Intravitreal anti-vascular endothelial growth factor with and without topical non-steroidal anti-inflammatory in centre-involving diabetic macular edema

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Purpose: Intravitreal anti-vascular endothelial growth factor (VEGF) therapy is the mainstay in the management of center-involving diabetic macular edema (CI-DME). Topical nonsteroidal anti-inflammatory drugs (NSAIDs) have been used to treat CI-DME as well. Whether there is any benefit of using both together has not been explored. The aim of this study was to compare visual acuity and OCT outcomes in patients with CI-DME who receive intravitreal anti-VEGF with and without topical NSAIDs in CI-DME.

Methods: This was a retrospective observational study in two centers in India. The study compared visual and OCT parameters of patients with CI-DME treated with intravitreal anti-VEGF monotherapy (group 1, N = 100) versus intravitreal anti-VEGF therapy with topical NSAIDs (group 2, N = 50) over 1-year follow-up. Continuous and categorical parameters were compared using parametric and nonparametric tests, respectively. Results: Over the 1-year follow-up, group 2 received more mean number of intravitreal injections (group 1: 2.26 ± 1.71 vs. group 2: 3.74 ± 2.42; P < 0.0001). There were no differences between the groups in visual acuity and OCT thickness at 1-year follow-up. Conclusion: Combination therapy of topical NSAIDs with intravitreal anti-VEGF did not show any beneficial effects in terms of visual outcomes, reduction in central subfoveal thickness, or reduction in the mean number of injections in our study.

Key words: Diabetic macular edema, intravitreal anti-VEGF, topical nonsteroidal anti-inflammatory drugs

Intravitreal anti-VEGF therapy is the mainstay in the management of center-involving diabetic macular edema (CI-DME). Inflammation plays a role in the development of DME. Though topical nonsteroidal anti-inflammatory drugs (NSAIDs) have a prophylactic and therapeutic role in pseudophakic cystoid macular edema, their role in augmenting the effect of anti-VEGF therapy for CI-DME is uncertain. Topical nepafenac is a commonly prescribed NSAID for inflammatory macular edema. Topical nepafenac 0.1% three times daily for 1 year in eyes with non-center-involving DME with good visual acuity has been shown not to have a meaningful effect on optical coherence tomography (OCT)-measured retinal thickness. However, topical nevanac is still used extensively in management of DME, usually along with intravitreal injections. There is no evidence whether this combination offers any benefit in terms of reduction of need for intravitreal injection and whether there is any visual benefit. The aim of this study was to compare visual acuity and OCT outcomes in patients with CI-DME who receive intravitreal anti-VEGF with and without topical NSAIDs in CI-DME.

Methods

This retrospective observational study was conducted in two tertiary eye care centers between January and December 2019. Institutional ethics committees of each participating center granted a waiver for this study in view of the secondary nature of data analysis. Patient data were anonymized before transferring into an excel sheet. Written informed consent is routinely obtained from patients before instituting any invasive treatment. A retrospective chart review of consecutive patients with diabetes was performed to identify treatment naïve DME cases initiated on various treatments during 2016–17 and who completed 1 year follow-up. Those with hazy media, ocular comorbidities, previous vitrectomy, and incomplete ocular record at baseline were excluded.

The data collected included demography, duration of DM, systemic comorbidities, type of treatment for DM, level of glycated hemoglobin (HbA1C), grade of DR, phenotype of DME, and lens status. All these data were collected at baseline. Across all participating centers, international clinical DR severity scale was used for grading of DR. Best-corrected visual acuity (BCVA) at baseline and at 1 year were recorded. The study compared visual and OCT parameters of patients with CI-DME treated with intravitreal anti-VEGF monotherapy (group 1, N = 100) versus intravitreal anti-VEGF therapy with topical NSAIDs given (group 2, N = 50) for 1 year. Group 1 received 0.5 mg intravitreal ranibizumab or biosimilar of ranibizumab (Razumab). Group 2 received 0.5 mg intravitreal ranibizumab or biosimilar of ranibizumab.

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ranibizumab (Razumab) along with topical nepafenac 0.1% eye drops twice a day for 12 months. Consecutive patients with CI-DME initiated on therapy were included. Patients with CST $\leq$300 $\mu$m at baseline but having foveal cysts and best-corrected visual acuity $\leq$6/12 were also classified as CI-DME and included in the study. Best-corrected visual acuity on Snellen chart and CST on Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA) were recorded at baseline, 3, 6, and 12 months in both groups. The outcomes were visual acuity $\geq$6/12 or $<6/12$ and central subfield thickness (CST) $\leq$300 $\mu$m, 300–500 $\mu$m, and $>500$ $\mu$m at each follow-up visit (3, 6, and 12 months). Data collected for each patient included demographic characteristics, duration of diabetes, severity of diabetic retinopathy, and history of prior intravitreal anti-VEGF therapy or laser photoagulation. Continuous and categorical parameters were compared using parametric and nonparametric tests, respectively.

**Results**

At baseline, group 1 (anti-VEGF alone) and group 2 (anti-VEGF + NSAIDs) were compared [Table 1]. Group 2 had patients with longer duration of diabetes (4.14 ± 0.82 vs. 3.77 ± 0.88 years), had more patients with prior history of intravitreal anti-VEGF injections (100% vs. 90%), and had more patients with severe stage of NPDR (4% vs. 15%) than group 1. Over 1-year follow-up, group 2 received more mean number of intravitreal injections (group 1: 2.26 ± 1.71 vs. group 2: 3.74 ± 2.42; $P < 0.0001$).

Table 2 shows the visual and OCT outcomes in the two groups for comparison. In both groups, there was visual improvement at 1-year follow-up [Vision $>6/12$ in group 1: 50 (54.3%) and in group 2: 17 (43.6%)]. Similarly, in both groups, there was a reduction in OCT central subfield thickness [OCT CST $<300$ $\mu$m in group 1: 47 (57.3%) and in group 2: 18 (41.9%)]. However, there were no statistical differences between both visual and OCT outcomes in both groups. To understand the influence of confounding variables, we performed a subgroup analysis of longer duration of diabetes (>5 years), severe grade of DR (severe NPDR/PDR), and more number of injections (>3 injections). There were no statistically significant differences in visual outcome and OCT between the anti-VEGF monotherapy and anti-VEGF + NSAIDs in these groups.

**Discussion**

In this study, we found that the addition of an NSAID to ranibizumab or its biosimilar is not superior to ranibizumab monotherapy in improving visual outcomes or reducing the CST in CI-DME. The mean number of anti-VEGF injections in the two groups was more in the combination group, indicating that the addition of NSAIDs to people having anti-VEGF therapy for CI-DME is of no benefit. Figs. 1 and 2 show the OCT of two patients from each of the study groups through 1-year follow up. Our study supports the findings by Pinna et al. and not Callahan et al. A comparative randomized prospective study was done in which topical NSAIDs or placebo were combined with intravitreal bevacizumab and dexamethasone for refractory DME. The NSAIDs used in their study included bromfenac, nepafenac, and ketorolac. This study also found that adding a topical NSAID did not result in any additional visual improvement, similar to our study patients who received a topical NSAID showed a statistically significantly greater reduction in retinal thickness compared to those who received a placebo. The NSAID group also required less frequent intravitreal injections than the placebo group, which was not seen in our study. Another study explored NSAIDs through the intravitreal route combined with anti-VEGF injections. Intravitreal diclofenac was combined with bevacizumab and compared with intravitreal bevacizumab monotherapy alone. This study found that the combination therapy reduced CST more than bevacizumab alone but not visual acuity.

| Table 1: Baseline characteristics of study groups |
|-------------------------------------------------|
| **Group 1** (Anti-VEGF alone) **N=100** | **Group 2** (Anti-VEGF + NSAID) **N=50** | **P** |
| Age; years (Mean±SD) | 57.37±8.25 | 57±8.77 | 1.000 |
| Gender N (%) | | | |
| Women | 19 (19.0) | 16 (32.0) | 0.07 |
| Men | 81 (81.0) | 34 (68.0) | 0.07 |
| Mean duration of Diabetes in years; Mean±SD | 3.77±0.88 | 4.14±0.82 | 0.01 |
| Grade of DR n (%) | | | |
| Mild NPDR | 24 (24.0) | 9 (18.0) | 0.40 |
| Moderate NPDR | 36 (36.0) | 5 (10.0) | 0.0008 |
| Severe NPDR | 15 (15.0) | 27 (54.0) | 0.0001 |
| PDR or Prior PRP | 25 (25.0) | 9 (18.0) | 0.33 |
| No. of previous intravitreal injections | | | |
| 1-2 | 39 (56.6) | 12 (24.5) | 0.000 |
| 3 and above | 51 (62.2) | 37 (74.0) | 0.112 |
| Lens status | | | |
| Phakic | 67 (67.0) | 38 (76.0) | 0.25 |
| Pseudophakic | 33 (33.0) | 12 (24.0) | 0.26 |

DME=Diabetic macular edema; NPDR=Nonproliferative diabetic retinopathy; DR=Diabetic retinopathy; PDR=Proliferative diabetic retinopathy; PRP=Panretinal photoagulation
Table 2: Visual and OCT outcomes in study groups

| Visual outcome          | Variable | Group 1 | | Group 2 | | P |
|-------------------------|----------|---------|---|---------|---|---|
|                        | Baseline | 1 year  | --- | Baseline | 1 year | --- |
| Overall                 | >6/12*   | 49 (49.5) | 50 (54.3) | 15 (30) | 17 (43.6) | 0.797 |
|                         | <6/12    | 50 (50.5) | 42 (45.7) | 35 (70) | 22 (56.4) | 0.397 |
| Duration of diabetes    | >5 years | 42 (85.7) | 31 (75.6) | 30 (85.7) | 22 (100) | 0.985 |
| Stages of DR            | <6/12    | 26 (52) | 21 (52.5) | 27 (77.1) | 19 (86.4) | 0.742 |
|                         | Severe/PDR | 24 (52.2) | 23 (60.5) | 25 (73.5) | 14 (63.6) | 0.224 |
| Number of Injections    | >3 injections | 170x748 | 170x748 | 170x748 | 170x748 | 170x748 |
| OCT outcome             | Overall  | 49 (49) | 47 (57.3) | 8 (16.0) | 18 (41.9) | 0.066 |
|                         | <300 µm** | 36 (36) | 30 (36.6) | 27 (54.0) | 22 (51.2) | 0.952 |
|                         | 301-500 µm | 15 (15) | 5 (6.12) | 15 (30.0) | 3 (7.0) | 0.529 |
| Duration of diabetes    | >5 years | 37 (78.8) | 41 (89.1) | 8 (100) | 13 (72.2) | 0.445 |
|                         | 301-500 µm | 30 (85.7) | 20 (74.1) | 22 (81.5) | 22 (100) | 0.330 |
|                         | 500-700 µm | 13 (92.9) | 6 (100) | 13 (86.7) | 3 (100) | 0.748 |
| Stages of DR            | <300 µm  | 18 (36.7) | 11 (23.4) | 5 (62.5) | 10 (55.6) | 0.704 |
|                         | Severe/PDR | 14 (42.4) | 14 (46.7) | 20 (74.1) | 20 (90.9) | 1.000 |
|                         | 501-700 µm | 8 (53.3) | 1 (20.0) | 11 (73.3) | 1 (33.3) | 0.830 |
| Number of Injections    | <300 µm  | 23 (54.8) | 19 (57.6) | 4 (50.0) | 11 (61.1) | 0.061 |
|                         | >3 injections | 13 (46.4) | 15 (53.6) | 22 (84.6) | 18 (85.7) | 0.484 |
|                         | 301-500 µm | 7 (58.3) | 4 (80.0) | 11 (73.3) | 5 (71.4) | 0.076 |
|                         | >3 injections | 7 (58.3) | 4 (80.0) | 11 (73.3) | 5 (71.4) | 0.076 |

DR=Diabetic retinopathy; Severe=Severe Nonproliferative diabetic retinopathy; PDR=Proliferative diabetic retinopathy; *Best corrected visual acuity; **Central subfield macular thickness

Figure 1: (a: Baseline, b: 3 months, c: 6 months, d: 1 year): Structural OCT of a patient with central involving diabetic macular edema treated with intravitreal anti-VEGF injection alone (group 1) through a 1-year follow-up
Figure 2: (a: Baseline, b: 3 months, c: 6 months, d: 1 year): Structural OCT of a patient with center-involving diabetic macular edema treated with intravitreal anti-VEGF injection along with topical NSAIDs (group 2) through a 1-year follow-up. There was no statistical difference noted in the central subfield thickness between the two groups.

Topical NSAIDs have commonly been used as initial monotherapy for treatment of pseudophakic cystoid macular edema. A combination of topical NSAIDs and anti-VEGF injections have also been employed for treatment of chronic pseudophakic cystoid macular edema. Both nepafenac and bromfenac treated eyes with pseudophakic edema showed reduced retinal thickness at 12 and 16 weeks. Nepafenac also produced a sustained improvement in visual acuity. These observations show that the inflammatory component of CI-DME is different from pseudophakic macular edema. There is sufficient evidence that CI-DME respond to steroids suggesting that the inflammatory component of CI-DME responds to steroids and not NSAIDs.

This study has many limitations, which include the retrospective nature of the study. As the OCT thickness values were recorded as three groups (≤300 µm, 300–500 µm, and >500 µm), a change in thickness could not be calculated. In addition, the two groups were not matched at baseline in terms of duration of diabetes and severity of diabetic retinopathy, which might have played a role in the final treatment outcomes.

Conclusion

In conclusion, combination therapy of topical NSAID with intravitreal anti-VEGF did not show any beneficial effects in terms of visual outcomes, reduction in CST, or reduction in the mean number of injections in our study. Although our study is limited by its retrospective nature, our findings support the available evidence that it is of no benefit to add NSAIDs to augment the effect of anti-VEGFs in the management of CI-DME in routine clinical practice.

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Conflicts of interest

There are no conflicts of interest.

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