Ocular Complications of Intravitreal Avastin: a Report from Tobruk Medical Center

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Abstract: A retrospective statistical study was done at the ophthalmology department of Tobruk Medical Center on all the patients who received intravitreal medication with Avastin (anti-VEGF (anti-vascular endothelial growth factor)) in the period between August 1st and December 31st, 2018. It is aimed to report the complications of the intravitreal injection (IVI) and how they were managed. Out of the 56 recorded patients, there were 32 (51.9 %) females, all the patients received multiple intravitreal injections, with a total number of 131 injections. The average age of the patients was 56.5 years (ranged from 40-70 years). The most common complications after intravitreal injection were subconjunctival hemorrhage (19%), discomfort/pain (13.7%), blurring of vision (6 %), leaking at injection site (4.6%), floaters (3 %), and increase intraocular pressure (IOP) in (13.7%). Six cases out of the eighteen that had high IOP received Diamox (Acetazolamide) Tab. 250 mg one-two hours before the time of injection which did not prevent the post-injection spike of IOP and that was statistically not significant (P=0.09). Thirteen eyes (10 %) developed sudden loss of vision due to sudden increase in IOP immediately after the injection, and all the cases of the high IOP were managed by anterior chamber paracentesis and the vision also improved. Endophthalmitis was recorded in only one case (0.8%), at the third-day post intracocular Avastin injection, the causative microorganism was unknown and treated with intravitreal antibiotics (vancomycin) along with topical and systemic antibiotics and steroids, but the patient did not recover until pars plana vitrectomy was done to him, and the patient recovered his preoperative vision. The patients who had glaucoma or rubeosis iridis suffered significantly (P = 0.01) from an increase in IOP levels (digitally measured) after injection with Avastin, while most other patients who didn't have both pathologies did not suffer from an increase in IOP. Concluded that despite Anti-VEGF has a dramatic effect on the quality of life by improving the central vision, it can cause serious complications that could be prevented by early diagnosis and treatment.

Keywords: Avastin; Complications; Intravitreal Injection; Tobruk

INTRODUCTION

Sub-retinal neovascularization and pathologic ocular angiogenesis are common causes of progressive, irreversible impairment of central vision, and dramatically affect the quality of life. Anti-vascular endothelial growth factor (anti-VEGF) therapy has improved the quality of life for many patients with age-related macular degeneration, diabetic retinopathy, and other ocular diseases involving neovascularization and edema. In these pathologies, the inhibition of intraocular VEGF is the only therapy that can preserve vision. (Semeraro et al., 2015).

Adverse events following intravitreal anti-VEGF injections have no relation to underlying ocular disease; Common complications of
intravitreal injection (IVI) are injection site discomfort, subconjunctival hemorrhage, vitreous reflux, transient intraocular pressure (IOP) elevation, and defective vision. The patient may also develop floaters, vitreous or retinal hemorrhage, and retinal detachment. (Frenkel et al., 2010). The most dreaded complications of intravitreal injection are endophthalmitis and loss of vision. (Aiello et al., 2004).

The intravitreal injection can cause an immediate rise in intraocular pressure IOP (spike) that is not merely the result of added volume, but also for the properties of the injected drug. The sudden increased intraocular pressure (IOP), due to various reasons, causes corneal edema and damage to the endothelial cells with optic nerve damage and can lead to significant loss of vision. (Fang et al., 2006).

Intraocular pressure spikes after intravitreal injections of Anti-VEGF are common, and in most cases transient, and usually return to baseline in a few minutes. (Qureshi et al., 2016). The increase of the IOP may take longer to normalize in patients with glaucoma and need to be monitored. In patients who develop high IOP spikes, the use of ocular massage, topical IOP reducing agent, oral medication, and anterior chamber tap can be used as means to reduce IOP to prevent optic nerve damage and possibility central retinal artery occlusion. (Uyar, et al., 2019). In patients who have primary open-angle glaucoma or ocular hypertension, the intravitreal injection is not considered a contraindication. It requires closer observation and the use of topical medical therapy. (Frenkel et al., 2010; Aiello et al., 2004).

Post intravitreal injections endophthalmitis is a serious inflammation within the eye due to bacterial or fungal infection, including involvement of the vitreous and/or aqueous humor. It usually causes irreversible damage to retinal photoreceptors that may lead to loss of vision, even with intensive medical and surgical management. The post intraocular injection’s endophthalmitis is rare. It accounts for 0.03%-0.072% of all cases of anti-vascular endothelial growth factor (VEGF) injection (Hoevenaars, et al., 2012; Park, et al., 2014). The most common causative organisms are Coagulase-negative staphylococci, Staphylococcus aureus, and Streptococci viridians. The post anti-VEGF injection endophthalmitis, in general, has a moderate visual outcome of 6/60 if managed properly in comparison with other types of endophthalmitis (Dhoot, et al., 2013; Solborg et al., 2013).

Although matters have improved recently with fast diagnosis and better management of endophthalmitis, this disease is still serious and can lead to destructive complications to the eye that may be irreversible, and sometimes cause blindness. (Barry, et al., 2013). In most cases of post intravitreal endophthalmitis, the bacterial endotoxins and other bacterial products appear to cause a direct cellular inflammatory effect. The inflammation is most often in the first 3-4 days after the operation. (Solborg, et al., 2013). The most commonly reported causes of endophthalmitis after surgery are from the patient's conjunctival flora, contamination of sterilized instruments, disposable supplies, prepared solutions, surgical field, or the intraocular lens. (Dancer, et al., 2012; Damasceno et al., 2015).

**Aim of the study:** This article is intended to highlight important aspects of post-injection complications and how to deal with these complications to avoid the risk of a serious outcome, which may lead to permanent vision loss.

**MATERIALS AND METHODS**

A retrospective study was done through data collection from the Statistical office in Tobruk Medical Center. Statistical analysis was performed using Microsoft Office Excel program.
The indications for the Avastin injections in the study group

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Avastin indication</th>
<th>No. of total injected eyes (injections)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DME</td>
<td>Cystoid macular edema</td>
<td>125</td>
</tr>
<tr>
<td>BRVO</td>
<td>Cystoid macular edema</td>
<td>3</td>
</tr>
<tr>
<td>AMD</td>
<td>Wet age-related macular degeneration</td>
<td>2</td>
</tr>
<tr>
<td>OI</td>
<td>Ruberosis iridis</td>
<td>1</td>
</tr>
</tbody>
</table>

In the present study, most of the cases with DME had cystoid macular edema (95.4%). Some of these patients were having other ocular pathologies as shown in table 2.

Table:(2). Patients with other ocular pathologies associated with DME

<table>
<thead>
<tr>
<th>Total DME cases</th>
<th>DME ass. with ruberosis iridis</th>
<th>DME ass. With COAG</th>
<th>DME ass. With retinal neovascularization</th>
</tr>
</thead>
<tbody>
<tr>
<td>125</td>
<td>9</td>
<td>5</td>
<td>7</td>
</tr>
</tbody>
</table>

About 93 eyes (71%) developed complications because of the intravitreal injection. There were some transient and easily treatable complications that did not lead to dangerous or permanent insult to the eyes like subconjunctival hemorrhage, eye pain/discomfort, floaters, and blurred vision. Other rare but serious complications such as endophthalmitis, vitreous hemorrhage, and transient loss of vision due to an acute increase in IOP at the time of
injection were also recorded. Serious complications, like retinal detachment and central artery occlusion, were not recorded in this study. (table 3).

Table: Complications after intraocular Avastin injection in the study group (93 out of 131 eyes (injection))

<table>
<thead>
<tr>
<th>Complication</th>
<th>Time in days of complications after the injections</th>
<th>Number of eyes (%) with complications</th>
<th>Gender</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subconjunctival hemorrhage</td>
<td>Soon after injection</td>
<td>25 pts. (19%)</td>
<td>15 F  10 M</td>
</tr>
<tr>
<td>Discomfort/pain</td>
<td>First post injection day</td>
<td>18 pts. (13.7%)</td>
<td>10 F  8 M</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>First post injection day</td>
<td>8 pts. (6%)</td>
<td>4 F  4 M</td>
</tr>
<tr>
<td>Floaters</td>
<td>First post injection day</td>
<td>4 pts. (3%)</td>
<td>3 F  1 M</td>
</tr>
<tr>
<td>Increase IOP</td>
<td>Day of injection</td>
<td>18 pts. (13.7%)</td>
<td>11 F  7 M</td>
</tr>
<tr>
<td>Sudden loss of vision</td>
<td>Soon after injection</td>
<td>13 pts. (10%)</td>
<td>7 F  6 M</td>
</tr>
<tr>
<td>Leak at site of injection</td>
<td>Soon after injection</td>
<td>6 pts. (4.6%)</td>
<td>5 F  1 M</td>
</tr>
<tr>
<td>Endophthalmitis</td>
<td>Third day post the injection</td>
<td>1 pts. (0.8%)</td>
<td>1 M</td>
</tr>
</tbody>
</table>

IOP; Intraocular pressure.

There was no statistical significance for the post-Avastin injection complications among gender ($P = 0.46$).

There were eighteen eyes (13.7%) complicated with increase IOP post-Avastin injection (11 females and 7 males), out of them; Six had received Diamoxy (Acetazolamide) Tablet 250 mg one-two hours before the time of injection. Cases with glaucoma or rubeosis iridis had no statistically significant difference from those free from it ($P = 0.09$). In both groups, the rise of IOP was relieved with anterior chamber tap.

Thirteen eyes (10%) developed a sudden increase in the IOP on the operating table immediately after the injection (digitally measured IOP showed hard resistance along with corneal edema and decrease vision), which resolved by anterior chamber tap. On the first postoperative day, all of them regained the baseline vision they had before the injection.

The patients who had glaucoma or rubeosis iridis suffered significantly ($P = 0.01$) from increase IOP (digitally measured) after injection with Avastin, while most other patients who didn’t have both pathologies didn’t suffer from an increase in IOP.

Endophthalmitis was recorded only in one eye (0.8%) on the third day after the injection. The diagnosis of endophthalmitis was made clinically (patient had severe pain, redness, decreased vision associated with hypopyon, and vitreous opacities detected by ultrasonography). The patient was treated with intravitreal antibiotics (vancomycin) along with topical and systemic antibiotics and steroids, but he did not recover until pars plana vitrectomy was done to him.

DISCUSSION

The Needle Gauge for the intravitreal medication injection is not only important for patient comfort, but also for a safe injection procedure and efficient outcome. The most commonly used needle size ranges from 27 to 30 gauge. Pulido et al., (2007) confirmed that smaller scleral holes and less structural damage occur with decrease needles gauge, independently on the injection technique used, such as the tunneled or the perpendicular technique. Oztas, et al., (2016) reported the location of intravitreal medication should be made through the pars plana, between 3.5 and 4mm from the limbus; posterior to 4 mm can lead to an increased risk of retinal detachment, while a more anterior location increases the risk of traumatic cataract formation. They also recommended avoiding injection in per sclerotomy areas, to prevent
vitreous incarceration and a persisting scleral hole.

Tufan, et al., (2013) confirm the intravitreal injection can be safely performed in 360 degrees through the pars plana. Patients who receive an injection of Avastin may experience less severe side effects related to the preparation procedure. These side effects may include eye pain, subconjunctival hemorrhage, vitreous floaters, inflammation of the eye, and visual disturbances. Other possible complications and side effects of the procedure and administration of Avastin, but not recorded in this study, include but are not limited to retinal detachment, cataract formation, hypotony, permanent damage to the retina or cornea, and bleeding (Hoguet, et al., 2019). The volume change of the vitreous cavity may be the main reason for immediate IOP increasing after Anti-VEGF intravitreal injections. The volume of the vitreous cavity in the human eye is approximately 4 ml, and the volume of Avastin injected into the vitreous is 0.1 ml. Therefore, the increase in fluid volume of the vitreous cavity is 2.5% approximately, which may cause immediate IOP elevation (Song et al., 2016). Transient vision loss is a poorly understood complication of intravitreal injections, (Fang et al., 2006; Uyar, et al., 2019) reported the increased intraocular pressure (IOP) causes corneal edema and damage to the endothelial cells with optic nerve damage and can lead to significant loss of vision. Long-term deformation can cause a significant effect on the endothelial function and it may result in endothelial dysfunction. (Fang et al., 2006) suggested high IOP may affect the function of the endothelial pump and induced corneal edema. It also reduces intraocular blood flow, induces hypoxia and oxidative stress and as a result, could damage the optic nerve. Transient IOP spikes mostly leave the healthy eye without permanent damage to the vascular optic nerve. (Callegan et al., 2002) confirm the IOP has to be rigorously controlled in patients vulnerable to vascular optic nerve damage, which are patients with glaucoma as well as patients predisposed to anterior ischemic optic neuropathy.

While the development of targeted molecular therapy to inhibit vascular endothelial growth factor (VEGF) has revolutionized the treatment and visual prognosis of highly prevalent retinal diseases such as diabetic retinopathy and age-related macular degeneration, each intravitreal injection of these agents carries a risk of endophthalmitis which can be visually devastating (Sachdeva et al, 2016). The post-IVI injection endophthalmitis is rare, accounting for 0.03% - 0.072% of all cases of anti-endothelial vascular growth factor (VEGF) injections (Hoevenaars, et al, 2012; Park, et al., 2014). In most cases of post-intravitreal medication, the endophthalmitis is acute, occurring mostly in <28 days after the injection (Hoveenaars et al., 2012 and Shah et al., 2011), it should be suspected in cases of persistent vitritis following treatment, and these cases may require vitrec-
tomy to remove the infected vitreous (Sachdeva, et al, 2016). Similarly, in the present study, this serious post-operative endophthalmitis was recorded in one case (0.8%), it occurred in the first 3 days after the injection, not responding to intravitreal antibiotics and improved by vitrectomy. There are several limitations to the present study. First, the most important limitation is that the IOP was measured digitally because of the unavailability of a non-contact tonometer, and fear that a contact tonometer may increase the risk of infection. Second, the central corneal thickness was not measured in this study, and the effect would be investigated in an advanced study. In addition, this study only focused on the short-term effect of the acute rise in IOP, so we recommend investigating the long term effects in future studies.

CONCLUSION

Despite Anti-VEGF having a dramatic effect on the quality of life by improving the central vision in ocular angiogenic disease processes, it can cause different complications, which could be transient like intraocular pressure spikes, or serious like endophthalmitis, that could be prevented by early diagnosis. Apart from glaucoma patients, routine prophylactic use of IOP-lowering medications is essentially ineffective in preventing IOP spikes after intravitreal injection, and routine monitoring of IOP in glaucoma patients receiving intravitreal anti-VEGF therapy is recommended. Also, post-anti-VEGF injection complications are not related to gender.

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REFERENCES


المضاعفات التي تحدث للعين بعد حقن الأفاستين داخل العين: تقرير من مركز طبرق الطبي

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المستخلص: تم إجراء دراسة إحصائية أثر رجعي على جميع المرضى الذين تلقوا الأدوية بالحقن داخل العين (أفاستين) في قسم طب العيون في مركز طبرق الطبي في الفترة بين 01 أغسطس 2018 إلى 31 ديسمبر 2018. تهدف هذه الدراسة إلى تحليل المضاعفات التي تحدث للعين داخل الجسم替え، وهي تشير إلى زيادة نسب الالتهاب الفيقاري والدمار في العين (Diamox) بمحفزات ضغطية، من خلال 250 مجم نتائج صغيرة وتبسيط ضغط العين بفضل استخدام Diamox في ضغط عينين من بينهم ست حالات تلقى فور قرص Diamox. هذه النتائج تشير إلى زيادة نسب الالتهاب، والدواء الديفتروبيد، ولكن ذلك لم يمنع ارتفاع ضغط العين بعد الحقن وكان غير معتمد إحصائيًا (P = 0.09). أما فقدان الرؤية بشكل مفاجئ فقد حدث في 13 عينة (10% من الحالات) بسبب الزوايا المفاجئة في ضغط العين مباشرة بعد عملية الحقن. وفي جميع الحالات تم خفض ضغط العين بواسطة نبضة العين الأدمية لغض تقليل السائل، وقد استجابة جميعهم لعملية خفض ضغط العين مع التحسن في الرؤية أيضاً، تم تسجيل الالتهاب بالعين في حالة واحدة فقط (8.7%)، في اليوم الثالث بعد حقن أفاستين داخل العين، في كل الكائنات الحية القدرة غير معروفة وعولجت بالمضادات الحيوية داخل الحلق (فلافاميسين) تجنبًا إلى جانب مضادات حيوية الموضعية والجهازية والستيرويدية، لكنه لم يمثل للشفاء قبل إجراء عملية استئصال السائل الزجاجي لاسترداد المريض رؤية ملهمة كانت قبل الحقن، والمرضى الذين يعانون من الزرق (الزاقلاء) أو داء الصلبة كانوا يعانون من ارتفاع في ضغط العين ذو دلالة إحصائية (P = 0.01) عند مقارنته بالمرضى الذين لا يعانون من هذه المرض، بالرغم من أن حقن أفاستين له تأثير إيجابي كبير على جودة الحياة من خلال تحسن الرؤية، إلا أنه قد يحدث مضاعفات حرجة من الممكن علاجها بدون أن ترك أي آثار جانبية إذا تم تداركاها في مرحلة مبكرة بالطريقة العلاجية المناسبة.

الكلمات المفتاحية: أفاستين؛ المضاعفات؛ الحقن داخل الجسم الزجاجي، طبرق.