

The effect of the hypertensive phase on the long-term outcomes of Ahmed glaucoma valve (AGV) implantation

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Abstract

Background

To investigate the long-term effect of hypertensive phase(HP) on the clinical outcomes of Ahmed Glaucoma Valve (AGV) implantation.

Method

The records of patients with different etiologies of glaucoma who underwent AGV implantation were retrospectively reviewed. HP was defined as the IOP> 21 mm Hg during the first three months after surgery. The main outcome measure was cumulative success defined as 5 < IOP< 21 mmHg and 20 % reduction from the baseline with or without IOP lowering medications. The secondary outcome measures were intraocular pressure (IOP) and the number of glaucoma medications.

Results

A total of 120 patients (28 patients of HP, 92 patients without HP) with an average age (\pm SD) of 48.9 ± 19.6 years and a mean follow-up of 4.5 ± 1.4 years were enrolled. The mean duration of survival was 5.3 ± 0.5 years in HP which was significantly shorter than 6.4 ± 0.2 years in non-HP. (log Rank= 4.2, P= 0.04) Mean IOP and number of IOP lowering agents were higher in postoperative visits at 1,2, 3, and 4 years in HP patients compared with non-HP. (All Ps < 0.01) Higher Baseline IOP was significantly associated with higher rates of surgical failure. Neovascular glaucoma was the only factor associated with the occurrence of HP in a logistic regression model. (Odds ratio: 3.14 CI: 1.2-8.1).

Conclusion

In the long-term follow up the duration of survival was significantly longer in the non-HP group. In the non-HP group, the success rate was significantly higher than the HP group

Introduction

Recently, glaucoma drainage devices (GDD) have been widely used in the surgical management of patients with refractory glaucoma or failed previous glaucoma surgeries. Primary GDDs implanting in glaucoma patients has been recently evaluated to have an association with lower rates of success in comparison to Trabeculectomy. [1, 2]

The hypertensive phase (HP) occurs in approximately 56 to 82 % of those patients undergoing GDD implantation, so it is considered as a natural phase following the prior hypotensive phase observed in the first 3 weeks postoperatively.[3, 4] The exact mechanism underlying the HP is poorly understood yet. However, the exaggerated process of wound healing around the implant still is the most acceptable mechanism.[3] The timing of the HP, starting over the first postoperative weeks, reaching a peak after 1 month, and is partially resolved over three to six months, supports the role of fibrosis formation and its

maturation as major causes of the HP. [5] Egress of inflammatory mediators and cytokines from the aqueous humor to the subconjunctival space around the shunt is proposed as a stimulator of fibrous formation.

Higher baseline intraocular pressure (IOP)[6], the type and material of the device[7], the intrinsic characteristics of the devices like opening and closing pressure of the tube[8], and longer axial length[9] have been reported as the risk factors for the development of HP. Tsai et al.[10] reported a significantly higher mean IOP after one month in patients undergone Ahmed Glaucoma Valve (AGV) implantation compared to the patients who undergone Bearveldt glaucoma implantation (BGI). The results of Ahmed versus Bearveldt[11] study and Ahmed and Bearveldt comparison[12] study supported the finding of higher IOP in the AGV group after one month from the operation, while the early postoperative IOP on day 1 and a week later were lower in the AGV group. Similarly, the use of the Molteno device is associated with lower IOP compared with the AGV.[13]

Considering HP as a natural phenomenon after GDD implantation was questioned by some authors in their studies. In this regard, Nouri-Mahdavi and Capriolli[14] demonstrated the worse IOP outcome and a higher need for glaucoma medication by passing 6 to 9 months from the AGV implantation. The authors hypothesized whether the HP is a spectrum of a failing AGV or is a transient phenomenon with no worse outcome. Multiple reports after Nouri-Mahdavi's study confirmed the worse success rates after the HP development.[15, 9] However, to the best of our knowledge, the data on the long-term effect of HP on the surgical outcome is still limited.

The present study aimed to investigate the long-term effect of HP on AGV implantation outcome and the factors contributing to the development of HP. We hypothesized that HP could affect the long-term outcomes of AGV implantation.

Methods

The records of all glaucoma patients who undergone AGV implantation between Jan 2010 and Jan 2019 were retrospectively reviewed in the present study. All surgeries were performed in two tertiary glaucoma practice centers (Rassoul Akram and Imam Hossein Hospitals). The study protocol was approved by a local ethics committee and adhered to the tenets of the Declaration of Helsinki.

The patients who undergone AGV implantation and were followed-up for at least 3 years, were included. The exclusion criteria consisted of age less than 18 years old and any intraocular surgery within the follow-up period HP was defined as follows: IOP > 21 mm Hg (with or without IOP lowering medication) within the postoperative 3-month period after a successful IOP reduction to < 22 mm Hg during the first postoperative week, and not resulted from tube obstruction, retraction, or valve malfunction. HP resolution was defined as an IOP < 22 mm Hg along with (1) a reduction in the IOP by ≥ 3 mm Hg with the same number of medications or less, or (2) a reduction in at least 1 medication with a change of IOP < 3 mm Hg. According to the above-mentioned definition, we categorized the included patients either in the

HP group or in the non-HP group. Besides, if the HP has started within the first 5 weeks postoperatively, the HP was considered as early HP.

Surgical technique and post-operative visits.

All surgeries were performed by two glaucoma specialists (NN, MY) using the uniform method for the surgery. Under general or local anesthesia, a fornixbased conjunctival flap was made in the superotemporal quadrant after priming the AGV (model FP7, New World Medical, Rancho Cucamonga, CA, USA), and the plate was then secured to the sclera with an 80 nylon suture, located approximately 10 mm behind the surgical limbus. The tube was then inserted into the anterior chamber using a 23-gauge needle. The anterior part of the tube was covered with a scleral patch graft (5*5 mm). Thereafter, the conjunctiva was secured with 8-0 Vicryl sutures. At the end of the surgery, we inferotemporally used subtenon Methylprednisolone. Postoperatively, all the patients were prescribed Ciprofloxacin eye drop 4 times per day for 10 days as well as Betamethasone eye drop every 2 h for a 2-week period that was tapered over the next 8–12 weeks by considering the inflammation of the surgical area. The patients were then examined on a postoperative day 1, and afterward, weekly for 4 weeks, and finally, every 1–3 months, based on the clinical judgment. Glaucoma medications were started in a stepwise fashion when the target pressure was not achieved or when the HP was diagnosed. If no contradiction was present, aqueous suppressants were the first choice.

Data Gathering

The following data were extracted from the patients' records: age, sex, stage and type of glaucoma, preoperative and postoperative IOP, number of medications, intraoperative and postoperative complications, previous intraocular surgeries, and systemic diseases.

Statistical analysis

The primary outcome measures were cumulative success defined as $5 < \text{IOP} < 21$ mm Hg and at least 20 % reduction compared to the baseline level with or without medications. The secondary outcome measures were IOP and the number of glaucoma medications. The normality of data was tested using Kolmogorov-Smirnov test and Q-Q plot. Mean was presented for variables with a normal distribution like IOP, Median for variables without normal distribution like glaucoma medication, and frequency and standard deviation were used to describe the obtained data. To evaluate the changes in IOP and glaucoma medication at different intervals, linear mixed models were used. Moreover, to compare IOP and glaucoma medications between the groups, student T-test and Mann-Whitney were used, respectively. Complete success was defined as the intraocular pressure between 5 and 21 mmHg and 20 percent reduction compared to the baseline level without glaucoma medication. The qualified success was defined in the same way without considering the use of any glaucoma medication.

Kaplan Meier survival analysis was used to assess the cumulative probability of success. Cox proportional Hazard model was also applied to predict the risk factors of failure. A binary logistic regression model was used by Backward wald to evaluate the factors affecting the occurrence of HP. All statistical analyses were performed using SPSS (Version 25, IBM, Chicago, Illinois). A P-value less than 0.05 was considered statistically significant.

Results

The records of 120 included patients were reviewed in this study. The mean (\pm SD) duration of follow-up was 4.5 ± 1.4 years. The average age (\pm SD) of the study participants was 48.9 ± 19.6 (ranged from 1 to 88) years old. Twenty-eight (23.3 %) patients experienced the hypertensive phase during the study period. IOP lowering agents also started in 19 patients with advanced glaucoma that required a lower IOP based on the targeted pressure between the second and the fourth weeks. The exact decision on the occurrence of HP was difficult in these patients. These patients were categorized as non-HP if the IOP was estimated to be lower than 22 after the adjustment for the effect of drugs. The patients who experienced the hypertensive phase were compared to the patients without HP in terms of age, sex, baseline IOP, baseline medication, and glaucoma type. (Table 1)

Table 1
Characteristics of the study participants.

		Group with HP	Group without HP	P-value
Age	Years	47.3 \pm 18.5	49.5 \pm 20.0	0.61
Sex	Male (N, %)	13 (48.1 %)	56 (60.8%)	0.19
	Female	15 (51.9 %)	36 (39.1%)	
Glaucoma type	POAG	2 (7.1 %)	19 (15.8%)	0.12
	CACG	2 (7.1 %)	9 (7.5 %)	
	PCG	4 (14.3 %)	5 (4.1 %)	
	NVG	11 (39.3 %)	16 (13.3 %)	
	Other	9 (32.1 %)	71 (59.2%)	
POAG: Primary open-angle glaucoma; CACG: chronic angle-closure glaucoma; PCG: Primary congenital glaucoma; NVG: Neovascular glaucoma				

The mean duration of survival (\pm SE) in the HP group was 5.3 ± 0.5 years, which was significantly shorter compared to the patients without HP that had 6.4 ± 0.2 years. (Log Rank = 4.2, P = 0.04) The cumulative probability of success was 78.6 %, 75 %, and 70.3% at years 1, 2, and 4 in the HP group, respectively. In addition, the corresponding value in the control group was 94.6 %, 91.3 %, 86.4%, and 84.3 % at 2, 3, 4, and 5 years, respectively. The cumulative probability of success was 63.6 % in the group experiencing

early HP (11 patients) at the end of the first and fifth years, while the corresponding values in the group with late HP (17 patients) were 88.2 % and 74.1 %, respectively. However, the longer duration of survival in the group with late HP did not reach a statistically significant level. (Log Rank = 0.58, P-value = 0.44) HP was resolved in 10 (37%) patients within 6 to 12 months. (Fig. 1).

Complete success (success without IOP lowering medications) occurred in 14.2 % of the non-HP patients versus in 0 HP patients. (P = 0.02, Table 2) A Cox proportional hazard regression model was identified to predict the factors affecting surgical failure. Baseline levels of IOP and glaucoma medication remained in the model, while baseline IOP was found to predict surgical failure significantly. (Table 3).

Table 2
Failure and success (complete and Qualified) at the final follow-up of each patients.

	HP	Non-HP	
Failure N (%)	8 (6.7%)	11 (9.2%)	0.05*
Success N (%)			
Qualified Success	20 (16.7%)	64 (53.3%)	0.02**
Complete success	0 (0%)	17 (14.2%)	
*Based on chi-square test. **Based on Fisher exact test. Complete success was defined as the intraocular pressure between 5 and 21 mmHg and 20 percent reduction from the baseline without glaucoma medication. Qualified success was defined in the same way without considering the use of glaucoma medication.			

Table 3
Results of regression model predicting factors affecting surgical failure in total patients.

Variable	Hazard Ratio	Confidence Interval 95 %		P-value
		Lower band	Upper band	
Age	0.99	0.96	1.02	0.65
Sex	1.0	0.39	2.51	0.99
Glaucoma Type	0.76	0.23	2.44	0.65
Presence of HP	2.17	0.83	5.71	0.11
Baseline Medication **	2.41	0.96	6.05	0.06
Baseline IOP	1.07	1.02	1.12	0.002*
*Based on the Cox Proportional Hazard Regression Model, backward Wald				
**Categorical variable less than 2 and more than 2 medications				

The mean IOP of the group with HP has significantly decreased from 29.6 ± 9.7 mmHg (Mean number of meds = 3.07 or with a median number of medications = 3) at baseline to 19.3 ± 6.7 mmHg after 5 years with a median of 3 glaucoma medication. The mean of the reduction in IOP was 31 % after 5 years. Correspondingly, an average IOP has significantly decreased from 27.4 ± 7.8 mm Hg with the mean number of 3.04 or with the mean number of medication = 3) at baseline to 16.4 ± 5.6 mm Hg after 5 years. The median number of glaucoma medications and the mean of the reduction in IOP was 2 and 36 %, respectively. (Table 4, Fig. 2) As shown in Table 5, the mean number of glaucoma medications was higher in the HP group compared to the group without HP at all intervals. In the fifth year, the median number of glaucoma medications in the HP and control groups was 3 and 2, respectively. (Fig. 3)

Table 4
Intraocular pressure between two groups with and without HP within the study period.

IOP	N	Group with HP (Mean \pm SD)	N	Group without HP (Mean \pm SD)	P-value*
Baseline	28	29.6 ± 9.7	92	27.4 ± 7.8	0.22
Month 6	28	18.3 ± 6.5	92	13.9 ± 4.9	< 0.001
P from baseline ¥		< 0.001		< 0.001	
Year 1	28	17.5 ± 5.3	92	14.9 ± 4.9	0.004
P from baseline ¥		< 0.001		< 0.001	
Year 2	28	17.9 ± 5.2	92	15.2 ± 4.9	0.011
P from baseline ¥		< 0.001		< 0.001	
Year 3	28	18.1 ± 6.8	92	15.3 ± 4.7	0.013
P from baseline ¥		< 0.001		< 0.001	
Year 4	23	19.8 ± 7.0	58	16.0 ± 5.3	0.010
P from baseline ¥		< 0.001		< 0.001	
Year 5	20	19.3 ± 6.7	45	16.4 ± 5.6	0.070
P from baseline ¥		< 0.001		< 0.001	
¥ based on the linear mixed model; * Based on independent T-test; HP: Hypertensive phase; SD: Standard Deviation;					

Table 5
Number of Glaucoma medication in groups with and without HP.

Glaucoma Medication		Group with HP		Group without HP		P-value*
		Mean ± SD	Median (IQ 25, 75)	Mean ± SD	Median (IQ 25, 75)	
Baseline	Mean ± SD	3.1 ± 1	3 (3, 4)	3.0 ± 1.1	3 (3, 4)	0.7
Month 6	Mean ± SD	2.3 ± 0.9	2 (2,3)	1.2 ± 0.9	1 (0,1)	< 0.001
P from baseline		< 0.001		< 0.001		
Year 1	Mean ± SD	2.6 ± 0.9	3 (2,3)	1.2 ± 1.2	1 (0, 2)	< 0.001
P from baseline		< 0.001		< 0.001		
Year 2	Mean ± SD	2.9 ± 0.8	3 (2,3)	1.5 ± 1.3	2 (0, 2)	< 0.001
P from baseline		0.002		0.001		
Year 3	Mean ± SD	2.9 ± 0.8	3 (3,3)	1.9 ± 1.4	2 (1, 3)	< 0.001
P from baseline		0.062		< 0.001		
Year 4	Mean ± SD	3.1 ± 0.9	3(2,4)	1.8 ± 1.4	2 (1, 3)	< 0.001
P from baseline		0.87		0.032		
Year 5	Mean ± SD	2.9 ± 0.9	3 (2, 4)	2.0 ± 1.3	2 (1, 3)	< 0.001
P from baseline						
*based on the Mann-Whitney test.						

The average of IOP in eleven patients experiencing early HP was 28.4 ± 3.9 mm Hg and in 17 patients in the late HP group, it was 28.9 ± 4.7 mm Hg. (P-value: 0.4) In year 1, despite the use of glaucoma medications, IOP in 6 (22.2 %) patients remained higher than 21. In a binary logistic regression model, neovascular glaucoma secondary to CRVO or DM was related to the higher odds of hypertensive phase (Odds ratio: 3.14 CI: 1.2–8.1), while age, baseline IOP, baseline glaucoma medications, and sex were not the predictors of HP. (Table 6)

Table 6
Results of the regression model predicting factors affecting the presence of HP in total patients.

Variable	Hazard Ratio	Confidence Interval 95 %		P-value*
		Lower band	Upper band	
Age	.986	.962	1.010	0.98
Sex	1.931	.792	4.711	0.14
Glaucoma Type**	3.143	1.216	8.119	0.018
Baseline Medication	1.119	.724	1.730	0.61
Baseline IOP	1.002	.948	1.060	0.93
*based on binary logistic Regression, backward Wald.				
**Categorical variable, neovascular glaucoma, or not.				

Complications

Tube exposure occurred in 5 patients treated with conjunctival free graft. Five patients experienced choroidal detachment, of them 4 were conservatively managed and one underwent choroidal drainage. Corneal decompensation was observed in 2 patients who were conservatively managed. Two groups were compared in terms of overall complications. (4 vs 11 in HP vs non-HP, Chi-square test, P = 0.74)

Discussion

The results of the present study show lower surgical success, higher IOP, and more glaucoma medications in patients experiencing HP after AGV implantation. Besides, the observed difference remained in the long-term period of 5 years, which is shown for the first time to the best of our knowledge.

Our results are in line with those of the previous reports investigating the effect of HP on the IOP outcome. Nouri-Mahdavi and Caprioli[14] found a higher mean IOP and more required glaucoma medications by passing 6 to 12 months from surgery in eyes with an HP. Similarly, Jung [9] reported higher IOP in the HP group compared to the non-HP group after 1 year, while the difference in surgical success did not reach a significant level. Subsequently, Jeong et al.[15] reported lower IOP control and worse success in eyes with HP after 2 years from the operation. Our study with a longer duration of follow-up has also shown a lower rate of success in the HP group.

Similar to Nouri-Mahdavi et Caprioli's study[14], we considered the IOP more than 21 mm Hg after 3 months, as a surgical failure, rather than an HP. Although the exact mechanism underlying HP has not been exactly clarified yet, various mechanisms have been proposed in this regard. The most plausible explanation relates the HP to the normal wound healing process, consequent fibrosis formation, and bleb

encapsulation.[3] The histopathological studies investigating the wound healing process after GDD implantation reported a difference between the staged processes and procedures in which the aqueous flow is immediately established like AGV.[16] The mechanical pressure of the aqueous or the pro-inflammatory cytokines present in AC was hypothetically indicated to result in a full-thickness thick bleb wall around the plate.[17]

The HP usually peaks after one month, which accords to the timing of fibrosis formation around the AGV plate. In contrast, Jung et al.[18] using anterior segment optical coherence tomography demonstrated thinner wall of the bleb accordant with the timing of HP and then postulated the collagen cross-linking as the mechanism underlying the pathophysiology of thinner bleb and HP. Moreover, the HP was not resolved in approximately two-third of the included patients. Besides, all HP patients needed glaucoma medication in the first year.

Moreover, there is a potential role for steroids as an inducer of high IOP after the surgery. Correspondingly, Yuen et al.[19] reported lower HP rates in patients receiving nonsteroidal inflammatory drugs (NSAID), as a substitute for the topical steroid. Besides, the inflammatory cytokine level was found to be correlated with higher IOP in the glaucomatous eyes with an HP.[20] However, it still seems unclear whether these cytokines are stimulated with high IOP or they are contributing to the development of the HP. Intrinsic characteristics of the implanted device might also play a role in the HP since the HP more frequently occurs after AGV implantation compared to Baerveldt[11, 21] or Molteno devices.[13] The valved nature of the AGV and lower surface area has been proposed as the possible cause of a higher prevalence of HP after AGV implantation.

In this study, we estimated the prevalence of HP lower than the reports in the literature.[3] The incidence of HP widely differs among different studies. The earlier studies reported higher prevalence rates (56% [14] and 82%[5]), while more recent studies estimated lower prevalence rates (31 % [7, 9]). Because of the worse outcome after HP, multiple methods were proposed to prevent the HP including intraoperative and postoperative triamcinolone[22] or antimetabolite injection[23], early start of glaucoma medications[24], and medical suppression of aqueous humor soon after the surgery[17]. Pakravan et al.[24] reported the HP difference as 66.0 % and 23.4 % ($P < 0.001$) in groups with the early start of fixed dorzolamide and timolol, respectively. In another study, intraoperative sub-tenon Triamcinolone injection resulted in the HP difference between the two study groups. (26 % vs 52%, $P = 0.027$ respectively). The use of Ketorolac in comparison to steroid eye drops has also led to lower HP occurrence (31% vs 53 %, $P = 0.27$)¹⁹. However, we did not apply the specific proposed methods for the prevention of the hypertensive phase. The IOP lowering medications were started either when the IOP passed the target pressure or when there was a pattern of the continuous rising of IOP between follow-up visits.

Another interesting result of the present study is the worse outcome in the group experiencing early HP compared with the group of late-onset HP. Since the difference did not reach a statistically significant level, making a clear conclusion is not possible. However, in our experience, it was shown that HP entails a heterogeneous group of patients with different outcomes. Furthermore, Cheng et al.[8] investigated the

opening and closing pressures in the AGVs and then hypothesized that high opening pressure (cutoff of 18 mm Hg) and low closing pressure (cutoff less than 7 mm Hg) were both related to the early hypertensive phase, while they did not affect the late HP. Therefore, we assume that there may be some tube-related factors affecting early HP that remain for a longer duration compared to late HP and consequently result in a worse outcome.

Several factors were reported in different studies as the risk factors for the HP development, including higher baseline IOP and long axial length[9]. In the present study, the only factor found to be associated with HP development was the presence of neovascular glaucoma. Also, it was indicated that more prevalent inflammatory cytokines in the aqueous of the patients with NVG[25] result in the more prominent fibrovascular reaction, so they might be the underlying mechanisms. In contrast to the previous reports, higher baseline IOP was not a factor affecting HP development, while it could predict the long-term success in a Cox proportional hazard regression model.

Our limitations are also included, but they are not limited to the retrospective nature of the study, small sample size, and different types of glaucoma.

In conclusion, we reported worse IOP outcomes, higher needs to glaucoma medications, and lower success rates in patients who experienced a hypertensive phase in the 5 years postoperatively. Patients experiencing HP in the earlier period after the surgery might also have a worse outcome compared to the patients experiencing HP for a period of 1.5 to 3 months after the procedure. In this regard, larger studies are required to investigate the possible difference between two groups of HP.

Declarations

- **Ethics approval and consent to participate:** All procedures in this study were approved by the Ethics Committee of the Eye Research Center, Rassoul Akram Hospital, Iran University of Medical Sciences, Tehran, Iran. Written informed consent was obtained from each participant.
- **Availability of data and materials:** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.
- **Competing interests:** The authors declare no conflict of interest.
- **Funding:** No funding was received

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Figures

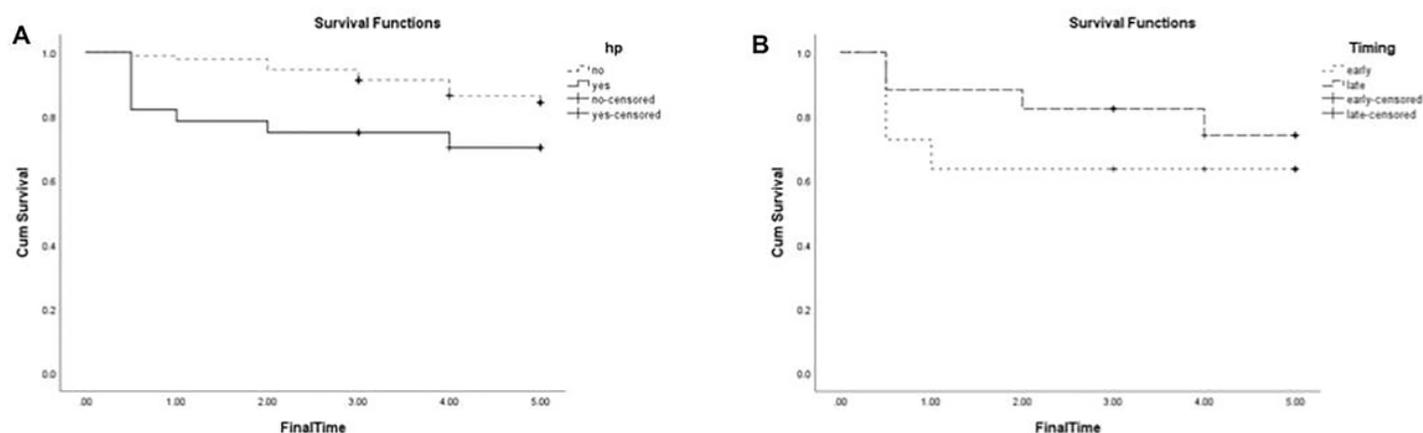


Figure 1

Kaplan-Meier plot demonstrating lower survival in patients with HP (n= 28, continuous line) and without HP (n= 92, Dotted line).

IOP

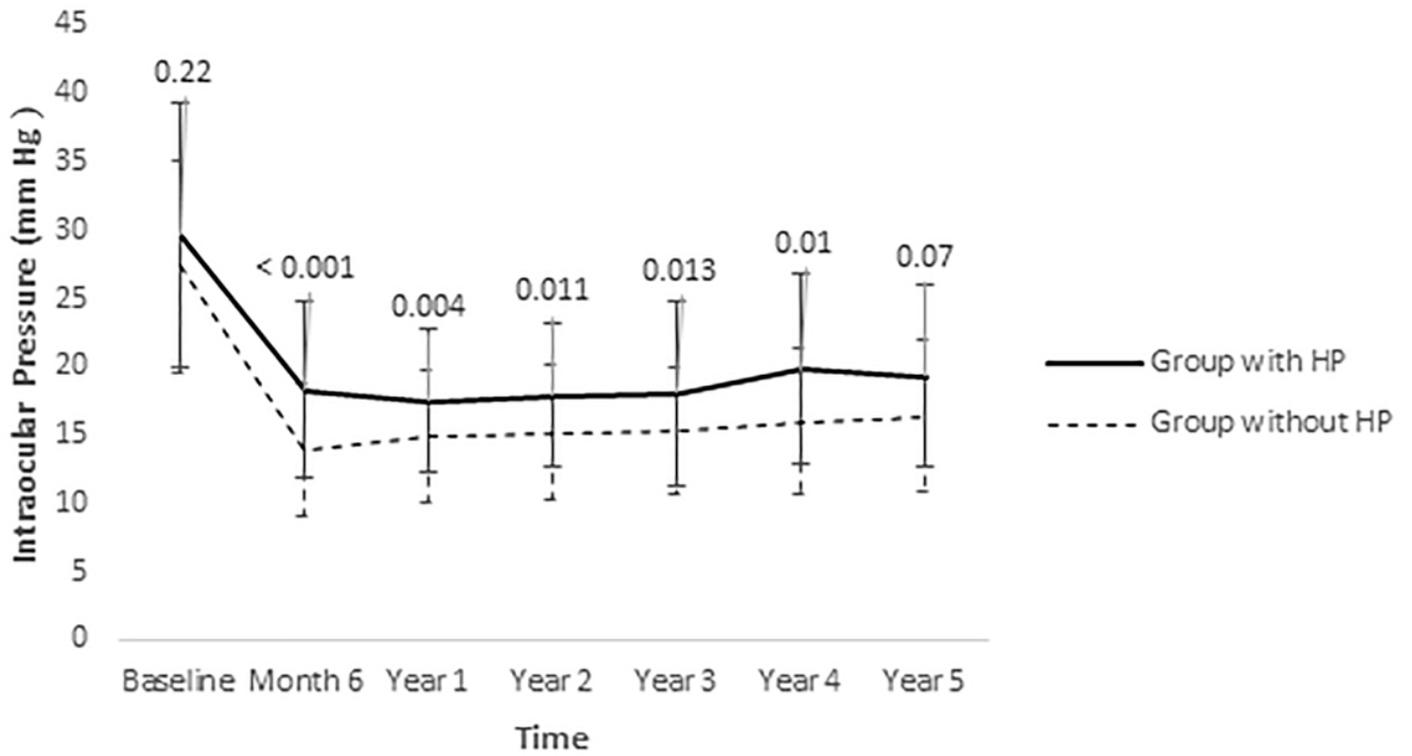


Figure 2

The line chart demonstrates Intraocular pressure (IOP) in a group with the hypertensive phase (black line) and groups without hypertensive phase (dotted line).

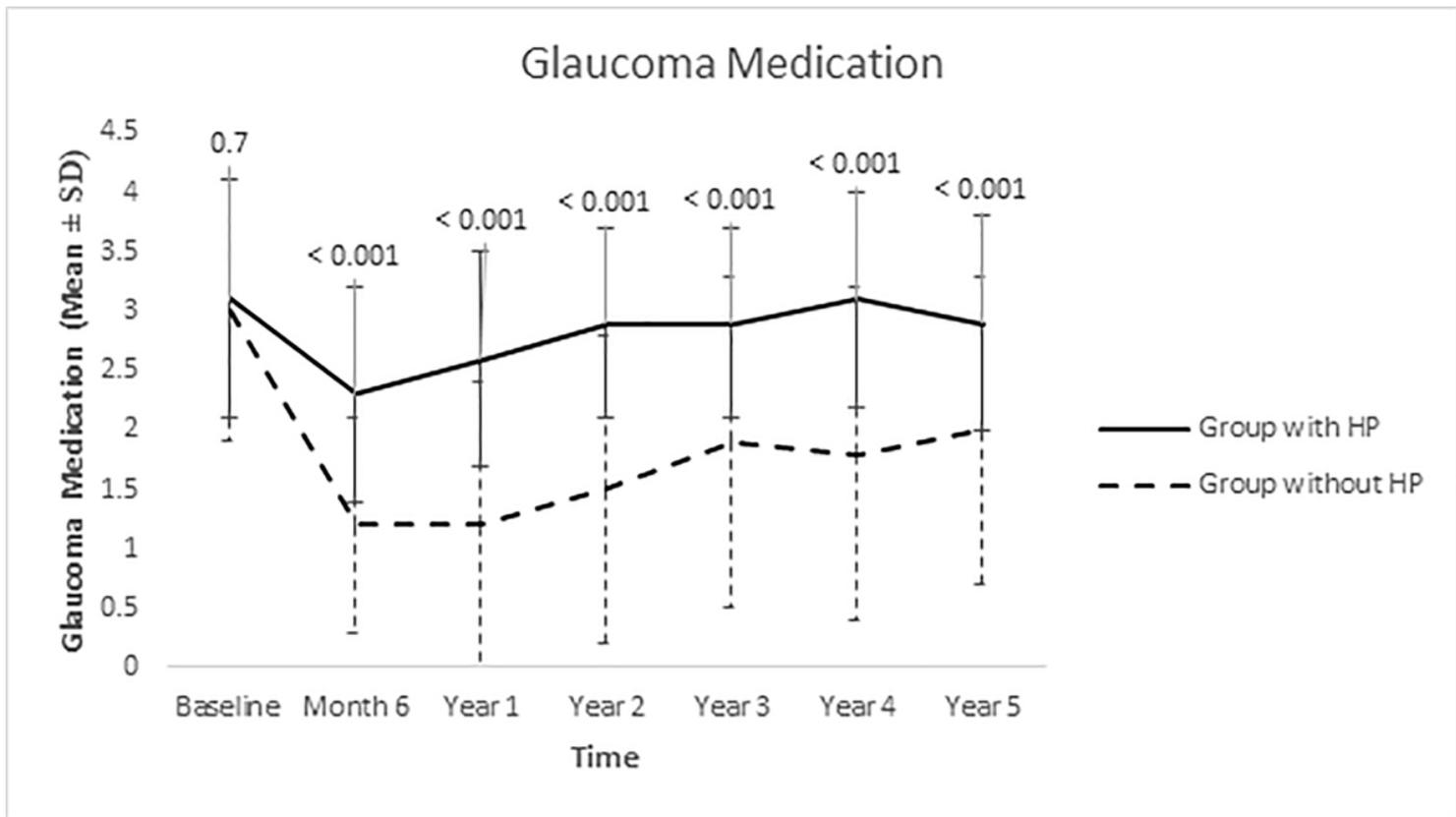


Figure 3

Glaucoma medication in the group with the hypertensive phase and without hypertensive phase