Risk of surgical failure and hemorrhagic complications associated with antithrombotic medication in glaucoma surgery

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Title: Risk of surgical failure and hemorrhagic complications associated with antithrombotic medication in glaucoma surgery

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Key messages

- While perioperative use of anti-thrombotic drugs is more likely to increase the chance of hemorrhagic complications at and after glaucoma surgery, discontinuing these substances may induce systemic life-threatening vascular events.
- The present relatively large sample study has demonstrated that anti-thrombotic drugs did not affect success rates for *ab interno* trabeculotomy, trabeculectomy, nor long tube shunt surgery at one year.
- Perioperative bleeding complications such as hyphema and vitreous hemorrhage were significantly higher in anti-thrombotic drug users for trabeculectomy and tube shunt surgeries, but not for trabeculotomy.

Abstract

Purpose: The purpose of this retrospective study was to determine the extent to which the use of antithrombotic drugs during glaucoma surgery contributes to surgical failure and postsurgical hemorrhagic complications.

Methods: Glaucoma surgeries were categorized into three groups: trabeculotomy (TLO), trabeculectomy (TLE), and long-Tube shunt surgery (Tube). At 1 year after surgery, the following criteria for surgical success were met: intraocular pressure (IOP) in the 5–21 mmHg range, IOP reduction of at least 20% from the preoperative level, and no additional glaucoma surgeries. We compared the percentages of the success rates and hemorrhagic complications between antithrombotic medication users and nonusers. Furthermore, we adjusted the preoperative factors between the two groups using a propensity score analysis in TLO and TLE surgeries.

Results: A total of 910 glaucoma surgeries were included, with TLO, TLE, and Tube accounting for 353, 444, and 113 surgeries, respectively. Preoperative antithrombotic medications were administered to 149 patients in all glaucoma surgeries: 37 patients used only anticoagulants, 102 used only antiplatelets, and 10 used both. There was no significant difference in the success rates of any of the procedures. The hemorrhagic complications (hyphema and vitreous hemorrhage rate) were significantly higher in the patients who underwent TLE and Tube. The surgical success rates of TLO and TLE were not significantly different after the two groups were matched by propensity score.

Conclusion: The perioperative use of antithrombotic drugs did not affect success for any of the procedures. However, it increased early postoperative hemorrhagic complications for TLE and Tube.

Key Words: glaucoma surgery, antithrombotic medication, surgical failure, hemorrhagic complication

Statements and Declarations

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Availability of data and material: The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Authors' contributions: Conceptualisation: SM and MN; Data sampling: FT, MO, YM, and KU, Data analysis: FT, SM and YY-N; Drafting: FT, SM and MN; Critical reading and reviewing: MS, TK, YY-N and MN, Submission: MN.

Ethics approval This study was approved by the Institutional Review Board of the Kobe University Graduate School of Medicine (No. 200091).

Consent to participate: Opt-out consent was obtained from all patients. This method was used for participant recruitment in the study. Information regarding the research, their involvement, and where their participation is presumed unless they decline to participate was provided to the potential participant.

Introduction

Many developed countries such as Japan, the U.S., and EU countries are experiencing a super-aging population. The number of patients facing the risk of cardiovascular or cerebrovascular events, such as stroke or myocardial infarction, is increasing rapidly in the elderly at least partially due to intensified atherosclerotic changes. This has led to a significant increase in the number of patients taking antithrombotic drugs. [1].

Glaucoma is one of the leading causes of blindness worldwide [2]. Lowering of intraocular pressure (IOP) is the solely established intervention to slow or halt the progression of glaucomatous optic neuropathy. Although medication is usually deemed first-line therapy, particularly in patients with primary open angle glaucoma, many patients still require surgical intervention to reduce IOP. Given that aging is also a well-known risk factor in the development of glaucoma, the number of elderly glaucoma patients who are taking antithrombotic agents and need to undergo glaucoma surgery has been increasing.

The dilemma is that the perioperative use of antithrombotic drugs is more likely to increase the chance of hemorrhagic complications at and after glaucoma surgery. At the same time, discontinuing these substances may induce systemic life-threatening vascular events. For example, aspirin cessation raised the incidence of major cardiovascular events by threefold [3]. Discontinuation of anticoagulants also increased the incidence of events that could lead to death [4, 5]. Because of the low risk of intraocular hemorrhage, many reports recommend performing cataract surgery, particularly phacoemulsification, without discontinuing antithrombotic drugs [6-12]. However, the decision to discontinue antithrombotic substances around glaucoma surgery is challenging for clinicians due to an elusive risk per benefit balance, and thus varies among facilities and reports. A survey for glaucoma surgeons in the UK reported that only 32.3% and 31.2% of them routinely discontinue warfarin and aspirin, respectively [13]. In contrast, a Brazilian study showed that 82.7% of them discontinued warfarin and aspirin [14]. Furthermore, while MIGS (minimally/micro invasive glaucoma surgery) has grown in popularity, little is known about the impact of antithrombotic therapy on MIGS [15]. There was no comprehensive study to address the question of whether continuation or discontinuation of

antithrombotic agents affects success and complications of glaucoma surgeries.

This study has investigated whether and to what extent the perioperative use of antithrombotic drugs in glaucoma surgery decreased the surgical success and/or increased hemorrhagic complications. Quasi-randomized studies regarding the history of antithrombotic drugs have also been conducted with propensity score matching analyses to address these issues [16, 17].

Methods

(Subjects)

The Institutional Review Board of Kobe University approved this study (No. 200091), which complied with the Declaration of Helsinki. This was a retrospective, observational study, so informed consent was not required. However, patients could withdraw consent any time after reviewing information about this study on the hospital homepage as an opt-out choice.

All glaucoma patients aged 20 years or older who underwent glaucoma surgeries from January 2015 to May 2019 and followed for at least one year after surgery at Kobe University Hospital were included in this study. If both eyes underwent surgery or the same procedure was repeated on the same eyes, only the first eye and the first procedure, respectively, were enrolled.

Collected clinical data of the patients were as follows: age, sex, glaucoma type, operative procedure (i.e., *ab interno* trabeculotomy [16, 18-21], trabeculectomy [22], or long-Tube shunt[23-25]), a history of antithrombotic drug use, preoperative and postoperative intraocular pressure (IOP), and mean deviation (MD) value of Humphrey visual field (HVF). Postoperative values were used for those at one year after surgery. For antithrombotic drug users, the type of medication (i.e., an anticoagulant, an antiplatelet aggregation drug, or both) and whether or not the medication was discontinued at the perioperative period were also extracted.

IOP was measured using a Goldmann applanation tonometer twice per session, and the average value was used. If the difference between the two measurements exceeded 1 mmHg, we obtained the third measurement. The median of the three measurements was the IOP of the session. The Swedish interactive threshold algorithm standard 30-2 program of the HVF analyzer (Carl Zeiss-Meditec,

Dublin, CA, USA) has been used to measure the visual field.

Antithrombotic agents were discontinued during an appropriate perioperative period to eliminate the pharmacological action of those agents only with permission from the internal physicians prescribing the drugs and if the patients were at a lower risk of systemic vascular events with short term discontinuation of the drugs [4].

(Primary outcome)

The primary outcome included the success at one year after surgery and surgery-related hemorrhagic complications. Surgical success meant satisfying all of the following three criteria at one year after surgery: IOP within 5–21 mmHg, IOP reduction of at least 20% from preoperative IOP, and no additional glaucoma surgery. When postoperative IOP at 1 year fell without the above range at two consecutive visits after one month postoperatively and later, surgical failure has been flagged regarding IOP, and the earlier visit was the point of failure. In the case of trabeculectomy, the performance of a filtering bleb revision with Mitomycin C was counted as the additional glaucoma surgery and, thus, was the event of surgical failure. Surgery-related hemorrhagic complications were vitreous hemorrhage, or layered hyphema formation and choroidal hemorrhage observed after the surgery.

(Surgical Procedure)

The glaucoma surgeries conducted were divided into three groups: *ab interno* trabeculotomy (TLO) using the Tanito's microhook (Inami & Co., Ltd., Tokyo, Japan) or Trabectome, trabeculectomy (TLE) with adjunctive use of 3-min 0.04% Mitomycin C and a deep sclerectomy, and long-Tube shunt surgery (Tube). The details for TLO [16, 18-21] and TLE [22] procedures were described elsewhere. For Tube, either the Ahmed Glaucoma Valve (FP-7; New World Medical, Rancho Cucamonga CA, USA) or Baerveldt Glaucoma Implant (BGI 101-350; Abbott Medical Optics, Chicago, IL, USA), only both of which are officially approved for use in Japan, were used. As reported, the Tube was inserted into the ciliary sulcus, or the vitreous cavity in case of preoperative avitreous patients, instead of the anterior chamber in an attempt to reduce corneal endothelial damage [23-25].

(Statistical analyses)

Proportions of the surgical success and surgery-related hemorrhagic complications in each surgical procedure were compared using Fisher's exact test between the groups with and without perioperative anti-thrombotic drugs. Other quantifiable values were compared using the Mann–Whitney U test.

Non-experiencer was defined as a patient who has never used an antithrombotic medication. In contrast, an experiencer was defined as a patient who used antithrombotic medications perioperatively and discontinued those drugs before surgery. A sub-analysis has also been conducted by comparing the outcomes between patients who continued those drugs and those who discontinued them preoperatively within experiencers.

In this study, there were significant differences in age between the experiencers and non-experiencers both in the TLO and TLE populations. Several previous reports elucidated that older age was associated with surgical success in TLO [26-28]. Therefore, it would introduce bias if patients with different backgrounds, including age, are compared. A common approach for adjusting observational data is propensity score matching [16, 17]. We used 1:1 matching with the propensity scores analysis based on the logistic regression analysis to quasi-randomize explanatory variables of age, sex, glaucoma types, and preoperative IOP and MD values over the antithrombotic drug use, and then the surgical success and surgery-related hemorrhagic complications were compared between the antithrombotic drug experiencers and the non-experiencers. As such, 50 and 44 patients each in the TLO and the TLE group, respectively, were extracted and compared, while the propensity score matching did not extract enough number of patients to the statistical comparison in the Tube group.

All statistical analyses were performed using MedCalc (MedCalc Software Ver20, Ostend, Belgium). A P value of <0.05 was defined as statistically significant.

Results

Table 1 summarizes the demographic data of a total of 910 enrolled patients (one eye per patient), which comprises 353, 444, and 113 patients who received TLO, TLE, and Tube, respectively.

In total, 149 patients (16.4%) had a history of taking routine preoperative antithrombotic medications. 37 patients (4.1%) took only anticoagulants, 102 patients (11.2%) took only antiplatelet agents, and

10 patients (1.1%) took both in all three types of surgeries. In patients with TLO, 64 (18.1%) used antithrombotic drugs, of which 45 took antiplatelets only, 13 took anticoagulants only, and 6 took both. In patients with TLE, 70 (15.8%) took antithrombotic drugs, of which 43 took antiplatelets alone, 23 took anticoagulants alone, and 4 took both. In patients with Tube, 15 (13.3%) took anti-thrombotic drugs, of which 14 took antiplatelets only, 1 took anticoagulants only, and none did both.

Table 2 summarizes the number of previous glaucoma surgery for each procedure. All cases in TLO patients did not have previous glaucoma surgeries. The TLE group included 326 patients with first surgeries and 118 with a previous history of TLO. The Tube group included 28 patients with first surgeries and 12 patients who experienced TLO only, 50 who experienced TLE only, and 23 who experienced both TLO and TLE.

Figure 1 depicts histograms of the eyes with surgical success and failure at 1 year after surgery, stratified by antithrombotic therapy experience in three types of glaucoma surgeries. The surgical success was compared between those who had never taken antithrombotic medications (non-experiencers) and those who routinely used these drugs irrespective of their continuation or discontinuation (experiencers) in each surgical procedure. In patients who underwent TLO, non-experiencers comprised 115 patients (39.8%) with failure, while experiencers comprised 21 (32.8%) with failure. In patients who underwent TLE, non-experiencers had 109 patients (29.1%) with failure, whereas experiencers had 18 (25.7%) with failure. In patients who underwent Tube, non-experiencers had 12 (12.2%) patients with failure, while experiencers had 3 patients (20%) with failure. There were no significant differences in the success rate between the non-experiencers and the experiencers in all of the three operative procedures (TLO, $p = 0.32$; TLE, $p = 0.67$; Tube, $p = 0.42$; Fisher's exact test).

Figure 2 and Supplemental Table 1 demonstrate the proportion of surgery-related hemorrhagic complications and the contents stratified by antithrombotic therapy experience in the three types of glaucoma surgeries. In the TLO group, non-experiencers comprised 108 cases (37.4%) with hemorrhagic complications, while experiencers consisted of 26 (40.7%), indicating no significant difference in the hemorrhagic complication rate between the two groups ($p = 0.63$, chi-square test). In TLO, the leading cause of hemorrhagic complications was layered hyphema (38.0%, 134 patients out

of 353). Layered hyphema occurred in 108 cases (37.4%) in the non-experiencers group and 26 cases (40.7%) in the experienced group. In the TLE group, non-experiencers comprised 65 cases (17.4%) with hemorrhagic complications. In comparison, experiencers comprised 23 cases (32.9%) with complications, indicating a significantly higher proportion of patients with hemorrhagic complications in the experiencers ($p < 0.01$, chi-square test). Layered hyphema was also most common in TLE (18.9%, 84 out of 444); 62 cases (16.6%) had hyphema in the non-experiencer group and 22 (31.4%) in the experiencer group. In the Tube group, non-experiencers consisted of 12 cases (12.2%) with hemorrhagic complications, whereas experiencers had five cases (33.3%) with the complications, indicating the significantly higher proportion of patients with hemorrhagic complications in the experiencers ($p < 0.05$, Fisher's exact test). In this study, choroidal hemorrhage occurred in one patient who was a non-experiencer in the TLE group. In Tube, among the non-experiencers, only hyphema occurred in seven cases (7.1%) and only vitreous hemorrhage in five (5.1%), while among the experiencers, hyphema occurred in two cases (13.3%) and vitreous hemorrhage in three (20.0%).

Table 3 shows a propensity score adjusted comparison of demographics and surgical outcome in patients with TLO. There were no significant differences in patient backgrounds between the two groups. The surgical success rate, postoperative IOP at 1 year, and proportion of hemorrhagic complications did not differ between the experiencers and the non-experiencers. When the transient IOP elevation was defined as an increase in IOP equal to 25 mmHg or higher within two weeks after surgery, the number of patients with the transient IOP elevation was 22 (44%) in the non-experiencers and 25 (50%) in the experiencers with no significant difference between the two groups ($p = 0.84$ Fisher's exact test).

Table 4 summarizes a propensity score adjusted comparison of demographics and surgical outcome in patients with TLE. No significant difference has been observed in the preoperative parameters between the experiencers and the non-experiencers except age. There were no significant differences in the surgical success rate and the postoperative IOP at one year between the two groups. In comparison, the proportion of hemorrhagic complications of 30% (13 out of 44) in the experiencers was significantly higher than that of 11% (5 out of 44) in the non-experiencers ($p < 0.05$, Fisher's exact

test).

In order to assess whether discontinuation of the antithrombotic drugs impacted the surgical outcomes in experiencers, the number of patients with success or failure and with or without the hemorrhagic complications in the experiencers who underwent the three types of glaucoma surgeries has been counted. There were no significant differences in the proportion of surgical success at 1 year or the hemorrhagic complications between those who discontinued the antithrombotic agents perioperatively and those who continued those agents in the experiencers with any types of surgery; i.e., TLO, TLE, or Tube, as shown in Table 5.

Collectively, the preoperative antithrombotic medications did not affect surgical success or major surgery-related complications in patients who received TLO. In contrast, those medications did not impact surgical success at one year but increased the risk of postoperative hemorrhagic complications in patients who received either TLE or Tube, irrespective of continuation or discontinuation of those drugs perioperatively.

Discussion

The present study demonstrated that among 910 consecutive glaucoma patients who received either one of the three surgical procedures, TLO, TLE, and Tube, at a tertiary medical hospital, 16.4% had a history of routine anti-thrombotic drug use perioperatively and perioperative anti-thrombotic drug use did not affect the success rate for any types of surgery. At the same time, it significantly increased the risk of hemorrhagic complications at and after TLE and Tube, but not TLO.

Regarding the proportion of antithrombotic drug use among patients who received intraocular surgery, Cobb et al. reported that 15.0% (55 out of 367) and 1.3% (5 out of 367) took antiplatelets and anticoagulants, respectively [29]. The proportion of counterparts in the present study was 12.3% and 5.2%, respectively, which was comparable in total with the study by Cobb et al. However, there was a relatively lower proportion of antiplatelet users and the relatively higher proportion of anticoagulant users in the present study compared with their study. However, the lower proportion of the antiplatelet users in the present study may represent the fact that the primary preventive effect of aspirin on

cardiovascular events had not been proven in the elderly Japanese population [30]; thus, the power of recommendation for aspirin medication in Japan is lower than those overseas, despite that the Japanese population comprises the higher proportion of the elderly (Japan, 28.1% vs the UK, 18.7% in 2018)[31].

The present observation that the antithrombotic drug users were more likely to undergo hemorrhagic complications after TLE compared with the nonusers is consistent with previous studies [9,29,32]. It is quite reasonable because TLE includes procedures that dissect many tissues; i.e., the conjunctiva, the sclera, and the iris, which is inevitably associated with bleeding.

In contrast, it was unexpected that no significant difference in the proportion of the hemorrhagic complications after TLO was observed between the antithrombotic users and the nonusers. One possible reason for this is hyphema after TLO originates from blood reflux due to abrupt loss of the aqueous humor drainage resistance at the trabecular meshwork rather than bleeding caused by tissue dissection. This is particularly the case in the *ab interno* approach without any damage on the conjunctiva and the sclera. TLO causes blood reflux and subsequent postoperative hyphema very frequently, ranging from 36.7% in our previous report [20] to 41% from others [33]. Such high incidence of blood reflux may mask additional bleeding that could be potentially more prone to occur in the eyes of those antithrombotic drug users.

Conversely, no comprehensive study was found to evaluate the effect of antithrombotic drugs on surgery-related hemorrhagic complications after a long-Tube shunt. The present study is the first to report that the antithrombotic drug users exhibited a higher proportion of hemorrhagic complications after Ahmed glaucoma valve or Baerveldt glaucoma implant surgery than the nonusers as in the case with TLE, specifically when the tube was placed at the ciliary sulcus or the vitrous cavity. The result is reasonable considering the invasiveness of the procedures.

Despite the higher proportion of the hemorrhagic complications in the antithrombotic drug users who received TLE or Tube than the nonusers, no significant difference was found in the surgical success rate at one year postoperatively between the antithrombotic drug users and the nonusers for any types of glaucoma surgeries. This held true even after adjusting for known confounders by propensity score

matching in the case of TLO and TLE. Furthermore, even after the antithrombotic drug users were subdivided into those who discontinued these drugs perioperatively and those who continued them, the surgical success rate and the proportion of the hemorrhagic complications were similar between the two subdivision groups for any types of surgeries. Tanito et al. previously demonstrated that, though an *ab externo* approach, hyphema formation did not contribute to the final surgical success after TLO [28]. Cobb et al. reported that aspirin medication increased postsurgical intracameral hemorrhage but did not change the final postoperative IOP outcomes after TLE [29]. The present findings support these previous observations. Conversely, hyphema is a risk factor of TLE failure for neovascular glaucoma [34]. Although our study included a small number of NVG patients (TLO, 0 cases; TLE, 23 cases; Tube, 23 cases), most of them underwent the Goldmann perimetry instead of the HVF test. Thus, MD values could not be obtained in these patients, resulting in the dropout of these cases during the propensity score matching. For this reason, in this study, assessing the effect of antithrombotic agents on surgical success and the hemorrhagic complications of glaucoma surgeries in NVG patients was impossible.

In this study, we allocated Trabectome in a TLO surgery because this procedure aims to reconstruct the physiological aqueous outflow facility and is free from an aqueous filtration mechanism unlike traditional *ab externo* TLE. However, one may claim that Trabectome is *ab interno* TLE surgery, because it dissects the inner wall of the Schlemm canal [35]. Therefore, we conducted an additional analysis in which Trabectome was allocated to TLE (Supplemental Figure 1 and Supplemental Table 2, 3). This re-allocation unchanged the outcomes of TLO, where antithrombotic agents didn't influence the proportion of surgical success and hemorrhagic complication rates. On the other hand, the difference in the hemorrhagic complication rate between eyes with TLE in the antithrombotic drug users and non-users disappeared by propensity score matching analysis with keeping the similar success rates between the two groups (Supplemental Table 3). We consider this is because Trabectome does not allow aqueous humor to be filtrated unlike the traditional TLE as mentioned above despite a higher bleeding complications than the conventional TLE.

Given that the antithrombotic drug use did not affect either success rate or hemorrhagic complication

event rate after TLO, irrespective of perioperative continuation or discontinuation, the present observations and the previous report imply that the perioperative discontinuation of the antithrombotic drug could be unnecessary. This idea may be guarded because subjects with an indication for TLO are in general patients with an early stage of glaucoma; thus, the short term hemorrhagic complication may not seriously influence the quality of life of patients unless the fellow eye is blind.

In contrast, in TLE and Tube, antithrombotic drug users were more likely to undergo hemorrhagic complications, irrespective of continuation or discontinuation. However, the surgical success rate was not different from the nonusers. These results indicate that antithrombotic drug users would have a higher chance of reduced quality of vision, at least for the short term, due to hemorrhagic complications than the nonusers. Given that the subjects indicative of TLE or Tube are in general in the more advanced stage of glaucoma in both eyes compared to those indicative of TLO, deciding to perform these two procedures is challenging for both patients and clinicians when the patients use antithrombotic drugs, particularly when the fellow eyes are blind. Meticulous risk/benefit analysis is warranted for glaucoma and systemic conditions, particularly cardiovascular status. Shared decision-making processes must determine if TLE or Tube would be performed with continued use of antithrombotic drugs or with the perioperative discontinuation of these drugs, or these surgeries would be given up.

This study has several limitations. First, the study was conducted at a single institute, and the subjects are only Japanese in ethnicity. Although the sample size of 910 is relatively large, our findings cannot be generalized until a larger survey involving multiple institutes would reach the same conclusion. Second, due to its retrospective nature of the study, a bias may have existed where surgeons attempted to make more intensive coagulative manipulation during TLE or Tube surgery for patients with antithrombotic drug use. Third, the magnitude of causative effect for the hemorrhagic complications may vary among different antithrombotic substances [15]. A subgroup analysis for each antithrombotic drug may be ideal but is not straightforward given that as many as eight types of antithrombotic agents are already available. Fourth, we could not show longitudinal data like Kaplan–Meier analysis because we just calculated the two points of IOP, preoperative and postoperative 1 year. Fifth, antithrombotic

drug use changes biomarkers, including the prothrombin time-international normalized ratio (PT-INR), and activates partial thromboplastin time (APTT), eventually affecting the hemorrhagic risk [9]. This study did not monitor or, thus, assess such biomarkers. However, the quasi-randomization by the propensity score matching revealed that the success rate of TLO and TLE was similar between the antithrombotic drug users and the nonusers as aforementioned, suggesting these biomarkers may not have an essential role in the surgical success of glaucoma surgery.

In conclusion, antithrombotic drug use did not influence surgical success at 1 year postoperatively of *ab interno* trabeculotomy, trabeculectomy, or long-Tube shunt surgeries with the ciliary sulcus or vitreous cavity fixation. However, antithrombotic drug use increased the chance of hemorrhagic complications after trabeculectomy and long-Tube shunt surgeries. Meticulous risk per benefit consideration and shared decision-making processes are warranted to determine if TLE or Tube would be performed in antithrombotic drug users.

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Table1: Preoperative patient demographics

	Trabeculotomy	Trabeculectomy	Long-Tube shunt	Total
Number of patients	353	444	113	910
Non-anti-thrombotic drug users	289 (81.9%)	374 (84.2%)	98 (86.7%)	761 (83.6%)
Anti-thrombotic drug users	64 (18.1%)	70 (15.8%)	15 (13.3%)	149 (16.4%)
Antiplatelet only	45 (12.7%)	43 (9.7%)	14 (12.4%)	102 (11.2%)
Discontinued	22	18	3	43
Continued	23	25	11	59
Anticoagulant only	13 (3.7%)	23 (5.2%)	1 (0.9%)	37 (4.1%)
Discontinued	8	12	1	21
Continued	5	11	0	16
Both-drug users	6 (1.7%)	4 (0.9%)	0 (0%)	10 (1.1%)
Discontinued	3	1	0	4
Continued	3	3	0	6

Table 2: The number of previous glaucoma surgery for each procedure

	TLO (n = 353)	TLE (n = 444)	Tube (n = 113)
No previous operation	353	326	28
Previous TLO	0	118	12
Previous TLE	0	0	50
Previous TLO and TLE	0	0	23

TLO, trabeculotomy; TLE, trabeculectomy; Tube, long-Tube shunt

Table 3: A propensity score adjusted comparison of background and outcome between patients who received *ab interno* trabeculotomy with and without the perioperative anti-thrombotic medications

	Non-experiencer (n = 50)	Experiencer (n = 50)	P value
Median age (IQR)	77.0 (73.0, 81.0)	76.5 (71.3, 81.0)	0.69†
Right eye (%)	24 (48)	19 (38)	0.32*
Men (%)	28 (56)	31 (62)	0.69*
Glaucoma type			
Primary open-angle glaucoma (%)	23 (46)	20 (40)	0.69*
Pseudoexfoliation glaucoma (%)	16 (32)	19 (38)	0.54*
Steroid-induced glaucoma (%)	1 (2)	3 (6)	0.62*
Other secondary glaucoma (%)	10 (20)	8 (16)	0.62*
Preoperative HVF MD (IQR), dB	−9.9 (−17.7, −4.9)	−10.5 (−15.4, −5.0)	0.64†
Preoperative IOP (IQR), mmHg	28.0 (23.0, 36.8)	28.0 (24.0, 34.0)	0.64†
Postoperative IOP (IQR), mmHg	17.5 (13.3, 22.0)	15.0 (12.3, 18.8)	0.17†
Success rate (%)	26 (52)	33 (66)	0.22*
Hemorrhagic complication rate (%)	22 (44)	20 (40)	0.84*
Transient IOP elevation	22 (44)	25 (50)	0.69*

IQR, interquartile range; IOP, intraocular pressure; HVF, Humphrey visual field test; MD, mean deviation; † Mann–Whitney U test, * Fisher's exact test

Table 4: A propensity score adjusted comparison of background and outcome between patients who received trabeculectomy with and without the perioperative anti-thrombotic medications

	Non-experiencer (n = 44)	Experiencer (n = 44)	P value
Median age (IQR)	75.0 (68.8, 79.3)	74.0(68.0,82.0)	0.92†
Right eye (%)	24 (55)	18 (41)	0.29*
Men (%)	29 (66)	29 (66)	1.00*
Glaucoma type			
Primary open-angle glaucoma (%)	21 (48)	24 (55)	0.53*
Pseudoexfoliation glaucoma (%)	15 (34)	11 (25)	0.48*
Neovascular glaucoma (%)	1 (2)	0 (0)	1.00*
Other secondary glaucoma (%)	7 (16)	9 (20)	0.78*
Preoperative HVF MD (IQR), dB	−19.6 (−22.9, −15.4)	−20.7 (−25.0, −15.3)	0.87†
Preoperative IOP(IQR), mmHg	24.5 (20.8, 32.0)	23.5 (20.0, 30.5)	0.74†
Postoperative IOP(IQR), mmHg	13.5 (9.0, 18.0)	11.0 (8.0, 16.0)	0.16†
Previous TLO (%)	15 (34)	16 (36)	0.77†
Success rate (%)	31 (70)	33 (75)	0.81*
Hemorrhagic complication rate (%)	5 (11)	13 (30)	<0.05*

IQR, interquartile range; IOP, intraocular pressure; HVF, Humphrey visual field test; MD, mean deviation;† Mann–Whitney U test, * Fisher's exact test

Table 5. A comparison of success rates and hemorrhagic complications between patients who continued anti-thrombotic medications and those who discontinued them among routine users of these medications in each glaucoma surgical procedure

	TLO (n = 64)		TLE (n = 70)		Tube (n = 15)	
	Discontinue	**Continue**	**Discontinue**	**Continue**	**Discontinue**	**Continue**
Success	21	22	24	28	3	9
Fail	12	9	7	11	1	2
P value	0.60*		0.78*		1.0*	
Hemorrhage (+)	20	18	24	23	3	7
Hemorrhage (-)	13	13	7	16	1	4
P value	1.0*		0.13*		1.0*	

* Fisher's exact test

Supplemental Table 1. The proportion and contents of hemorrhagic complications in the three types of glaucoma surgeries

	TLO	**TLE**	**Tube**
Non-experiencers	289	374	98
Layered hyphema	108(37.4%)	62(16.6%)	7(7.1%)
Vitreous hemorrhage	3(1.0%)	4(1.1%)	6(6.1%)
Choroidal hemorrhage	0(0%)	1(0.3%)	0(0%)
Experiencers	64	70	15
Layered hyphema	26(40.6%)	22(31.4%)	2(13.3%)
Vitreous hemorrhage	3(4.7%)	4(5.7%)	3(20.0%)
Choroidal hemorrhage	0(0%)	0(0%)	0(0%)

Supplemental Table 2: A propensity score adjusted comparison of background and outcome between patients who received ab interno trabeculotomy after re-allocating Trabectome to trabeculectomy with and without the peri-operative anti-thrombotic medications

	None (n=41)	Continue/discontinue (n=41)	P value
Median age (IQR)	79.0(75.0,82.0)	77.0(72.0, 81.0)	0.40†
Right eye (%)	16(39)	14(34)	0.66*
Men (%)	15(37)	24(59)	0.076*
Glacoma type			
Primary open angle glaucoma (%)	21(51)	14(34)	0.18*
Pseudoexfoliation glaucoma (%)	12(29)	18(44)	0.18*
Steroid-induced glaucoma (%)	0(0)	2(5)	0.49*
Other secoudary glaucoma (%)	8(20)	7(17)	1.0*
Preoperative HVF MD(IQR), dB	-11.9(-16.8,-7.4)	-11.4(-16.2,-5.7)	0.46†
Preoperative IOP(IQR), mm Hg	25.0(22.0,31.0)	28.0(24.0,34.0)	0.20†
Postoperative IOP(IQR), mm Hg	16.0(12.0,20.0)	14.0(12.0,18.0)	0.56†
Transient IOP elevation (%)	16(39)	18(44)	0.66*
Success rate (%)	28(68)	30(73)	0.81*
Hemorrhagic complication rate (%)	13(32)	14(34)	1.0*

IQR, interquartile range; IOP, intraocular pressure; HVF, Humphrey visual field test; MD, mean deviation;† Mann–Whitney U test, * Chi-square test

Supplemental Table 3: A propensity score adjusted comparison of background and outcome between patients who received trabeculectomy after re-allocating Trabectome to trabeculectomy Trabectome with and without the peri-operative anti-thrombotic medications

	None (n=54)	Continue/discontinue (n=54)	P value
Median age (IQR)	74.0(68.3,82.0)	74.5(68.0,82.0)	0.74†
Right eye (%)	18(33)	24(44)	0.25*
Men (%)	24(44)	36(67)	<0.05*
Glaucoma type			
Primary open angle glaucoma (%)	29(54)	31(57)	0.85*
Pseudoexfoliation glaucoma (%)	18(33)	12(22)	0.28*
Neovascular glaucoma (%)	0(0)	0(0)	1.0*
Other secoudary glaucoma (%)	7(13)	11(20)	0.44*
Preoperative HVF MD(IQR), dB	-18.1(-22.5,-12.2)	-18.3(-24.7,-12.1)	0.68†
Preoperative IOP(IQR), mm Hg	24.5(20.0,35.5)	24.0(20.0,31.5)	0.80†
Postoperative IOP(IQR), mm Hg	13.0(10.0,16.8)	11.0(8.3,18.0)	0.37†
Previous TLO (%)	16(30)	16(30)	0.95†
Success rate (%)	42(78)	36(67)	0.21*
Hemorrhagic complication rate (%)	14(26)	18(33)	0.53*

IQR, interquartile range; IOP, intraocular pressure; HVF, Humphrey visual field test; MD, mean deviation;† Mann–Whitney U test, * Chi-square test

Figure legend

Figure 1: Histograms of the eyes with surgical success and failure stratified by anti-thrombotic therapy experience in three types of glaucoma surgeries

Black bars indicate patients with success at one year, while white bars denote patients with failure. None designates patients who had never taken anti-thrombotic medications, while experiencers are those who routinely used these drugs irrespective of their continuation or discontinuation peri-operatively. n.s., not significant.

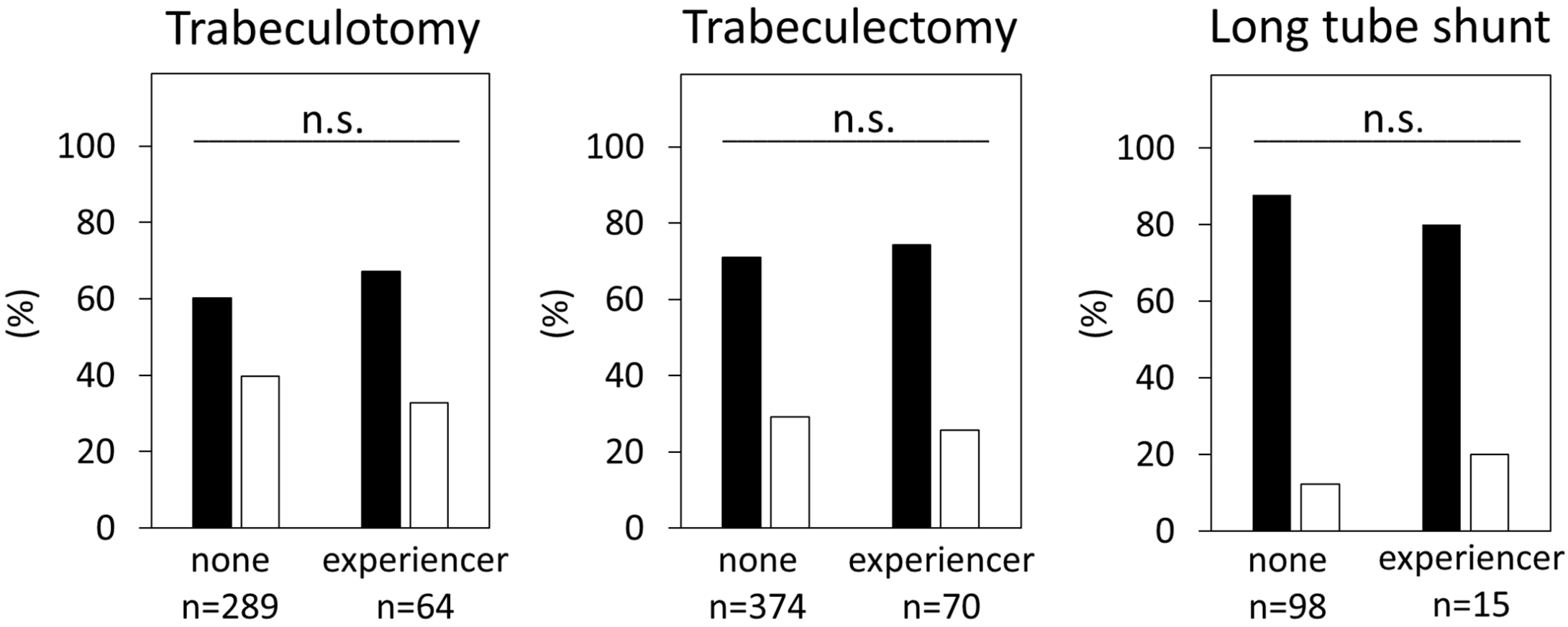
Figure 2: Histograms of the eyes with and without surgery-related hemorrhagic complications stratified by anti-thrombotic therapy experience in three types of glaucoma surgeries

The black bar indicates patients without hemorrhagic complications, while the white bar denotes patients with complications. Designations are the same as in Figure 1. n.s., not significant; *, $p < 0.05$.

Supplemental Figure legend

Supplemental Figure 1　: Histograms of the eyes with surgical successes and hemorrhagic complications stratified by anti-thrombotic therapy experience in TLO after re-allocating Trabectome to TLE

A indicates TLO patients without Trabectome, while B denotes TLE patients including Trabectome. Black bars indicate patients with success or without hemorrhagic complications, while white bars denote patients with failure or hemorrhagic complications. Designations are the same as in Figure 1. n.s., not significant. *, $p < 0.05$.


Trabeculotomy
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Trabeculectomy
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experiencer
n=70
Long tube shunt
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100
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n=98
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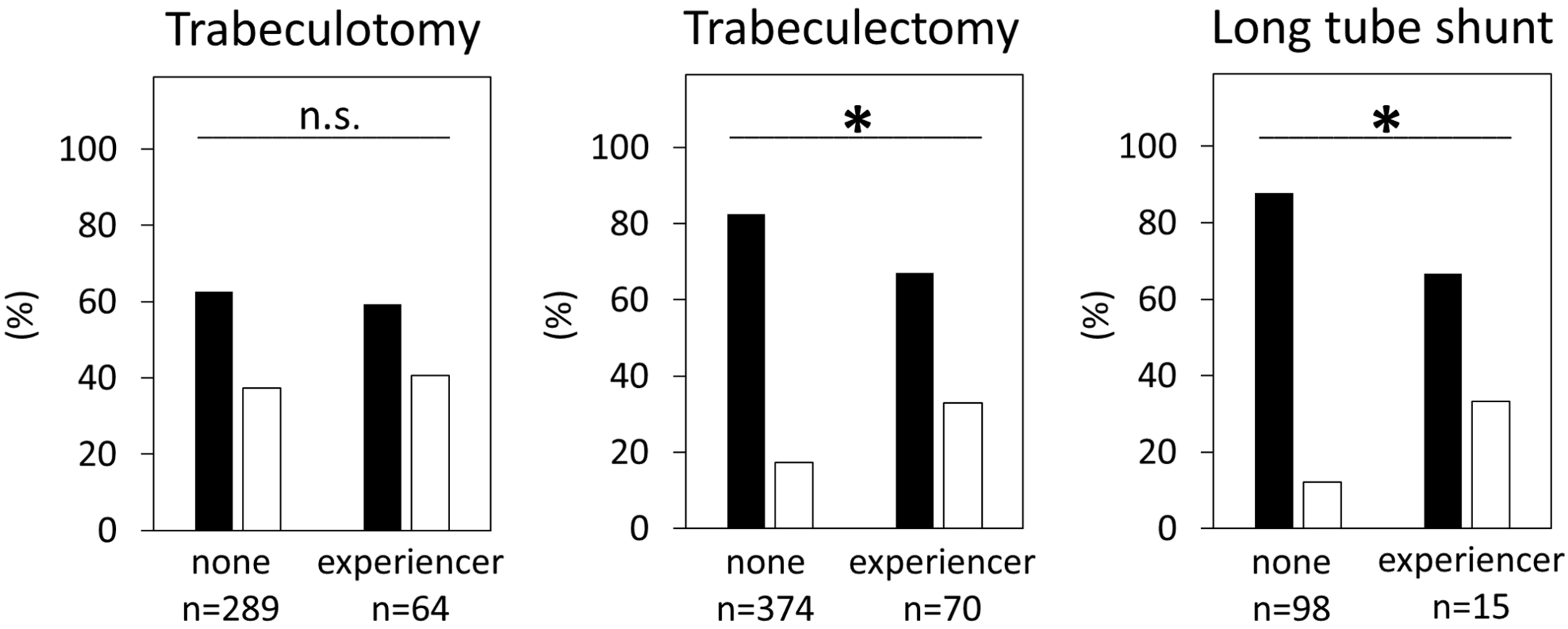
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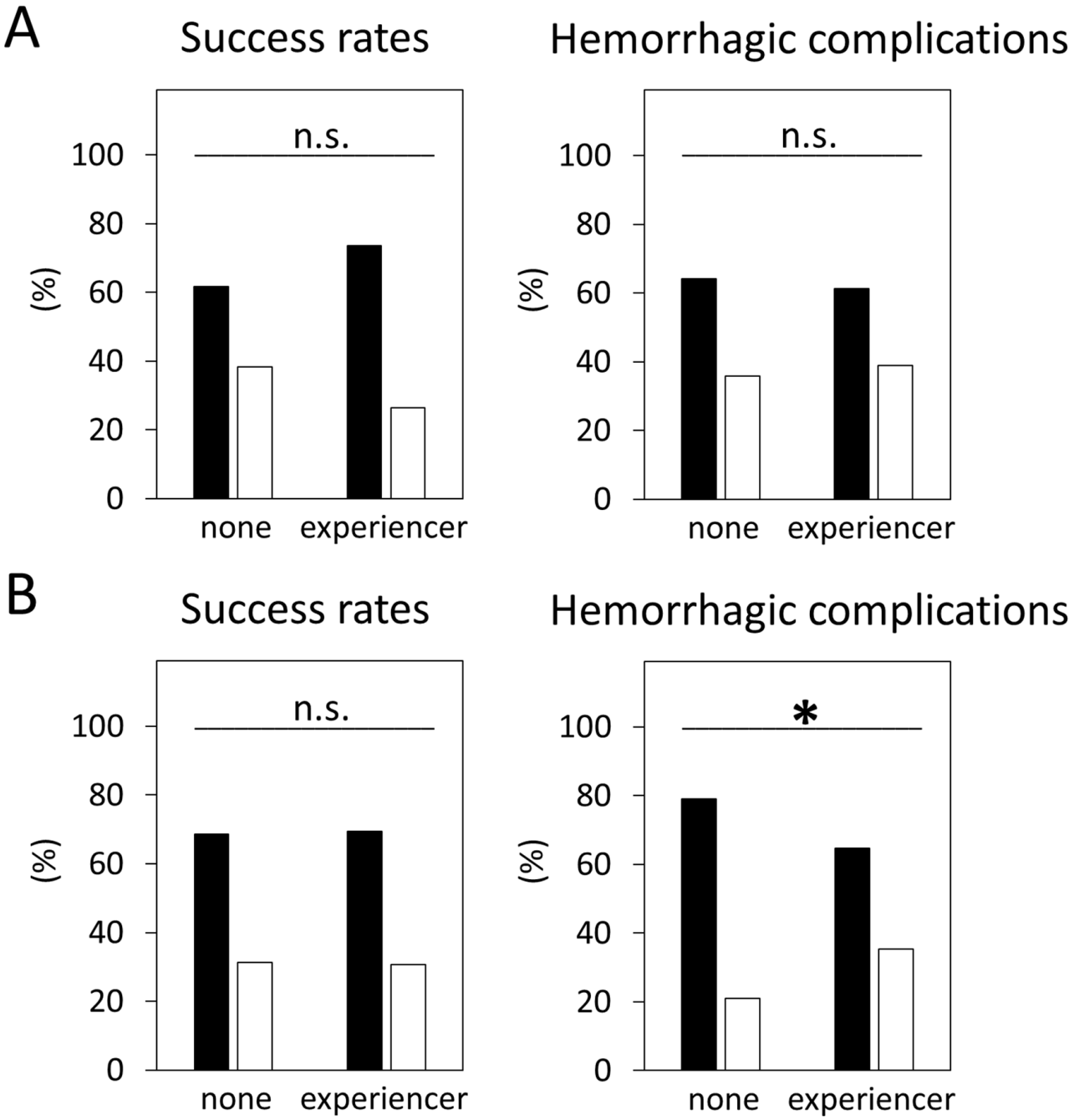
A
Success rates
Hemorrhagic complications
n.s.
n.s.
100
80
60
40
20
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(%)
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B
Success rates
Hemorrhagic complications
n.s.
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