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의학박사 학위논문

시신경 유두출혈이 동반된 녹내장 안에서 항혈전제 / 항응고제의 복용이 녹내장 진행에 미치는 영향

Effect of Antiplatelet / Anticoagulant use on Glaucomatous progression in Glaucoma eyes with Optic disc hemorrhage

울 산 대 학 교 대 학 원

의 학 과

이 지 윤

시신경 유두출혈이 동반된 녹내장 안에서 항혈전제 / 항응고제의 복용이 녹내장 진행에 미치는 영향

지 도 교 수　　성 경 림

이 논문을 의학박사 학위 논문으로 제출함

2017 년　12 월

울 산 대 학 교 대 학 원

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울 산 대 학 교 대 학 원

2017 년 12 월

<국문요약>

제목

시신경 유두 출혈이 동반된 녹내장 안에서 항혈전제 / 항응고제의 복용이 녹내장 진행에 미치는 영향

연구 목적

시신경 유두 출혈이 동반된 녹내장 안에서 항혈전제 / 항응고제의 복용이 녹내장 진행에 미치는 영향을 알아보고자 함.

연구 방법

개방각 녹내장 환자 119 명의 119 안을 대상으로 의무기록을 통한 후향적 연구를 시행함. 36 개월 이상의 경과 관찰 기간을 가지며 한 번 이상의 시신경 유두 출혈이 있는 환자들로, 항혈전제 / 항응고제 복용 유무, 시신경 유두 출혈의 위치, 시신경 유두 출혈 빈도 횟수를 기준으로 녹내장 진행 기준 반영 지표들과 상관 관계를 분석하였음.

연구 결과

119 명 중 19 명의 환자가 항혈전제 / 항응고제를 매일 복용하고 있었다. 전체 환자의 평균 경과 관찰 기간은 74.8 개월이었으며, 항혈전제 / 항응고제 복용군은 77.2 개월, 대조군은 74.4 개월이었다. 항혈전제 / 항응고제 평균 복용 기간은 96.3 개월이었으며, 가장 많이 복용하는 약은 aspirin(52.6%)이었다. 시신경 유두 출혈 빈도의 총 횟수가 항혈전제 / 항

응고제군 (n, 1.78)에서 대조군 (n, 1.66)에 비해 잦았으나, 통계적으로 유의하지 않았으며(p=0.601), 대조군 (27.6 개월)에서 녹내장 진행까지의 경과 관찰 기간이 항혈전제 / 항응고제군 (66.2 개월)에 비해 더 짧았다 (p=0.016). 또한, 전체 그룹에서 항혈전제 / 항응고제의 복용이 녹내장 진행을 지연시켰고 (hazard ratio (HR), 0.576, p=0.046), 경과 관찰 기간 동안의 높은 평균 안압이 녹내장 진행의 악화와 연관을 보였다(HR, 1.107, p=0.014). 항혈제 / 항응고제군 안에서는 평균 RNFL thickness(HR, 1.165, p=0.008)와 MD(HR, 0.672, p=0.003)가, 대조군에서는 안압하강(HR, 0.937, p=0.075)이 적을수록, 시신경 유두출혈 빈도(HR, 1.244, p=0.064)가 잦을수록 녹내장 진행과 관련성을 보였다.

한편, 반복적인 시신경 유두 출혈을 보인 군에서 일회성의 시신경 유두 출혈군에 비해 Visual field guided progression analysis 상, 빠른 진행을 보였으나 (-1.34 ± 1.79 %/year, -0.42 ± 0.95 %/year, p=0.004, 각각) 각 군에서 항혈전제 / 항응고제이 차지하는 비율은 일회성 출혈군에서 12.5%, 반복성 출혈군에서 21.2%로 유의한 차이를 보이지 않았다(p=0.201).

결론

항혈전제 / 항응고제군과 대조군간의 시신경 유두 출혈 빈도 및 녹내장 진행과 관련된 지표들간에서 통계적으로 유의한 차이를 발견할 수 없었다. 이는 항혈전제 / 항응고제를 복용하는 녹내장 환자의 시신경 유두에서 관찰되는 출혈은 녹내장의 진행과 관련되기 보다는, 전반적인 출혈 경

향의 증가로 인해 관찰되는 현상으로 해석된다.

차 례

표 및 그림목차

<Abstract>

Purpose

To analyze whether the use of antiplatelet (AP) / anticoagulant (AC) drugs affects the progression of glaucoma in glaucomatous eyes with optic disc hemorrhage (DH).

Method

A retrospective longitudinal study performed in a tertiary hospital setting. Data were reviewed for 119 eyes from 119 glaucoma patients who were followed for more than 36 months and in whom a DH was observed at least once during the follow - up period. Patients clinical characteristics were analyzed especially in terms of AP / AC use, location of DHs, and number of incidence of DH. Cox proportional hazard model and Kaplan - Meier survival analysis with the log rank test were used to identify the association between AP / AC use, DH and glaucoma progression.

Results

Nineteen out of 119 patients took daily AP / AC drugs. The total follow-up period was 74.8 month: 77.2 month for the AP / AC use group (AG),

and 74.4 month for the no use group (NG) (p=0.606). Although the total number of incidence of DH between two groups was insignificantly different (AG 1.78, NG 1.66 p= 0.601), the follow-up period till progression was shorter in NG than in AG (AG, 66.2 months, NG 27.6 months, p=0.016). The mean duration of AP / AC use was 96.3 months and the most frequently used drug was aspirin (52.6%). In the total groups analysis, use of AP / AC drugs was against the glaucomatous progression (hazard ratio (HR), 0.576, p=0.046), but higher mean intraocular pressure (IOP) was a risk factor for accelerating glaucoma progression (HR, 1.107, p=0.014). In the AG, average RNFLT and MD were significant risk factors for glaucomatous progression (HR, 1.165, p=0.008, HR, 0.672, p=0.003, respectively). In the NG analysis, a lesser reduction in IOP (HR, 0.937, p=0.075) and a higher frequency of DH (HR, 1.244, p=0.064) were marginally associated with progression. Visual field guided progression analysis was faster in multiple DH group than one DH group (-1.34 ± 1.79 %/year, -0.42 ± 0.95 %/year, p=0.004, respectively). However, the patient's ratio of AG vs NG showed no significant difference between one DH (12.5%) and multiple DHs (21.2%) (p=0.201)

Conclusion

The incidence of DH and visual field guided progression analysis between AG and NG were statistically insignificant. Those results implied the DH observed in AG was not a risk factor for the glaucoma progression, but rather was a result of increased bleeding tendency.

<Introduction>

Glaucoma is an optic neuropathy defined as structural damages to the optic nerve head accompanied with characteristic functional defect in visual field (VF). According to previous studies, various risk factors including high intraocular pressure (IOP)[1], old age[2], family history[3,4] and myopia[5] have been related to the development of glaucoma.

Disc hemorrhage (DH) has been frequently observed in glaucoma patients, and several studies have shown that it is related to rapid structural and functional disease progression. In other words, progression of neuroretinal rim notching or thinning, or widening of retinal nerve fiber layer (RNFL) defect were observed after DH according to previous publications.[6,7] Other studies have reported that faster rate of VF deterioration or new VF defects as a consequence of DH.[8,9] However, pathogenesis and mechanism of DH in glaucoma have not been fully elucidated.

Given that glaucoma frequently develops in old age and older patients are at

greater risk of chronic systemic vascular diseases such as hypertension, ischemic heart disease, and diabetic mellitus, considerable portion of patients are taking anticoagulant or antiplatelet (AP / AC) drugs. Those medications can cause alteration of optic disc hemodynamics and thus DHs are sometimes observed even in patients with healthy non glaucomatous optic discs who are taking such medications.[10-12] Further, positive relationships were found between use of AP and frequency of DH in previous studies [13] [14].

Given that DH is a complex phenomenon, that results from diverse factors such as mechanical disruption of the RNFL, vascular disturbances and other causes, the clinical course of glaucoma may be different by such factors. Hence, in this study, we aimed to compare the longitudinal clinical course of open angle glaucoma accompanied by DH in patients taking AP / AC medications and in those not taking AP / AC medications. We also explored the effect of AP / AC use on glaucoma progression.

<Method>

Study Population

This is a retrospective longitudinal study with review of the medical records of 296 eyes of 296 patients who visited the glaucoma clinic and met the inclusion criteria between March 2007 and April 2017. The institutional review board of Asan Medical Center approved this study, and the study was executed in accordance with the principles of the Declaration of Helsinki. Written informed consent was exempted due to retrospective nature of the study design.

All subjects underwent a comprehensive ophthalmologic examination, including a review of systemic diseases and medical histories including the use of anticoagulant / antiplatelet medications such as aspirin, clopidogrel, warfarin and cilostazol etc, the duration and number of medications used, measurement of best-

corrected visual acuity (BCVA), refraction, slit-lamp biomicroscopy, Goldmann applanation tonometry, gonioscopy, central corneal thickness assessment (DGH-550;DGH Technology, Inc., Exton, PA, USA), funduscopic examination, stereoscopic optic disc and red-free RNFL photography (AFC-210; Nidek, Aichi, Japan), ganglion cell inner plexiform layer (GCIPL) and RNFL imaging (Cirrus HD-OCT; Carl Zeiss Meditec), standard automated perimetry (Humphrey Field analyzer with Swedish Interactive Threshold Algorithm standard 24–2 test; Carl Zeiss Meditec). Baseline IOP was defined as IOP measured before starting glaucoma medication, and reduction in IOP was defined as baseline IOP minus the mean follow - up IOP during treatment. Patients were followed every 6 to 9 months with the OCT and VF exams, disc/RNFL photographs and IOP measurement. Patients included in the study were primary open angle glaucoma patients with follow-up more than 36 months in whom a disc hemorrhage was observed during at least one follow - up period visit and for whom the results of at least five reliable OCT and VF examinations performed at different

visits available. Glaucoma was diagnosed by the presence of retinal nerve finer layer (RNFL) defects or glaucomatous optic disc changes (neuroretinal rim thinning, disc excavation, or disc hemorrhage) and corresponding visual field (VF) defects as confirmed by at least 2 reliable VF examinations. Only reliable VF test results (i.e., false-positive errors <15%, false-negative errors <15%, and fixation loss <20%) were included in the study. Glaucomatous VF defects were defined as a cluster of 3 or more non-edged contiguous points on a pattern deviation plot with a P value of less than 0.05 (with at least having a P value of less than 0.01) as confirmed by at least 2 consecutive examinations, a pattern standard deviation with a P value of less than 0.05, or glaucoma hemifield test results outside normal limits. If both eyes of a patient were eligible, one eye was selected at random and included in the study. Patients with any ophthalmic or neurologic disease known to affect the optic nerve head or VF were excluded. If surgical or laser treatment was performed during the study follow-up

period, only data obtained in the period before the treatment, which should be longer than 36 months were analyzed.

Assessment of optic disc hemorrhage

All stereoscopic optic disc/RNFL photographs were thoroughly reviewed by two glaucoma specialists independently (KRS, JYL). All DHs were evaluated and recorded on a chart to depict their locations and shapes. We defined a DH as an isolated flame or splinter hemorrhage on the optic disc or crossing the disc border or in the peripapillary area. A non-recurrent DH was defined as a DH that occurred in an eye that had no other DH in the follow – up period, while, a recurrent DH was defined as the enlargement of an earlier DH or a new DH elsewhere. The total number of DHs was the sum of non-recurrent and recurrent DHs.

Definition of glaucoma progression

Glaucoma progression was evaluated in either structural or functional aspects. Structural progression was assessed by observing changes in the optic disc and RNFL, either by comparing serial optic disc photo and serial red - free fundus photograph or by using RNFL and cup disc ratio guided progression analysis (GPA) provided by a Cirrus spectral -domain OCT.[15] The criteria for progression on optic disc photos included changes in notching or thinning of the neuroretinal rim, changes in the vessel contour of the optic disc and an increase in cup disc ratio. For RNFL progression, the criteria were increments in the depth or width of existing RNFL defects or the appearance of newly occurring RNFL defects.

RNFL thickness was measured using the optic disc cube protocol of a Cirrus OCT running version 6.0 software (Cirrus OCT; Carl Zeiss Meditec, Inc., Dublin, CA). Images exhibiting involuntary saccade, misalignment, or blinking artifacts and those

with a signal strength of <6 were discarded. Images featuring algorithm segmentation failure were also excluded after visual inspection.

Eyes were classified as with or without progressive RNFL thinning using the GPA software of Cirrus OCT. At least 5 OCT examinations are necessary to generate a GPA report, which was an inclusion criterion for this study. The superior and inferior RNFL thicknesses were plotted against the duration of follow-up. If progression was suspected, the RNFL thickness at each visit was indicated as “possible loss” or “likely loss.” Progression was identified if the observed change from two baseline examinations to a test value that exceeded the test–retest variability of the system. If the “‘possible loss” criterion was met on 2 successive visits, the patient was considered to show “likely loss.” We considered that “likely loss” in the superior region, inferior region, average ratio or cup disc ratio reflected progressive structural changes and thus glaucomatous progression.

VF progression was evaluated by either trend or event based analysis employing GPA. In trend-based linear regression analysis using a newly introduced global index, the visual field index, a significantly negative slope ($p < 0.05$) indicated VF progression. In event - based analysis, progression was defined as a significant deterioration from the baseline pattern deviation at three or more of the same test points on three consecutive examinations.[16]

Statistical Analysis

We used the independent t- test or Mann-Whitney U test for continuous variables and the chi- square test or Fishers' exact test for categorical factors according to the normality of the data to compare demographics and progression - related parameters between the AP / AC use group (AG) and the no use group (NG).

Also, subgroup analysis was performed to confirm the effect of the location of DH and the number of DHs, by classifying patients into superior DH and inferior DH groups, and the one DH group and multiple DHs group. The same statistical methods were used to compare the characteristics of the subgroups. Cox proportional hazard model was adopted to analyze the putative risk factors including AP / AC use as a covariate for progression in total groups. Subgroup analysis was performed for exploration of risk factors in each AG and NG. Univariate and multivariate Cox analyses were carried out and adjusted hazard ratios (HRs) were calculated. Kaplan - Meier survival analysis with the log rank test were used to compare glaucoma progression in the AG and NG, and in the one DH and multiple DHs subgroups. All statistical analyses were performed with SPSS version 15.0 (SPSS Inc., Chicago, IL, USA) and $P < 0.05$ was considered statistically significant.

<Results>

From the 296 patient charts recruited, 119 met the entry criteria and were included for further analysis. One hundred seventy-seven charts were excluded for the following reasons: previous glaucoma surgery with follow-up period less than 36 months (n = 76), previous refractive surgery (n = 27), closed angle on gonioscopy (n = 39), lack of systemic medical information (n= 13), lack of documented glaucoma examinations including VF test, OCT, optic disc photographs and red -free fundus photographs less than five times (n= 22).

A total of 119 eyes of 119 patients consisting of 19 patients in the AG and 100 patients in the NG were included in the final analysis. Those 19 AG patients had been taking daily AP/ACs with a mean duration of 96.3 ± 53.1 months: 5 patients with less than 5 years of AP or AC uses, 9 patients with 5 to 10 years, 5 patients with over 10 years. In terms of combination on the use of AP or AC drugs, 10 patients with AP drugs only, 2 patients with AC drugs only, 7 patients with both AP and AC drugs were

identified. Among the drugs, the most used ones were aspirin (52.6%), clopidogrel (21.1%), warfarin (15.8%), or cilostazol (10.5%) followed the order.

Of the 119 subjects, 61 were male and 58 were female and the mean age was 59.6 ± 11.2 years old. Table 1 summarizes the demographic and clinical characteristics of the participants. The total follow - up period was 74.8 ± 22.0 months for all patients and the follow - up period till progression was 49.8 ± 22.7 months. The follow -up period till progression was significantly different between two groups, 61.2 ± 23.5 months for AG and 47.6 ± 22.0 months for NG (p=0.016). Presence of family history of glaucoma was more frequent in the NG than in the AG (p<0.001), while presence of systemic diseases such as hypertension, diabetes mellitus and, dyslipidemia was more frequent in the AG than in the NG (p=0.003, p=0.001, p=0.007, respectively). The mean number of the optic disc/RNFL photographs was 10.2 ± 2.6 per eye, which was not significantly different between two groups. Total number of DH detected was 1.6 ± 0.9, which was not different among two groups (AG; 1.8 ± 0.9, NG;

1.6 ± 1.0, p=0.601). However, reduction in IOP during the follow – up showed greater in NG than in AG (AG; 0.2 ± 3.1, NG; 2.2 ± 3.4 mmHg, p=0.022), and VF PSD was higher in NG than in AG (AG; 2.9 ± 2.7, NG; 4.6 ± 4.0, p=0.022).

Progression rates determined by VF and Cirrus OCT GPA were compared between two groups (Table 2). None of parameters differed significantly between the two groups.

According to the Cox proportional hazard analysis, mean IOP, total number of DH, PSD, and use of AP or AC were possibly associated with glaucoma progression in univariate analysis of total group (Table 3). In multivariate analysis, higher mean follow - up IOP (HR=1.1, p=0.014) was associated with glaucomatous progression while use of AP or AC was protective against progression (HR=0.6, p= 0.046). Kaplan-Meier analysis revealed a greater cumulative probability of glaucoma progression was found in the NG than in the AG, but statistical significance was borderline (p=0.081).

Meanwhile, subgroup analysis of the AG revealed that thicker average RNFL and worse VF MD were associated with progression of glaucoma in multivariate Cox analysis (Table 4) while a smaller reduction in mean follow - up IOP, and greater total number of disc hemorrhages were marginally associated with glaucomatous progression in the NG (p= 0.075, p= 0.064 respectively) (Table 5).

Figure 2 describes the patterns of disc hemorrhages in each group, the frequency of hemorrhage includes recurrent hemorrhage. In both groups the inferior region of the optic disc had the greatest number of hemorrhages. Hemorrhage in the superior region of the disc were more common in the AG than the NG. Recurrent DH detection rates were 52.6 % (10 eyes of 19 eyes) in the AG and 39 % (39 eyes of 100 eyes) in the NG, but the difference was not significant (p= 0.268).

We also compared the patients according to numbers of DHs (Table 8, Table 9). More patients in the multiple DH subgroup (93.6%) showed significant glaucoma

progression than those in one DH subgroup (77.8%) (p=0.021). The percentage of patients using AP or AC drugs (21.3%) was similar in the two subgroups (p=0.201), but the number of medication used at last follow-up was significantly higher in the multiple DH subgroup (1.30 ± 0.66) than in one DH subgroup (1.00 ± 0.59) (p=0.014), and VF GPA showed faster progression in multiple DH subgroup (-1.34 ± 1.79) than in one DH subgroup (-0.42 ± 0.95) (p=0.004). In OCT related parameters, only the inferior RNFL thickness GPA showed slightly faster progression rate in multiple DH (-1.98 ± 2.09) than in one DH (-1.35 ± 1.41) (p=0.085).

<Discussion>

In this study, we found that a higher mean IOP was a risk factor for accelerating glaucoma progression, whereas use of AP / AC drugs was not likely to lead to the progression in the total group analysis supported by Kaplan-Meier analysis. On the contrary, NG group showed greater cumulative probability of progression with marginal significance. Disc hemorrhage (DH) is widely considered to be a significant

risk factor for the development and progression of glaucoma.[17] However, the etiology and pathogenesis of DH is still unclear and controversy about the relationship between DH and glaucoma progression is going on. According to previous studies[16,18], DH is an independent risk factor for VF progression and recently, Kim et al[19] reported that DH was associated with a 2.5 fold higher probability of progression of normal tension glaucoma. These findings suggested that IOP reduction is not able to fully prevent the disease from deteriorating, and indeed and non-IOP factors such as hypertension[20,21], diabetes[13,20,21] have been found to be associated with glaucomatous aggravation. Use of aspirin[13] is a risk factor for glaucoma progression. Kim et al found a marginal association between use of aspirin and DH (p, 0.079) and Grodum et al[22] reported a positive association between those two factors, although the study subjects were not divided into glaucoma patients and healthy participants.

DH can originate from ischemic microinfarction in the optic disc, as well as from mechanical rupture of small blood vessels due to structural changes in the

lamina cribrosa.[20,23] Since aspirin prevents thromboxane A2 production by inhibiting cyclooxygenase, resulting in interfering with platelet aggregation, use of aspirin could boost the risk of developing DH. In addition, due to the DH mechanism described above, patients on aspirin tend to have vascular diseases that eventually result in DH.[10,11]

Therefore, we decided to analyze whether use of AP / AC drugs affected glaucoma progression and to establish its true influence on the disease. We limited participants to those with glaucoma. However, since in our patient' pool, there were a few patients on APs only, we included them with patients using AC drugs such as warfarin, clopidogrel, or cilostazol. Although their pharmacological dynamics and mechanisms are quite different, it is unquestionable that these medications all increase bleeding tendency. According to the results of multivariate analysis, the use of AP / AC drugs was protective against glaucoma progression. These observations suggest that use of AP / AC drugs may increase the frequency of DH or hamper the

absorption of DHs but that these effects are not related to glaucoma progression because they may not be caused by purely glaucomatous structural neuroretinal rim loss.

In our study, slightly higher incidence of DH and according to GPA outcome, faster progression rate except inferior RNFL area were observed. However, neither the difference of incidence between the two groups nor the difference of GPA was statistically significant. This could mean that the more frequent observation of DH in the AG is related to the greater bleeding tendency, despite the more frequent DHs, there was no definite glaucomatous progressive change in such patients.

Analysis restricted to the AG showed that average RNFL thickness and MD were associated with glaucoma progression, and these are well known risk factors for glaucoma progression[1,24-26]. Meanwhile, in the NG, the higher total DH incidence and smaller reduction in IOP was marginally associated with progression. Taking all these findings together, it seems that in each group, universe indices known as risk factors,

affect disease status whereas taking AP / AC drugs do not render the optic disc more vulnerable.

The present study has several limitations. Firstly, the imbalance between the numbers of patients in the two groups: the fact that there were many patients in the NG and relatively few in the AG might affect the statistical analysis. However, other variables including total follow-up period and number of optic disc/RNFL photographs taken did not differ significantly. Therefore, statistical analyses were possible, and the results were conclusive. Secondly, there were patients taking medications in the NG other than AP or AC drugs. Since according to previous studies [14,21], systemic disease such as hypertension and diabetes mellitus can affect the progression of glaucoma, it is impossible to rule out effects of these systemic medications on hemodynamic changes in the optic disc. Thirdly, the use of AP / AC drugs was reviewed at baseline only and some patients may have started or discontinued AP/ AC drugs during the follow - up period. Further studies are required to compensate for these limitations.

<Conclusion>

To the best of our knowledge, this study is the first to explore the effect of use of AC / AP drugs on glaucoma progression. We conclude that glaucoma patients using AP / AC drugs have more frequent DHs but do not undergo more progressive structural and functional changes. This finding should be considered in the treatment of glaucoma patients who have DHs and take AP / AC drugs.

Table 1. Demographics and clinical characteristics of the Antiplatelet / Anticoagulant use Group (AG) and the No use group (NG).

	Total (n = 119)	**AG (n=19)**	**NG (n=100)**	**P value***
Total Follow - up period (Month)	74.82 ± 21.96	77.21 ± 19.86	74.36± 22.40	0.606
Follow - up period till Progression (Month)	49.76 ± 22.73	61.16 ± 23.49	47.59 ± 22.04	0.016
Age (year)	59.57 ± 11.18	66.21 ± 10.75	58.31 ± 10.86	0.004
Laterality (OD/OS) (n)	58 / 61	11 / 8	47 / 53	0.428
Sex (M/F) (n)	61 / 58	14 / 5	47 / 53	0.040
Previous op history (n)	14 (11.76%)	4 (21.1%)	10 (10.0%)	0.170
Number of glaucoma medications at last follow up (n)	1.12 ± 0.63	1.26 ± 0.73	1.09 ± 0.61	0.276
Family history of glaucoma (n)	7 (5.88%)	0 (0 %)	7 (7.0 %)	<0.001
Hypertension (n)	39 (32.77%)	12 (63.2 %)	27 (27.0 %)	0.003
Diabetes (n)	23 (19.33%)	9 (56.3 %)	14 (14.0 %)	0.001
Hypercholesterolemia (n)	23 (19.33%)	8 (42.1 %)	15 (15.0 %)	0.007
BCVA	0.96 ± 0.15	0.91 ± 0.17	0.96 ± 0.15	0.228
SE (Diopters)	-1.93 ± 3.05	-1.47 ± 2.95	-2.01 ± 3.07	0.501
Baseline IOP (mmHg)	15.95 ± 3.46	14.74 ± 2.98	16.18 ± 3.51	0.095
Mean IOP (mmHg)	14.08 ± 2.80	14.50 ± 2.54	14.01 ± 2.85	0.482

Reduction in IOP (mmHg)	1.87 ± 3.39	0.24 ± 3.12	2.18 ± 3.37	0.022
CCT (㎛)	524.83 ± 28.23	527.18 ± 24.95	524.50 ± 28.80	0.770
VF MD (dB)	-3.21 ± 4.19	-2.79 ± 4.23	-3.29 ± 4.20	0.637
VF PSD (dB)	4.35 ± 3.86	2.87 ± 2.69	4.63 ± 3.99	0.022
Number of total photo exams (n)	10.20 ± 2.63	10.68 ± 3.09	10.11 ± 2.55	0.386
Number of disc hemorrhage (n)	1.62 ± 0.91	1.78 ± 0.86	1.66 ± 1.01	0.601
Average RNFL thickness (㎛)	80.02 ± 10.37	78.21 ± 9.15	80.36 ± 10.60	0.411
Average cup/disc ratio	0.74 ± 0.08	0.74 ± 0.05	0.73 ± 0.09	0.860
Vertical cup/disc ratio	0.73 ± 0.08	0.72 ± 0.07	0.74 ± 0.08	0.455
Rim area	0.86 ± 0.19	0.89 ± 0.18	0.85 ± 0.19	0.409

***Mann-Whitney U test**

For categorical analysis, Fisher's exact test was performed.

Table 2. Comparison of glaucoma progression in terms of functional and structural changes using guided progression analysis (GPA)

	Total (n=119)	**AG (n=19)**	**NG (n=100)**	**P value***
VF GPA (%/year)	-0.74 ± 1.45	-1.53 ± 2.01	-0.61 ± 1.31	0.106
OCT average RNFL GPA	-0.84 ± 0.88	-0.97 ± 1.16	-0.81 ± 0.83	0.507
OCT C/D ratio GPA	0.003 ± 0.01	0.005 ± 0.11	0.003 ± 0.01	0.409
OCT Superior RNFL GPA	-1.27 ± 1.48	-1.82 ± 2.12	-1.17 ± 1.33	0.239
OCT Inferior RNFL GPA	-1.62 ± 1.75	-1.39 ± 1.82	-1.66 ± 1.75	0.560

Table 3. Univariate and Multivariate Cox-Proportional Hazards Models testing the association between Parameters and Glaucoma Progression in the total groups

	Univariate		**Multivariate**	
Factor	Exp (B)	P value	Exp (B)	P value
Age	.990	.285		
sex	.958	.830		
SE	.989	.736		
IOPbaseline	1.011	.650		
Mean IOP	1.104	.018	1.107	.014
Reduction in IOP	.967	.221		
Avg C/D ratio	.408	.493		
avgRNFL	1.011	.290		
Number of Total DH	1.152	.188	1.139	.223
CCT	1.003	.526		
Medication Number	1.102	.495		
MD	.982	.430		
PSD	1.033	.199	1.025	.362

Use of antiplatelet or anticoagulant drugs	.597	.061	.576	.046
Combination on the use of antiplatelet or anticoagulant drugs				
None				
Antiplatelet only	.595	.162	.460	.211
Anticoagulant only	.345	.291	.268	.269
Both	.669	.312	.468	.176
Duration of antiplatelet or anticoagulant use				
Never				
< 5 years	1.249	.630	1.347	.575
≥ 5, <10 years	.489	.071	.554	.298
≥ 10 years	.461	.134	.468	.176

Table 4. Univariate and Multivariate Cox-Proportional Hazards Models Testing the Association between Parameters and Glaucoma Progression in the Antiplatelet / Anticoagulant use Group (AG)

	Univariate		**Multivariate**	
Factor	Exp (B)	P value	Exp (B)	P value
Age	1.051	.083	1.057	.097
sex	1.157	.807		
SE	1.240	.141	1.101	.666
IOP baseline	1.125	.199	1.205	.276
Mean IOP	1.239	.072	.907	.659
Reduction in IOP	1.004	.965		
Avg CDratio	.547	.895		
Avg RNFL	1.054	.176	1.165	.008
Number of Total DH	1.028	.944		
CCT	1.016	.416		
Medication N	1.033	.920		
MD	.861	.098	.672	.003

PSD	1.246	.133	1.129	.782
Combination on the use of antiplatelet or anticoagulant drugs				
Antiplatelet only				
Anticoagulant only	.647	.684		
Both	1.020	.972		
Duration of antiplatelet or anticoagulant use				
< 5 years				
≥ 5, <10 years	.329	.076	.662	.650
≥ 10 years	.236	.063	.148	.083

Table 5. Univariable and Multivariable Cox-Proportional Hazards Models Testing the Association between Parameters and Glaucoma Progression in the No use group (NG)

	Univariate		**Multivariate**	
Factor	Exp (B)	P value	Exp (B)	P value
Age	.980	.130	.982	.077
sex	.858	.483		
SE	.972	.445		
IOP baseline	.985	.619		
Mean IOP	1.086	.054	1.060	.223
Reduction in IOP	.934	.070	.937	.075
Average C/D ratio	.462	.562		
Average RNFL thickness	1.007	.545		
Number of Total DH	1.167	.163	1.244	.064
CCT	1.002	.636		
Medication N	1.135	.442		
MD	.999	.975		
PSD	1.012	.646		

Table 6. Characteristics of Patients according to number of incidents of Disc Hemorrhage.

	One DH (n, 72)	**Multiple DH (n, 47)**	**P value**
Anticoagulant (Y / N) (n)	9 / 63	10 / 37	0.201
Age (year) (n)	58.25 ± 11.22	61.60 ± 10.93	0.111
Sex (M / F) (n)	37 / 35	24 / 23	0.972
Glaucoma Progression (Y / N) (n)	56 / 16	44 / 3	0.021
Family history (Y / N)(n)	5 / 59	2 / 39	0.729*
HTN (Y / N) (n)	21 / 51	18 / 29	0.300
DM (Y / N) (n)	12 / 60	11 / 36	0.363
Hyperlipidemia (Y / N) (n)	12 / 60	10 / 37	0.012
Total Follow-up period (Month)	74.18 ± 21.44	75.79 ± 22.92	0.698
Follow-up period to progression (Month)	50.86 ± 22.71	49.51 ± 25.88	0.765
BCVA	0.95 ± 0.17	0.96 ± 0.14	0.726
SE (Diopters)	-1.90 ± 2.89	-1.79 ± 3.25	0.863

Baseline IOP (mmHg)	16.28 ± 2.89	16.11 ± 3.97	0.786
Mean IOP (mmHg)	14.06 ± 2.70	14.13 ± 2.97	0.891
IOP reduction (mmHg)	2.22 ± 2.75	1.98 ± 3.76	0.684
CCT (㎛)	521.52 ± 30.93	533.33 ± 23.60	*0.061*
Medication at Last Follow-up (n)	1.00 ± 0.59	1.30 ± 0.66	0.014
Number of disc/RNFLphoto exams (n)	9.10 ± 2.45	8.42 ± 1.98	0.426
Number of Total DH (n)	1.63 ± 0.94	1.92 ± 0.90	0.195
Number of VF test (n)	10.33 ± 2.72	10.45 ± 3.23	0.837
Baseline MD (dB)	-3.24 ± 4.60	-3.15 ± 3.50	0.904
Last MD (dB)	-3.35 ± 5.16	-4.27 ± 5.14	0.334
Baseline PSD (dB)	4.34 ± 4.20	4.36 ± 3.30	*0.985*
Last PSD (dB)	4.92 ± 4.35	6.23 ± 4.82	0.126
VF GPA (%/year)	-0.42 ± 0.95	-1.34 ± 1.79	0.004

* For categorical analysis, the chi-square test was used (For the analysis of numbers of patients below 5, Fisher's exact test was adopted)

Independent t -test was used for the analysis

Table 7. Retinal Nerve Fiber Layer and Optic Nerve Head Parameters of Patients according to frequency of incidents of Disc Hemorrhage

	One DH (n, 72)	**Multiple DH (n, 47)**	**P value**
Baseline Average C/D ratio	0.74 ± 0.08	0.73 ± 0.09	0.879
Baseline Rim area	0.86 ± 0.19	0.86 ± 0.18	0.967
Baseline Disc area	2.09 ± 0.42	2.11 ± 0.51	0.793
Baseline average RNFL Thickness (㎛)	79.30 ± 10.69	81.11 ± 9.88	0.354
Baseline Superior RNFL thickness (㎛)	100.82 ± 15.89	103.60 ± 18.92	0.390
Baseline Nasal RNFL thickness (㎛)	61.94 ± 7.79	63.91 ± 8.67	0.200
Baseline Inferior RNFL thickness (㎛)	90.25 ± 21.58	92.11 ± 17.92	0.625
Baseline Temporal RNFL thickness (㎛)	63.26 ± 10.76	65.13 ± 11.35	0.368

Last Average C/D ratio	0.75 ± 0.09	0.76 ± 0.07	0.346
Last Rim area	0.86 ± 0.20	0.84 ± 0.19	0.647
Last Disc area	2.04 ± 0.44	2.06 ± 0.47	0.807
Last average RNFL Thickness (μm)	76.03 ± 9.90	76.26 ± 8.38	0.897
Last Superior RNFL thickness (μm)	95.56 ± 15.63	96.47 ± 17.94	0.770
Last Nasal RNFL thickness (μm)	62.49 ± 7.77	64.09 ± 6.86	0.253
Last Inferior RNFL thickness (μm)	83.68 ± 20.47	83.19 ± 17.12	0.892
Last Temporal RNFL thickness (μm)	61.40 ± 11.33	61.21 ± 10.56	0.927
Average RNFL thickness GPA	-0.71 ± 0.80	-0.98 ± 0.96	0.113
Average C/D GPA	0.002 ± 0.01	0.005 ± 0.01	0.189
Superior RNFL thickness GPA	-1.18 ± 1.59	-1.32 ± 1.29	0.631
Inferior RNFL thickness GPA	-1.35 ± 1.41	-1.98 ± 2.09	0.085

Independent t -tests were used for the analysis

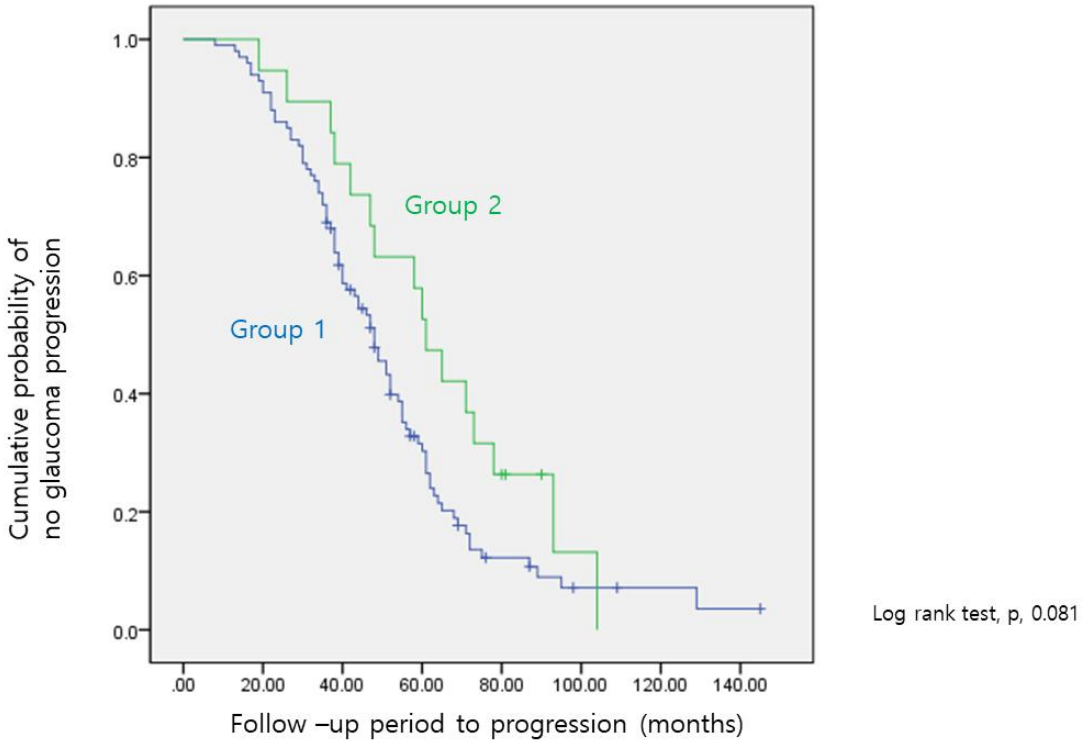

Figure 1. Kaplan-Meier analysis of the probability of no glaucomatous progression in patients in the No use group (Group1) and the Antiplatelet / Anticoagulant use Group (Group2).

Log rank tests comparing the control group and the anticoagulant group showed borderline significant differences (p, 0.081).

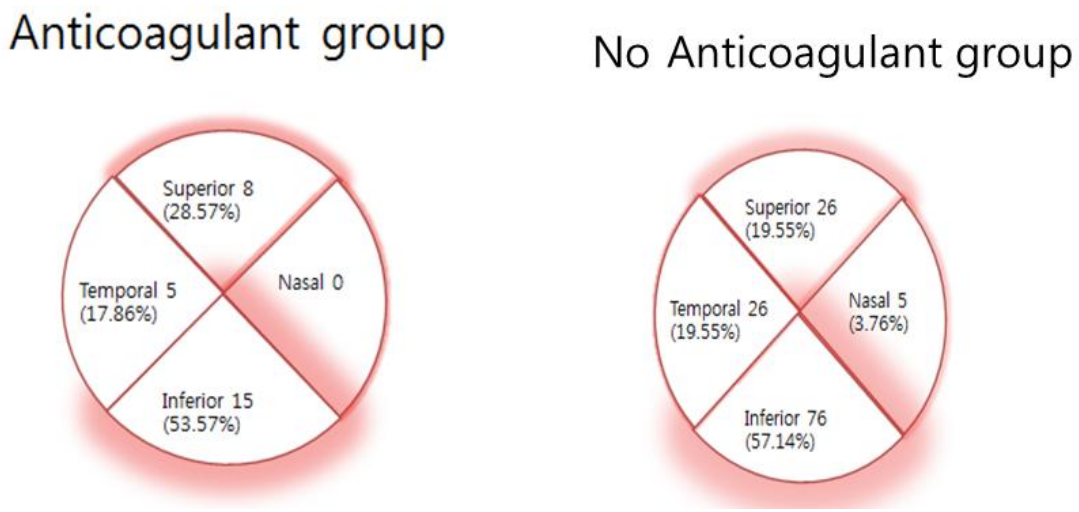

Figure 2. Analysis of disc hemorrhage patterns including recurrent hemorrhages

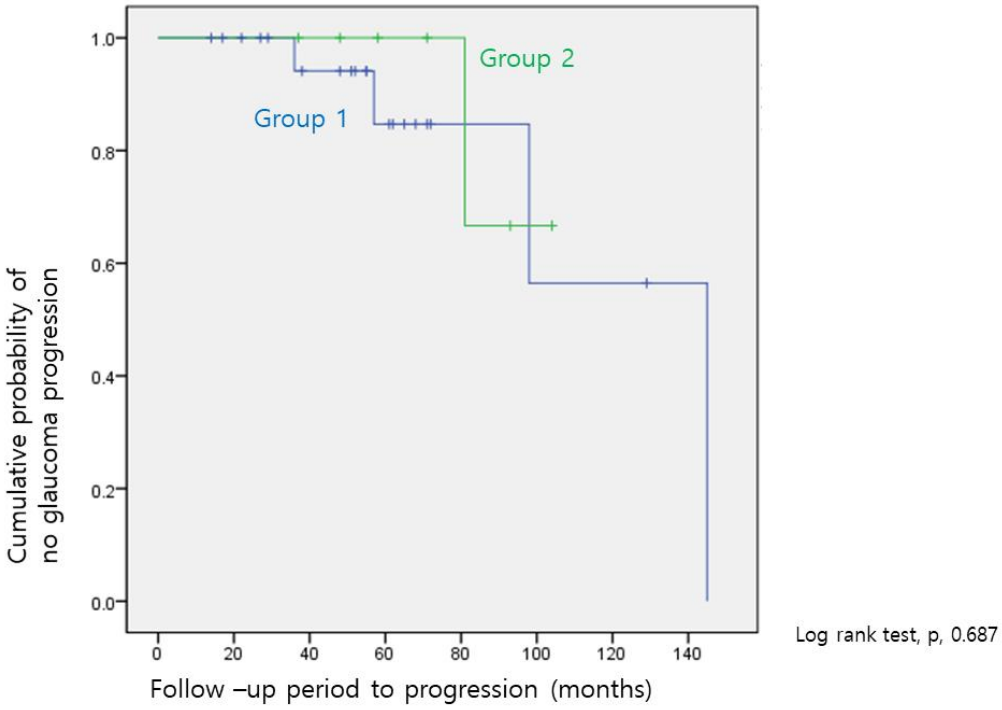

Figure 3. Kaplan-Meier analysis of the probability of no glaucomatous progression in the No use Group (Group1) and the Antiplatelet / Anticoagulant use Group (Group2) with superior disc hemorrhages.

Log rank tests comparing the groups did not reveal statistically significant differences (p, 0.687).

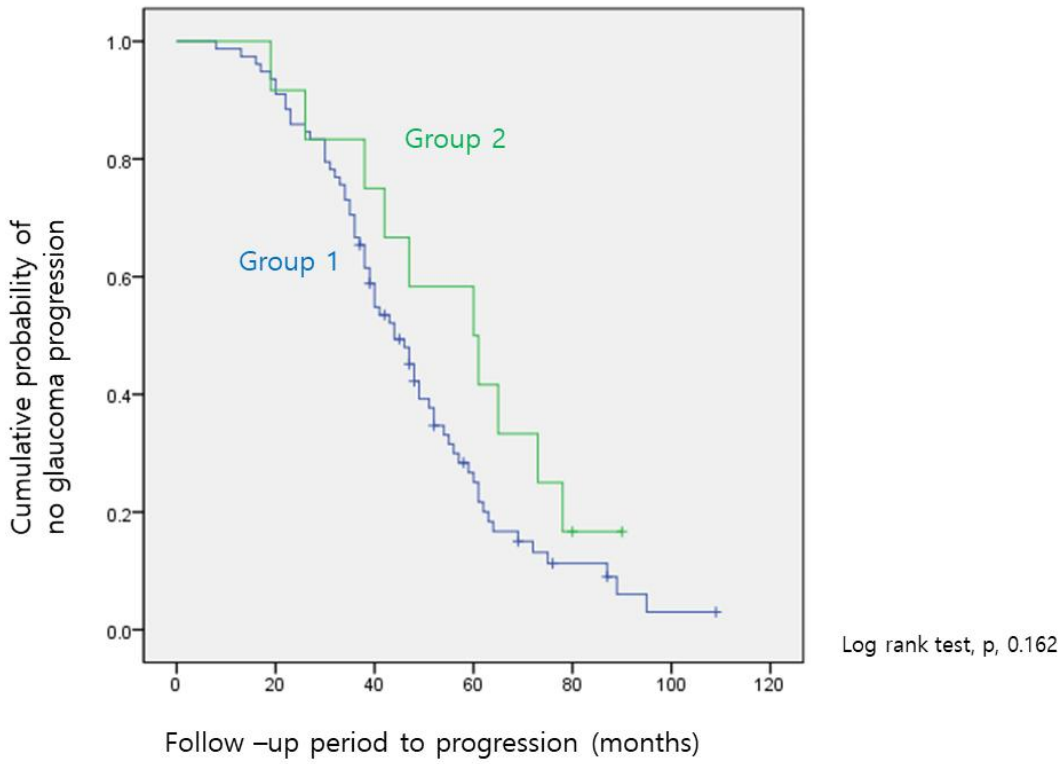

Figure 4. Kaplan-Meier analysis of the probability of no glaucomatous progression in the No use Group (Group1) and the Antiplatelet / Anticoagulant use Group (Group2) with inferior disc hemorrhages.

Log rank tests comparing the groups did not reveal statistically significant differences (p, 0.162).

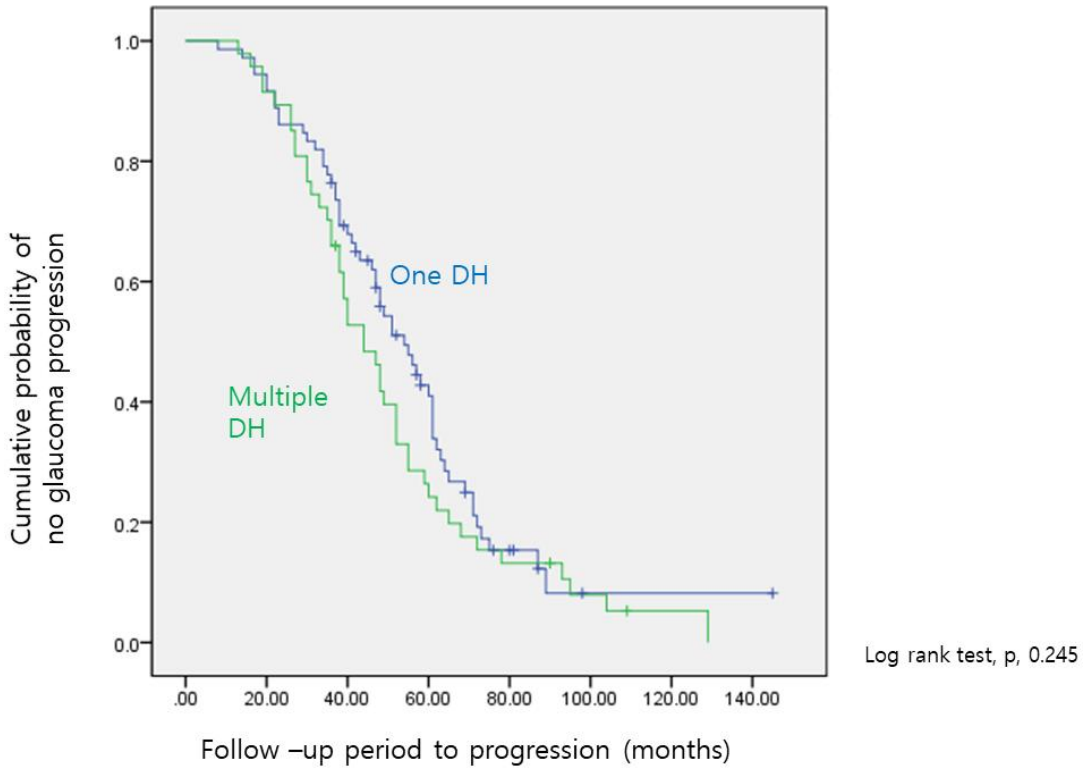

Figure 5. Kaplan-Meier analysis of the probability of no glaucomatous progression in patients with one disc hemorrhage versus multiple disc hemorrhages

Log rank tests comparing the groups did not reveal statistically significant differences (p, 0.162).

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