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Original Article

Intracameral ranibizumab injection combined with Ex-PRESS mini glaucoma shunt implantation versus Ahmed valve surgery in treatment of neovascular glaucoma

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Abstract: *Purpose:* The purpose of this study was to evaluate the efficacy and safety of intracameral ranibizumab (ICR) injection combined with Ex-PRESS mini glaucoma shunt implantation in the treatment of neovascular glaucoma (NVG), and comparison with Ahmed valve surgery. *Methods:* Thirty-one NVG patients (31 eyes) from the First Affiliated Hospital of Chongqing Medical University, between January 1, 2013 and January 1, 2016, are included in this prospective, interventional clinical study. Sixteen NVG eyes were given 50-μL intracameral ranibizumab (1.25 mg) before undergoing Ex-PRESS mini glaucoma shunt implantation. Ahmed valve implantation surgery was performed in fifteen eyes. Best corrected visual acuity (BCVA), intraocular pressure (IOP) and surgical complications were evaluated before and after the surgery. *Results:* IOP was significantly decreased following ICR injection combined with Ex-PRESS mini glaucoma shunt implantation. There was a significant BCVA improvement in sighted eyes of the ICR group. ICR injection combined with Ex-PRESS mini glaucoma shunt implantation had less postoperative complications and lower failure ratio than Ahmed surgery. *Conclusions:* The study revealed that ICR injection combined with Ex-PRESS mini glaucoma shunt implantation is an effective and safe treatment for NVG. Compared with Ahmed surgery, ICR injection combined with Ex-PRESS mini glaucoma shunt implantation had less complications and a higher success ratio.

Keywords: Intracameral ranibizumab injection, Ex-PRESS shunt implantation, Ahmed valve surgery, neovascular glaucoma

Introduction

Neovascular glaucoma (NVG) is a serious condition that frequently results in severe visual impairment and with poor prognosis [1]. It is an intractable glaucoma secondary to neovascularization of the iris and the anterior chamber angle, and it is caused by ischemia and hypoxia of the retina in ocular ischemic diseases like proliferative diabetic retinopathy (PDR), central retinal vein occlusion (CRVO), etc. [1, 2]. Identification of the underlying diseases is essential for effective treatment.

Hypoxic retinal tissue produces diffusible angiogenic factors, including vascular endothelial growth factor (VEGF), in an attempt to revascularize the hypoxic area. VEGF was found highly expressed in neovascular membranes and ocular fluids of neovascular ocular diseases such as PDR, CRVO, and also NVG [3, 4]. Ranibizumab (Lucentis), the Fab fragment of recombinant humanized IgG1kmurine monoclonal antibody against VEGF-A, was approved for the treatment of ocular neovascular diseases such as wet age-related macular degeneration [5, 6]. Utilization of ranivizumab has been expanded to treat many diseases with macular edema such as PDR, CRVO and NVG in recent years [7, 8]. Similar to its intravitreal administration (IVB), it has been reported that intracameral injection of ranivizumab is effective in regressing anterior chamber neovascularization [9]. Considering the positive effects, ranivizumab injection shows promise in improving surgical success by reducing complications, included

bleeding, and inflammation in eyes with NVG [10-12]. However, the administration route, amount, and timing of ranivizumab injections required to achieve beneficial results remain unknown.

The Ex-PRESS mini glaucoma shunt implant (Alcon Laboratories Inc., Fort Worth, TX, USA) is a biocompatible, unvalved, stainless steel drainage device designed to offer fast, simple, and safe glaucoma surgery [13]. The efficacy of the Ex-PRESS shunt is similar to that of a standard trabeculectomy, while complications are lower than those of other glaucoma drainage devices and standard trabeculectomies [14].

Our study was designed to test the efficacy of intracameral ranibizumab (ICR) injection combined with Ex-PRESS mini glaucoma shunt implantation on patients with NVG. We also compared its efficacy and safety with the conventional treatment, Ahmed valve surgery, to evaluate advantages and disadvantages of these two therapies separately.

Subjects and methods

Patients and inclusion criteria

The study was a prospective interventional study including 31 patients with 31 NVG eyes. NVG patients were treated in the ophthalmology department of the First Affiliated Hospital of Chongqing Medical University, Chongqing, China, between January 1, 2013 and January 1, 2016. The study design conformed to the tenets of the Declaration of Helsinki. All patients were aware of their therapy. An informed consent form was signed by every patient.

Patients included in the study met the following criteria: (1) age > 20 years; (2) diagnosed as NVG with rubeosis; (3) IOP > 21 mmHg with the maximum use of anti-glaucoma drugs. Exclusion criteria included: (1) active ocular infection; (2) previous glaucoma filtering surgery; (3) previous anti-VEGF treatment; (4) any contraindication of intraocular injection or surgery, such as high risk of bleeding, pregnancy, and infection, et al. NVG patients received one of two types of treatment: ICR injection and subsequent Ex-PRESS mini glaucoma shunt implantation, or Ahmed valve implantation surgery. Main medical history and previous treatments were recorded.

Intracameral injection and surgical technique

All injections of 50 μL volume, containing 1.25 mg ranivizumab, were performed through a temporal paracentesis by single-use 30-G needle under topical anesthesia in the operating room by the same ophthalmologist. Before ranivizumab injection, 0.1 mL of aqueous was aspirated to reduce IOP. Intraocular pressure spike did not occur in any patient. After the injection, 0.3% tobramycin was prescribed for several days.

Glaucoma shunt implantations were performed in a separate session by the same surgeon after confirmation of complete or partial regression of neovascularization. The interval between ICR and shunt surgery (mean 10.4 days; range 2-14 days) was determined by considering the level of IOP and the severity of optic nerve damage.

All operations were performed under local anesthesia using the Dahan and Carmichael technique [15]. After creating a fornix-based conjunctival incision, a 5 × 5-mm partial thickness scleral flap dissection was made in the supratemporal quadrant in 10 (62.5%) and the infratemporal quadrant in 6 (37.5%) eyes where the angle was the widest on preoperative evaluation.

Mitomycin C (0.2 mg/mL) was applied for 2 minutes under both the conjunctival and the scleral flaps to prevent invasion of the sclera insertion area by the surrounding fibroblastic activity and rinsed with 0.9% NaCl. The anterior chamber was entered using a 25-G needle, and the P-200 Ex-PRESS shunt was inserted using its applicator, with no iridectomy. The scleral flap was sutured with 2 10-0 nylon sutures, and the conjunctiva was closed to the limbus using 8-0 polyglactin sutures.

Ahmed valve implantation surgery was performed on fifteen NVG eyes and the procedure was described as follows. A fornix-based conjunctival and Tenon's flap was created in the superotemperal quadrant. The Ahmed valve implantation (Model FP7, New World Medical, Inc.) was inserted into the Tenon's capsule and fixed on the sclera 8 mm posterior to the limbus with 8-0 sutures. A 4 mm × 4 mm square scleral flap was made, a corneoscleral track was made by a 23-gauge needle, and the tube was

Table 1. Baseline characteristics of included patients

	ICR and Ex-PRESS (n = 16)	Ahmed valvesurgery (n = 15)	*P* value
Age (y)	60.4 ± 11.1	62.6 ± 12.5	0.025[1]
Sex (female/male)	10/6	6/9	0.047[2]
Etiology			
PDR	6	5	
CRVO	2	2	> 0.05[2]
BRVO	6	7	
PDR and CRVO	1	0	
Lens status			
Phakic	13	12	> 0.05[2]
Pseudophakic	3	3	
IOP, mmHg	51.1 ± 7.2	47.8 ± 9.3	> 0.05[1]
BCVA			
HM or LP	3	3	
0.01-0.1	7	6	> 0.05[2]
0.2-0.5	6	6	
BCVA, logMAR	2.3 ± 0.9	2.2 ± 1.1	0.717[1]

BCVA = best-corrected visual acuity; BRVO = branch retinal vein occlusion; CRVO = central retinal vein occlusion; HM = hand motions; IOP = intraocular pressure; LP = light perception; PDR = proliferative diabetic retinopathy; [1]Student's *t*-test; [2]x^2 test.

inserted into the anterior chamber through the scleral flap. The tube was fixed to the episclera with 8-0 sutures.

The patients used a topical regimen of 0.1% dexamethasone and 0.3% tobramycin 4 times per day during the first month postoperatively. The dexamethasone dosage was tapered 6-12 weeks after surgery.

Outcome measurement and follow-up

Best corrected visual acuity (BCVA), IOP (Goldmann applanation tonometer), angle status, and full ophthalmic examination were taken before and after surgery. BCVA was recorded using logMAR equivalent. The new vessels of the iris were observed by slip lamp. Surgical complications were also recorded. The patients were followed up for at least 6 months and the IOP and BCVA were recorded on day 1, week 1, then monthly after the operation. The staff members performing the BCVA and IOP assessment were not involved in implementing the surgeries. The efficacy of the treatment was evaluated by the success of the surgery. Complete success was defined as postoperative IOP between 5 and 21 mmHg with at least a 30% reduction from baseline and no need for additional glaucoma surgery. Partial success was defined as IOP < 21 mmHg with topical anti-glaucoma medicines. The failure criteria included lack of IOP control with glaucoma medications, devastating operative or postoperative complications, loss of light perception, or the need for additional glaucoma surgical intervention. Laser suture lysis and bleb needling were not considered to be criteria for failure in our report.

Statistical analysis

In all groups, the arithmetic mean and standard deviation were calculated. Quantity and percentage distribution were calculated to determine qualitative characteristics. Data were tested for normality using the Shapiro-Wilk test. Between-group comparisons were made using Student's test. Within-group differences, obtained from data taken at different time points, were evaluated using paired Student's test and Wilcoxon signed-rank test for parametric and nonparametric data, respectively. X^2 test of independence for two variables was used to compare quantitative characteristics. Values of < 0.05 were considered statistically significant. Analyses were carried out using the SPSS and NCSS statistical packages.

Results

Baseline characteristics

Demographic data and preoperative clinical characteristics of the 31 eyes of 31 patients are presented in **Table 1**. Sixteen NVG eyes underwent ICR injection and subsequent Ex-PRESS mini glaucoma shunt implantation (ICR group). Fifteen eyes underwent Ahmed valve implantation surgery (Ahmed group). All 31 eyes (100%) had evident iris and/or angle neovascularization and active retinal pathology with angle-closure glaucoma secondary to peripheral anterior synechiae (PAS) extended over 270°. However, none of the eyes had 360° degrees of synechial closure.

Table 2. Intraocular pressure (IOP) mean values, median values, standard deviations, and range in the ICR and Ahemed groups at specific times after surgery

Time	ICR group			Ahmed group			P
	Mean (SD)	Median	Range	Mean (SD)	Median	Range	
Pre-op	51.1 ± 7.2	50.00	40-60	47.8 ± 9.3	46.00	38-54	0.877
Week 1	17.2 ± 9.0	16.00	11-21	15.3 ± 6.3	15.00	12-18	0.411
Month 1	17.8 ± 11.8	16.00	13-20	15.4 ± 4.1	16.00	13-18	0.582
Month 3	15.0 ± 4.1	16.00	13-17	15.7 ± 2.6	16.00	14-18	0.427
Month 6	15.0 ± 3.5	15.5	12-28	15.3 ± 2.9	16.00	14-17	0.733

Student's *t*-test.

Table 3. BCVA (logMAR) in the ICR and Ahmed groups at specific times after surgery

Time	ICR group	Ahemed group
Pre-op	2.3 ± 0.9	2.2 ± 1.1
Week 1	1.8 ± 0.9	1.9 ± 1.2
Month 1	1.7 ± 0.9	2.2 ± 0.8
Month 3	1.7 ± 0.8	2.1 ± 1.0
Month 6	1.6 ± 0.7	2.0 ± 1.1

Student's *t*-test.

Table 4. Intraoperative and postoperative complications

	ICR group (n = 16)	Ahmed group (n = 15)
Intraoperative	0	0
Early postoperative[1]		
Shallow or no anterior chamber	0	3 (20.00%)
Hypotony	0	3 (20.00%)
Hyphema	0	1 (6.67%)
Exudative inflammation	0	1 (6.67%)
Subtotal	0	8 (53.33%)
Late postoperative[2]		
Hyphema	1 (6.25%)	1 (6.67%)
Choroid detachment	1 (6.25%)	2 (13.33%)
High IOP	1 (6.25%)	2 (13.33%)
Tube occlusion by iris	0	2 (13.33%)
Subtotal	3 (18.75%)	7 (46.67%)
Total	3	15

[1]Early postoperative: within one week after the surgery; [2]Late postoperative: after one week of the surgery.

There were no differences in gender and age between the two groups, and there were no differences among the causes between two groups. The baseline IOP was 51.1 ± 7.2 mmHg in the ICR group and 47.8 ± 9.3 mmHg in the Ahmed group. Baseline BCVA of sighted eyes was 2.3 ± 0.9 in the ICR group and 2.2 ± 1.1 in the Ahmed group. No differences were found in baseline IOP (P > 0.05) and BCVA (P = 0.717) between the two groups.

Intraocular pressure

In the ICR group, IOP was significantly decreased (week 1, 17.2 ± 9.0 mmHg, P < 0.001; month 1, 17.8 ± 11.8 mmHg, P < 0.001; month 3, 15.0 ± 4.1 mmHg, P < 0.001; and month 6, 15.0 ± 3.5 mmHg, P < 0.001) after treatment compared with the baseline IOP (51.1 ± 7.2 mmHg). There was also a significant drop of IOP in the NVG eyes of the Ahmed group (week 1, 15.3 ± 6.3 mmHg, P < 0.001; month 1, 15.4 ± 4.1 mmHg, P < 0.001; month 3, 15.7 ± 2.6 mmHg, P < 0.001; month 6, 15.3 ± 2.9 mmHg, P < 0.001). There were no differences of IOP between the two groups at week 1 (P = 0.411), month 1 (P = 0.582), month 3 (P = 0.427) and month 6 (P = 0.733) (**Table 2**).

Visual acuity

Visual acuity was relatively low in all NVG patients. Mean BCVA of sighted eyes (n = 25) was 2.25 ± 1.0 (ICR 2.3 ± 0.9, Ahmed 2.2 ± 1.1), and 6 eyes showed light perception (LP) or Hand movement (HM) (**Table 1**). Results showed that there was a significant BCVA improvement at week 1, month 1, month 3, and month 6 in the ICR group (week 1, 1.8 ± 0.9, P = 0.014; month 1, 1.7 ± 0.9, P = 0.013; month 3, 1.7 ± 0.8, P = 0.013; month 6, 1.6 ± 0.7, P = 0.012) compared with the baseline, although the improvement was relatively modest. BCVA was not significantly increased in the Ahmed group (week 1, 1.9 ± 1.2, P = 0.154; month 1, 2.2 ± 0.8, P = 0.198; month 3, 2.1 ± 1.0, P = 0.186; month 6, 2.0 ± 1.1, P = 0.168) (**Table 3**). Visual acuity of all NVG patients in both groups maintained stable after one month, except 1 patient in the ICR group and 2 in the Ahmed group who lost preoperative light perception at month 6.

Complications

No major intraoperative complication was found in either the ICR or the Ahmed group. There were less postoperative complications in the ICR group than in the Ahmed group (**Table 4**), especially in the early postoperative period (within one week of the surgery). Three (20%) eyes were found with low IOP (hypotony, IOP ≤ 5 mmHg), 3 (20%) eyes with shallow anterior chamber or no anterior chamber which needed additional surgery, and 1 (6.67%) eye with hyphema and 1 (6.67%) eye with exudative inflammation in the Ahmed group. There were no the same complications in the ICR group. In the late postoperative period (after one week), 7 eyes (46.67%) with complications (hyphema, choroid detachment, high IOP and Tube occlusion by iris) were found in the Ahmed group. There were fewer complications in the ICR group (3 eyes, 18.75%).

In the ICR group, 10 eyes (62.5%) maintained IOP < 21 mmHg without anti-glaucoma medications (complete success), 5 eyes (31.25%) maintained IOP < 21 mmHg with medications (partial success), 1 eye (6.25%) failed to control IOP even with anti-glaucoma medications. In the Ahmed group, 9 eyes (60%) had complete success, 2 eyes (13.33%) had partial success and 4 eyes (26.67%) failed.

Discussion

Neovascular glaucoma remains a therapeutic challenge. Because the prognosis for NVG is poor, treatment should be performed whenever possible. Both elevated IOP and the underlying cause of the disease must be treated immediately [1, 2]. Conventional treatment remains still failed due to the recurrence of neovascularization [16]. In our study, we evaluated the efficacy of ICR injection combined with Ex-PRESS mini glaucoma shunt implantation in treating NVG patients, and which we also compared with treatment of Ahmed valve surgery. Our results show that ICR injection reduces new vessels of the iris, ICR combined with Ex-PRESS mini glaucoma shunt implantation effectively controlled IOP, and partially improved BCVA. Compared with the Ahmed valve surgery, the ICR combined with Ex-PRESS mini glaucoma shunt implantation treatment had less postoperative complications and lower failure ratios.

It has been shown that the VEGF concentration increases in both the aqueous and vitreous humor in patients with NVG [4]. This suggests that VEGF may play an important role in intraocular neovascularization. Thus, using an anti-VEGF agent blocks the pathogenesis of NVG. There are reports indicating that intraocular injection of bevacizumab can block the process of NVG [17, 18]. There are various routes of bevacizumab administration, including subconjunctival, intracameral, and intravitreal injection. Although intravitreal administration is the most effective route for intraocular tissue, the pigmentary epithelium of the retina seems to be more vulnerable to the toxic effect of bevacizumab. It has been stated that intracameral administration is simple, minimally aggressive, and has an immediate onset of action in the structures of the anterior segment [19, 20]. On the hand, the study by Klettner and Roider revealed ranibizumab was more efficient than bevacizumab in neutralizing VEGF *in vitro* [21]. Due to the off-label use of bevacizumab in eye diseases, ranibizumab (Lucentis) should be more suitable in treating NVG. Desai et al. [22] found that intravitreal injection of ranibizumab was an effective adjunctive treatment to Ahmed tube surgery in open-angle glaucoma. A study by Li et al. [23] found that IVR combined vitrectomy, lensectomy, retinal photocoagulatin, and trabeculectomy could control IOP and improve BCVA for NVG patients with vitreous hemorrhage. In accordance with these studies, we revealed that the treatment of ICR injection combined with Ex-PRESS mini glaucoma shunt implantation induced regression of iris new vessels, significantly lowered IOP, and partially improved BCVA in NVG patients. The high ratio of complete and partial success supported the efficacy of ICR injection combined with Ex-PRESS mini glaucoma shunt implantation in treatment of NVG.

Glaucoma drainage devices (GDDs) are designed to divert aqueous humor from the anterior chamber to an external reservoir [24]. These devices appear to be useful as a primary procedure in patients with a high likelihood of trabeculectomy failure, such as those with uveitic, neovascular, and aphakic glaucomas [25-27]. However, GDD may be associated with severe late postoperative complications [28]. In our study, we compared the efficacy and complications of ICR injection combined with Ex-PRESS

mini glaucoma shunt implantation treatment with Ahmed valve surgery on NVG. Our results showed that while Ahmed valve surgery also significantly lowered IOP and partially improved BCVA, compared with ICR injection combined with Ex-PRESS mini glaucoma shunt implantation. Ahmed valve surgery also markedly increased the postoperative complications, especially in the early postoperative stage, such as shallow or no anterior chamber, hyphema and hypotony. These complications ultimately increased the probability of failure from the Ahmed surgery. Results showed that there was lower failure ratio in the ICR group compared with the Ahmed group.

In conclusion, our study revealed that compared with Ahmed surgery, Ex-PRESS mini glaucoma shunt implantation with preoperative ICR had less complications and a higher success ratio. ICR injection combined with Ex-PRESS mini glaucoma shunt implantation is thus an effective and safe treatment for NVG. However, the relatively short follow-up period in our study needs to be considered. Preoperative low vision and absence of PRP can be considered as poor prognostic factors.

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Disclosure of conflict of interest

None.

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