Study of Corneal Endothelial Changes after Intravitreal Injection of Ranibizumab (Lucentis) in Cases of Retinal Vein Occlusion

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Abstract: Introduction: Intravitreal ranibizumab (Lucentis®) is an effective short-term treatment for (retinal neovascularization) and persistent macular edema secondary to retinal vein occlusion (RVO). Intravitreal ranibizumab may cause changes in the corneal endothelium. Aim: The aim of this study is to evaluate corneal endothelial changes after intravitreal injection of Ranibizumab (Lucentis) in cases of Retinal Vein Occlusion. Patients and Methods: This prospective case series study included 30 patients with RVO to evaluate corneal endothelial changes by Specular microscopy after intravitreal injection of ranibizumab. Results: There was an insignificant difference between before and one month after the last intravitreal injection as regard to endothelial cell density, coefficient of variation in cell size and hexagonality of endothelial cells (P = 0.614, 0.677 and 0.687). Conclusion: Repeated intravitreal injections of ranibizumab (Lucentis®) don’t seem to cause substantial changes in the corneal endothelium by specular microscopy after one month after finishing three times of injection in RVO patients.

Keywords: Corneal Endothelial, Ranibizumab (Lucentis), Retinal Vein

1. Introduction:
Retinal vein occlusion (RVO) is a common vascular disorder of the retina and one of the most common causes of vision loss worldwide. Specifically, it is the second most common cause of blindness from retinal vascular disease after diabetic retinopathy. There are central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO) (1,2). Retinal venous occlusion is classified into non ischemic type which represents 75% of cases at which the cause of diminution of vision is due to macular edema and ischemic type which represents the rest of the ratio at which cause of diminution of vision is due to macular ischemia. Fluorescein angiography (FA) provides information mainly about retinal vascular system, also permits localization and qualitative evaluation of abnormal vascular permeability (3).

Loss of vision may result from persistent macular changes as: macular edema, macular ischemia or neovascular glaucoma (4). In eyes with macular edema resulting from RVO, the increased retinal thickness could be measured by Optical coherence tomography (OCT) which also demonstrate the microstructural abnormalities of the macular area with Cystoid macular edema (CME). Vascular endothelial growth factors (VEGF) is a stimulus for persistent capillary leakage, neovascularization and macular edema that result from retinal vein occlusion (5).

Ranibizumab (trade name Lucentis) is a monoclonal antibody fragment (Fab). It is an anti-angiogenic (antiVEGF). Intravitreal ranibizumab (Lucentis) is an effective short-term treatment for (retinal neovascularization) and persistent macular edema secondary to retinal vein occlusion. Intravitreal ranibizumab may cause changes in the corneal endothelium (6).

The corneal endothelium is a monolayer of 350,000 to 500,000 specialized cells that cover the posterior surface of the cornea. The primary physiological function of the corneal endothelium is to maintain the health and transparency of the corneal stroma. The endothelium must serve two functions to maintain the health and clarity of the stroma. It must control hydration (maintain stromal deturgescence) and it must be permeable to nutrients and other molecules from the aqueous humor. The endothelium maintains stromal deturgescence by functioning both as a barrier to fluid movement into the cornea and an active pump that moves ions and draws water.
osmotically from the stroma to the aqueous humor. The combined leaky barrier and fluid pump has sometimes been called a pump-leak mechanism (5).

Specular microscopy is a non-invasive photographic technique that allows you to visualize and analyze the corneal endothelium and is used to determine the number of cells per square millimeter of corneal endothelium that facilitates rapid and accurate diagnosis of corneal endotheliopathies which affect the structure and function of the corneal endothelium and it is used to detect endothelial damage or disease that was not seen by slit lamp examination (6).

2. Patients and Methods:
This prospective case series study included 30 patients with retinal vein occlusion who are selected from Tanta University Ophthalmology outpatient clinic to evaluate corneal endothelial changes by Specular microscopy after intravitreal injection of Ranibizumab (Lucentis).

Inclusion criteria:
 Patients with retinal vein occlusion either ischemic or non-ischemic who were treated with intravitreal injection of Ranibizumab (Lucentis).

Exclusion Criteria:
1. Patients with contraindication to Ranibizumab (Lucentis) injection e.g. history of myocardial infarction, cerebrovascular stroke or ocular infection.
2. Patients with other corneal diseases that affect the visualization of corneal endothelium e.g. corneal dystrophy, corneal opacity and previous corneal surgery.
3. Patient with chronic systemic diseases e.g. Diabetes Mellitus and renal failure.

History taking and examination to all patients as the following:

History:
1. Personal history including age, sex and occupation.
2. History of the present illness: progressive diminution of vision.
3. History of systemic illness e.g. Diabetes Mellitus, Hypertension.
4. Past history of previous ocular surgery, trauma.
5. Family history of similar condition.

Examination:

Table 1: Side of RVO in the studied patients

<table>
<thead>
<tr>
<th>Side of RVO</th>
<th>Patients (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right</td>
<td>16 (53.3%)</td>
</tr>
<tr>
<td>Left</td>
<td>14 (46.7%)</td>
</tr>
</tbody>
</table>

Table 2 shows an insignificant difference between before and one month after the last intravitreal injection as regard to SP:ECD (P = 0.614).
Table 2: Corneal endothelium measurements (SP: ECD) of the studied patients before and one month after the last intravitreal injection

<table>
<thead>
<tr>
<th>SP: ECD (cells/mm²)</th>
<th>Mean ± SD</th>
<th>Post</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2716.07 ± 261.56</td>
<td>2681.93 ± 259.15</td>
<td>0.614</td>
</tr>
<tr>
<td></td>
<td>2187-3208</td>
<td>2157-3189</td>
<td></td>
</tr>
</tbody>
</table>

Table 3 shows an insignificant difference between before and one month after the last intravitreal injection as regard to SP:HEX (P = 0.677).

Table 3: Corneal endothelium measurements (SP: HEX) of the studied patients before and one month after the last intravitreal injection

<table>
<thead>
<tr>
<th>SP: HEX (%)</th>
<th>Mean ± SD</th>
<th>Post</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50.7 ± 4.76</td>
<td>50.57 4.89</td>
<td>0.677</td>
</tr>
<tr>
<td></td>
<td>42-64</td>
<td>42-64</td>
<td></td>
</tr>
</tbody>
</table>

Table 4 shows an insignificant difference between before and one month after the last intravitreal injection as regard to SP:CV (P = 0.687).

Table 4: Corneal endothelium measurements (SP: CV) of the studied patients before and one month after the last intravitreal injection

<table>
<thead>
<tr>
<th>SP: CV (%)</th>
<th>Mean ± SD</th>
<th>Post</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>39.03 ± 3.32</td>
<td>38.87 ± 2.73</td>
<td>0.687</td>
</tr>
<tr>
<td></td>
<td>31-43</td>
<td>32-43</td>
<td></td>
</tr>
</tbody>
</table>

4. Discussion:

To our knowledge, our study is the first one to evaluate corneal endothelial changes by specular microscopy after intravitreal injection of Ranibizumab (Lucentis) in RVO cases only. Other studies were in other diseases (e.g. macular edema and age-related macular degeneration) or in small number of RVO cases.

Perez-Rico et al. (10) evaluated the effect of monthly intravitreal injections of (0.05 mL, 0.5 mg) ranibizumab for 3 consecutive months on the corneal endothelium in patients with choroidal neovascularization in age-related macular degeneration. There were no significant difference in SP: endothelial cell density (ECD) before injection and at 7 days and 6 months after the first intravitreal ranibizumab injection.

Guzel et al (11) investigated intravitreal injection of 1.25mg/0.05ml ranibizumab for three consecutive months on corneal endothelium of patients with diabetic macular edema. There was no significant difference in SP: endothelial cell density (ECD) before injection and 1 month after the first and third injections.

Coskun (12) evaluated the intravitreal injections of ranibizumab administered due to diabetic retinopathy and macular edema to the corneal endothelium. No significant difference was seen in SP: endothelial cell density (ECD) measurements.

Ryu et al (13) evaluated the effect of intravitreal injection on the corneal endothelium of ranibizumab in various diseases (16 patients with age-related macular degeneration; one patient with diabetic macular edema; 2 patients with RVO with ME and one patient with uveitis). The mean SP: endothelial cell density (ECD) wasn’t significantly different before and 1 month after injection in any of the 4 groups.

Joshi et al (14) evaluated the effect of intravitreal 0.5 mg/0.05 ml of ranibizumab on corneal endothelial cell count in phakic and pseudophakic eyes. There was no significant change in SP: endothelial cell density (ECD) before and after intravitreal injection over one month of follow-up.

In our study, there was an insignificant difference between before and one month after the last intravitreal injection as regard to SP: endothelial cell density (ECD) (P = 0.614).

Perez-Rico et al. (10) found no significant differences in the SP: hexagonality (HEX) before injection and at 7 days and 6 months after the first intravitreal ranibizumab injection.

Guzel et al (11) found no significant difference in SP: hexagonality before injection or 1 month after the first and third injections.

Coskun (12) evaluated the intravitreal injections of ranibizumab administered due to diabetic retinopathy and macular edema to the corneal endothelium. No significant difference was seen in SP: hexagonality (HEX) measurements.

In our study, there was an insignificant difference between before and one month after the last intravitreal injection as regard to SP: hexagonality (HEX) (P = 0.677).
Perez-Rico et al. (10) found no significant differences in SP: coefficient of variation of cell area (CV) before injection and at 7 days and 6 months after the first intravitreal ranibizumab injection.

Guzel et al. (11) found no significant difference in SP: coefficient of variation of cell area (CV) before injection or 1 month after the first and third injections.

Coskun (12) evaluated the intravitreal injections of ranibizumab administered due to diabetic retinopathy and macular edema to the corneal endothelium. No significant difference was seen in SP: coefficient of variation of cell area (CV) before injection and at 7 days and 6 months after the first intravitreal ranibizumab injection.

In our study, there was an insignificant difference between before and one month after the last intravitreal injection as regard to SP: coefficient of variation of cell area (CV) (P = 0.687).

Recommendations:
- Further studies with larger sample size, in multi-center and different countries are needed to generalize our results.
- Also, studies for a larger duration of follow-up 6 to 12 months should be performed.

References: