

## Research Article



## Comparison of Retinal Nerve Fiber Layer Thickness Changes after Intravitreal Bevacizumab in Patients of Diabetic Macular Edema

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**Abstract** | Diabetic macular edema is one of the leading causes of visual loss in diabetic patients. However, the impact of medicinal treatment on the occurrence of macular edema remained elusive.

**Objectives:** This study was designed to determine the effect of intravitreal bevacizumab in patients of diabetic macular edema.

**Methods:** An interventional study was conducted on patients that underwent pre-injection and one-month post-injection OCT for RNFL thickness. OCT was performed by researchers and findings were recorded accordingly. The retinal nerve fiber layer thickness was measured in superior, inferior halves and total average thickness. Pre- and post-injection OCT were conducted and macular thickness were documented.

**Results:** The mean retinal nerve fiber layer thickness was decreased in superior and inferior halves as well as in the total thickness.

**Conclusion:** Intra vitreal bevacizumab decreases the retinal nerve fiber layer thickness. Large randomized controlled trials are required to establish or rule out any association between this decrease in thickness and incidence of glaucoma in such patients.

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**Keywords** | Diabetic macular edema, Retinal nerve fiber layer thickness, OCT.

### Introduction

Intra vitreal administration of drugs has become a popular mode of treatment of various vitreoretinal disorders including diabetic macular edema, proliferative diabetic retinopathy, and viral infections of posterior segment<sup>(1, 2, 3)</sup>. Diabetes mellitus is one of the most prevalent metabolic diseases, which affect the eye within years and if the blood sugar level is not kept under control then it can lead to a blind eye within years. Most common ocular involvement of the eye in diabetes is that of retinal vessels classified

as diabetic retinopathy and one of the features of diabetic retinopathy is macular edema<sup>(4, 5)</sup>. Now a days the most prevalent treatment option for diabetic macular edema is intra vitreal anti VEGF injections<sup>(6)</sup>. In Pakistan, the most commonly used anti-VEGF agent is bevacizumab also known as Avastin. The Bevacizumab is a monoclonal anti body which is injected into the vitreous cavity through pars plana. The duration of action of single injection is around four weeks after which it has to be repeated if indicated. Intra vitreal anti VEGF agents reduce the permeability of vessels in addition to helping in absorption of already

present fluid within the retinal layers<sup>(7)</sup>. Retinal nerve fiber layer is an important layer of retina in relation to the development of glaucoma. This is the layer which is affected when the glaucomatous damage occurs due to raised IOP<sup>(8,9)</sup>. So the diseases which affect the retina i.e. diabetes may also affect this layer particularly<sup>(10)</sup>. Also during the treatment of various retinal diseases, anatomy of this layer may be changed thereby rendering it more susceptible to glaucomatous damage. Literature shows that surgery of the posterior segment does affect the thickness of RNFL as do the intra vitreal injections.

## Materials and Methods

It was a quasi-experimental study and all patients (n=64) presented during the study period of one year fulfilling the inclusion and exclusion criteria were considered. The patients diagnosed with diabetic macular edema on fundus examination were included in study. The patients diagnosed with any other macular edema, retinal disease or any coexisting ocular disease were excluded from study. Informed consent was obtained from all the patients and the procedure was explained to them. Pre injection retinal nerve fiber layer thickness was measured on OCT and recorded on proforma. All the patients were administered intra vitreal bevacizumab 1.25mg/0.05ml injection.

After aseptic measures, a point was identified in the supero temporal quadrant of the globe which was about 4mm from limbus. The measurement was performed with the help of calipers. From that point, the needle entry was made and bevacizumab was administered into vitreous cavity. After that needle was withdrawn and the site of entry was held pressed with a corneal forceps in order to prevent any reflux of drug from the entry site. The eye was then cleaned and pad was applied. Post operatively antibiotic drops were prescribed for a period of one week. All the patients were called on next day for anterior and posterior segment examination. The patients were followed

at one month for RNFL thickness measurement. The OCT was conducted by the researcher and findings were recorded. The data was entered in SPSS and independent sample t-test was applied for the comparison of pre and post injection thickness.

## Results

Out of the 64 patients, 30 were male and 34 were female. The mean age of male patients was  $55.71 \pm 4.16$  and in female patients it was  $55.93 \pm 4.14$ . In the operated eye mean Pre injection superior RNFL thickness was  $95.28 \pm 5.43$  and in the non-operated eye mean pre injection superior RNFL thickness was  $94.93 \pm 5.08$ . In the operated eye mean post injection superior RNFL thickness was  $94.06 \pm 5.03$  and in the non-operated eye the mean post injection superior RNFL thickness was  $94.63 \pm 4.97$ . The mean change in superior RNFL thickness in operated eye was  $1.21 \pm 1.45$  while it was  $0.30 \pm 0.62$  in the non-operated eye ( $p$  0.0001).

In the operated eye mean pre injection inferior RNFL thickness was  $96.17 \pm 4.73$  and in the non-operated eye mean pre injection inferior RNFL thickness was  $94.42 \pm 3.67$ . In the operated eye mean Post injection inferior RNFL thickness was  $94.90 \pm 4.40$  and in the non-operated eye the mean post injection inferior RNFL thickness was  $93.58 \pm 3.57$ . The mean change in inferior RNFL thickness in operated eye was  $1.27 \pm 1.87$  while it was  $0.84 \pm 0.95$  in the non-operated eye ( $p$  0.0001) (Table 1).

In the operated eye mean pre injection total RNFL thickness was  $95.73 \pm 4.21$  and in the non-operated eye mean pre injection total RNFL thickness was  $94.66 \pm 3.31$ . In the operated eye mean post injection total RNFL thickness was  $94.34 \pm 4.27$  and in the non-operated eye the mean post injection total RNFL thickness was  $94.10 \pm 3.19$ . The mean change in total RNFL thickness in operated eye was  $1.38 \pm 1.76$  while it was  $0.56 \pm 0.57$  ( $p$  0.0001) (Table 2).

**Table 1:** Changes in RNFL thickness in superior and inferior quadrants

Sr No	RNFL thickness	Superior		Inferior	
		Operated eye	Non operated eye	Operated eye	Non operated eye
1	Pre injection	$95.28 \pm 5.43$	$94.93 \pm 5.08$	$96.17 \pm 4.73$	$94.42 \pm 3.67$
2	Post injection	$94.06 \pm 5.03$	$94.63 \pm 4.97$	$94.90 \pm 4.40$	$93.58 \pm 3.57$
3	Change in thickness	$1.21 \pm 1.45$	$0.30 \pm 0.62$	$1.27 \pm 1.87$	$0.84 \pm 0.95$

*p* value 0.0001 (Operated eye)

In the operated eye mean central macular thickness pre injection was  $512.12 \pm 89.28$  microns while post injection it was  $429.03 \pm 72.94$  microns. In the non-operated eye mean central macular thickness pre injection was  $215.34 \pm 8.16$  microns while it was  $214.60 \pm 7.91$  microns. The mean difference in macular thickness in the operated eye was  $83.09 \pm 36.90$  microns while in the non-operated eye it was  $0.73 \pm 1.75$  microns (Table 3).

**Table 2:** Total changes in rnfl thickness after intravitreal avastin

Sr No	Change in RNFL thickness	Total thickness	
		Operated eye	Non operated eye
1	Pre injection	$95.73 \pm 4.21$	$94.66 \pm 3.31$
2	Post injection	$94.34 \pm 4.27$	$94.10 \pm 3.19$
3	Change in thickness	$1.38 \pm 1.76$	$0.56 \pm 0.57$

*P 0.0001 (Operated eye)*

**Table 3:** Changes in macular thickness in both eyes

Sr No	Macular thickness	Eye	
		Operated eye	Non-operated eye
1	Pre injection	$512.12 \pm 89.28$	$215.34 \pm 8.16$
2	Post injection	$429.03 \pm 72.94$	$214.60 \pm 7.91$
3	Change in thickness	$83.09 \pm 36.90$	$0.73 \pm 1.75$

## Discussion

This research had found the changes in RNFL thickness after one injection of intravitreal bevacizumab for diabetic macular edema. It is well known that posterior segment surgery or pan retinal photocoagulation alter the thickness of retinal nerve fiber layer. But very few studies have been performed to study the effect of various intravitreal injections on RNFL thickness. In this study the results showed that RNFL thickness was decreased in superior and inferior halves in addition to a decrease in total average thickness. The authors also compared the changes in RNFL thickness in the fellow eye before and after intravitreal bevacizumab injection. The study showed that the RNFL thickness was decreased in all the quadrants and the decrease in RNFL thickness was symmetrical in both the superior and inferior halves of the operated eye. The non-operated eye also showed symmetrical decrease in RNFL thickness. None of the patient was diagnosed with glaucoma during the follow up period.

Intra vitreal anti VEGF injection as a very convenient outpatient procedure. After aseptic measures the injection is administered in the vitreous cavity, the eye is padded and the patient can go home immediately after the procedure. Other researchers had reported similar findings. El-Ashry M et al<sup>(11)</sup> have studied changes in RNFL thickness in twenty four patients after phacoemulsification with intra ocular implant. The mean pre-operative RNFL thickness was  $84.9 \pm 16.5$  while the mean post-operative RNFL thickness was  $93.0 \pm 17.6$ . So in their study cataract extraction increased the RNFL thickness which was clinically significant.

Aydin A et al<sup>(12)</sup> have studied RNFL thickness changes after trabeculectomy. They documented an increase of  $0.5 \mu\text{m}/\text{mm}$  reduction of intraocular pressure. So they concluded that 30 % IOP reduction as a result of trabeculectomy leads to an increase in RNFL thickness.

Pareja-Esteban J et al<sup>(13)</sup> have studied RNFL changes after cataract extraction. The mean pre-operative RNFL thickness was  $90.71 \pm 19.93$  while post-operative RNFL thickness after one day was  $88.30 \pm 20.59$  and at one month it was  $97.45 \pm 14.30$  microns. The results were not statistically significant.

Demntyev DD et al<sup>(14)</sup> have studied changes in RNFL thickness after LASIK. In their study, mean pre-operative thickness was  $104.2 \pm 9.0$  while mean post-operative thickness after one week was  $101.9 \pm 6.9$  and at three months it was  $106.7 \pm 6.1$ . The changes in RNFL thickness were statistically insignificant.

Yamashita T et al<sup>(15)</sup> have analyzed changes in RNFL thickness in patients presenting with or without visual field effects after pars plana vitrectomy and internal limiting membrane peeling aided with indocyanine green. They concluded that the RNFL thickness decreased more in patients with defects in the visual field as compared to the patients who did not develop any visual field defects.

Young-Joon J et al<sup>(16)</sup> have studied changes in RNFL thickness after intra vitreal anti VEGF therapy in 20 patients. They concluded that the average total RNFL thickness decreased from  $98 \pm 6.8$  to  $96.3 \pm 4.2$  after six months of anti VEGF therapy. This thickness in the inferior zone decreased from  $120.9 \pm 10.1$  to  $120.7 \pm 9.3$  and the thickness in the superior zone decreased from



122.8±10.2 to 121.8±6.5. This decrease in the RNFL thickness was clinically and statistically insignificant.

Hatata RM et al<sup>(17)</sup> have studied changes in RNFL thickness after intravitreal triamcinolone acetonide in patients of macular edema. In their study mean average RNFL thickness changes from 91.63±10.5 to 90.83±10.11. The mean superior RNFL thickness decreased from 104.57±15.3 to 103.08±15.3. The mean inferior RNFL thickness changed from 118.9±19.95 to 111.8±19.95. The decrease in RNFL thickness was clinically and statistically insignificant.

Martinez JM et al<sup>(18)</sup> have studied the RNFL thickness changes after multiple injections of intravitreal Ranibizumab in patients of wet age related macular degeneration. In their study significant retinal nerve fiber layer thinning was observed. Base line RNFL thickness was 105.7±12.2 which significantly reduced to 100.2±11.0 after twelve months.

During literature search various studies were found which showed that RNFL thickness increased after vitreo retinal surgery but no study was found which concluded an increase in RNFL thickness after intravitreal bevacizumab. Lee YH et al<sup>(19)</sup> studied the RNFL thickness changes after Pars Plana vitrectomy to achieve retinal reattachment. In their study the RNFL thickness pre-operatively was 120.7±13.5 which was increased post-operatively i.e. 124.7±24.5 at six months, 124.0±16.6 at twelve months and 123.8±14.3 at twenty four months. This increase in RNFL thickness was significant.

Lee SB et al<sup>(20)</sup> have studied retinal nerve fiber layer changes after pars plana vitrectomy for epiretinal membrane. Their comparison between the involved and non-involved eye showed that the mean RNFL thickness was increased at baseline (112.88±12.66 & 102.94±11.58) and at 1 month (112.63±15.43 & 102.95±11.49) but decreased at 12 months (94.47±13.53 & 103.57±9.0).

Entazari M et al<sup>(21)</sup> studied RNFL thickness changes after two intra vitreal bevacizumab injections for neovascular age related macular degeneration. They studied RNFL thickness changes in all four quadrants at week 12 and 24 post injection. In their study the RNFL thickness was reduced from baseline at 24 weeks except for the inferior quadrant in which it was increased.

## Conclusions

In our study the mean RNFL thickness decreased after treatment with intravitreal bevacizumab in patients of diabetic macular edema.

## Author's Contribution

**Muhammad Shaheer:** Conceived and designed the study, collected the data and wrote the article.

**Asad Aslam Khan:** Supervised the research, reviewed the manuscript and drafted the intellectual content.

**Nasir Ahmed and Tehseen Mahmood Mahju:** Diagnosis and selection of patients and administering the intravitreal injection.

**Ummarah Rasheed:** Performed statistical analysis.

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