Week 1	Study	40	5.9	2.1	6.631	0.0005**
	Control	40	3.5	0.9		
Month 1	Study	40	7.5	1.9	9.391	0.0005**
	Control	40	4.4	0.8		
Month 3	Study	40	9.7	1.1	20.093	0.0005**
	Control	40	5.2	0.9		

Independent-samples t-test, **Highly statistically significant ($p<0.01$). n: Number of eyes, SD: Standard deviation

Table 6. Comparison of corneal fluorescein staining between the groups

Fluorescein staining score	Group	n	Mean	SD	t	p
Day 0	Study	40	3.23	0.89	3.826	0.0005**
	Control	40	3.98	0.86		
Week 1	Study	40	3.03	1.03	3.051	0.003**
	Control	40	3.63	0.70		
Month 1	Study	40	2.45	0.78	4.787	0.0005**
	Control	40	3.20	0.61		
Month 3	Study	40	1.33	0.66	8.589	0.0005**
	Control	40	2.60	0.67		

Independent-samples t-test, **Highly statistically significant ($p<0.01$). n: Number of eyes, SD: Standard deviation

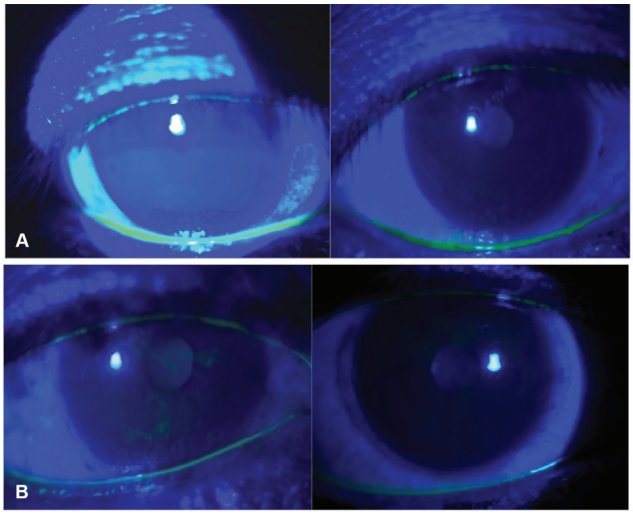

Figure 2. Pre- and posttreatment corneal fluorescein staining in the study group (A) and control group (B)

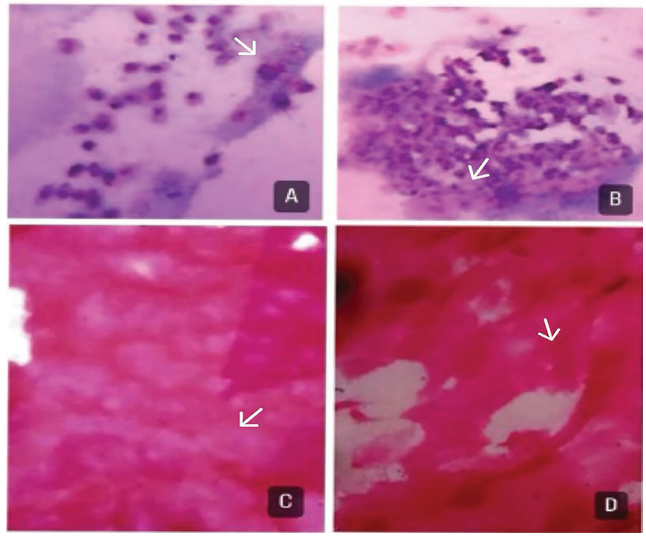

Figure 3. Pre- and posttreatment conjunctival impression cytology images from the study group. A) Complete loss of cohesion with enucleated cells and severe keratinization (grade 3) on day 0 (Papanicolaou stain, 40x). B) Loss of cohesion in the form of clusters with a nucleus-to-cytoplasm ratio of 1:3 to 1:4 (grade 1) after 3 months of treatment (Papanicolaou stain, 40x). C) Mucin spot/occasional goblet cells (grade 3) on day 0 (periodic acid-Schiff stain, 40x). D) Mild reduction of goblet cells (grade 1) after 3 months of treatment (periodic acid-Schiff stain, 40x)

Table 7. Comparison of impression cytology scores between the groups

Impression cytology score	Group	n	Mean	SD	t	p
Day 0	Study	40	1.98	0.83	0.291	0.772
	Control	40	2.03	0.70		
Month 3	Study	40	0.98	0.83	5.039	0.0005**
	Control	40	1.90	0.81		

Independent-samples t-test, **Highly statistically significant (p<0.01). n: Number of eyes, SD: Standard deviation

Table 8. Summarized results

Main outcome measures	Study group (mean±SD)		Control group (mean±SD)		p*
	Day 0	Month 3	Day 0	Month 3	
OSDI	71.95±9.10	38.90±9.00	72.00±8.91	61.55±10.14	0.0005
BCVA (logMAR)	0.12±0.11	0.10±0.11	0.12±0.14	0.13±0.16	0.325
TMH (µm)	188.38±.56.37	262.20±48.74	199.13±.55.31	208.18±56.57	0.0005
TBUT (s)	3.63±0.84	7.28±1.66	3.75±1.33	5.05±1.22	0.0005
Schirmer's (mm)	4.3±2.1	9.7±1.1	3.2±1.0	5.2±0.9	0.0005
CFS score	3.23±0.89	1.33±0.66	3.98±0.86	2.60±0.67	0.0005
CIC score	1.98±0.83	0.98±0.83	2.03±0.70	1.90±0.81	0.0005

*p values for intergroup comparison of month-3 values. OSDI: Ocular Surface Disease Index, BCVA: Best corrected visual acuity, logMAR: Logarithm of the minimum angle of resolution, TMH: Tear meniscus height, TBUT: Tear break-up time, CFS: Corneal fluorescein staining, CIC: Conjunctival impression cytology, SD: Standard deviation

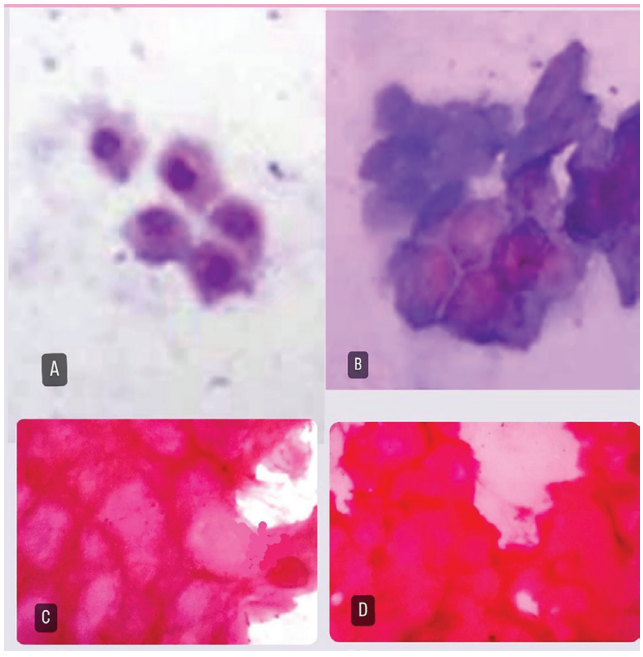

Figure 4. Pre- and posttreatment conjunctival impression cytology images from the control group. A) Scattered cells with a nucleus-to-cytoplasm (N:C) ratio ≥ 1:5 (grade 2) on day 0 (Papanicolaou stain, 40x). B) Loss of cohesion in the form of clusters with N:C of 1:3 to 1:4 (grade 1) after 3 months (Papanicolaou stain, 40x). C) Moderate reduction of goblet cells (grade 2) on day 0 (periodic acid-Schiff stain, 40x). D) Moderate reduction of goblet cells (grade 2) after 3 months (periodic acid-Schiff stain, 40x)

Table 9. Main outcomes after 3 months of autologous platelet-rich plasma treatment

Main outcome measures	Result	Study group (n=20)	Control group (n=20)
OSDI	Severe dry eye	0 (0%)	11 (55%)
	Moderate dry eye	5 (25%)	9 (45%)
	Mild dry eye	13 (65%)	1 (5%)
	Normal	2 (10%)	0 (0%)
BCVA	≥1 line gain	5 (25%)	1 (5%)
	No gain	15 (75%)	14 (70%)
	Loss	0 (0%)	5 (25%)
CIC	Improvement	20 (100%)	0.5 (2.5%)
	No change	0 (0%)	16 (80%)
	Worsening	0 (0%)	3.5 (17.5%)
CFS	Stain negative	9 (45%)	0 (0%)
	Improvement	11 (55%)	9 (45%)
	No change	0 (0%)	8 (40%)
	Worsening	0 (0%)	3 (15%)

n: Number of patients, OSDI: Ocular Surface Disease Index, BCVA: Best corrected visual acuity, CIC: Conjunctival impression cytology, CFS: Corneal fluorescein staining

Discussion

DED is a major problem that affects millions of people globally and is currently one of the leading reasons individuals see an ophthalmologist.[5] It lowers quality of life with incapacitating symptoms and frequent lubricant instillations.

The most commonly used therapy for dry eye is still the conventional approach, such as using artificial tears.[8] According to Drew et al.[9], there is a notable resemblance between tears and plasma since they originate from the same source and may have similar effects on the ocular surface. In an observational study by Alio et al.[10], improvements were noted in corneal staining, conjunctival impression cytology, conjunctival hyperemia, and symptoms in individuals with symptomatic dry eye treated with aPRP. These differences in impression cytology and corneal staining have been associated with tissue regeneration, which may be linked to the superior regenerative capacity of aPRP over autologous serum. According to a study by López-Plandolit et al.[11], Schirmer's test results and clinical symptoms also improved, but the degree of conjunctival metaplasia did not change significantly.

A decrease in OSDI score was seen with both treatment modalities in our group. By 3 months, the mean OSDI improved to 38.90 in the study group versus 61.55 in the controls (p=0.0005). The substantial improvement in symptomatology we observed with aPRP is similar to that reported in other studies.[10,11] Numerous studies have demonstrated a significant decrease in OSDI scores when using plasma rich in growth factors in dry eyes.[11,12,13,14,15]

Regarding visual changes, the improvements in BCVA in the study group, while potentially clinically relevant, did not reach statistical significance when compared to the control group over the study duration. In their study, Alio et al.[10] discovered that only 28% of patients receiving aPRP had a visual improvement of one line or more. In contrast, studies by Emam et al.[16], García-Concha et al.[12], and Rawat et al.[13] showed statistically significant improvement in BCVA in the aPRP-treated groups. Epithelial damage and tear film instability are factors contributing to visual deterioration in dry eye. Improvement in these factors with treatment leads to improved visual acuity.[17,18]

The study group exhibited a substantial increase in tear meniscus height from 188.38 µm at baseline to 262.20 µm at 3 months. This was significantly greater than the change from 199.13 µm to 208.18 µm seen in controls (p=0.0005). The progressive increase in tear meniscus height in the study group suggests that aPRP treatment may be effective in enhancing tear film stability over time, which could be beneficial for patients with tear film-related eye conditions. Similar results were also reported by Alio et al.[10] and observed in a retrospective study by Murtaza et al.[19] in eyes with evaporative dry eye secondary to meibomian gland disease.

In our study, significant changes in TBUT from baseline were observed at 1 month. The improvement in the study group was even more pronounced at 3 months (7.28 s vs. 5.05 s

in the control group, p=0.0005). This suggests enhanced ocular surface health and may reflect the therapeutic benefits of aPRP in maintaining a stable tear film. Emam et al.[16] reported that aPRP as a monotherapy led to a significant increase in TBUT when compared to artificial tears (hyaluronic acid). After aPRP therapy, Alio et al.[10] observed that 46% of the subjects showed an improvement in TBUT of more than 2 seconds. Rawat et al.[13] also reported that TBUT increased by more than 2 seconds in 42.6% and 1-2 seconds in 57.4% of cases in their aPRP group.

We assessed the effect of therapies on tear film volume in our sample by examining Schirmer's test results. Schirmer's test shows high variability, both in repeated measurements and between examiners. Hence, it is advised to perform all tear parameter testing is the same room conditions (temperature, humidity, and air flow). These environmental factors are important in all dry eye investigations, but especially during Schirmer's test. In our sample, the study group showed a marked increase in tear production by 1 week. This trend continued, with mean Schirmer's test results increasing to 7.5 mm at 1 month and 9.7 mm at 3 months. Both of these values were significantly higher than those in the control group (4.4 mm and 5.20 mm, respectively; p=0.0005). These treatment outcomes may also be attributable to the greater capacity of aPRP for ocular surface regeneration and its impact on acinar cells in the lacrimal glands. Indeed, Avila et al.[20] discovered that Schirmer's test findings were much enhanced by aPRP injections administered in close proximity to the lacrimal gland. According to García-Conca et al.[12], Schirmer's values after using aPRP increased significantly when compared to artificial tears (p<0.05). However, Rawat et al.[13] found no appreciable differences in Schirmer's values in their comparison of aPRP and artificial tears.

The present study revealed a substantial decrease in corneal fluorescein staining scores in both groups. By 3 months, the study group achieved a remarkable mean score of 1.33, significantly lower than the controls' score of 2.60 (p=0.0005). Alio et al.[10] reported similar outcomes, and Rawat et al.[13] also found that aPRP treatment significantly reduced corneal fluorescein staining grade according to the Oxford scale in severe dry eye cases.

Nelson and Wright[21] stated that there is a notable decrease in the quantity of goblet cells in DED. This reduction has been found to have an impact on the stability of the tear film. According to Amparo et al.[22], there was a 17% decrease in cell counts over the interpalpebral region in individuals with dry eyes. We observed in our sample that there was significant improvement in conjunctival impression cytology grade after aPRP therapy. While no difference between the groups was observed on day 0, the grade of conjunctival metaplasia was highly significantly lower in the study group at 3 months. Similar results were reported by Alio et al.[10] and García-Conca et al.[12] for the use of aPRP eye drops in DED and diabetic patients, respectively.

Study Limitations

Our study has some limitations. This is a single-center study; hence the results cannot be generalized to all populations. Secondly, we used 20% aPRP in this study, but 100% aPRP may be more beneficial and can be used in severe to very severe cases.[1] Determining the platelet concentration in the prepared eye drop (which was not performed in this study) may demonstrate a clearer correlation with treatment response.

Conclusion

aPRP eye drops have a distinct edge over conventional treatments when it comes to treating ocular surface illnesses. Rich in cytokines and growth factors, the regenerative qualities of aPRP facilitate a more efficient and natural healing process, accelerating recovery and improving tissue regeneration. This research will add to the literature because it shows that even 20% aPRP is better than conventional treatment. The dry eye parameters are also supported by impression cytology findings, which has not been done in previous studies of aPRP.

Ethics

Ethics Committee Approval: The study was initiated after approval from the ethics council of MLN Medical College, Prayagraj (ECR/922/Inst/UP/RR-22 on 5/7/2023).

Informed Consent: Informed consent was obtained from all individuals who participated in the study.

Declarations

Authorship Contributions

Surgical and Medical Practices: K.D., S.S., S.P.S., Concept: K.D., S.S., S.K., Design: S.P.S., S.K., V.K.S., Data Collection or Processing: K.D., S.S., S.P.S., Analysis or Interpretation: K.D., S.S., S.K., V.K.S., Literature Search: K.D., S.S., S.K., V.K.S., Writing: S.K.S., S.K., V.K.S.

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Original Article

Comparative Analysis of Automated vs. Expert-Designed Machine Learning Models in Age-Related Macular Degeneration Detection and Classification

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Abstract

Objectives: To compare the effectiveness of expert-designed machine learning models and code-free automated machine learning (AutoML) models in classifying optical coherence tomography (OCT) images for detecting age-related macular degeneration (AMD) and distinguishing between its dry and wet forms.

Materials and Methods: Custom models were developed by an artificial intelligence expert using the EfficientNet V2 architecture, while AutoML models were created by an ophthalmologist utilizing LobeAI with transfer learning via ResNet-50 V2. Both models were designed to differentiate normal OCT images from AMD and to also distinguish between dry and wet AMD. The models were trained and tested using an 80:20 split, with each diagnostic group containing 500 OCT images. Performance metrics, including sensitivity, specificity, accuracy, and F1 scores, were calculated and compared.

Results: The expert-designed model achieved an overall accuracy of 99.67% for classifying all images, with F1 scores of 0.99 or higher across all binary class comparisons. In contrast, the AutoML model achieved an overall accuracy of 89.00%, with F1 scores ranging from 0.86 to 0.90 in binary comparisons. Notably lower recall was observed for dry AMD vs. normal (0.85) in the AutoML model, indicating challenges in correctly identifying dry AMD.

Conclusion: While the AutoML models demonstrated acceptable performance in identifying and classifying AMD cases, the expert-designed models significantly outperformed them. The use of advanced neural network architectures and rigorous optimization in the expert-developed models underscores the continued necessity of expert involvement in the development of high-precision diagnostic tools for medical image classification.

Keywords: Age-related macular degeneration, AutoML, convolutional neural networks, EfficientNet V2, optical coherence tomography

Introduction

Age-related macular degeneration (AMD) is a major cause of vision loss in individuals over the age of 55 and is projected to affect up to 288 million people globally by 2040.[1] AMD primarily involves the macula, leading to the degeneration of photoreceptors and the retinal pigment epithelium (RPE).[1] Clinically, AMD manifests in two forms: dry AMD, characterized by the presence of drusen, and wet or exudative AMD, which is associated with abnormal blood vessel growth, often resulting in rapid and severe vision loss.[1,2] Optical coherence tomography (OCT) is a critical tool for diagnosing and monitoring AMD, providing high-resolution, cross-sectional images of the retina that allow clinicians to identify key lesions, such as drusen, RPE abnormalities, and choroidal neovascular membranes. OCT is particularly valuable for distinguishing between dry and wet AMD, monitoring disease progression, and evaluating treatment responses in patients receiving anti-vascular endothelial growth factor therapy.[1]

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Deep learning (DL) models, particularly convolutional neural networks (CNNs) designed by expert engineering, have demonstrated success in medical image analysis. Several studies using those DL models showed significant achievement in the diagnosis and classification of AMD.[3,4,5,6,7,8,9,10,11] Early studies, such as that by Rasti et al.[3], relied on relatively small datasets and simpler models like Multi-scale Convolutional Mixture of Experts and AlexNet but achieved noteworthy classification performance despite limited data.[4] As datasets grew in size and complexity, more sophisticated architectures such as ResNet and DenseNet were introduced, often coupled with ensemble learning approaches to further improve accuracy, sensitivity, and specificity, surpassing 99% in many cases.[7,8] Recent advancements, particularly those made since 2020, have focused on hybrid models that combine CNNs with recurrent neural networks to handle longitudinal data, along with the integration of self-attention mechanisms to enhance feature extraction.[9,10] Table 1 summarizes previous studies that have utilized DL models for the diagnosis and classification of AMD. Although they achieved successful results, they require considerable technical knowledge to build, which poses a challenge for physicians lacking technical expertise. More recently, the utilization of code-free automated machine learning (AutoML) platforms has emerged as a promising approach for medical image classification, potentially allowing physicians to develop models without extensive coding knowledge.[12] AutoML systems automate key aspects of the ML pipeline-including data preprocessing, feature selection, and model optimization, thereby reducing the barrier to entry for non-experts in ML and enabling healthcare professionals to focus on clinical applications rather than technical complexities.[13] Several studies have evaluated the success of AutoML in ophthalmic diseases, including diabetic retinopathy, retinal vein occlusion, and cataract surgery phases.[14,15,16]

To the best of our knowledge, no prior study has compared the performance of AutoML models with expert-designed models in the detection and classification of AMD using OCT images. Therefore, in this study we aimed to assess and compare the performance of these two techniques to investigate whether physicians can independently leverage AutoML tools to create accurate and reliable classification models, or if engineering expertise remains crucial for optimal performance.

Materials and Methods

This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Dokuz Eylül University Ethics Committee (protocol code: 2024/37-06, date of approval: 06.11.2024). Given that the study utilized publicly available datasets and involved no direct interaction with patients or identifiable data, the need for patient consent was waived.

Optical Coherence Tomography Data

We utilized an open dataset of macula-centered spectral domain OCT scans from the Optical Coherence Tomography Image Database dataset published by Gholami et al.[17] in 2020 as well as the Kaggle dataset published by Kermany et al.[18] in 2018. Two experienced ophthalmologists (C.D.E. and D.Ö.) evaluated these OCT images and grouped them into dry AMD and wet AMD. Wet AMD was identified by the presence of intraretinal fluid, subretinal fluid, and/or subretinal hyperreflective material, consistent with the clinical diagnostic criteria. The dry AMD group included cases with drusen and without signs of exudation. Geographic atrophy cases were not included in this study. Images with any other concurrent retinal disease and images with insufficient quality due to any kind of noise were excluded. To assess the consistency of image labeling, inter-rater reliability between the two ophthalmologists was evaluated using Cohen's kappa coefficient. The Cohen's kappa score was 0.987, indicating excellent agreement in the classification of OCT images. Any discrepancies were resolved through consensus before finalizing the dataset for model training. In total, 500 macula-centered OCT images were included in each group. As a control group, 500 normal spectral domain OCT images without any retinal pathologies from the same datasets were included. All images were cropped to 900x300 pixels and converted to JPEG format.

Building the Models

The dataset was divided, with 80% of the images in each group used for training the models and the remaining 20% allocated for testing. Subsequently, four distinct models were developed and tested using LobeAI for AutoML and within the Python environment for the expert-designed models. Model I was trained to differentiate wet AMD from normal images, Model II to differentiate dry AMD from normal images, and Model III to differentiate wet AMD from dry AMD. Additionally, Model IV was constructed using all pathological and normal OCT images to evaluate model performance in a complex classification task. Both model types were trained and tested using the same dataset to ensure a fair comparison of their performance.

Automated Machine Learning Models

The Lobe software (version 0.10.1130.5) was obtained from the official website (https://www.lobe.ai/) and installed on a personal computer. Upon installation, the images were uploaded to the program and labeled with three specific tags: wet AMD, dry AMD, and normal. The Lobe application automatically creates five random variations of each image during the training process. It utilizes techniques such as adjusting brightness, saturation, and contrast, modifying hue, as well as applying rotation, zoom, and noise reduction. Therefore, no further data augmentation methods were implemented. This application employs transfer learning, a method that utilizes pre-trained models on related tasks to enhance performance on the current task, allowing for high accuracy even with a limited dataset. The ResNet-50 V2 CNN architecture was chosen by selecting the "optimize for accuracy" option in the Project Settings menu. He et al.[19] introduced ResNet-50, a 50-layer CNN known for its effectiveness in image classification and other vision tasks. It features 16 residual blocks grouped into 4 sets, using convolutional layers with batch normalization and ReLU activation. The core concept is the skip connection, which directly transfers the input to the block's output, aiding in

deep network optimization. The model concludes with global average pooling and a fully connected layer with SoftMax. After the training phase, the model underwent further refinement using the application's built-in "model optimization" feature to improve performance. Statistical analyses for the AutoML models were performed using MedCalc website (https://www.mdcalc.com/). Sensitivity, specificity, and accuracy were calculated for distinguishing pathological OCT images from normal images, as well as for identifying each specific type of AMD. Additionally, a confusion matrix was generated via Confusion Matrix Generator for Model IV to offer a more comprehensive evaluation of its performance.[20]

Expert-Designed Models

The expert-designed model was developed by an artificial intelligence specialist (U.B.) with a background in computer engineering and biomedical technologies and expertise in image processing, machine learning, and DL applications in clinical settings. The expert was responsible for designing the model architecture, implementing preprocessing and augmentation techniques, optimizing hyperparameters, and validating model performance.

EfficientNet models, introduced by Tan and Le[21], aim to deliver high performance with fewer parameters and floating-point operations per second compared to architectures like ResNet or VGG. They introduce "compound scaling," a method that optimally balances model depth, width, and resolution. Depth refers to the number of layers, width to the number of channels per layer, and resolution to the input image size, allowing EfficientNet to scale efficiently across different dimensions.

For our models, the training and evaluation process for OCT images commenced with the computation of dataset statistics, where the mean (μ) and standard deviation (σ) were derived from the training set. Data preprocessing and augmentation were subsequently performed, with transformations defined for the training, validation, and test sets based on these statistics. The dataset was then partitioned into training and validation subsets, and DataLoaders were constructed accordingly. The model, based on a custom EfficientNetV2 architecture, was initialized for the classification task, and He initialization was applied. The loss function employed was label smoothing cross-entropy. Hyperparameter optimization was conducted using Optuna, an automated framework designed to minimize the need for manual tuning by systematically exploring the hyperparameter space and identifying optimal configurations.[22] In Optuna, the search space for learning rate (α), dropout rate (p), and weight decay (λ) was first delineated, then the optimal hyperparameters ($\theta^* = \{\alpha^*, p^*, \lambda^*\}$) were determined by maximizing validation accuracy. During the training phase, the optimizer was initialized with the optimal learning rate (α^*) and weight decay (λ^*), while the best dropout rate (p^*) was incorporated into the model, to reduce the risk of overfitting. The model was trained across multiple epochs, with each epoch comprising a training phase in which model parameters were updated, followed by a validation phase to evaluate performance on the validation set. Model checkpoints were saved whenever an improvement in validation accuracy was observed. Upon completion of training, statistical metrics for the final model (M^*) were computed directly within the Python environment. Sensitivity, specificity, precision, recall, and F1 score were calculated using the scikit-learn library based on the model's predictions. Additionally, a confusion matrix was generated programmatically within Python to visualize classification performance. The summary of expert model parameters and training settings are given in Supplementary Table 1.

Results

The ML models developed using the Lobe application demonstrated the capability to differentiate between normal-appearing OCT images and those with wet or dry AMD, achieving sensitivities of 92.00% and 90.00% and specificities of 94.00% and 91.00%, respectively. In contrast, the expert-designed models for distinguishing wet and dry AMD from normal OCT images achieved sensitivities of 100.00% and 99.00% and specificities of 99.00% and 100.00%, respectively.

The AutoML Model III, which was designed to classify wet versus dry AMD, attained an accuracy of 86.00%, indicating lower performance compared to the models that distinguished wet AMD (accuracy: 93.00%) and dry AMD (accuracy: 90.50%) individually from normal OCT images. In comparison, the expert-designed Model III exhibited an accuracy of 99.50%, approaching near-perfect performance. The performance metrics for all models are summarized in Table 2.

The AutoML Model IV, which incorporated all pathological images in comparison to normal OCT images, achieved an accuracy of 89.00% with a weighted F1 score of 0.88. Conversely, the expert-designed Model IV model achieved an accuracy of 99.67% and a weighted F1 score of 0.97. The confusion matrices for Model IV, both AutoML and expert-designed, are presented in Figure 1.

Discussion

This comparative analysis of expert-designed custom models utilizing EfficientNet V2 and AutoML models employing transfer learning with ResNet-50 V2 revealed significant differences in performance and highlights the critical role of expert engineering in specialized medical imaging tasks. In the most complex task of detecting AMD in the entire OCT database, the expert model achieved an exceptional overall accuracy of 99.67%, with F1 scores of 0.99 or higher across all classes. This high level of performance indicates that the model is not only accurate in its positive predictions but also effective in identifying nearly all relevant instances of AMD in OCT images. The minimal misclassification rates reinforce the model's reliability and trustworthiness for clinical applications, where precise classification is crucial for patient diagnosis and treatment planning. In contrast, the AutoML model attained a lower overall accuracy of 89.00%, with F1 scores ranging from 0.8725 to 0.9045 in binary classifications. This shortcoming could have significant clinical implications, as misdiagnosis or delayed diagnosis of AMD can lead to progressive vision loss and affect treatment outcomes.

Table 1. Summary of studies on AMD classification using OCT images from 2017 to 2024, detailing datasets, models, performance metrics, and key findings

Year	Study	Dataset	Model	Performance metrics	Remarks
2017	[3]	148 OCT volumes (50 normal, 48 dry AMD, 50 DME), 45 public acquisitions	Multi-scale convolutional mixture of expert (MCME)	AUC: 0.998; Precision: 98.86%; Recall: 99.36%; F1-score: 99.34%	MCME with minimal pre-processing outperformed conventional models
2018	[4]	83,484 OCT images (healthy, dry AMD, wet AMD, DME)	AlexNet (fully trained)	Accuracy: 97.1%; Sensitivity: 99.6%; Specificity: 98.4%	AlexNet achieved better performance than transfer learning for AMD classification
2019	[5]	83,484 OCT images (healthy, dry AMD, wet AMD, DME)	ResNet (18 layers), AlexNet	Accuracy: 99.5%; Sensitivity: 98.0%; Specificity: 100%	ResNet outperformed AlexNet in dry and wet AMD detection
2019	[6]	185 normal OCT, 535 AMD with fluid, 514 AMD without fluid	VGG16 (transfer learning)	AUC: 0.999; Accuracy: 99.2%; AUC: 0.992; Accuracy: 95.1%	Two-step transfer learning model for normal vs. AMD and fluid vs. non-fluid AMD
2020	[7]	281 training patients, 69 test patients (longitudinal OCT)	DenseNet + RNN	AUC: 0.85 (low treatment); AUC: 0.81 (high treatment); R^2: 0.22	End-to-end DL model for predicting treatment needs performed better than traditional models
2020	[8]	108,309 training images, 1,000 test images	Ensemble of 3 ResNet152 models	Accuracy: 98.9%; Sensitivity: 98.9%; Specificity: 99.6%	CNN ensemble achieved superior classification by combining ResNet152 models
2022	[9]	4927 OCT images (neovascular AMD, PCV, non-wet AMD)	Stacked Autoencoder-VGG16	F1: 86.81%; Accuracy: 88.28%; Precision: 86.34%; Recall: 87.28%	Self-attention VGG16 with contrastive learning improved AMD subtype classification
2023	[10]	OCT scans from 94 patients, 20,482 B-scans	ResNet + Random Forest + RNN	Random forest: Accuracy: 95%; RNN: Accuracy: 71%	Feature extraction for treatment prediction, with RNN for sequential data prediction
2024	[11]	1285 OCT B-scans from 167 patients	Explainable artificial intelligence (AI)-based system	Accuracy: 90.82%; Kappa: 89.10%	Multi-stage AI system mimicked retinal specialists in AMD detection

AMD: Age-related macular degeneration, OCT: Optical coherence tomography, DME: Diabetic macular edema, PCV: Polypoidal choroidal vasculopathy, AUC: Area under curve, CNN: Convolutional neural network, RNN: Recurrent neural network

Table 2. Key metrics of AutoML and expert-designed models

	Sensitivity (95% CI)		Specificity (95% CI)		Precision		Recall		F1 score	
	AutoML	Expert	AutoML	Expert	AutoML	Expert	AutoML	Expert	AutoML	Expert
Model I: wet AMD vs. normal	92.00 (84.84 to 96.48)	100.00 (96.38 to 100.00)	94.00 (87.40 to 97.77)	99.00 (94.55 to 99.97)	93.88 (87.36 to 97.14)	99.00 (94.55 to 99.82)	92.00 (85.00 to 95.89)	99.00 (94.45 to 99.82)	92.93	99.00
Model II: dry AMD vs. normal	90.00 (82.38 to 95.10)	99.00 (94.55 to 99.97)	91.00 (83.60 to 95.80)	100.00 (96.38 to 100.00)	90.90 (83.65 to 93.12)	100.00 (96.30 to 100.00)	90.00 (82.56 to 94.47)	99.00 (95.80 to 100.00)	90.45	99.50
Model III: wet AMD vs. dry AMD	85.00 (76.40 to 91.35)	99.00 (94.55 to 99.97)	87.00 (78.80 to 92.89)	100.00 (96.38 to 100.00)	86.73 (76.72 to 90.69)	100.00 (94.55 to 100.00)	85.00 (75.80 to 92.24)	99.00 (94.55 to 99.82)	85.86	99.50

AMD: Age-related macular degeneration, CI: Confidence interval, AutoML: Automated machine learning

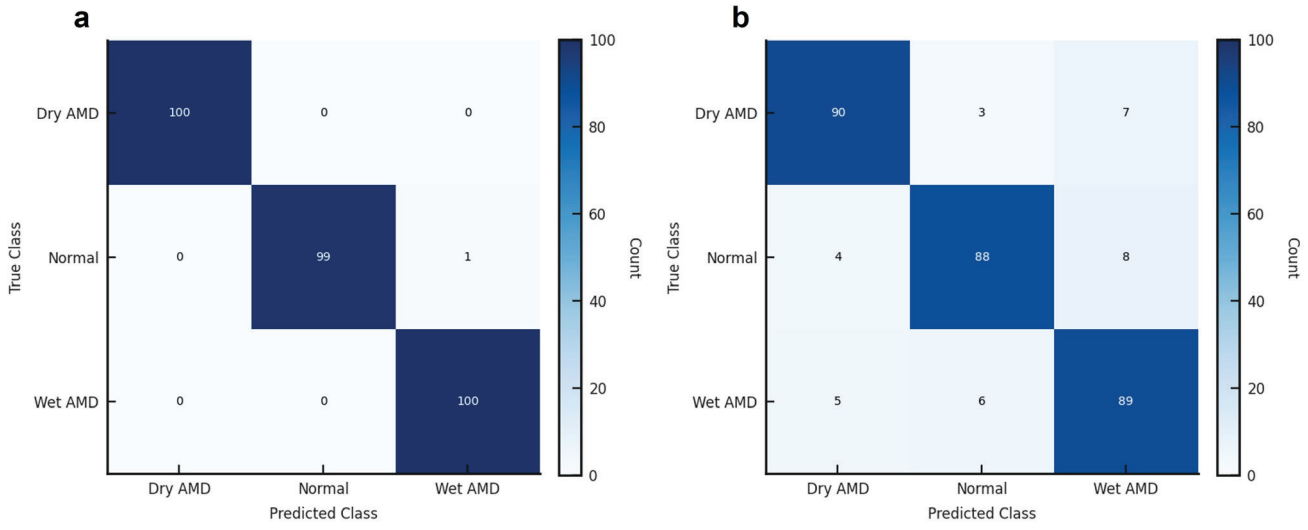

Figure 1. Confusion matrices of Model IV incorporating all age-related macular degeneration subtypes and normal controls. a) Expert-designed model. b) Auto machine learning model
AMD: Age-related macular degeneration

The superior performance of the expert model can be attributed to several key factors. Firstly, the advanced architecture of EfficientNet V2 employs a compound scaling method that simultaneously scales network depth, width, and resolution, allowing it to capture intricate patterns in OCT images more effectively.[21] This capability is crucial for distinguishing subtle differences between AMD classes. EfficientNet V2 also integrates channel attention mechanisms, enabling the model to selectively focus on the most informative channels while suppressing less relevant ones. This strategic attention enhances feature representation, contributing to improved model accuracy. Similar to our study, a recent study by Kansal et al.[23] evaluated the performance of these two CNN algorithms, ResNet-50 and EfficientNetB0, on multi-disease lung X-ray datasets encompassing coronavirus disease-2019 (COVID-19), bacterial and viral pneumonia, and normal cases. The results demonstrated the superior performance of EfficientNetB0, which achieved a training accuracy of 0.98 and a testing accuracy of 0.99. In contrast, the ResNet-50 model attained a comparatively lower training accuracy of 0.83 and a testing accuracy of 0.96, highlighting the effectiveness of EfficientNetB0 in this context. In a study conducted by De La Fuente et al.[24], a small, imbalanced dataset of esophagogastroduodenoscopy images supplemented with synthetic images was classified into three categories, and the classification performance of two DL models was evaluated. The results demonstrated that EfficientNet V2 achieved an overall accuracy of 92.19% and an overall F1 score of 91.03. In comparison, the ResNet-50 algorithm yielded lower performance, with an overall accuracy of 89.49% and an overall F1 score of 88.74. These findings underscore the superior performance of EfficientNet in image classification tasks.

Tailored preprocessing and data augmentation significantly enhance a model's ability to generalize in ML studies. While the Lobe app generates five random variations of each image, expert models might benefit from more targeted and diverse augmentation techniques. Also, parameters such as learning rate, dropout rate, and weight decay were meticulously tuned to maximize validation accuracy via Optuna in our study, resulting in improved generalization and model performance in expert models.[22] This finding is supported by Lacerda et al.[25], who demonstrated that hyperparameter optimization with the Optuna framework increased their CNN model's sensitivity from 0.94 to 0.97 and accuracy from 0.87 to 0.88 in diagnosing COVID-19 pneumonia from chest CT images. In contrast, LobeAI provided standard settings for model optimization without allowing fine-tuning of specific hyperparameters, potentially limiting performance in complex classification tasks.

We observed that both AutoML and expert models were more successful in distinguishing wet AMD from normal cases compared to dry AMD from normal cases. This finding aligns with the existing literature, which suggests that the phenotypic characteristics of wet AMD (choroidal neovascularization, intraretinal cysts, and subretinal fluid) are more distinct and pronounced, thereby facilitating easier classification through imaging-based models.[26] From a clinical perspective, the higher classification accuracy for wet AMD is advantageous because early and accurate diagnosis of this subtype is crucial for timely intervention, which can prevent significant vision loss. Moreover, as we expected, lower success in classifying wet vs. dry AMD was observed compared to normal vs. any type of AMD models. This could stem from the overlapping features and subtle differences between dry and wet AMD, which make it challenging for an automated system to reliably differentiate the two subtypes without confusion.[2]

The AutoML Model IV, which classified all pathological images against normal OCT images, achieved an accuracy of 89.00% and a weighted F1 score of 0.88. While these metrics demonstrate reasonable differentiation between pathology and normality, the expert-designed model excelled with an accuracy of 99.67% and a weighted F1 score of 0.97. The AutoML model's reliance on ResNet-50 V2 and generic pre-processing steps may limit its effectiveness in specialized domains like medical image analysis. ResNet-50 V2, while powerful, may not capture fine-grained features in OCT images as efficiently as EfficientNet V2. Moreover, AutoML platforms often use default settings that may not be optimal for specific tasks, leading to suboptimal architectures and insufficient hyperparameter tuning. These findings suggest that models developed with expert engineering input can outperform those generated solely through AutoML platforms, particularly in complex tasks requiring high precision.

Study Limitations

Despite these promising results, certain limitations should be acknowledged. The dataset, while sufficient for this study, may not fully capture the variability found in broader patient populations. Future research should incorporate larger and more diverse datasets to improve the assessment of model generalizability. Additionally, newer AutoML platforms like Google Vertex AI, Microsoft Azure AutoML, and Amazon SageMaker enable users without coding experience to optimize parameters, potentially enhancing performance.[27] However, these platforms impose trial limits for modeling, requiring payment once the limit is exceeded.

Conclusion

This study presents a novel comparison of AutoML and expert-designed ML models for AMD classification using OCT images. Our findings show that while the Lobe AI AutoML platform offers clinicians a convenient way to develop ML models, expert input remains crucial for optimizing performance in specialized tasks. The expert-designed EfficientNet V2 model demonstrated superior accuracy and sensitivity, highlighting the value of advanced architectures, customized data augmentation, and fine-tuned hyperparameters. Combining the accessibility of AutoML with expert oversight could further enhance model performance while maintaining ease of use for clinicians. Collaborative efforts between engineers and healthcare professionals are essential to develop AI solutions that are both effective and clinically viable, ultimately contributing to improved patient care.

Ethics

Ethics Committee Approval: This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Dokuz Eylül University Ethics Committee (protocol code: 2024/37-06, date of approval: 06.11.2024).

Informed Consent: Given that the study utilized publicly available datasets and involved no direct interaction with patients or identifiable data, the need for patient consent was waived.

Declarations

Authorship Contributions

Surgical and Medical Practices: C.D.E., Concept: C.D.E., M.A.S., Design: C.D.E., D.Ö., M.A.S., Data Collection or Processing: D.Ö., U.B., Analysis or Interpretation: C.D.E., U.B., Literature Search: C.D.E., U.B., Writing: C.D.E., U.B.

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Original Article

Pattern of RNFL Damage in Early- and Late-Stage Primary Open-Angle Glaucoma Using the Disc Damage Likelihood Scale and Optical Coherence Tomography

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Abstract

Objectives: To determine patterns of peripapillary retinal nerve fiber layer (RNFL) damage in early- and late-stage glaucoma based on the Disc Damage Likelihood Scale (DDLS).

Materials and Methods: This cross-sectional, multi-center study involved 267 eyes of 135 patients aged 18 years or older with suspected or diagnosed glaucoma. Exclusion criteria were high refractive errors, media opacities, trauma history, and systemic conditions affecting the optic disc. After a comprehensive ocular examination, the DDLS was used for glaucoma staging. Disease severity was classified into three zones: green, orange, and red. RNFL thickness was measured in four quadrants using optical coherence tomography. Patterns of RNFL damage were analyzed, especially in terms of the ISNT (inferior>superior>nasal>temporal) rule, and compared between the three groups.

Results: The male-to-female ratio was 1.59:1 and the mean age was 45.12±15.76 years. There were statistically significant differences among the groups for average, inferior, superior, and temporal RNFL thickness ($p<0.00001$). However, the difference in nasal RNFL was insignificant. The ISNT rule was the commonest pattern in the study participants (64.4%) and progressive loss of pattern was observed with increased disease severity.

Conclusion: This study revealed an association between disease severity and RNFL thinning in the inferior, superior, and temporal quadrants, while nasal RNFL showed no significant association with disease severity. The ISNT rule was more frequently observed in the early stages and diminished with advanced glaucoma. These results highlight RNFL thinning based on the DDLS as an important marker for glaucoma monitoring.

Keywords: Primary open-angle glaucoma, retinal nerve fiber layer, Disc Damage Likelihood Scale

Introduction

In 2020, approximately 3.6 million people worldwide suffered vision loss due to glaucoma, contributing to about 11% of blindness in adults over the age of 50 years.[1] This staggering number may even be an underestimate since the current definition of glaucoma requires visual field loss for diagnosis. Many individuals may have glaucoma without documented visual field loss, highlighting the critical need for early detection and intervention to prevent or delay progression.

In glaucoma, structural damage to the optic nerve often occurs before visual field loss detectable by standard perimetry. Therefore, quantitative analysis of the retinal nerve fiber layer (RNFL), optic nerve head (ONH), and macular cube with ganglion cell layer thickness are considered more reliable for assessing glaucoma.

Among the optic disc parameters, the ISNT rule (inferior>superior>nasal>temporal) has widely been discussed as a key diagnostic tool in glaucoma. It is frequently violated in glaucoma patients because the neuroretinal rim (NRR) is often preferentially affected in the inferior and superior quadrants of the optic disc.[2] However, studies have primarily relied on optic disc photographs or subjective assessments by ophthalmologists. Only a few studies have utilized scanning techniques to measure RNFL thickness for assessing the ISNT rule in glaucoma detection and progression. Moreover, there are conflicting results

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regarding the clinical usefulness of the ISNT rule in glaucoma screening.[3,4,5] The ISNT rule also varies depending on optic disc size.[6] To address the impact of disc size on the NRR, we employed the Disc Damage Likelihood Scale (DDLS), which considers disc size when ranking the severity of optic nerve damage, thus providing a more accurate assessment of glaucoma progression. We used optical coherence tomography (OCT) scans to quantitatively measure peripapillary RNFL (pRNFL) thickness in different quadrants to evaluate the ISNT pattern across various stages of glaucoma, classified according to the DDLS. To date, no other study has analyzed RNFL patterns in primary open-angle glaucoma (POAG) based on DDLS grading.

The aim of this study was to determine patterns of pRNFL damage in early- and late-stage glaucoma based on the DDLS.

Materials and Methods

A cross-sectional, observational, multi-center study was conducted at Mughal Trust Eye Hospital and Lahore General Hospital from April 2023 to April 2024. The study was conducted according to the Declaration of Helsinki and approval was obtained from the Mughal Eye Hospital Trust Review Board (0264/IRB/MEHT, dated March 2023). Patients were recruited after obtaining informed consent. Patients over 18 years old with suspected or diagnosed glaucoma were included. Glaucoma suspects were defined as patients who had either higher than normal intraocular pressure (defined as between 10 and 21 mmHg) or optic disc cupping but with normal visual fields and normal RNFL.

There were 267 eyes of 135 patients that qualified for the study. Patients with refractive error of more than ±5.0 diopters (D) sphere and ±3.0 D cylinder, media opacities, history of trauma, neurological and systemic abnormalities affecting the optic disc, pigment dispersion, pseudoexfoliation, ocular inflammation, and OCT with poor signal strength were excluded. Patients with best corrected visual acuity (BCVA) of 6/60 or better and clear media were included in this study.

After taking a detailed medical and ocular history, patients underwent a thorough ocular examination which included BCVA, intraocular pressure measurement, slit-lamp examination, and fundoscopy using a 78D lens. The measured optic disc size was adjusted by multiplying by 1.1 to correct for the magnification error from the 78D lens. Both the average and vertical cup-to-disc ratios, as well as the rim-to-disc ratio, were documented.

The observations agreed between the two observers and in cases of disagreement, opinion of a third observer was sought. DDLS stage was first determined based on optic disc size and neural rim width. Glaucoma stage was then classified based on DDLS stages using the Glaucoma Color Graph (Figure 1).[7] Amount of disc damage was categorized as green (DDLS 1-4, not definite disc damage; n=153), orange (DDLS 5-7, asymptomatic glaucoma damage; n=62), or red (DDLS 8-10, glaucomatous disease or disability; n=52).

Visual fields were assessed using the Humphrey 24-2 SITA-Fast strategy. RNFL thickness was measured using SD-OCT (Cirrus), and only images with good signal strength were included in the analysis. The parameters recorded included average RNFL thickness, along with superior, temporal, inferior, and nasal quadrant pRNFL thickness. The average RNFL thickness and the mean RNFL thickness in each of the four quadrants were calculated and compared with severity of glaucoma based on DDLS.

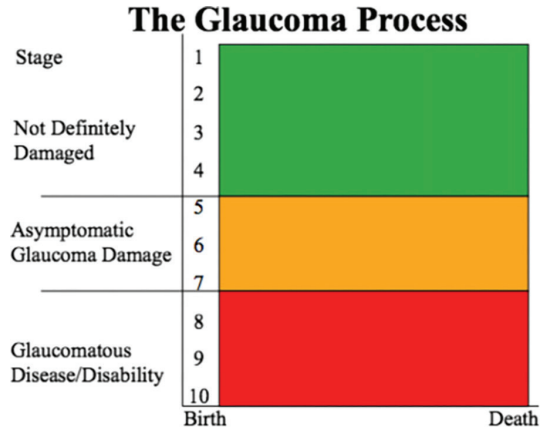

Figure 1. Grading of disease based on the Disc Damage Likelihood Scale. Adapted from Spaeth and Paulus,[7] 2010. Image available through Creative Commons Attribution-NonCommercial-NoDerivs 3.0

Statistical Analysis

The Shapiro-Wilk test was used to test normality of continuous variables. Quantitative variables were presented as mean±standard deviation, and qualitative variables as percentages. The Mann-Whitney U test was used to compare the RNFL thickness with normative data derived from a previous study.[8] The Kruskal-Wallis test with post-hoc Dunn's test was done to compare RNFL thickness among the groups. The chi-square test was used to compare the frequency of the ISNT pattern among the groups. A p value of <0.05 was considered significant.

Results

A total of 267 eyes of 135 patients were included in the study. There were 134 right and 133 left eyes. The mean intraocular pressure was 18.2±6.4 mmHg. The mean age was 45.12±15.76 years.

There was no statistically significant difference in pRNFL thickness by gender ($p>0.05$). Comparison with normative data showed statistically significant differences between the control values from the previous study and the different groups in this study (Table 1).

Comparisons between the groups revealed statistically significant differences among the groups for average, inferior, superior, and temporal RNFL thickness ($p<0.00001$). However, the difference for nasal RNFL thickness was statistically insignificant (Table 1). Post-hoc analysis (adjusted using Bonferroni correction) showed that the green group consistently had greater RNFL thickness compared to the red group for the inferior, superior, and temporal quadrants. However, differences between the orange and red group were less pronounced or not

significant. No significant differences in nasal RNFL thickness were found between any of the groups.

The different patterns of RNFL thickness damage observed in the groups are shown in Table 2. The ISNT rule was the commonest pattern among the study participants (64.4%). It was present in 79.7% of eyes in the green group, 46.8% of those in the orange group, and 40.4% in the red group, indicating significant progressive loss of ISNT pattern with disease severity (p<0.00001).

Discussion

In this study, highly statistically significant differences were found in average, inferior, superior, and temporal RNFL thickness across the groups, while the difference in nasal RNFL thickness was not significant. The ISNT rule was followed by 79.7% of patients in the green group, 46.8% in the orange group, and 40.4% in the red group. A notable difference in the pattern of RNFL thickness damage was found between the green and orange groups, but no significant difference was observed between the orange and red groups in terms of adherence to the ISNT rule.

Although gender is not typically considered a risk factor for POAG, the male-to-female ratio in our study was 1.59:1. This is contrary to previous data in which 60.8% of patients with glaucoma were female.[9] The average age of the patients in our study was 45.12±15.76 years, while another study reported a mean age of 54.5±13.6 years, with 66.9% males and 33.1% females.[10]

We found an average RNFL thickness of 90.85±12.95 µm in glaucoma suspects (green group), 78.00±14.16 µm in early glaucoma cases (orange group), and 68.00±14.96 µm in advanced glaucoma cases (red group). Comparatively, another study reported RNFL thickness of 101.58±5.24 µm in normal eyes, 92.35±5.56 µm in glaucoma suspects, and 79.00±7.97 µm in glaucoma patients (p<0.001 for all pairwise comparisons).[11]

Patients with preperimetric glaucoma exhibit a significantly thinner RNFL compared to healthy individuals. Among all RNFL thickness values, average and inferior RNFL thickness are reported to provide useful information about the severity of RNFL damage. However, as RNFL thickness shows a floor effect in the late stages, these measurements provide complementary information to perimetry reports and clinical observation.[12]

The lack of a difference in nasal RNFL thickness despite progressive reductions in the inferior, superior, and temporal quadrants across the groups in our study reinforces that nasal thickness is generally not a reliable indicator for predicting the progression of glaucoma. There is a common perception that RNFL thickness is preserved in the temporal quadrant even in the late stage of the disease, which is responsible for the preserved central vision. However, this is not always true, as temporal RNFL thickness was also significantly reduced in our patients.

Xu et al.[13] reported an average global thickness of 66.38±11.13 µm in patients with moderate POAG. In our

Table 1. Comparison of normative data[8] for RNFL thickness and the mean values for different stages of primary open-angle glaucoma

RNFL thickness (µm)	Normal*	Green (n=153)	Orange (n=62)	Red (n=52)	p value**
Average	101.43±8.63	90.85±12.95	78.00±14.16	68.00±14.96	<0.00001
Inferior	135.34±20.40	110.63±22.94	95.07±25.38	79.08±26.78	<0.00001
Superior	129.15±16.87	104.47±22.46	94.98±19.98	82.06±19.96	<0.00001
Nasal	79.73±12.05	65.55±11.81	62.83±12.28	62.82±16.44	0.058
Temporal	71.95±7.73	62.42±14.26	59.90±15.73	55.92±15.42	0.002

*All groups differed significantly from normative values (Mann-Whitney U test, p<0.00001 for all), **All parameters except nasal RNFL thickness differed significantly among the glaucoma severity groups (Kruskal-Wallis test, p<0.05). RNFL: Retinal nerve fiber layer

Table 2. Frequency of patterns of RNFL damage by glaucoma severity group

Pattern	Green, n (%)	Orange, n (%)	Red, n (%)	Total, n (%)
ISNT*	122 (79.7)	29 (46.8)	21 (40.4)	172 (64.4)
Non-ISNT	31 (20.3)	33 (53.2)	31 (59.6)	95 (35.6)
SITN	10 (6.5)	9 (14.5)	9 (17.3)	28 (10.5)
STIN	1 (0.7)	1 (1.6)	2 (3.9)	4 (1.5)
SINT	20 (13.1)	16 (25.8)	11 (21.2)	47 (17.6)
STNI	0	2 (3.2)	2 (3.9)	4 (1.5)
SNIT	0	4 (6.5)	6 (11.5)	10 (3.8)
SNTI	0	1 (1.6)	1 (1.9)	2 (0.8)
All	153	62	52	267

*The frequency of the ISNT pattern differed significantly among the groups (chi-square test, p<0.00001). RNFL: Retinal nerve fiber layer, I: Inferior, S: Superior, N: Nasal, T: Temporal

study, however, the thickness ranged from 90.85±12.95 µm in early disease to 68.00±14.96 µm in patients with more advanced damage. Among the four quadrants, inferior RNFL thickness offered the best diagnostic capability for glaucoma. This is further supported by Hood et al.,[14] who reported that RNFL thinning is more pronounced in the inferior retina, which corresponds to the superior visual field.

The ISNT rule is widely regarded as a valuable tool for glaucoma screening. However, Silim et al.[15] found that among the 65.6% of eyes that violated the ISNT rule, only 34.7% showed abnormal OCT results, raising questions about the rule's reliability. In this study, the most common pRNFL thickness pattern across all stages of glaucoma was ISNT, followed by SINT, where the superior quadrant was thicker than the inferior quadrant, likely due to more severe damage in the inferior RNFL thickness. This pattern was also observed in another study.[16] However, in advanced disease, RNFL defects extended through nearly all sectors. Contrary to the early inferior thinning, superior thinning in early glaucoma was reported by El-Naby et al.[17] and Soliman et al.[18], supporting the SINT rule. However, the concentric nature of RNFL thickness damage may explain why some glaucoma patients retain the ISNT pattern despite disease progression.

The specificity of the ISNT rule is influenced by several factors, including disc size, disc tilt, and vascular patterns within the disc. Normal eyes that violate this rule often have longer axial lengths and larger disc areas. These eyes are also associated with ISNT rule violations.[19] However, since we used the DDLS for glaucoma staging, which accounts for disc size, this effect was mitigated to some extent. Despite this, the ISNT rule should not be relied upon as the sole criterion for diagnosing or monitoring glaucoma progression.

Beyond the ISNT rule, the IT (inferior rim wider than the temporal rim) and ST rules (superior rim wider than the temporal rim) have also been described in the literature.[20] However, when evaluating the impact of optic disc size and disease severity on the diagnostic performance of these three NRR rules, all were found to have better sensitivity in eyes with smaller discs. A Japanese study further suggested that the IST pattern, rather than the ISNT pattern, was more effective for glaucoma screening.[21] Contrary to this, Law et al.[4] demonstrated that only evaluating the inferior and superior rim (IS rule) yielded better specificity than the ISNT rule in differentiating glaucomatous eyes from normal eyes.

The early RNFL loss typically observed in the inferior and superior quadrants can be attributed to the backward bowing of the lamina cribrosa at the upper and lower poles compared to the mid-nerve head. The more pronounced deformation and remodeling in these regions may lead to RNFL loss being most commonly found in the inferior and superior quadrants in glaucoma.

In another study, the NRR in healthy participants did not follow the ISNT rule, except that the smallest rim area was consistently located in the temporal disc region when Heidelberg retinal tomography (HRT) was used.[22] However, the rim thickness in the superior and inferior sectors was found to be similar based on HRT measurements. It was also found that a greater number of normal eyes adhered to the IST rule compared to the ISNT rule when RNFL thickness was measured using HRT and OCT.[23]

Kostianeva-Zhelinska et al.[24] reported that the inferior and superior RNFL quadrants were specific sites for early glaucomatous damage in POAG. This finding was also confirmed by Singh et al.[25]

Very conflicting results were reported by Abera and W Gessesse[26] They found that temporal and superior thickness performed poorly while average, nasal, and inferior thickness had better diagnostic value.

It must be kept in mind that the floor effect occurs earlier in the pRNFL than the macular region. In these situations, it is advisable to use macular OCT and visual field 10-2 testing. Not only this, but RNFL thickness in patients with high myopia, ONH swelling, and small or tilted ONHs can be misleading. In these instances, macular area parameters are better reference points.[27]

Study Limitations

Although the present study is unique in grading the disease in terms of DDLS, it is limited by the cross-sectional design. Without following the same patients over time, the study cannot fully assess the progression of RNFL thinning or confirm whether DDLS reliably predicts long-term outcomes. The study was focused on structural changes (RNFL thinning). Further work can be done to find the functional relationship using the same scale which would be important to fully understand the impact of the observed RNFL damage.

Conclusion

This study revealed an association between disease severity and RNFL thinning in the inferior, superior, and temporal quadrants, while nasal RNFL showed no significant association with disease severity. The ISNT rule was more frequently observed in the early stages and diminished with advanced glaucoma. These results highlight RNFL thinning based on the DDLS as an important marker for glaucoma monitoring.

Ethics

Ethics Committee Approval: Mughal Eye Hospital Trust Review Board (0264/IRB/MEHT, dated March 2023).

Informed Consent: Informed consent was obtained from the patients.

Declarations

Authorship Contributions

Surgical and Medical Practices: N.U., T.G.M., Concept: N.U., T.G.M., R.M.S, Design: N.U., T.G.M., R.M.S, Data Collection or Processing: N.U., T.G.M., Analysis or Interpretation: N.U., T.G.M., R.M.S, Literature Search: N.U., T.G.M., Writing: N.U., T.G.M.

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Original Article

Real-Life Effectiveness and Safety of Selective Laser Trabeculoplasty as Primary, Adjunctive, and Substitutive Therapy

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Abstract

Objectives: To assess real-world outcomes of selective laser trabeculoplasty (SLT) in naive patients compared to SLT as adjunctive treatment (AT), investigating SLT's intraocular pressure (IOP) reduction and its potential to decrease topical medication.

Materials and Methods: Patients undergoing SLT with no prior glaucoma surgery or laser treatment were grouped based on the intended objective: SLT as primary treatment (PT), SLT as AT, and SLT as substitutive treatment (ST). Survival in the PT and AT groups was defined as ≥20% IOP reduction from baseline and IOP ≤21 on two consecutive visits with the same or fewer medications and no additional glaucoma procedure, including repeat SLT. Survival in the ST group was defined as decreasing topical medication while maintaining or reducing IOP.

Results: The study included 120 eyes of 120 patients with a mean follow-up of 32.7 months. The PT group showed superior IOP reduction than the AT group at 24-36 months (22.1% vs. 14.5%, p=0.039). Non-responders comprised 28.6% of the PT group and 37.0% of the AT group. The PT group demonstrated better survival rates than the AT group at 12, 24, and 36 months (69.0% vs. 47.1%, 38.8% vs. 31.4%, and 31.1% vs. 23.5%, respectively). In the ST group, 34.2% of patients were successful at 12 months, increasing to 38.3% at 24 months. At 24 months, 50.0% of patients had reduced at least one medication.

Conclusion: SLT showed two-thirds effectiveness, with one-third being non-responders. It was more effective as PT, with higher IOP reduction and success rates. SLT reduced topical medication in half of patients.

Keywords: Selective laser trabeculoplasty, glaucoma, SLT, laser glaucoma therapy

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Introduction

Elevated intraocular pressure (IOP) is the primary modifiable risk factor in the progression of glaucoma. Despite the availability of topical IOP-lowering medications, which are often used as first-line treatment,[1] their effectiveness is frequently undermined by issues such as non-compliance and side effects, leading to less than 50% of patients continuing treatment after 1 year.[2] While surgical options are effective, they are not without risks, underscoring the need for less invasive alternatives.

Selective laser trabeculoplasty (SLT) presents a minimally invasive, cost-effective alternative that does not require daily patient compliance.[3,4,5,6] Demonstrating IOP-lowering efficacy comparable to that of a single topical antihypertensive drug,[6,7,8,9] SLT is also considered safer and more repeatable than argon laser trabeculoplasty.[3,10,11] The procedure targets pigmented trabecular meshwork cells with a Q-switched, frequency-doubled, 532-nm neodymium-doped yttrium aluminum garnet (Nd:YAG) laser to increase aqueous outflow and reduce IOP.[12,13,14] Although transient side effects like mild anterior chamber inflammation and temporary IOP spikes occur, they generally resolve without long-term consequences.[8,15]

Initially overshadowed by new and effective pharmacological treatments,[16,17,18] SLT has gained prominence as both a primary and adjunctive treatment (AT) due to increasing concerns over medication overuse and non-adherence.[19,20] Hypotensive outcomes of SLT vary across studies, influenced by patient

characteristics such as glaucoma stage,[5,6] baseline IOP,[21,22] prior treatments,[22] and methodological differences. In the LiGHT trial, 74% of patients who underwent primary SLT remained drop-free at 36 months.[22] However, further real-world studies are needed to validate these findings.

This study aimed to assess the real-world effectiveness of SLT in reducing IOP when used as primary treatment (PT) in treatment-naïve patients, as an AT in medicated patients, and as substitutive treatment (ST) for those with controlled IOP facing adherence or tolerability issues.

Materials and Methods

Patients

This single-center review analyzed real-world patients who underwent SLT between June 2017 and January 2022, with a minimum 12-month follow-up. Only one randomly selected eye per patient was included, and those with prior glaucoma surgeries or laser treatments (SLT or argon laser trabeculoplasty) were excluded. While the study was prospectively designed, including patient recruitment, data extraction was conducted retrospectively. The research adhered to the Declaration of Helsinki and received approval from the Barcelona Clinic Hospital Ethics Committee (HCB/2022/0959, 23/02/2022). All patients provided consent for the review of their clinical data for this purpose.

Patients were grouped based on the treatment objective: SLT as PT, SLT as AT for medicated patients needing further IOP reduction, and SLT as ST for patients with controlled IOP but facing tolerability or adherence issues.

Procedure

SLT was performed by multiple ophthalmologists using the OPTIMIS Fusion® laser system (Quantel Medical, Cournon-d'Auvergne, France), equipped with a Q-switched 532-nm Nd:YAG laser. The procedure followed a 360-degree protocol without overlapping impacts, utilizing a 400-µm spot size and a 4-ns duration. Laser power started at 0.6 mJ and was incrementally increased until microbubbles appeared, with a maximum power of 1.2 mJ. A total of 95-105 spots were necessary to complete the 360 degrees. A Volk Optical SLT lens and 1% methylcellulose were used during the procedure. Preoperatively, patients received 2% pilocarpine hydrochloride (Mizar Farmacéutica S.L., Barcelona, Spain) and 5 mg/mL apraclonidine drops (Iopimax®, Alcon-Couvreur N.V.). Postoperative care included topical diclofenac 1 mg/mL (Angelini Pharma España, Barcelona, Spain) administered every 8 hours for 1 week, in addition to the continuation of pre-laser hypotensive medication, which was discontinued as needed.

Measures

Baseline data, including age, sex, diagnosis, pseudophakia, angle pigmentation, number of topical medications, visual acuity, and Goldmann applanation tonometry measurements, were collected from electronic medical records. Primary outcomes were changes in IOP and the number of hypotensive drops used.

IOP changes and medication usage were recorded at 3, 6, 12, 24, and 36 months. A 1-month margin was allowed for data collection (±0.5 months of the target time point) after 3 months due to the retrospective nature of the study. Data from 24 to 36 months post-SLT were grouped for some analyses, using the most recent assessment. Alternative procedures for IOP control, such as surgery or repeat SLT sessions, were documented. Patients requiring additional procedures were censored at their last visit before the intervention.

For survival analysis, failure in the PT and AT groups was defined as an IOP reduction of <20% from baseline at two consecutive visits, IOP ≥21, an increase in glaucoma medications from baseline, or any further glaucoma procedure, including repeat SLT. In the ST group, survival was defined as maintaining the same or lower IOP while reducing at least one medication from baseline without requiring additional glaucoma procedures.

Statistical Analysis

Statistical analysis was conducted using STATA 17 software (StataCorp LLC). For the initial characterization of the groups, chi-squared tests and either analysis of variance (ANOVA) or Kruskal-Wallis tests were employed. Intergroup comparisons of IOP changes between the PT and AT groups were performed using multivariable linear regression models including previously described related variables. For the survival analysis, Kaplan-Meier survival analysis and multivariable Cox regression were conducted. For the ST group, the mean number of medications used at each time point was compared to baseline using paired-samples Wilcoxon tests. Results are expressed as frequency and percentage or means and standard deviation (SD) with 95% confidence intervals (CI).

Results

A total of 120 eyes with a mean follow-up time of 32.7 months (SD: 6.1 months) were included in the analysis. Of these, 103 eyes (86%) had a follow-up of at least 24 months. Table 1 displays the baseline demographic and clinical characteristics. There were statistically significant differences (attributable to group designs) among the three groups in baseline IOP ($p<0.001$) and baseline number of treatments ($p<0.001$). However, no statistical differences were found for age, sex, pseudophakia, angular pigmentation, or diagnosis. Similarly, when comparing baseline characteristics between the PT and AT groups, significant differences were found in baseline IOP ($p<0.001$) and number of treatments ($p<0.001$), as well as age ($p=0.016$). No differences were found for sex ($p=0.51$) or angle pigmentation ($p=0.49$). IOP was measured in all patients between 6 and 24 hours after treatment, and no instances of IOP exceeding pre-laser levels were detected.

Selective Laser Trabeculoplasty as Primary versus Adjunctive Treatment

The study included 42 eyes in the PT group and 27 eyes in the AT group, with mean follow-up times of 32.7 months (SD: 5.9) and 30.7 months (SD: 6.9), respectively. The difference in

follow-up time between the two groups was not statistically significant (p=0.2).

Change in Intraocular Pressure

The mean percentage IOP reduction from baseline for the PT vs. AT groups was 17.3% (95% CI, 13.6 to 21.0) vs. 10.0% (95% CI, 2.5 to 17.5) at 12 months and 21.3% (95% CI, 16.1 to 26.5) vs. 13.2% (95% CI, 6.1 to 20.3) at 24 months (Table 2). In the raw multivariable linear regression, the differences in percentage IOP reduction were significant at 6 months (p=0.03), 12 months (p=0.06), and 24 months (p=0.06). In the multivariable linear regression adjusted for age, baseline IOP, baseline number of topical treatments, and pseudophakia, the PT group had 9.4% greater IOP reduction than the AT group (95% CI, -5.2 to 24.0; p=0.2) at 12 months and 25.1% greater (95% CI, 1.4 to 48.8; p=0.02) at the 24-36 months period (Table 2 and Figure 1). The multivariable analysis showed that higher baseline IOP was a strong predictor for a more significant SLT effect (p=0.002), and a higher baseline number of IOP-lowering medications was associated with a lower SLT effect (p=0.01). Age was not a predictor (p=0.4).

Survival Analysis

Twelve eyes (28.6%) in the PT group and 10 eyes (37.0%) in the AT group did not respond to SLT, given that they failed to achieve an initial 20% IOP reduction or an IOP under 21 mmHg. If non-responders are included in the survival analysis, the probability of success in the PT group was 52.4% at 6 months and decreased to 43.9%, 27.8%, and 22.2% at 12, 24, and 36 months post-SLT, respectively. For the AT group, the success rate was 37.0% at 6 months and declined to 29.6%, 19.8%, and 14.8% at 12, 24, and 36 months, respectively.

Among those with initial response, the PT group showed a success rate of 73.3% at 6 months, which declined to 60.0%, 38.8%, and 31.1% at 12, 24, and 36 months post-SLT, respectively. In the AT group, the success rate was 58.8% at 6 months and declined to 47.1%, 31.4%, and 23.5% at 12, 24, and 36 months, respectively (Table 2).

The median survival for responders in the PT group was 24 months, while it was 12 months in the AT group (p=0.05). The multivariable Cox regression model adjusted for the same factors revealed no significant differences between the groups (hazard ratio: 1.08, 95% CI, 0.5 to 2.6), with a p value of 0.86. Kaplan-Meier graphs are displayed in Figure 2.

Selective Laser Trabeculoplasty as Substitutive Treatment

The ST group included 51 eyes. The mean follow-up time was 33.8 months (SD: 5.6), and 48 eyes (94%) completed at least 24 months of follow-up. SLT successfully achieved a reduction in hypotensive medication while maintaining equal or lower IOP in 39.5%, 34.2% and 38.3% of the eyes at 6, 12, and 24 months.

The mean number of medications at baseline was 1.63 (SD: 0.7) with a mean IOP of 18.6 mmHg (SD: 3.9). The mean medication reduction was statistically significant at all time points, with a reduction of 0.65 medications (95% CI, 0.43 to 0.87) at 12 months and 0.52 medications (95% CI, 0.29 to 0.75) at 24 months. By 24 months, 50.0% (95% CI, 35 to 65) of patients had reduced at least one medication, and 10.4% (95% CI, 3.5 to 23) had discontinued two medications from baseline (Figure 3 and Table 3).

Table 1. Baseline description by groups

	SLT as primary treatment n=42		SLT as adjunctive treatment n=27		SLT as substitutive treatment n=51	
Follow-up (months)	32.7	(5.9)	30.7	(6.9)	33.8	(5.6)
Age (years)	60.0	(11.0)	67.1	(11.8)	62.4	(14.8)
Sex female	23	56.1%	11	42.3%	25	49.0%
Pseudophakia	15	35.7%	15	55.6%	21	41.2%
Mean baseline IOP (mmHg)	22.8	(2.9)	19.9	(3.7)	18.6	(3.9)
Mean baseline number of medications	0.0	(0.0)	2.0	(0.8)	1.6	(0.7)
Angular pigmentation	1.7	(0.7)	1.5	(0.6)	1.7	(0.8)
Diagnosis						
POAG	9	21%	8	30%	10	20%
PXG	3	7%	1	4%	4	8%
OHT	20	47%	7	26%	20	39%
PACG	4	10%	2	7%	2	4%
Pigmentary glaucoma	3	7%	0.0	0%	4	8%
NTG	0	0%	4	15%	3	6%
Others	3	7%	5	19%	8	16%

Values are expressed as mean (standard deviation) or frequency and percentage. SLT: Selective laser trabeculectomy, IOP: Intraocular pressure, POAG: Primary open-angle glaucoma, PXG: Pseudoexfoliative glaucoma, OHT: Ocular hypertension, PACG: Primary angle-closure glaucoma, NTG: Normal tension glaucoma

Table 2. Survival and mean percentage IOP reduction over time with SLT as primary and adjunctive treatment

	Primary SLT treatment						Adjunctive SLT treatment					
	Eyes	Failed	Partial success	Complete success	Cumulative survival	Cumulative survival on patients with initial response	Mean percentage IOP reduction (95% CI)	Eyes	Failed	Partial success	Complete success	Cumulative survival	Cumulative survival on patients with initial response	Mean percentage IOP reduction (95% CI)
Initial response (1 month)	40	18	0	22	71.4%	-	21.7% (25.7-17.7)	27	12	0	15	63.0%	-	17.0% (23.0-11.0)
3 months	40	22	0	18	59.5%	83.3%	18.1% (22.6-13.6)	25	14	0	11	51.9%	82.4%	12.6% (19.6-5.6)
6 months	33	21	1	11	52.4%	73.3%	18.0% (23.1-12.9)	25	19	1	5	37.0%	58.8%	9.5% (15.6-3.4)
12 months	37	23	1	13	43.9%	60.0%	17.3% (21.0-13.6)	24	16	2	6	29.6%	47.1%	10.0% (17.5-2.5)
24 months	38	18	9	11	27.8%	38.8%	21.3% (26.5-16.1)	24	16	1	7	19.8%	31.4%	13.2% (20.3-6.1)
36 months	29	11	6	12	22.2%	31.1%	24.5% (32.7-16.4)	14	7	1	6	14.8%	23.5%	10.9% (28.2 – -6.5)

IOP: Intraocular pressure, SLT: Selective laser trabeculectomy, CI: Confidence interval

Secondary Effects and Failure

None of the treated eyes showed significant anterior segment inflammation and no transient increase in IOP was recorded. Patients reported no pain or discomfort during the procedure.

We identified 22 non-responders: 12 in the PT group (28.6%) and 10 in the AT group (37.0%), with no significant difference between these rates (p=0.46). The mean age of non-responders was 66.5 years (SD: 10.6), while that of responders was 61 years (SD: 12.5). This difference was also statistically non-significant (p=0.08).

The mean pre-SLT IOP among non-responders was 19.95 mmHg (SD: 3.6). In contrast, responders had a significantly higher mean pre-SLT IOP of 22.4 mmHg (SD: 3.2) (p=0.006). This finding supports the hypothesis that lower baseline IOP is associated with poorer SLT efficacy. The mean number of prior treatments was 0.9 (SD: 1.15) for non-responders and 0.7 (SD: 1.1) for responders (p=0.52).

Failure requiring a secondary glaucoma procedure was observed as follows:

PT group: One eye required SLT retreatment at 12 months, while another underwent non-penetrating deep sclerectomy at 34 months.

AT group: Two eyes required additional SLT at 20 months, and one eye underwent drainage implant surgery using an SL-Molteno3 device (NovaEye Medical, Fremont, USA) at 24 months.

ST group: Four eyes underwent SLT retreatment (one at 7 months, two at 12 months, and one at 25 months). Additionally, one eye underwent Xen® gel stent implantation (AbbVie, Illinois, USA) at 8 months, and another underwent subliminal transscleral laser cyclophotocoagulation (SubCyclo-Quantel, Cournon d'Auvergne, France) at 12 months.

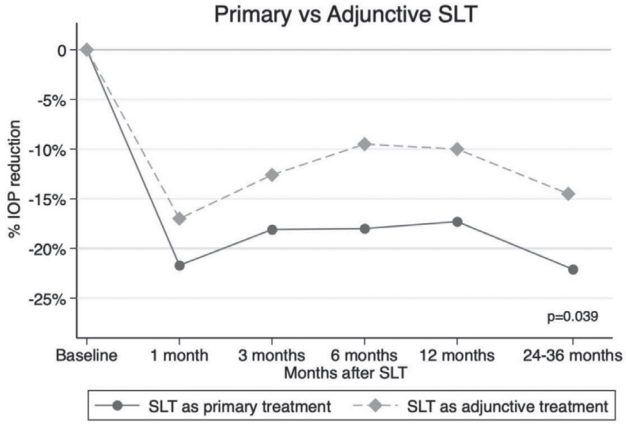

Figure 1. Percentage IOP reduction over time in the primary and adjunctive treatment groups. P value for multivariable linear regression model adjusted for age, baseline IOP, previous number of medications, and pseudophakia

SLT: Selective laser trabeculoplasty, IOP: Intraocular pressure

Discussion

This study evaluated the impact of SLT in three real-world scenarios. Compared to the group in which SLT was used as adjunctive therapy, SLT was more effective as PT, achieving greater IOP reductions (21.3% vs. 13.2% at 24 months and 24.5% vs. 10.9% at 36 months), a lower proportion of non-responders (28.6% vs. 37.0%), and a higher 24-month survival rate among responders (38.8% vs. 31.4%). In the group in which SLT replaced medication, 50.0% of eyes maintained the same or lower IOP while reducing at least one medication by the 24-month follow-up.

In real-world settings, SLT is often considered for newly diagnosed glaucoma or ocular hypertension in patients without prior hypotensive treatment. However, when baseline IOP exceeds certain thresholds, SLT is generally not recommended, as it is unlikely to achieve target pressures. In such cases, treatment typically progresses to topical hypotensive or surgery, depending on the condition of the optic nerve.

Accordingly, IOP in the PT group was mildly elevated (mean 22.8 mmHg) with no prior hypotensive treatment. In contrast, in eyes that underwent SLT as adjunctive therapy, patients were already on hypotensive medication, and the objective was to further reduce IOP due to disease progression or an increase in IOP. In this scenario, it must be assumed that a 20% reduction would be sufficient. If this reduction was deemed insufficient, surgical intervention would be considered. This means that patients with high IOP were not selected for adjunctive SLT but were instead considered for surgical treatment. Consequently, IOP in the AT group was expected to be normal or only mildly elevated, as reflected in the data.

The small but significant age difference between groups suggests that patients with a longer history of glaucoma treatment tend to be older. Therefore, as expected, the PT and AT groups showed significant differences in preoperative IOP, number of hypotensive medications, and age, all of which are known prognostic factors that influence SLT efficacy.[23]

In this study, only higher preoperative IOP and a lower number of preoperative medications were identified as predictive factors for greater treatment efficacy (p=0.02 and p=0.01, respectively). However, when adjusted for age, preoperative IOP, and number of medications, the PT group still achieved better

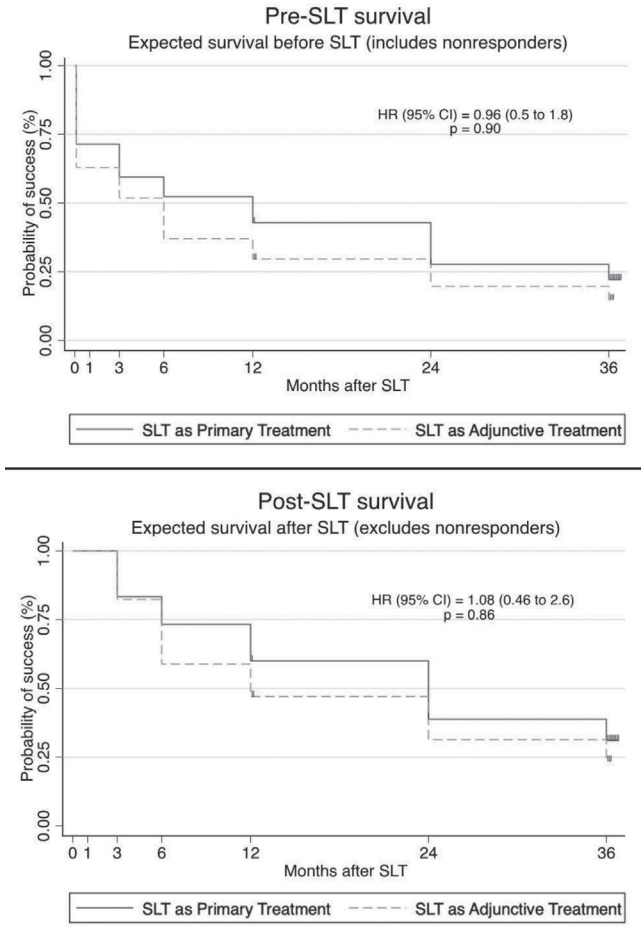

Figure 2. A Kaplan-Meier graph was used to compare SLT survival between the primary and adjunctive treatment groups. The first graph includes all patients in the study, representing expected survival prior to SLT. The second graph represents patients who demonstrated an initial response, excluding those with IOP reduction <20% at first month (non-responders). This graph represents survival after SLT was initially effective. Although there are differences in survival between the two graphs, the overall shape and the differences among the groups remain similar. This suggests that excluding non-responders may lead to an overestimation of the effect of SLT but not its duration over time. P values were obtained using multivariable Cox regression, adjusting for age, baseline IOP, the previous number of medications, and pseudophakia

SLT: Selective laser trabeculoplasty, HR: Hazard ratio, CI: Confidence interval, IOP: Intraocular pressure

Table 3. Success rates, mean percentage IOP reduction, and mean number of medications after SLT as substitutive treatment

	Eyes	Success (%)	Mean percentage IOP reduction (95% CI)	Mean n of medication reduced (95% CI)
Baseline	51	-	Baseline IOP: 18.6 mmHg (SD: 3.9)	Baseline n of meds: 1.63 (SD: 0.66)
3 months	49	26.5%	10.6% (4.8 to 16.4)	0.45 (0.29 to 0.61)
6 months	43	39.5%	7.2% (1.1 to 13.3)	0.58 (0.40 to 0.76)
12 months	41	34.2%	4.4% (-1.6 to 10.5)	0.65 (0.43 to 0.87)
24 months	47	38.3%	5.2% (-2.1 to 12.6)	0.52 (0.29 to 0.75)
36 months	41	19.5%	8.6 % (1.1 to 16.1)	0.52 (0.22 to 0.83)

IOP: Intraocular pressure, SLT: Selective laser trabeculectomy, CI: Confidence interval, SD: Standard deviation

efficacy, with 25.1% greater IOP reductions than the AT group at 24 to 36 months.

We did not examine the differences in SLT efficacy according to angle anatomy or in phakic versus pseudophakic cases. Nevertheless, it can be anticipated that pseudophakic patients are typically older and therefore may have more advanced glaucoma. Consequently, pseudophakia is expected to be more prevalent in the AT and ST groups, as noted in the group descriptions. Additionally, the average pigmentation of the cases was very similar across the groups (1.7, 1.8, and 1.7).

Reported SLT 2-year success rates vary widely (40-85%).[24] The LiGHT trial, a multicenter randomized study, demonstrated that 74.2% of patients undergoing SLT required no drops at 36 months to maintain target IOP.[5,22] However, the study included only naïve patients and allowed second SLT sessions, which may have influenced the results.

This study underscores the importance of assessing SLT's real-world impact, where success rates appear lower. Findings by Khawaja et al.[25] align closely with this study, showing 12- and 24-month survival rates of 45% and 27%, respectively, under similar success definitions. Many studies use less stringent criteria, excluding factors like increased medication use or repeat SLT sessions from failure definitions, which can bias success rates upward.[26,27] To avoid this, follow-up in this study was truncated at the last visit before additional glaucoma procedures.

Additionally, non-responders are often excluded or omitted in other studies.[25,28] In contrast, this study highlights their presence. We argue that this group should always be acknowledged and analyzed to provide a comprehensive understanding of SLT outcomes. When analyzing non-responding eyes, only higher pre-SLT IOP was identified as a predictive factor for treatment response. A larger sample size may be required to better assess the influence of other variables associated with the initial response to SLT.

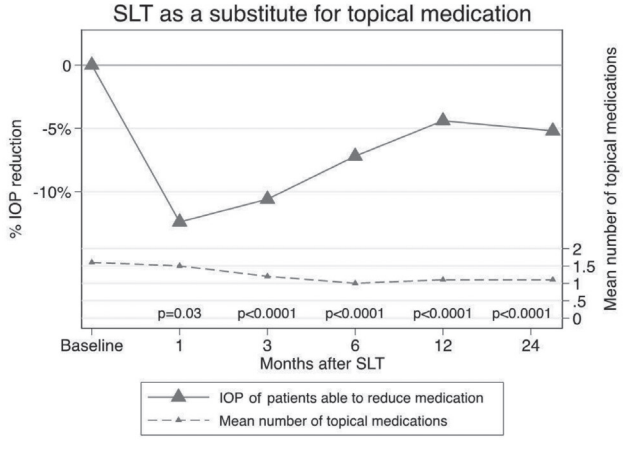

Figure 3. Percentage IOP reduction and mean number of treatments over time on SLT as substitutive treatment. P values for paired Wilcoxon test for mean number of medications at each time point compared to baseline

SLT: Selective laser trabeculoplasty, IOP: Intraocular pressure

Moreover, we acknowledge the importance of further analyzing non-responders to SLT to better understand predictors of treatment failure. While this study primarily aimed to assess a patient profile that can help anticipate the response to SLT, we recognize that a more detailed evaluation of non-responders, considering factors such as age, baseline IOP, and prior medications, would provide valuable insights for refining patient selection criteria. If data availability permits, a more in-depth stratification of non-responders could be explored in future analyses.

Despite 24-hour IOP monitoring, no cases of post-laser ocular hypertension were detected. This is believed to be attributable to the preoperative administration of pilocarpine and apraclonidine, which are known to control post-laser pressure spikes. Furthermore, the continuation of preoperative hypotensive treatment during the initial postoperative weeks likely contributed to this outcome.

This study included all patients who underwent SLT, excluding those with previous glaucoma surgeries or laser treatments. Patients were classified based on clinical criteria without randomization, leading to inherent statistical differences between groups. The PT group was younger, had a lower rate of pseudophakia, and exhibited higher baseline IOP compared to those already on hypotensive treatments. These differences, when adjusted for baseline variables (IOP, age, pseudophakia, and number of topical medications), allowed a more nuanced understanding of SLT's real-world effects.

After adjustment, IOP reduction was 9.4% greater in the PT group than the AT group at 12 months (95% CI, -5.2 to 24.0; p=0.2) and 25.1% greater at 24-36 months (95% CI, 1.4 to 48.8; p=0.04). Baseline IOP emerged as the main predictor of SLT response, with higher baseline IOP correlating with a greater SLT effect (p<0.001 at 24 months), consistent with findings from other studies.[21,22,25,26]

Conversely, a higher number of pre-laser antihypertensive drugs was associated with a reduced SLT effect. Some authors have also observed this,[23] whereas other studies indicated no differences based on pre-SLT treatments.[25,28] This suggests the higher SLT efficacy in the PT group may be due to their elevated baseline IOP, which predicts a stronger response, while the extensive pre-laser medication use in the AT group correlates with a diminished effect. These findings highlight how baseline characteristics influence SLT outcomes and emphasize the need for tailored approaches based on patient profiles.

Limited research has explored the differences in SLT response between naïve and previously treated patients. In a study by Gračner[29], 59 patients underwent 180-degree SLT and were followed up for a mean of 19.6 months. The author reported a similar 24-month survival rate between the PT and AT groups but found a slightly greater IOP reduction in the PT group (28.10% vs. 24.82%; p=0.041). Similarly, McIlraith et al.[30] observed significantly less IOP reduction in pretreated eyes compared to primary SLT treatment. In this study, multivariable analysis showed significantly greater IOP reduction in the PT group compared to the AT group (22.1% vs. 14.5% at

24-36 months; p=0.04), though survival rates did not differ significantly (p=0.64).

Success in survival analysis was defined as at least 20% IOP reduction without additional medications or treatments, consistent with literature standards.[22,24,25,31] Non-responders and those requiring additional procedures, including second SLT sessions, were considered failures, and follow-up was truncated at the last visit before further treatment. While some studies permit multiple SLT sessions,[32] this study focused on the effect of a single session, and follow-up was truncated for 5 patients who underwent a second SLT.

Survival analysis was conducted in two scenarios: including and excluding non-responders. When non-responders were censored, the 2-year survival rate was 42.0% for the PT group and 26.9% for the AT group. Including non-responders, these rates dropped to 29.3% and 16.3%, respectively. Non-responders were found to have significantly lower baseline IOP than responders (mean difference, -2.5 mmHg; 95% CI, 0.7 to 4.2; p<0.06), aligning with prior findings that lower baseline IOP was a determinant of lower SLT efficacy.[33] Pillunat et al.[34] suggested that below a specific IOP level, such as 14 mmHg, we should not anticipate an effective response to SLT. The efficacy of SLT in normotensive glaucoma remains uncertain.[24] While Nitta et al.[35] found SLT effective for this subtype, they noted that a higher baseline IOP predicts a stronger response. Further research is needed to clarify these findings. Some patients may experience only modest effects or fail to respond entirely, emphasizing the need for caution when interpreting studies reporting 100% response rates or excluding non-responders from survival analyses.

There are limited data on SLT as a substitute for hypotensive medication,[36] and its efficacy in eyes under maximal anti-hypertensive treatment is modest.[37] However, SLT can benefit patients with poor adherence, intolerance, or a preference to avoid topical treatments by reducing the need for medications and their associated side effects. In the ST group, SLT eliminated the need for one medication in 50% of treated eyes and two medications in 10.4%. This suggests potential for partial treatment reduction in non-compliant or intolerant patients, delaying the need for surgery. Poor adherence to topical treatments significantly contributes to glaucoma progression,[25,38,39] and SLT may serve as a more effective substitute for the third or fourth drug in polytherapy, particularly when adherence declines or efficacy diminishes.[40]

Multivariable analysis revealed that a higher number of pre-SLT medications was associated with reduced SLT efficacy in the AT group. Nevertheless, medication withdrawal indicates SLT is at least as effective as the last drug in half of the patients, offering continuous IOP control without reliance on adherence. Unlike topical treatments, which lose effect over time, SLT provides consistent pressure reduction throughout the day.[21]

Study Limitations

This research has some limitations. The study excluded patients with previous glaucoma surgeries or laser treatments, which limits the understanding of SLT's efficacy in treating more advanced or complex cases of glaucoma. Although it had a reasonable sample size of 120 eyes, the division into three groups, combined with a significant dropout rate, might have compromised the statistical power necessary to detect meaningful differences, particularly in subgroup analyses. The follow-up period was capped at 36 months, which does not provide information on the long-term outcomes or the durability of SLT's effectiveness over extended periods. Additionally, despite the prospective design for patient recruitment, the retrospective nature of data extraction could have introduced biases. Finally, the lack of randomization in assigning patients to the treatments could lead to selection bias. This occurs when patients' characteristics influence their treatment (topical, laser, or surgery), potentially skewing the results and affecting the overall conclusions of the study. These limitations highlight the need for future studies to incorporate a randomized design, include a broader spectrum of glaucoma cases, extend the duration of follow-up, and ensure consistent and standardized data collection to enhance the reliability and applicability of the findings.

Conclusion

In this real-world setting, SLT was shown to be effective in approximately two-thirds of patients, with around one-third of patients being non-responders. SLT was more effective as initial treatment than as AT, with greater IOP reduction and higher success rates in the PT group at 12, 24, and 36 months. SLT was found to be effective in reducing topical medication, reducing at least one topical medication in more than half of patients.

Ethics

Ethics Committee Approval: The research adhered to the Declaration of Helsinki and received approval from the Barcelona Clinic Hospital Ethics Committee (HCB/2022/0959, 23/02/2022).

Informed Consent: The patients' informed consent was obtained.

Declarations

Authorship Contributions

Surgical and Medical Practices: O.G-C., S.Dj., S.P., C.A.A-P., E.A., E.M., S.D.,

Concept: O.G-C., S.P., S.D., Design: D.O-G., G.S-D., S.D., Data Collection or Processing: S.Dj., O.G-C., Analysis or Interpretation: D.O-G., G.S-D., Literature Search: D.O-G., O.G-C., G.S-D., M.C., Writing: D.O-G., O.G-C., S.Dj., G.S-D., M.C., S.P., C.A.A-P., E.A., E.M., S.D.

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Original Article

Gonioscopy-Assisted Transluminal Trabeculotomy versus Bent Ab Interno Needle Goniectomy in Patients with Open-Angle Glaucoma

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Abstract

Objectives: To compare the efficacy and safety of gonioscopy-assisted transluminal trabeculotomy (GATT) and bent ab interno needle goniectomy (BANG) in patients with open-angle glaucoma (OAG).

Materials and Methods: This retrospective comparative study included 65 eyes diagnosed with OAG that underwent GATT (34 eyes) or BANG (31 eyes). Intraocular pressure (IOP) was measured using Goldmann applanation tonometry at baseline and during follow-up visits. Success was categorized as qualified (IOP ≤21 mmHg with ≥20% reduction) and complete (same criteria without medication). Complications and the need for further surgery were recorded.

Results: Preoperative mean IOP was 32.9±6.1 mmHg for GATT and 31.8±5.4 mmHg for BANG. At the final visit, mean IOP was reduced to 15.8±4.5 mmHg in the GATT group (51.9% reduction) and 17.9±5.7 mmHg in the BANG group (43.7% reduction). The complete success rate was 88.2% for GATT and 61.3% for BANG. Early failures were more frequent in BANG, while GATT showed fewer but later failures. Both procedures had minimal complications, with transient hyphema being the most common.

Conclusion: In this study, GATT provided greater and more sustained IOP reduction and higher long-term success rates compared to BANG, making it a more reliable option for managing OAG.

Keywords: Open-angle glaucoma, bent ab interno needle goniectomy, gonioscopy-assisted transluminal trabeculotomy

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Introduction

Glaucoma is a degenerative condition of the optic nerve that can lead to permanent vision impairment if not treated. Among its various forms, open-angle glaucoma (OAG) is the most widespread, affecting millions of people worldwide, and its prevalence continues to rise with the aging population.[1] The primary therapeutic goal in glaucoma management is to reduce intraocular pressure (IOP) to prevent further optic nerve damage. First-line treatments typically involve topical medications or laser trabeculoplasty.[2] However, topical therapy in particular is associated with drawbacks, including poor patient adherence, ocular surface toxicity, and long-term cost burden.[3,4]

When IOP cannot be adequately controlled through medical or laser treatments, surgical options become essential. Conventional procedures like trabeculectomy and aqueous shunt implantation are known for their effectiveness in reducing IOP but are often linked to considerable postoperative complications such as hypotony, infections, and bleb-related problems.[5] These drawbacks have driven the advancement of minimally invasive glaucoma surgery (MIGS) techniques, which focus on achieving substantial IOP reduction while offering improved safety and faster recovery times.[6]

Two notable MIGS procedures are gonioscopy-assisted transluminal trabeculotomy (GATT) and bent ab interno needle goniectomy (BANG). GATT involves a 360-degree trabeculotomy using a suture or microcatheter to open Schlemm's canal circumferentially, thereby enhancing aqueous outflow through the collector channels.[7] In contrast, BANG utilizes a bent 25- or 26-gauge needle to create a targeted goniotomy, excising a segment of the trabecular meshwork (TM) to facilitate aqueous drainage.[8] Both techniques have shown promising outcomes in reducing IOP and dependence on glaucoma medications while minimizing the risk of severe complications.

Despite these advancements, limited comparative data exist on the efficacy and safety of GATT and BANG in managing OAG.[9] Given the importance of optimizing surgical outcomes,

this study seeks to evaluate and compare the effectiveness of these procedures in lowering IOP, reducing the need for medications, and minimizing complication rates in patients with OAG.

Materials and Methods

The study was conducted in accordance with the principles of the Declaration of Helsinki and received ethical approval from the Ethics Committee for Scientific Research in Health Sciences of Kırşehir Ahi Evran University Faculty of Medicine (decision no: 2024-16/138, date: 10/08/2024). Prior to participation, informed consent was obtained from all individuals included in the study.

Patient Population

This retrospective comparative study included patients diagnosed with OAG who underwent either GATT or BANG between November 2022 and February 2024 at Ahi Evran University Training and Research Hospital. The eligibility criteria included adult patients with a confirmed diagnosis of primary open-angle glaucoma (POAG), pseudoexfoliation glaucoma (PXG), or pigmentary glaucoma. All participants had a preoperative IOP of 21 mmHg or higher, despite being on maximum tolerated medical therapy. Exclusion criteria consisted of a history of prior glaucoma surgery, significant corneal pathology that obstructed angle visualization, or undergoing cataract surgery during the follow-up period. Patients with advanced or end-stage glaucoma (mean deviation [MD] worse than -12 dB on visual field [VF] testing) were also excluded from the study. In cases where both eyes underwent surgery, only the right eye was included in the analysis to maintain statistical independence and avoid intra-subject correlation.

All surgeries in this study were performed by a single glaucoma surgeon (A.Y.Ü.). Patients were allocated to either GATT or BANG using a sequential allocation approach. Early in the study period, patients primarily underwent GATT. When the BANG technique was later described and adopted, subsequent patients were allocated to BANG. This method creates a historically controlled case series, where the patient allocation was influenced by the chronological introduction of the BANG procedure.

Surgical Technique

GATT was performed under local anesthesia using a standard operating microscope. A 2.2-mm temporal clear corneal incision was made to access the anterior chamber. The anterior chamber was filled with a cohesive viscoelastic agent (Protectalon 1.4%, VSY Biotechnology, Leinfelden-Echterdingen, Germany) to maintain space and protect the intraocular structures. Under direct gonioscopic visualization using a Volk TVG surgical goniolens, a 23-gauge microvitreoretinal blade was used to create a small goniotomy in the nasal TM, exposing Schlemm's canal. A 5-0 Prolene suture with a blunted tip was inserted through the goniotomy into Schlemm's canal. The suture was carefully advanced circumferentially along the canal for 360 degrees. If resistance was encountered, the device was redirected in the opposite direction to achieve complete cannulation. Once the suture traversed the full circumference of Schlemm's canal, the distal end was grasped with microsurgical forceps, and the proximal end was pulled to create a 360-degree trabeculotomy by unroofing the TM. After completing the trabeculotomy, the viscoelastic was removed from the anterior chamber by irrigation-aspiration. The anterior chamber was then reformed with balanced salt solution (BSS). Care was taken to tamponade any blood reflux by maintaining appropriate IOP. At the end of the procedure, the corneal incision was hydrated to ensure a watertight seal, and a combination steroid and antibiotic drop (Moxidexa 5 mg/1 mg, Abdi İbrahim Pharmaceuticals, İstanbul, Türkiye) was administered.

BANG was carried out under local anesthesia with the patient positioned supine. A 2.2-mm temporal clear corneal incision was created to access the anterior chamber. The chamber was then filled with a cohesive viscoelastic agent (Protectalon) to preserve space and stabilize the ocular structures during the procedure. A 25-gauge hypodermic needle was manually bent at approximately a 30-degree angle close to its distal tip to facilitate precise engagement with the TM. Under direct gonioscopic visualization of the nasal angle using a Volk TVG surgical goniolens, the bent needle was introduced through the corneal incision and advanced toward the nasal TM. The needle tip was engaged with the TM, and a 90-degree goniotomy was performed by excising a segment of the TM. The needle was carefully swept along the targeted area to remove the TM, ensuring that Schlemm's canal was opened without damage to adjacent tissues. After completing the goniotomy, the viscoelastic was removed from the anterior chamber by gentle irrigation-aspiration. BSS was used to reform the anterior chamber and maintain appropriate IOP. The corneal incision was hydrated to achieve a watertight seal, and a combination antibiotic and steroid drop (Moxidexa) was applied.

Main Outcome Measures

The primary outcome measure was postoperative IOP reduction. IOP was measured using Goldmann applanation tonometry at each follow-up visit. To ensure consistency, all measurements were taken during morning hours (between 8:00 and 11:00 AM) to minimize diurnal variation. IOP was recorded preoperatively and at the following postoperative time points: 1 day, 1 week, 1 month, 3 months, 6 months, 12 months, and the final follow-up visit. The final visit was defined as the visit at which surgical failure was detected for patients who experienced surgical failure, and as the last follow-up visit for those who did not. Success was categorized as qualified success and complete success. Qualified success was defined as an IOP of 21 mmHg or lower with a reduction of at least 20% from baseline, with or without the use of medications, and no need for additional glaucoma surgery. Complete success was defined as achieving the target IOP without the use of any glaucoma medications or additional surgical interventions. Secondary outcome measures included changes in the number of glaucoma medications required postoperatively, visual acuity assessed using the logarithm of the minimum angle of resolution (logMAR) scale,

and the incidence of complications. Visual acuity was evaluated preoperatively and at each follow-up visit. Furthermore, MD values in automated VF testing were extracted for analysis. Retinal nerve fiber layer (RNFL) thickness was measured using spectral-domain optical coherence tomography, focusing on global RNFL thickness. Complications such as early IOP spikes, hyphema, and the need for further glaucoma surgery were also documented. An IOP spike was defined as a pressure increase exceeding 30 mmHg within the first week postoperatively.

Statistical Analysis

Data analysis was carried out using SPSS software (version 22.0; IBM Corp., Armonk, NY, USA). Continuous variables were summarized as mean values with corresponding standard deviations, while categorical variables were represented as percentages. Group comparisons between GATT and BANG were performed using independent-samples t-test for continuous variables exhibiting normal distributions, whereas the Mann-Whitney U test was applied for non-parametric data. Categorical variables were assessed using the chi-square test or Fisher's exact test, as appropriate. To evaluate the cumulative likelihood of achieving both qualified and complete surgical success over the follow-up period, Kaplan-Meier survival analysis was employed. A p value of less than 0.05 was deemed indicative of statistical significance.

Results

The study included a total of 65 eyes, with 34 in the GATT group and 31 in the BANG group. The mean age was 60.6±13.0 years in the GATT group and 61.1±12.2 years in the BANG group. Both groups had a similar sex distribution, with 47.1% females in the GATT group and 45.2% in the BANG group. The mean glaucoma duration was 7.4±4.1 years in the GATT group and 5.7±3.8 years in the BANG group (p=0.725). The mean follow-up duration was 13.4±4.3 months for GATT and 11.8±3.8 months for BANG, which did not differ significantly between the groups. Phakic and pseudophakic eyes were evenly distributed, and PXG was the most common diagnosis, accounting for 58.8% of cases in the GATT group and 48.4% of those in the BANG group. Table 1 provides a comprehensive overview of the baseline demographic and clinical profiles of the study participants.

The preoperative IOP was similar between the groups, averaging 32.9±6.1 mmHg in the GATT group and 31.8±5.4 mmHg in the BANG group. Postoperative outcomes revealed substantial IOP reductions in both groups. At postoperative 1 month, the mean IOP decreased to 14.4±5.2 mmHg in the GATT group, representing a 56.2% reduction, and to 19.1±6.0 mmHg in the BANG group, representing a 39.9% reduction. The difference between the two groups at this time point was statistically significant (p=0.002). At 3 months, the mean IOP was 14.1±4.4 mmHg in the GATT group, a 57.2% reduction, compared to 16.6±3.8 mmHg in the BANG group, a 47.8% reduction (p=0.025). At 6 months, the reduction in IOP remained more pronounced in the GATT group, with mean values of 14.6±4.1 mmHg compared to 16.3±2.7 mmHg in the BANG group, but the difference did not reach statistical significance (p=0.064). By the final follow-up, the GATT group demonstrated a mean IOP of 15.8±4.5 mmHg, corresponding to a 51.9% decrease from baseline. In contrast, the BANG group exhibited a mean IOP of 17.9±5.7 mmHg, reflecting a 43.7% reduction. The difference in final IOP between the groups was not statistically significant (p=0.108). Table 2 shows the efficacies of the two surgical techniques in detail.

Both procedures resulted in a significant reduction in the number of glaucoma medications used postoperatively. In the GATT group, the mean number of medications decreased from 3.4±0.6 preoperatively to 0.3±0.9 at the final follow-up, whereas in the BANG group, the mean number of medications decreased from 3.3±0.7 to 0.9±1.2. This reduction was statistically greater in the GATT group (p=0.036).

Preoperative visual acuity was similar between the groups, with a mean logMAR of 0.15±0.23 in the GATT group and 0.16±0.24 in the BANG group. At the final follow-up, visual acuity remained stable, with a mean logMAR of 0.18±0.24 in the GATT group and 0.21±0.28 in the BANG group (p=0.603).

A subgroup analysis of PXG patients revealed no significant differences in final IOP levels between pseudophakic and phakic patients (p=0.421). Both groups demonstrated significant medication reduction (p=0.285), and the surgical success rates were comparable (p=0.537).

MD on VF testing and central RNFL thickness values were comparable at baseline. The mean preoperative MD was -7.5±3.7 dB in the GATT group and -6.8±3.5 dB in the BANG

Table 1. Baseline demographical and clinical characteristics of the patients

	GATT group (n=34)	BANG group (n=31)	Total (n=65)	p
Mean age (years)	60.6±13.0	61.1±12.2	60.8±12.5	0.879[a]
Age range (years)	29-81	40-80	29-81	
Female, n (%)	16 (47.1)	14 (45.2)	30 (46.2)	0.878[b]
Glaucoma duration (years)	7.4±4.1	5.7±3.8	6.6±4.0	0.725[c]
Mean follow-up time (months)	13.4±4.3	11.8±3.8	12.7±4.1	0.108[a]
Lens status, n (%)				0.859[b]
Phakic	15 (44.1)	13 (41.9)	28 (43.1)	
Pseudophakic	19 (55.9)	18 (58.1)	37 (56.9)	
Diagnosis, n (%)				0.622[b]
POAG	13 (38.2)	14 (45.2)	27 (41.5)	
PXG	20 (58.8)	15 (48.4)	35 (53.8)	
PG	1 (2.9)	2 (6.5)	3 (4.6)	

[a]Independent samples t-test, [b]Chi-square test, [c]Mann-Whitney U test. GATT: Gonioscopy-assisted transluminal trabeculotomy, BANG: Bent ab interno needle goniectomy, POAG: Primary open-angle glaucoma; PXG: Pseudoexfoliation glaucoma, PG: Pigmentary glaucoma

Table 2. Efficacy data of the two different surgical procedures				
	GATT (n=34)	**BANG (n=31)**	**Total (n=65)**	**p**
Visual acuity (logMAR)				
Preoperative	0.15±0.23	0.16±0.24	0.16±0.23	0.966[c]
Last visit	0.18±0.24	0.21±0.28	0.20±0.26	0.603[c]
Further glaucoma surgery, n (%)	3 (8.8)	5 (16.1)	8 (12.3)	0.463[b]
Early IOP spike, n (%)	3 (8.8)	0 (0)	3 (4.6)	0.091[d]
IOP (mmHg)				
Preoperative	32.9±6.1	31.8±5.4	32.4±5.8	0.424[a]
Month 1	14.4±5.2	19.1±6.0	16.6±6.1	**0.002**[a]
Month 3	14.1±4.4	16.6±3.8	15.2±4.3	**0.025**[a]
Month 6	14.6±4.1	16.3±2.7	15.4±3.6	0.064[a]
Month 12	14.5±2.9	16.2±2.2	14.8±2.8	0.278[a]
Final	15.8±4.5	17.9±5.7	16.8±5.2	0.108[a]
Number of medications				
Preoperative	3.4±0.6	3.3±0.7	3.3±0.6	0.252[c]
Final	0.3±0.9	0.9±1.2	0.6±1.1	**0.036**[c]
Central RNFL thickness (µm)				
Preoperative	79.0±13.1	77.8±15.7	78.5±14.3	0.737[a]
Final	74.8±13.0	70.9±14.2	72.9±13.5	0.249[a]
Mean deviation in VF				
Preoperative	-7.5±3.7	-6.8±3.5	-7.2±3.6	0.362[c]
Final	-9.2±4.1	-8.0±3.4	-8.6±3.8	0.208[c]

[a]Independent samples t-test, [b]Chi-square test, [c]Mann-Whitney U test, [d]Fisher's exact test. GATT: Gonioscopy-assisted transluminal trabeculotomy, BANG: Bent ab interno needle goniectomy, logMAR: Logarithm of the minimum angle of resolution, IOP: Intraocular pressure, RNFL: Retinal nerve fiber layer, VF: Visual field

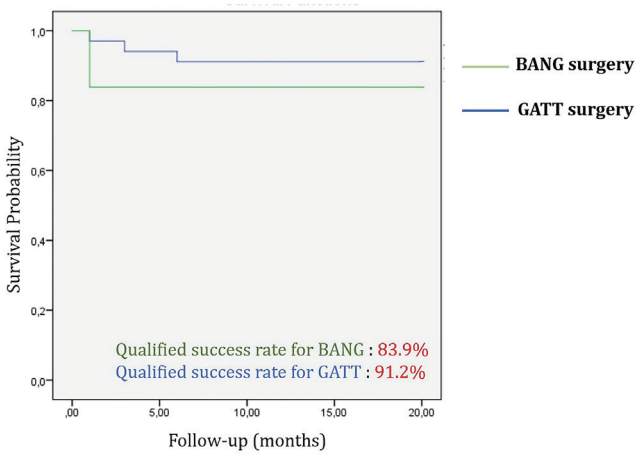

Figure 1. Kaplan-Meier analysis of qualified surgical success in gonioscopy-assisted transluminal trabeculotomy (GATT) and bent ab interno needle goniectomy (BANG). Qualified success was defined as IOP ≤21 mmHg and 20%≥ IOP reduction from baseline without further glaucoma surgery. Qualified success rates did not differ significantly between the groups (p=0.361, Breslow test)
IOP: Intraocular pressure

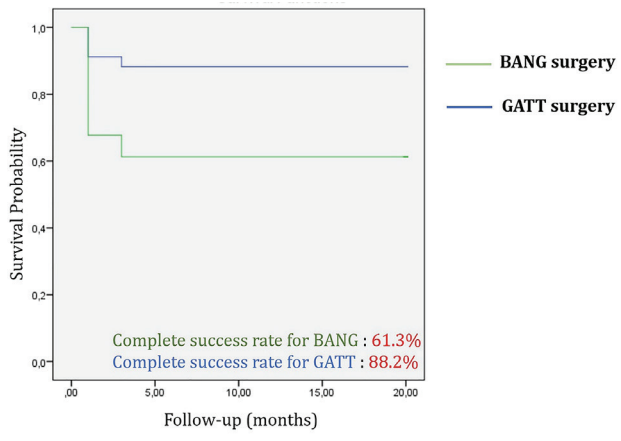

Figure 2. Kaplan-Meier analysis of complete surgical success in gonioscopy-assisted transluminal trabeculotomy (GATT) and bent ab interno needle goniectomy (BANG). Complete surgical success was defined as IOP ≤21 mmHg and 20%≥ IOP reduction from baseline without any further antiglaucoma medication or glaucoma surgery. The rate of complete success was significantly higher for GATT than BANG (p=0.012, Breslow test)
IOP: Intraocular pressure

group (p=0.362). The final MD values were -9.2±4.1 dB for GATT and -8.0±3.4 dB for BANG (p=0.208).

Similarly, the baseline RNFL thickness was 79.0±13.1 µm in the GATT group and 77.8±15.7 µm in the BANG group (p=0.737). At the final visit, RNFL thickness was 74.8±13.0 µm for GATT and 70.9±14.2 µm for BANG (p=0.249).

Kaplan-Meier survival analysis indicated higher success rates in the GATT group compared to the BANG group. The qualified success rate, defined as achieving an IOP of 21 mmHg or lower with at least a 20% reduction from baseline with or without medication, was 91.2% in the GATT group and 83.9% in the BANG group (p=0.361) (Figure 1). The complete success rate, defined as achieving the same IOP target without the use of medications, was 88.2% for the GATT group and 61.3% for the BANG group (p=0.012) (Figure 2). All patients requiring further surgical intervention due to uncontrolled IOP underwent trabeculectomy (3 patients [8.8%] in the GATT group and 5 patients [16.1%] in the BANG group). The need for a second surgical intervention was observed primarily within the first 6 months postoperatively (at 1, 3, and 6 months in the GATT group and at 1 month in the BANG group).

Both procedures resulted in minimal complications. Early IOP spikes were noted in 3 patients (8.8%) in the GATT group and none in the BANG group, with no significant difference (p=0.090). Hyphema was observed in all patients, with varying degrees in both groups. It resolved spontaneously within a week in most cases, except for 2 GATT patients who required anterior chamber washout by postoperative week 3.

Discussion

This study explored the therapeutic outcomes and safety considerations of GATT and BANG in treating patients with OAG, highlighting important differences in IOP reduction trends and surgical success rates between the two procedures. Both GATT and BANG significantly reduced IOP and the need for glaucoma medications, reinforcing their viability as MIGS techniques. However, the magnitude, stability, and durability of these outcomes differed notably between the groups. The GATT group demonstrated a substantial and sustained reduction in IOP throughout the follow-up period. At the first postoperative month, the mean IOP in the GATT group dropped from a baseline of 32.9±6.1 mmHg to 14.4±5.2 mmHg, reflecting a 56.2% reduction. This marked decrease remained consistent, with the final IOP stabilizing at 15.8±4.5 mmHg, corresponding to a 51.9% reduction overall. This stability in IOP reduction suggests that the 360-degree trabeculotomy performed in GATT effectively enhances aqueous outflow through Schlemm's canal, providing extensive and long-lasting improvement in outflow facility. The Kaplan-Meier analysis showed a qualified success rate of 91.2% and a complete success rate of 88.2% for GATT, indicating that the procedure achieves reliable IOP control with a reduced dependency on medications.

In contrast, the BANG group exhibited a less pronounced and less stable IOP reduction trend. The mean IOP decreased from 31.8±5.4 mmHg preoperatively to 19.1±6.0 mmHg at the first postoperative month, representing a 39.9% reduction. Over time, the IOP reduction plateaued, with the final mean IOP stabilizing at 17.9±5.7 mmHg, corresponding to a 43.7% reduction. The limited extent of TM excision in BANG, which addresses only a 90-degree segment, may account for the lower efficacy compared to the 360-degree approach of GATT. This partial goniotomy likely leaves residual outflow resistance, preventing sustained IOP control. The Kaplan-Meier analysis reflected this difference, with the qualified success rate for BANG at 83.9% and the complete success rate significantly lower at 61.3%. This suggests that BANG patients are more likely to require ongoing medication to maintain target IOP levels.

Surgical failure rates also showed a divergent trend between the two groups. In the BANG group, failures tended to occur early in the follow-up period, likely due to initial healing responses or incomplete trabeculotomy. Once this early period passed, IOP control remained relatively stable, even as medication dependence increased. Conversely, the GATT group experienced fewer surgical failures, but these continued to emerge over time, suggesting a progressive decline in effectiveness. This ongoing failure trend may be due to the natural wound healing response that can lead to fibrosis or scarring of the TM and Schlemm's canal. This scarring may gradually reduce the outflow capacity restored by the 360-degree trabeculotomy, causing IOP to rise again and leading to surgical failure in some patients.

The outcomes of this study align with and expand upon the findings of previous research comparing GATT and BANG. Ayub et al.[9] reported that both GATT and BANG effectively reduced IOP in patients with primary POAG, but the extent of IOP reduction was greater with GATT. Our study similarly showed a more pronounced IOP reduction in the GATT group, with a 56.2% decrease at postoperative 1 month compared to 39.9% in the BANG group. Furthermore, Grover et al.[10] documented a mean IOP reduction of 44% at 12 months and 37.3% at 24 months following GATT, underscoring the procedure's ability to provide sustained IOP control. Rahmatnejad et al.[11] reported a 63.0% overall success rate at 12 months, with a significant IOP decrease from 26.1 mmHg to 14.6 mmHg, indicating variability in GATT outcomes. Moreover, Aktas et al.[12] compared outcomes in POAG and PXG, showing a higher success rate in PXG (97.6%) than in POAG (86.8%) in the first year after GATT. In contrast, BANG studies such as those by Bukke et al.[13] demonstrated only a 31.8% reduction in IOP at 12 months when combined with phacoemulsification. The superior efficacy of GATT may be attributed to its 360-degree trabeculotomy, which addresses the entire circumference of Schlemm's canal, whereas BANG's limited 90-degree goniotomy may leave residual resistance to aqueous outflow. These comparative results emphasize that GATT offers more comprehensive and durable IOP control, making it a preferable option for patients requiring substantial IOP reduction.

The surgical success rates and complication profiles observed in our study are consistent with findings in the existing literature. In our study, the GATT group achieved a complete success rate of 88.2%, which is close to the 85% success rate reported by Dar et al.[14] for patients with advanced glaucoma undergoing GATT. Additionally, Liu et al.[15] reported a 45% IOP reduction at 4 years with a cumulative failure rate of 53.9%, suggesting that while GATT is effective, failures can occur over the long term. In comparison, BANG studies like those by Bukke et al.[13] reported an overall success rate of 87.5% at 12 months when combined with phacoemulsification, though isolated BANG procedures often showed lower success rates. Complications such as transient hyphema were the most common adverse events in both GATT and BANG.

Our comprehensive analysis of IOP reduction trends, surgical success rates, and complication profiles over an extended follow-up period demonstrated superior and sustained efficacy of GATT in achieving long-term IOP control compared to BANG. These findings may offer valuable guidance for clinicians in tailoring surgical interventions according to individual patient needs and disease severity. The inclusion of detailed failure trends also underscores the importance of considering the extent of TM intervention when predicting long-term outcomes. Furthermore, this study highlights the clinical significance of early versus late surgical failures, helping to refine postoperative expectations and management strategies. By filling these gaps, our research enhances the understanding of MIGS efficacy and supports evidence-based decision-making in glaucoma management.

Study Limitations

This study has several limitations. The retrospective design and sequential allocation of patients introduce potential biases, limiting the validity of direct comparisons between GATT and BANG. The lack of true randomization and the single-surgeon setting may affect the generalizability of the results to broader populations and varying skill levels. The sequential selection of surgical techniques may have resulted in increased surgeon experience over time, potentially influencing the outcomes in favor of later-performed procedures. Additionally, the sample size is relatively small, and the follow-up period may not fully capture long-term outcomes or late failures. Future studies should include larger, multicenter, randomized controlled trials to minimize bias and enhance generalizability. Longer follow-up periods are needed to assess the durability of IOP control and the frequency of late failures.

Conclusion

This study shows that GATT achieves greater and more sustained IOP reduction compared to BANG in OAG. The higher long-term success rate with GATT highlights its reliability, providing valuable guidance for MIGS selection.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the principles of the Declaration of Helsinki and received ethical approval from the Ethics Committee for Scientific Research in Health Sciences of Kırşehir Ahi Evran University Faculty of Medicine (decision no: 2024-16/138, date: 10/08/2024).

Informed Consent: Prior to participation, informed consent was obtained from all individuals included in the study.

Declarations

Authorship Contributions

Surgical and Medical Practices: A.Y.Ü., Concept: A.Y.Ü., Z.A., Design: A.Y.Ü., R.K.Ü., Data Collection or Processing: A.Y.Ü., R.K.Ü., Analysis or Interpretation: A.Y.Ü., R.K.Ü., Z.A., Literature Search: A.Y.Ü., R.K.Ü., Writing: A.Y.Ü., R.K.Ü.

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Review

Binocular Approaches in Amblyopia Treatment Based on Dichoptic Stimulation

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Abstract

The discovery that binocular dysfunction may play a critical role in the development of amblyopia has led to the development of a novel approach based on contrast-rebalanced binocular stimulation of both eyes. This approach, known as dichoptic stimulation, enables the treatment of amblyopia by facilitating the cooperation of both eyes. Dichoptic treatment approaches are founded on the theoretical premise that binocular imbalance plays a significant role in both monocular and binocular impairments in amblyopia, and that preserving binocular function capacity is essential. Therefore, these approaches are designed to promote the collaborative functioning of the eyes, enhance stereopsis, and improve binocular fusion. This review systematically examines and synthesizes the existing literature on dichoptic stimulation techniques aimed at improving binocular function in the treatment of amblyopia. Based on various studies in the literature, the fundamental principles of these treatment methods are outlined, and the results obtained in comparison to traditional monocular treatments are highlighted. The clinical efficacy of dichoptic treatment methods is evaluated in terms of their contribution to enhancing binocular function in amblyopia. Additionally, information is provided regarding the outcomes, treatment durations, efficacy levels, and potential side effects of these treatment approaches in different patient groups. This review offers a comprehensive assessment of the integration of dichoptic treatment approaches into clinical practice, highlighting both their advantages and disadvantages, and aims to provide a guiding perspective on their future use.

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Keywords: Amblyopia, binocular dysfunction, binocular therapies of amblyopia, dichoptic stimulation

Introduction

Binocular Dysfunction and Amblyopia

Amblyopia is defined as a visual impairment caused by abnormal binocular interaction and disproportionate fusional suppression in one or both eyes during early visual development with no underlying abnormality or pathology detected with routine eye examination.[1,2,3] Although amblyopia can occur in both eyes, it was historically considered a monocular condition because visual acuity is typically affected in only one eye. Consequently, traditional amblyopia treatments aimed to improve the monocular visual acuity of the amblyopic eye by suppressing the other (dominant) eye, which was thought to be healthy.[4-23] While these treatments could be effective in enhancing the visual acuity of the amblyopic eye, they did not prevent the occurrence of residual or recurrent amblyopia, ocular motor problems, fine motor issues, and contrast sensitivity abnormalities in many individuals.[24,25]

The discovery that binocular vision is necessary for the amelioration of experimentally induced amblyopia in animal models led to the hypothesis that binocular dysfunction plays a critical role in the development of amblyopia.[26] Subsequent findings that balanced contrast in the two eyes can lead to binocular vision were regarded as evidence of latent binocular abilities in amblyopic individuals.[27,28] Given that binocular dysfunction is thought to be an important factor in the development of amblyopia, many researchers suggest that binocular approaches may play a significant role in the treatment of amblyopia.[3,24,29] This perspective has led to the development of a new dichoptic stimulation approach that relies on binocular stimulation conditions forcing both eyes to collaborate on a visual task by balancing the contrast differences between them.[29]

Dichoptic stimulation involves presenting different images to each eye and posing a visual task that can only be completed by combining information from both eyes.[24] These stimuli can be provided using red/green anaglyph glasses (glasses with one red and one green lens, used to view stereoscopic pictures/video consisting of two images of the same object/scene taken from slightly different angles), shutter glasses (glasses that brighten and darken quickly in sync with the monitor, thus allowing a common background to be presented to both eyes but allowing the rich, moving image to be presented only to the amblyopic eye), polarized glasses, virtual reality (VR) headsets, or low-pass filters that reduce brightness in the dominant eye.

Dichoptic contrast stimulation involves presenting different images with varying contrast levels to each eye, while maintaining the same background contrast for both eyes. The dichoptic manipulation of contrast is achieved by reducing the contrast of the signal seen by the dominant eye to a point where binocular combination is possible, thus eliminating suppression from the dominant eye. This delicate balance point can vary for each amblyopic individual. It is thought that allowing the eyes to combine information under balanced contrast conditions and repeatedly exposing the amblyopic individual to these stimuli will progressively strengthen binocular fusion, eventually resulting in smaller interocular contrast differences.[24,27,28]

Dichoptic approaches are based on the assumption that the amblyopic visual system retains its binocular functional capacity (latent binocular abilities).[3,24] The primary objective of dichoptic approaches is to restore binocular fusion and stereopsis, with the expected secondary outcome of improved visual acuity in the amblyopic eye.[3] To achieve this, complementary dichoptic stimuli are employed, such that the visual task can only be resolved if both left and right eye information is integrated.[24]

The purpose of the present review is to evaluate dichoptic stimulation approaches for the treatment of amblyopia in light of published studies on the subject. Binocular approaches are examined in three sections: the first section covers dichoptic stimulation approaches designed to restore monocular visual acuity; in the second section we discuss monocular perceptual learning and dichoptic stimulation approaches aimed at restoring binocular function; and the third section addresses active and passive dichoptic stimulation approaches and dichoptic contrast manipulation designed to restore binocular function.

1. Approaches Using Dichoptic Stimulation to Improve Monocular Visual Acuity

The aim of these approaches is to develop an amblyopia treatment alternative to patching therapy, enhancing visual acuity in a fun, binocular format for children.[30]

Interocular Binocular Treatment System

Interocular binocular treatment system (I-BiT™) is a VR-based computer system that uses dynamic stimuli for preferential stimulation of the amblyopic eye without the need for patching. The original I-BiT™ system features a 3D cyberscope,[30] which allows rapid light and dark alternation synchronized with the monitor, presenting a common background to both eyes while a rich, dynamic image is delivered only to the amblyopic eye. In this setup, two completely separate but visually related images can be presented independently to each eye, similar to a synoptophore.[31,32] In this system, images are presented to the eyes with various methods.[30] These methods have been used to develop different video clips and games. In the video clips, the amblyopic eye sees a moving video, while the dominant eye sees a stationary background. The games used in the I-BiT™ system include a version of Pac-Man (Bandai Namco Entertainment Inc., Japan) and a racing game. Studies implementing I-BiT™ are summarized in Table 1.[33,34,35,36]

The I-BiT™ system was tested in a pilot study involving 6 children aged 5-7 years with anisometropic, strabismic, or combined anisometropic/strabismic amblyopia in which traditional treatments were refused or failed.[33] The study involved 1-2 treatment sessions per week, with each session including 20 minutes of video viewing and a few minutes of interactive gameplay. Treatment continued until the visual acuity of the amblyopic children stabilized (11-22 months), showing a mean improvement of 10 letters in logarithm of the minimum angle of resolution (logMAR) visual acuity.[33]

In a multicenter, randomized controlled trial involving 75 patients aged 4-8 with strabismic, anisometropic, or mixed amblyopia, the I-BiT™ system produced a visual acuity improvement of 0.067 logMAR after 10 weeks.[32] However, no gains were observed in stereoacuity. It was concluded that dichoptic stimulation with I-BiT™ did not provide a significant advantage for the amblyopic eye. The limited success in the study was attributed to the short treatment duration, a high rate of previous treatment failures among the participants, and the disadvantage of strabismic amblyopia in dichoptic stimulation studies.[34]

I-BiT™ is considered an effective supplementary method for amblyopia treatment, but no sustained improvement in visual acuity was observed after it was discontinued.[35] Issues with adherence in the I-BiT™ system have been pointed out, mainly due to the prototype's unsuitability for young children and inability to be used at home.[32,34] Researchers also emphasized the need for dichoptic images to be presented in alignment with each eye's fovea for success in strabismic and mixed amblyopia cases.[31]

2. Approaches Using Monocular Perceptual Learning and Dichoptic Stimulation to Restore Binocular Function

Research has shown that performing a challenging visual task repeatedly can enhance perceptual performance, particularly in adults and older children in whom traditional treatments have limited success in improving visual acuity.[22,23] However, the limited improvement in visual acuity and the restriction of perceptual learning due to monocular occlusion as a routine treatment for amblyopia have been noted. To overcome these limitations, researchers have developed alternatives with the aim of providing perceptual learning under binocular conditions.

Table 1. Studies implementing I-BiT™ to improve monocular visual acuity

Studies	Study type	Sample size	Amblyopia type	Age	Treatment duration	Session duration/ frequency	Adherence	Stereoacuity improvement	Visual acuity improvement	Side effects
Waddingham et al.[33] 2006	Pilot	6	Anisometropic, strabismic, or mixed	5-7	11-22 months	20 min, 2 days/week	100%	N/A	10 letters	None
Herbison et al.[32] 2013	Pilot	10	Anisometropic, strabismic, or mixed	4-8	6 weeks	30 min, 1 day/week	90%	N/A	0.18 logMAR	None
Herbison et al.[34] 2016	Randomized controlled	75	Anisometropic, strabismic, or mixed	4-8	6 weeks	30 min, 1 day/week	>90%	None	0.060 logMAR	Diplopia
Rajavi et al.[35] 2016	Randomized controlled	50	Anisometropic	3-10	4 weeks	30 min, 5 days/week	N/A	N/A	0.17 logMAR	N/A
Rajavi et al.[36] 2019	Randomized controlled	38	Anisometropic	3-10	4 weeks	30 min, 5 days/week	87.5%	None	0.08 logMAR	N/A

I-BiT™: Interocular binocular treatment system, N/A: Not applicable (not assessed or reported in study), logMAR: Logarithm of the minimum angle of resolution

Push-Pull Perceptual Learning Training Protocol

The visual sensory system can be shaped by competition from binocular stimulus interactions and reciprocal inhibition between the two eyes.[37] In normally developed adults, reciprocal inhibition between the eyes is generally balanced. However, disruption of this balance results in sensory eye dominance.[37] It is thought that almost all individuals exhibit some degree of sensory eye dominance.[38] When this dominance becomes excessive, it leads to disturbances in binocular vision through both excitatory and inhibitory mechanisms.[37] Amblyopia is described as a condition in which excessive interocular inhibition of the amblyopic eye occurs as a result of extreme sensory eye dominance.[39]

It has been reported that amblyopic individuals exhibit more pronounced sensory eye dominance compared to healthy controls with clinically normal visual acuity.[40] Push-pull perceptual learning training (PPLT) was developed as a protocol to reduce excessive sensory eye dominance in amblyopia and improve stereopsis by simultaneously affecting the excitatory stimuli of the amblyopic eye and the inhibitory stimuli of the dominant eye.[37] Traditional amblyopia treatments, such as occluding the dominant eye, do not directly address sensory eye dominance.[37] PPLT is fundamentally designed to regulate the binocular balance of excitatory and inhibitory interactions by suppressing the dominant eye's perception (pull) and stimulating the amblyopic eye's perception (push). It has been noted that this training protocol effectively reduces sensory eye dominance, improves stereoacuity, and significantly contributes to sensory plasticity even in people with clinically normal binocular vision.[37,38,39,40] This method has been proposed as a potentially effective treatment for amblyopia. However, the only clinical study on PPLT conducted so far involved 36 children aged 4-17 with anisometropic amblyopia and 33 with normal visual acuity. The 20-minute training sessions stimulated both the visual cortex and the temporal lobe, highlighting the importance of this method for regaining stereoacuity in anisometropic amblyopia.[41] The persistence of learning effects for more than 4 months after training suggests that PPLT induces long-term cortical plasticity.[38]

Lazy Eye Shooter

Lazy Eye Shooter is a therapeutic video game created by modifying the first-person action game Unreal Tournament 2004 (Epic Games, 2004, CA, USA). In this method, the amblyopic individual views the same game scene on two different screens using a stereoscope or video glasses (Figure 1). This approach simultaneously provides perceptual learning, video gameplay, and dichoptic stimulation. Amblyopic individuals are asked to play a specially designed action video game with monocular perceptual learning tasks, Gabor patches,[42] and dichoptic stimulation. Gabor patches are sinusoidal gratings featuring a pattern of diagonal black and white stripes enclosed within a square frame.[43] They are commonly used in studies of amblyopia, particularly in the context of perceptual learning. In the dichoptic presentation method developed by Bayliss et al.[43], the same image (except for the Gabor patches) is shown to each eye with reduced contrast for the dominant eye, with the aim of encouraging binocular fusion. As part of the game, participants are required to shoot at targets containing a Gabor patch while ignoring those without it.[43]

In a study comparing Lazy Eye Shooter with occlusion therapy in 38 adults aged 19-66, the game group showed a significant improvement in visual acuity (0.14±0.01 logMAR) after 40 hours of treatment.[44] Significant improvements were also observed in stereoacuity, with a mean gain of 0.18±0.05 log seconds of arc (arcsec). Additionally, participants who received dichoptic and perceptual learning training showed markedly enhanced contrast ssensitivity and reading speed and reduced fear of losing vision in the dominant eye, with these improvements remaining stable even after 2 months.

However, this therapeutic approach has some limitations. Due to the inclusion of violent elements (weapons, blood, and violence), Lazy Eye Shooter cannot be used for children.[44] The

Figure 1. Lazy Eye Shooter game. Two game screens are shown. The good eye is shown the dimmed screen (right) and the amblyopic eye is shown the screen with the extra object (Gabor patch; left) (Reproduced from Bayliss JD, Vedamurthy I, Bavelier D, Nahum M, and Levi D, "Lazy eye shooter: A novel game therapy for visual recovery in adult amblyopia", *2012 IEEE International Games Innovation Conference*, Rochester, NY, USA, 2012, pp. 1-4, with permission from *IEEE Proceedings*)

requirement to play the game for approximately 40-50 hours can also lead to boredom among participants. Additionally, the Gabor patches as currently designed interrupt the flow of the game and affect the player's concentration.[43,44]

3. Approaches Using Dichoptic Stimulation with Contrast Manipulation to Restore Binocular Function

Interactive Approaches

Falling Blocks

Falling Blocks is a modified version of the game Tetris (Tetris Inc., Honolulu, HI, USA). Tetris was chosen for dichoptic stimulation due to its block-based structure, which enables effective contrast customization.[45] In the initial prototype developed, the contrast balance ratio was calculated individually for each person to determine how blocks should be presented to the amblyopic and dominant eyes. The amblyopic individual advances to higher levels by creating rows of blocks without gaps. At higher levels, the difficulty of the game is raised by recalculating the contrast balance ratio and increasing the block fall speed, while maintaining an effect that does not significantly impact game performance.[45]

The dichoptic stimulation in this game can be presented in various ways. Knox et al.[46] performed this application using VR glasses in an office setting, while To et al.[45] used a touch-sensitive iPod® Touch (Apple® Inc., Cupertino, CA, USA) without requiring additional equipment in an office setting. However, due to the need for a fixed head position and excellent fine motor skills for manipulating the blocks, this design was not suitable for younger amblyopic children.[47] Consequently, the game was modified to be played on a larger iPad® (Apple® Inc., Cupertino, CA, USA) held at reading distance while wearing red/green anaglyph glasses.[47,48,49,50,51] Game elements are presented with 100% contrast to the amblyopic eye and lower contrast to the other eye. The contrast used for the dominant eye is adjusted based on the game duration and previous day's performance, with changes ranging from an increase of 10% to a reduction or no change. Studies implementing Falling Blocks are summarized in Table 2.[47,48,50,51,52,53,54,55,56]

Two multicenter randomized clinical trials conducted by the Pediatric Eye Disease Investigator Group (PEDIG) compared the effects of Falling Blocks therapy and occlusion therapy on amblyopic eye visual acuity.[50,51] These studies involved 385 children aged 5-12 and 100 adolescents aged 13-16 with strabismic (≤4 prism diopters [PD]), anisometropic, or mixed-type amblyopia. In the trials, a 16-week home-based treatment of 1 hour per day with the binocular Falling Blocks game was compared to 2 hours per day of recommended occlusion therapy. The touch device recorded game play duration and dominant eye contrast automatically. Over the 16-week period, the binocular treatment group completed at least 75% of the prescribed treatment 22% of the time in the 5-12 age group and 13% of the time in the 13-16 age group. Improvements were observed in amblyopic eye visual acuity, with a mean gain of 1.05 lines (0.31 lines difference favoring occlusion) in the 5-12 age group and 0.74 lines (0.52 lines difference favoring occlusion) in the 13-16 age group. However, no significant changes in stereoacuity measurements were reported in the binocular treatment groups compared to baseline values.[50,51]

Overall, studies involving Falling Blocks therapy suggest that this treatment may provide more significant improvements in visual acuity and stereoacuity in amblyopic adults.[45,47,48,49,50,51] Differences in study outcomes may be attributed to whether the contrast balance points were individualized, age-related differences in attention or motivation, and variations between controlled laboratory and home settings.[48] PEDIG has suggested that visual acuity improvements with Falling Blocks therapy are not as effective as 2 hours per day of occlusion therapy.[50,51] Possible reasons for these results include the timing of initial and final evaluations and differences in treatment duration. In some studies, patients were assessed after shorter treatment periods (4 weeks),[45,47,48] while in the PEDIG trials they were evaluated after

Table 2. Studies implementing active dichoptic stimulation and dichoptic contrast manipulation designed to regain binocular function

Studies	Study type	Sample size	Amblyopia type	Age	Treatment duration	Session duration/ frequency	Adherence	Stereoacuity improvement (mean, log arcsec)	Visual acuity improvement	Side effects
Falling Blocks										
Li et al.[48] 2014	Case-control	75	Anisometropic, strabismic, or mixed	4-12	4 weeks	4 hours/week	N/A	11%	0.08±0.01 logMAR	N/A
Birch et al.[47] 2015	Case-control	50	Anisometropic, strabismic, or mixed	3-7	4 weeks	4 hours/week	59%	None	0.14±0.02 logMAR	N/A
Holmes et al.[50] 2016	Randomized controlled	385	Anisometropic, strabismic, or mixed	5-12	16 weeks	1 hour/week	22%	None	1.05 lines	Heterotropia, diplopia
Manh et al.[51] 2018	Randomized controlled	100	Anisometropic, strabismic, or mixed	13-16	16 weeks	1 hour/week	13%	None	3.7 letters or 0.74 lines	Heterotropia, diplopia
Dig Rush										
Kelly et al.[52] 2016	Randomized controlled	28	Anisometropic, strabismic, or mixed	4-10	2 weeks	5 days/week, 1 hour/day	100%	None	0.15±0.08 logMAR	None
Kelly et al.[54] 2018	Randomized controlled	41	Anisometropic, strabismic, or mixed	4-10	2 weeks	5 days/week, 1 hour/day	94%	4.46±0.79	0.14±0.09 logMAR	N/A
Holmes et al.[55] 2019	Randomized controlled	138	Anisometropic, strabismic, or mixed	7-12	8 weeks	5 days/week, 1 hour/day	97%	None	2.3 letters	Heterotropia, diplopia
Manny et al.[56] 2022	Randomized controlled	182	Anisometropic, strabismic, or mixed	4-6	8 weeks	5 days/week, 1 hour/day	78%	None	1.3 logMAR	Diplopia

N/A: Not applicable (not assessed or reported in study), logMAR: Logarithm of the minimum angle of resolution, arcsec: Seconds of arc

a longer period (16 weeks).[50,51] However, Li et al.[49] proposed that visual acuity improvements from binocular treatment can persist for up to 12 months. Another reason for the lack of a larger effect may be that participants lost interest in the game, highlighting the importance of addressing compliance issues and developing more engaging treatment alternatives such as immersive children's games, binocular first-person action games, and binocular film watching.

Dig Rush

Dig Rush is an action-adventure game played on an iPad using red/green anaglyph glasses. Detailed information about the game is presented by Kelly et al.[52] The red/green anaglyph glasses enable the presentation of distinct game elements to each eye. In the game, high-contrast elements (miners and monsters) can be seen by the amblyopic eye, while the low-contrast elements (mining cart, gold, and fire) can be seen by the dominant eye (Figure 2).[53] The game starts with the amblyopic eye's contrast set to 100%, while the contrast level of the dominant eye can be adjusted by the clinician. Success in the game leads to an increase in the dominant eye's contrast, while a lack of success over 30 minutes results in a reduction in contrast. The touch device automatically records gameplay duration and dominant

Figure 2. Dig Rush. High-contrast red elements (miners and fireball) are seen by the amblyopic eye. Low-contrast blue elements (gold and platforms) are seen by the dominant eye. Gray elements (rocks and ground) are seen by both eyes (Reproduced from Boniquet-Sanchez and Sabater-Cruz[53] with permission from *Vision*)

eye contrast, adjusting the contrast based on the success rate.

Studies concerning Dig Rush are summarized in Table 2. In two multicenter randomized controlled trials, PEDIG compared the effects of Dig Rush on amblyopic eye visual acuity with those of using glasses alone.[55,56] The first of these studies included 138 children aged 7-12 with strabismic (≤4 PD), anisometropic, or mixed amblyopia, and objective adherence to the therapy was 58% at 4 weeks and 56% at 8 weeks. The binocular treatment group showed an improvement in amblyopic eye visual acuity of 1.3 letters at 4 weeks and 2.3 letters at 8 weeks. However, no significant differences were observed in stereoacuity measurements compared to baseline values.[55]

The age groups included in Dig Rush studies vary. Kelly et al.[52,54] included children aged 4-10, while the PEDIG studies[55,56] involved children aged 7-12 and 4-6. Differences in results among these studies have been attributed to the varying age groups.[54,55] Older age groups may have a history of previous amblyopia treatments (e.g., occlusion and atropine) or may have reached a treatment plateau with limited additional improvement from new therapies, making them less responsive to binocular treatments. Younger age groups and/or children who have not undergone amblyopia treatment previously might be more responsive to binocular treatments. However, when the same protocol was applied to children aged 4-6, visual acuity improvements observed at 4 weeks were not maintained at 8 weeks. Variability in adherence to the prescribed treatment duration has also been suggested as a reason for inconsistent results.[54,55] In the studies by Kelly et al.,[52,54] higher adherence rates (87-100%) were linked to significant improvements in visual acuity and binocular outcomes. In contrast, the PEDIG study found adherence rates of 56-75% among children aged 7-12 years.[55] PEDIG attributed this to the design of the Dig Rush game, which was assumed to be more appealing to younger children, and therefore anticipated higher adherence in a subsequent study involving children aged 4-6 years. However, contrary to expectations, lower adherence rates of 43-57% were observed in this younger age group.[56] These findings suggest that adherence to the Dig Rush game may vary depending on age group and individual characteristics, highlighting the importance of accounting for age-related differences when evaluating the effectiveness of game-based therapies.

Vivid Vision®

Vivid Vision® (Vivid Vision Inc., San Francisco, CA, USA) games provide a dichoptic visual experience using VR glasses. Originally named Diplopia, the games are now known by the company's name, Vivid Vision®. In Diplopia mode, designed in 2014 by Blaha (who himself suffered from strabismus and amblyopia) and Gupta[57], each eye receives a different image, compelling the eyes to work together to succeed in the game. The aim is to limit the information given to each eye, requiring the player to integrate both visual inputs into a single coherent image.

In a pilot study involving 17 adults aged 17-69 with anisometropic amblyopia, after 4 weeks of Vivid Vision® games played in twice-weekly sessions lasting 40 minutes, there were significant improvements in both visual acuity and stereoacuity in the amblyopic eye (Figure 3).[58] These improvements were correlated with in-game test measurements, and no persistent diplopia or other adverse effects were reported.[59]

However, Vivid Vision® games have limitations. Developers note that simulator sickness[60] caused by VR glasses poses a significant barrier, especially for children. Additionally, the VR glasses' inability to monitor changes in accommodation and the design not fitting well around the head are other reasons why the system cannot be used for younger children. There is also concern about the risk of abnormal retinal correspondence developing in strabismic amblyopia cases.

Passive Approaches

Contrast-Balanced Dichoptic Movies

Dichoptic films consist of long-format versions of popular animated films or television programs presented in a dichoptic format. These films can be viewed using polarized[61,62,63] or shutter glasses,[64] VR headsets,[65] or specialized devices[66] without additional imaging equipment. An example of such a film is shown in Figure 4.

In a pilot study involving 8 patients aged 4-10 years with strabismic (≤5 PD), anisometropic, or mixed amblyopia, the impact of watching dichoptic films in a laboratory setting for 2 weeks, 3 times a week was evaluated in terms of visual acuity, stereoacuity, and interocular suppression.[61] A significant improvement in mean visual acuity of 2.0 logMAR was reported in the amblyopic eye. No significant changes were observed in stereoacuity or interocular suppression. This level of improvement was notably greater in the younger age group (3-6 years) and in cases of severe amblyopia (≥0.7 logMAR).[62] In cases of anisometropic amblyopia with measurable stereoacuity values (170 arcsec) at the start of treatment, there was a significant increase in stereoacuity (85 arcsec) following treatment.[64] Additionally, this gain in stereoacuity was significantly related to both the initial visual acuity of the amblyopic eye and the absolute improvement in visual acuity. Studies in which passive dichoptic approaches were implemented are summarized in Table 3.

In a study involving 17 amblyopic individuals with a mean age of 34 years, it was demonstrated that patching the amblyopic eye for 2 hours prior to therapeutic film sessions resulted in significant visual acuity improvement in the amblyopic eye, with sustained gains observed during a 1-month follow-up.[63] That study indicated that short-term monocular deprivation might activate binocular brain plasticity mechanisms through changes in excitatory/inhibitory balance, potentially enhancing dichoptic training outcomes.[63]

These findings constitute preliminary evidence that passive dichoptic film training can improve stereoacuity in older children and amblyopic adults. Furthermore, a 2-week treatment period with films viewed 3 times a week was found to be more effective in enhancing visual acuity and stereoacuity than patching for 2 hours daily.[66]

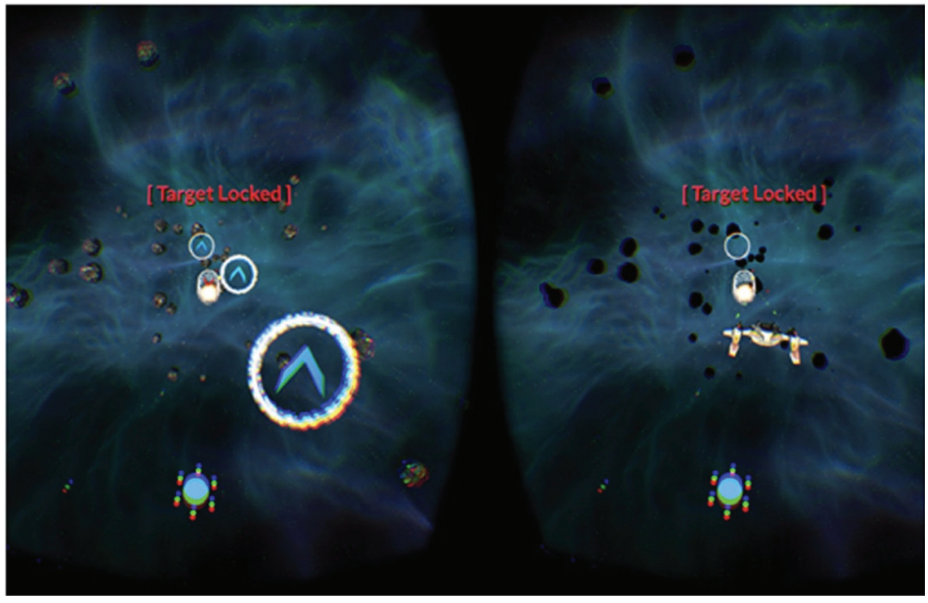

Figure 3. Vivid Vision® Ring Runner. This space game is designed with a dichoptic environment in which the central part of the image is different. Colored doors and asteroids can only be seen with the amblyopic eye, while the spaceship can only be seen with the dominant eye. The spaceship is presented to the dominant eye to prevent cheating, because if all objects in the game are seen with the amblyopic eye, there is a risk that the patient can monocularly use the amblyopic eye by closing the dominant eye (Reproduced from Žiak et al.[58] with permission from *BMC Ophthalmology*)

The most recent development in dichoptic films is Luminopia™ One (Luminopia Inc., Cambridge, MA, USA) digital therapy. As the first FDA-approved digital therapy, Luminopia™ One allows children aged 4-7 with anisometropia and/or mild strabismus, under the supervision of an ophthalmologist, to watch approximately 700 hours of popular television programs and films through a VR headset.[67] Given the issues associated with VR headset use in younger children, Luminopia™ One has been specifically designed with adjustable interpupillary distance and a secure strap system to accommodate children's heads. The device's therapeutic visual input, delivered to each eye via the VR headset, is controlled by a software application preloaded onto a smartphone.

Following encouraging results from a pilot study,[68] a multicenter randomized controlled trial was conducted to compare full-time refractive correction to 12 weeks of dichoptic therapy using Luminopia™ One for 1 hour per day, 6 days per week.[65] The results of the trial demonstrated that after 12 weeks of treatment, amblyopic eye visual acuity was significantly better in the dichoptic treatment group compared to the full-time refractive correction group.

Controversial Aspects of Dichoptic Stimulation-Based Binocular Approaches

Research involving binocular approaches using dichoptic stimulation has increased interest in the development of amblyopia treatments that directly address binocular dysfunction by promoting binocular vision and reducing inhibitory interactions within the visual cortex.[3,24] Although improvements in stereoacuity have been reported in pilot studies,[39,41,43,47,58,64] these

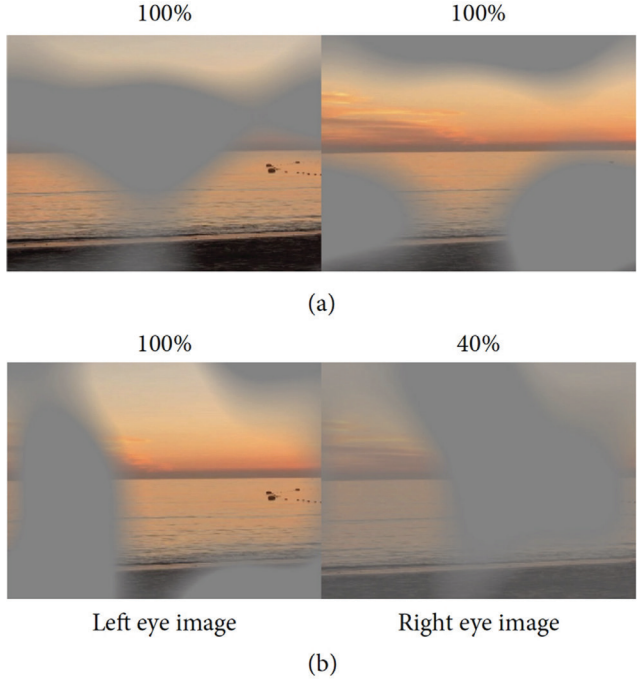

Figure 4. Dichoptic film sections (a, b) at 10-second intervals. a) 100% contrast of the images are presented to both eyes. b) High contrast image is presented to the amblyopic eye, while low contrast image is presented to the dominant eye. (Reproduced from Sauvan et al.[63] with permission from *Neural Plasticity*)

Table 3. Studies implementing passive dichoptic stimulation and dichoptic contrast manipulation designed to regain binocular function

Studies	Study type	Sample size	Amblyopia type	Age (y)	Treatment duration	Session duration/ frequency	Adherence	Stereo acuity improvement	Visual acuity improvement	Side effects
Dichoptic movies										
Li et al.[61] 2015	Prospective cohort	8	Anisometropic, strabismic, or mixed	4-10	2 weeks	3 days/week	N/A	None	2 logMAR	N/A
Birch et al.[62] 2019	Prospective cohort	27	Anisometropic, strabismic, or mixed	4-10	2 weeks	3 days/week	N/A	None	0.15±0.10 logMAR	N/A
Sauvan et al.[63] 2019	Prospective cohort	17	Anisometropic, strabismic, or mixed	9-67	2 weeks	3 days/week	N/A	N/A	0.08 logMAR	N/A
Jost et al.[66] 2022	Randomized controlled	60	Anisometropic, strabismic, or mixed	3-7	2 weeks	3 days/week	95%	0.12 log arcsec	0.07 logMAR	N/A
Bossi et al.[64] 2017	Cohort	22	Anisometropic, strabismic, or mixed	3-11	8 weeks	1 hour/day	68%	165±182 log arcsec	0.39±0.25 logMAR	None
Luminopia™ One										
Xiao et al. 2022[65]	Randomized controlled	105	Anisometropic, strabismic, or mixed	4-8	12 weeks	1 hour/day, 6 days/week	88.2%	None	0.18 logMAR	Headache, heterotropia

N/A: Not applicable (not assessed or reported in study), logMAR: Logarithm of the minimum angle of resolution, arcsec: Seconds of arc

results have not been corroborated by multicenter randomized controlled trials. Key uncertainties remain regarding the optimal reduction in contrast in the dominant eye, the rate of contrast progression throughout treatment, and whether therapy should continue once equal contrast is achieved.[50,51] The variability in amblyopia severity among individuals underscores the necessity for personalized determination of initial and ongoing contrast ratios for each amblyopic patient.[45] Additionally, the lack of a stereoacuity test that measures thresholds between 0 and 2000 arcsec has led to a decrease in the number of individuals with measurable stereoacuity at baseline, and the use of different stereoacuity tests across heterogeneous age groups may lead to non-comparable results.[46] Furthermore, there is concern about whether the improvements observed with binocular therapy are due to learning effects. However, studies evaluating the visual acuity of the dominant eye no significant increases, suggesting that improvements in the amblyopic eye are not likely to be a result of learning.[50,51,55,56,61,62,63,64]

To effectively deliver dichoptic-based binocular therapy, reach the maximum number of patients, and compete with monocular approaches, there is a pressing need for home-based treatment alternatives.[45] However, the most effective models in vision therapy are typically office-based, doctor-supervised, and tailored to individual patient goals. Moreover, inconsistencies between electronic records of adherence to binocular therapy and parent-reported adherence, uncertainties about actual use of the required equipment, and the possibility that the therapy may not be administered by the amblyopic patient themselves raise questions about the reliability of home-based treatments.[50,51,55,56]

In studies on binocular therapy involving participants with strabismic or mixed-type amblyopia, only those with a deviation angle of 4-5 PD or less following surgery or glasses were included. Researchers have emphasized that results should not be generalized to other forms of amblyopia, such as those with a greater deviation angle or deprivation amblyopia (e.g., congenital cataracts).[52,54]

Since the mechanism of action of dichoptic stimulation-based binocular treatments may involve anti-suppression pathways, concerns have been raised that these therapies could be associated with new-onset diplopia. However, diplopia has been rarely reported in these studies.[50,56]

Although interest in binocular approaches for amblyopia rehabilitation grows, the number of studies investigating the effect of dichoptic stimulation on the crowding phenomenon remains quite limited.[69,70] It is known that contrast sensitivity loss in amblyopia increases the crowding effect under monocular conditions. In perceptual learning-based amblyopia treatments, it has been observed that as monocular contrast sensitivity increases, the crowding effect decreases.[71] Early research has shown that crowding can occur dichoptically, but comparisons across studies are complicated by the selective nature of different types of stimuli (such as stimulus similarity, context, and attention).[72] A few pilot studies of binocular approaches have suggested that balancing the contrast gap between the eyes through dichoptic stimulation may reduce the crowding effect.[73] However, the lack of comprehensive research in this area hinders our understanding of how binocular approaches may alleviate

the crowding effect, thereby limiting their potential as effective interventions in visual rehabilitation.

Conclusion

Dichoptic-based binocular therapies present promising advances in the treatment of amblyopia by directly addressing binocular dysfunctions and promoting binocular vision. These approaches aim to reduce inhibitory interactions within the visual cortex, potentially improving stereoacuity and alleviating the crowding effect. Pilot studies have shown positive outcomes, but these findings remain unconfirmed by large-scale, multicenter randomized controlled trials. Key uncertainties persist regarding optimal contrast reduction, progression rates, and the duration of therapy once equal contrast is achieved. Additionally, the variability in amblyopia severity among patients highlights the need for personalized treatment protocols. While home-based treatment models could increase accessibility and patient reach, concerns about adherence and the reliability of self-administered therapy raise questions about their effectiveness. Furthermore, the potential for new-onset diplopia, though rare, remains a consideration due to the mechanisms of anti-suppression pathways involved. Despite these challenges, the development of dichoptic therapies holds significant promise for amblyopia treatment, particularly if future research addresses current limitations and further clarifies the mechanisms behind the crowding effect and its reduction.

Declarations

Authorship Contributions

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Review

Ab Interno Goniotomy/Goniectomy Techniques

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Abstract

Minimally invasive glaucoma surgeries (MIGS), such as Kahook Dual Blade (KDB), bent ab interno needle goniectomy (BANG), gonioscopy-assisted transluminal trabeculotomy (GATT), OMNI, Trabectome, Streamline, and TrabEx+, have significantly advanced the treatment of glaucoma by improving aqueous humor outflow and reducing intraocular pressure (IOP). These innovative procedures target the trabecular meshwork (TM) and Schlemm's canal, offering effective alternatives to more invasive filtration surgeries. By enhancing the natural drainage pathways, MIGS can achieve notable reductions in IOP and minimize the need for long-term glaucoma medications. Each device has a distinct mechanism of action. The KDB excises a strip of TM, while BANG uses a bent hypodermic needle for controlled goniectomy. GATT performs a 360-degree trabeculotomy using a microcatheter or Prolene (polypropylene) suture to open Schlemm's canal. OMNI combines canaloplasty and trabeculotomy in a single procedure. The Trabectome ablates TM tissue with electrical energy, whereas Streamline performs viscodilation to expand outflow channels. TrabEx+ facilitates goniectomy with integrated irrigation and aspiration. Clinical studies have shown these MIGS techniques to be both safe and effective, with fewer complications compared to traditional surgeries like trabeculectomy or tube shunt implantation. MIGS procedures are particularly appealing due to their reduced recovery time and lower risk profile. However, further research is essential to establish their long-term efficacy and durability. Continued advancements and comprehensive long-term studies will ensure that MIGS provide sustainable and reliable benefits for glaucoma patients, optimizing treatment strategies in clinical practice.

Keywords: Minimal invasive glaucoma surgery, goniotomy, goniectomy

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Introduction

Glaucoma is a leading cause of irreversible blindness worldwide, characterized by progressive optic neuropathy associated with elevated intraocular pressure (IOP). It is a multifactorial disease, and timely management of IOP remains the most effective strategy to prevent disease progression. Despite advancements in medical and laser therapies, many patients require surgical intervention to achieve adequate IOP control. Traditional glaucoma surgeries, such as trabeculectomy and tube shunts, have long been the standard options for managing advanced disease. While effective, these procedures are invasive, associated with significant risks such as hypotony, infection, bleb-related complications, and prolonged recovery periods.

To address these limitations, the past two decades have witnessed the emergence of minimally invasive glaucoma surgeries (MIGS), which aim to enhance aqueous humor outflow with minimal disruption to ocular structures. First introduced in the early 2000s, MIGS techniques have revolutionized glaucoma management by offering safer, less invasive alternatives to traditional surgeries. Unlike trabeculectomy, MIGS procedures are often performed via an ab interno approach, eliminating the need for conjunctival dissection and reducing the risk of postoperative complications. Additionally, MIGS techniques are associated with shorter operative times, quicker recovery,

and better preservation of conjunctival integrity, making them particularly advantageous for patients who may require future surgical interventions.

The necessity for MIGS stems from their ability to bridge the gap between medical therapy and more invasive surgical options. With an expanding range of devices and techniques, MIGS can be tailored to address specific anatomical and physiological challenges of glaucoma, offering versatility in treatment approaches. These procedures have demonstrated significant success in lowering IOP and reducing dependence on glaucoma medications, particularly in patients with mild to moderate glaucoma. Moreover, the ability to combine MIGS with cataract surgery has further broadened their applicability and appeal.

This review aims to provide an overview of MIGS techniques, highlighting their evolution, applications, and outcomes. By comparing different MIGS procedures, we seek to elucidate their roles in modern glaucoma management and their advantages over traditional surgical approaches.

Kahook Dual Blade Goniotomy

Technical Information

The Kahook Dual Blade (KDB; New World Medical) is an ophthalmic knife specifically designed for ab interno goniotomy. It functions by engaging, stretching, and removing a strip of diseased trabecular meshwork (TM) tissue in both pediatric and adult glaucoma patients.[1] This MIGS device was cleared by the United States Food and Drug Administration (FDA) in 2015 under a 510(k) class I exemption. The device features a unique design that facilitates precise tissue removal. Key elements include a distal 230-µm-wide footplate with a pointed tip for penetrating target tissue, a ramp for tissue elevation, and a pair of posteriorly integrated elevated parallel blades that stretch and excise TM tissue.[2,3] Literature consistently demonstrates that the KDB procedure significantly reduces IOP and dependence on glaucoma medications across a wide range of glaucoma types and severities, with a safety profile favorable to traditional incisional procedures.

Surgical Application

Excisional goniotomy with the KDB is performed under direct gonioscopic visualization. An intraoperative image of KDB goniotomy can be found in Figure 1A. The device is introduced into the anterior chamber via a temporal peripheral clear corneal incision, targeting the nasal TM. The pointed tip creates an opening, while the footplate seats against the anterior wall of Schlemm's canal. The device advances through the canal, lifting TM onto the ramp and directing it toward the dual blades, facilitating clean tissue excision. This process maximizes the width of the excised TM strip while minimizing collateral damage to surrounding structures.[4]

Three excisional approaches are available, as described by Dorairaj et al.[2]: 1) *Mark and meet*: The device creates an initial opening at one end, is removed, re-enters the TM at the opposite end, and excises the tissue strip between the two points. 2) *Outside-in*: The device creates an incision at one end and cuts to the midpoint, then makes a connecting cut from the opposite end for complete strip excision. 3) *Inside-out*: The device engages the midpoint of the excision, moves to one end, rotates 180 degrees, and returns to excise the strip in two halves or leaves them in place, based on surgeon preference.

Indications

KDB is indicated for 1) *Open-angle glaucoma (OAG)*: As a standalone procedure or in combination with phacoemulsification, addressing mild to severe disease, 2) *Angle-closure glaucoma (ACG)*: Combined with goniosynechialysis (GSL) to manage peripheral anterior synechiae (PAS) and reduce IOP.

Literature Review

KDB excisional goniotomy can be performed as a standalone procedure or in combination with phacoemulsification in the treatment of OAG and across the spectrum of disease severity. In a multicenter retrospective analysis, ElMallah et al.[5] evaluated the safety and efficacy of standalone KDB goniotomy in a sample of 42 eyes with predominantly mild to severe primary open-angle glaucoma (POAG; 85.7%) and reported mean percentage reductions from baseline in IOP (-27.7%; -19.3%) and glaucoma medications (-32.6%; -12.5%) at 6 and 12 months, respectively, with 40.5% of eyes experiencing reduction by >1 IOP-lowering medications at 12 months. Dorairaj et al.[6] evaluated clinical outcomes of KDB goniotomy combined with phacoemulsification in a prospective, multicenter case series of 52 eyes. The authors found significant percentage reductions in IOP (-26.2%) and glaucoma medications (-50.0%) by month

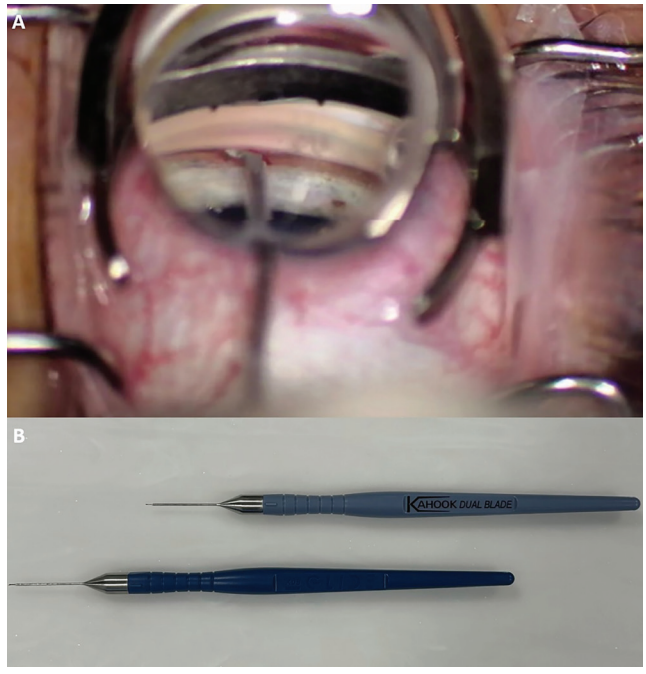

Figure 1. A) Intraoperative image of the Kahook Dual Blade goniotomy procedure; B) Image of the first-generation Kahook Dual Blade model (top) and the second-generation Kahook Dual Blade Glide® model (bottom)

12, with an IOP reduction of >20% from baseline in 57.7% of eyes and reduction in glaucoma medication burden by >1 medications in 63.5% of eyes. Reports have also compared the outcomes of standalone KDB goniotomy to phacoemulsification with KDB goniotomy. In a single-center retrospective report of 90 patients with mild to severe POAG or pseudoexfoliative glaucoma (PEXG), Barkander et al.[7] found KDB goniotomy to produce significant percentage reductions in IOP (-39.5%; -37.3%) and number of glaucoma medications (-11.4%; -30.3%) at 24 months when performed as a standalone procedure and when combined with phacoemulsification, respectively. The authors noted a lower rate of postoperative hyphema (4% vs. 26%; p=0.008) and lower risk of subsequent glaucoma surgery (p=0.026) in the combined group, suggesting additional benefits of the KDB procedure when performed in combination with phacoemulsification.[7] The follow-up time of most KDB studies in the current literature ranges from 6 to 24 months, but two studies have found the procedure to exhibit excellent reductions in IOP (by 24.7-39.0%) and glaucoma medication burden (by 33.3-50.0%) at 36 months when combined with phacoemulsification in eyes with OAG.[8,9] Additionally, long-term (60-month) success has also been demonstrated in eyes with mild to moderate OAG on >1 IOP-lowering medications at baseline, regardless of phacoemulsification status.[10]

While KDB goniotomy is indicated for the treatment of OAG and ocular hypertension, success has been demonstrated when treating ACG. Across multiple retrospective studies of a cohort of 42 eyes with ACG, Dorairaj et al.[11,12,13] showed that KDB-assisted GSL and excisional goniotomy with phacoemulsification induced significant mean percentage reductions in both IOP (-48.8%; -47.2%; -47.1%) and glaucoma medications (-91.7%; -91.7%; -76%) at 6, 12, and 24 months, respectively. By 24 months, no subsequent glaucoma surgeries were required in the study cohort and all eyes had achieved >20% IOP reduction from baseline, with 69% becoming medication-free. The authors suggested that the excellent safety and efficacy seen with this combined procedure were due in part to its ability to address PAS present, which cannot be accomplished with phacoemulsification alone. Al Habash and Albuainain[14] prospectively analyzed outcomes of this combined procedure in 11 eyes with ACG and of KDB goniotomy with phacoemulsification performed in 37 eyes with OAG. At 24 months, significant percentage reductions in mean IOP (-31.4%; -32.1%) and glaucoma medications (-56.3%; -62.7%) were observed in eyes with ACG and OAG, respectively, with no secondary surgical reinterventions required in either group.

A recent study compared the outcomes of standalone KDB goniotomy with other MIGS techniques. A single-center retrospective study by Boopathiraj et al.[15] compared KDB goniotomy to the Xen gel stent in moderate to severe OAG. At 36 months, KDB goniotomy achieved a 23.5% reduction in IOP (from 23.2±6.0 mmHg to 16.6±5.4 mmHg) and a 30.8% reduction in medication burden (from 2.2±1.4 to 1.1±0.7). These outcomes were comparable to Xen, which reduced IOP by 22.1% and medication burden by 25.6%. However, the KDB group showed fewer surgical reinterventions (11.5% vs. 42.2% in the Xen group), suggesting that KDB may have a lower long-term complication rate and a reduced need for additional surgeries.[15]

Complications

Reported complications include 1) *Transient hyphema*: Common but resolves with conservative treatment. 2) *IOP spikes*: Observed postoperatively but manageable. 3) *Hypotony*: Cyclodialysis cleft, though rare (approximately 1.2% of cases), can lead to significant complications such as hypotony maculopathy. A recent case study demonstrated that minimally invasive direct internal cyclopexy (MIDIC) can effectively address cyclodialysis clefts associated with KDB goniotomy.[16] MIDIC avoids conjunctival or scleral incisions, making it an appropriate option for patients who may require future trabeculectomy. This technique has shown success in resolving hypotony maculopathy and restoring visual acuity, as well as maintaining long-term IOP control.[16]

Patients undergoing KDB should be monitored for signs of persistent hypotony, such as choroidal detachment and hypotony maculopathy. Management options include conservative treatment with cycloplegics or surgical repair using cyclopexy for refractory cases. Recommendations include early detection and tailored intervention based on the severity of complications.

Future Advancements

The second-generation KDB device, KDB Glide®, received FDA approval in 2020. An image of both KDB models can be found in Figure 1B. Enhancements include beveled edges and rounded footplate corners for smoother passage through Schlemm's canal. Preclinical data suggest superior TM excision capabilities compared to other devices like TrabEx™, 360° trabeculectomy with Prolene (polypropylene) sutures, and iAccess® Trabecular Trephine. Further studies are anticipated to confirm these findings.[17,18]

OMNI Surgical System

Technical Information

The OMNI surgical system (Sight Sciences Inc., Menlo Park, CA, USA) combines canaloplasty and trabeculotomy through a single corneal incision, addressing multiple points of resistance in the aqueous humor outflow pathway. The device, approved by the FDA in December 2017 and launched in March 2018, includes a disposable handpiece with a cannula tip for delivering a microcatheter, an advancement wheel for microcatheter deployment and retraction, and a port for loading an ophthalmic viscosurgical device (Figure 2A). This system allows for microcatheterization and viscodilation of Schlemm's canal followed by trabeculotomy, making it a versatile option for treating mild to moderate glaucoma.[19]

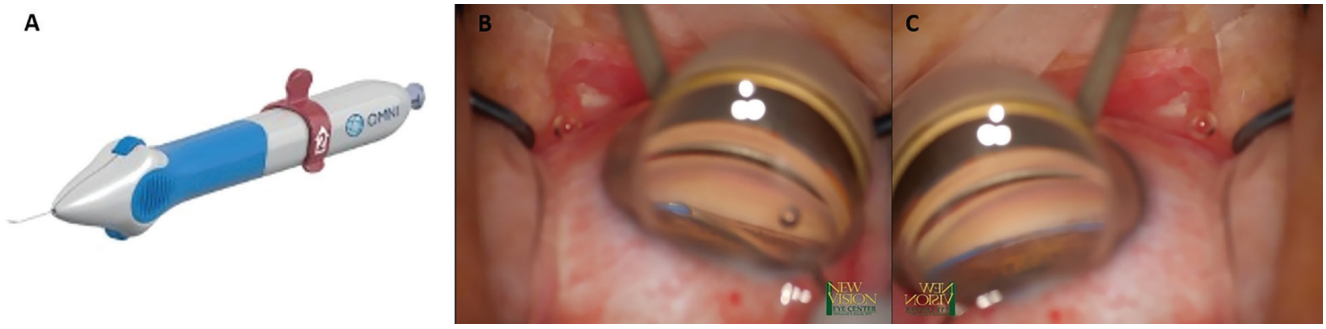

Figure 2. A) OMNI surgical system; B) OMNI device introducing the suture into the Schlemm's canal; C) Appearance of the suture in the canal

Surgical Application

The surgical procedure begins with a temporal corneal incision. The microcatheter is inserted into Schlemm's canal for viscodilation (Figure 2B), targeting resistance in both proximal (TM and Schlemm's canal inner wall) and distal (collector channels) portions of the outflow pathway. Trabeculotomy follows canaloplasty, addressing TM resistance and enhancing aqueous outflow (Figure 2C). The OMNI device avoids scleral dissection or conjunctival disruption and leaves no implant in the eye, which contributes to its minimally invasive profile.

Indications

The OMNI device is indicated for mild to moderate glaucoma and can be used as a standalone procedure or in combination with cataract surgery. It is particularly suited for pseudophakic patients and in cases where enhancing outflow at multiple levels is critical.

Literature Review

Outflow resistance arises from various parts of the physiological outflow pathway. In primates, up to 75% of this resistance is attributed to the TM, specifically the juxtacanalicular tissue.[20,21] The inner wall of Schlemm's canal, on the other hand, contributes 10% or less to the resistance in normal eyes.[22] Studies suggest that in eyes with POAG, the cross-sectional area of Schlemm's canal is on average 54% lower, and mean outflow facility is 55% lower compared to normal eyes. These findings suggest atrophy of Schlemm's canal as a potential source of resistance.[23] Another point of resistance is observed at the collector channel ostia, as demonstrated in bovine eyes, where increased IOP led to the herniation of the inner wall and juxtacanalicular tissue into the ostia of the collector channels.[24]

Combining canaloplasty and trabeculotomy addresses both proximal (TM and inner wall of Schlemm's canal) and distal (Schlemm's canal and collector channels) points of conventional outflow resistance.[25] The canaloplasty part of the procedure opens the distal outflow pathway, including the collector channel ostia, and subsequent trabeculotomy removes the resistance due to the TM. Using the OMNI system also has the advantage of avoiding scleral dissection, sparing the conjunctiva, and not leaving an implant inside the eye.[26] This provides an efficient and safe MIGS option for glaucoma patients.

The ROMEO study is a retrospective multicenter study that evaluated the efficacy and safety profiles of the OMNI system in mild to moderate glaucoma (with IOP ≤36 mmHg on ≤4 medications).[26,27,28] In pseudophakic patients who underwent standalone canaloplasty and trabeculotomy, the rate of success (defined as 20% reduction in IOP from baseline or IOP between 6 and 18 mmHg on the same or fewer medications without glaucoma reoperation) was 72.9% at 1 year. Patients with high baseline IOP (>18 mmHg) showed a statistically significant reduction of IOP from 21.8±3.3 mmHg on 1.7±1.3 medications at baseline to 15.6±2.4 mmHg on 1.2±1.3 medications at 1 year. However, in patients with low baseline IOP (≤18 mmHg), IOP reduced from 15.4±2.0 mmHg preoperatively to 13.9±3.5 at postoperative month 12 (p=0.24), with a decrease in medication burden from 2.0±1.3 at baseline to 1.3±1.3 at month 12 (p=0.003). The percentages of patients who used the same number of medications or fewer than at baseline were 91.7% and 89.5% among patients with baseline IOP >18 mmHg and ≤18 mmHg, respectively. No difference in IOP reduction based on the extent of canaloplasty or trabeculotomy was noted. Most of the reported complications in that study were mild and transient. Mild postoperative inflammation was noted in 12.5% of the eyes, 10.5% of the patients required additional glaucoma procedures, IOP spikes occurred in 5% of the eyes, and corneal edema, clinically significant hyphema (layered and >1 mm and/or persisting for 1 week or more and/or required a secondary intervention), and decreased visual acuity were reported in 4.2% of the eyes.[26]

After 2 years of follow-up, the patients with high baseline IOP who underwent combined canaloplasty/trabeculotomy with cataract surgery had an IOP reduction from a preoperative mean of 21.7 mmHg on 2.2 medications to 15.6 mmHg on 1.4 medications.[27] On the other hand, standalone canaloplasty/trabeculotomy resulted in an IOP reduction from 22.1 mmHg on 1.9 medications to 14.7 mmHg on 1.64 medications. The overall success rate of the cohort was 75% at 2 years, compared to 80.2% at 1 year, which suggests the persistence of the IOP-lowering effect of the canaloplasty/trabeculotomy surgery in the majority of patients. Around one-third of patients were medication-free at 2 years, compared to 12% at baseline.[28]

In the prospective GEMINI study, 360° canaloplasty and 180° trabeculotomy performed with the OMNI surgical system at the time of phacoemulsification resulted in a reduction of unmedicated diurnal IOP from 23.8±3.1 mmHg at baseline to 15.6±4.0 at month 12, with 84.2% of eyes achieving IOP reductions of ≥20% from baseline. Similarly, the mean IOP reduction was 6.2 mmHg at 24 months and 6.9 mmHg at 36 months, with the proportion of eyes with ≥20% reduction in IOP being 77% and 78% at 24 and 36 months, respectively. Moreover, significantly fewer medications were reported at months 12, 24, and 36 (0.4±0.9, 0.4±0.9, and 0.3±0.6, respectively, vs. 1.8±0.9 at baseline). Seventy-four percent of the enrolled patients were medication-free at 36 months. Transient hyphema (>1 mm) was the most commonly reported adverse event in the study, occurring in 6% of the treated eyes, and none of the patients experienced decreased visual acuity due to the procedure. One patient required glaucoma reoperation to control IOP at month 30.[29,30] One of the important risk factors for glaucoma progression is IOP fluctuations.[31] In the post-hoc analysis of the diurnal IOP from the GEMINI study at three different time points (9 am, 12 pm, and 4 pm), it was found that after treatment, the peak IOP was around 8 mmHg lower and IOP fluctuations were 1 mmHg lower than baseline. Additionally, postoperative IOP measurements at each diurnal time point were statistically significantly lower than the corresponding time points preoperatively.[32]

The OMNI device can be used in conjunction with other MIGS to enhance IOP lowering and decrease the number of glaucoma medications.[33] In a retrospective study by Dickinson et al.[34] the success rates (meeting target IOP without medications or further surgical intervention) were 44.5% in patients who underwent phacoemulsification with the Hydrus microstent alone versus 70.0% in the phacoemulsification-Hydrus-canaloplasty (using the OMNI device) group at 6 months (p=0.04). The percentage of medication reduction was 67% in the microstent group alone compared to 88% in the microstent-canaloplasty group (p<0.05). None of the patients in either group required glaucoma reoperation to control IOP. The authors postulated that the increased success rate of the microstent-canaloplasty group was likely due to the downstream dilating effect of canaloplasty, which reverses the herniated tissue in the collector channels and possibly provides a larger outflow area distal to the Hydrus implant. Additionally, the viscodilation of Schlemm's canal might make the correct positioning of the Hydrus implant in the canal easier. Similarly, in patients with inadequate IOP control after iStent (Glaukos, San Clemente, CA, USA) implantation, canaloplasty and trabeculotomy using the OMNI device resulted in a 23% reduction of IOP and an 18% decrease in medication burden.[35] The additive IOP- and medication-lowering effects of combined or sequential MIGS procedures should be weighed against the cost of these procedures.[36,37]

In our experience, we prefer to perform canaloplasty/trabeculotomy after completing cataract surgery in combined cases using a temporal approach, as most of the active collector channels are thought to be located inferiorly and nasally.[38] Additionally, we tend to perform 360° canaloplasty with 180° trabeculotomy (instead of 360° trabeculotomy) since the success rates of 360° and 180° trabeculotomy were comparable.

Complications

The most commonly reported complications with OMNI include mild and transient postoperative inflammation (12.5%), IOP spikes (5%), and hyphema (>1 mm), noted in 4.2% of cases. These adverse events typically resolve with conservative management. Performing 360° canaloplasty with 180° trabeculotomy instead of full 360° trabeculotomy reduces the likelihood of complications such as hyphema while maintaining efficacy. Rare cases of corneal edema and transient vision changes have also been reported.[39,40]

Gonioscopy-Assisted Transluminal Trabeculotomy

Technical Information

Gonioscopy-assisted transluminal trabeculotomy (GATT) is a MIGS introduced in 2014.[41] It involves the ab interno cannulation of Schlemm's canal through a single or dual corneal incision, providing a less invasive alternative to traditional filtering surgeries. The procedure directly addresses TM dysfunction and the adjacent inner wall of Schlemm's canal, enhancing aqueous outflow and reducing IOP. GATT has demonstrated efficacy across a variety of glaucoma types, including primary and secondary OAG, ACG, pediatric, and juvenile glaucoma, offering a versatile option for different patient populations.

Surgical Application

GATT is performed via an ab interno approach, minimizing surgical trauma and postoperative complications. Following standard sterile preparation, a paracentesis track is created as an entry site. Viscoelastic is injected to maintain the depth of the anterior chamber. An illuminated microcatheter is introduced into the anterior chamber, positioned at the nasal angle, and a goniotomy is performed. The microcatheter is carefully advanced circumferentially through Schlemm's canal using microsurgical forceps to ensure complete traversal. Once the microcatheter completes its passage, a 360-degree trabeculotomy is performed. Residual viscoelastic and blood are cleared using a bimanual irrigation-aspiration system. Postoperative care typically includes corticosteroid and antibiotic drops.

GATT is most suitable for ACG patients with manageable PAS. Combining GATT with GSL is key to opening angles with PAS and allowing access to Schlemm's canal. The surgical technique for ACG differs from standard GATT by incorporating GSL using a blunt spatula, which ensures visualization of the TM and facilitates canal cannulation.

Variations in Technique and Instrumentation

Prolene GATT: A novel adaptation of the GATT technique involves thermally marking and blunting the tip of a 5-0

Prolene® (polypropylene) suture for enhanced visualization during the procedure (Figure 3). This modification maintains similar safety to the use of an illuminated microcatheter but is more cost-effective. This approach allows for good visualization of the suture tip during the circumnavigation of Schlemm's canal, contributing to the ease and effectiveness of the surgery.[42,43]

Prolene GATT with Marker Suture: This method utilizes a Prolene® suture for canalization and an additional Vicryl® (polyglactin 910) suture as a marker, enabling the surgeon to estimate the degree of Schlemm's canal cannulated. The technique proved to be safe and effective, even in partial canalizations, offering a low-cost alternative to illuminated microcatheters. The use of the marker suture aids in tracking the progress and success of the procedure.[44]

Trabectome-initiated GATT (TIGATT): The TIGATT procedure, a modification of GATT, replaces the initial goniotomy incision with an ab interno trabeculectomy ablation using the trabectome. This approach showed promising results in a preliminary case series, offering a feasible alternative with comparable safety and efficacy to traditional GATT and trabectome surgeries.[45] The authors proposed that conducting TM ablation by trabectome could be advantageous, as the initial incision of the TM may result in bleeding and obstruct the surgeon's field of vision. This approach offers a clearer view of Schlemm's canal lumen and its outer wall, while also reducing the likelihood of needing to reapproximate the wound in the trabectome-treated portion of the angle. Patients undergoing TIGATT experienced significant IOP reduction and a decrease in medication use, highlighting its potential effectiveness in glaucoma management.[45]

Hemi-GATT: Hemi-GATT involves treating only 180 degrees of the Schlemm's canal, compared to the 360 degrees in traditional GATT. This approach is adaptable to anatomically difficult cannulations and may have an improved safety profile. It allows for future interventions if necessary, providing a stepwise approach to glaucoma management. Evidence suggests that treating fewer degrees might not compromise the efficacy of the procedure.[46]

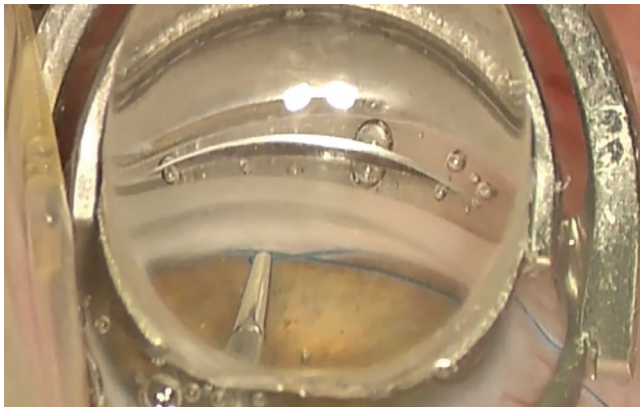

Figure 3. Prolene (polypropylene) gonioscopy-assisted transluminal trabeculotomy. The suture is in the canal and the distal tip is grasped

Indications

GATT is indicated for a wide range of glaucoma types, including primary and secondary OAG, ACG, pigmentary glaucoma, pediatric glaucoma, and glaucoma refractory to conventional medical treatments. Its minimally invasive nature and ability to avoid conjunctival disruption make it a preferred option for patients who may require future surgeries.

Literature Review

The effectiveness of GATT has been demonstrated in several studies. Dar et al.[47] reported a mean IOP reduction from 19.3 mmHg to 13.2 mmHg in advanced OAG, achieving a 91% success rate for IOP ≤18 mmHg at 6 months. Faria et al.[48] observed a significant decrease from 24.85 mmHg to 12.58 mmHg at 24 months in cases resistant to medical therapy, with a success rate of 64.9% for standalone GATT procedures. Liu et al.[49] documented a 45% IOP reduction at 4 years across various OAG types, though with a cumulative failure rate of 53.9%.

GATT's efficacy extends to PEXG, with Aktas et al.[50] reporting a higher success rate in PEXG (97.6%) compared to POAG (86.8%) in the first year. Grover et al.[51] demonstrated an average IOP reduction of 9.2 mmHg in POAG and 14.1 mmHg in secondary OAG at 24 months, highlighting its broader applicability. Furthermore, Rahmatnejad et al.[52] reported an overall success rate of 63.0% at 12 months, with IOP reductions from 26.1 mmHg to 14.6 mmHg.

Beyond primary glaucomas, GATT has shown promise in other types. Parikh et al.[53] documented an IOP reduction from 37.8 mmHg to 12.2 mmHg at 12 months in uveitic glaucoma, with an 81% success rate and a reduction in glaucoma medications from 4.6 to 2.2. Belkin et al.[54] observed a decrease in IOP from 31.4 mmHg to 13.8 mmHg in uveitic glaucoma over 1 year. Aktas et al.[55] reported an IOP reduction from 31.0 mmHg to 15.6 mmHg in vitrectomized patients, with a success rate of 93.3%. Similarly, Smith et al.[56] demonstrated significant decreases in IOP and medication dependency in eyes with prior keratoplasty. Hopen et al.[57] emphasized the effectiveness of GATT in pediatric patients with steroid-induced glaucoma, achieving IOP reduction through 360° GATT.

GATT has proven effective in ACG, with Fontana et al.[58] reporting a reduction from 30.27 mmHg to 15.20 mmHg at 1 year and a 93-100% success rate at 6 and 12 months. Sharkawi et al.[59] documented reductions from 21.4 mmHg to 12.1 mmHg at 24 months, with a 78% success rate. Additionally, Chira-Adisai et al.[60] found IOP reductions from 21.8 mmHg to 15.1 mmHg over 2 years in ACG.

In primary congenital glaucoma (PCG), Aktas et al.[61] noted significant IOP reductions (from preoperative mean of 31 mmHg to 17.8 mmHg) and a decrease in medication count, while Elhusseiny et al.[62] reported a reduction in mean IOP from 25.7 mmHg to 11.5 mmHg. Grover et al.[63] also observed a mean

decrease in IOP of 12.5 mmHg in PCG and juvenile glaucoma. Haidu and Aktas[64] found postoperative IOPs of 10 and 11 mmHg at 6 months in a child with Klippel-Trenaunay-Weber syndrome. These outcomes collectively suggest that GATT is a versatile and effective surgical option across various glaucoma types.

Complications

The most commonly reported complication of GATT is transient hyphema. Naftali Ben Haim et al.[65] noted IOP spikes in 24% of 217 eyes, often associated with medication withdrawal. The average duration of IOP spikes was 4.9 days, and these spikes were linked to GATT failure. Gunay et al.[66] reported PAS formation in 38.3% of nasal quadrants and 25.3% of temporal quadrants at 6 months post-surgery, which could limit long-term outcomes. Rao et al.[67] identified causes of IOP spikes, including retained viscoelastic and uncontrolled hypertension, often associated with PAS in multiple quadrants or fibrotic TM tissue. Another rare but severe complication is the wipe-out phenomenon, as reported in patients undergoing GATT combined with phacoemulsification.[68] Wipe-out is characterized by sudden postoperative vision loss, central visual field deterioration, and decreased visual acuity, often seen in patients with advanced glaucoma. This underscores the importance of cautious patient selection, particularly for those with advanced optic nerve damage. Other rare complications include persistent mydriasis, delayed-onset hyphema, panscleritis, cystoid macular edema, intracapsular hematoma, Descemet membrane separation, and transient myopia due to supraciliary effusion.[69,70,71,72,73,74,75]

Bent Ab interno Needle Goniectomy

Technical Information

Bent ab interno needle goniectomy (BANG) is a cost-effective alternative to commercially available TM-based glaucoma procedures. This technique employs a bent 25-gauge hypodermic needle to create a goniotome, forming two cutting edges for TM removal. Unlike commercialized devices with a fixed 90-degree bend, the needle bevel can be adjusted to a 75-degree angle, facilitating smoother travel within Schlemm's canal and reducing resistance encountered along curved canalicular structures (Figure 4A). Histological studies confirm that the excised tissue is indeed TM, demonstrating the procedure's targeted effectiveness.

Surgical Application

The BANG procedure involves creating a goniotome by bending the distal 1 mm of a sterile 25-gauge hypodermic needle toward the bevel using a needle driver. For standalone procedures, a 1.4-mm incision suffices, while a temporal incision is utilized when combined with cataract surgery. The bent needle is used to excise the nasal TM, effectively lowering resistance and facilitating aqueous outflow (Figure 4B). The shorter needle design may limit access to all angles from a temporal approach, highlighting the importance of precise adjustments for surgical efficacy.

Indications

BANG is indicated for patients with OAG seeking a low-cost alternative to other MIGS. It can be performed as a standalone procedure or combined with cataract surgery, making it a versatile option for various patient needs.

Literature Review

Initial data on the efficacy of the BANG procedure is promising but limited in scope. Shute et al.[76] analyzed outcomes from 41 eyes of 23 OAG patients undergoing BANG, either as a standalone procedure (2 eyes) or combined with phacoemulsification (39 eyes). The average preoperative IOP was 17.4±4.1 mmHg on 1.1±1.4 topical glaucoma medications. At 6 months postoperatively, the mean IOP decreased to 13.3±2.5 mmHg, with 73% of patients achieving ≥20% IOP reduction (p=0.01). Additionally, 73% of patients required at least one fewer medication, and 41% achieved IOP ≤12 mmHg.

Despite these promising results, the absence of comparative studies among goniotomy devices and limited long-term data highlights the need for further research. Current efforts include multicenter, longitudinal studies aimed at assessing the long-term efficacy and safety of the procedure.

Complications

The BANG procedure shares a complication profile similar to other TM-based surgeries, although specific reports are sparse due to the limited volume of published data. Potential complications may include transient hyphema, IOP spikes, and mild postoperative inflammation, consistent with findings in similar goniotomy techniques. The straightforward nature of the BANG technique and the use of readily available materials suggest a favorable safety profile, but more data are needed to confirm this assumption.

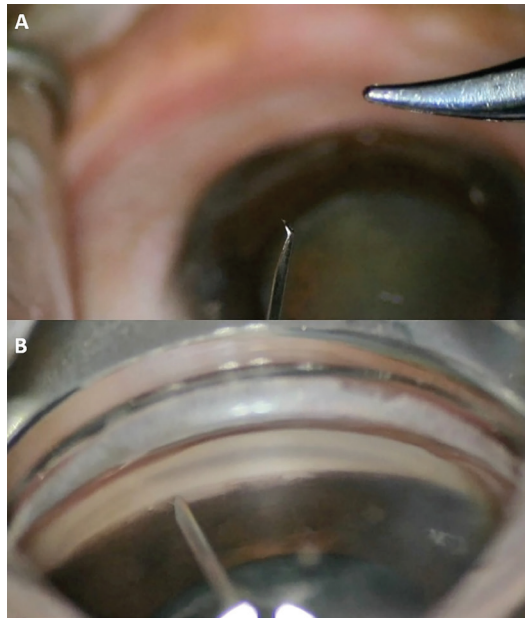

Figure 4. A) The tip of a 25-gauge hypodermic needle is bent; B) The needle tip is inserted along Schlemm's canal for goniectomy

Trabectome

Technical Information

The Trabectome, developed by NeoMedix Corporation, is a surgical device approved by the FDA in 2004 for the treatment of glaucoma. It is designed to enhance aqueous humor outflow by ablating a strip of the TM and the inner wall of Schlemm's canal using high-frequency electrical energy (Figure 5).[6,77] This technique minimizes tissue damage while facilitating direct outflow of aqueous humor into Schlemm's canal, reducing IOP. The procedure's minimally invasive nature results in less postoperative inflammation and scarring compared to traditional glaucoma surgeries. However, the high-frequency ablation method is associated with a higher risk of intraoperative blood reflux, a temporary complication that can obscure the surgical field and potentially prolong surgery duration. Despite this, the Trabectome has demonstrated consistent efficacy in reducing IOP and dependence on glaucoma medications.

Surgical Application

The Tabectome procedure begins with the creation of a small corneal incision. The device is inserted under gonioscopic visualization to access the TM. High-frequency electrical energy is used to ablate a portion of the TM and the inner wall of Schlemm's canal, creating a pathway for improved aqueous humor outflow. Careful technique is required to manage potential blood reflux from Schlemm's canal, which typically resolves spontaneously and does not significantly impact postoperative outcomes. Postoperatively, anti-inflammatory and antibiotic medications are prescribed to minimize inflammation and infection risk.

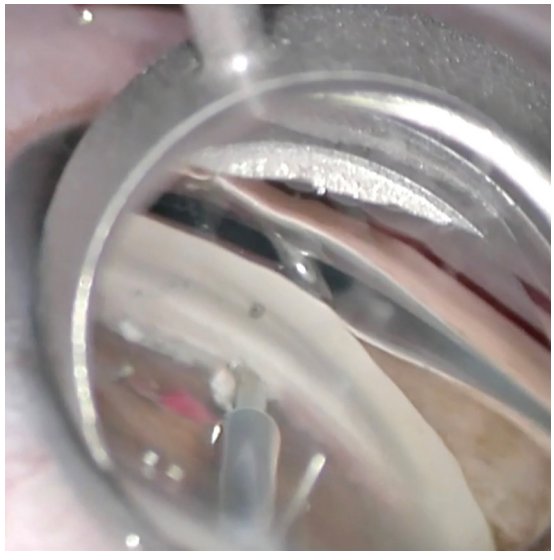

Figure 5. Tip of the Trabectome device, ablating and removing the trabecular meshwork strip

Indications

The Trabectome is indicated for patients with OAG, particularly those seeking a minimally invasive procedure to improve aqueous outflow and reduce IOP. It can be performed as a standalone procedure or in combination with cataract surgery, offering flexibility for a range of patient needs.

Literature Review

The Trabectome has been extensively studied, with results consistently demonstrating its efficacy and safety in managing glaucoma. Studies have shown that the Trabectome achieves significant reductions in IOP, with average decreases ranging from 20% to 40% depending on the patient population and follow-up duration. For example, Mosaed et al.[78] reported an IOP reduction from 24.6 mmHg to 16.4 mmHg at 12 months in patients with POAG, with a simultaneous reduction in glaucoma medications. In a multicenter study, Kaplowitz et al.[79] reported that the Trabectome lowered IOP by approximately 31% to a final IOP near 15 mmHg while reducing the number of medications by less than one, with a low rate of serious complications. When combined with phacoemulsification, the Trabectome has shown additive effects in IOP reduction. Minckler et al.[80] reported a decrease from 21.1 mmHg to 15.6 mmHg at 12 months in patients undergoing combined Trabectome-phacoemulsification procedures. Although the Trabectome is generally effective, its success may vary based on patient factors such as age, disease severity, and baseline IOP. Additionally, while the device is effective in reducing IOP, its outcomes may be less predictable in secondary glaucomas compared to POAG.

Complications

The most commonly reported complication of Trabectome surgery is intraoperative blood reflux from Schlemm's canal, which occurs due to the direct connection created between the anterior chamber and the canal. Although this reflux can obscure the surgical field, it typically resolves spontaneously without impacting long-term outcomes. Other complications include transient hyphema, postoperative IOP spikes, and mild inflammation, all of which are generally self-limiting and manageable with standard postoperative care.

Other Procedures

TrabEx+ surgery, an ab interno trabeculectomy, offers a minimally invasive approach to managing glaucoma by removing the TM to enhance aqueous humor outflow and IOP. Utilizing a serrated dual-bladed device with integrated irrigation and aspiration ports, TrabEx+ maintains the anterior chamber stability during surgery, eliminating the need for ocular viscoelastic devices. A recent study reported significant outcomes with TrabEx+, showing an average IOP reduction from 31.3 mmHg preoperatively to 20.9 mmHg postoperatively over a follow-up period of up to 38 months. Additionally, the study found that 73% of eyes achieved over a 20% reduction in IOP

without requiring additional surgeries or increased medication, highlighting the procedure's efficacy.[81]

TrabEx+ surgery was performed as a standalone procedure or combined with cataract surgery, with both methods showing substantial IOP reductions and a decrease in the need for glaucoma medications. The incorporation of irrigation and aspiration ports into the TrabEx+ device stabilizes the anterior chamber during surgery, improving surgical precision and reducing complications. Despite these benefits, some patients experienced postoperative complications, such as hyphema and transient IOP spikes, which were managed medically in most cases. Overall, the early results of TrabEx+ surgery demonstrate its potential as a safe and effective option for reducing IOP in glaucoma patients, with the added benefit of minimizing the need for postoperative glaucoma medications. Gosling et al.[81] underscored the need for further long-term research to fully establish the procedure's efficacy and safety profile over extended follow-up periods. These findings align with the growing trend of utilizing MIGS to provide safer and more effective alternatives to traditional filtration surgeries.

The Streamline® (New World Medical) is a MIGS system aimed at enhancing aqueous humor outflow by targeting Schlemm's canal. Unlike trabeculotomy, it employs canaloplasty, involving cannulation and viscodilation of Schlemm's canal. The device features a disposable stainless-steel cutting cannula within a polymer sleeve, introduced through a corneal incision. Upon retraction, it creates a 150-µm goniotomy and injects viscoelastic material to dilate the canal and collector channels, reducing IOP. FDA-approved in 2021, initial trials show promising IOP reduction and medication decrease at 6 months.[82] Further studies are needed to assess its long-term efficacy and safety.

Conclusion

This review of various MIGS procedures highlights advancements in techniques aimed at reducing IOP by enhancing aqueous humor outflow. Devices like the TrabEx+, Streamline, and KDB demonstrate significant IOP reductions and decreased medication dependence with favorable safety profiles. These MIGS procedures offer less invasive alternatives to traditional filtration surgeries and show promising short-term results. However, further long-term studies are needed to fully establish their efficacy and safety, ensuring sustainable benefits for glaucoma patients. Table 1 provides a comparative summary of various ab interno goniectomy techniques, highlighting their pressure-lowering effects, strengths, weaknesses, and recommended clinical applications.

Additionally, the success of angle surgeries heavily relies on the surgeon's proficiency in gonioscopy, which is critical for proper angle assessment, surgical planning, and intraoperative visualization. Gonioscopy training should be emphasized as a cornerstone in the skill set of ophthalmic surgeons performing angle surgeries. Enhanced gonioscopy proficiency can improve surgical outcomes, reduce complications, and expand the accessibility of MIGS procedures by increasing surgeon confidence and competence.

Table 1. Summary of ab interno goniectomy techniques

Technique	Pressure-lowering effect	Strengths	Weaknesses	Recommended for
GATT	30-50% reduction	Minimally invasive; effective in various glaucomas	Requires skill; hyphema risk	Mild to advanced OAG
Trabectome	20-40% reduction	Minimal inflammation; combines with phaco	Blood reflux; less predictable in PEXG	Early to moderate OAG
BANG	Comparable to marketed devices	Cost-effective; simple setup	Limited data; potential for IOP spikes	Mild to moderate OAG, resource-limited settings
OMNI	20-30% reduction	Targets proximal and distal resistance	Device cost; mild transient inflammation	Mild to moderate glaucoma
KDB	25-40% reduction	Safe and effective; combines with cataract surgery	Hyphema; less efficacy in advanced stages	Mild to moderate glaucoma

GATT: Gonioscopy-assisted transluminal trabeculotomy, BANG: Bent ab interno needle goniectomy, KDB: Kahook Dual Blade, PEXG, Pseudoexfoliative glaucoma, IOP: Intraocular pressure, OAG: Open-angle glaucoma

Declarations

Authorship Contributions

Surgical and Medical Practices: Z.A., S.D., M.S., I.W., A.S., M.K., Concept: Z.A., A.Y.Ü., Design: Z.A., Data Collection or Processing: Z.A., S.D., M.S., A.Y.Ü., I.W., A.S., M.K., Analysis or Interpretation: Z.A., S.D., M.S., A.Y.Ü., I.W., A.S., M.K., Literature Search: Z.A., S.D., M.S., A.Y.Ü., I.W., A.S., M.K., Writing: Z.A., S.D., M.S., A.Y.Ü., I.W., A.S., M.K.

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A Promising Outcome of the Augmented Modified Hummelsheim Procedure in a Challenging Case of Inferior Rectus Hypoplasia

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Keywords

Vertical deviation, inferior rectus hypoplasia, augmented modified Hummelsheim procedure, case report

Dear Editor,

Inferior rectus (IR) hypoplasia/aplasia is a rare abnormality. In Asia, cumulative data from the Japanese population from 1930-2009 recorded only 16 cases of IR aplasia.[1] This condition presents with various clinical signs, including abnormal head posture (AHP) with head tilt, incomitant hypertropia, limitation of infraduction, incyclotorsion on retinal imaging, and a forced duction test showing complete laxity for upward deviation and variable tightness for downward deviation. The pathogenesis is believed to result from either an aberrant insertion or a failure in the condensation of the common inferior mesoderm complex.[2] Misdiagnosis is common in IR hypoplasia due to its similarity to other more prevalent causes of IR underaction. These include disorders affecting the oculomotor nucleus, nerve, myoneural junction, or extraocular muscles (e.g., congenital anomalous bands).

Orbital imaging, such as computed tomography or magnetic resonance imaging (MRI), is the definitive non-invasive diagnostic modality. However, surgery remains the gold standard for both invasive diagnosis and treatment of IR hypoplasia.[3] The main goal of surgical treatment is to achieve ocular alignment in primary position, followed by improving ocular movement and addressing cosmetic concerns. The choice of surgical approach depends on the degree of ocular deviation, ocular motility limitation, and severity of muscle dysgenesis. With various surgical techniques available, surgeons must adapt and select the most suitable technique based on intraoperative findings.[4] In this case report, we present the successful management of a challenging case of IR hypoplasia using the augmented modified Hummelsheim procedure.

A 25-year-old female, who provided written informed consent for publication, presented with esotropia and hypertropia in the right eye without reported diplopia. She had a right head tilt and slight face turn since early childhood, with no history of trauma (Figure 1A). Visual acuity in the right eye was 6/6 with correction of 0.75 sphere and 0.75 cylinder (160° axis). The left eye exhibited 6/6 emmetropia. The prism alternate cover test showed 12 prism diopter (PD) esotropia and 15 PD hypertropia of the right eye in the primary position, with vertical deviation worsening in downward/outward gaze (Figure 1B). A three-step test revealed weakness of the right IR muscle, while fundus photography showed 11° incyclotorsion (Figure 1C). Further investigation with MRI suggested that the muscle belly was located far retroglobally (Figure 1D). No abnormalities were noted in the left eye.

The initial diagnosis was congenital IR palsy and atrophy, and the patient was planned for transposition surgery. A forced duction test was performed intraoperatively and yielded negative results. Subsequently, an exploration of the four rectus muscles was conducted. The lateral and medial rectus were identified. However, upon exploring the inferior sector to a distance of up to 15 mm from the limbus, only two ciliary arteries were found on Tenon's capsule or the sheath, with no identifiable IR muscle. This finding led to a revised diagnosis of congenital IR hypoplasia/aplasia (Figure 1E). The

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patient underwent a modified Hummelsheim procedure, with the muscle halves positioned as if the IR muscle were still intact, along with scleral augmentation sutures 5 mm behind the original insertion (Figure 1F). Postoperatively, there were significant improvements in ocular alignment, AHP, and funduscopic incyclotorsion, as well as partial improvement in infraduction ocular movement from -4 to -2 (Figure 1G, H, I).

In rare cases, establishing a definitive diagnosis can be particularly challenging. In congenital IR hypoplasia, careful interpretation of orbital imaging and intraoperative findings is crucial. Our case demonstrated a distinct difference between the anterior and posterior segments of the muscle belly on sagittal MRI, with intraoperative identification of ciliary arteries leading to a revised diagnosis of hypoplasia. In this case, the surgeon performed a modified procedure involving lateral and medial rectus muscle/tendon splitting to simulate the presence of an IR. This was followed by augmentation with Mersilene sutures on the sclera (augmented modified Hummelsheim) to correct vertical misalignment, along with medial rectus recession of the contralateral eye to address esotropia.

The muscle-splitting technique was specifically designed to preserve the anterior ciliary vessels of each muscle.[4,5] The technique was further developed with the addition of an equatorial fixation suture (augmented suture) by Scott Foster to enhance the verticalization of the transposed muscle

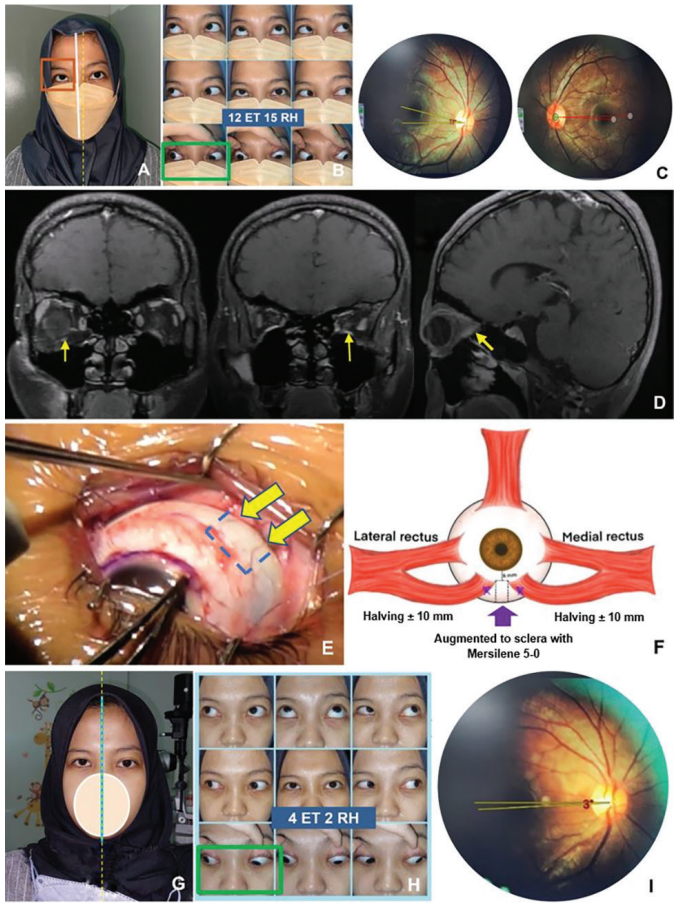

Figure 1. A) Right head tilt and face turn. B) Ocular movement limitation of -4 in depression, more prominent during inferotemporal gaze (green box). C) Posterior pole imaging: incyclotorsion of 11 degrees in right eye (RE), normal in left eye. D) Coronal and sagittal magnetic resonance imaging: a thin muscle sheath was found on the anterior segment of the RE. It became thicker, forming a muscle band on the posterior segment in lieu of the inferior rectus (IR) (yellow arrow). E) Intraoperative findings: two ciliary arteries (two yellow arrows) where the IR should be (blue dash line). F) Augmented modified Hummelsheim procedure: special approaches included transposing the horizontal muscle with a gap between the muscle halves to simulate the presence of an IR. Additionally, Mersilene (polyester) suture augmentation to the sclera (purple knots) was implemented due to the absence of the IR belly (purple arrow). G) At postoperative 6 months, no abnormal head posture was observed. H) Deviation and ocular movement (green box) were improved. I) Incyclotorsion was reduced to 3 degrees (RE)

ET: Esotropia, RH: Right hypertropia

and maximize tonic force. Couser et al.[6] performed an augmented Hummelsheim procedure for total abducens nerve palsy and reported consistently good outcomes. Additionally, the modified Hummelsheim procedure resulted in a lower incidence of anterior segment ischemia, a complication linked to inadequate blood supply to the anterior ciliary arteries caused by muscle manipulation.[4,5,6] Other modification techniques include the modified Nishida, which involves splitting the temporal halves of the muscle without tenotomy. Although this technique requires further evaluation of its efficacy, it is reported to be more beneficial for incomitant horizontal strabismus.[7,8]

In conclusion, a thorough examination and intraoperative exploration are essential for establishing a definitive diagnosis in rare cases of IR hypoplasia. The augmented modified Hummelsheim procedure has demonstrated promising outcomes in improving ocular alignment in the primary position and correcting AHP, consistent with the main goal of the procedure.

Ethics

Informed Consent: Written informed consent for publication obtained.

Declarations

Authorship Contributions

Surgical and Medical Practices: A.P.B., Concept: F.P., A.P.B., Design: F.P., A.P.B., Data Collection or Processing: F.P., A.P.B., Analysis or Interpretation: F.P., A.P.B., Literature Search: F.P., Writing: F.P., A.P.B.

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Ptosis Repair by "PEANUTS" MMCR: "Pelin's Easy and Needle Up To Stretch" Müller's Muscle Conjunctival Resection Without the Putterman Clamp

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Keywords

Aponeurotic ptosis, Müller's muscle conjunctival resection, Putterman clamp, phenylephrine test

Dear Editor,

Müller's muscle-conjunctival resection (MMCR) is a common surgical procedure used in the management of mild to moderate ptosis cases. Patients who have levator function ≥10 mm and respond to the 2.5-10% phenylephrine test are generally eligible for this procedure.[1] MMCR was first described by Putterman and Urist[2] in 1975. The procedure involves holding and stretching the posterior lamellar tissues using a T-shaped, serrated, and concavely curved ptosis clamp designed by and named after Putterman.[3] In this correspondence, we describe our procedure–a variation of the original MMCR technique in which a 21-gauge needle is used instead of the Putterman clamp–and present the results of three ptosis patients operated with this technique. This study adhered to the tenets of the Helsinki Declaration.

The study included three patients with mild to moderate aponeurotic ptosis (1-3 mm) and levator function >14 mm who were responsive to the 2.5% phenylephrine test. The exclusion criteria were a history of eyelid and corneal surgery or trauma, any irregularity of the eyelid contour or eyelid skin, and ocular surface abnormalities. For each eye, the margin reflex distance (MRD1) was measured by holding a penlight at eye level and recording the distance from the corneal light reflex to the upper eyelid margin in the primary position. A millimeter ruler was placed next to the eye for measurement. The resection amount was determined according to preoperative MRD1.

Before the surgery, informed consent was obtained from every patient. For local anesthesia, 0.1 mL of 2% lidocaine with 1:100,000 epinephrine was injected medially and temporally below the skin. The upper eyelid was everted over a Desmarres retractor to expose the superior tarsal border and conjunctiva. According to the measured ptosis, a caliper was set between 4 mm and 5 mm to measure above the superior tarsal border. The

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resection length was marked with a disposable fine-tip cautery in the central region, then in the nasal and temporal regions after measuring 6-7 mm to each side. A 21-gauge needle was inserted into the conjunctiva and Müller's muscle temporally and advanced along the mark to exit nasally 6-10 mm away from the superior punctum and hold the tissues taut, similar to the Putterman clamp. The Desmarres retractor was then removed. Then, a 6-0 Prolene suture was passed full thickness through the eyelid laterally. A running horizontal mattress stitch was made adjacent to the superior tarsal border, through conjunctiva and the superior tarsal border on one side and through conjunctiva and Müller's muscle on the other side. The suture was then externalized medially on a 1-mm silicone bolster. Subsequently, the suture was passed back toward the conjunctiva, run in the opposite direction, and externalized and secured laterally on another 1-mm silicone bolster. The lateral ends of the suture were tied on this bolster to prevent cheese-wiring of the tissues. The conjunctiva and Müller's muscles stretched on the 21-gauge needle were excised with Stevens scissors held parallel and adjacent to the plane of the horizontal mattress suture, carefully avoiding any possibility of cutting the sutures (Figure 1). The excised tissue was left on the needle.

We call our modified technique "Pelin's Easy and Needle Up To Stretch (PEANUTS)" MMCR. Follow-ups of the three patients operated using this technique were conducted for at least 6 months. After postoperative examinations on day 1 and at 1 week, 1 month, 3 months, and 6 months, all the patients showed successful ptosis repair, which was defined as improvement (2-3 mm) in MRD1 and eyelid symmetry within 1 mm. Regular upper eyelid contours were obtained in all patients. Details of the cases are summarized in Table 1.

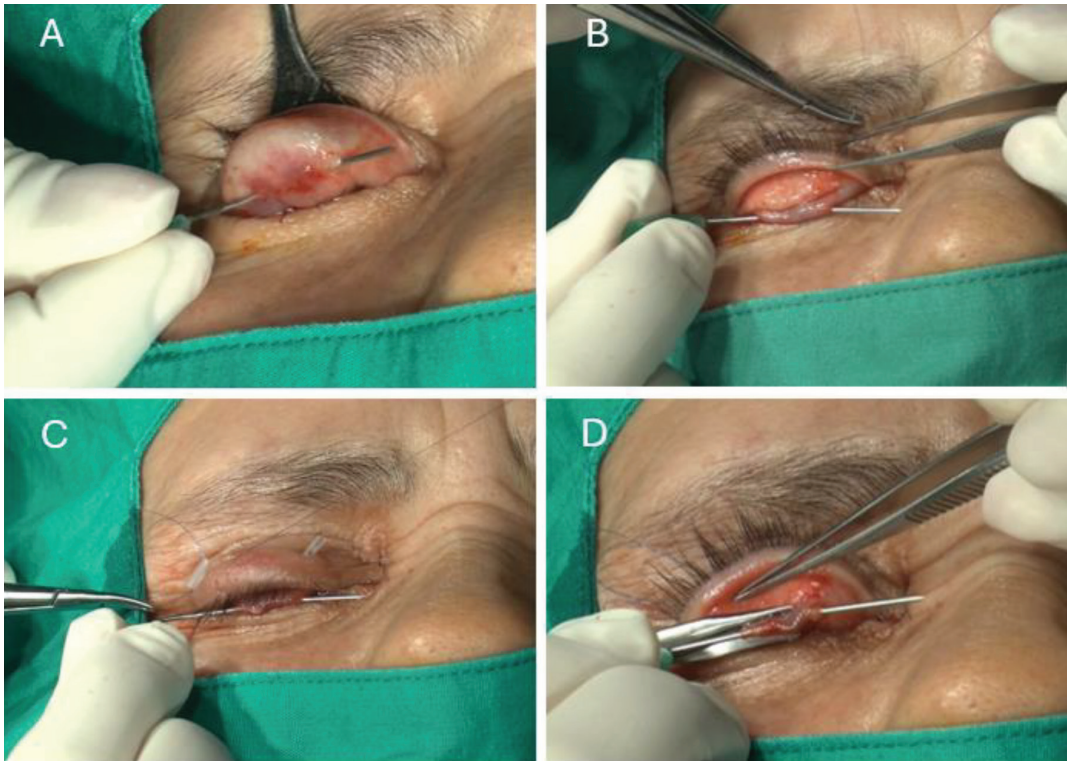

Figure 1. Surgical technique. A) A 21-gauge needle is inserted into the conjunctiva and Müller's muscle at the marking. B) The tissues are held taut with the 21-gauge needle while a 6-0 Prolene suture is used to make a running horizontal mattress stitch. C) Small silicone bolsters are left on the skin of the eyelid where the sutures are externalized, and the two ends of the suture are tied laterally. D) The conjunctiva and Müller's muscle are excised with Stevens scissors

Table 1. Clinical data of PEANUTS MMCR cases

Case no.	Age (years)	Sex	Eye	Preoperative MRD1 (mm)	Postoperative MRD1 (mm)	Complications	Follow-up duration (months)
1	46	F	Right	3	5	None	6
2	50	F	Right	2	4.5	None	6
3	44	F	Right	2.5	5	None	6

PEANUTS: Pelin's Easy and Needle Up To Stretch, MMCR: Müller's muscle-conjunctival resection, F: Female, MRD1: Margin reflex distance 1

The Putterman clamp was designed by Allen M. Putterman in 1972 to replace the two curved hemostats used in Fasanella-Servat ptosis surgery. Its main advantages include easier manipulation and increased stability compared to the hemostats.[3] During MMCR, the use of the Putterman clamp has been reported to secure the posterior lamellar tissues for resection and yield favorable surgery outcomes.[4,5] Various modifications of the original MMCR technique have also been described.[6,7] One modification with the clamp is Carruth's simplified MMCR internal ptosis repair technique, where traction sutures are not used and there is a single knot external to the eyelid.[7]

Despite the many advantages of the Putterman clamp, its limited availability, substantial cost, and need for sterilization after each surgery restrict its use. Moreover, due to the bulkier nature of the clamp, visualization of the tissues is restricted during surgery, making it challenging to position the clamp properly at the superior tarsal border. Inadvertent inclusion of tarsus into the clamp is also possible. In addition, the conjunctiva and Müller's muscle secured with the Putterman clamp can occasionally slip out of the ends of the clamp.

In this case series, we describe a variation of the original MMCR technique that utilizes a 21-gauge needle instead of the Putterman clamp to hold and stretch the conjunctiva and Müller's muscle for resection. The PEANUTS MMCR is an easy and effective ptosis repair technique with certain advantages over the original MMCR. In particular, the 21-gauge needle is a disposable, single-use tool that is easy to manipulate, widely available, and less costly than the Putterman clamp. We observed that the 21-gauge needle provided stable traction on the conjunctiva and Müller's muscle, similar to the Putterman clamp. The 21-gauge needle also allowed better visualization of the tissues intraoperatively, with a lower risk of slipping away. However, one disadvantage associated with the 21-gauge needle is its less stable nature compared to the clamp and that it may require steadier hands to operate with.

We aimed to define an alternative variation to the MMCR performed with the Putterman ptosis clamp. The PEANUTS MMCR technique was effective in our three cases, with surgical results comparable to previous MMCR procedures performed with the Putterman clamp. However, this study is limited by the small number of patients. A large series is needed to assess the consistency of the favorable outcomes of this technique.

Ethics

Informed Consent: Informed consent was obtained from all patients before surgery.

Declarations

Authorship Contributions

Surgical and Medical Practices: P.K., Concept: P.K., C.Ö., Design: P.K., C.Ö., Data Collection or Processing: G.D.Ş., E.A., Analysis or Interpretation: P.K., G.D.Ş., Literature Search: G.D.Ş., E.A., Writing: P.K., G.D.Ş., C.Ö., E.A.

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