Intravitreal Diclofenac Versus Intravitreal Triamcinolone for Diabetic Macular Edema

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Abstract

Aim of Study: To investigate the effect and safety of intravitreal injection of Diclofenac versus intravitreal triamcinolone in the treatment of diabetic macular edema.

Patients and Methods: A total of 30 eyes with Diffuse Diabetic Macular Edema (DME) were included in this study. Patients were randomly allocated to either intravitreal Diclofenac sodium (IVD) injection (500 µg/0.1mL) or intravitreal triamcinolone acetonide (IVTA) injection (4mg/0.1mL). Patients were followed-up weekly for one month and then monthly for six months. Serial exams included dilated fundus examination, Intraocular Pressure (IOP) and best corrected visual acuity (BCVA) measurements. The response to treatment was monitored by evaluating the central macular thickness (CMT) using optical coherence tomography (OCT), the BCVA and noting the incidence of any adverse events at one, three and six months.

Results: Evaluation of the postoperative mean CMT revealed a statistically significant reduction at one, three and six months in both groups compared with the preoperative values. No statistically significant difference between both groups was observed. There was a statistically significant improvement in the mean BCVA at one month in both groups but this improvement was statistically insignificant at the other follow-up visits. No major side effects were reported in both groups.

Conclusion: Intravitreal diclofenac injection is safe and effective when compared to intravitreal triamcinolone injection in diabetic macular edema.


Introduction

NEARLY half of the world’s diabetic population has some degree of diabetic retinopathy [1]. DME is a leading cause of blindness in these patients.

The prevalence of DME in the diabetic population is 10%, but the prevalence is dramatically increased in eyes with more severe retinopathy [2].

For decades, Argon Laser Photocoagulation (ALP) was considered the gold standard treatment of DME. However, the limited improvement in BCVA and the potential complications of ALP, has driven the research for alternative therapies [3]. Several options have been suggested, with varying results as far as efficacy and safety. The use of intravitreal agents showed great promise. The most widely studied drugs include triamcinolone [4], bevacizumab [8], ranibuzimab [6] and aflibercept [7].

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are potent cyclooxygenase (COX) inhibitors with potential antiproliferative and antiangiogenic effects. NSAIDs are not associated the main side effects of IVTA especially, cataract and elevated IOP [8]. Since topical administration of NSAIDs does not deliver sufficient drug quantities to the posterior segment [9], intravitreal administration of NSAIDs may prove a viable option for treating DME.

Diclofenac, an NSAID, exerts its action by inhibition of both the COX and lipoxygenase pathways [10]. Although diclofenac has been used topically in the treatment of inflammatory conditions, intravitreal delivery is a promising alternative. It has shown good early results in pilot studies [11,12].

Aim of study:

The aim of this study is to investigate the effect and safety of intravitreal injection of Diclofenac on DME versus intravitreal triamcinolone injection.
Patients and Methods

A total of 30 eyes with Diffuse DME were included in this study. All patients were recruited from the Research Institute of Ophthalmology outpatient clinic from 2012 to 2013. Diabetic patients of both sexes aging more than 18 years suffering from DME with a CMT more than 400 µm were included. Media clarity, good pupillary dilation and subject cooperation sufficient for adequate fundus imaging and the ability to return for regular study visits were required. Exclusion criteria included BCVA better than 0.8 LogMAR, uncontrolled glycemic levels and uncontrolled hypertension. Any ocular condition that might potentially result in macular edema e.g. Uveitis were also excluded.

Patients were randomized to one of the two treatment options using a computer-generated randomized allocation schedule (Random Allocation Software, Version 1.0). Group A underwent IVD injection and group B underwent IVTA injection. All patients signed an informed consent. Preoperative best corrected visual acuity (BCVA), Intraocular pressure (IOP), central macular thickness (CMT) using optical coherence tomography (OCT) were recorded. Baseline fundus fluorescein angiography (FFA) and clinical examination were done.

Patients in group A underwent intravitreal injection of 500 µg Diclofenac sodium. Commercially available diclofenac prescribed for systemic use (Voltaren; Novartis Pharma AG., Switzerland) was diluted to obtain the desired concentration. Group B patients received 0.1ml of 4mg/0.1ml triamcinolone acetonide (Kenacort). Povidone iodine was applied to the conjunctiva and lids for five minutes before injection. All injections were performed in the operating theater using topical anesthesia. At the conclusion of the procedure the optic disc perfusion was assessed and anterior chamber paracentesis was performed to relieve high intraocular pressure if needed.

Patients were followed-up weekly for one month and then monthly for six months. Serial exams included dilated fundus examination, IOP and BCVA measurements. The response to treatment was monitored by evaluating the CMT using OCT at one, three and six months and comparing the results of both groups.

Results

Data were statistically described in terms of mean standard deviation (SD), median and range, or frequencies (number of cases) and percentages when appropriate. All statistical calculations were done using computer programs SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

The study included thirty eyes diagnosed with DME divided in two groups. The mean age was 59.4±6.9 years in group A and 57.7±5.5 years in group B with a 60% males in both groups. There was no significant statistical difference regarding baseline mean CMT, BCVA & IOP between both groups, (Table 1).

The CMT in both groups showed a statistically significant difference at one, three and six months between pre-and post-operative values. Comparison between the two study groups revealed no statistically significant difference at all follow-up visits. Both groups showed statistically significant lower mean CMT at all points shown in Fig. (1), (Table 2).

The reduction ratio, defined as the baseline foveal thickness minus the foveal thickness after injection divided by the baseline foveal thickness, in both groups is shown in Fig. (2).

At one month postoperative, all patients in both groups showed reduction in CMT. At three months postoperative, all patients in group A maintained or had more reduction in CMT compared to only 46% of patients in group B. At six months postoperative, 66% of patients in group A maintained or had more reduction in CMT compared to only 20% of patients in group B, Fig. (3). Another observation, is that patients in group A in whom the macular edema recurred, none exceeded the preoperative values, while only 0.07% (1/15) exceeded the preoperative values in group B.

In both groups there was a statistically significant improvement in the mean BCVA at one month. However, there failed to be any statistically significant improvement at any follow-up visit, Fig. (4). Comparison between both groups revealed no statistically significant difference between both groups at one, three and six months postoperatively.

In group A there was no statistically significant increase in the mean IOP at all follow-up visits. In group A the mean IOP at one, three and six months did not change more than 1 mmHg. Evaluation of the postoperative IOP revealed an increase in the mean IOP at one, three and six months in group B compared with the preoperative mean IOP. No major side effects was reported in either group during the follow-up period.
Table (1): Comparison between the study groups as regards the mean baseline BCVA, IOP and CMT.

<table>
<thead>
<tr>
<th>Study group</th>
<th>CMT (µm)</th>
<th>BCVA (LogMAR)</th>
<th>IOP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>528.93±90.545</td>
<td>0.980±0.2396</td>
<td>15.07±3.712</td>
</tr>
<tr>
<td>Group B</td>
<td>512.53±81.610</td>
<td>0.900±0.1852</td>
<td>15.07±3.011</td>
</tr>
</tbody>
</table>

Table (2): Comparison within and between the study groups as regards mean CMT, preoperative, 1 month, 3 months and 6 months postoperatively.

<table>
<thead>
<tr>
<th>Study group</th>
<th>Preoperative</th>
<th>Postoperative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 month</td>
<td>3 month</td>
</tr>
<tr>
<td>Group A</td>
<td>528.93±90.545</td>
<td>372.13±75.942</td>
</tr>
<tr>
<td>Group B</td>
<td>512.53±81.610</td>
<td>325.73±86.544</td>
</tr>
</tbody>
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Fig. (1): Mean CMT (µm) between the study groups over the study period.

Fig. (2): Mean CMT reduction (reduction ratio) between the study groups.

Fig. (3): Percentage of patients with reduction of CMT at one, three and six months.

Fig. (4): Mean BCVA between the study groups over the study period.
Discussion

Laser photocoagulation, the gold standard treatment of DME [3] for more than two decades, has been challenged by the use of intravitreal therapeutic agents. The most notable are anti-VEGFs. Anti-VEGF agents theoretically could block VEGF from activating its receptors, preventing increased vessel permeability, thus decreasing DME. In 2010, the DRCR.net published convincing evidence that ranibizumab with or without prompt laser, leads to superior BCVA outcomes compared with laser alone [13]. The main drawbacks of anti-VEGF treatment are the high cost and frequent dosing intervals. Numerous reports suggested that by inhibiting expression of VEGF as well as other proinflammatory cytokines, corticosteroids could reduce capillary permeability [14], thus decreasing DME. Preliminary studies with short follow-up suggested steroids are superior to laser. However, in 2008, the DRCR.net published data showing that despite early results favoring 4mg IVTA at 4 months, IVTA was not shown to be superior to ALP. The results also showed that laser yielded better mean visual acuity at 2 years [15]. The high incidence of complications especially cataract and increased IOP limited its use to pseudophakic patients as a first line treatment [16].

Considering all the limitations of the available treatment options, NSAIDs may prove a noteworthy alternative. NSAIDs theoretically seem to share many pharmacological effects of steroids, including an effect on angiogenesis [17]. Their effectiveness is almost comparable to the short term effects of steroids, minus the complications. The role of topical NSAIDs as a therapy for DME has been shown in many studies [18]. Soheilian in 2010 established the safety and efficacy of a single IVD injection (500mcg/0.1mL) based on electroretinography recordings [19]. Intravitreal ketorolac (500 mcg/0.1mL) showed significant improvement in VA but there was no change in macular thickness [20]. Maldonado in 2011 used a larger dose of ketorolac (3000mcg/0.1mL) in patients with DME refractory to laser. At one month, 28% of patients had an improvement in VA of at least five letters, while there was no significant difference in macular thickness [21]. Elbendary in 2011 demonstrated significant decrease in the CMT following single IVD injection at three months. However, they did not report a statistically significant improvement in visual outcome after the 12 week follow-up [12].

In the view of promising preliminary results of intravitreal NSAIDs, we conducted a randomized, prospective study to compare the morphological and visual acuity outcomes associated with a single intravitreal injection of diclofenac sodium versus triamcinoloneacetonide in the management of DME.

Evaluation of the postoperative mean CMT revealed a statistically significant reduction at one, three and six months in both groups compared with the preoperative mean CMT. However, the comparison between both study groups revealed no statistically significant difference at all follow-up visits. The reduction ratio at one month in the IVD group was 29.6% compared with 36.4% in IVTA group. This revealed a superior initial reduction effect of triamcinolone acetone over diclofenac. At three months, the reduction ratio in IVTA injected eyes stabilized at 36.3%, while it increased in the diclofenac group to 38.2%. At six months, the ratio dropped to 30% in the triamcinolone group, indicating loss of its reduction effect. On the contrary, the ratio increased in the diclofenac group to 40%, indicating a more solid and longer lasting therapeutic effect of IVD on the CMT.

There was a statistically significant improvement in the mean BCVA at one month in both groups. This effect was statistically insignificant at three and six months in both groups. Although, the mean CMT decreased from 528.93 ± 90.545 µm to 317.13 ± 95.541 µm six months in the IVD group, the average improvement in BCVA was considerably less than expected. BCVA changed from a mean of 0.980±0.2396 LogMAR to 0.929 ± 0.2158 LogMAR over six months duration. The relatively limited improvements in vision in both groups may be explained by the fact that chronic retinal edema causes irreversible neural cell loss over time in the diabetic retina. Due to the experimental nature of this study, only patients with V.A ≤0.2 Snellen acuity were included. The initial poor V.A may be explained by the presence of irreversible ischemic changes. Ischemia can be documented using FFA, but the lack of a standardized quantification technique, limits the ability to follow-up this vision affecting parameter.

However, these results were surprising considering the half lives of both drugs. Compared to the longer half-life of triamcinolone, which is 18.6 days in a nonvitrectomized eyes, intravitreal diclofenac lasts only hours in the vitreous [22]. Diclofenac is a drug with a small molecule (318.13 Daltons) and has a short half-life in the vitreous (2.87 hours). Methods of increasing the half-life of diclofenac in the vitreous may include its pharmacokinetic model and lipophilicity, as well as the delivery system. An animal study revealed that a
less soluble form of the drug, such as diclofenac acid rather than diclofenac sodium, will remain in the vitreous cavity for up to 24 days. This has the potential of sustaining therapeutic levels in the posterior segment for a few months [23].

Although the biggest drawbacks of steroids were its side effects profile, we did not encounter serious side effects in both groups. Of the 24 phakic patients in both groups none developed cataract. There were no reports documenting the development of cataract due to the use of NSAIDs in the literature, a finding this study further confirms. Increased IOP after IVTA injection is the other major drawback of steroids [24]. In our study, 40% of IVTA patients experienced a steroid response of at least 5mmHg at one month. Of these, 13% had an increase of at least 10mmHg at 1 month. At 3 month follow-up, further 13% developed late onset increase in IOP. At 6 month 9 of the 10 patients on treatment were controlled medically using at least 1 anti-glaucoma medication. Only one patient failed to respond and required filtration surgery. No patients in the IVD group experienced any meaningful change in the IOP. In 2011, Elben-dary reported significant reduction of IOP when using IVD [12] Also, Shimura recorded significant reduction of IOP with topical diclofenac after cataract surgery [25]. Many ocular structures contain more than one subtype of PG receptors that may elicit synergistic or antagonistic responses. IVD may preferentially inhibit the action of PG on a subtype of receptors rather than others, leading to reduction of IOP. We also did not experience any of the most serious ocular adverse effects associated with intravitreal injections including endophthalmitis, traumatic injury of the lens, and retinal detachment [26].

The main limitations in this study include the small sample size, short term follow-up and the poor preoperative visual acuity values. Long term studies are needed to assess NSAIDs safety and effectiveness and thereby establishing their potential role in the treatment of DME. The results in this study demonstrated the short term effectiveness and safety of intravitreal NSAIDs. The effects is comparable to the short term effect of other treatment modalities especially IVTA and anti-VEGFs. Although DME responded to IVD treatment, BCVA improvements were modest and did not mirror the CMT reductions. Studies to investigate this paradoxical effect are needed to determine its exact role in the complex algorithm of DME treatment. These studies may have less strict inclusion criteria such as duration of DME, CMT recordings and visual acuities at presentation.

Studies to assess monthly IVD injections as determined by clinical response may also show more potential for its use. Strategies suggested by the DCRC.net network for the treatment of DME using ranibizumab may be implemented, albeit using diclofenac sodium. If these studies yield solid therapeutic responses, alternative modes of delivery as sustained delivery implants may also be explored. Strategies that combine the potential benefits of both anti-VEGFs and NSAIDs may also be investigated especially in patients who developed tachyphylaxis to anti-VEGF.

References


