• Meta-Analysis •

Dexamethasone implant in naive versus refractory patients with diabetic macular edema: a Meta-analysis

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Abstract

● **AIM:** To evaluate the efficacy and safety of the intravitreal dexamethasone implant in naive and refractory patients with diabetic macular edema (DME).

● **METHODS:** PubMed, Embase, Web of Science, and Medline databases were searched. The main outcomes were best-corrected visual acuity (BCVA) and central retinal thickness (CRT). The secondary outcomes included mean number of injections, intraoperative or postoperative complications including intraocular pressure (IOP) elevation and cataract.

● **RESULTS:** Ten comparative studies involving a total of 1000 DME eyes including 402 naive eyes and 598 refractory eyes were selected. The postoperative BCVA in the naive group was significantly better than in the refractory group [mean difference (MD) -0.11, 95% confidence interval (CI) -0.17 to -0.05, *P*=0.0003; MD 8.69, 95%CI 5.08 to 12.30, *P*<0.00001)]. Additionally, the naive group got greater improvement of BCVA change as well as more gains of BCVA letters than the refractory group [MD 7.71, 95%CI 2.02 to 13.40, *P*=0.008; odds ratio (OR) 2.99, 95%CI 2.05 to 4.37, *P*<0.00001]. The subgroup analysis revealed that the naive group had significantly higher BCVA gains of ≥5, ≥10, and ≥15 letters compared to the refractory group (*P*=0.002, 0.0001, 0.003, respectively). No significant difference was detected between the two groups in either postoperative CRT (MD -22.36, 95%CI -46.39 to 1.66, *P*=0.07) or the overall mean number of injections (MD -0.08, 95%CI -0.38 to 0.22, *P*=0.61). Intraoperative and postoperative complications including the elevation of IOP (OR 0.47, 95%CI 0.20 to 1.13, *P*=0.09) and cataract (OR 1.78, 95%CI 0.97 to 3.24, *P*=0.06) showed no significant differences between the two groups during the follow-up time.

● **CONCLUSION:** Intravitreal dexamethasone implants for DME can improve anatomical and functional outcomes in both naive and refractory eyes and have a well-acceptable safety profile. Moreover, naive eyes maintain better visual outcomes than refractory eyes. It provides further evidence of better visual response when used for naive eyes as first-line therapy.

● **KEYWORDS:** diabetic macular edema; dexamethasone implant; refractory eyes; systemic review
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INTRODUCTION

The pathogenesis of diabetic macular edema (DME) is multifactorial. The up-regulation of vascular endothelial growth factor (VEGF) and inflammatory mediators leading to the destruction of blood-retinal barrier plays the major role in the pathogenesis of DME[1-2]. The current guidelines recommend anti-VEGF injections as the first-line treatment of DME[3-4]. However, the limitations of anti-VEGF injections include frequent injections, low treatment compliance and the induction of resistance[5-6]. Not all patients responded adequately to these agents and the suboptimal responsed to anti-VEGFs also suggested that other inflammatory mediators were involved in the pathogenesis of DME, not only VEGF[7-8]. Dexamethasone intravitreal implant is a biodegradable implant containing sustained-release dexamethasone, which can inhibit many processes known to be involved in DME progression by suppressing inflammatory mediators and VEGF[9-10]. As suggested by the EURETINA guidelines for the management of DME[3], dexamethasone implants were mainly used for the treatment of patients who were pseudophakic or considered insufficiently responsive to, or unsuitable for, anti-VEGF therapy. Studies hare indicated that for refractory DME patients who did not sufficiently respond to anti-VEGF injections, dexamethasone may be a valuable option[11-14]. In

addition, more and more evidence supported the benefits of dexamethasone implants for naive DME patients as first-line therapy in recent years and studies reported that naive patients can obtain better visual outcomes compared to refractory DME patients[15-18].

Therefore, the purpose of this study was to conduct Meta-analysis to evaluate the efficacy and safety of the intravitreal dexamethasone implant in naive and refractory patients with DME.

MATERIALS AND METHODS

Search Strategy The PubMed, Embase, Web of Science, and Medline databases were searched. All related articles were published before 1 December 2023 in English. The following search terms were used: (dexamethasone OR DEX OR intravitreal dexamethasone implant) AND (macular edema OR DME OR naive macular edema OR refractory macular edema).

Inclusion and Exclusion Criteria All studies included in this Meta-analysis followed the inclusion and exclusion criteria. Inclusion criteria: 1) patients with DME; 2) a comparison of the dexamethasone implant in naive and refractory DME patients, refractory macular edema was considered patients previously managed with at least 3 monthly anti-VEGF injections with a poor clinical response (reduction of less than 10% of retinal thickness or reduction of central macular thickness less than 50 μm); 3) records of best-corrected visual acuity (BCVA) and central retinal thickness (CRT); 4) a follow-up time of not less than 6mo after the first dexamethasone injection. The exclusion criteria included patients with other eye diseases besides DME, studies with insufficient data, animal trials, case reports, review articles and non-English language articles.

Data Collection and Quality Assessment Two reviewers independently extracted the data and evaluated the quality. If the two reviewers disagreed, a third reviewer analyzed the data and quality.

The following variables were extracted from each study: first author, publication year, sample size, location, design, postoperative follow-up time and measured outcomes. The main measured outcomes were BCVA and CRT. The secondary measured outcomes included mean number of injections, intraoperative or postoperative complications including intraocular pressure (IOP) elevation, cataract formation and/or progression. All included studies were assessed by the Newcastle-Ottawa scale, which provided a score from a possible total of nine stars[19-20]. Publication bias was assessed using funnel plot of the data.

Data Synthesis and Analysis The results of individual studies were pooled using Review Manager software (V.5.3, the Cochrane Collaboration, Oxford, England). A P value <0.05 was considered a statistically significant difference between studies. The I^2 statistic test was used to assess the heterogeneity between studies. I^2 ranges from 0 to 100%[21-22]. If there was significant heterogeneity between studies ($I^2 \geq 50\%$), a random-effect model was employed. Otherwise, a fixed-effect model was used. The results were presented as the mean±standard deviation (SD) with a 95% confidence interval (CI) for continuous variables and odds ratio (OR) with 95%CI for categorical variables.

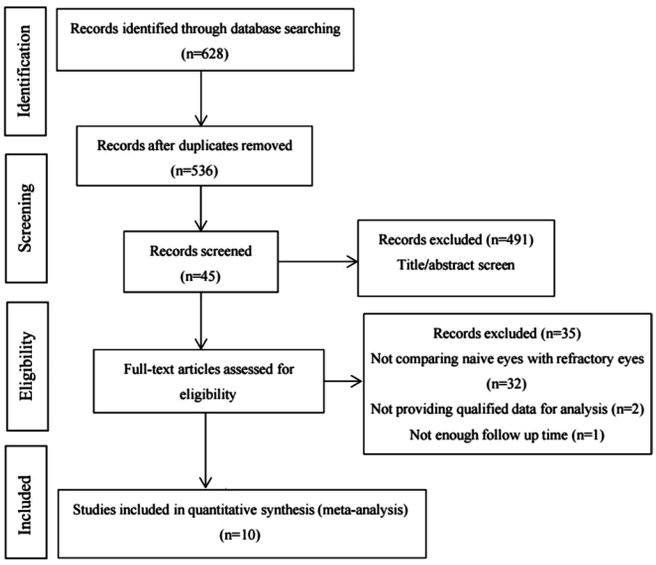

Figure 1 Selection of studies.

RESULTS

Search Results A total of 628 relevant studies were identified through our initial search, and 536 studies remained after removing duplicates. By screening titles and abstracts, 491 studies were excluded. After assessing the full-text articles, 10 of these studies[15-18,23-28] were eligible for inclusion (Figure 1).

Characteristics of the Included Studies The summary characteristics and quality assessment of the included 10 studies were showed in Table 1[15-18,23-28]. Nine studies were retrospective comparative studies and one study was prospective[18]. A total of 1000 eyes (402 naive eyes versus 598 refractory eyes) with DME receiving dexamethasone implant were analyzed. Among them, 402 eyes were treatment-naive with no prior intravitreal therapies while 598 refractory eyes were considered insufficiently responsive to previously intravitreal drugs therapies. The follow-up time was at least 6mo (6–24mo). In the included ten studies, Chhablani *et al*[23] referred that total number of additional anti-VEGF injections required was 1±2.3 and Iglicki *et al*[26] mentioned eyes treated with additional anti-VEGF injections were eleven eyes. Patients in another eight studies were only treated with dexamethasone implants over the study periods. The Newcastle-Ottawa scale was used to present the risk of bias for the included studies. The scores ranged from 7 to 9. The quality of the studies was medium to good. No significant

Table 1 Main characteristics and quality assessment of the included studies

Study	Participants		Location	Design	Outcome measures	Follow up (mo)	Quality scores
	Naive eyes	Refractory eyes					
Wang, 2021[17]	41	34	China	Retrospective	BCVA, CRT, complications, number of injections	6	8
Bux, 2022[25]	64	64	Italy	Retrospective	BCVA, CRT, complications, number of injections	6	8
Iglicki, 2019[26]	71	59	Multicenter study	Retrospective	BCVA, CRT, complications, number of injections	24	9
Neves, 2021[27]	34	19	Portugal	Retrospective	BCVA, CRT, complications, number of injections	6	8
Castro-Navarro, 2019[16]	29	55	Spain	Retrospective	BCVA, CRT, complications, number of injections	6	8
Escobar-Barranco, 2015[18]	36	40	Spain	Prospective	BCVA, CRT, complications, number of injections	6	7
Ruiz-Medrano, 2021[28]	21	108	Spain	Retrospective	BCVA, CRT, number of injections	12	9
Chhablani, 2016[23]	15	64	Multicenter study	Retrospective	BCVA, CRT, complications, number of injections	12	8
Medina-Baena, 2020[24]	24	19	Spain	Retrospective	BCVA, CRT, complications, number of injections	12	8
Zarranz-Ventura, 2020[15]	67	136	Spain	Retrospective	BCVA, CRT, complications, number of injections	24	8

BCVA: Best-corrected visual acuity; CRT: Central retinal thickness.

difference was detected in either preoperative BCVA (mean difference (MD) -0.03, 95%CI -0.07 to 0.01, *P*=0.15, Figure 2A; MD 3.02; 95%CI -3.24 to 9.27; *P*=0.34; Figure 2B) or the preoperative CRT (MD 10.76; 95%CI -6.23 to 27.76; *P*=0.21; Figure 2C) between the naive group and refractory group.

Outcomes

Best-corrected visual acuity The postoperative BCVA in the naive group was significantly better than in the refractory group (MD -0.11, 95%CI -0.17 to -0.05, *P*=0.0003, Figure 2D; MD 8.69, 95%CI 5.08 to 12.30, *P*<0.00001, Figure 2E). In the subgroup analysis, whether at months 6 or 12, the postoperative BCVA was also significantly better in the naive group (MD -0.17, 95%CI -0.27 to -0.08, *P*=0.0005; MD -0.07, 95%CI -0.11 to -0.02, *P*=0.008; Figure 2D). Additionally, the naive group got greater improvement of BCVA change (MD 7.71, 95%CI 2.02 to 13.40, *P*=0.008; Figure 2F) as well as more gains of BCVA letters (OR 2.99, 95%CI 2.05 to 4.37, *P*<0.00001; Figure 2G) than the refractory group. The subgroup analysis of gains of BCVA letters revealed that the naive group had significantly higher BCVA gains of ≥5, ≥10, and ≥15 letters compared to refractory group (*P*=0.002, *P*=0.0001, *P*=0.003, respectively; Figure 2G).

Central retinal thickness No significant difference was detected in the overall postoperative CRT between two groups (MD -22.36, 95%CI -46.39 to 1.66, *P*=0.07; Figure 2H) . In the subgroup analysis of postoperative CRT, there was also no significant difference between two groups at either month 6 (MD -19.45, 95%CI -48.37 to 9.47, *P*=0.19; Figure 2H) or month 12 (MD -8.43, 95%CI -55.55 to 38.69, *P*=0.73, Figure 2H), while the CRT of the naive group decreased significantly at month 24 (MD -60.46, 95%CI -112.30 to -8.62, *P*=0.02; Figure 2H).

Mean number of injections The average number of injections of the naive group and the refractory group during the follow-up time were 1.69 *vs* 1.81 at month 6, 1.85 *vs* 1.79 at month 12, and 2.69 *vs* 2.21 at month 24, respectively. The total mean number of injections during the follow-up time between the naive group and the refractory group also showed no statistical difference (MD -0.08, 95%CI -0.38 to 0.22, *P*=0.61). In the subgroup analysis, the refractory group needed more injections than the naive group at month 6 (MD -0.23, 95%CI -0.37 to -0.09, *P*=0.001). However, the mean number of injections in refractory group was not significantly different from that in naive group at month 12 (MD -0.15, 95%CI -0.83 to 0.54, *P*=0.68) and month 24 (MD 0.19, 95%CI -1.01 to 1.38, *P*=0.76).

Intraoperative and Postoperative Complications The elevation of IOP showed no significant difference between the refractory group and the naive group (OR 0.47, 95%CI 0.20 to 1.13, *P*=0.09). The included eyes were mostly well controlled with topical hypotensive medication and only one eye needed glaucoma surgery which had pre-existing glaucoma and was already on IOP-lowering medication prior to first injection[15]. Additionally, there was no significant difference in eyes undergoing cataract surgery after dexamethasone implantation between the two groups during the follow-up time (OR 1.78, 95%CI 0.97 to 3.24, *P*=0.06). No other serious complications were reported.

Publication Bias Publication bias of the main outcomes was assessed by using funnel plot of the data. No significant publication bias was observed.

DISCUSSION

Outcomes Analysis To the best of our knowledge, this Meta-analysis was the first to assess the efficacy and safety of intravitreal dexamethasone implant in naive and refractory patients with DME. We reviewed ten comparative studies involving a total of 1000 DME eyes including 402 naive eyes and 598 refractory eyes that received dexamethasone implant.

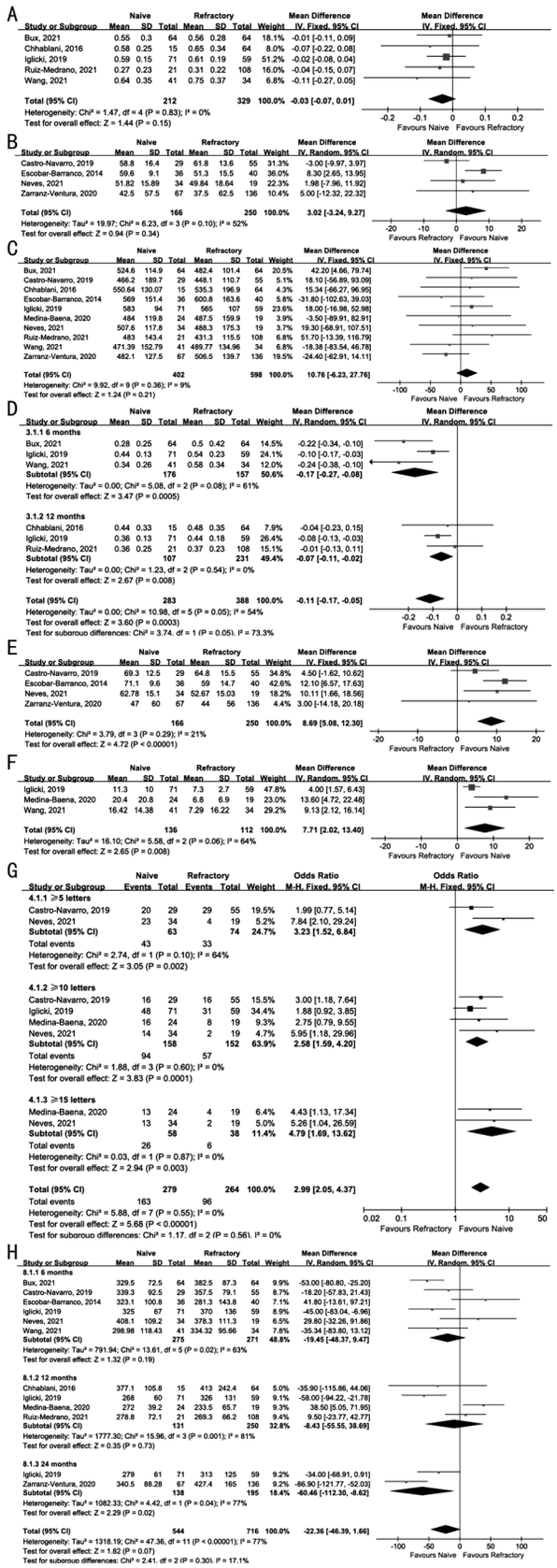

Figure 2 Forest plot Preoperative BCVA (logMAR, A), preoperative BCVA (ETDRS, B), preoperative CRT (C), postoperative BCVA (logMAR, D), postoperative BCVA (ETDRS, E), mean change of BCVA (ETDRS, F), BCVA gains of ≥5, ≥10 and ≥15 letters (ETDRS, G), and postoperative CRT (H) between the naive group and the refractory group with diabetic macular edema. BCVA: Best-corrected visual acuity; ETDRS: Early Treatment Diabetic Retinopathy Study; CRT: Central retinal thickness.

The included studies showed that both the naive group and the refractory group had improvement in visual acuity and decrease in foveal thickness. The pooled outcomes from this Meta-analysis indicated that the naive group could achieve significantly better visual outcomes than the refractory group. However, no significant difference was detected between the two groups in either postoperative CRT or overall mean number of injections. Additionally, intraoperative and postoperative complications including the elevation of IOP and cataract showed no significant differences between the two groups during the follow-up time.

Best-corrected Visual Acuity LogMAR and ETDRS eye charts were used in our included studies. Considering the differences of the two eye charts, we conducted analyses individually including the preoperative BCVA (logMAR), the preoperative BCVA (ETDRS), the postoperative BCVA (logMAR), the postoperative BCVA (ETDRS), the mean change of BCVA (ETDRS), the BCVA gains of ≥5, ≥10, and ≥15 letters (ETDRS) between the naive group and the refractory group with DME. This Meta-analysis showed compared to the refractory group, the naive group maintained better mean BCVA at months 6 and 12, and achieved greater improvement of BCVA change as well as more gains of BCVA letters. The proportions of patients gaining BCVA improvement ≥5, ≥10, and ≥15 letters were all significantly higher in the naive group than in the refractory group. These finding suggested naive DME patients could respond better in terms of visual acuity, consistent with previously published studies[15-18]. The functional outcome of refractory eyes was not as well as that of naive eyes, which might be related to the delayed initiation of dexamethasone treatment. The long-standing DME in eyes refractory to anti-VEGF injections frequently showed disruption of the inner segment and outer segment layer and the external limiting membrane[29-30]. Therefore, it adversely affected the functional results. Additionally, studies mentioned that in the case of failure of clinical response to anti-VEGF agents, a rapid switch to dexamethasone therapy might be necessary to prevent further irreversible damage to the retinal structures[25-26,31].

Central Retinal Thickness The natural history of the disease may be affected by the baseline demographic and clinical characteristics, such as age, sex and baseline CRT[32-35]. The included ten studies in our article controlled these confounding factors, and there was no statistically significant difference in preoperative CRT between the two groups. All the included studies reported both groups acquired significant decrease of postoperative CRT compared with preoperative CRT, indicating that dexamethasone implantation had effective significance in reducing edema in the two groups. While comparing the refractory group and naive group, no significant

difference was detected in postoperative CRT between the two groups. The results of this Meta-analysis showed that although a similar decrease of CRT (anatomical outcomes) was found in both refractory and naive groups, the visual acuity (functional outcomes) improved more in the naive group. As reported by previous studies, the differences between the functional and anatomical outcomes of DME suggested that retinal thinning might also be related with the atrophy of the outer layer of the retina that prevented visual improvement, which was more common in long-standing DME[31,36]. In addition, different subtypes of DME might also affect the reduction in CRT. Castro-Navarro *et al*[16] compared the impact of the subtypes of DME on the dexamethasone implant outcomes and found that the anatomical response in serous retinal detachment (SRD) subtype was significantly better than that observed in the Sponge-like diffuse retinal thickening (DRT) subtype, although the changes in BCVA were similar. These findings partially agreed with the study of Koytak *et al*[37] who found no significant difference between the two groups in BCVA, whereas the cystoid macular edema and SRD subtypes showed greater reduction in CRT than the DRT subtype. However, Chhablani *et al*[23] did not find any relationship between dexamethasone implant response and the subtypes of DME on OCT. The effect of different dexamethasone subtypes on the dexamethasone implant outcomes needs further research to confirm.

Intraoperative and Postoperative Complications The major concern for dexamethasone implant were the risks of ocular hypertension, cataract and ocular infection. Several large-scale studies have reported that 14% to 42% DME patients receiving dexamethasone implant had the risk of ocular hypertension and required topical hypotensive medication[26,31,38-41]. In the included ten studies comparing the refractory eyes with naive eyes, the incidence of ocular hypertension during the follow-up time (6 to 24mo) was 8% to 27% and all of them were well controlled with topical treatment with no significant difference detected between the refractory group and naive group. Among the included studies, four studies[15,23-24,26] mentioned dexamethasone implant was safe even in patients with ocular hypertension taking IOP-lowering medication at baseline. Four studies[15,18,24,27] reported multiple injections didn't have the cumulative effect on the IOP increase. These findings suggested that dexamethasone implant could be safely used in both refractory and naive eyes with DME, but with regular IOP check was mandatory. Additionally, the included studies suggested 0 to 20% DME patients underwent cataract surgery after dexamethasone implantation during the follow-up time (6 to 24mo) and no significant difference was detected between the refractory group and the naive group. No infectious endophthalmitis or other serious ocular complications, such as retinal detachment or anterior chamber migration of dexamethasone implant were reported. The dexamethasone injections were well tolerated in all included DME patients.

Mean Number of Injections At month 6, the included three studies reported that the mean number of injections was lower in naive *vs* refractory group and the subgroup analysis suggested the difference was statistically significant[16-17,25]. However, no significant difference was detected in the mean injection number between two groups either at month 12 or at month 24. Among them, two studies showed that the injections in the naive group was lower than that in the refractory group[15,24], whereas the other two studies indicated the opposite result that injections was higher in the naive group[26,28]. Data regarding the difference in the number of injections between naive and refractory DME eyes remains inconclusive and needs further investigation with larger sample size and longer follow-up time.

Limitations and Prospects A total of 9 retrospective studies and one prospective study involving 1000 eyes were eligible under our strict inclusion and exclusion criteria. The retrospective design was one of the limitations. Nevertheless, we carefully compared the selection bias and the influence of confounders among the included studies. No significant difference was detected in either preoperative BCVA or the preoperative CRT. Considering the difference of the follow-up time in each study, the subgroup analyses were performed. However, the difference of the duration or the subtypes of DME might affect the functional and anatomical outcomes after dexamethasone implantation. Further studies with subgroup analysis of subtypes of DME and more standard-designed studies with prospective randomized control are needed to provide more reliable evidence in evaluating the effect.

In conclusion, intravitreal dexamethasone implants for DME can improve anatomical and functional outcomes in both naive and refractory eyes and has a well-acceptable safety profile. Moreover, naive eyes maintained better visual outcomes than refractory eyes. This is the first Meta-analysis that compares the dexamethasone therapy in both refractory and naive DME eyes and provide further evidence of better visual response when used for naive eyes as first-line therapy.

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