IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 20, Issue 7 Ser.7 (July. 2021), PP 53-57
www.iosrjournals.org

Effect of Laser Photocoagulation and Intravitreal Injection of Steroid and Anti-Vegf on Diabetic Macular Edema; a Retrospective Comparative Analysis

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Abstract
Introduction*: Diabetic Macular Edema (DME) is the retinal thickening as a result of exudation from incompetent macular vasculature.*
Metabolic alterations and inflammation are most important in the pathogenesis of DME. VEGF is a potent angiogenic factor and is responsible for DME. Long standing DME has an inflammatory component and is more responsive to corticosteroids, which are also antiangiogenic.
Materials and methods: *A comparison between photocoagulation and intravitreal injection (triamcinolone/ranibizumab) in patients with DME and also to evaluate the visual outcomes in these patients.*
A retrospective comparative study was conducted at tertiary eye care centre from August 2020 to March 2021 for 45 eyes of 30 patients diagnosed with diabetic macular edema. Treatment given included either laser photocoagulation, intravitreal triamcinolone injection or intravitreal ranbizumab (anti-VEGF).
Results: *In our study, we found that there is significant improvement seen in best-corrected visual acuity in the laser photocoagulation group at 12 weeks. Intravitreal injection of triamcinolone acetate was effective in reducing the foveal thickness and improved visual acuity for a short term, but the visual acuity and moderate reduction in foveal thickness persisted. Intravitreal injections of anti-VEGF also reduced the central foveal thickness but not to a significant extent.*
Conclusion: *Intravitreal injections show improvement in visual acuity and reduction in CFT more than laser photocoagulation.*
Amongst intravitreal injections, triamcinolone was found to be superior to anti-VEGF as it had a prolonged effect and the need for retreatment was less in comparison to anti-VEGF.
Keywords: *diabetic macular edema, intravitreal injection, triamcinolone, ranibizumab, laser photocoagulation.*

Date of Submission: 28-06-2021 Date of Acceptance: 12-07-2021

I. Introduction

Diabetic macular edema (DME) is the retinal thickening as a result of exudation from the incompetent macular vasculature. If retinal edema is peripheral to macula it is usually not vision threatening. To calibrate the severity of edema ETDRS (Early Treatment Diabetic Retinopathy Study) stated the term CLINICALLY SIGNIFICANT MACULAR EDEMA. (1)

The ETDRS (2) defined clinically significant macular edema as:

- Retinal thickening involving the center of the macula, or
- Hard exudates within 500µm of the center of the macula (if associated with retinal thickening), and
- An area of macular edema greater than one-disc area but within 1 disc diameter of the center of the macula.

Metabolic alterations and inflammation are most important in the pathogenesis of diabetic macular edema (DME). The exact pathogenesis of DME is still unclear, however it is known that it is known that diabetic retinopathy is a neovascular disease of retina. Chronic hyperglycemia related accumulation of advanced glycated end products causes disruption of the blood retinal barrier (BRB), due to altered glial cells, loss of pericytes, endothelial cell death, leukostasis in retinal vasculature, up regulation of expression of vascular endothelial growth factor (VEGF) which in turn causes increased vasopermeability.

VEGF is a potent angiogenic factor and is responsible for DME (3). VEGF is an important mediator of blood retinal barrier breakdown, which increases in diabetic patients and in turn leads to fluid leakage and the

development of macular edema. Several randomized controlled clinical trials have shown the efficacy of anti-VEGF treatments for DME.

It is reported that long standing DME has more of an inflammatory component and are more responsive to corticosteroids, which are also antiangiogenic [(4).] Corticosteroids provide a powerful anti-inflammatory and anti-edematous effects by targeting not only the synthesis of pro-inflammatory mediators involved in DME (IL-6, IL-8, MCP-1, ICAM-1, etc.) but also decrease VEGF synthesis. Corticosteroids block the arachidonic acid pathway; hence down regulate the synthesis of thrombaxnes, leukotrienes, and prostaglandins. Consequently the BRB improves density and activity of tight junctions in retinal capillary endothelium enhances and retinal oxygenation ameliorates. [(5)]

Type 2[(6)] diabetes and duration of diabetes strongly correlated with the prevalence and incidence of macular edema, retinopathy progression and other diabetic complications [(7,8).]

Various imaging modalities are now common in clinical use for the diagnosis of DME includes fundus photography, optical coherence tomography (OCT) and fundus fluorescein angiography (FFA).
FFA is useful in the classification of DR and to understand the response to treatment [(9).]

Management of DME comprises of strict metabolic control and changes in modifiable risk factors and ocular treatment. In our study, we aim to compare the treatment modalities available to us in the form of intravitreal injections and fundus laser photocoagulation.

II. Materials And Method

A retrospective comparative study was conducted at a tertiary eye care centre from August 2020 to March 2021.
Study design: Retrospective comparative study.
Study location: Tertiary eye care centre in western regional institute of Gujarat.
Study duration: August 2020 to March 2021
Sample size: 30 patients (45 eyes, 15 patients with bilateral disease and 15 patients with unilateral disease).
Sample size calculation: we have taken every consecutive patient from OPD of our centre who had DME.
Subjects and selection method: The study population was drawn from diabetic patients who presented to the tertiary eye care centre and were divided into 2 groups based on the treatment they received which included either intravitreal injections of either triamcinolone or anti-VEGF and another group which received laser photocoagulation.

Inclusion criteria:
1. Age 30 years and above
2. Diabetic patients
3. Pre-treatment Central foveal thickness (CFT) >280μm
4. Patients had received treatment for DME in the form of either laser photocoagulation or intravitreal injection (triamcinolone/anti-VEGF) with documented 6 months follow ups.

Exclusion criteria:
1. Patients with retinal disease other causes for macular edema
2. Pre treatment CFT ≤ 280μm with macular edema
3. Poor fixation for OCT examination
4. Significant macular ischemia (determined by FFA)
5. Received any previous treatment for macular edema.
6. Known allergy for triamcinolone or ranibizumab.

Procedure methodology:

After written informed consent a detailed questionnaire was used to collect data of the recruited patients retrospectively. The questionnaire included socio-demographic data, lifestyle habits, history of any systemic illness and if on treatment or not for the same, any significant family history, and smoking or drinking habits. As well as data regarding past eye diseases, eye surgeries.

A detailed eye examination was done which included best corrected visual acuity (BCVA) with the help of Snellen's chart for distance and Jaeger's chart for near vision, anterior segment examination with a slit lamp, detailed fundus evaluation by indirect ophthalmoscopy and evaluation by a 90D on the slit lamp, intraocular pressure by a non-contact tonometer, pre-operative OCT for central foveal thickness, FFA was done before and after treatment performed at 1 week, 4 weeks, and 12 week post treatment.

Patients were divided into 3 groups as per the treatment they received which included laser photocoagulation, intravitreal triamcinolone injection or intravitreal ranibizumab (anti-VEGF).

Patients belonging to ranibizumab treated group (26.6%) were given retreatment in the form of re-injection after 4 weeks of treatment. Patients belonging to triamcinolone treated group (13.3%) were given retreatment in the form of re-injection after 10 weeks of the first injection.

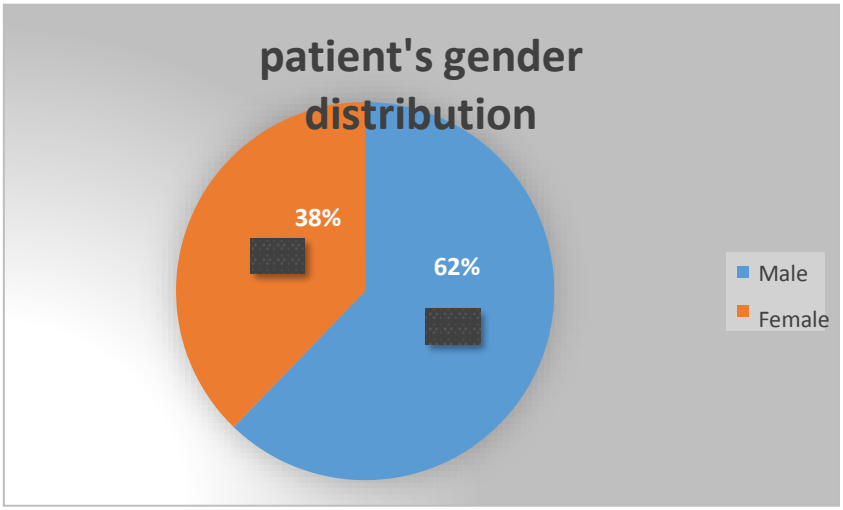
Statistical analysis:
An appropriate statistical analysis was applied on the collected data and results were obtained.

III. Results

In our study, there were 10 patients within 30 to 45 years, 25 patients in 46-60 years and 10 patients in above 61 years.

Chart 1 denotes the patients gender distribution.

Chart 1



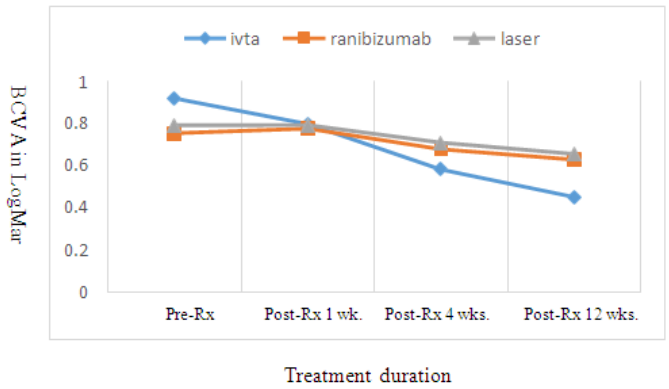
In patients treated with laser photocoagulation the mean BCVA improved from 0.80 to 0.79 post treatment week 1 which is statistically significant (p value=0.0001) which in turn improved to 0.71 at post treatment 4 weeks which is also statistically significant (p value=0.0004) and 0.65 at 12 weeks which is statistically significant (p value= 0.0008).

In the triamcinolone treated group, the mean BCVA improved from 0.92 to 0.79 at post treatment week 1 which is statistically significant (p value= 0.0011), which in turn improved to 0.58 at week 4 (p value= 0.0002) and to 0.45 (p value= 0.00004) at week 12, which are both statistically significant.

In the ranbizumab treated group, the mean BCVA worsened from 0.75 to 0/77 post treatment, and improved to 0.64 post 1 month which is statistically significant (p value= 0.00005) and improved to 0.62 at post treatment 3 months which is also statistically significant (p value=0.00013).

On comparing all the groups, the patients who received intravitreal triamcinolone showed greatest improvement in the post treatment BCVA at the end of 3 months. (Chart 2).

Chart 2

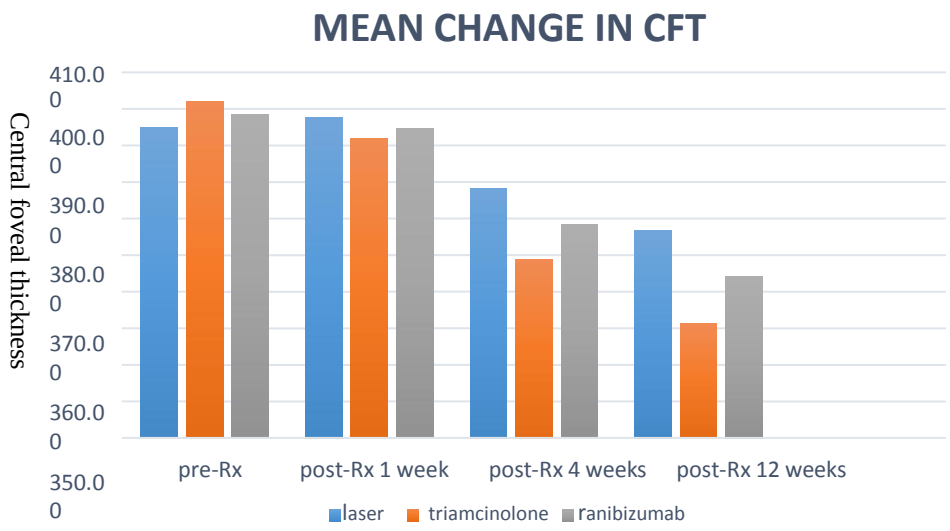


The central foveal thickness of 15 laser photocoagulation treated patients shows the changes at 1 week, 4 weeks and 12 weeks. The mean CFT, which was 394.93µm, reduced to 397.60µm at post treatment week 1 which is statistically not significant (p value=0.60). It reduced to 378.13µm at post treatment 4 weeks (p value= 0.034) and to 366.87µm at 12 weeks (p value=0.0043), which are both statistically significant.

The changes in CFT of 15 patients after triamcinolone injections were noted. The mean CFT, which was 402.13µm, reduced to 358.9µm at post treatment week 1 which is statistically not significant (p value=0.52). It reduced to 358.9µm at post treatment 4 weeks (p value= 0.024) and further reduced to 341.3µm at post treatment week 12 (p value =0.00513), which are both statistically significant.

Similarly, 15 patients treated with anti-VEGF (ranibizumab) were considered. The mean CFT was 398.53µm reduced to 394.77µm at post treatment week 1 which is statistically not significant (p value 0.57). It further reduced to 368.50 µm at post treatment 4 weeks which is statistically significant (p value= 0.024) and further reduced to 354.07µm at post-treatment at 12 weeks which is statistically not significant (p value=0.32). (Chart 3)

Chart 3



IV. Discussion

DME is one of the main reasons of visual impairment in patients with diabetic retinopathy [(10)]. A recent analysis of 35 population based studies in many countries indicate that global, age standardized prevalence of DR and DME in diabetic patients younger than 80 years of age is approximately 35% and 7.5% respectively [(11)].

Our study shows that our patient cohort consisted of 17 females and 28 males, with no gender predominance.

From our study we noted that there is a significant improvement in BCVA in the laser photocoagulation group (p value <0.01) at 12 weeks. However a study done by lee et al [(!2)] showed no significant improvement of BCVA at three month after laser treatment. There is a significant improvement seen in BCVA in the intravitreal triamcinolone group (p<0.01) like few studies shown the same data [(13)]

Avitabile et el. [(14)] showed better visual acuity outcome and reduced central macular thickness in 22 eyes that received intravitreal triamcinolone compared to 21 eyes that received laser treatment. Similarly, in our study the laser photocoagulation treated group, the mean BCVA improved from 0.80 to 0.79 at post-treatment week 1 which is statistically significant (p value= 0.0001) which in turn improved to 0.71 at post-treatment 4 weeks which is also statistically significant (p value = 0.0004) and 0.65 at post-treatment 12 weeks which is statistically significant (p value= 0.0008). In comparison to laser treated group, the triamcinolone treated group showed mean BCVA improved from 0.92 to 0.79 at post-treatment week 1 which is statistically significant (p value= 0.0011) which in turn improved to 0.58 at post- treatment 4 weeks which is also statistically significant (p value =0.0002) and 0.45at post-treatment 12 weeks which is statistically significant (p value=0.00004).

We also noted that the CFT in patients treated with intravitreal triamcinolone reduced at post 12 weeks, which is statistically significant.

In the triamcinolone group patients only 13.3% required re treatment while in ranibizumab group 26.6% required retreatment.

Paccola et al [(15)]. reported that a single IVTA had more effect on reduction of Central Macula thickness

(CMT) in patients with DME compared with one intravitreal bevacizumab (IVB) during an eight-week period. Oh et al. [16] also reported that CMT reduction was maintained until three months after IVTA injection, while in the IVB group, CMT reduction was maintained until two months after injection.

In our study, the CFT decreased with both intravitreal triamcinolone and anti-VEGF, but a prolonged maintenance was seen in patients who had received triamcinolone. None of the patients belonging to laser treated group required retreatment up to 12 weeks.

V. Conclusion

We conclude that intravitreal injection (triamcinolone>anti-VEGF) showed improvement in visual acuity and reduction in CFT more than laser photocoagulation group.

However, within the intra-vitreal injection group post treatment improvement in visual acuity and reduction in CFT are seen in triamcinolone group more than anti-VEGF group.
The need for retreatment was seen more with anti-VEGF group in comparison to intravitreal triamcinolone and laser photocoagulation.

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Dr. Apoorvi Batra, et. al. "Effect of Laser Photocoagulation and Intravitreal Injection of Steroid and Anti-Vegf on Diabetic Macular Edema; a Retrospective Comparative Analysis." *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, 20(07), 2021, pp. 53-57.