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Changes in glaucoma medication numbers after cataract and glaucoma surgery

A nationwide population-based study

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Abstract

To determine whether cataract or glaucoma and combined cataract and glaucoma surgery (CGS) affect glaucoma medication usage.

We recruited patients who received new diagnoses of glaucoma, either primary open-angle glaucoma (POAG) (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 365.1) or primary angle-closure glaucoma (PACG) (ICD-9-CM code 365.2), between 1998 and 2011 and had undergone cataract surgery alone (CS), glaucoma surgery alone (GS), or CGS under the National Health Insurance program in Taiwan. CS, GS, and CGS in all the patients were performed after the glaucoma diagnosis date. The patients were subdivided into CS, CGS, and GS groups. The number of glaucoma medications, including prostaglandin analogs, β-blockers, carbonic anhydrase inhibitors, α-agonists, pilocarpine, and a combination of drugs, in each prescription, were compared before and after surgery.

The mean number of glaucoma medications in each prescription before the surgery increased from approximately 0.5/1 (CS/CGS + GS) to a peak of 1.75/3 within 3 months before the index date. The mean number of glaucoma medications in each prescription reduced to 0 (CS group) and to approximately 0.5 (CGS and GS) at the end of the 3-year follow-up period. The mean number of glaucoma medications in each prescription significantly reduced at the time points within 6 months, between 6 months and 2 years, and during 2 to 3 years after surgery in each group. At the end of the 3-year period, the reduction effect was most evident in the CS group. Similar trends were also observed in the POAG and PACG group.

CS, GS, and CGS significantly reduced the number of glaucoma medications used by the glaucoma patients.

Abbreviations: CGS = combined cataract and glaucoma surgery, CS = cataract surgery alone, GEE = generalized estimating equations, GS = glaucoma surgery alone, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, IOP = intraocular pressure, NHIRD = National Health Insurance Research Database, PACG = primary angle-closure glaucoma, POAG = primary open-angle glaucoma, RR = relative ratio.

Keywords: cataract, glaucoma medication, glaucoma surgery

1. Introduction

Several studies have shown that cataract extraction plays a crucial role in the controlling intraocular pressure (IOP) in comorbid glaucoma.[1–4] A recent large clinical trial showed that clear lens extraction was more efficacious in IOP control and more cost-effective than laser peripheral iridotomy, and it has been suggested as a first-line treatment for primary angle-closure glaucoma (PACG).[5] However, the role of phacoemulsification in treating primary open-angle glaucoma (POAG) remains controversial.[5] No strong evidence from large randomized

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The NHIRD encrypts personal data of patients to protect their privacy and provides researchers with anonymous identification numbers associated with relevant claims data, including sex, date of birth, medical services received, and prescriptions. Therefore, patient consent is not required before accessing their data from the NHIRD. This study fulfilled the condition for exemption by the Institutional Review Board (IRB) of China Medical University (CMUH104-REC2-115-CR3). Furthermore, the IRB waived the patient consent requirement.

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trials elucidating the role of phacoemulsification is yet available, and available data have been interpreted inconsistently.[6–11] To enhance our understanding of this crucial problem, we designed a study to determine whether cataract surgeryalone (CS) or glaucoma surgery alone (GS) and combined cataract and glaucoma surgery (CGS) affects glaucoma medication usage in Taiwanese patients by using data from the National Health Insurance Research Database (NHIRD). We recruited patients who received new diagnoses of glaucoma (International Classification of Disease, Ninth Revision, Clinical Modification [ICD-9-CM] code 365) between 1998 and 2011 and had undergone either CS, GS, or CGS. To our knowledge, this study is among the few studies worldwide that have investigated this crucial topic by using a large claims database.

2. Patients and methods

2.1. Data source

In Taiwan, the National Health Insurance (NHI) program, launched by the government in 1995, covers all citizens except prison inmates. In this study, patient records were obtained from the NHIRD, which is released and maintained by the National Health Research Institutes. The NHIRD covers approximately 99% of Taiwan's population and provides registration files and inpatient, outpatient, and pharmacy claims data for all insured individuals (http://www.nhi.gov.tw/english/index.aspx). Longitudinal data of medical history records are linked to an encrypted personal identification number of each patient. The diagnostic codes in the NHIRD follow the format of the ICD-9-CM.

2.2. Data availability statement

The data set used in this study is managed by the Taiwan Ministry of Health and Welfare (MOHW). Approval of our application by the MOHW was required to access this data. Any researcher interested in accessing this dataset can submit an application form to the MOHW requesting access. The staff of MOHW can be contacted at stcarolwu@mohw.gov.tw or No.488, Sec. 6, Zhongxiao E. Rd., Nangang Dist., Taipei City 115, Taiwan (R. O.C.) (Phone: +886-2-8590-6848) for further assistance. All relevant data are presented within the paper.

2.3. Study patients

Patients who received new diagnoses of glaucoma (ICD-9-CM code 365), both POAG (ICD-9-CM code 365.1) and PACG (ICD-9-CM code 365.2), between 1998 and 2011 and underwent CS (phacoemulsification or extracapsular lens extraction), GS (trabeculectomy), or CGS after glaucoma diagnosis were identified. The identified patients were divided into 3 groups: CS, CGS, and GS, but patients aged <20 years were excluded. The study index date was the last date of CS or GS. We compared the number of glaucoma medications, including prostaglandin analogs (PGAs), β-blockers, carbonic anhydrase inhibitors (CAIs), α-agonists, pilocarpine, and a combination of drugs, of each prescription before and after surgery over a 3-year follow-up period.

2.4. Statistical analysis

Differences in the distribution of age and sex among the 3 groups were compared using the Chi-square test (for categorical variables) or *t* test (for continuous variables). The difference between the mean number of glaucoma medications in each prescription before and after index date among the 3 groups was measured using the sign test. Generalized estimating equations (GEEs) adjusted for age and sex by using Poisson's distribution and log link were used to compare the relative changes in the number of glaucoma medications in each prescription before surgery (6 months) and after surgery (within 6 months, between 6 months and 2 years, and during 2–3 years). Relative ratio (RRs) and 95% confidence intervals (CIs) obtained from the GEE model indicated the after-to-before (with reference to the index date) average number of glaucoma medications required simultaneously. All *P* values less than .05 were considered significant.

3. Results

Figure 1 shows the flow chart of patient selection process.

3.1. Demographic data of the patients

The patients in the CS group were older than those in the CGS and GS groups, and 55.7% of the total 4369 patients were women (Table 1). The patients in the GS group were the youngest among the 3 groups, and 64.6% of them (216 patients) were men. Among the groups, the mean number of glaucoma medications in each prescription before the surgery increased from approximately 0.5/1 (CS /GS + CGS) at 6 months before the index date to 1.75/3 within 3 months before the index date (Fig. 2). The mean number of glaucoma medications of each prescription reduced to 0 (in the CS group) and approximately 0.5 (in the GS and CGS groups) at the end of the 3-year period after the index date.

3.2. Changes in the number of glaucoma medications before and after surgery

The mean numbers of glaucoma medications in each prescription significantly reduced within 6 months, between 6 months and 2 years, and during 2 to 3 years in all the groups (Table 2). At the end of the 3-year period, the reduction effect was most clearly visible in the CS group (RR = 0.19, 95% CI = 0.18–0.20). Significant reductions were also observed in the other 2 groups (RR = 0.31 with 95% CI = 0.27–0.35 and RR = 0.23 with 95% CI = 0.20–0.27 in the CGS and GS groups, respectively). Similar trends were also observed in the POAG or PACG groups.

3.3. Changes in number of glaucoma medication stratified by age and sex

Further analyses stratified by age and sex are presented in Table 3. We stratified the patients in the 3 groups by age and sex to evaluate differences attributable to differences in surgery different age groups and sex groups. We observed significant reductions in all strata among all the groups.

4. Discussion

Our results showed that CS, GS, or CGS significantly reduced glaucoma medication usage in the Taiwanese patients, which indirectly indicated the IOP-lowering effect of these surgical procedures. Moreover, another crucial finding was that the glaucoma patients in the CS group were considerably older than those in the other 2 groups (mean age: 69.0 years). The patients in the GS group were the youngest among the 3 groups (mean age: 56.3 years). To our knowledge, clinicians in clinical practice

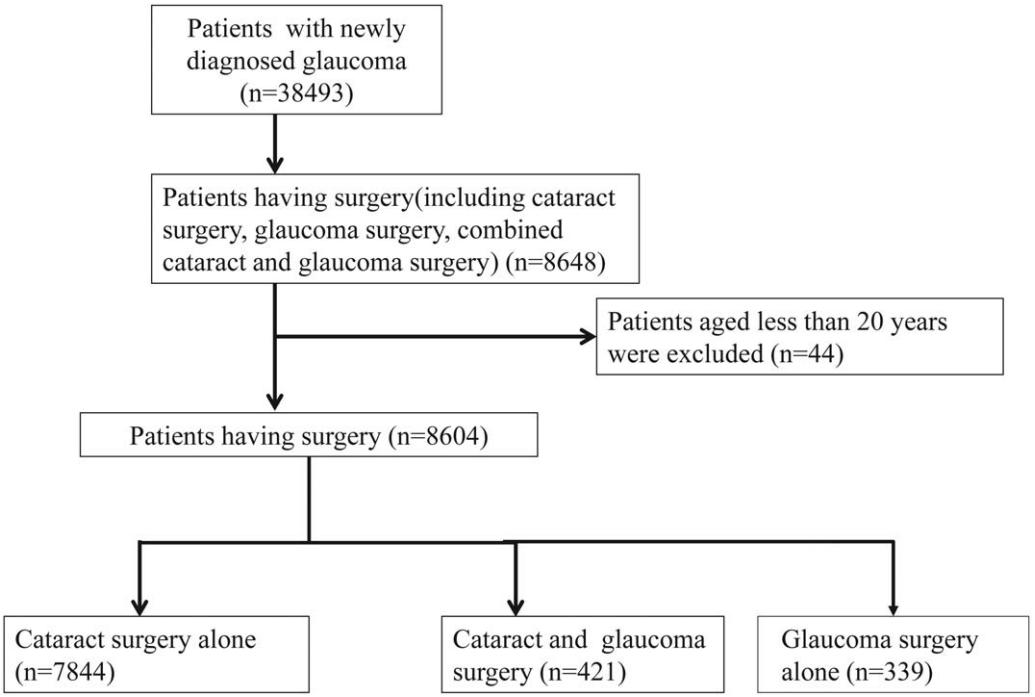

Figure 1. Flowchart depicting the patient selection process.

Table 1

Demographic data of patients.

Variable	Cataract surgery alone (N = 7844)	Cataract and glaucoma surgery (N = 421)	Glaucoma surgery alone (N = 339)	*P* value
Age, years				<.001
≤49	378 (4.82)	16 (3.80)	114 (33.6)	
50–64	1910 (24.4)	113 (26.8)	111 (32.7)	
65+	5556 (70.8)	292 (69.4)	114 (33.6)	
Mean (SD)*	69.0 (10.2)	68.6 (9.65)	56.3 (15.5)	<.001
Sex				<.001
Female	4369 (55.7)	193 (45.8)	120 (35.4)	
Male	3475 (44.3)	228 (54.2)	219 (64.6)	

Chi-square test.
* *t* test.

consider decision making for glaucoma treatment a major challenge. Crucial factors, including the level of IOP, severity of cataract, corneal condition, and optic nerve function, should be considered simultaneously to arrive at the correct decision.

For glaucoma patients without cataract, trabeculectomy is clearly the first choice for reducing IOP. Therefore, the mean age of the patients in this group is less than the mean ages of the patients in the other groups. However, for glaucoma patients

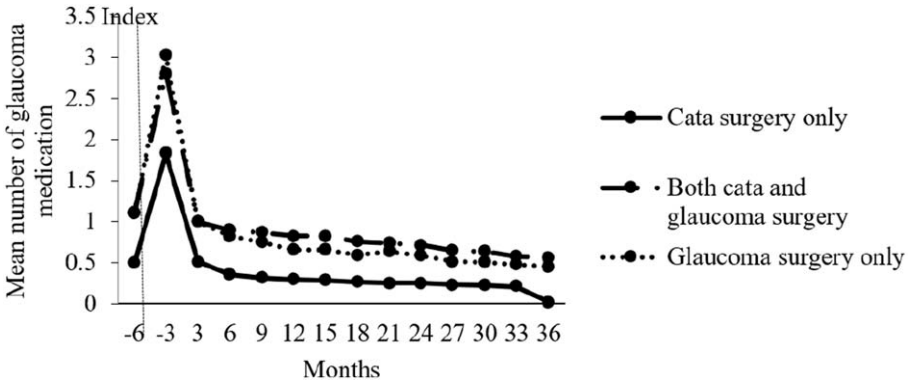

Figure 2. Mean number of glaucoma medications before and after the index date among patients undergoing different types of surgery.

Table 2

Changes in the number of glaucoma medication.

	6 months before surgery	6 months after surgery	Change			6 months to 2 years after surgery	Change			2-3 year after surgery	Change		
	Mean, SD	Mean, SD	Mean, SD	P value*	Relative ratio, 95% CI†	Mean, SD	Mean, SD	P value*	Relative ratio, 95% CI†	Mean, SD	Mean, SD	P value*	Relative Ratio, 95% CI†
Cataract surgery alone	1.22 (1.30)	0.39 (0.75)	−0.82 (1.02)	<.001	0.32 (0.31, 0.34)	0.36 (0.80)	−0.86 (1.16)	<.001	0.30 (0.28,0.31)	0.23 (0.63)	−0.99 (1.24)	<.001	0.19 (0.18, 0.20)
Cataract + glaucoma surgery	2.83 (1.48)	1.21 (1.18)	−1.62 (1.35)	.001	0.43 (0.39, 0.46)	1.31 (1.35)	−1.52 (1.55)	<.001	0.46 (0.42,0.51)	0.86 (1.13)	−1.96 (1.66)	<.001	0.31 (0.27,0.35)
Glaucoma surgery alone	3.04 (1.43)	1.16 (1.12)	−1.88 (1.51)	<.001	0.38 (0.35, 0.42)	1.17 (1.28)	−1.87 (1.64)	<.001	0.38 (0.34,0.43)	0.71 (1.05)	−2.33 (1.72)	<.001	0.23 (0.20, 0.27)
POAG													
Cataract surgery alone (N=545)	1.52 (1.30)	0.47 (0.79)	−0.99 (1.04)	<.001	0.31 (0.28, 0.36)	0.42 (0.81)	−1.10 (1.24)	<.001	0.28 (0.24, 0.32)	0.27 (0.70)	−1.26 (1.30)	<.001	0.18 (0.14, 0.22)
Cataract + glaucoma surgery (N=18)	3.61 (1.42)	0.92 (1.34)	−2.00 (1.53)	<.001	0.26 (0.17, 0.40)	1.72 (1.67)	−1.89 (2.14)	.002	0.48 (0.30, 0.76)	1.06 (1.30)	−2.56 (2.09)	<.001	0.29 (0.16, 0.54)
Glaucoma surgery alone (N=24)	3.33 (1.74)	1.09 (1.14)	−1.92 (1.38)	<.001	0.35 (0.24, 0.50)	1.04 (1.16)	−2.29 (1.71)	<.001	0.31 (0.21, 0.47)	0.38 (0.92)	−2.96 (1.92)	<.001	0.11 (0.04, 0.30)
PACG													
Cataract surgery alone (N=1103)	1.78 (1.40)	0.47 (0.79)	−1.31 (1.20)	<.001	0.26 (0.24, 0.29)	0.41 (0.85)	−1.37 (1.31)	<.001	0.23 (0.21, 0.26)	0.24 (0.67)	−1.54 (1.36)	<.001	0.14 (0.12, 0.16)
Cataract + glaucoma surgery (N=53)	3.32 (1.57)	0.92 (1.34)	−2.40 (1.56)	<.001	0.28 (0.20, 0.40)	1.30 (1.65)	−2.01 (1.78)	<.001	0.39 (0.29, 0.54)	0.72 (1.12)	−2.60 (1.82)	<.001	0.22 (0.14, 0.33)
Glaucoma surgery alone (N=54)	3.41 (1.31)	1.09 (1.14)	−2.31 (1.65)	<.001	0.32 (0.24, 0.43)	1.02 (1.34)	−2.39 (1.64)	<.001	0.30 (0.21, 0.42)	0.57 (0.90)	−2.83 (1.56)	<.001	0.17 (0.11, 0.26)

* Sign test.
† GEE model adjusted for age, and sex.

with cataract, deciding between CGS and CS is complicated.[1,12] A recent meta-analysis of 37 treatment arms revealed that phacoemulsification causes a reduction in IOP.[1] For angle-closure glaucoma (ACG), the results showed a decrease of 6.4 mmHg in IOP at final follow-up (≥12 months). The open-angle glaucoma (OAG) group exhibited an overall IOP change of 2.7 mmHg from baseline. However, the authors noted some sources of bias, including loss to follow-up, washout, medication use, and lack of a control group. Therefore, the role of CS in reducing IOP remains unconfirmed in OAG eyes. However, CS (or clear lens extraction) is a suitable option for reducing IOP in ACG eyes according to the results of a large-scale randomized clinical trial.[5,13] Furthermore, clear lens extraction exhibited higher efficacy and was more cost-effective than laser peripheral iridotomy and should, therefore, be considered as a feasible first-line treatment.[5,14] Another meta-analysis showed low-quality evidence that CGS may result in more effective IOP control at 1 year than CS.[12] Several factors, such as visual field tests and quality of life, have not been considered in these studies. Additional studies evaluating clinically crucial outcomes are required to provide evidence to support treatment recommendations for glaucoma patients with cataract.[12]

Some meaningful results should be stated and discussed. First, the mean numbers of glaucoma medication usage at 6 months before surgery were 1.22 (±1.30), 2.83 (±1.48), and 3.04 (±1.43) in the CS, CGS, and GS groups, respectively. In actual clinical practice, the decision of timing surgical intervention for glaucoma patients depends not only on the level of IOP but also on the number of glaucoma medications used. In the GS group, the number of glaucoma medications used was 3.04, which indicated that the patients simultaneously required 3 types of glaucoma medication to control IOP. Hence, GS was the best choice for this group. However, in the CS group, the number of glaucoma medications was only 1.22, which indicated that patients needed less than 2 types of glaucoma medications for IOP control. For this group, CS would be sufficient for IOP control.

Regarding the short-term and long-term effects of the surgical procedures, we followed up the patients for up to 3 years after the index date. The mean number of glaucoma medications in each prescription reduced to 0 (in the CS group) and approximately 0.5 (in the GS and CGS groups). Furthermore, the mean number of glaucoma medications in each prescription significantly decreased within 6 months, between 6 months and 2 years, and during 2 to 3 years after surgery in all the groups. Further analyses stratified by age and sex also showed significant reductions in glaucoma medication numbers in all the subgroups. All these findings support the notion that surgical procedures effectively control IOP by reducing the usage of glaucoma medication. Furthermore, a similar trend was observed in the POAG or PACG groups. A similar study was proposed by Chang et al; they reported that the prescriptions of glaucoma medications reduced considerably after CS. Although the percentage reduction in the demand for antiglaucoma medications after CS was significantly larger in PACG patients than in POAG patients, the reduction was sustained for 5 years in the PACG and POAG patients.[15] Our results are consistent with these meaningful findings and suggest that CS significantly reduced medication usage in the glaucoma patients.

Despite obtaining meaningful results, our study had the following limitations.[16] First, we defined glaucoma by relying entirely on claims data (ICD-9-CM coding); this approach may be less accurate than conducting individual diagnoses through a standardized procedure. In a study that uses a claims database;

Table 3

Changes in the number of glaucoma medication stratified by age and sex.

	6 months before surgery	6 months after surgery	Change			6 months to 2 years after surgery	Change			2–3 years after surgery	Change		
	Mean, SD	Mean, SD	Mean, SD	*P* value*	Relative Ratio, 95% CI†	Mean, SD	Mean, SD	*P* value*	Relative ratio, 95% CI†	Mean, SD	Mean, SD	*P* value*	Relative ratio, 95% CI†
Cataract surgery alone													
Age, years													
≤49	1.44 (1.38)	0.55 (0.92)	−0.89 (1.08)	<.001	0.38 (0.33, 0.43)	0.54 (1.04)	−0.91 (1.22)	<.001	0.37 (0.32,0.44)	0.27 (0.70)	−1.18 (1.32)	<.001	0.19 (0.14, 0.24)
50-64	1.26 (1.29)	0.40 (0.77)	−0.86 (1.02)	<.001	0.32 (0.30, 0.34)	0.37 (0.83)	−0.88 (1.21)	<.001	0.30 (0.27,0.33)	0.25 (0.66)	−1.01 (1.26)	<.001	0.20 (0.18, 0.22)
65+	1.19 (1.29)	0.38 (0.73)	−0.80 (1.02)	<.001	0.32 (0.31, 0.34)	0.34 (0.76)	−0.84 (1.15)	<.001	0.29 (0.28,0.30)	0.22 (0.62)	−0.97 (1.22)	<.001	0.18 (0.17, 0.20)
Sex													
Female	1.18 (1.28)	0.37 (0.73)	−0.81 (1.01)	<.001	0.31 (0.30, 0.33)	0.33 (0.76)	−0.84 (1.14)	<.001	0.28 (0.27,0.30)	0.21 (0.59)	−0.97 (1.20)	<.001	0.18 (0.17, 0.19)
Male	1.26 (1.31)	0.43 (0.77)	−0.84 (1.04)	<.001	0.34 (0.32, 0.35)	0.40 (0.84)	−0.87 (1.20)	<.001	0.31 (0.29,0.33)	0.25 (0.68)	−1.02 (1.28)	<.001	0.20 (0.18, 0.21)
Cataract and glaucoma surgery													
Age, years													
≤49	3.06 (1.48)	1.56 (1.31)	−1.50 (1.51)	.001	0.51 (0.35,0.74)	1.31 (1.35)	−1.75 (2.08)	.01	0.43 (0.25,0.75)	1.00 (1.100	−2.06 (1.88)	.003	0.33 (0.18, 0.58)
50-64	2.77 (1.45)	1.11 (1.11)	−1.66 (1.38)	<.001	0.40 (0.34,0.47)	1.20 (1.31)	−1.57 (1.63)	<.001	0.43 (0.36,0.53)	0.89 (1.26)	−1.88 (1.63)	<.001	0.32 (0.25, 0.41)
65+	2.84 (1.49)	1.23 (1.19)	−1.61 (1.33)	<.001	0.43 (0.39,0.47)	1.35 (1.36)	−1.49 (1.50)	<.001	0.47 (0.43,0.53)	0.85 (1.09)	−1.99 (1.67)	<.001	0.30 (0.26, 0.35)
Sex													
Female	2.78 (1.50)	1.13 (1.16)	−1.65 (1.39)	<.001	0.41 (0.36,0.46)	1.24 (1.42)	−1.53 (1.59)	<.001	0.45 (0.39,0.52)	083 (1.17)	−1.95 (1.69)	<.001	0.30 (0.25, 0.36)
Male	2.87 (1.46)	1.27 (1.19)	−1.60 (1.32)	<.001	0.44 (0.40,0.49)	1.36 (1.28)	−1.51 (1.53)	<.001	0.47 (0.42,0.53)	0.89 (1.11)	−1.98 (1.65)	<.001	0.31 (0.27, 0.37)
Glaucoma surgery alone													
Age, years													
≤49	3.31 (1.46)	1.31 (1.25)	−2.00 (1.52)	<.001	0.40 (0.34,0.47)	1.32 (1.39)	−1.99 (1.60)	<.001	0.40 (0.33,0.48)	0.82 (1.09)	−2.49 (1.67)	<.001	0.25 (0.19, 0.32)
50-64	2.78 (1.44)	1.05 (0.99)	−1.74 (1.52)	<.001	0.38 (0.31,0.45)	1.05 (1.14)	−1.73 (1.60)	<.001	0.38 (0.31,0.46)	0.61 (0.94)	−2.17 (1.78)	<.001	0.22 (0.16, 0.30)
65+	3.01 (1.37)	1.12 (1.11)	−1.89 (1.50)	<.001	0.37 (0.31,0.44)	1.12 (1.29)	−1.89 (1.71)	<.001	0.37 (0.30,0.46)	0.68 (1.11)	−2.32 (1.72)	<.001	0.23 (0.17, 0.31)
Sex													
Female	2.87 (1.46)	1.17 (1.16)	−2.05 (1.51)	<.001	0.36 (0.31,0.43)	1.14 (1.34)	−2.08 (1.72)	<.001	0.35 (0.29,0.44)	0.73 (1.16)	−2.49 (1.81)	<.001	0.23 (0.17, 0.30)
Male	2.94 (1.41)	1.16 (1.11)	−1.78 (1.51)	<.001	0.39 (0.35,0.45)	1.18 (1.25)	−1.76 (1.59)	<.001	0.40 (0.35,0.46)	0.69 (0.99)	−2.24 (1.67)	<.001	0.24 (0.19, 0.29)

* Sign test.

† GEE model adjusted for age, and sex.

clinical information regarding IOP level, anterior chamber depth, visual acuity, visual field findings, and optic nerve evaluations are not available. To improve patient selection accuracy, we selected patients with both diagnostic and surgery codes. Furthermore, in actual clinical practice, the optimal timing for decision making for selection of the surgical procedure for each glaucoma patient is 6 months before surgery. Therefore, we evaluated the medication usage 6 months before surgery. We did not recruit patients based on medication usage coding because not all glaucoma patients used glaucoma medications 6 months before surgery. Second, laboratory and imaging data were not available in the individual chart records. The NHIRD is used primarily for insurance purposes and has not been validated entirely for research; thus, uncontrolled confounding factors such as visual field severity, IOP readings, and potential biases may have affected our retrospective case–control study. Third, despite the large sample size, the study cohort consisted of Taiwanese patients; hence, these findings are not adequately applicable to other populations. Fourth, patients with glaucoma received CS, GS or CGS, depending on the decisions of their doctors; therefore, the result might not be representative of the entire population. Future prospective longitudinal study, including other outcomes such as quality of life, clinical severity information, and cost-effectiveness analysis, are required to provide evidence to support treatment recommendations.

Our study had the following strengths. First, the strength of the database is excellent because of the large sample randomization. Moreover, we could follow-up the patients over time to assess glaucoma medication usage before and after these surgical procedures.[17] Second, the database includes data on a broad range of people with different sociodemographic profiles, unlike some smaller studies in which patients are recruited from specific regions. The study populations selected in these studies might not be representative of the entire population.[17] Third, our study is the first to evaluate glaucoma medication usage before and after CGS, CS, or GS in a purely Chinese population by using a large claims database. Our findings can provide a strong foundation for further longitudinal research.

In conclusion, CGS, CS, and GS significantly reduced the number of glaucoma medication used by the glaucoma patients. A similar trend was observed in the POAG and PACG groups.

Author contributions

Design and conduct: Hsin-Yi Chen, Cheng-Li Lin, Chia-Hung Kao
Analyze the data: Hsin-Yi Chen, Cheng-Li Lin, Chia-Hung Kao
Write the manuscript: Hsin-Yi Chen, Cheng-Li Lin, Chia-Hung Kao
Modify the manuscript: Hsin-Yi Chen, Chia-Hung Kao
Final approval of manuscript: Hsin-Yi Chen, Cheng-Li Lin, Chia-Hung Kao
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Data curation: Hsin-Yi Chen, Cheng-Li Lin, Chia-Hung Kao.
Formal analysis: Cheng-Li Lin.
Funding acquisition: Chia-Hung Kao.
Investigation: Chia-Hung Kao.
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Project administration: Chia-Hung Kao.
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