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LITERATURE REVIEW

COMBINATION OF DEXAMETHASONE IMPLANT AND ANTI-VEGF IN THE MANAGEMENT OF DIABETIC MACULAR EDEMA: A SYSTEMATIC REVIEW

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ABSTRACT

Background: *Anti Vascular Endothelial Growth Factor (anti-VEGF) and dexamethasone implant (DEX) are suggested as the first and second-line therapy for Diabetic Macular Edema (DME). However, persistent DME were found after six months of routine anti-VEGF injection. Intravitreal steroids have the advantage to control the inflammatory component of DME. Combining intravitreal anti-VEGF and DEX may reduce macular edema more effectively and more quickly theoretically. Hence, we aim to review the efficacy of adding DEX to anti-VEGF in treating DME.*

Methods: *Literatures were obtained using comprehensive searching on PubMed and Proquest using the keywords "Dexamethasone implant", "anti-VEGF therapy", and "Diabetic Macular Edema" including their synonyms between 2018 to 2023. Non-English studies, animal studies, review articles, case studies, and editorial letters were excluded. This result was presented following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines.*

Results: *A total of 3 studies with 265 eyes were included. All of the studies had Central Foveal Thickness (CFT) and Best Corrected Visual Acuity (BCVA) as the main outcomes. Improved CFT was seen in all of the studies (all $p<0.05$) with ΔCFT (200,40 µm in 6 months and 413 µm in 12 months). Most studies showed improved visual acuity after 8 months of injections which were shown by ΔBCVA (8,84 letters in 6 months and 21,6 letters in 12 months) and increased intraocular pressure as an adverse effect of steroids.*

Conclusion: *Combination of DEX and anti-VEGF showed improvement in CFT and BCVA. Further studies are required due to the controversial intravitreal steroids' ocular adverse effect.*

Keywords: *Dexamethasone implant; Anti-VEGF therapy; Diabetic Macular Edema*

INTRODUCTION

Diabetic Macular Edema (DME) is one of the main factors contributing to visual loss in patients with diabetic retinopathy (RDP).[1] It is characterized by diffuse retinal thickening, subretinal fluid, that leads to decreased visual acuity or even leading to vision loss. DME can occur in 2.7% to 11% of individuals with diabetic retinopathy.[1,2] Type of diabetes and duration of the disease have a direct impact on the prevalence rate of DME.[2] Over 10,000 new incidences

of blindness are caused by DME each year[2,3] The increasing prevalence of diabetes worldwide highlights the importance of diabetic macular edema as a global health issue.[2,3]

The pathogenesis of DME is not thoroughly known as it involves a complex process involving various factors. Several vasoactive factors (e.g., VEGF, protein kinase C [PKC], heparin, angiotensin II, PEDF, metalloproteases) and biochemical pathways may be affected by sustained hyperglycemia in diabetes, which may influence the progression of structural and functional changes in diabetic retinopathy.[2,3] Proliferation of new blood vessels that are weak can rupture causing vitreous hemorrhage, damage to the blood-retinal barrier (BRB) due to disruption of endothelial tight junction proteins. Other multiple proinflammatory cytokines, such as insulin-like growth factor-1 (IGF-1), interleukin-6 (IL-6), and PKC-beta, also promote the expression of VEGF and BRB disruption. Aqueous levels of VEGF and IL-6 significantly correlate with macular edema severity in diabetic patients.[4,5] Effective therapies are required to address these complex processes involved in the pathogenesis of DME.

Currently, anti-Vascular endothelial growth factor (Anti-VEGF) is approved as the first-line therapy of DME. Intravitreal injection treatment using anti-VEGF aims at vascular regression, and has been shown to be superior to macular laser photocoagulation. According to research, the use of Anti-VEGF can improve visual acuity and significant reduction in foveal thickness in eyes with DME.[3,4,5] However, in some cases persistent macular edema was found in the eyes that have been treated with at least 6 months of intravitreal anti-VEGF injections.[3] Corticosteroids injection as an anti-inflammatory agent can reduce breakdown of the blood-retinal barrier and inhibit other inflammatory cytokines. Injections of corticosteroids that control the inflammatory component can reduce macular edema more effectively and quickly to prevent vision loss due to DME.[6] As second-line therapy of DME, Corticosteroid injection is a promising therapy method for DME unresponsive to previous therapy. [4,6]

The aim of this literature review is to evaluate the efficacy of adding intravitreal dexamethasone to anti-VEGF in treating patients with DME in terms of improvement in anatomical and functional of the eyes.

METHODS

Eligibility criteria

The participants included in this review were adult patients with diabetic macular edema. Studies on patients with other causes of macular edema such as age-related degeneration, vascular problems, and others were excluded from this study. Animal studies

were also not included in this review. The studies had to include a comparison between the intervention, combination of dexamethasone implants and anti-VEGF therapy, with the comparator, anti-VEGF therapy. Papers that only report one of the others were excluded from the study. The outcome of interest was retinal thickness and visual outcomes.

Information sources

A literature search was done on two medical databases being Pubmed and Proquest on (insert date) by the author.

Search Strategy

Table 1. shows the following search strategies were used in the literature search.

Medical database	**Search strategy**
Pubmed	"dexamethasone implants" AND "management" OR "therapy" AND "diabetic macular edema"
Proquest	"dexamethasone implants" AND "management" OR "therapy" AND "diabetic macular edema"

Selection process

Studies were retrieved by an author and imported into a reference management application (insert name of application). The imported studies were then checked for duplicates and removed with the "remove duplicates" function available in the application. Studies were then reviewed in duplicate by two authors independently in accordance with the eligibility criteria mentioned above. The selection process included an initial title and abstract screening followed by a full-text screen of the articles included. Any conflicts were discussed and decided between the two authors.

Data collection process

Data collection was done independently in-duplicate with the following form.

Author (year)	Study design	Participants	Effect of treatment	Side effects

Data items

List of data items in this study is listed in Table 2.

Table 2. Data items in this study

Variable	Operational definition	Method of collection	Type of data
Age	Age of participants during therapy	Methods section	Discrete
Types of diabetes mellitus	Diabetes mellitus type I or diabetes mellitus type II	Methods section	Nominal
Duration of diabetes	The number of years patient has had diabetes at the time of therapy	Methods section	Continuous
Visual acuity	Patient's ability to distinguish between two letters or images in the Snellen chart measured as best corrected visual acuity (BCVA)	Methods and results section	Ordinal
Follow-up	Time of measurement for visual acuity	Methods section	Ordinal
Anatomic outcome	Any information on anatomic changes such as central subfield thickness (CST), sub foveal neuroretinal detachment (SND), etc.	Results section	-
Intraocular pressure	Intraocular pressure of baseline and post-therapy	Methods and results section	Continuous
Cataract progression	Increase or decrease in cataract density from baseline	Methods and results section	Nominal

Study risk of bias assessment

The risk of bias tools used in the review were the *Joanna Briggs Institute quality assessment tool for analytical cross-sectional studies* and the *Risk of Bias in Non-randomized Studies – Of Interventions (ROBINS-I)* tool. The domains assessed in the included studies:

1. Confounding bias
2. Selection bias
3. Classification bias
4. Deviation bias
5. Missing data bias
6. Measurement of outcome bias
7. Selective reporting bias

The results of the appraisal from *Joanna Briggs Institute quality assessment tool for analytical cross- sectional studies* were summarized into a table and given a subjective appraisal for quality of evidence with guidance from GRADE. The highest score given for a non-randomized observational study was moderate. Studies that received 0 to 3 "Yes" from the

checklist were appraised as very low. Studies with 4 to 6 “Yes” from the checklist were appraised as low. Lastly, studies with 7 to 8 “Yes" were appraised as moderate.

The studies were then appraised with the same review matrix for risk of bias with the *ROBINS-I* assessment tool. Each type of bias was assessed with a set of questions and appraised in regard to the guidelines within the *ROBINS-I* assessment tool. Each question was either appraised as potential markers for low risk of bias or high risk of bias. Finally, the type of bias in each domain was categorized into low, moderate, serious, critical risk by assessing the number of potential markers. The authors had adapted the assessment of each bias from the guidelines given in the ROBIN-I assessment tool. A low risk of bias was given when all the questions were appraised as potential markers for low risk of bias. A moderate risk of bias was given when one question was appraised as a potential marker for high risk of bias. Serious and critical risk was subjectively given if the study was deemed to be problematic or if no useful evidence could be extracted.

Effect measures (narrative approach)

Synthesis methods

A qualitative analysis was done and presented with a narrative approach. A quantitative analysis was not done.

Reporting of bias assessment (none, a meta analysis was not done)

Certainty assessment (none)

RESULTS

A total of 3 studies comparing additional DEX to anti-VEGF alone in treating DME in the period between 2018-2023 were included. Figure 1. Shows the PRISMA flow chart summarizing the results of search and reasons of exclusion. This review included two continuous clinical trials and a randomized clinical trial involving 197 eyes.

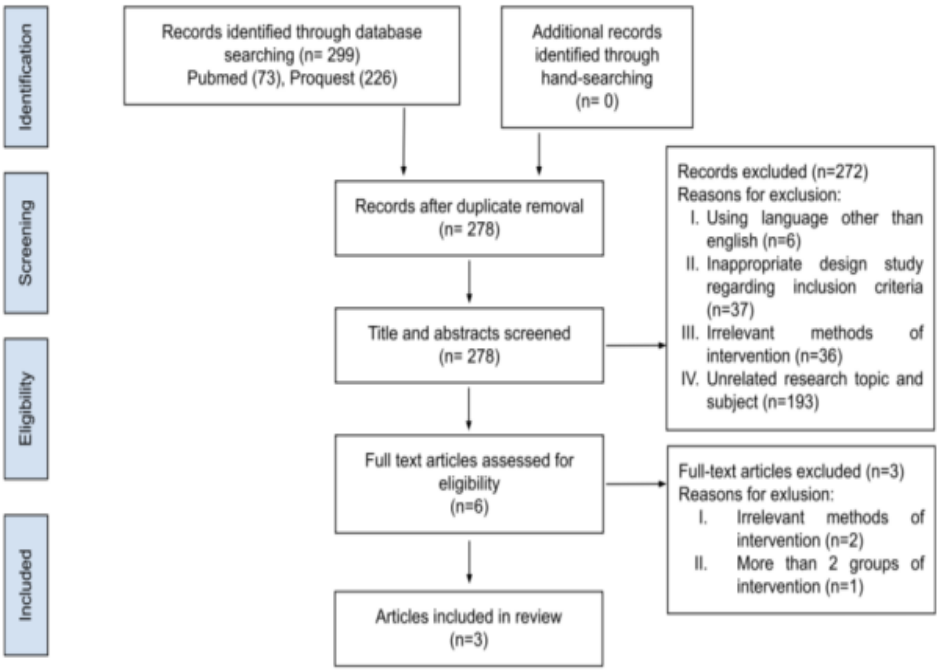

Figure 1. Articles included in this study selected with PRISMA Guideline

All included studies used dexamethasone implant and ranibizumab as their therapeutic intervention, which research arms were divided into two: ranibizumab alone (monotherapy) and dexamethasone implant as an adjuvant to ranibizumab (combined therapy).

Study Participants

A total of 162 participants from 3 studies were included, with the age ranging between 49-86 years. Maturi et al involved participants with both types of diabetes mellitus (DM Type 1 and Type 2), while Kaya et al participants were all Type 2 DM. In both studies, durations of DM ranging between 10-21 years and some received insulin therapy.[5]

Effect of Treatment

Follow up regarding the treatment received was done in 1, 6, 12, and 24 months, with the aim of visual acuity improvement and reduced central fundus thickness (CFT).

Visual acuity outcomes

Randomized controlled trial by Maturi et al showed an improvement of visual acuity after 6 months of follow up in both arms.[5] The mean visual acuity letter scores baseline was 63±12 (Snellen equivalent 20/63) for combined therapy arms, while it was 63±13 (Snellen

equivalent 20/63) for monotherapy arms. After six months, mean visual acuity were improved to 66±13,4 (Snellen equivalent 20/50, mean improvement was 2,7±9,8) for combined therapy and 66±15,1 for monotherapy (Snellen equivalent 20/50, mean improvement was 3,0±7,1). Even though more eyes in combined therapy had visual acuity improvement, it was suggested that there were also more eyes whose visual acuity worsened in the same group. Other factors such as early cataract formation should be considered in those dual therapy arm patients who never undergone cataract surgery before.

In a clinical intervention study by Kaya et al, the patients in both groups (monotherapy and combined therapy) were examined monthly over the first year of the study and they continuously showed steady improvement of visual acuity until the last follow up visit.[4] In the first month, there was an improvement of visual acuity into 54,5±23 (increased by +6,5 letters from baseline) for the combined therapy group and 54,2±14 (increased by +2,2 letters from baseline) for the monotherapy group. The visual acuity in the combined therapy group continually increased to 68,5±23 (improved by +20,5 letters from baseline) and 69,6±23 (improved by +21,6 letters from baseline) at month 6 and 12 respectively. On the other hand, for the monotherapy arms, the visual acuity increased to 60,9±14 (improved by +8,9 letters from baseline) and 61,6±14 (improved by +9,6 letters from baseline) at month 6 and 12 respectively. It was significantly shown that more than half patients in combined therapy groups reached Snellen BCVA ≥20/40 at month 12 compared with ranibizumab monotherapy groups ($p=0,013$).[8] A statistically significant vision improvement was found in the combined therapy group compared with the ranibizumab monotherapy group after 8 months of injection ($p<0,001$). Further study by Kaya et al was done to determine the visual acuity improvement at 24 months after therapeutic intervention. At month 24, 65,4% patients in combined therapy group and 26,2% patients in ranibizumab monotherapy group had gained a statistically significant visual acuity improvement.[9] But, it was found that the average changes in visual acuity from month 12 to month 24 was not significant and tended to remain constant.

Anatomic outcomes

Study by Maturi et al showed a significant reduction in central subfield thickness (CST) in both groups.[5] After six months of therapy, the reduction in CST was 111 μm and 37 μm in combined therapy and ranibizumab monotherapy respectively. Kaya et al had the same findings supporting Maturi et al study, where it was demonstrated that reduction in CFT happened in both study groups, where it was greater in the combined therapy group.[5] According to Kaya et al study results, the reduction of CFT was more significant in the combined therapy group than

ranibizumab monotherapy group. There was a reduction in CFT thickness by 370 μm and 413 μm in month 6 and 12 respectively for the combined therapy group, compared to 250 μm and 282 μm in month 6 and 12 respectively in ranibizumab monotherapy group.[8] Besides, there was a significant improvement in subfoveal neuroretinal detachment (SND) in the combined therapy group after 12 months ($p < 0,0001$). Reversely, there were no significant SND changes in ranibizumab monotherapy group, compared to the baseline ($p=0,097$). Further examination was done at month 24 and it was found the CFT reduction in combined therapy throughout the study is significantly greater than in ranibizumab monotherapy group ($p<0.001$) and the baseline CFT reduction at month 12 was maintained through month 24 in both groups.[9] Differences in results between groups was observed to be statistically significant at 2 months and after.

Side Effects

Intraocular pressure

Among studied eyes by Maturi et al, 19 of 65 eyes (29%) in combined therapy group experienced increased intraocular pressure (IOP), while there was none of this adverse event in ranibizumab monotherapy group.[5] This same side effect was observed in 12 of 34 eyes (25,3%) in the combined therapy group and 6/34 (18%) in ranibizumab monotherapy group by Kaya et al.[5] It was reported that at least 5 mmHg IOP elevation from the baseline had happened. Furthermore, twelve eyes from combined therapy groups had high IOPs and were successfully lowered by observation or topical antiglaucoma agents. After 24 months, IOP was reexamined and the number of IOP elevations in the combined therapy group increased to 38% (13/34) while the other group remained the same.[9]

Cataract Progression

Three of sixty-five eyes (5%) in combined therapy groups by Maturi et al received post-randomization cataract extraction while there was none in the other group. However, this finding was not statistically significant ($p=0,24$).[5]

During the first year of study, Kaya et al found the increased cataract density by two or more from baseline in 11,8% (4/34) eyes in the combined therapy group and 5,9% (2/34) in ranibizumab monotherapy group.[8] At month 24, there were increased cataract density detected in 27% (6/22) eyes in combined therapy group and in 12,5% (3/24) eyes in ranibizumab monotherapy group.[9]

DISCUSSION

In this systematic review, we screened 299 journal articles and selected 3 articles which compare additional DEX to anti-VEGF alone in treating DME. Significant CFT improvements were seen in all studies. Most of the studies also showed improvement of BCVA after 8 months of DEX implant injections. The ocular side effects of intravitreal steroid injection is still controversial, one study stated that the combined therapy group experienced increased intraocular pressure and in another study also stated increased cataract density in the combined therapy group. Further studies required to assess the controversial effects of intravitreal steroid injection compared to its benefit in improving CFT and BCVA outcome in patients with DME.

There were very few of the systematic reviews conducted to review the comparison between combination therapy and anti-VEGF therapy in treatment of DME. Furthermore, most of the study did not have the same timeline for outcome assessment which is why further studies are required to assess when the combination therapy gave the best outcome in treatment of DME.[7]

From the studies we reviewed, we found all studies consistently reported improvement of visual acuity and reduction in CFT in combined group after several times of evaluation. Furthermore, other studies showed potential benefit of DEX injection as a single therapy.The mean BCVA change was 5.2±11.1 letters along with changes in CRT of -89.6±143.3 μm after the first year evaluation. Moja et al, found no significant differences in visual outcome between the eyes treated only with DEX implants and the eyes given combined treatment.

In this systematic review of RCT, prospective, consecutive, clinical intervention study, evidence suggest that the results demonstrate that simultaneous intravitreal DEX implant and ranibizumab injection is superior to ranibizumab monotherapy and results in both significant visual acuity gains and revealed superior anatomical outcomes.

The most common side effects associated with DEX implants are cataract progression and IOP elevation. At month 24 compared to month 12 in the double protocol group, there was no significant increase in the cataract development and IOP elevation secondary to corticosteroid treatment.[10] Increased IOP developed in more eyes in the combination group than in the ranibizumab-only group.

It is possible that vision loss in some phakic eyes in the combination group that had not undergone cataract surgery was due to early cataract formation. A prespecified subgroup analysis suggested that pseudophakic eyes, on average, had a better visual acuity outcome with combination treatment than with ranibizumab therapy alone and that phakic eyes had a better outcome with ranibizumab therapy alone than with the combination treatment.

The 12 months results of this study demonstrated that the simultaneous double-protocol therapy significantly improved visual outcomes and significantly decreased CFT compared with ranibizumab monotherapy. Moreover, the morphological changes are usually associated with active inflammation.

Besides, they stated that the decrease in retinal thickness was observed mostly in patients with the combination therapy. The fact that reduced macular thickening was significantly improved in the combination group without improvement in BCVA suggests that the addition of the dexamethasone implant may have occurred after photoreceptor death

DME is one of the leading causes of visual impairment, which generally first line treatment is anti-VEGF. Often, DME treated with anti-VEGF alone showed incomplete response or even failed.(1) On the other side, corticosteroids have been shown to be effective as an addition to anti-VEGF due to its effect on inhibits inflammatory cytokines and enhance blood-retinal barrier.(3) Current study shows better improvement on DME using combination therapy, in the terms of visual acuity and anatomic outcomes. Although side effects have been found in several cases, looking into the outcomes and its impact on the better quality of life, combination therapy on DME together with close monitoring of its side effects should be taken into consideration in making therapeutic clinical decisions for DME treatment.

CONCLUSION

Combination of DEX and VEGF showed improvement in CFT and BCVA even though there were several side effects reported in the use of DEX for management of Diabetic Macular Edema. Therefore, further studies are required to assess the intravitreal steroids' ocular adverse effects.

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Conflicts of interest

The authors declare that there are no conflicts of interest in this article

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