

Management of Diabetic Macular Edema using Intravitreal Bevacizumab versus Intravitreal Triamcinolone: Systematic Review and Meta-Analysis

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Abstract

Background and aim: Triamcinolone, as an ocular steroid, plays an anti-inflammatory, anti-angiogenic, and cost-effective role in the treatment of DME. Meanwhile, the humanized monoclonal antibody bevacizumab shows promising anti-VEGF results when used as an off-label therapeutic option because it is less expensive than most anti-VEGF agents. This work aims to determine the efficacy and safety of Intravitreal Bevacizumab (IVB), versus Intravitreal Triamcinolone (IVT) in Diabetic Macular Edema (DME) patients. **Methodology:** A systematic search was performed over different medical databases to identify ophthalmology studies, which studied the outcome of the IVB group versus the IVT group of DME patients. We conducted a meta-analysis process on Best-Corrected Visual Acuity (BCVA) and Central Macular Thickness (CMT), as primary outcomes, and on Intraocular Pressure (IOP) as a secondary outcome. Eight studies were identified involving 564 eyes, 285 in the IVB group, and 279 in the IVT group. Our meta-analysis process showed a highly significant decrease in mean CMT in the IVB group compared to the IVT group ($p=0.043$). But, there was a non-significant difference in mean BCVA and IOP between groups ($p>0.05$) respectively. **Conclusion:** To conclude, this study compares the efficacy and safety of Intravitreal Bevacizumab (IVB), versus Intravitreal Triamcinolone (IVT) in Diabetic Macular Edema, according to our results IVB was more effective than IVT in CRT reduction but no difference between both in best-corrected visual acuity and on Intraocular Pressure (IOP) parameters.

Keywords: Diabetic macular edema; Intravitreal bevacizumab; Intravitreal triamcinolone

Abbreviations: PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT: Randomized Controlled Trial; OR: Odds Ratio; SMD: Standard Mean Difference; CI: Confidence Interval

Introduction

Diabetes Mellitus (DM) affects over 422 million people globally. [1] Approximately 33% of diabetic patients develop diabetic-related eye damage. [2] In patients with T1DM, the 10-year incidence of diabetic retinopathy is about 36%, whereas the 20-year incidence of T2DM is 84% in those on insulin and 53 percent in those not taking insulin. [3] Diabetic retinopathy is a microvascular condition characterised by the thickening of the retinal nerve fiber layer peripapillary. [4]

Diabetic Macular Edema (DME) is the most common cause of visual loss in diabetic retinopathy. DME can develop at any stage of retinopathy and is characterised by edema and retinal thickness. [5] In DME, Chronic hyperglycemia increases vascular permeability and angiogenesis in DME through up regulating Vascular Endothelial Growth Factor (VEGF). [6] Furthermore, a substantial body of evidence suggests that inflammatory mediators play a role in the pathophysiology of DME, contributing significantly to vascular permeability and the development of edema. [7] Macular Laser Photocoagulation

(MLP), anti-VEGF agents, ocular corticosteroids treatments for DME. [8] MLP was the primary treatment for DME, and it was found to be effective in limiting vision loss. Intravitreal anti-VEGF injections have quickly become the standard of care due to their ability to adjust both visual and anatomical outcomes, as well as the avoidance of laser-related complications such as subretinal fibrosis and laser scars. [9] Triamcinolone, as an ocular steroid, plays an anti-inflammatory, anti-angiogenic, and cost-effective role in the treatment of DME, as evidenced by several studies. [10]

Meanwhile, the humanised monoclonal antibody bevacizumab shows promising anti-VEGF results when used as an off-label

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therapeutic option because it is less expensive than most anti-VEGF agents. Triamcinolone, on the other hand, requires fewer injections, and one Intravitreal Triamcinolone (IVT) injection may be as effective as three Intravitreal Bevacizumab (IVB) injections for the treatment of DME. [11] This implies that IVT has the potential to reduce injection-related complications while also improving patient compliance. However, rates of Intraocular Pressure (IOP) increase, and cataract development is expected to be higher in eyes treated with steroids. [12] This work aims to determine the efficacy and safety of Intravitreal Bevacizumab (IVB), versus Intravitreal Triamcinolone (IVT) in Diabetic Macular Edema (DME) patients.

Methodology

Our review came following the (PRISMA) statement guidelines. [13] Basic searching was done over the pubmed, cochrane library, and google scholar using the following keywords: Diabetic Macular Edema, Intravitreal Bevacizumab, Intravitreal Triamcinolone. RCTs, clinical trials, and comparative studies, which studied the outcome of the IVB group versus the IVT group of DME patients, will be reviewed. Outcome measures included Best-Corrected Visual Acuity (BCVA) and Central Macular Thickness (CMT), as primary outcomes, and on Intraocular Pressure (IOP) as a secondary outcome. The included studies should be in English, a journal published article, and a human study describing DME patients. The excluded studies were either animal or non-English studies. We found 150 records, 90 excluded because of the title; 60 articles are searched for eligibility by full-text review; 21 articles cannot be accessed; 13 studies were reviews and case reports; 11 were not describing functional outcome; the desired drug not used in 7 studies. The studies which met all inclusion criteria were 8 studies.

Statistical analysis

Pooled Standard Mean Differences (SMDs), with 95% Confidence Intervals (CI) assessed, using a statistical package (MedCalc, Belgium). The meta-analysis process was established via I²-statistics (either the fixed-effects model or the random-effects model), according to the Q test for heterogeneity.

The included studies were published between 2011 and 2021. Regarding the type of included studies, all studies were RCTs. Regarding patients' characteristics, the total number of eyes in all the included studies was 564 eyes, 285 in the IVB group and 279 in the IVT group, while their average follow-up time was (28.6 weeks). The mean age of all patients was (59.8 years), with all patients received a 0.125 ml dose of Bevacizumab [Table 1]. Our meta-analysis included 8 studies comparing 2 different groups of patients; with a total number of eyes (N=564) [Table 2]. [14-22]

Each outcome was measured by

Standard Mean Difference (SMD)

- For BCVA (LogMar).
- For CMT (µm).
- For (IOP) (mmHg).

Concerning the primary outcome measures, we found 8 studies that reported BCVA. I² (inconsistency) was 83.9%, Q test for heterogeneity (p<0.0001), so random-effects model was carried out; with overall SMD=-0.259 (95% CI=-0.679 to 0.161). The random-effects model of the meta-analysis process revealed a non-significant difference in mean BCVA in the IVB group compared to the IVT group (p>0.05) [Figure 1]. We found 8 studies reported CMT. I² (inconsistency) was 85.3%, Q test for

Table 1: Patients and study characteristics.

N	Author	Type of study	Number of eyes			Age (average years)	Follow-up time (average weeks)	Dosage (ml)
			Total	IVB group	IVT group			
1	Marey et al. [14]	RCT	60	30	30	57.66	12	1.25
2	Lim et al. [15]	RCT	75	38	37	58.4	48	1.25
3	Shoeibi et al. [16]	RCT	78	41	37	59.1	49	1.25
4	Sonoda et al. [17]	RCT	51	26	25	61	12	1.25
5	Kasiri et al. [18]	RCT	60	30	30	59.5	12	1.25
6	Riazi-Esfahani et al. [19]	RCT	92	46	46	62	24	1.25
7	Rodrigues et al. [20]	RCT	65	33	32	61	48	1.25
8	Sultan et al. [21]	RCT	83	41	42	---	24	1.25

Table 2: Summary of outcome measures in all studies.

N	Author	Primary outcomes				Secondary outcome	
		BCVA (LogMar)		CMT (µm)		IOP (mmHg)	
		IVB group	IVT group	IVB group	IVT group	IVB group	IVT group
1	Marey et al.	0.22	0.18	445.06	492.3	15.47	14.83
2	Lim et al.	0.62	0.65	447	449	15	14
3	Shoeibi et al.	0.88	0.92	414.6	417.7	15.4	16.1
4	Sonoda et al.	0.48	0.39	495.7	503.9	13.1	13.7
5	Kasiri et al.	0.63	0.59	417	451	14.9	14.4
6	Riazi-Esfahani et al.	0.35	0.38	462	466	---	---
7	Rodrigues et al.	0.5	0.6	447.2	478	18.5	18.4
8	Sultan et al.	0.61	0.8	210.16	294.3	15.2	16.9

Discussion

This work aims to determine the efficacy and safety of Intravitreal Bevacizumab (IVB), versus Intravitreal Triamcinolone (IVT) in Diabetic Macular Edema (DME) patients. The included studies were published between 2011 and 2021. Regarding the type of included studies, all studies were RCTs. Regarding patients' characteristics, the total number of eyes in all the included studies was 564 eyes, 285 in the IVB group, and 279 in the IVT group, while their average follow-up time was (28.6 weeks). The mean age of all patients was (59.8 years), with all patients received a 0.125 ml dose of Bevacizumab. Our meta-analysis

heterogeneity ($p < 0.0001$), so random-effects model was carried out; with overall $SMD = -0.457$ (95% $CI = -0.899$ to -0.0145). The random-effects model of the meta-analysis process revealed a highly significant decrease in mean CMT in the IVB group compared to the IVT group ($p = 0.043$) [Figure 2].

Concerning the secondary outcome measure, we found 7 studies that reported IOP. I^2 (inconsistency) was 75%, Q test for heterogeneity ($p < 0.0001$), so random-effects model was carried out; with overall $SMD = 0.0242$ (95% $CI = -0.340$ to 0.388). The random-effects model of the meta-analysis process revealed a non-significant difference in mean IOP in the IVB group compared to the IVT group ($p > 0.05$) [Figure 3].

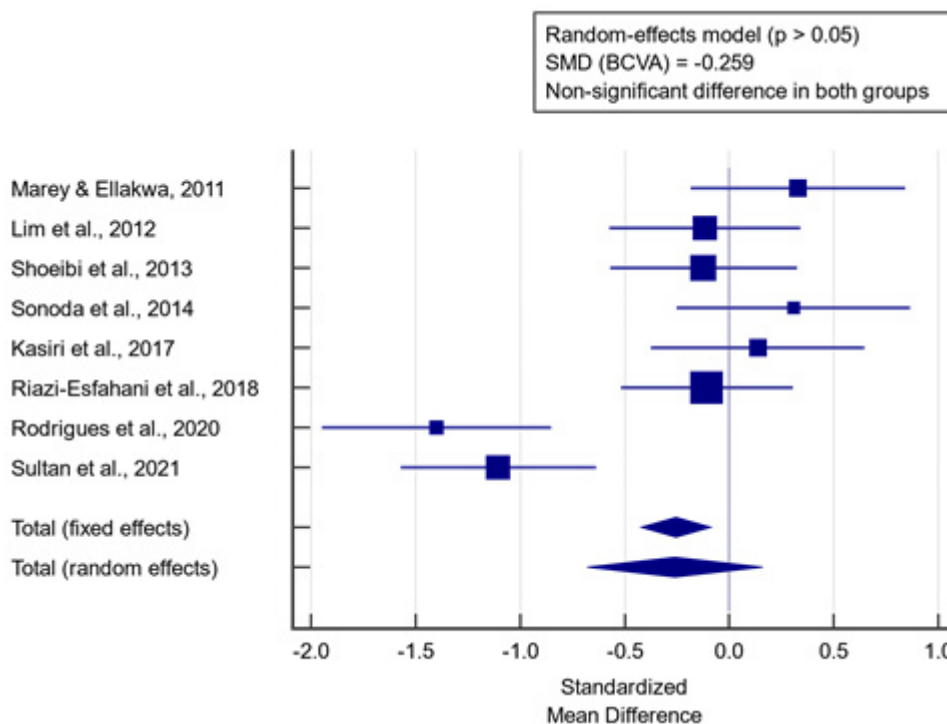


Figure 1: Forest plot (BCVA).

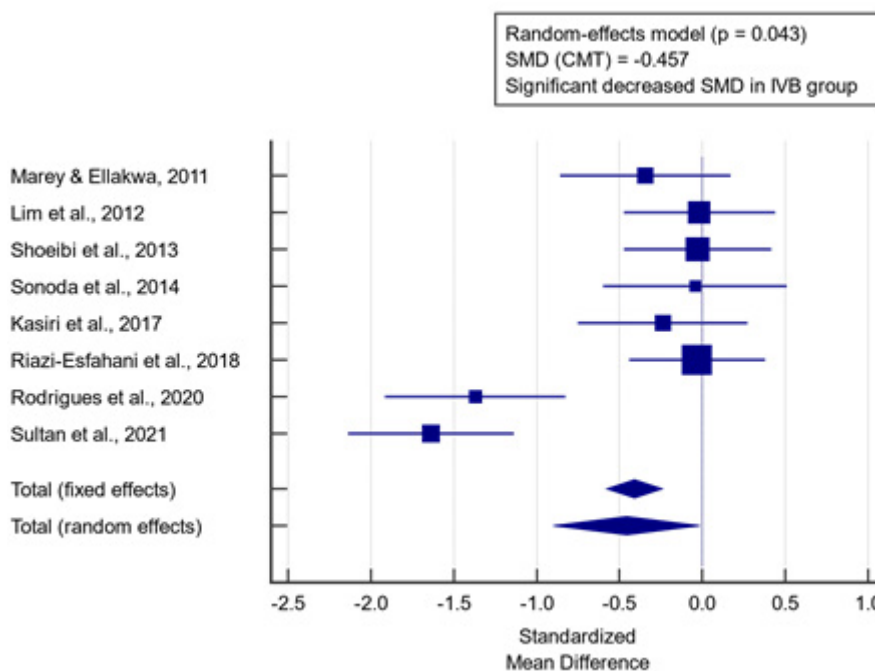


Figure 2: Forest plot (CMT).

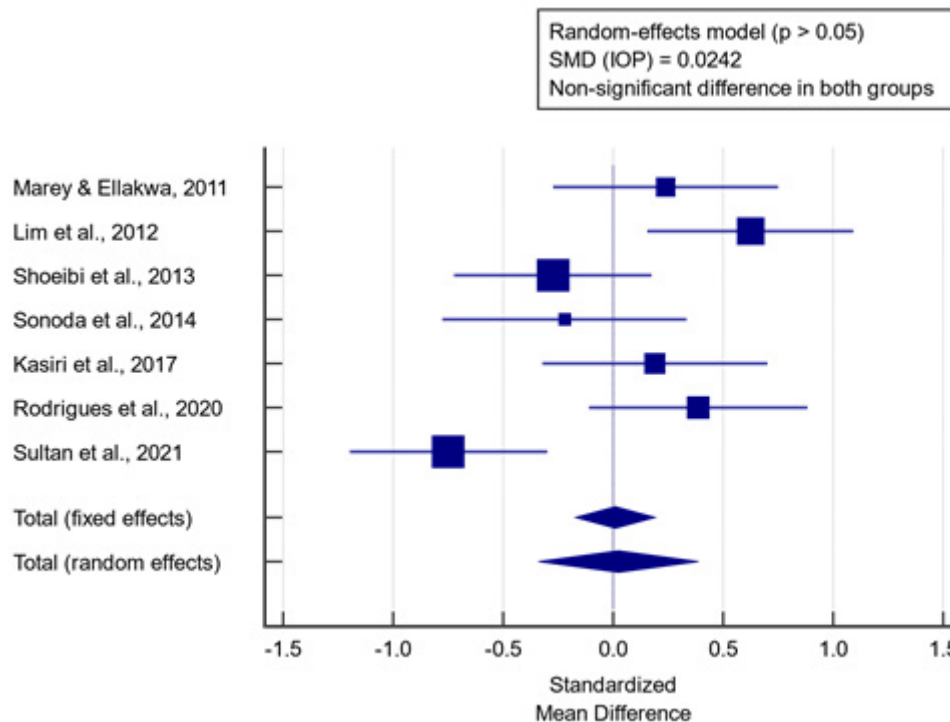


Figure 3: Forest plot (IOP).

included 8 studies comparing 2 different groups of patients; with a total number of eyes (N=564). Concerning the primary outcome measures, we found 8 studies that reported BCVA.

Using Random-effects model of the meta-analysis process revealed a non-significant difference in mean BCVA in the IVB group compared to the IVT group ($p > 0.05$) which came in agreement with Meena et al.; Kandasamy et al.; Penha et al.; Neto et al. [23-25] Meena et al. discovered a rapid increase in visual acuity in both groups within a few weeks of the first injection, with a mean BCVA improvement of 0.3230.200 and 0.2360.187 log MAR from baseline in the IVT and IVB groups, respectively, at 6 weeks following injections. Patients continued to improve, with acuity improving at 87.5 percent and 75 percent of patients at the final appointment. The IVT group appeared to have more character than the IVB group, albeit there was no statistical difference, which could be due to the study's small sample size.

Kandasamy et al. reported that while TA had a statistically significant morphological advantage over BVB, there was no statistically significant difference in BCVA between the two groups, despite the TA group having slightly better visual outcomes. [23] Penha et al. reported that, in comparison to the baseline, both groups improved their BCVA and decreased their CMT after 6 months. In all follow-up periods, there was no statistically significant difference in BCVA between the groups ($p = 0.29$). [24]

Neto et al. reported that when comparing baseline and 6-month follow-up values, statistically significant improvements in BCVA and decreased foveal retinal thickness were observed in all groups ($P < 0.001$). The differences between the groups, however, were not statistically significant ($P > 0.05$). [25] Concerning the primary outcome measures, we found 8 studies

reported CMT. Using the Random-effects model of the meta-analysis process revealed a highly significant decrease in mean CMT in the IVB group compared to the IVT group ($p = 0.043$) which came in agreement with Liu et al.; Ramezani et al. [26,27] Liu et al. reported that At 6 and 12 weeks, IVB was slightly more successful than IVTA in lowering CRT in DMT patients, but BCVA improvement did not differ significantly between the two therapies.

Ramezani et al. reported that CMT reduction was statistically significant in both groups in within-group analysis, 83 104 and 151 122 microns in the IVB group versus 89 105 and 75 89 microns in the IVT group at 3 and 6 months, respectively; however, the difference between the two groups reached a significant level ($p = 0.002$) in favor of the IVB group only at 6 months. [27] Concerning the secondary outcome measure, we found 7 studies that reported IOP. Using the Random-effects model of the meta-analysis process revealed a non-significant difference in mean IOP in the IVB group compared to the IVT group ($p > 0.05$) which came in agreement with Abdel-Maboud et al.; [1], Meena et al.; Nguyen et al. [28]

Abdel-Maboud et al. reported that IVB vs. IVT. In terms of IOP, both groups were comparable at 12 weeks with single and repeated injections and 24 weeks with single and repeated injections, both groups had equivalent IOP. Furthermore, no clear conclusions can be taken at the 4-week follow-up, whether with single or repeated injections, because each analysis only included one trial. [1] Meena et al. reported that The IVT group had a greater mean elevation than the IVB group, but the difference was not statistically significant. Nguyen et al. found, In the IVT and IVB groups; there was no more than a 15 mm Hg increase in IOP. [28]

On the other hand Ramezani et al. reported that at 3, 4, and 6

months, the IVT group's mean IOP was considerably greater. The IVB group showed no significant change in mean IOP throughout all follow-up visits, demonstrating within-group analysis, however, the IVT group showed a substantial IOP rise at each follow-up visit, demonstrating from the within-group analysis. [27]

Conclusion

To conclude, this study compares the efficacy and safety of Intravitreal Bevacizumab (IVB), versus Intravitreal Triamcinolone (IVT) in diabetic macular edema, according to our results IVB was more effective than IVT in CRT reduction but no difference between both in best-corrected visual acuity and on Intraocular Pressure (IOP) parameters.

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Authorship

All the listed authors contributed significantly to the conception and design of study, acquisition, analysis, and interpretation of data and drafting of the manuscript, to justify authorship.

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