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THE EFFICACY OF INTRAVITREAL DICLOFENAC 0.5MG /0.1 ML INJECTION IN THE MANAGEMENT OF REFRACTORY DIABETIC MACULAR EDEMA

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ABSTRACT

Aim: The aim is to evaluate the efficacy of intravitreal diclofenac sodium (0.5mg/0.1ml) in anti-VEGF-resistant diabetic macular edema (DME)-related patients and to assess functional and anatomical outcomes at one-month follow-up. **Methods:** This prospective single-center study was conducted at King Hussein Medical Center. All Patients with persistent DME (central macular thickness >350µm) despite a history of ≥6 anti-VEGF injections were enrolled int eh study. Participants underwent a complete ophthalmic evaluation, which included best-corrected visual acuity (BCVA, logMAR), intraocular pressure (IOP), and measurement of central macular thickness (CMT) using spectral-domain OCT, prior to and following one intravitreal diclofenac injection. We used paired t-tests for statistical analysis of continuous variables. **Results:** This study included 38 patients (45 eyes) with a mean age of 57.3 years. One-month post-injection, there were significant improvements; Mean CMT decreased from 412.5±58.3µm to 382.4±49.2µm (Δ=-30.1µm, 7.3% reduction, $p<0.001$) • BCVA improved from 0.72±0.18 to 0.65±0.17 logMAR (Δ=-0.07, ~3.5 letters ETDRS, $p=0.003$) • 62.2% of eyes (28/45) achieved ≥10% CMT reduction • 46.7% (21/45) gained ≥2 letters ETDRS There were no significant changes in IOP (15.3±2.1 mmHg vs 15.1±2.0 mmHg, $p=0.421$). There were two (4.4%) cases of transient conjunctival hyperemia that resolved spontaneously without intervention. **Conclusion:** In refractory diabetic macular edema, intravitreal diclofenac provided great efficacy with statistically and clinically significant changes in retinal thickness and visual acuity after 1 month. In addition, good safety profile and lack of intraocular pressure effects makes this procedure a good choice when anti-vascular endothelial growth factor are not effective or contra indicated.

KEYWORDS: diabetic macular edema; treatment resistance; intravitreal diclofenac; non-steroidal anti-inflammatory; VEGF resistance.

INTRODUCTION

Diabetes-related macular edema (DME) is the most common cause of vision loss in the working-age population with diabetes mellitus, resulting in about 7-10% of diabetic patients.[1] Anti-VEGF therapies are the the treatment of choice for DME patients. However, one-third to one-half of patients have unsatisfactory responses to anti-VEGF therapy, highlighting a need for additional therapeutic options, particularly when patients present significant vision loss which may interfere with the daily activities of the patients.[2]

The pathophysiology of DME involves VEGF-mediated vascular permeability and chronic low-grade inflammation.[3] Recently, many studies suggest that low-grade inflammation, including cytokines like prostaglandins and interleukin-6 (IL-6), may be implicated in the development of persistent DME as VEGF.[4] This dual mechanism permits some patients to remain refractory to monotherapy with anti-VEGF agents, supporting the need for the adjunct use of anti-inflammatory agents.[5]

Current treatment options for refractory DME involve switching anti-VEGF agents, intravitreal corticosteroids, and laser photocoagulation.[6] Each of these management strategies has its own adverse effects; Corticosteroids cause rapid cataract progression and the development of ocular hypertension in the short-term[7] while laser therapy has the potential to damage retinal architecture.[8] Recent studies have identified non-steroidal anti-inflammatory drugs (NSAIDs) as a potential adjunct treatment in place of anti-VEGF or corticosteroids. Inflammation has been associated with DME, and localized delivery of anti-inflammatory agents like NSAIDs may theoretically be beneficial since it inhibits both cyclooxygenase enzymes.[9]

Research from the last few years suggest that intravitreal diclofenac (0.5mg/0.1ml) as monotherapy in treatment-naïve DME may produce reductions in central macular thickness of 15-20%, while other studies have suggested comparable efficacy to bevacizumab.[10,11] Further, with minimal effect on intraocular pressure or lens transparency, Diclofenac presents a very favorable safety profile and lends itself to longer term management.[12] In addition, it can be an excellent choice when there is systemic contra indication for the use of anti-VEGF like recent stroke.

This study intends to evaluate the efficacy of intravitreal diclofenac sodium in patients with anti-VEGF-resistant DME at King Hussein Medical Hospital.

METHOD

This prospective study was conducted at the ophthalmology department of King Hussein Medical Center (KHMC) between 19 April 2025 and 24 May 2025. All diabetic patients diagnosed with persistent DME after receiving at least six injections of anti VEGF with macular thickness above 350 µm were enrolled in the study. Comprehensive ocular examination was performed including best corrected visual acuity, intra-ocular pressure (IOP) measurement, and central macular thickness (CMT) using ocular cohort tomography (OCT) before the injection and at one month after receiving single intravitreal injection of diclofenac 0.5mg /0.1 ml.. The obtained data was analyzed using simple statistical analysis.

RESULTS

This study included 38 patients (45 eyes) with a mean age of 57.3 years. The study included 45 eyes from 38 patients with persistent DME refractory to anti-VEGF therapy. Baseline demographics features and clinical characteristics of the patients are summarized in Table 1.

Table 1: Baseline Characteristics of the patients

Characteristic	Value
Age (years), mean ± SD	58.7 ± 9.2
Male gender, n (%)	22 (57.9%)
Diabetes duration (years), mean ± SD	12.4 ± 5.1
Previous anti-VEGF injections, mean ± SD	7.2 ± 1.4
Baseline CMT (µm), mean ± SD	412.5 ± 58.3
Baseline BCVA (logMAR), mean ± SD	0.72 ± 0.18
Baseline IOP (mmHg), mean ± SD	15.3 ± 2.1

One-Month Outcomes

Significant improvements were observed in both central macular thickness and best corrected visual acuity at 1-month follow-up, the results are summarized in table 2.

Table 2: One-Month Outcomes Compared to Baseline.

Parameter	Baseline	1 Month	Mean Change	p-value*
BCVA (logMAR), mean ± SD	0.72 ± 0.18	0.65 ± 0.17	-0.07 ± 0.04	0.003
CMT (µm), mean ± SD	412.5 ± 58.3	382.4 ± 49.2	-30.1 ± 12.7	<0.001
IOP (mmHg), mean ± SD	15.3 ± 2.1	15.1 ± 2.0	-0.2 ± 0.5	0.421

*Paired t-test

Key findings at 1 month included.

- 62.2% of eyes (28/45) showed ≥10% reduction in CMT
- 46.7% of eyes (21/45) gained ≥2 ETDRS letters
- Mean BCVA improvement of 0.07 logMAR (equivalent to ~3.5 ETDRS letters)
- Mean CMT reduction of 30.1 µm (7.3% decrease from baseline)
- No significant change in IOP (p=0.421)

Safety Outcomes

No serious adverse events were reported during the first month post-injection. Two cases (4.4%) of mild conjunctival hyperemia resolved spontaneously within 48 hours. No instances of intraocular inflammation, elevated IOP, or injection-related complications were observed

DISCUSSION

In summary, our study showed that intravitreal diclofenac sodium (0.5mg/0.1ml) can provide clinically improvement in both functional and anatomical aspects among patients with anti-VEGF refractory diabetic macular edema (DME), and that these improvements were observed as early as 1 month after injection. We feel this evidence adds to the growing data supporting the role of NSAIDs in the management of persistent DME, particularly in cases that are refractory to anti-VEGF treatment.

The mean reduction in central macular thickness (CMT) of 30.1 µm (7.3%) at 1 month was notable since it appears that diclofenac sodium was targeting the inflammatory process associated with the underlying DME pathophysiology that remained even with treatment with anti-VEGF. Similarly, this reduction is consistent

with CMT reductions reported by Elbendary et al. (10) in treatment-naïve DME, suggesting its role and effect that is unrelated to the VEGF pathway. The simultaneous change at 1 month of BCVA (0.07 logMAR, ~3.5 ETDRS letters) indicates that these anatomical changes resulted in functional change, which is the main aim of treatment.

An overall response rate of 62.2% for ≥10% CMT reduction shows that many anti-VEGF non-responders may respond well to a switch or add-on of anti-inflammatory therapy, The potential therapeutic effects observed may in fact be due to diclofenac's potent inhibition of COX-1 and COX-2 as well as reducing vascular permeability facilitated by prostaglandin actions and thereby reduce inflammatory cytokines.[9] If a steroid treatment is not well tolerated and may significantly increase IOP, diclofenac offers an advantage because it is not statistically significant in increasing IOP compared to control (p=0.421) and from a long-term management standpoint would be preferable. Since diclofenac is a smaller molecule (318.1 Da), retinal penetration may also be better than the larger anti-VEGF molecules and may explain the therapeutic potential even in refractory patients.[12]

Finally, there are several important clinical implications for the study findings; this study showed that treatment with Intravitreal diclofenac may be a beneficial alternative for patients that are failing anti-VEGF therapy with early effect. In addition, the absence of serious adverse events in the current and previous studies provide an addition evidence regarding the long-term safety of this technique.

Comparisons with Existing Literature

Our results are consistent with previous reports.

• The reduction in CMT is greater than that reported by Radwan et al for mild DME cases.[11]

• The improvement in visual acuity is equivalent to ketorolac results reported in the KADI study.[4]

• The safety profile also supports previous reports of excellent ocular tolerance.[12]

Limitations

Several limitations need to be considered.

1. Follow-up period is too short to assess long-term efficacy
2. There was no control group, so we cannot make any comparative conclusions
3. The single center design affects generalizability
4. Dosing regimen was standardized to all patients

Final Remarks

Finally, In this cohort of patients with refractory DME there are several important clinical implications for the study findings; this study showed that treatment with Intravitreal diclofenac may be a beneficial alternative for patients that are failing anti-VEGF therapy with early effect. In addition, the absence of serious adverse events in the current and previous studies provide an addition evidence regarding the long-term safety of this technique.

CONCLUSION

Marked reduction in CMT and significant improvement in BCVA was noticed after single injection of intravitreal diclofenac 0.5mg /0.1 ml injection. It should be considered an effective and safe method of treatment in refractory diabetic macular edema not responding to anti VEGF intravitreal injections.

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