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Incidence and risk factors of early transient intraocular pressure elevation after canaloplasty for primary open-angle glaucoma

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Glaucoma is one of the most common optic neuropathies, featuring progressive retinal ganglion cell damage and visual field loss (Tham et al., 2014; Xu et al., 2020). Currently, the only effective treatment for this condition is the reduction of intraocular pressure (IOP) (Palmberg, 2001; Heijl et al., 2002). Canaloplasty is a proven bleb-independent surgery with good efficacy and safety profiles in primary open-angle glaucoma (POAG) (Gołaszewska et al., 2021). However, early transient postoperative IOP elevation has been reported in up to 30% of cases (Riva et al., 2019), similar to that commonly observed in other internal drainage glaucoma surgeries such as implantation using iStent (0%–21.0%), CyPass (10.8%), and Hydrus (4.8%–6.5%) (Lavia et al., 2017). This complication may be a predictor of poor reserve in the outflow system and is potentially associated with surgical failure. Nonetheless, the exact pathophysiology of glaucoma remains unknown, and studies clarifying the risk factors for postoperative IOP elevation have been scarce.

In light of previous work, we speculated that both pre- and postocular factors are responsible for the postoperative dysfunction of the outflow system, which results in early transient postsurgical IOP elevation. Moreover, we analyzed the incidence and risk factors of IOP elevation within the first three postoperative months following canaloplasty, with the goal of optimizing the postoperative care of patients and clarifying the underlying mechanisms.

Among the 77 eyes of 73 consecutive Chinese POAG patients who underwent canaloplasty with records for 12 months of follow-up, 16 eyes were excluded for the following reasons: trabeculectomy was performed in four eyes (5.2%) due to the failure of 360° catheterization during the operation; nine eyes (11.7%) required additional trabeculectomy within three months postoperatively due to persistent IOP elevation, despite that medical treatments were considered early failures; and three eyes (3.9%) were excluded because of incomplete or unreliable data during the one-year follow-up. Both eyes met the inclusion criteria in four patients, where only one eye was randomly selected. Finally, 57 eyes of 57 patients were included in the analysis.

Patients were divided into subgroups with normal IOP (NIOP) and high IOP (HIOP) based on the presence of early transient IOP elevation, defined as IOP>21 mmHg (1 mmHg=0.133 kPa), which reduced to ≤21 mmHg within one week to three months postoperatively. The baseline demographics are summarized in Table 1. The participants were predominantly male (73.7%), and the majority presented advanced POAG (59.5% and 55.0% in the NIOP and HIOP groups, respectively) according to the Hodapp-Anderson-Parrish criteria (Wang et al., 2020). The mean ages of patients with NIOP and HIOP were (47.27±12.72) and (47.25±17.24) years, respectively. Patients with HIOP had longer glaucoma duration than those

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Table 1 Baseline and ocular characteristics of the study participants

Characteristics	NIOP (n=37)	HIOP (n=20)	P value
Age (years)	47.27±12.72	47.25±17.24	0.99
Gender (female/male)	10/27	5/15	0.87
OD/OS	19/18	10/10	0.92
Previous intraocular surgery*	0.31±0.63	0.11±0.32	0.11
Glaucoma duration (years)	2.57±2.33	4.39±6.87	0.28
Glaucoma stage			0.77
Early	8 (21.6%)	6 (30.0%)	
Moderate	7 (18.9%)	3 (15.0%)	
Late	22 (59.5%)	11 (55.0%)	
Preoperative IOP (mmHg)	30.08±10.62	28.26±9.79	0.53
Maximum recorded preoperative IOP (mmHg)	35.10±11.22	30.28±10.53	0.12
Preoperative medications	2.58±1.05	2.55±1.19	0.91
BCVA	0.78±0.29	0.78±0.27	0.96
Cup-to-disc ratio	0.82±0.15	0.79±0.15	0.35
Mean deviation (dB)	−15.64±9.98	−15.45±10.64	0.95
RNFL thickness (μm)	68.82±17.73	71.78±18.87	0.58
AL (mm)	25.07±2.25	25.30±3.53	0.77
Postoperative $IOP_{min\text{-}1w}$ (mmHg)	9.16±2.76	12.76±3.70	**<0.01**
Postoperative $IOP_{min\text{-}1w}$≥12 mmHg	5 (13.5%)	12 (60.0%)	**<0.01**
Follow-up period (months)	22.70±14.43	24.60±16.85	0.66
Qualified success rate for IOP≤21 mmHg	91.9%	85.0%	0.72
Complete success rate for IOP≤21 mmHg	78.4%	45.0%	**0.01**
Qualified success rate for IOP≤18 mmHg	86.5%	75.0%	0.28
Complete success rate for IOP≤18 mmHg	73.0%	35.0%	**<0.01**
Qualified success rate for IOP≤15 mmHg	59.5%	30.0%	**0.03**
Complete success rate for IOP≤15 mmHg	54.1%	15.0%	**<0.01**

* Previous intraocular surgery included anti-glaucoma, cataract, and vitreoretinal surgeries. Data are expressed as mean±standard deviation (SD), number (percentage), or percentage, except for gender. Significantly different P values were written in bold. OD, right eye; OS, left eye; IOP, intraocular pressure; BCVA, best-corrected visual acuity; RNFL, retinal nerve fiber layer; AL, axial length; min, minimum; $IOP_{min\text{-}1w}$, lowest recorded IOP during the first postoperative week; Postoperative $IOP_{min\text{-}1w}$≥12 mmHg, the number of eyes with postoperative $IOP_{min\text{-}1w}$ above 12 mmHg; NIOP, normal IOP; HIOP, high IOP.

with NIOP ((4.39±6.87) vs. (2.57±2.33) years), although the difference was not statistically significant.

HIOP occurred in 20 eyes (35.1%) with an average initial onset time of postoperative (2.45±1.40) weeks and a duration of (1.66±1.79) weeks. In all patients with HIOP, the IOP reduced to ≤21 mmHg during the first three postoperative months, with a mean follow-up time of (24.60±16.85) months. Surgical success was defined as postoperative 5 mmHg<IOP≤21 mmHg at each postoperative visit with (qualified success) or without (complete success) the use of anti-glaucoma medication and without additional surgical therapy. At 12 months, the cumulative complete and qualified success rates for all participants were 66.7% and 89.5% at IOP≤21 mmHg, respectively.

Previous studies have shown that IOP in severe glaucoma eyes needs to be better controlled to achieve a better surgery outcome and the average value was 12 mmHg in those stable eyes (Chandler, 1970; Warjri et al., 2021). Accordingly, the number of eyes with postoperative $IOP_{min\text{-}1w}$ (lowest recorded IOP during the first postoperative week) above 12 mmHg was compared between the two groups. Compared to the NIOP group, patients in the HIOP group had significantly higher postoperative $IOP_{min\text{-}1w}$ ((12.76±3.70) vs. (9.17±2.76) mmHg), and more cases were observed with $IOP_{min\text{-}1w}$≥12 mmHg (60.0% vs. 13.5%), and lower complete success rates (45.0% vs. 78.4%) (all P<0.01).

In the entire cohort, IOP significantly reduced from (29.43±10.27) mmHg to (12.98±5.80) mmHg at Day 1, (14.85±3.05) mmHg at three months, and (14.73±3.60) mmHg at one year (all P<0.01). Compared to IOP at baseline, the mean IOP reduction in all participants was (37.81±26.31)% at the last follow-up, with a mean reduction of (2.05±1.33) medications. Fig. 1 shows the longitudinal pre- and postoperative outcomes in terms of mean IOP, number of medications, and best-corrected visual acuity (BCVA) in the

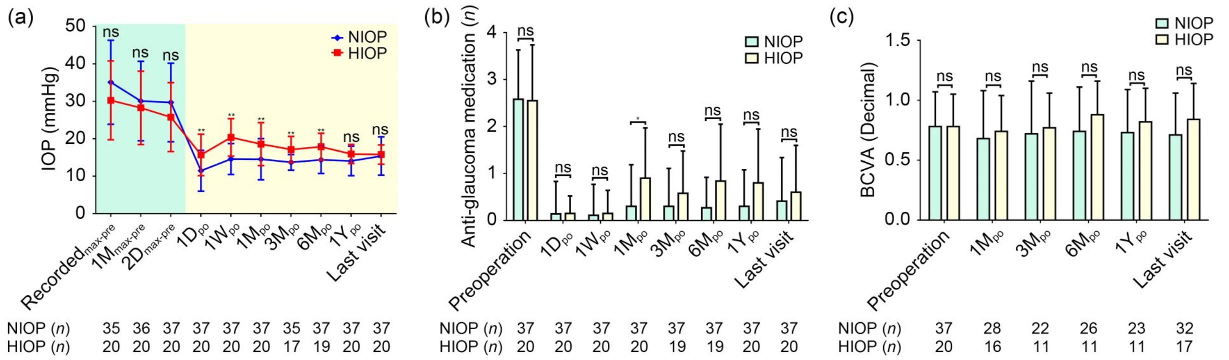

Fig. 1 Pre- and postoperative intraocular pressure (IOP) (a), anti-glaucoma medication (b), and best-corrected visual acuity (BCVA) (c) in the normal IOP (NIOP) and high IOP (HIOP) groups. Data are expressed as mean±standard deviation (SD). ** ***P*≤0.01,** * ***P*≤0.05. ns, non-significant; max-pre, the maximum preopeative value; po, postoperative; D, day; W, weak; M, month; Y, year.**

HIOP and NIOP groups. From Day 1 to 6 months postoperatively, patients in the HIOP group had a significantly higher IOP than those in the NIOP group (all $P<0.01$). The mean BCVA remained stable during the one-year follow-up period.

HIOP and complete success were significantly negatively correlated at one year postoperatively ($r=-0.34$, $P=0.01$). The variables compared between NIOP and HIOP with $P<0.15$, including recorded $IOP_{max\text{-}pre}$ (the highest preoperative IOP value), $IOP_{min\text{-}1w}$, $IOP_{min\text{-}1w}\geqslant$ 12 mmHg, and number of previous intraocular surgery, were selected for further linear logistic regression analysis to evaluate the risk factors for HIOP. Among them, the only unique risk factor was $IOP_{min\text{-}1w}\geqslant 12$ mmHg (hazard ratio: 10.29, 95% confidence interval (CI): 2.72–38.84, $P<0.01$) after adjusting for age, gender, and the eye laterally.

Canaloplasty, a bleb-independent surgery that focuses on the dilation of Schlemm's canal to facilitate the drainage of aqueous humor through the physiological route, is an increasingly popular procedure for POAG. In this study, the one-year qualified and complete success rates were 89.5% and 66.7%, respectively. These results were similar to those of previous studies that demonstrated the remarkable safety and efficacy of canaloplasty with qualified success rates between 86.2% and 95.5% (for IOP≤21 mmHg) and failure rates between 5% and 14% (Lewis et al., 2011; Brusini, 2014; Seuthe et al., 2016). However, our success rates might have been overestimated due to the exclusion of early failures. Significant reductions in IOP and the number of medications were observed; however, little is known about early transient postoperative IOP elevation.

While direct comparison is unfeasible, the incidence of HIOP in the present study (35.1%) was higher than that previously reported for Schlemm's canal-based drainage surgeries, such as Ab interno viscocanaloplasty (22.2%) (Gillmann et al., 2021) and Hydrus implantation (4.8%–6.5%) (Lavia et al., 2017). In our study, the most likely cause was the high prevalence of advanced glaucoma (57.9%), which might have severely disturbed aqueous humor outflow (AHO). This hypothesis is supported by the findings of prior studies that collector channels and intrascleral plexus sclerosis are destroyed in advanced glaucoma (Fellman and Grover, 2014).

Early transient IOP elevation indicates the transient dysfunction of the AHO system, either due to the excessive production of obstructive materials or due to pathological changes in the outflow system. Brusini (2014) has suggested that viscoelastic substances and inflammatory cytokines can decrease outflow through the trabecular meshwork (TM) and collector channels. However, surgery-related viscoelastic substances or inflammation-induced IOP elevation usually diminish within one week; therefore, they cannot explain the longer duration of HIOP.

Another presumed cause is corticosteroid-induced IOP elevation. While our patients received steroids for 2–4 weeks, HIOP was usually elevated at one week and reduced later, even with the continued use of steroids. Moreover, according to another study conducted by our group (Hu et al., 2022), the HIOP developed in two out of ten corticosteroid-induced glaucoma eyes after penetrating canaloplasty with the continued use of steroid, implying that HIOP may go beyond steroid usage.

Preoperative anatomical differences in AHO may be correlated with postoperative IOP elevation. Qi et al. (2020) found that in myopic eyes undergoing cataract surgery, eyes with early elevated IOP had smaller vertical diameter and area of Schlemm's canal, as well as lesser TM thickness and width compared to those in the non-elevation group. Nonetheless, owing to the retrospective nature of this study, information on the structural characteristics of AHO was not available, and thus we could not evaluate these anatomical differences.

Compared to the NIOP group, patients in the HIOP group had a higher average postoperative IOP_{min-1w}, and IOP_{min-1w}≥12 mmHg was the only unique risk factor for HIOP. Moreover, HIOP was significantly negatively correlated with one-year complete success, implying that eyes with HIOP may have poorer AHO pump function and increased risk of surgical failure.

Healthy TM cells can phagocytose debris and particulate material in the aqueous humor to maintain an unobstructed AHO (Buller et al., 1990), and Schlemm's canal plays an important role in regulating IOP (Johnstone et al., 2021). This indicates that the postoperative AHO anatomy might be reshaped during disease or surgery, which could account for alterations in the microenvironment of the related cells (including TM cells and endothelial cells of Schlemm's canal and its downstream pathways). These factors may impact IOP regulation. This hypothesis is supported by the findings of Yoshikawa et al. (2018), who evaluated the morphological changes in AHO canals by optical coherence tomography (OCT) in glaucoma patients before and after trabecular-targeted minimally invasive glaucoma surgery.

Alterations in the pre- and post-trabecular outflow system may be reversible in eyes with mild pathological AHO and rescue high IOP, whereas the circumferential opening of Schlemm's canal after surgery may not have a significant effect on IOP in eyes with high distal post-trabecular outflow system resistance. We speculate that in the early postoperative (≤3 months) stage, the main reason for HIOP may be the reversible distal outflow resistance, while surgical failure may be due to TM dysfunction; therefore, identifying the precise mechanism requires further research.

This study has several limitations. First, it had a single-center design, and only Chinese patients were included. Second, a selection bias could have resulted from the retrospective design, and the exclusion of patients with persistent IOP elevations and generally advanced glaucoma. These must have had a negative impact on the evidence intensity of these results. Third, the postoperative follow-up duration was only one year, and it is possible that further changes in the AHO patterns, collector channel entrances, and deep scleral plexus after canaloplasty may affect long-term prognosis.

Conclusively, HIOP, which was more likely to develop in eyes with higher postoperative IOP_{min-1w}, was associated with significantly lower one-year complete success rates than NIOP. Approximately 40% of the patients who underwent canaloplasty experienced early postoperative IOP elevation. Among these, 70% had transiently elevated IOP and 30% showed persistently high IOP, who were deemed to be subjects of surgical failure. These patients are difficult to distinguish at the early stage. Thus, regular follow-ups within three months postoperatively and timely IOP lowering are recommended for cases with early elevated IOP. Moreover, detection in the morphological (e.g., Schlemm's canal scanning by OCT) and functional changes (e.g., aqueous humor outflow facility) of the distal AHO may aid the evaluation of the outflow state, and thus needs further exploration.

Materials and methods

Detailed methods are provided in the electronic supplementary materials of this paper.

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Author contributions

Lijuan XU: methodology, software, data acquisition and analysis, writing–original draft, revision, and funding acquisition; Xinyao ZHANG and Yang CAO: data acquisition and analysis; Yin ZHAO, Juan GU, Wenqing YE, and Jinxin LI: data acquisition; Xiaojie WANG: data analysis; Ruiyi REN:

methodology, writing−reviewing and editing, revision, and supervision; Yuanbo LIANG: conceptualization, methodology, writing–reviewing and editing, funding acquisition, and supervision. All authors have read and approved the final manuscript, and therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Lijuan XU, Xinyao ZHANG, Yang CAO, Yin ZHAO, Juan GU, Wenqing YE, Xiaojie WANG, Jinxin LI, Ruiyi REN, and Yuanbo LIANG declare that they have no conflict of interest.

This cross-sectional study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of the Eye Hospital of Wenzhou Medical University (KYK[2014] No. 47). Written informed consent was exempted due to the nature of retrospective study.

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Supplementary information

Materials and methods