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ORIGINAL ARTICLE

COMPARATIVE EVALUATION OF INTRAVITREAL DICLOFENAC PLUS BEVACIZUMAB VERSUS BEVACIZUMAB ALONE IN THE TREATMENT OF NAÏVE DIABETIC MACULAR EDEMA: A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

OBJECTIVE: To evaluate the therapeutic effects of intra-vitreal injection Bevacizumab combined with Diclofenac-Na versus intra-vitreal Bevacizumab alone in the treatment of naïve diabetic macular edema.

METHODS: In this prospective, randomized interventional clinical trial, 40 eyes of 40 participants were enrolled for trial conducted at an Ophthalmology department of Qazi Hussain Medical Complex, Nowshera. Twenty eyes each included in the intra-vitreal Bevacizumab and bevacizumab plus diclofenac group via random sampling technique. The main outcome variable was a change in best-corrected visual acuity (BC-VA) in log MAR at 4th, 12th and 24th week. The secondary outcomes included mean change in central subfield thickness (CSFT) of macula and possible injection-related side effects.

RESULTS: Marked improvement in BC-VA was observed in both therapeutic groups (mean change in log MAR: 0.324±0.411 and 0.562±0.388 for bevacizumab alone and combination group, respectively). The difference in BC-VA change was in favor of combination group; however, the level didn't achieve statistical significance (p = 0.08). Significant decrease in CSFT was noted in both groups (mean reductions: 178.02 ± 166.42, 214.55 ± 132.65) for bevacizumab and combination, respectively). Comparison of CSFT changes between groups revealed that combination decreased CSFT more than bevacizumab, but the difference was statistically insignificant (p = 0.07). Neither injection related side effects nor any marked change in intraocular pressure was observed in either groups.

CONCLUSION: In diabetic macular edema, superiority of combination therapy over Bevacizumab alone was evident, esp. with regard to structural improvement in macula.

Clinical Trial Registration Number: IRCT20220607055097N1

KEYWORDS: Diclofenac (MeSH); Bevacizumab (MeSH); Macular Edema (MeSH); Diabetic Retinopathy (MeSH); Retina (MeSH); Intravitreal, Anti-Inflammatory Agents, Non-Steroidal (MeSH).

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INTRODUCTION

Diabetic macular edema (DME) commonly afflicts diabetic population with more than a decade duration of the disease along with other risk factors and is the main reason for reduced vision among diabetics.[1] Various therapeutic modalities have been devised such as intra-vitreal injections and pharmacological therapies to treat diabetic maculopathy.[2,3] The safety and effectiveness of focal/grid laser for DME was first shown by Early Treatment for Diabetic Retinopathy Study (ETDRS).[4] Nowadays, intra-vitreal (IV) injections have become more widespread; both IV triamcinolone and IV anti-vascular endothelial growth factor (VEGFs) agents have proven their worth.[5,6] Despite, being less invasive and effective in the treatment of DME, still controversies surrounds them with more facts gathering due to extensive exploration through various trials. Due to destructive nature of laser therapies, extensive knowledge about the pathogenesis of diabetic retinopathy and numerous evidences and trials have been done on intra-vitreal anti-VEGFs, now increasing number of ophthalmologists are preferring them as compare to laser therapy.[6-8] These different intra-vitreal agents have peculiar mechanism of action on different receptors in retinal tissues. Triamcinolone and NSAIDs acts by blocking Prostaglandins (PGs) induced inflammatory cascades, while anti-VEGFs like Bevacizumab/Ranibizumab are used to block VEGFs.[2,3,5,6,8] Believing the assumption that diabetic maculopathy is actually the result of multiple inter-connected pathological pathways, mainly merging on a common pathway of vascular instability and altered proliferation necessitating repeated injections to control it with safety concerns regarding repeated doses.[1,2,7,8] This emphasizes upon the need for development of combination therapy to target multiple pathways i.e. PGs and VEGFs, at the same time.

The rationale for undertaking this trial is to see the cocktail effect of intravitreal

TABLE I: THE BASELINE CHARACTERISTICS OF PARTICIPANTS BETWEEN THE TWO STUDY GROUPS

Variable		IV-B (20)	IV-B/D (20)	p value
Mean age (years) ± SD		59.76 ± 7.242	62.56 ± 7.684	0.231
Gender	Male (N %)	08 (40%)	10 (50%)	0.263
	Female (N %)	12 (60%)	10 (50%)	0.104
Best corrected visual acuity		0.81 ± 0.38	0.96 ± 0.45	0.497
Central subfield thickness of macula (mm)		553.88 ± 173.55	578.89 ± 151.88	0.090

IV-B= Intra-vitreal Bevacizumab, IV-B/D= Intra-vitreal Bevacizumab & Diclofeanac

TABLE II: VISUAL ACUITY (LOG MAR) MEASURED AT BASELINE AND FOLLOW UPS BETWEEN THE TWO STUDY GROUPS

Variable	IV-B (20)	IV-B/D (20)	p value btw groups
At baseline	0.812 ± 0.389	0.968 ± 0.458	0.104
At 4 week	0.723 ± 0.408	0.740 ± 0.372	0.848
At 12 week	0.644 ± 0.352	0.614 ± 0.432	0.655
At 24 week	0.488 ± 0.363	0.406 ± 0.286	0.565
Change (24 week-baseline)	0.324 ± 0.411	0.562 ± 0.388	0.08
p value (within groups)	0.002	< 0.001	

IV-B= Intra-vitreal Bevacizumab, IV-B/D= Intra-vitreal Bevacizumab & Diclofeanac, Log MAR= Logarithm of Minimum angle of resolution

TABLE III: CENTRAL SUBFIELD THICKNESS OF MACULA (μM) BETWEEN TWO GROUPS AT BASELINE AND FOLLOW UPS

Variable	IV-B (20)	IV-B/D (20)	p value btw groups
At baseline	553.88 ± 173.55	566.89 ± 151.88	0.497
At 4 week	471.45 ± 129.69	455.63 ± 111.10	0.195
At 12 week	412.66 ± 145.45	398.42 ± 162.12	0.362
At 24 week	375.86 ± 192.56	352.34 ± 145.74	0.642
Change (24 week-baseline)	178.02 ± 166.42	214.55 ± 132.65	0.074
p value (within groups)	0.001	< 0.001	

IV-B= Intra-vitreal Bevacizumab, IV-B/D= Intra-vitreal Bevacizumab & Diclofeanac.

TABLE IV: INTRA-OCULAR PRESSURE VALUES BETWEEN TWO GROUPS AT BASELINE AND FOLLOW-UPS

Intra-Ocular Pressure (mm Hg)	IV-B (20)	IV-B/D (20)	p value btw groups
At baseline	14.50 ± 2.20	14.63 ± 2.67	0.810
At 4 week	14.83 ± 2.24	14.66 ± 2.43	0.738
At 12 week	14.60 ± 1.88	14.73 ± 2.04	0.885
At 24 week	14.26 ± 2.14	14.52 ± 2.32	0.674
Change (24 week-baseline)	-0.24 ± 1.45	-0.11 ± 1.68	0.566
p value (within groups)	0.224	0.712	

IV-B= Intra-vitreal Bevacizumab, IV-B/D= Intra-vitreal Bevacizumab & Diclofeanac.

diclofenac with bevacizumab as this combination hasn't not yet been tested locally and very few studies have been done globally.[9,10] We formulated the present trial to target this pathway by adjunctive use of intra-vitreal diclofenac-Na (IV-D) to a well proven intra-vitreal Bevacizumab (IV-B), and compared it with IV-B alone. We would explore, if such a cocktail can bring any better functional and structural changes for DME patients.

METHODS

This prospective, randomized, interventional clinical trial was conducted at Ophthalmology Department of Qazi Hussain Medical Complex, Nowshera from September 2020 to March 2021. The study was approved by the Institutional Ethical Review Board (IERB). The trial was registered with Iranian registry of clinical trials with the trail id # IRCT20220607055097N1 www.irct.ir

The 'ETDRS' criteria was utilized for enrollment of treatment naïve eyes of DME, defined as any hard exudates/dot blot hemorrhages, retinal thickening/edema within 500μm from the center of the fovea or involving the very center, examined clinically on fundoscopy.[4]

Exclusions included:

1) Any history of prior retinal laser therapy
2) History of prior intravitreal injections any type
3) Any intra-ocular procedure done within last 6 months
4) Rubeosis iridis
5) Any glaucomatous eye damage
6) Evidence of ischemic maculopathy, defined as an enlarged foveal avascular zone (FAZ) ≥ 1500μm;
7) Best corrected visual acuity (BCVA) of ≥6/12 or ≤6/120;
8) significant media opacity precluding fundus view
9) Associated morbid conditions like, monocularity, pregnancy, diabetic nephropathy grade 3 and HbA1c ≥ 10.

Patients fulfilling the criteria were selected for recruitment in the study through non-probability convenient sampling technique. Informed consent was taken before enrollment from all patients, a separate informed consent was also taken for the possible serious side effects of intra-vitreal injections.

One eye of each patient was recruited in a total no. of 40 patients. Participants selected for the study were allocated to one of the following treatment groups via lottery method.

I. IV-B group of 1.25 mg/0.05 ml of Bevacizumab (Avastin; Roche, Ltd)

II. IV-B/D group of 500 μg/0.1 mL of Diclofenac sodium (Inj. VorenR Asian Continental, Pak.) diclofenac-Na is available in 75 mg/3 ml. After aspiration of 1 ml (containing 25 mg), 4 ml of balanced salt solution was added. Therefore, each 1 ml contains 5 mg diclofenac. Then 0.1 cc containing 500 μg of diclofenac plus 1.25 mg/0.05 mL of Bevacizumab.

Injections were given at baseline, 04th week, 8th week and 12th week with 27-gauge insulin syringes through the supero-temporal quadrant in the IV-B group and via supero-temporal and supero-nasal quadrants in the IV-B/D group. In the later, drugs were injected separately so as to avoid contamination. All injections were performed under aseptic conditions using Povidone Iodine 5% (applied two times, separated by 5 minutes) and anesthetic eye drops (two times, 3 minutes apart) with insertion of a lid speculum. The study drugs were injected at baseline and then every 4th weekly unless visual acuity was 6/6 or there was no improvement or worsening in response to the previous two injections (PRN protocol after 3 initial doses).

Before intervention, all the participants were subjected to ophthalmic assessment i.e. BC-VA, slit lamp biomicroscopy, applanation tonometry, fundus examination, retinal images and spectral-domain optical coherence tomography (OCT). Such assessments were recorded at 4th, 12th and 24th week after intervention. To find out any serious reaction/effects, visits were also planned after 7 days of injection to look for any intraocular pressure (IOP) rise and anterior chamber (AC) reactivity. OCT scans were acquired by spectral domain optical coherence tomography (OCT, 3D- optical coherence tomography, Topcon, Japan). BC-VA was recorded from Snellen's chart and converted into logarithm of minimum angle of resolution (log MAR).

The main determinant of the trial was post injection BC-VA in log MAR. The secondary outcomes were post-injection change in central subfield thickness (CSFT) as shown in OCT scans. Possible intra-vitreal associated adversities like raised IOP, AC reactivity, and lens opacification were among other secondary outcome measures.

Study outcome variables were taken as dependent while interventions were taken as independent variables. The outcome variables were quantified and taken as numerical variables and were presented as mean±standard deviation, while interventions were taken as categorical variables and were represented in the form of percentages and frequencies. We used two test for our categorical variables, while independent T-test was utilized for numerical variables. Paired T-test was applied for significance within groups while for analyzing the significance between the groups we used Mann Whitney test to compensate for the data normalization. For statistical analysis we used SPSS version 25.0 (IBM Corp. USA). The study was set at a confidence interval of 95 while the significance of tests was set at <5%

RESULTS

Forty eyes of 40 patients were equally distributed into two groups of 20 participants each, one group was given combination IV-B/D and another was given IV-B only. Participants ranged from 45 to 78 years with mean age of 62.44±7.94 years. Twenty-two (55%) patients were female and 18 (45%) were male. Patients in both the groups were comparable with regard to age, sex, CSFT and BC-VA (Table I).

Mean BC-VA (log MAR) in both groups at the beginning and at 4th, 12th and 24th week are depicted in Table II. At the end of 24th week statistically significant improvement in BC-VA was observed in both groups (p= 0.002 in IV-B and p= < 0.001 in IV-B/D); But we didn't achieve any statistically significant difference between the groups as far as improvement in BC-VA was concerned as shown in Table II (p = 0.08).

CSFT values in two therapeutic arms at the baseline and at 4th, 12th and 24th week are shown in Table III. After 24th week, statistically significant decrease in CSFT was observed in both groups. (p= 0.001 in IV-B and p= < 0.001 in IV-B/D). However, CSFT reduction between groups had shown that IVB/D was more effective than IVB, but the difference between the two didn't achieve statistical significance (p = 0.07) (Table III). Similarly, IOP values in both groups at baseline and at 4th, 12th and 24th week are displayed in Table IV. At the end of 24th week, no statistically significant difference in IOP was observed neither within the groups nor between them (p = 0.56). No, intra-vitreal related adversities like endophthalmitis, retinal detachment or vitreous hemorrhage was observed and no systemic thromboembolic event was observed.

DISCUSSION

Diabetic macular edema (DME) is a chronic condition and its management is difficult due to its recurrence, aggravation and its huge impact on central vision of the patients requiring strict surveillance and prolonged duration of treatment and patients may undergo multiple intra-vitreal injections along with laser therapy to make it dry.[2–8,11] The current trial has been undertaken to show whether combination of diclofenac sodium plus Bevacizumab (IV-B/D) is effective in the long term for resolution of treatment naïve DME as compare to standard Bevacizumab alone (IV-B) and to see its effects on the structural component (CSFT) of DME as well as its functional component (BC-VA). We explored in the trial that DME anatomically improved better in the IV-B/D as compare to IV-B alone although the difference between the groups didn't achieve statistical significance, however from visual perspective not much difference was observed between groups with statistically insignificant results. Though we observed some visual improvement in both groups and in fact the IV-B/D did slightly better than IV-B, but the degree of improvement didn't reach the level of statistical significance between them, this could be attributed to the inadequate sample size and inherent errors associated with statistical analysis formulae. Studies conducted on different intra-vitreal anti-VEGFs showed that anatomical improvement is not always associated with better visual outcome particularly in DME cases and same findings were observed as in our study.[11,12] The factors that could possibly prevent visual improvement in DME cases after restoration of its anatomy includes, fovealar atrophic changes, RPE changes, sub-foveal exudation, ischemic maculopathy, and intra-vitreal injection related toxicities.[12]

In the latest literature available the role of inflammation in the causation of DME is inevitable.[13] By looking into the depth of inflammatory cascade, whenever

there is any tissue injury, arachidonic acid is released which is converted into PGs and TX-A2 by COX enzymes and to LTs by 5-LOX.[13,14] It is to be emphasized here that PGs can induce vascular proliferation. PG-E2, is the predominant PG in the retina, which liberates VEGFs, this finding has been well observed in Muller cells culture.[8,13–16] Interestingly steroids which are powerful immune-suppressants can effectively decrease the production of VEGFs.[17] By recollecting all our knowledge regarding inflammatory and angiogenic pathways involved in the pathogenesis of DME, hitting them with agents having peculiar role in these pathways by combining them to effectively block the production of various PGs and VEGFs, such combinations may utilize the drugs like Steroids, NSAIDs and anti VEGFs.

Some past studies have utilized these concepts of inflammatory induced VEGFs release into retinal tissues by incorporating intra-vitreal steroids (IV-S), as a therapeutic regimen with wonderful results both as a mono-therapy and in combination in the management of DME, we did the same experiment by using rather safe alternative to steroids i.e. NSAIDs which is free from the side effects which are intrinsic to steroids like raised IOP and cataract formation.[2,3,11]

The number of studies published in the favor of NSAIDs use in DME are less due to relatively weak immune-suppressant effect. Their mechanism of action involves inhibition of arachidonic acid leading to reduced production of PGs, along with suppression of COX and LOX pathways. This twin ability widens its spectrum of use and place it somewhere near to steroids with additional benefit of being less implicated in the causation of cataract and raised IOP.[8,14,18]

In one popular study it was reported that nepafenac 0.1 % is very effective in the management of of cystoid macular edema (CME) and DME.[19] Similar observation was noted in another study suggesting that topical Diclofenac prevents early event in the development of CME post cataract extraction among diabetics, we took the idea from topical NSAIDs and used it intravitreally for more enhanced and localized effect at the tissue receptor level in the retina and our results showed improvement in both macular thickness and visual acuity in combination group with slight edge over bevacizumab alone suggesting the synergistic role of diclofenac in resolution of DME.[20]

Study conducted in 2008 revealed that topical Nepafenac 3times/day for 3 months showed promising results in patients with DME, findings similar to our study results in which our combination group showed more efficacy in improving macular edema vs. bevacizumab alone.[21]

Two years later another study reported that topical Bromfenac was effective in prevention of CME in post cataract cases among diabetics, similar observation was noted in our study in which our combination group did well than IV-B alone though the difference was not statistically significant.[22] In the recent past a study on topical NSAIDs, esp. Nepafenac and Bromfenac, showed promising results along with IV-S/ Anti VEGFs in the treatment of long standing pseudo-phakic CME, which somehow resembles our combination group of IVB/D with beneficial effect on DME and slightly on the vision.[23] By understanding the role of topical NSAIDs in both CME and DME the scientists administered them intravitreally to explore further their anti-inflammatory properties. Trials done in 2010[24] and 2011 [11] revealed marked visual improvement by intravitreal ketorolac in DME, finding from this study explains that our combination group was slight better than IV-B alone due to role of diclofenac as an anti-inflammatory agent with its role in suppression of DME and indirectly improving the visual acuity. Soheilian et al in his study reported the efficacy of IV-D in the treatment of macular edema due to different pathological entities of retina, esp. in DME.[25] Similarly other researchers in 2011 explored that the efficacy of IV-D is almost identical to IV- triamcinolone in the management of DME.[15] Soheilian et al[8] in 2016 found out that IV-D has almost similar efficacy to IV-B in the management of DME, by combining them as in our trial the results were further potentiated in terms of better anatomical and functional outcomes when compared with IV-B.[25]

We observed no injection related adverse effects, neither locally nor systemically. Furthermore, none of our patients developed cataract or raised IOP during the trial period. Few studies suggested that Diclofenac-Na when given either intravitreally or topically can actually cause reduction in IOP but not yet confirmed, whether it is by chance observation or some mechanism comes into play to reduce it, however we observed no, IOP changes in both groups.[9,10,21]

The limitations of our study included small sample size, lack of control group for assessing the real response of therapies in comparison, low power of the statistical analysis tests used, short term follow up and non-blinding nature of the study.

The results of our study should be taken in the light of the results of three previous studies regarding the use of IV-D in DME.[8,15,25]

CONCLUSION

In DME, superiority of IV-B/D combination therapy over IV-B mono-therapy was evident, esp. with regard to structural changes. In our exploration for DME treatment we advocate Diclofenac combination with Bevacizumab for improved and sustained outcome.

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AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

AA: Concept and study design, acquisition, analysis and interpretation of data, drafting the manuscript, critical review, approval of the final version to be published

MR: Analysis and interpretation of data, drafting the manuscript, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST

Authors declared no conflict of interest

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DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request

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