LATE-ONSET OCULAR HYPERTENSION AFTER VITRECTOMY

A Multicenter Study of 6,048 Eyes

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Purpose: To determine the incidence and risk factors for late-onset ocular hypertension (LOH) after vitrectomy.

Methods: From the electronic medical records of consecutive patients who underwent primary vitrectomy, from January 2010 to December 2015, at 5 tertiary vitreoretinal centers in Italy, patient demographics, systemic, ophthalmic, operative, and postoperative data were drawn. Main outcome measure was the presence of LOH, defined as intraocular pressure >21 mmHg detected more than 2 months after vitrectomy on at least 2 consecutive visits.

Results: Among 6,048 patients, LOH was found in 294 (4.9%) vitrectomized eyes and in 87 (1.4%) fellow eyes, (chi square; $P < 0.001$). Multivariable logistic regression showed that significant risk factors for developing LOH included intraoperative triamcinolone use (odds ratio [OR], 7.62; $P < 0.001$), longer axial length (OR, 1.55; $P = 3.023$), preoperative higher intraocular pressure (OR, 1.81; $P = 0.003$), and postvitrectomy pseudophakic/aphakic status (OR, 2.04; $P < 0.001$). Decision-tree analysis showed that the stronger predictor of LOH was intraoperative triamcinolone use ($P < 0.001$). Secondary predictors were a preoperative intraocular pressure more than 15 mmHg ($P < 0.001$) in eyes that use triamcinolone, and postvitrectomy pseudophakic/aphakic status ($P = 0.007$) in eyes that did not use triamcinolone.

Conclusion: Late-onset ocular hypertension occurred in 4.9% of vitrectomized eyes. The main risk factors were intraoperative use of triamcinolone and postvitrectomy pseudophakic/aphakic status.

RETINA 00:1–9, 2018

From the beginning, pars plana vitrectomy has gained wide-spread popularity thanks to the numerous technological advances that have improved its efficacy and safety; over the past decade, the overall rate of vitrectomies has increased around 30% in the United States, and vitrectomy has become the third most common ocular surgery after cataract and laser refractive surgery, with approximately 225,000 procedures performed in the United States each year.[1,2]

The indications for this surgery continue to widen and also pathologies leading to a mild visual impairment, such as vitreous floaters, are now treated; the threshold level of visual acuity has dropped progressively, and the visual outcome is becoming the primary goal of this surgery.[3] Therefore, detecting long-term vitrectomy complications has become increasingly important, particularly when taking into consideration that lifetime risks of such complications could be remarkable, as patients tend to be younger.[2]

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None of the authors has any financial/conflicting interests to disclose.

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Late-onset ocular hypertension (LOH) has been described as a long-term complication of vitrectomy,[4,5] and it may threaten the visual outcome of the surgery as a result of glaucomatous damage. Previous studies have estimated an incidence ranging from 2% to 19%,[4–9] which could be underestimated because of the low amount of long-term results.

Furthermore, the possible risk factors associated with its development have not been completely identified. Only a few variables have been identified, namely family history of open-angle glaucoma and pseudophakic status.[2,7,8] However, no study has had a large enough sample to provide a systematic assessment of risk factors associated with this complication. Identification of risk factors may facilitate clinicians to identify high-risk patients, allowing for early detection and treatment of this condition and preventing irreversible damage.

The aim of this study was to assess the incidence of LOH after vitrectomy and to evaluate risk factors associated with its development.

Methods

In this retrospective multicenter cohort study, were included all consecutive patients who had undergone primary pars plana vitrectomy only in one eye with unaffected fellow eye from January 2010 to December 31, 2015, at 5 tertiary vitreoretinal centers in Italy: the centers were the Eye Clinic of the University of Catania, the Eye Clinic of the University of Ancona, the Eye Clinic of the University of Bari, the Eye Clinic of the University of Sassari, and the Eye Clinic of the University of Napoli. The institutional review board at the coordinating center (University of Catania, Italy) and at the other participating centers approved the study; informed consent was obtained from all subjects. The study protocol and data collection conformed to the tenets of the Declaration of Helsinki.

Exclusion criteria both in vitrectomized and in fellow eyes included: any preexisting diagnosis of ocular hypertension or any type of glaucoma or an intraocular pressure (IOP) >18 mmHg, any previous ocular surgery except uncomplicated cataract surgery, eyes with a history of chronic steroid use (either topical or systemic), a history of anterior segment inflammation or ocular inflammatory disease, previous intravitreal or periocular steroid injections, and a diagnosis of iris neovascularization. In vitrectomized eyes were excluded: eyes that underwent pars plana vitrectomy for ocular trauma, endophthalmitis, and choroidal hemorrhage, those that received silicone oil as tamponade, or intraoperative intraocular steroids with therapeutic purpose. Moreover, patients suffering from postoperative complications, such as acute IOP increase, corneal dysfunction, angle closure, suprachoroidal hemorrhage, or those who received postoperatively topical steroids longer than 2 months, and those who underwent further surgery after primary vitrectomy, except cataract surgery, were excluded. Only eyes with documented gonioscopic findings indicating that the anterior chamber angle was open were included.

Patient demographics, ophthalmic, systemic, operative, and postoperative data were drawn from electronic medical records. In each center, 2 separate investigators, previously qualified in the methods of chart abstraction, were committed the task of reviewing the charts of patients separately. Chart abstractors were blinded as to the aim of the study.

Age and sex were analyzed as demographic data. Systemic factors included history of diabetes, hypertension, and cardiovascular diseases. Ophthalmic features included axial length, preoperative lens condition, and preoperative IOP measured with a Goldmann applanation tonometer. Operative data included indication for vitrectomy (diabetic retinopathy, rhegmatogenous retinal detachment, epiretinal membrane, macular hole, dropped lens/intraocular lens, and other indications), type of surgical procedure (combined vitrectomy and phacoemulsification or vitrectomy alone), use of laser photocoagulation (extensive photocoagulation: 360°/panretinal photocoagulation; localized photocoagulation; and no photocoagulation), use of cryotherapy, size of tools (20, 23, 25, or 27 gauge), use of triamcinolone acetonide as vitreous dye, use of brilliant blue dye for epiretinal membrane/outer limiting membrane, type of tamponade agent (air, SF6, C3F8, or no tamponade), and use of scleral buckling. Postoperative data included final lens status, postoperative IOP, and cataract surgery.

Late-onset ocular hypertension after vitrectomy was defined by the presence of an IOP >21 mmHg detected more than 2 months postoperatively on at least 2 consecutive examinations.[5] As a clinical standard, and per protocol, all IOP assessments were performed by Goldmann applanation tonometer.

The interval between vitrectomy and LOH diagnosis was assessed. The development of ocular hypertension, defined by an IOP >21 mmHg, in the fellow eye was also assessed.

Statistical Analysis

The full number of vitrectomy procedures was identified, and the overall incidence rate of LOH was calculated; the rate of fellow untreated eyes

that developed an ocular hypertension was also determined.

Kaplan–Meier survival analyses were applied to assess the development of LOH in vitrectomized eyes and in fellow untreated eyes; survival curves were compared by the log-rank (Mantel–Cox) test.

In the group of vitrectomized eyes, potential risk factors for LOH were identified in univariate analyses, using the chi-square or Fisher exact tests for categorical variables, and Mann–Whitney tests for quantitative variables. Odd ratio was also calculated; for the continuous variables, Exp(B) from binary logistic regression has been used. Risk factors that were significant at the $P < 0.2$ level in the univariate analysis were included in the multivariable logistic regression analysis.

Risk factors were also evaluated comparing vitrectomized eyes that had received triamcinolone acetonide as vitreous dye versus those that had not received triamcinolone.

The predicting capability of the variables using a regression based on conditional inference decision trees was also investigated. Risk models were developed using a decision-tree induction from class-labeled training records: the development of LOH was the dependent variable, and the other attributes were the predictor variables; the individual records are the tuples for which the class label is known, as previously described.[10]

All differences were considered to be statistically significant at a 5% probability level, and all reported *P* values are 2-sided. Statistical analysis used IBM SPSS Statistics for Windows (Version 21.0; IBM Corp, Armonk, NY).

Results

Overall, 7,004 eyes that underwent vitrectomy at 5 surgical units between January 2010 and December 2015 were screened: 956 were excluded (109 for preexisting glaucoma or ocular hypertension, 25 for previous uveitis, 432 had previous surgery, 14 had vitrectomy for endophthalmitis, 8 had vitrectomy for ocular trauma, 2 had vitrectomy for choroidal hemorrhage, 179 received silicone oil tamponade, 38 had postoperative complications, and 149 had further surgery), and 6,048 eyes were included in the analysis. The mean ± SD age was 66.2 ± 9.6 years. Patients were followed at every month in the first 3 months, then at about 3 months to 6 months. Mean postoperative follow-up duration was 39 ± 18 months, and overall, 5,899 eyes (97.54%) were followed for more than 6 months.

The mean ± SD baseline IOP in the eyes that underwent vitrectomy was 14.3 ± 1.9 mmHg and 14.6 ± 1.8 mmHg in the fellow eyes ($P < 0.001$). The mean ± SD final IOP was 14.9 ± 3.0 mmHg ($P < 0.001$ vs. baseline) in eyes that underwent vitrectomy and 14.6 ± 2.6 mmHg in the fellow eyes ($P = 0.126$).

Late-Onset Ocular Hypertension Incidence

Overall, the incidence of LOH was 4.85% (294/6,048) in the eyes that underwent vitrectomy and 1.43% (87/6,048) in the fellow untreated eye (chi square; $P < 0.001$). In all centers, the eyes with LOH received topical hypotonizing agents.

In patients who developed LOH, mean baseline IOP was 14.5 ± 2.0 mmHg in vitrectomized eyes and 14.1 ± 1.4 mmHg in fellow eyes ($P = 0.005$). In patients who did not develop LOH, mean baseline IOP was 14.3 ± 1.0 mmHg in vitrectomized eyes ($P = 0.028$ vs. other group) and 14.4 ± 1.6 mmHg ($P < 0.001$) in fellow eyes.

In the eyes that developed LOH, the mean IOP at diagnosis was 23.9 ± 1.8 mmHg, with a mean IOP increase of 9.6 ± 1.3 mmHg; the mean IOP increase in eyes that did not develop LOH was 0.5 ± 0.7 mmHg.

Overall, ocular hypertension was found in both eyes in 8 patients (8/6,048, 0.1%), only in vitrectomized eye in 286 patients (286/6,048, 4.7%), only in fellow eye in 79 patients (79/6,048, 1.3%), and in neither eye in 5,699 patients (5,675/6,048, 93.8%).

Figure 1 shows the results of Kaplan–Meier survival analyses for vitrectomized eyes and fellow eyes. The number of eyes with LOH increased over time in both groups, and it was significantly higher in vitrectomized eyes (the log-rank test $P < 0.001$) (hazard ratio 3.38, 95% confidence interval [CI] 2.76–4.13).

Univariate Analysis

Univariate analysis showed that in vitrectomized eyes, significant variables related with increased risk of LOH included: longer axial length (25.9 ± 1.6 mm in the hypertension group, 25.1 ± 1.8 mm in controls; odds ratio [OR], 1.23 [95% CI 1.18–1.30]; $P < 0.001$), preoperative higher IOP (14.5 ± 2.0 mmHg in the hypertension group, 14.3 ± 1.0 mmHg in controls; OR, 1.07 [95% CI 1.01–1.14]; $P = 0.022$), preoperative pseudophakic/aphakic status (35.7% of the hypertension group, 28.4% of controls; OR, 1.40 [95% CI 1.09–1.79]; $P = 0.009$), presence of rhegmatogenous retinal detachment (51.4% of the hypertension group, 44.8% of controls; OR, 1.30, [95% CI 1.03–1.65]; $P = 0.031$), use of triamcinolone acetonide (71.4% of the hypertension group, 28.4% of controls;

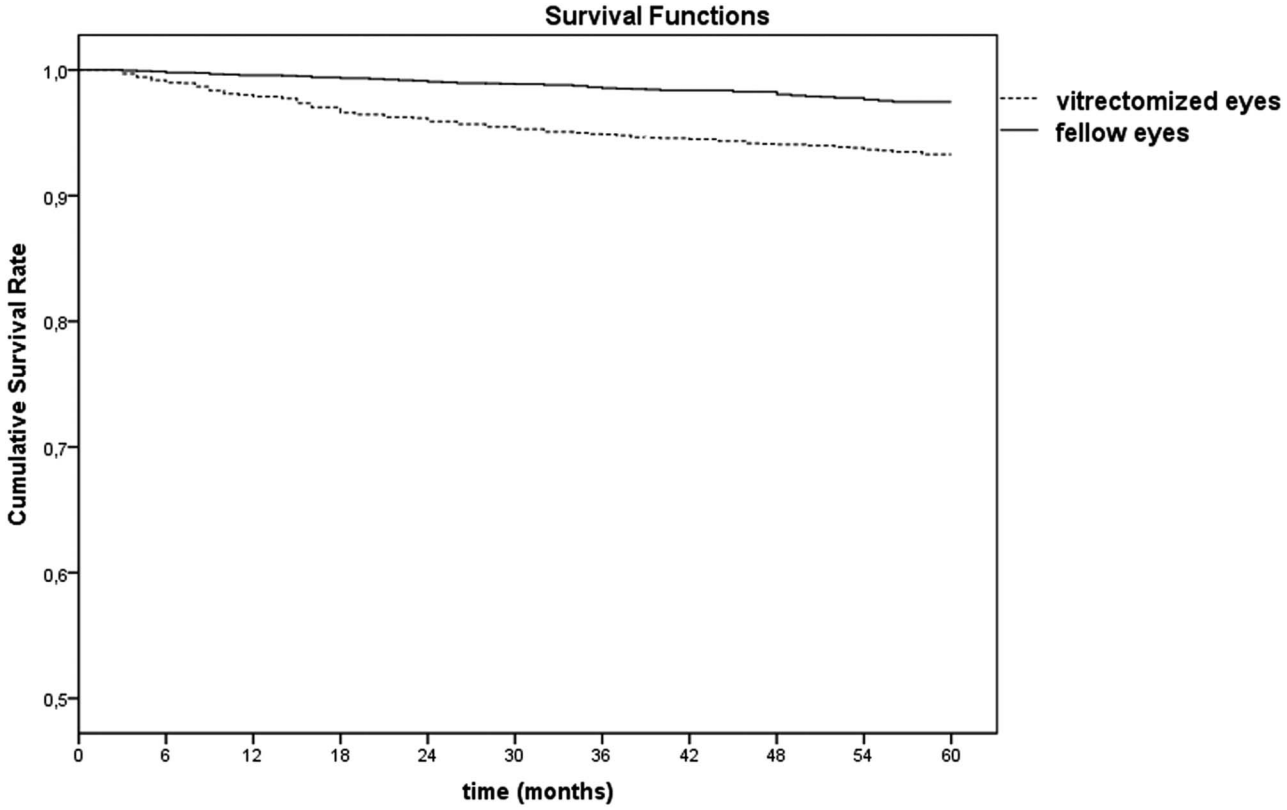

Fig. 1. Kaplan–Meier estimates of LOH in vitrectomized and fellow eyes.

OR, 6.09 (95% CI 4.71–7.86); $P < 0.001$), and postvitrectomy pseudophakic/aphakic status (73.5% of the hypertension group, 61.1% of controls; OR, 1.76 (95% CI 1.35–2.30); $P < 0.001$) (Table 1).

Univariate analysis showed that there was no difference in the incidence of various risk factors between eyes that had received or not triamcinolone (Table 2).

Multivariable Analysis

Significant variables at univariate analysis were taken forward to multivariable analysis. A regression model was constructed for the risk of developing LOH in vitrectomized eyes. Significant risk factors for developing LOH included longer axial length (OR, 1.55 [95% CI 1.19–2.23]; $P = 0.023$), higher preoperative IOP (OR, 1.81 [95% CI 1.37–2.38]; $P = 0.003$), intraoperative triamcinolone (OR, 7.62 [95% CI 5.85–10.06]; $P < 0.001$), and postvitrectomy pseudophakic/aphakic status (OR, 2.04 [95% CI 1.57–2.75]; $P < 0.001$) (Table 3).

Decision-Tree Analysis

The outcome of the decision-tree analysis for prediction of LOH is shown in Figure 2. The most significant prediction factor was the use of triamcinolone acetonide ($P < 0.001$). Secondary predictors were a preoperative IOP ≥15 mmHg in the group that used triamcinolone acetonide ($P < 0.001$), and postvitrectomy pseudophakic/aphakic status in eyes that did not use triamcinolone acetonide ($P = 0.007$). Finally, the third related classification variable was an axial length ≥24.9 mm in phakic eyes that did not use triamcinolone acetonide ($P < 0.001$).

Discussion

We found that vitrectomy increases the risk of LOH, and that the most significant variables associated with its development are related with the use of triamcinolone, the higher preoperative IOP, and the pseudophakic status.

Our study showed that the incidence of LOH was 4.9% (294/6,048) in the eyes that underwent vitrectomy and 1.4% (87/6,048) in the fellow eye (chi square; $P < 0.001$).

Six retrospective studies have demonstrated an association between pars plana vitrectomy and increased risk of LOH or open-angle glaucoma development.[2,5,7–9,11]

Table 1. Univariate Analysis of Variables in Vitrectomized Eyes With and Without LOH

Variables	Vitrectomized Eyes With LOH, n = 294	Vitrectomized Eyes Without LOH, n = 5,754	*P*	OR (95% CI)
Demographics				
Mean ± SD age (years)	66 ± 7	66 ± 10	0.856	1.00 (0.99–1.01)
Male sex, n (%)	147 (50.0)	3,108 (54.0)	0.198	0.85 (0.67–1.08)
Systemic				
Hypertension, n (%)	145 (49.1)	2,684 (46.6)	0.403	1.11 (0.88–1.41)
Diabetes, n (%)	53 (18.0)	819 (14.2)	0.085	1.33 (0.98–1.80)
Cardiovascular diseases, n (%)	6 (2.0)	197 (3.4)	0.264	0.59 (0.26–1.34)
Ophthalmic				
Mean ± SD axial length (mm)	25.9 ± 1.6	25.1 ± 1.8	<0.001*	1.23 (1.18–1.30)
Mean ± SD preoperative IOP (mmHg)	14.5 ± 2.0	14.3 ± 1.0	0.022	1.07 (1.01–1.14)
Preoperative pseudophakic/ aphakic, n (%)	105 (35.7)	1,636 (28.4)	0.009*	1.40 (1.09–1.79)
Operative				
Rhegmatogenous retinal detachment, n (%)	151 (51.4)	2,575 (44.8)	0.031*	1.30 (1.03–1.65)
Macular hole, n (%)	24 (8.2)	588 (10.2)	0.299	0.78 (0.51–1.20)
Epiretinal membrane, n (%)	68 (23.1)	1,604 (27.9)	0.087	0.78 (0.59–1.03)
Diabetic retinopathy, n (%)	11 (3.7)	315 (5.5)	0.251	0.68 (0.36–1.24)
Dropped lens/IOL, n (%)	9 (3.1)	189 (3.3)	0.999	0.93 (0.47–1.83)
Others, n (%)	31 (10.5)	483 (8.4)	0.237	1.29 (0.88–1.89)
Combined vitrectomy and phaco, n (%)	111 (37.8)	1,879 (32.7)	0.080	1.25 (0.98–1.59)
20-gauge vitrectomy, n (%)	24 (8.2)	439 (7.6)	0.823	1.08 (0.70–1.65)
23-gauge vitrectomy, n (%)	123 (41.8)	2,276 (39.6)	0.471	1.01 (0.87–1.39)
25-gauge vitrectomy, n (%)	139 (47.3)	2,853 (49.6)	0.475	0.91 (0.72–1.15)
27-gauge vitrectomy, n (%)	8 (2.7)	186 (3.2)	0.752	0.84 (0.41–1.72)
No photocoagulation, n (%)	122 (41.5)	2,709 (47.1)	0.070	0.80 (0.63–1.01)
Localized photocoagulation, n (%)	121 (41.2)	2,184 (38.0)	0.299	1.14 (0.90–1.45)
Extensive photocoagulation, n (%)	51 (17.3)	861 (15.0)	0.303	1.19 (0.87–1.63)
Buckling, n (%)	1 (0.3)	28 (0.5)	—	0.70 (0.09–5.14)
Cryopexy, n (%)	6 (2.0)	91 (1.6)	—	1.30 (0.56–2.99)
No tamponade, n (%)	63 (21.4)	1,327 (23.1)	0.566	0.91 (0.68–1.21)
Air tamponade, n (%)	81 (27.6)	1,387 (24.1)	0.188	1.20 (0.93–1.57)
SF6 tamponade, n (%)	109 (37.1)	2,092 (36.4)	0.841	1.03 (0.81–1.31)
C3F8 tamponade, n (%)	41 (13.9)	948 (16.5)	0.288	0.82 (0.59–1.15)
Intraoperative triamcinolone, n (%)	210 (71.4)	1,634 (28.4)	<0.001*	6.09 (4.71–7.86)
Intraoperative brilliant blue, n (%)	42 (14.3)	949 (16.5)	0.060	0.72 (0.51–1.00)
Postoperative				
Postvitrectomy pseudophakic/ aphakic, n (%)	216 (73.5)	3,515 (61.1)	<0.001*	1.76 (1.35–2.30)
Cataract surgery, n (%)	23 (7.8)	499 (8.7)	0.689	0.89 (0.58–1.38)

*Statistically significant.
IOL, intraocular lens.

An increased risk of open-angle glaucoma after vitrectomy was first described by Chang who studied 453 eyes with a minimum follow-up of 6 months (mean 56.9 months) and found elevated IOP in 68 eyes. Vitrectomy was performed for several indications, including: vitreous hemorrhage, retinal detachment, dislocated intraocular lens, and retained lens fragments. Vitrectomized eyes had a greater risk of developing glaucoma, with a 67.6% of new glaucoma cases developed only in the vitrectomized eye; patients with glaucoma before vitrectomy required a greater number of medications in the vitrectomized eye than in the fellow eye.[2]

A 12% incidence of open-angle glaucoma was reported by Koreen et al in their study on 285 vitrectomized eyes. Vitrectomy had several indications: 26% of the eyes had a history of retinal detachment and 19% had previous scleral buckle.[8]

Luk et al,[9] in 101 eyes treated by vitrectomy for an idiopathic epiretinal membrane or idiopathic macular hole, after a minimum follow-up of 6 months, found that 8% of patients developed open-angle glaucoma, with a higher rate in pseudophakic than in phakic eyes.

Toyokawa et al,[5] in 767 eyes that received vitrectomy combined with cataract surgery, after a mean

Table 2. Univariate Analysis of Variable in Vitrectomized Eyes Receiving or Not Triamcinolone Acetonide (TA)

Variables	Vitrectomized Eyes With TA, n = 1,844	Vitrectomized Eyes Without TA, n = 4,204	*P*	OR (95% CI)
Demographics				
Mean ± SD age (years)	66 ± 7	66 ± 7	ns	1.00 (0.99–1.01)
Male sex, n (%)	986 (53.5)	2,269 (54.0)	0.740	0.98 (0.88–1.09)
Systemic				
Hypertension, n (%)	859 (46.6)	1,970 (46.9)	0.862	0.99 (0.89–1.10)
Diabetes, n (%)	271 (14.7)	601 (14.3)	0.708	1.03 (0.88–1.21)
Cardiovascular diseases, n (%)	64 (3.5)	139 (3.3)	0.806	1.05 (0.78–1.42)
Ophthalmic				
Mean ± SD axial length (mm)	25.1 ± 1.4	25.1 ± 1.4	0.490	1.01 (0.98–1.05)
Mean ± SD preoperative IOP (mmHg)	14.3 ± 1.1	14.3 ± 1.0	1.000	0.97 (0.92–1.02)
Preoperative pseudophakic/ aphakic, n (%)	537 (29.1)	1,204 (28.6)	0.729	10.2 (0.91–1.16)
Operative	1,844	4,204		
Rhegmatogenous retinal detachment, n (%)	829 (45.0)	1,897 (45.1)	0.920	0.99 (0.89–1.11)
Macular hole, n (%)	184 (10.0)	428 (10.2)	0.163	0.87 (0.73–1.05)
Epiretinal membrane, n (%)	499 (27.1)	1,173 (27.9)	0.522	0.96 (0.85–1.08)
Diabetic retinopathy, n (%)	111 (6.0)	215 (5.1)	0.169	1.19 (0.94–1.50)
Dropped lens/IOL, n (%)	72 (3.9)	126 (3.0)	0.081	1.32 (0.98–1.77)
Others, n (%)	149 (8.1)	365 (8.7)	0.471	0.92 (0.76–1.13)
Combined vitrectomy and phaco, n (%)	589 (31.9)	1,401 (33.3)	0.306	0.94 (0.84–1.06)
20-gauge vitrectomy, n (%)	143 (7.8)	320 (7.6)	0.888	1.02 (0.83–1.25)
23-gauge vitrectomy, n (%)	736 (39.9)	1,663 (39.6)	0.823	1.02 (0.91–1.14)
25-gauge vitrectomy, n (%)	907 (49.2)	2,085 (49.6)	0.791	0.98 (0.88–1.10)
27-gauge vitrectomy, n (%)	58 (3.1)	136 (3.2)	0.920	0.97 (0.71–1.33)
No photocoagulation, n (%)	860 (46.6)	1,971 (46.9)	0.888	0.99 (0.89–1.11)
Localized photocoagulation, n (%)	699 (37.9)	1,606 (38.2)	0.841	0.99 (0.88–1.11)
Extensive photocoagulation, n (%)	285 (15.5)	627 (14.9)	0.617	1.04 (0.90–1.21)
Buckling, n (%)	9 (0.5)	20 (0.5)	0.888	1.03 (0.47–2.26)
Cryopexy, n (%)	29 (1.6)	68 (1.6)	1.000	0.97 (0.63–1.51)
No tamponade, n (%)	409 (22.2)	981 (23.3)	0.343	0.94 (0.82–1.07)
Air tamponade, n (%)	437 (23.7)	1,031 (24.5)	0.512	0.96 (0.84–1.09)
SF6 tamponade, n (%)	683 (37.0)	1,518 (36.1)	0.507	1.04 (0.93–1.17)
C3F8 tamponade, n (%)	315 (17.7)	674 (16.0)	0.327	1.08 (0.93–1.25)
Intraoperative brilliant blue, n (%)	302 (16.4)	689 (16.4)	1.000	1.00 (0.86–1.16)
LOH	210 (11.4)	84 (2.0)	<0.001*	6.30 (4.86–8.17)
Postoperative				
Postvitrectomy pseudophakic/ aphakic, n (%)	1,126 (61.1)	2,605 (62.0)	0.527	0.96 (0.86–1.08)
Cataract surgery, n (%)	163 (8.8)	359 (8.5)	0.740	1.04 (0.86–1.26)

*Statistically significant.
IOL, intraocular lens.

follow-up of 48 months, found an ocular hypertension in 4% of eyes, with a mean interval after surgery of 31 months.

Wu et al,[7] in 198 patients treated for idiopathic epiretinal membrane, after an average follow-up of 47 months, found a sustained elevation of IOP in 19% of vitrectomized eyes and in 4% of the unoperated fellow eyes.

Govetto et al,[11] in a cross-sectional study, found that the prevalence of open-angle glaucoma was 9% in a group of 169 eyes vitrectomized for various indications and 2% in a groups of 143 nonvitrectomized eyes.

Three studies found no association between pars plana vitrectomy and development of LOH or open-angle glaucoma.[4,12,13]

Lalezary et al, in 101 eyes treated for chronic macular edema, tractional retinal detachment, vitreous hemorrhage, macular hole, and epiretinal membrane, with a follow-up of at least 1 year, found that no eye developed open-angle glaucoma, whereas an IOP increase greater than 4 mmHg was detected in 7% of eyes at 4 years and in 34% at 8 years. Subgroup analysis of 66 patients comparing study eyes with nonvitrectomized fellow eyes demonstrated no

Table 3. Independently Significant Risk Factors For Developing Postoperative LOH in the Multivariate Logistic Regression

Variables	OR	OR (95% CI)	*P*
Axial length	1.55	1.19–2.23	0.023
Preoperative IOP	1.81	1.37–2.38	0.003
Intraoperative triamcinolone	7.62	5.78–10.06	<0.001
Postvitrectomy pseudophakia/aphakia	2.04	1.57–2.75	<0.001

significant difference in rates of increased IOP of >4 mmHg.[4]

Similarly, Yu et al,[12] among 441 vitrectomized eyes, for a variety of indications including retinal detachment, macular pucker, macular hole, and choroidal neovascularization, found similar rates of open-angle glaucoma and ocular hypertension in vitrectomized (4 and 4%, respectively) and in fellow eyes (2 and 3%, respectively).

Mi et al,[13] in 234 consecutive patients treated for idiopathic epiretinal membrane or macular hole, after a mean follow-up of 4.4 years, found an incidence of late-onset glaucoma of 3% in vitrectomy eyes and 2% in the fellow control eyes, without a statistically significant difference.

When comparing the incidence and risk factors for ocular hypertension after vitrectomy among the different studies, an important issue to consider is that the definition of ocular hypertension, the inclusion criteria,

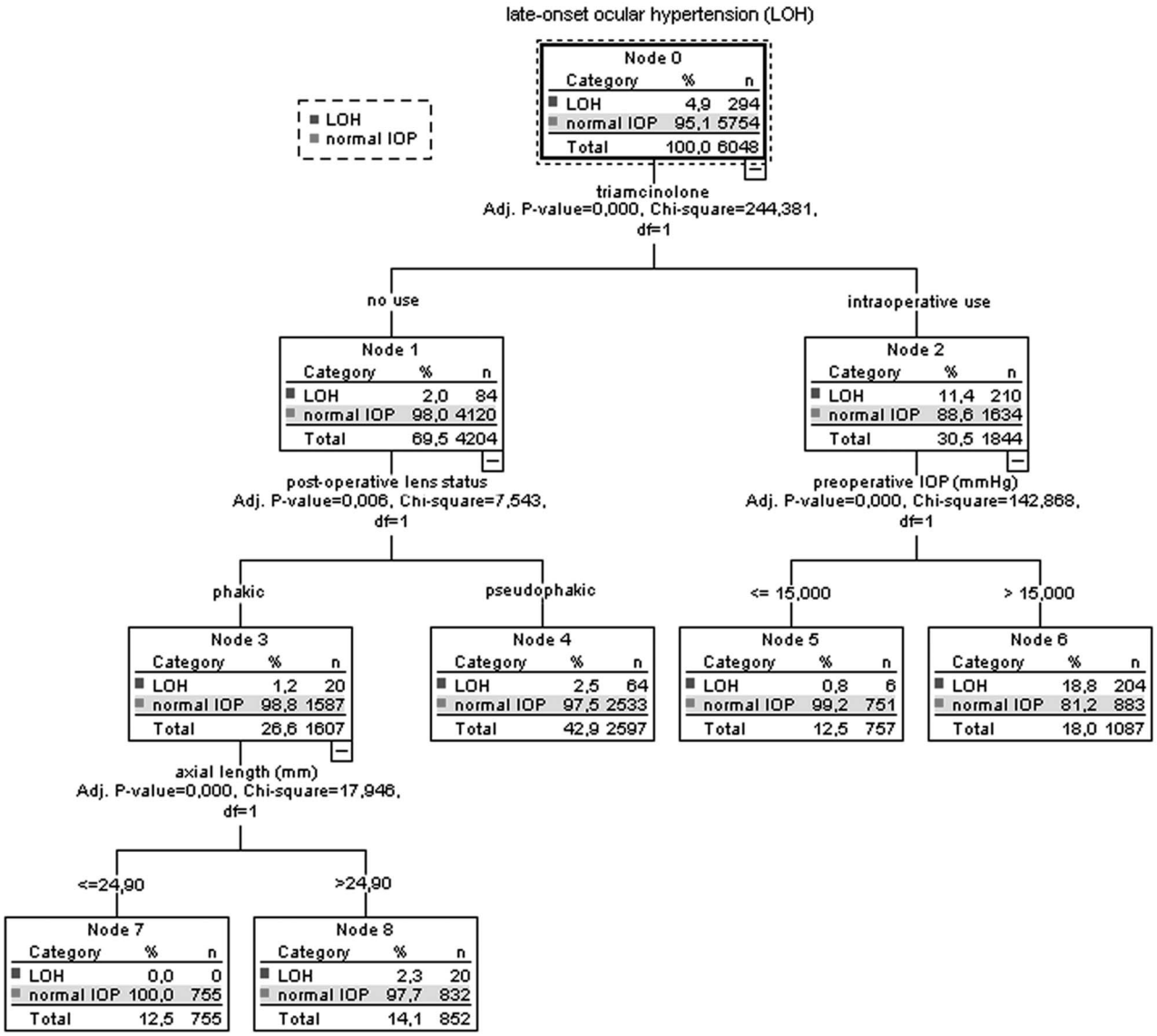

Fig. 2. Decision-tree algorithm of the variables associated with LOH in vitrectomized eyes.

the follow-up of the study, and the methods used to evaluate the IOP can differ significantly. Furthermore, because of an inadequate sample size, most of the studies lack a sufficient power to evaluate possible risk factors. Finally, given the low frequency of LOH, to determine the true incidence rate, it is necessary to have a control group.[4,6]

Regarding the possible risk factors, the results in the published studies are discordant. This is also because most of them used regression models, which are effective for examination of independent risk factors, but not to explain the priority and the interaction between them.

In our study, including more than 6,000 vitrectomized eyes, multivariate analysis showed that 4 factors had a significant effect on the incidence: use of triamcinolone during vitrectomy, higher preoperative IOP, postvitrectomy pseudophakic status, and preoperative longer axial length. We used a decision-tree analysis to analyze the interactions and priorities among them; this is a modeling procedure that has several advantages, including automatically capturing multilevel interactions among predictors, handling nonlinear relationships, rule generation, and ease of visualization and interpretation.[14] In addition, a decision-tree model can be successfully used in clinical settings since the primary related factors can be identified.[15]

The decision-tree model identified the use of triamcinolone as the main variable associated with LOH, particularly in eyes with higher values of IOP at baseline. In nonvitrectomized eyes, after intraocular or periocular steroid use, IOP increase and secondary glaucoma have been reported.[16,17] Also, in vitrectomized eyes, intravitreal triamcinolone, left in the eye at the end of surgery, may be associated with an IOP increase, whose rate and severity have not yet been well described. An elevated IOP has been reported in 9% of the eyes 1 day after vitrectomy with 4-mg intravitreal triamcinolone[18] and in 13% of eyes 1 month after vitrectomy with 1-mg intravitreal triamcinolone.[19]

Triamcinolone acetonide, which is largely water insoluble, can remain longer in the vitreal chamber when used as vitreous dye.[5] In a study comparing anatomical and functional outcomes after triamcinolone acetonide assisted and brilliant blue internal limiting membrane peeling in macular hole surgery, the incidence of postoperative glaucoma was 21% in eyes treated with triamcinolone and 2% in eyes with brilliant blue.[20]

Pseudophakic status is another variable associated with the incidence of ocular hypertension. Vitrectomy was correlated with subsequent open-angle glaucoma, particularly in the absence of the crystalline lens, in Chang's LXII Edward Jackson lecture.[2] Koreen et al[8] showed that an open-angle glaucoma developed in 12% of patients, in particular in 1% of phakic eyes and in 15% of nonphakic eyes.

It has been hypothesized that after vitrectomy, the increased levels of oxygen in the vitreous chamber can cause oxidative damage to the trabecular meshwork, leading to IOP elevation.[2,8] This process is presumably enabled or expedited when the lens is removed, either before or after vitrectomy, as the native lens metabolizes oxygen.[2,21,22]

In our study, the postvitrectomy pseudophakic status was significantly associated with the incidence of LOH.

A longer axial length has been significantly associated with open-angle glaucoma; in particular, eyes with axial lengths $\geq$25 mm had a 2.29 times higher chance of open-angle glaucoma than those with an axial length less than 25 mm.[23] In our study, the rate of phakic eyes that developed LOH was significantly higher among those with an axial length $\geq$24.9 mm.

Our study has several limitations, mainly because of the retrospective nature, such as selection bias and incomplete records. It was hard to determine the exact incidence of LOH related to the differences in the follow-up periods and to nonstandardized intervals of postoperative examinations. Furthermore, to exclude patients with a possible ocular hypertension before surgery, we had chosen as exclusion criteria an IOP $>$18 mmHg; this may have led to an underestimation of the incidence rate of LOH. Finally, some patients were lost to follow-up or returned to their referring physician. Also, how many patients developed a glaucoma, that is, had an alteration of the visual field with optic nerve damage related to IOP increase remain to be determined. This assessment, not easy in patients treated with vitrectomy for retinal detachment, macular hole, and epiretinal membrane, requires longer follow-up.

Nevertheless, our analysis using the nonvitrectomized fellow eye as a control and the large sample size strengthen our results compared with previously published reports.

In conclusion, vitrectomy represents a risk factor for the development of LOH; in our study, the use of triamcinolone, a high IOP before the vitrectomy and postvitrectomy pseudophakic status were the main variables associated with its incidence. Avoiding the use of triamcinolone, particularly in eyes with borderline IOP values, and monitoring ocular pressure for long periods after vitrectomy are potential strategies to reduce the incidence and effects of this complication.

Key words: late-onset ocular hypertension, vitrectomy.

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