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Original Article

Tunnelled scleral intravitreal injection with vitreous reflux assessed by AS-OCT

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Abstract: Purpose: To compare the outcomes of tunnelled scleral intravitreal injection (TSI) with straight intravitreal injection (SII) basing on the intraocular pressure (IOP) changes, occurrence and amount of vitreous reflux, and patients' discomfort. Methods: A randomized hospital-based study. Thirty patients with exudative age-related macular degeneration were randomly (1:1) assigned into two groups (TSI injection and SII injection). IOP was immediately measured before and after the intravitreal injection with 0.05 ml (0.5 mg) ranibizumab every 5 minutes until IOP <30 mmHg. The occurrence and amount of vitreous reflux were followed and recorded with anterior-segment optical coherence tomography (AS-OCT). Patients' discomfort during injection was evaluated with Wong-Baker faces pain rating scale. Results: IOP (mmHg ± SD) immediately increased to 32.03±3.22 mmHg in TSI group and 29.94±2.89 mmHg in SII group after injection, but without statistical significance (P=0.2202). The occurrence and amount of vitreous reflux were significantly lower in TSI than in SII groups (P<0.001). No difference was found between TSI and SII in Wong-Baker faces rating scale score (P=0.2089). Conclusion: Tunnelled scleral intravitreal injection is better than straight intravitreal injection. The occurrence and amount of vitreous reflux in TSI were lower than in SII group, which indicated that TSI could decrease the incidence of post-injection endophthalmitis and cause less drug loss.

Keywords: Age-related macular degeneration, anterior-segment coherence optical tomography, intravitreal injection, vitreous reflux, wong-baker faces rating scale

Introduction

It has been proved in MARINA, ANCHOR and CATT that ranibizumab is an effective treatment for exudative age-related macular degeneration, with enormous amount of intravitreal injections have been performed [1-3]. Intravitreal injection is regarded to be simple and safe, with few complications [4, 5]. The main post-injection concerns are disastrous endophthalmitis and short-term-increasing intraocular pressure (IOP) [6-8]. Drug injection leads to an increase of IOP, which could potentially cause retinal artery occlusion [9] or bleeding of neovascular tissue. The temporary IOP increase can also increase the incidence of vitreous reflux through the injection tunnel, which could potentially cause drug loss, even though the relationship of vitreous reflux and drug loss needs further investigation [10]. Benz et al. observed a negative relation between vitreous reflux out of the injection tract and post-injection IOP and a normalization of IOP within 30 minutes [7], then they found that IOP was an important factor affecting the reflux. Pascal et al. revealed a reduction of vitreous reflux in tunnelled scleral intravitreal injection by comparing with straight intravitreal injection, and they showed that the shape of the injection tunnel also played an important role [10].

Previous reports suggest that tunnelled scleral intravitreal injection may be painful and difficult to master, with potential risks of retinal tears, retinal detachments or lens injuries [11].

In this study we aimed to evaluate the post-injection IOP changes and vitreous reflux by AS-OCT, and patients' discomfort in the conjuntviva displacement intravitreal injection were compared with in the straight scleral intravitreal injection with 0.05 ml ranibizumab for the treatment of exudative age-related macular degeneration (AMD), in order to find better intravitreal injection technique.

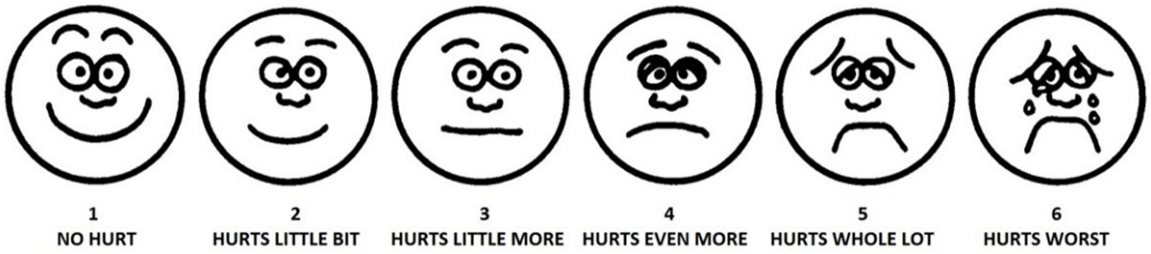

Figure 1. Wong-Baker faces rating scale for the assessment of patients discomfort before and after intravitreal injection.

Table 1. Baseline characteristics of the enrolled subjects

Baseline Information	
Age (years)	
Range	50-92
Mean	64±12.52
Sex	
Male	14 (46.67%)
Female	16 (53.33%)
Studied eye	
Right	13 (43.33%)
Left	17 (56.67%)
Lens status	
Phakia	20 (66.67%)
Pseudophakia	10 (33.33%)

Patients and methods

This study was randomized and single-center setting with 30 patients, diagnosed with neovascular AMD by fundus fluorescein angiography and optical coherence tomography. The protocol was accorded to the requirements of ethics committee in Hebei Medical University and the tenets of Helsinki Declaration. Written informed consent was obtained from each patient. Exclusion criteria: the patients with previous glaucoma or vitreoretinal surgery history, using IOP-controlling agents, IOP >25 mmHg before surgery, or inability to finish this study.

All the injections were operated by skillful retina specialist (JB An), IOP measurements were performed by the same investigator (NL Zhou), and AS-OCT (Heidelberg, Germany) and Wong-Baker faces rating scale score were performed by experienced investigator (B Zhang). Both NL Zhou and B Zhang were blind to the kind of injection techniques.

Intravitreal injection procedure

Preinjection and postinjection managements are the same for both procedures according to intravitreal injection guidelines [12]. After local anesthesia with Alcaine (Alcon, Belgium), 5% povidone-iodine solution (Linkwell, Shanghai) was used to disinfect conjunctiva sac and skin. All injections were performed using 30-gauge needle (Novartis, UK).

For TSI, the scleral injection site was 3.5 mm to 4.0 mm posterior to the limbus in the inferior temporal quadrant. First of all, the tip of the needle was inserted at 30 degree parallel to the limbus, and then at 90 degree aiming at the center of the globe.

In contrast, SII was performed at the same site of treatment, with 3.5 mm to 4.0 mm posterior to the limbus in the same quadrant using 30-gauge needle, only without scleral tunnel.

IOP measurement

IOP was measured with Goldman Applantation Tomometry (66 Vision, Suzhou) before injection (I_{pre}), instantly after injection (I_0), and every 5 minutes intervals (I_1, I_2, I_3, I_4, I_5, I_6) until IOP <30 mmHg. At each point, the IOP readings were recorded for analysis until the deviation of three records <0.5 mmHg.

Vitreous reflux measurement

After the measurement of I_0, the measurement of vitreous reflux was measured by AS-OCT with sections of 30 μm interval and a coverage of 6400 μm×1500 μm, centered at the midpoint of scleral site and conjunctiva site. And according to the largest diameter of vitreous reflux, the patients were categorized into 5 grade: Grade I (0-250 μm), Grade II (251-500 μm),

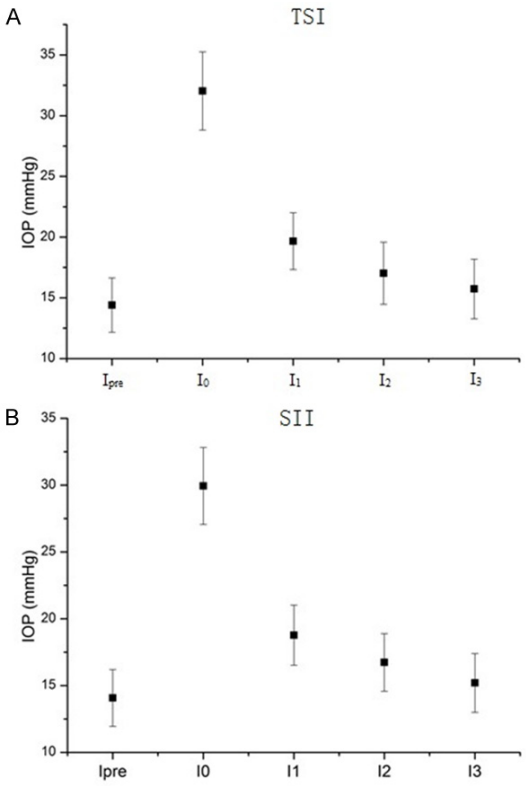

Figure 2. Scatter plots show the distribution of IOP before (Ipre), instantly after injection (I_0), 5 minutes after injection (I_1), 10 minutes after injection (I_2), and 15 minutes after intravitreal injection (I_3) with 0.05 ml ranibizumab. TSI: Tunnelled scleral intravitreal injection; SII: Straight scleral intravitreal injection.

Grade III (501-750 μm), Grade IV (751-1000 μm), or Grade V (>1000 μm).

Patents' discomfort score

Discomfort caused by TSI and SII was evaluated with Wong-Baker faces rating scale before and after injection (**Figure 1**).

Statistical analysis

Data are presented as frequencies or as mean ± SD. Normality of the distribution of data was assessed with the Kolmogorov-Smirnov test. IOP values in both groups were compared with paired t-test. The differences of IOP for each subject in both groups were compared using unpaired t-test. The different grade distributions of both techniques were compared using Wilcoxon test, as well as to the differences between pre-injecting and post-injecting Wong-Baker faces rating scale. Statistical analysis was performed using SAS V8 (SAS Institute Inc., USA). $P<0.05$ with the two-tailed considered significantly different.

Results

The main characteristics of subjects were listed in **Table 1**. The mean age and the female/male ratio were similar between the two groups ($P=0.900$ and $P=0.874$, respectively).

There was no difference of the pre-injection IOP between the two techniques ($P=0.4424$). IOP increased instantly after injection in both groups with $P<0.001$, but the increase of IOP between them were not significant ($P=0.2202$). For TSI group, IOP returned slowly to basic level 15 minutes later ($P=0.2071$). Compared with TSI, IOP of SII returned sooner to the prime stage within 10 minutes ($P=0.5093$), as shown in **Figure 2**.

The vitreous reflux was assessed with AS-OCT. We found that all the subconjunctival blebs of 30 patients were smaller than 1000 μm. All the details were shown in **Table 2**. Twelve of 15 in TSI were observed to have subconjunctival blebs smaller than 250 μm, and all the blebs of TSI were smaller than 500 μm. Only 1 of 15 in SII had bleb smaller than 250 μm. For the 15 blebs in SII, 6 were in the range of 500-750 μm, and 4 were in the range of 250-500 μm, with no bleb in SII bigger than 1000 μm. In TSI, the occurrence of vitreous reflux was significantly lesser (mostly <250 μm), as a liner and thin space between conjunctiva and superficial scleral with AS-OCT (**Figure 3**).

As to the Wong-Baker faces rating scale, the baseline scales of both groups were identical ($P=0.2083$). The post-injection scales of all the subjects were presented in **Table 3**. It suggested that most patients felt no hurt or a little bit during the injection in both groups.

Discussion

Our study showed that the IOP increased just after the intravitreal injection with 0.05 ml ranibizumab. In TSI group, the occurrence of vitreous reflux occurred was significantly lesser (mostly <250 μm), as a liner and thin space between conjunctiva and superficial scleral with AS-OCT (**Figure 3**), while patients' discomfort did not differ significantly between TSI and SII groups.

Table 2. The IOP changes pre-injection and post-injecton of both techniques (Mean ± SD mmHg)

	I_{pre}	I_0	I_1	I_2	I_3
TSI	14.4±2.20	32.03±3.22*	19.67±2.34*	17.03±2.56*	15.73±2.45#
SII	14.07±2.12	29.94±2.89*	18.7±2.25*	16.73±2.63#	15.2±2.20#

*Compared with I_{pre}, P<0.05; #Compared with I_{pre}, P>0.05.

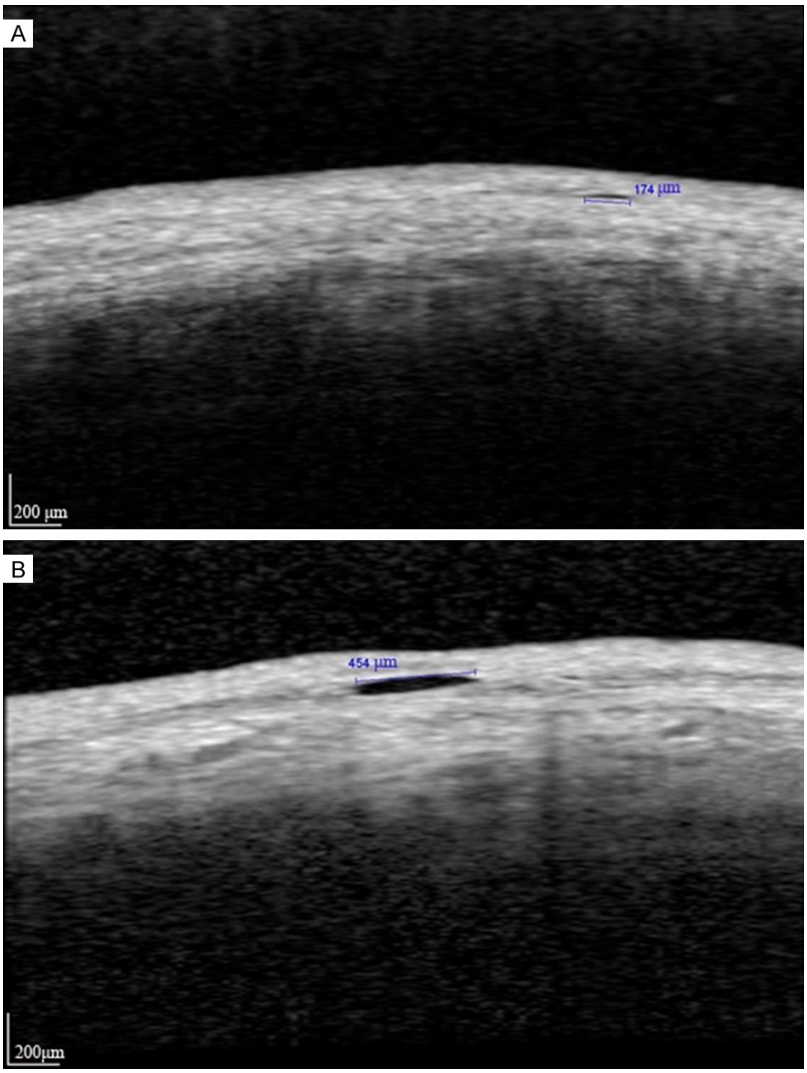

Figure 3. AS-OCT images of subconjunctival blebs: A. Shows the typical liner and thin space (174 μm) between conjunctiva and superficial scleral in patients with TSI; B. Shows the typical bleb (454 μm) with SII. TSI: Tunnelled scleral intravitreal injection; SII: Straight scleral intravitreal injection.

Table 3. Vitreous reflux assessed with AS-OCT (μm)

	I (0-250)	II (251-500)	III (501-750)	IV (751-1000)	V
TSI	12	3	0	0	0
SII	1	7	6	4	0

Z=-4.1249, P<0.001.

Pascal et al used tunnelled scleral injection and found a 10.96 mmHg of IOP increasing after the injection [11]. In our study, the post-injection increase was 17.63±3.53 mmHg in TSI, and 16.00±3.60 mmHg in SII groups. The most possible reason could be the less vitreous reflux of our procedures. Although IOP increased after injection, the differences of IOP change between the two techniques were not significant (P=0.2202). After 5 minutes, all eyes had an IOP <30 mmHg. Pascal reported the duration was 15 minutes. The only explanation was that our patients are younger and they have lower scleral rigidity [13].

In our study, we used AS-OCT to recorder the occurrence and amount of vitreous reflux. The resolution of AS-OCT was approximately 5 μm, so we can record every detail of subconjunctival blebs. Eduardo et al. found that the width of the subconjunctival bleb was 1.13±1.16 mm for injection with 0.1 ml TA by tunnelled scleral technique. This contrasted our findings, because the diameters of blebs with TSI were smaller than 1000 μm. The different volume might be the reason of this disparity. For the width of blebs in TSI <500 μm, the refluxed vitreous couldn't get access to conjunctiva sac, which would minimize the risk of endophthalmitis [14].

The common opinion among vitreoretinal surgeons

implied that tunnelled scleral injection technique was an optional technique [11]. Therefore, we adopted TSI in our study. The results of Wong-Baker faces rating scale suggested that TSI was not with more hurt than SII, but with less vitreous reflux. No retinal tear, retinal detachment, or lens injury was observed in this study.

From our results, we could conclude that the hurts of TSI technique are no more than SII technique but with less vitreous reflux. IOP increased instantly after the injection. However, IOP dropped below 30 mmHg within 5 minutes and returned to basic level within 15 minutes. Less vitreous reflux means less drug loss and lower risk of endophthalmitis. Taking all factors into account, we suggest that TSI technique be as the suitable method for intravitreal injection. As the incidence of endophthalmitis after intravitreal injection is extremely low, which is needed more observations to validate our conclusion. If TSI is successfully validated in a large-volume prospective cohort, it may benefit thousands of patients. Our future studies should investigate on the efficiency of TSI with variable volumes and types of medications.

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Disclosure of conflict of interest

None.

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