
Effect of topical 5% phenylephrine in reducing the incidence of subconjunctival hemorrhage after intravitreal injection

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ABSTRACT

Background and objective: Subconjunctival hemorrhage (SCH) is a common condition; one of its important causes is intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF), which is used to treat various ocular pathologies. In this study, we aimed to decrease subconjunctival hemorrhage with the use of a 5% phenylephrine hydrochloride topical drop.

Methods: Prospective, randomized, single-blind, multicenter study. One hundred patients (116 eyes) with different retinal pathologies were enrolled, divided into two groups: group 1, 50 patients (60 eyes), received one drop of phenylephrine, and group 2, 50 patients (56 eyes), received a drop of distilled water, fifteen minutes before intravitreal injection. Patients were examined by slit lamp for presence of subconjunctival hemorrhage 24 hours after the injection.

Results: The frequency of subconjunctival hemorrhage in the intervention group was 23.3% (14 of 60 eyes), notably less ($p=0.041$) than in the control group (41.1%, 23 of 56 eyes).

Conclusion: Administration of topical phenylephrine hydrochloride 5%, 15 minutes prior to intravitreal injection of anti-VEGF, appears to be an effective and straightforward approach for reducing or preventing subconjunctival hemorrhage (SCH) — a commonly reported complication following such injections. This strategy may contribute to improved patient comfort and compliance with ongoing intravitreal therapy.

Keywords: Subconjunctival hemorrhage, Intravitreal injection, Anti-vascular endothelial growth factor, Phenylephrine hydrochloride

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INTRODUCTION

Subconjunctival hemorrhage can be defined as bleeding in the space between the conjunctiva and episclera, due to damage of small blood vessels under the conjunctiva; it is self-resolving, painless, and causes no visual problems (1).

Subconjunctival hemorrhage (SCH) can occur as a benign condition or may indicate an underlying pathological issue, especially if it is unresolving or frequently recurring, so medical staff usually pay attention to such cases. Histologically, the conjunctiva has two parts: the tarsal conjunctiva, covering the under-surface of the eyelids, and the bulbar conjunctiva, lying over the sclera; SCH arises from superficial small blood vessels, with blood passing below the tenon capsule. A variety of causes can lead to SCH: older patients show it more frequently, due to vascular changes from diabetes, hypertension, hyperlipidemia, and anticoagulant therapy, while in younger individuals it may occur as a result of trauma or even spontaneously. Eye surgeries are considered one of the important risk factors for developing SCH, particularly in patients on antiplatelet or anticoagulant treatment (2, 3). Traumatic causes can come from direct injuries to the eye, such as blunt force, as well as from surgeries or needle piercing inside the eye.

Intravitreal medications have become one of the most widely used treatments in ophthalmology; they have modernized the management of multiple retinal pathologies and enhanced prognosis (4, 5). Antibiotics, steroids, antifungals, anti-vascular endothelial growth factors (anti-VEGFs), and many other medications can all be given via the intravitreal route.

Anti-VEGFs have proven to be an effective method for treating multiple retinal pathologies where the original problem is due to new vessel formation, as in diabetic macular edema, age-related macular

degeneration, neovascular glaucoma, and retinal vascular diseases. The commonly used anti-VEGFs in ophthalmology include aflibercept (Eylea), ranibizumab (Lucentis), pegaptanib (Macugen), and bevacizumab (Avastin). Some ophthalmologists use a protocol of monthly injections for three successive months according to clinical and optical tomographic findings, while others prefer a 'treat and extend' protocol for less frequent injections and better visual prognosis (6).

Intravitreal anti-VEGF therapies have been associated with both inflammatory and non-inflammatory adverse effects. Cataracts, elevated intraocular pressure, retinal artery occlusion, intraocular hemorrhage, and rhegmatogenous retinal detachment are non-inflammatory issues, while inflammatory responses can include sterile intraocular inflammation (SII), brolucizumab-associated retinal vasculitis (BARV), and infectious endophthalmitis. Although these problems don't happen often, they can have major effects on visual outcomes and need to be recognized and treated promptly to minimize eye damage (7).

It is common for people who have had intravitreal medication injections to experience subconjunctival hemorrhage. Widespread or bullous hemorrhages are usually thought to be harmless; however, they can cause mechanical problems such as difficulty closing the eyelids, ocular irritation, and, in very rare cases, secondary problems such as corneal dellen. The noticeable appearance of subconjunctival hemorrhage can also be upsetting for patients, which can affect satisfaction with the treatment overall. For these reasons, reducing the frequency and intensity of this problem is important both for clinical outcomes and for maintaining patients' trust in, and adherence to, treatment plans (8).

In line with the treatment protocols above, minimizing the side effects of anti-VEGF medications is important for better compliance and completion of treatment schedules.

This study looks into how phenylephrine's vasoconstrictor effects can help lower the incidence of subconjunctival bleeding. Although phenylephrine is a direct-acting sympathomimetic agent, it works mostly by stimulating alpha-1 adrenergic receptors. With a structure similar to epinephrine and ephedrine, phenylephrine has strong vasoconstrictor effects when injected intravenously or applied directly to mucosal tissues. In ophthalmology, topical application allows fast absorption through the eye and conjunctival surfaces, usually starting to act within minutes (9).

METHODS

Data Selection

The study was conducted at the Hawler and Eye Centre teaching hospitals in Erbil city, from the end of April to July 2025. It is a prospective, randomized, single-blind study. Participants gave their full agreement, and the ethical committee of the institute approved the study (meeting code 6, paper 6, dated 23/4/2025).

A total of 100 patients, aged 40 to 75, with various eye diseases who were going to receive intravitreal anti-VEGF therapy were enrolled. One hundred sixteen eyes were treated, as most patients received injections in one eye and some received injections in both. Patients who had eye surgery in the last month, acute angle-closure glaucoma, ongoing uveitis, or a history of acute cardiac syndrome or heart failure were not allowed to participate.

Study Plan

Patients were divided into two indistinguishable groups based on the order in which they were

enrolled: those with an odd enrollment number were placed in group 1, the intervention group, and those with an even number were placed in group 2, the control group.

A drop of 5% phenylephrine hydrochloride was given to group 1, and a drop of distilled water was given to group 2. Patients were not informed which drop they received. The drop was instilled into the conjunctival sac 15 minutes before the injection in both groups, and patients were asked to press on the medial canthus to reduce systemic absorption. Topical anesthesia with tetracaine hydrochloride 5 mg/1 mL solution was applied 5 minutes before therapy. Povidone-iodine 5% was then applied and left on for at least 3 minutes. The skin around the eye, eyelids, and eyelashes were cleaned with 5% povidone-iodine. A sterile periocular drape was used, and a sterile lid speculum was placed in the eye. Aflibercept 2 mg/0.05 mL was then injected using a 30-gauge needle.

A slit-lamp examination was performed 24 hours after the injection, and the presence of SCH was recorded. A hemorrhage size of less than 1 mm was considered negative, and one of 1 mm or greater was considered positive.

Data Analysis

Data were processed using SPSS version 26. The chi-square test was used to compare the sizes of two or more groups. When the expected frequency was less than 5 in more than 20% of cells, Fisher's exact test was used. An unpaired t-test was used to compare the outcomes of the two groups. A p-value ≤ 0.05 was considered statistically significant.

RESULTS

There was a total of 116 eyes, with 60 in the intervention group and 56 in the control group. The intervention group had a mean age ($\pm$ SD) of 61.6 ($\pm$ 8.5) years, while the control group had a mean

age of 59.3 (± 7.8) years ($p=0.129$). Sex distribution was not significantly different between groups, despite approximately two-thirds (65.5%) of the sample being female ($p=0.293$). Table 1 provides further detail.

The total incidence of subconjunctival hemorrhage was 31.9%; in the intervention group it was 23.3%, meaningfully less ($p=0.041$) than in the control group (41.1%) (Figure 1).

Table 1. Age and sex distribution

Variable	Intervention No. (%)	Control No. (%)	Total No. (%)	p
Age <60	23 (38.3)	24 (42.9)	47 (40.5)	0.620*
Age ≥ 60	37 (61.7)	32 (57.1)	69 (59.5)	
Mean ($\pm$ SD)	61.6 (± 8.5)	59.3 (± 7.8)		0.129**
Male	18 (30.0)	22 (39.3)	40 (34.5)	0.293*
Female	42 (70.0)	34 (60.7)	76 (65.5)	
Total	60 (100.0)	56 (100.0)	116 (100.0)	

*Calculated by chi-square test. **Calculated by unpaired t-test.

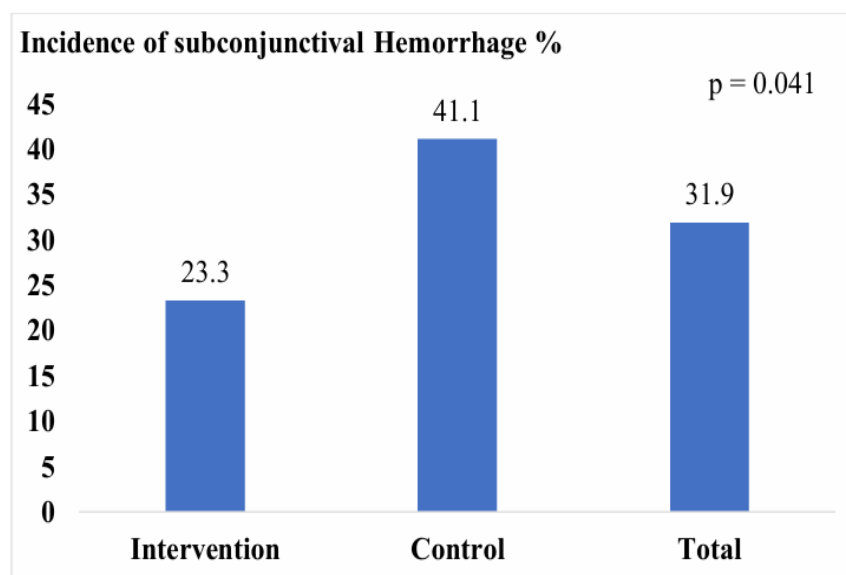


Figure 1. Incidence of subconjunctival hemorrhage by type of intervention

In the intervention group, no noteworthy association was found between the incidence of subconjunctival hemorrhage and age ($p=0.691$), sex ($p=1.000$), diabetes ($p=0.617$), hypertension ($p=0.751$), or ischemic heart disease ($p=1.000$). The

incidence of subconjunctival hemorrhage among those taking aspirin (37.5%) was significantly higher ($p=0.034$) but still lower than the corresponding rate in the control group (64.0%, $p=0.002$), as presented in Table 2.

Table 2. Incidence of subconjunctival hemorrhage by studied factors in the intervention group

Variable	Yes	No	Total	p
Age <60	6 (26.1)	17 (73.9)	23 (100.0)	0.691*
Age ≥60	8 (21.6)	29 (78.4)	37 (100.0)	
Male	4 (22.2)	14 (77.8)	18 (100.0)	1.000**
Female	10 (23.8)	32 (76.2)	42 (100.0)	
Diabetes: Yes	12 (22.2)	42 (77.8)	54 (100.0)	0.617**
Diabetes: No	2 (33.3)	4 (66.7)	6 (100.0)	
Hypertension: Yes	10 (25.6)	29 (74.4)	39 (100.0)	0.751**
Hypertension: No	4 (19.0)	17 (81.0)	21 (100.0)	
IHD: Yes	2 (22.2)	7 (77.8)	9 (100.0)	1.000**
IHD: No	12 (23.5)	39 (76.5)	51 (100.0)	
Aspirin: Yes	9 (37.5)	15 (62.5)	24 (100.0)	0.034*
Aspirin: No	5 (13.9)	31 (86.1)	36 (100.0)	
Total	14 (23.3)	46 (76.7)	60 (100.0)	

*Calculated by chi-square test. **Calculated by Fisher's exact test. IHD = ischemic heart disease.

In the control group, no important association was detected between the incidence of subconjunctival hemorrhage and age ($p=0.938$), sex ($p=0.091$), diabetes ($p=0.704$), hypertension ($p=0.389$), or ischemic heart disease ($p=0.688$). The incidence of

subconjunctival hemorrhage among those taking aspirin (64%) was significantly higher ($p=0.002$), as shown in Table 3.

Table 3. Incidence of subconjunctival hemorrhage by studied factors in the control group

Variable	Yes	No	Total	p
Age <60	10 (41.7)	14 (58.3)	24 (100.0)	0.938*
Age ≥60	13 (40.6)	19 (59.4)	32 (100.0)	
Male	6 (27.3)	16 (72.7)	22 (100.0)	
Female	17 (50.0)	17 (50.0)	34 (100.0)	0.091*
Diabetes: Yes	19 (39.6)	29 (60.4)	48 (100.0)	0.704**
Diabetes: No	4 (50.0)	4 (50.0)	8 (100.0)	
Hypertension: Yes	19 (44.2)	24 (55.8)	43 (100.0)	
Hypertension: No	4 (30.8)	9 (69.2)	13 (100.0)	0.389*
IHD: Yes	2 (28.6)	5 (71.4)	7 (100.0)	0.688**
IHD: No	21 (42.9)	28 (57.1)	49 (100.0)	
Aspirin: Yes	16 (64.0)	9 (36.0)	25 (100.0)	
Aspirin: No	7 (22.6)	24 (77.4)	31 (100.0)	0.002*
Total	23 (41.1)	33 (58.9)	56 (100.0)	

*Calculated by chi-square test. **Calculated by Fisher's exact test. IHD = ischemic heart disease.

Discussion

Subconjunctival hemorrhage (SCH) is a common complication following intravitreal anti-VEGF therapy. Despite its benign nature, SCH can negatively affect patient satisfaction and quality of life, as some individuals may withdraw from social interactions until the hemorrhage has fully resolved (8). As a result, considerable research has focused on identifying and managing the complications associated with frequent intravitreal injections.

This study found no significant association between the incidence of subconjunctival hemorrhage and sex, age, diabetes mellitus, ischemic heart disease, or hypertension, in either the intervention or control group. However, a statistically significant increase in the incidence of subconjunctival hemorrhage was observed among patients taking aspirin, with p-values of 0.034 and 0.002 in the intervention and control groups, respectively.

The overall incidence of subconjunctival hemorrhage was 31.9%; in the intervention group it was 23.3%, meaningfully less ($p=0.041$) than in the control group (41.1%).

Various methods have been investigated to prevent subconjunctival hemorrhage (SCH) following ocular procedures. Lagstein et al. (2017) (10) and Gonzalez-Saldivar et al. (2019) (11) investigated the effect of topical apraclonidine 0.5% and oxymetazoline 0.05%, respectively, in preventing subconjunctival hemorrhage after intravitreal injection, while Desco MC et al. (2021) (12) used topical brimonidine eye drops (2 mg/mL) to minimize SCH following 23G pars plana vitrectomy.

Lagstein et al. found no statistically significant difference in the incidence of SCH between groups, with 16 eyes (41%) in the apraclonidine group and 20 eyes (51.3%) in the control group ($p=0.503$),

while Gonzalez-Saldivar et al. reported a total SCH incidence of 61%, with 27 of 52 eyes (51%) in the intervention group receiving topical oxymetazoline.

Desco MC et al. found only a slight difference in SCH incidence between the intervention group receiving brimonidine eye drops (72.5%) and the control group (77.1%), $p > 0.05$, at the first postoperative visit (1–3 days after surgery).

In our study, the total incidence of SCH was 31.9% of 116 eyes, significantly lower than the 61% of 102 eyes reported by Gonzalez-Saldivar et al.

As a statistical comparison, the SCH incidence in the intervention group of our study (23.3%) was significantly lower than those reported by Lagstein et al., Gonzalez-Saldivar et al., and Desco MC et al. — 41% for apraclonidine, 51% for oxymetazoline, and 72.5% for brimonidine, respectively, at 1–3 postoperative days.

Activation of α_1 - and/or α_2 -adrenergic receptors in vascular smooth muscle cells leads to vasoconstriction. Phenylephrine, a selective α_1 -adrenergic receptor agonist, is a sympathomimetic compound that primarily induces vasoconstriction via α_1 stimulation. In contrast, oxymetazoline, an imidazoline derivative, exhibits a preferential binding affinity for α_2 over α_1 receptors, at an approximate ratio of 5:1. Brimonidine tartrate, another adrenergic agonist, displays significantly higher α_2 selectivity than α_1 , with a binding affinity ratio of approximately 1000:1 (13).

These facts may help explain the differences in efficacy observed among various medications used to reduce SCH following ocular procedures. Comparative findings suggest the lowest incidence of SCH with phenylephrine hydrochloride 5%, with oxymetazoline hydrochloride 0.025% (0.25 mg/mL) showing the smallest reduction in SCH among the three agents. Following absorption,

phenylephrine readily diffuses into vascularized tissues owing to its lipophilic properties, facilitating both central and peripheral pharmacologic effects; however, when administered in ophthalmic formulations, its distribution is largely confined to ocular structures, promoting effective pupillary dilation with minimal systemic exposure or adverse effects (9).

For these reasons, we chose phenylephrine 5% in our study to investigate its effectiveness in decreasing SCH following anti-VEGF injection, without the reduction in intraocular pressure that can occur with topical brimonidine, and to identify a more potent and safer agent for decreasing SCH than those used in the studies mentioned above (apraclonidine, oxymetazoline, and brimonidine), which can exert a stronger vasoconstrictive effect.

Additionally, topical phenylephrine (2.5 to 10%) has shown no or minimal effect on blood pressure and heart rate, which encouraged us to use it in our study without significant concern about possible cardiovascular effects (14).

Conclusion

The administration of topical phenylephrine hydrochloride 5%, 15 minutes prior to intravitreal injection of anti-VEGF (Eylea®), appears to be an effective and straightforward approach for reducing or preventing subconjunctival hemorrhage (SCH) — a commonly reported complication following such injections. This strategy may contribute to improved patient comfort and compliance with ongoing intravitreal therapy.

COMPETING INTEREST

The authors declare that they have no competing interests.

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