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Original Article

The therapeutic effect of Healaflow in glaucoma surgery

Liping Wu[1], Junjie Liu[2], Xiaoke Chang[1], Yijun Zheng[1]

[1]Department of Glaucoma and Cataract, Aier Eye Hospital Group Hankou Hospital of Wuhan Aier Eye Hospital, Wuhan, Hubei, China; [2]Department of Fundas, Aier Eye Hospital Group Hankou Hospital of Wuhan Aier Eye Hospital, Wuhan, Hubei, China

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Abstract: Objective: To explore the clinical effectiveness of Healaflow in primary angle-closure glaucoma surgery. Methods: From August 2018 to July 2019, 100 primary angle-closure glaucoma patients admitted to our ophthalmology department were divided into a control group (trabeculectomy alone) and an observation group (trabeculectomy + Halver), with 50 patients in each group, and 53 eyes in the control group and 56 eyes in the observation group. All the patients were followed up for half a year. The vision, intraocular pressure, bleb morphology, efficacy, and adverse reactions were evaluated. Results: There was no significant difference in the visual acuity between the two groups of patients during the follow-up ($P > 0.05$). The intraocular pressure levels in the two groups of patients during the follow-up were significantly lower than they were before the treatment ($P < 0.05$), and the difference in the intraocular pressure levels between the 6th month postoperative groups was significant ($P < 0.05$). During the last follow-up, 45 eyes in the control group developed functional filtration blebs, and 8 eyes had non-functioning filtration blebs. There were 55 functional filtration blebs and 1 non-functional filtration bleb in the observation group ($\chi^2 = 4.731$, $P = 0.030$). The total effective rate in the observation group was higher than it was in the control group (92.86% VS 77.36%, $\chi^2 = 4.058$, $P = 0.044$). During the follow-up period, the control group had 2 eyes with anterior chambers, 1 eye with low intraocular pressure, and 1 eye with an iris adhesion. The observation group had 1 eye with an anterior chamber, and no significant difference in the complications between the groups was evident ($P > 0.05$). Conclusion: Healaflow is of great value in maintaining functional filtration blebs and in controlling and stabilizing intraocular pressure. It is safe and reliable in clinical application, and it helps to reduce the unstable intraocular pressure after glaucoma surgery caused by scar adhesions in the filtration channel.

Keywords: Primary angle-closure glaucoma, Healaflow, trabeculectomy

Introduction

Glaucoma is an ocular disease with visual field impairment and optic nerve atrophy mainly manifested by abnormally increased intraocular pressure. Primary glaucoma accounts for 0.52% of China's non-selective population [1], and angle closure glaucoma is more common. Due to pupillary block or high iris pleural obstructions of the anterior chamber angle, the aqueous humor blocks the trabecular meshwork and closes the angle, causing an elevation in the intraocular pressure. At present, trabeculectomies and other filtering operations are mainly used to treat glaucoma [2, 3]. This procedure has the effect of reducing intraocular pressure immediately, but it is prone to formatting scars in the filtering channel, shallowing the anterior chamber. Complications such as low intraocular pressure, choroidal detachment, and cataracts are not conducive to controlling the postoperative intraocular pressure and will affect the surgical results. Healaflow is a new type of cross-linked sodium hyaluronate product [4], which can be slowly absorbed by the human body in order to achieve the anti-scarring effect after glaucoma surgery. However, since Healaflow is a new drug, there is still a lack of relevant clinical evidence. Its efficacy and safety still need to be determined. Therefore, this study examines primary angle-closure glaucoma medical records of patients who underwent trabeculectomy to observe the efficacy of Healaflow, aiming to further optimize the treatment of glaucoma and provide a clinical reference.

Materials and methods

General information

A total of 109 eyes of primary angle-closure glaucoma patients in our hospital from August

Table 1. General information of the two groups

	Control group (n = 50)	Observation group (n = 50)	χ^2/t	*P*
Gender			0.161	0.688
male	28 (56.00)	26 (52.00)		
female	22 (44.00)	24 (48.00)		
Age (years)	58.41±6.28	56.26±7.11	1.603	0.112
The eye position				
left	29 (58.00)	25 (50.00)	0.644	0.422
right	21 (42.00)	25 (50.00)		
Blood glucose (mmol/L)	9.17±1.35	9.33±1.26	0.613	0.541
Diastolic blood pressure (mmHg)	94.30±5.27	96.54±6.56	1.882	0.063
Systolic blood pressure (mmHg)	146.41±13.92	149.62±12.31	1.221	0.225
Preoperative intraocular pressure (mmHg)	25.48±5.24	27.23±5.16	1.683	0.096
Eye axis length (mm)	22.63±1.25	22.84±1.34	0.810	0.420
Preoperative vision	4.36±0.75	4.40±0.82	0.255	0.800
Type			0.437	0.509
Acute angle-closure glaucoma	16 (32.00)	13 (26.00)		
Chronic angle-closure glaucoma	34 (68.00)	37 (74.00)		

2018 to July 2019 were selected. Inclusion criteria: ① The disease conforms to the diagnosis of primary angle-closure glaucoma in "Ophthalmology" [5]. Acute angle-closure glaucoma presents with the acute increasing of the intraocular pressure, a closed angle of the chamber, and is accompanied by pain, congestion, blurred vision, and other symptoms of various eye injuries caused by acute high intraocular pressure, such as dilated pupils and iris atrophy. Chronic angle-closure glaucoma is characterized by repeated mild and moderate intraocular pressure increases, a narrowing of the angle of the room, and a closure of the angle of the eye under high pressure. The symptoms in the later stages are similar to those of primary open-angle glaucoma, with visible papillae and visual field damage. ② Patients who agreed to undergo a trabeculectomy, i.e., patients with acute and chronic anterior chamber angle closures, and the closure range exceeds 180°, and whose treatment was ineffective with drug or laser treatment, and patients with severe visual function or optic nerve damage, etc. ③ Patients undergoing glaucoma operations for the first time. ④ Patients with no intraoperative drug allergies. ⑤ Patients who signed the informed consent, and patients with complete clinical data. Exclusion criteria: ① Patients with severe conjunctival fascia adhesions, severe iris neovascularization, and severe iris lesions, pathological myopia, cataracts, or other eye diseases. ② Patients with secondary acute and chronic angle-closure glaucoma. The study was approved by the Medical Ethics Committee of our hospital.

The patients were divided into the control group, which was administered trabeculectomies alone according to the patients' wishes, and the observation group, which was treated using Healaflow in addition to trabeculectomies. There were 53 eyes in the control group, and 56 eyes in the observation group. The two groups shared similar baseline data (P > 0.05) (**Table 1**).

The control group underwent conventional trabeculectomies. Each patient was instructed to take a supine position, and we disinfected their eyes during the routine surgery. After opening the eyelid, we used a povidone-iodine solution to soak the bulbar conjunctival sac for 30 s and then we used 0.9% sodium chloride solution to fully rinse the eye. We then traversed a 4-0 suture through the superior rectus muscle and guided the eyeball downward. Then we mixed 2% lidocaine (Jichuan Pharmaceutical Group Co., Ltd., National Pharmaceutical Standard H20059049) and bupivacaine hydrochloride (Shanghai Zhaohui Pharmaceutical Co., Ltd., National Pharmaceutical Standard H2005-6442) in a 1:1 ratio and injected it under the conjunctiva. We then lifted the conjunctiva and

fascia and used the upper conjunctival dome as a base to make the conjunctival flap. Next we made a (3 × 4) mm, 1/2-thick scleral flap with the limbus as the base, and drew it downward, flatly, against the sclera to divide the interlaminar fibers. We then used a puncture knife to make an anterior chamber puncture along the transparent cornea at the edge of the corneal sclera. We pulled the scleral flap downward to expose the tissue so it could be removed completely. The deep layer of the corneal sclera was removed by about (1 × 2) mm. The peripheral iris in the deep corneal scleral incision was extracted and excised. The iris was restored and the scleral flap was reset, and its two free angles were intermittently sutured to the corresponding scleral position, and the tightness of the suture was adjusted according to the scleral valve filtration. After the incision of the bulbar conjunctival flap was sutured intermittently, balanced saline was injected into the corneal puncture port at 10 o'clock to form an anterior chamber, and the filtration was observed. If the conjunctival flap leaked, the bulbous conjunctival flap was sutured tightly. We then cut off the suspension line of the superior rectus muscle and relaxed the eyeballs. After the operation, we applied an appropriate amount of tobramycin dexamethasone eye ointment to the conjunctival sac. Finally, we covered the eye with gauze as a dressing.

The observation group underwent the same operation as the control group, but with these additional steps. After suturing the scleral flap, we avoided the anterior chamber and injected 0.02 ml of Healaflow (Swiss Aptissen) under the scleral flap. After the conjunctival flap was sutured, we injected 0.1 ml of Healaflow under the conjunctival flap.

Observation indicators

Vision assessment: A standard logarithmic visual acuity chart was used to evaluate the visual acuity changes between the two groups of patients before and after the first week, first month, third month, and sixth month after the surgery.

Evaluation of the intraocular pressure: A tonometer was used to measure the intraocular pressure values of the two groups of patients before and after the first week, the first month, the third month, and the sixth month.

Filtration evaluation: In the first month, the third month, and the sixth month after the surgeries, according to the morphology of the two groups of patients, they were divided into: type I (microvesicle type, thin-walled multi-cystic, no blood vessels), type II (diffused flat type), type III (absent type), and type IV (cyst-like wrapped type, cyst-like fluid cavity). Among them, the functional filtration vesicles were types I and II, and the rest were non-functional filtration vesicles.

Evaluation of the efficacy: According to the results of the last follow-up, the efficacy was divided into significantly effective (presenting functional filtration blebs, without using intraocular pressure-lowering drugs, the intraocular pressure can be maintained at 9~21 mmHg), effective (presenting functional filtration blebs, using ≤ 3 kinds of ocular hypotension; the drug controls the intraocular pressure), and ineffective (in the form of non-functional filtration blebs, intraocular pressure > 21 mmHg or < 9 mmHg, and remedial surgery such as secondary surgery is required).

The occurrence of adverse reactions: During the follow-up period, records were kept to record whether the two groups of patients had adverse reactions.

Statistical analysis

SPSS 17.0 statistical software was used for the data analysis. The measurement data were expressed as ($\bar{x} \pm s$), and the comparisons were done using t-tests. The count data were expressed as n (%), and we used chi-square (χ^2) tests to do the comparisons, and $P < 0.05$ indicated that a difference was statistically significant.

Results

Comparison of the vision between the two groups

In the first week after the surgeries, the vision improvement rates in the control and observation groups were 33.96% (18/53) and 35.71% (20/56). In the first month after the surgeries, the vision improvement rates in the control and observation groups were 37.74% (20/53) and 41.07% (23/56). In the third month after the surgeries, the vision improvement rates in the

Table 2. Comparison of the vision between the two groups [n, (%)]

	First week after surgery	First month after surgery	Third month after surgery	Sixth month after surgery
Control group (n = 53)	18 (33.96)	20 (37.74)	20 (37.74)	19 (35.85)
Observation group (n = 56)	20 (35.71)	23 (41.07)	24 (42.86)	21 (37.50)
χ^2	0.037	0.127	0.279	0.032
P	0.848	0.722	0.586	0.858

Table 3. Comparison of the intraocular pressure levels between the two groups ($\bar{x}\pm s$)

Time	Control group (n = 53)	Observation group (n = 56)	t	P
Preoperative	25.48±5.24	27.23±5.16	0.08	1.756
First week after surgery	15.43±1.03*	15.24±0.88*	1.037	0.302
First month after surgery	15.39±1.25*	15.76±1.14*	1.616	0.109
Third month after surgery	16.76±1.02*	17.22±1.58*	1.795	0.076
Sixth month after surgery	18.59±2.61*	17.10±1.52*	3.666	< 0.001

Note: * indicates P < 0.001 compared to the preoperative value.

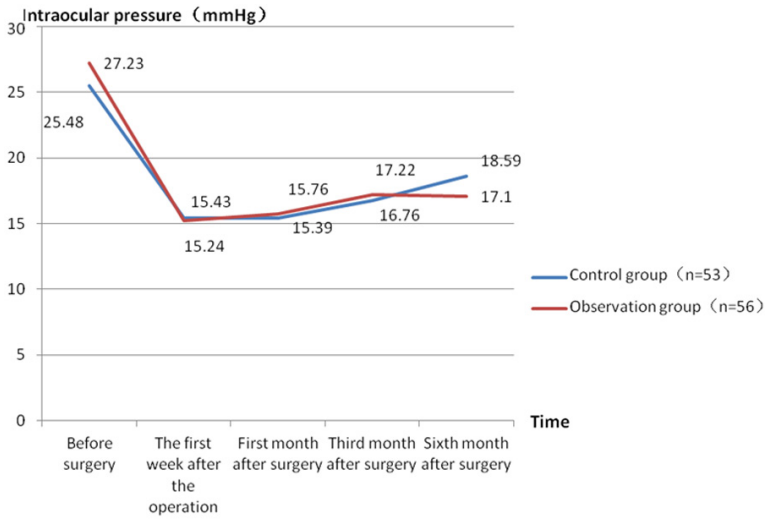

Figure 1. Trend chart of the intraocular pressure before and after the operations in two groups.

control and observation groups were 37.74% (20/53) and 42.86% (24/56). In the sixth month after the surgeries, the vision improvement rates in the control and observation groups were 35.85% (19/53) and 37.50% (21/56). During follow-up, the vision improvement rates between the two groups were all similar (all P > 0.05), as shown in **Table 2**.

Comparison of the intraocular pressure levels between the two groups

After the treatment, both groups of patients had remarkable antihypertensive effects and shared similar results in their intraocular pressure levels at each time point except for the sixth month after the surgeries (P < 0.05) , as shown in **Table 3** and **Figure 1**.

Comparison of the filtration between the two groups

Both groups of patients formed functional filtration blebs during the first month of observation. The observation group had 1 non-functional filtration bleb in the sixth month after the operations. It appeared in the third month and the sixth month, and there were non-functional filtering blebs in 3 eyes and 8 eyes in the control group. Moreover, in contrast to the earlier time point, there was a dramatic difference in the filtration between the two groups at the last follow-up (χ^2 = 4.731, P = 0.030), as shown in **Table 4**.

Comparison of curative effect between the two groups

After the treatment in the two groups, 12 eyes were ineffective in the control group and 4 eyes were ineffective in the observation group. The total effectiveness rates in the two groups were 77.36% (41 eyes) and 92.86% (52 eyes) (χ^2 = 4.058, P = 0.044), as shown in **Table 5**.

Comparison of the occurrences of adverse reactions between the two groups

During the follow-up period, the control group had 2 eyes with shallow anterior chambers, 1 eye with low intraocular pressure, and 1 eye with an iris adhesion. The observation group

Table 4. Comparison of the filtration between the two groups

Time	Control group (n = 53)		Observation group (n = 56)	
	Functional filtration bleb	Non-functional filtration bleb	Functional filtration bleb	Non-functional filtration bleb
First month after surgery	53	0	56	0
Third month after surgery	50	3	56	0
Sixth month after surgery	45	8	55	1

Table 5. Comparison of the curative effects between the two groups

Group	Excellent	Effective	Invalid	Total effectiveness
Control group (n = 53)	16	25	12	41 (77.36)
Observation group (n = 56)	22	30	4	52 (92.86)
X^2				4.058
P				0.044

had 1 eye with a shallow anterior chamber. The two groups differed slightly in their occurrences of complications (P > 0.05).

Discussion

Glaucoma treatment mainly aims to reduce the intraocular pressure. Aqueous humor, an important substance for regulating the intraocular pressure, fills the anterior and posterior chambers of the eye. The balance between the outflow and inflow rates of the aqueous humor is the key to maintaining stable intraocular pressure. In general, the aqueous humor completes outflow through the anterior chamber trabecular meshwork, the scleral venous sinus, the superior scleral vein, and the conjunctival vein [6]. However, patients with primary angle-closure glaucoma suffer from an obstruction of the aqueous humor outflow pathway due to a pupil block and/or an iris hyperplasia mechanism, causing abnormally increased intraocular pressure [7, 8]. In order to reduce the intraocular pressure rapidly [9, 10], trabeculectomies are performed to re-establish the external drainage channel of the aqueous humor using an artificial incision fistula, so that the aqueous humor flows out of the extraocular conjunctiva through the fistula and is then absorbed by the surrounding tissue. In this study, using a modified trabeculectomy, for example, we made the scleral flap slightly larger than the filtered incision, lowering scleral flap to obtain long-term intraocular pressure control, and we used adjustable sutures and anti-scarring drugs during surgery to prevent postoperative shallow anterior chambers, filtering channel scarring, and other complications to improve the surgical effect [11].

Healaflow is a sodium hyaluronate isotonic colloidal liquid with a cross-network structure that can be kept in the body for a long time. According to previous studies, its complete degradation in the body generally takes 3 months [12]. Through the structure and isotonic effect of Healaflow, it helps the aqueous humor flow at a moderate and uniform rate, greatly reducing postoperative complications such as shallow anterior chamber, low intraocular pressure, and choroidal detachment caused by strong filtration. In addition, by injecting Healaflow under the scleral flap and under the conjunctival flap, some patients can properly avoid iris incarnation caused by improper massage [13]. Several studies have shown that sodium hyaluronate can inhibit the expression of cytokines and the inflammatory factors, or it combines with other oxidizing systems to reduce the release of free radicals, thereby slowing the scarring and fibrosis processes of the filtration channel [14]. Therefore, it is possible to maintain the morphology of the filtering bleb and filtering channel by injecting Healaflow under the scleral flap or the conjunctiva flap to avoid tissue adhesion.

This study showed that the intraocular pressure of the two groups of patients was significantly reduced during the week after surgery (P < 0.05), and there was no significant difference between the groups within one week after the surgery (P > 0.05), indicating that regardless of whether the trabeculectomy uses an injection of Healaflow or not, the surgery can effectively reduce the intraocular pressure in patients with primary angle-closure glaucoma. During the follow-up period, there was no significant differ-

ence between the groups at one month and three months after the operations until the last follow-up. A possible explanation may be that in the first 3 months after the operation, the newly established aqueous humor channel can maintain a dynamic balance of the aqueous humor and the normal intraocular pressure, but it may be affected by inflammatory scarring, making the newly established channel obstructed as the postoperative time increases, which in turn raises the intraocular pressure, causing a significant difference in the intraocular pressure between the two groups [11]. However, Healaflow can slow down the accumulation of the inflammatory factors, fiber proliferation, and adhesion in the early postoperative stage, which changes the biological environment inside the filter bubble and thus delays or controls the scarring process of the filter bubble, so that the intraocular pressure can continue to be well controlled. It also shows that trabeculectomy combined with an injection of Healaflow helps to maintain the smoothness and shape of the filtration channel, confirming that Healaflow can effectively inhibit angiogenesis and exert anti-inflammatory effects [15]. In addition, the patients in both groups developed functional filtration blebs within one month after the surgeries, and no non-functional filtration blebs occurred in the observation group within 3 months. During the last follow-up, 8 eyes with non-functional filtration occurred in the control group compared with 1 eye in the observation group ($P < 0.05$), so the total effective rate in the observation group was significantly higher than the total effective rate in the control group ($P < 0.05$), indicating that the early filtration in the two groups were both good, regardless of whether the injection passage channel formation and the excessive filtration of aqueous humor are both good [16]. However, with the passage of time, the filtration vesicles shrink and become organic, which may be related to tissue repair and scleral channel blockage again. The filtration bleb in the observation group did not changed significantly. This was thought to be related to the effect of Healaflow on the filtration channel, that is, through the degradation and absorption process of Healaflow, it can slow down the inflammatory response and reduce the risk of the filter channel's tendency to scar [17, 18]. Healaflow is a viscoelastic non-thermogenic colorless and transparent isosmotic colloid liquid. It also has strong cohesion, supports and drains to alleviate tissue fibrosis, and can be gradually absorbed by tissues as a biological fermentation, non-animal origin material. This shows that Healaflow has a good anti-scarring effect in the treatment of primary angle-closure glaucoma and plays a key role in maintaining functional filtration blebs and improving the therapeutic effect [19-21]. In the follow-up observation of the complications of the two groups of patients, compared with the control group, there were no significant inflammatory reactions in the observation group, and only 1 eye had a shallow anterior chamber, and no anterior chamber hemorrhage, conjunctival flap dissolution, poor healing, ciliary body shedding, choroid complications such as detachment and malignant glaucoma occurred, but there was no significant difference in the complications between the two groups ($P > 0.05$). At the same time, the results showed a slight difference in the visual recovery between the two groups, indicating that the use of Healaflow in glaucoma filtering surgery is relatively safe and reliable. However, the following limitations were identified in this study. It was a monocentric study with a small number of participants and a short follow-up. A randomized controlled, multicenter, double-blind study with a large sample is needed to further confirm our findings.

In summary, the combined injection of Healaflow in primary angle-closure glaucoma trabeculectomies is of great value for maintaining functional filtration blebs, controlling and stabilizing the intraocular pressure levels, and thanks to Healaflow's anti-fiber property, it is safe, reliable, and effective at reducing scarring and supporting the drainage of the filtering blebs. It can help reduce the instability of the intraocular pressure after glaucoma surgery caused by scar adhesions in the filtering channel.

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Disclosure of conflict of interest

None.

Address correspondence to: Xiaoke Chang, Department of Glaucoma and Cataract, Aier Eye Hospital Group Hankou Hospital of Wuhan Aier Eye Hospital, 328 Ma Chang Road, Jianghan District, Wuhan City, Hubei Province, China. Tel: +86-18627877042; E-mail: 375006169@qq.com

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