

Visual outcomes of acute bacterial endophthalmitis treated with adjuvant intravitreal dexamethasone: A meta-analysis and systematic review

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Adjunctive treatment of bacterial endophthalmitis with intravitreal steroids is a topic of controversy among many ophthalmologists. The objective of this study is to evaluate the effects of intravitreal dexamethasone on the visual outcomes of patients with acute bacterial endophthalmitis through a systematic review and meta-analysis. A literature search of PubMed, Scopus, and Cochrane Library databases was performed to include studies on the visual outcomes of adjuvant intravitreal dexamethasone in patients with acute bacterial endophthalmitis. The review is based on the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) protocol. A total of 1545 articles met our search criteria and after further review, two randomized controlled trials and three retrospective case series were included in the final analysis. A total of 126 eyes were treated with intravitreal dexamethasone combined with antibiotics, and another 139 eyes were treated with antibiotics alone. All cases of endophthalmitis were post-operative or post-intravitreal injection, with pooled results demonstrating no visual benefit with supplementation of intravitreal dexamethasone. Our meta-analysis does not show any visual benefit from steroid supplementation and yet, considering a relatively small number of patients included in each study, larger randomized controlled trials are required to further clarify the role of steroids in the treatment of acute bacterial endophthalmitis.

Key words: Antibiotics, endophthalmitis, steroid

Endophthalmitis is a vision-threatening condition with varied causes, including surgical intervention, trauma, systemic infection, corneal ulcer, bleb-associated infection, and intravitreal injection. Early signs and symptoms of endophthalmitis include decreased vision, pain, red eye, hypopyon, and hazy media. Prompt treatment is necessary to reduce vision loss.^[1] The incidence of endophthalmitis remains low at 0.04% following cataract surgery.^[2] Standard treatment of endophthalmitis is based on the landmark Endophthalmitis Vitrectomy Study (EVS) published in 1995.^[1] The authors in the EVS study evaluated 420 patients diagnosed with endophthalmitis related to cataract surgery or secondary intraocular lens implantation and treated with systemic antibiotics and intravitreal amikacin and vancomycin. The authors concluded that the use of systemic antibiotics resulted in no difference in final visual acuity (VA). Additionally, patients who presented with light perception (LP) vision had improved visual outcomes with core vitrectomy rather than vitreous tap and injection alone.

All patients in this study received oral prednisone 30 mg twice daily for 5–10 days.^[1] The study, however, did not address the potential use of intravitreal steroids in the treatment of acute bacterial endophthalmitis following cataract surgery.

The mechanisms of intraocular damage in bacterial endophthalmitis are attributed to multiple etiologies, including

bacterial release of inflammatory toxins, bacterial enzymes causing damage to ocular tissues, and the host immune response.^[3] Thus, given the eye's robust inflammatory response in endophthalmitis, some investigators have supported the use of steroids in addition to antibiotics to enhance the final visual outcome. Additionally, steroids have been shown to play a role in treating bacterial meningitis by decreasing morbidity and mortality via stabilization of the blood–brain barrier, which is thought to have similar functions to the blood–retina barrier.^[4] Nevertheless, considering that the side effects of systemic steroids are extensive,^[5] intravitreal use of dexamethasone is sometimes a preferred option. At the same time, controversy remains over the potential benefits of this treatment modality. In the present study, we performed a meta-analysis of prior studies to evaluate the potential visual benefits of dexamethasone supplementation to intravitreal antibiotics in the treatment of acute bacterial endophthalmitis.

Methods

Data sources

Our study was conducted in accordance with the Preferred Reporting Items for Systematic review and

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Meta-Analysis (PRISMA) protocol [see PRISMA checklist in file 1]. A systematic search was conducted through the PubMed, Scopus, and Cochrane Library databases by using the search terms “endophthalmitis” AND “dexamethasone” from the date of database inception to December 2020. The Scopus database was accessed through the University of Texas Health Science Center San Antonio (UTHSCSA) library.

Selection criteria

Eligible articles included studies comparing final visual acuity outcomes of patients who received intravitreal antibiotics alone versus those given adjuvant intravitreal dexamethasone in the setting of postoperative or post-intravitreal injection endophthalmitis. The outcome evaluated in our study was final visual acuity, which was converted into logMAR acuities for quantitative analysis based on Snellen vision. Articles met inclusion criteria if the study included acute endophthalmitis cases due to intraocular surgery of any type (cornea, glaucoma, cataract, and vitrectomy) or post-intravitreal injection of medications. The type of intravitreal antibiotics used and the performance of the vitrectomy procedure were not considered as limiting factors for inclusion of studies in our meta-analysis. Excluded articles included reviews, animal experiments, case reports, and letters. Additional studies excluded, as detailed in supplementary Table 1, were those that included the use of systemic steroids, non-English articles, fungal endophthalmitis, chronic endophthalmitis, endophthalmitis due to other etiologies (trauma, suture removal, stitch abscess, endogenous, and corneal ulcer), lack of final visual acuity outcomes, or incomplete data required for statistical analysis.^[17-18,20,23-31] Two authors (CS and CZ) independently reviewed each title and/or abstract and eliminated studies based on the eligibility criteria. Subsequently, the studies were further narrowed by a review of the full-text articles. Discrepancies of eligible articles were discussed and resolved between the authors (CS and SB).

Data extraction

To avoid bias in the study, two authors (CS and CZ) independently extracted the raw data from the selected studies and a checklist was used to record the following information:

first author, year of publication, study location, study design, sample size, intravitreal antibiotics and dose, and follow-up time. The primary outcome was final visual acuity (VA). When the mean final visual acuity and standard deviation could not be obtained from the study, the authors reached out to the corresponding authors via email to obtain the raw data, for which Moisseiev *et al.* (2017) has kindly provided their raw data for our data analysis. Etiologies of endophthalmitis other than post-operative or post-intravitreal injection were excluded from the analysis.^[6] Considering that the selected studies had discrepancy in chart conversion of visual acuities of count finger or worse, the authors decided to minimize bias by normalizing visual outcomes of these studies with the following logMAR equivalents: count fingers (CF) as 1.8, hand motion (HM) as 2.3, light perception (LP) as 2.8, and no light perception (NLP) as 3.^[7] Any disagreements were resolved through discussion between the authors (SB and CS).

Quality assessment

The risk of bias from the included randomized controlled studies was assessed by two authors by using the Cochrane risk of bias Table in the following seven domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other potential sources of bias.^[8] Pending the degree of adequacy in each domain, the risk of bias was judged as low (adequate), high (inadequate), or unclear (not enough information available). Egger's and Begg's tests were not carried out due to a relatively small number of selected studies.

Statistical analysis

RevMan 5.4 software was used for all our statistical analyses, including calculation of inverse variance and 95% confidence interval of final visual acuity (VA) by using the random-effect model. The same software was also used for graphing the forest plot and assessment of statistical heterogeneity by using the Chi-square test.

Table 1: Characteristics of studies included in the meta-analysis

First Author, Year	Location, Type of Study	<i>n</i>		Antibiotics ± dexamethasone	Primary outcome
		Study	Control		
Manning <i>et al.</i> , ^[9] 2018	Netherlands, Randomized controlled trial	81	86	Vancomycin 0.2 mg/0.1 mL Gentamicin 0.05 mg/0.1 mL Dexamethasone 400 µg/0.1 mL	BCVA at 12 months
Gan <i>et al.</i> , ^[10] 2005	Netherlands, Randomized controlled trial	13	16	Vancomycin 0.2 mg/0.1 mL Gentamicin 0.05 mg/0.1 mL Dexamethasone 400 µg/0.1 mL	VA at 3 months, 12 months
Miller <i>et al.</i> , ^[11] 2004	USA, Retrospective case series	10	2	Vancomycin 1.0 mg/0.1 mL Ceftazidime 2.25 mg/0.1 mL Amikacin 0.4 mg/0.1 mL Gentamicin 0.1 mg/0.1 mL Tobramycin 0.1 mg/0.1 mL Dexamethasone 400 µg/0.1 mL	VA at 6 months and antibiotic sensitivities
Eifrig <i>et al.</i> , ^[12] 2003	USA, Retrospective case series	7	3	Vancomycin Ceftazidime Gentamicin Tobramycin Dexamethasone (no doses provided)	Final VA and rate of enucleation or evisceration
Moisseiev <i>et al.</i> , ^[6] 2017	USA, Retrospective chart review	15	32	Vancomycin 1.0 mg/0.1 mL Ceftazidime 2.25 mg/0.1 mL Dexamethasone 400 µg/0.1 mL	Improvement in VA and final VA
Total		126	139		

Results

Overall characteristics of included studies

A total of 1545 articles met our initial search criteria, and after further review of the inclusion/exclusion criteria, two randomized clinical trials and three retrospective case series were selected for our final analysis.^[6,9-12] A flowchart illustrating our literature selection process is displayed in Fig. 1 Two randomized studies specifically analyzed cases of endophthalmitis following cataract surgery, 167 cases by Manning *et al.* (2018), and 29 cases by Gan *et al.* (2005).^[9,10] The other studies included endophthalmitis due to various etiologies; thus, we extracted the data pertaining to post-surgical and post-intravitreal injection etiologies only. Thus, our meta-analysis included a total of 265 endophthalmitis cases, where 126 patients received treatment with dexamethasone (400 µg/0.1 mL) plus antibiotics, while 139 cases received intravitreal antibiotics alone [refer to Table 1 for details]. The dosage of dexamethasone was the same in all studies. However, one study (Eifrig *et al.* 2003) did not specify the dose. As summarized in Table 1, various antibiotics were used, which included vancomycin, gentamicin, ceftazidime, amikacin, and tobramycin.^[12] The primary outcome among all studies included final visual acuity.

Bias assessment

The included randomized controlled studies used random allocation of study participants into the intervention and control groups. The article by Gan *et al.* (2005) does not state whether a blinding process was used in the study, whereas the study by Manning *et al.* (2018) employed a double-blind approach.^[9,10] Gan’s study had to be terminated early as the dexamethasone formulation became unavailable during the investigation. Overall, the authors of this review believe Manning’s study to be at low risk of publication bias, whereas Gan’s study has unclear risk of publication bias as listed in

Fig. 2. We further lessened the risk of bias across studies by normalizing the discrepancy in logMAR conversion values for visual acuities of count finger (CF) or worse.

Regarding the non-randomized studies, the groups receiving steroids in two studies was relatively small (n = 2 in Miller’s study, and n = 3 in Eifrig’s study) compared to the antibiotic group (n = 10 in Miller’s study, and n = 7 in Eifrig’s study). Moreover, the causative etiology in these two studies was due to specific bacteria that may have led to worse outcomes (*Streptococcus pneumoniae* and *Pseudomonas aeruginosa* in Miller’s and Eifrig’s study, respectively). Lastly, in Moisseiev’s study, a majority of patients had preexisting pathology that limited good vision prior to the endophthalmitis event.

Study outcomes and pooled results

Of the randomized controlled studies, Manning *et al.* (2018) reported a statistically insignificant difference in final VA between the dexamethasone and placebo groups ($P = 0.90$), whereas Gan *et al.* (2005) reported a trend toward better visual outcomes at 3 and 12 months in the dexamethasone group without reaching statistical significance (3 months: $P = 0.055$, 12 months: $P = 0.080$).^[9,10] When using our own logMAR conversion for poor visual acuities, the mean BCVA at 12 months in Manning’s study was 0.65 ± 1.03 for the dexamethasone group and 0.74 ± 1.1 for the control group. For Gan’s study, the mean LogMAR acuities were 0.77 ± 0.70 and 1.27 ± 1.04 for the dexamethasone and control group, respectively. For both studies, the control group included antibiotic supplementation along with a placebo injection. As illustrated in Fig. 3, the inverse variance of the mean difference was -0.09 for Manning *et al.* (2018) and -0.50 for Gan *et al.* (2005), which is roughly equivalent to 5 and 25 Early Treatment Diabetic Retinopathy Study (ETDRS) letters, respectively.^[9,10,13] This difference, however, did not reach a statistical significance ($P = 0.27$)

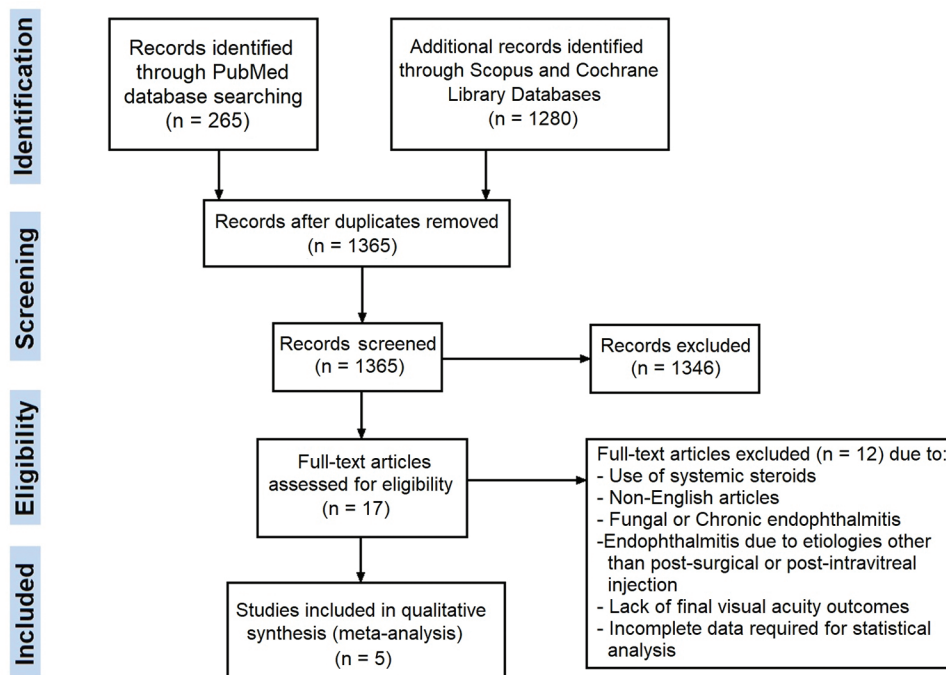


Figure 1: PRISMA flow diagram of the literature review

as demonstrated in Fig. 3A forest plot. Similarly, inclusion of the nonrandomized (Miller *et al.* 2004, Eifrig *et al.* 2003, and Moisseiev *et al.* 2017) studies did not change the conclusion of our meta-analysis as there was no significant difference between the dexamethasone-supplemented group compared to antibiotics alone ($P = 0.87$) in Fig. 3B.^[6,11,12]

It is worth noting that for Manning *et al.* (2018) study, cultures that grew gram-negative bacteria or gram-positive organisms other than coagulase-negative staphylococci were more likely to lead to light perception vision or evisceration.^[9] Meanwhile, those infected by coagulase-negative staphylococci were more likely to have better visual outcomes, with 93% of visual acuities ranging from logMAR 0.0 to logMAR 0.7 (Snellen equivalent of 20/20 to 20/100). Gan *et al.* 2005, on the other hand, reports that most patients grew *S. epidermidis* with final visual acuity ranging from logMAR 0.15 to logMAR 2.8 (Snellen equivalent of 20/30 to LP).^[10]

Subgroup analysis for pars plana vitrectomy

To understand the role of dexamethasone in patients undergoing pars plana vitrectomy (PPV), we performed a subgroup analysis of the Eifrig *et al.* (2003), Miller *et al.* (2004), and Gan *et al.* (2005) articles, where a number of patients received PPV.^[10,11,12] However, due to a small number of patients undergoing PPV in some of the selected articles, aggregate data meta-analysis could not be performed. Instead, we conducted an individual participant meta-analysis by compiling data from these three articles. Our analysis demonstrates that visual acuity (sample size, Mean ± SD) was not significantly ($P = 0.28$) different between dexamethasone (14, 2.13 ± 1.17) and the control (9, 1.83 ± 1.18) groups. Similarly, subgroup analysis of the results from Gan *et al.* (2005), Manning *et al.* (2018), and Moisseiev *et al.* (2017) demonstrates that

supplementation with dexamethasone does not affect the final visual outcome ($P = 0.99$) in patients that did not receive PPV [Fig. 4].^[6,9,10] Of note, none of the patients in Manning *et al.* (2018) and Moisseiev *et al.* (2017) studies had undergone PPV.^[6,9]

Discussion

Endophthalmitis due to bacterial infection leads to the release of toxins along with the host inflammatory response, which could irreversibly damage the retina.^[3] Thus, some investigators have supported the use of steroids to limit this response and improve visual outcomes in endophthalmitis. Nevertheless, controversy regarding the use of intravitreal steroids exists due to concerns of vulnerability to fungal infections, sequestration of neutrophils necessary for eliminating infection, retinal toxicity, and its effects on the pharmacokinetics of intravitreal antibiotics.^[14] Our meta-analysis shows that final visual outcomes were not improved in acute bacterial endophthalmitis patients receiving intravitreal dexamethasone. However, the limited number of samples and studies suggests the need for more prospective randomized studies to provide strong and convincing evidence of any potential effects, whether harmful or beneficial.

In a study by Meredith *et al.* (1996),^[15] rabbit models with *Staphylococcus aureus* endophthalmitis demonstrated worse inflammatory scores, more corneal opacities, and retinal necrosis when treated with intraocular dexamethasone. Another animal study by Kim *et al.* (1996)^[16] revealed no beneficial effect when adding intravitreal dexamethasone to ciprofloxacin in rabbits with *Pseudomonas aeruginosa* endophthalmitis treated at 6 and 12 h, possibly due to impairment of the bactericidal effects of the antibiotics. At

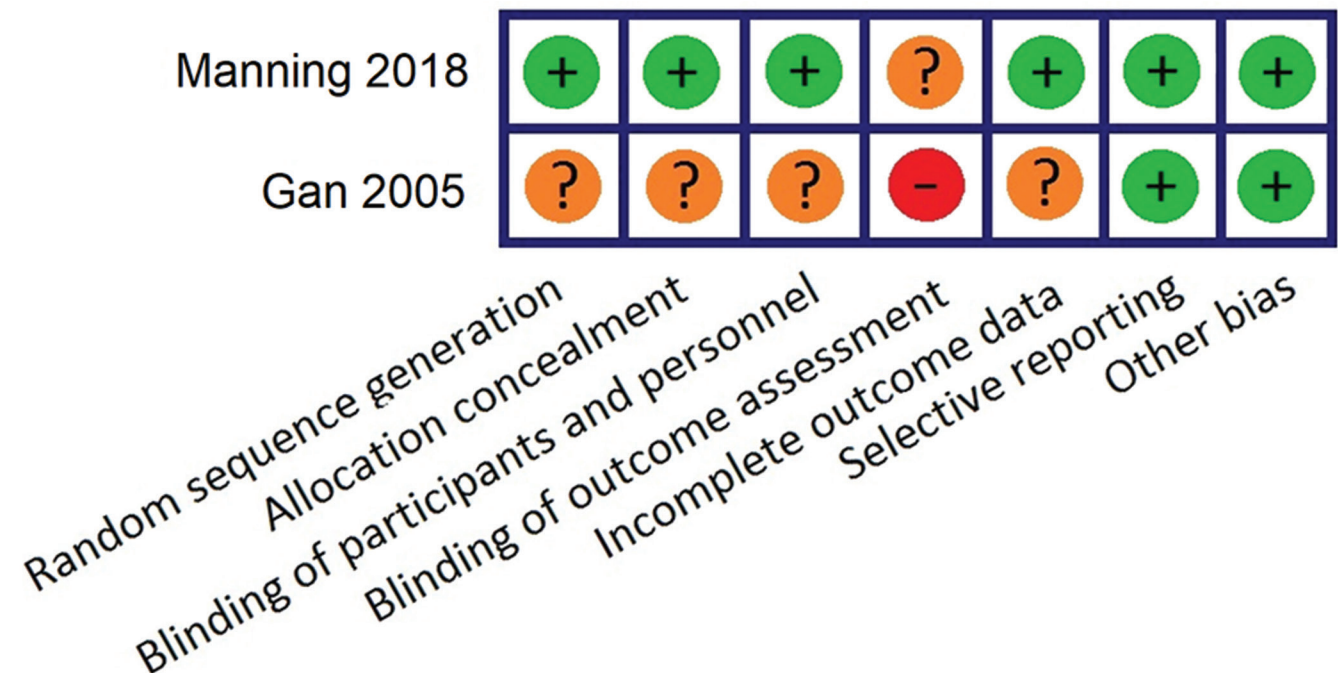


Figure 2: Methodological quality of studies demonstrated by Cochrane risk of bias table as low risk of bias (+ symbol), high risk of bias (- symbol), or unclear risk of bias (? Symbol)

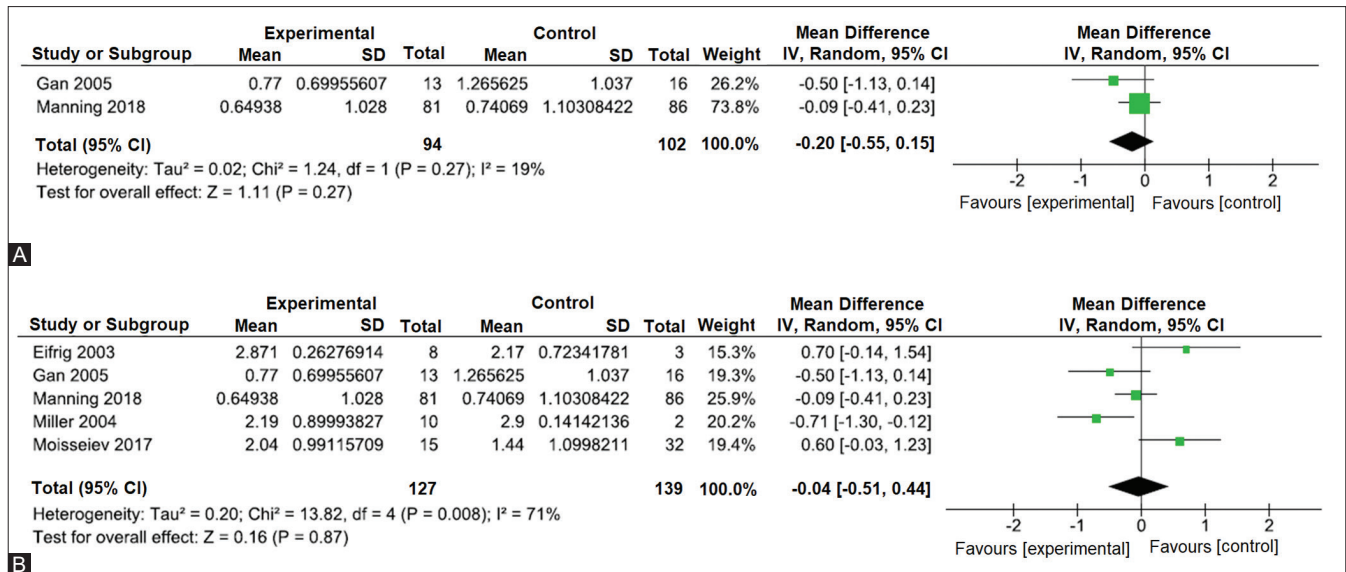


Figure 3: Forest plot showing the weighted mean difference of best-corrected visual acuity (BCVA) between endophthalmitis patients that received either dexamethasone [experimental] or placebo [control]. Note that values smaller than zero favor dexamethasone supplementation to intravitreal antibiotics, whereas values larger than zero favor injection of antibiotics with placebo. Panel A represents randomized studies. Panel B represents all studies (randomized and retrospective). [SD: standard deviation, IV: inverse variance, Random: Random-effect model, CI: confidence interval]

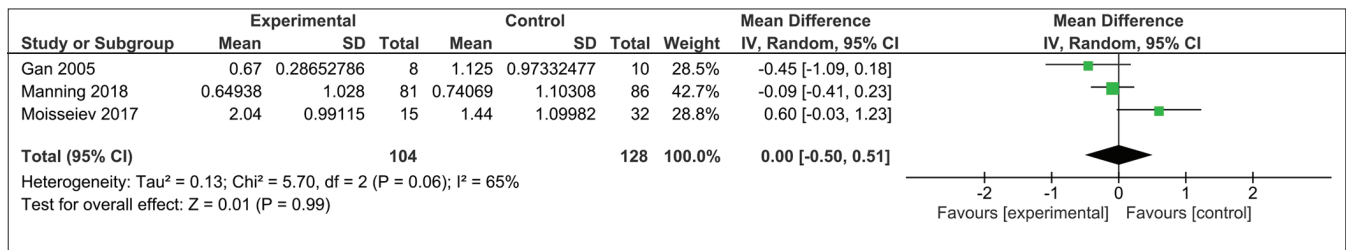


Figure 4: Forest plot of the weighted mean difference of best-corrected visual acuity (BCVA) for the subgroup of patients that did not receive Pars Plana Vitrectomy. No statistical significance is observed between the dexamethasone [experimental] or placebo [control] groups (P = 0.99). [SD: standard deviation, IV: inverse variance, Random: Random-effect model, CI: confidence interval]

the same time, while some studies conclude that intravitreal steroids provide no benefit in either inflammatory or visual outcomes,^[17] there are also other studies that provide evidence of added benefit from steroid supplementation. A study by Das *et al.* (1999) suggested intravitreal dexamethasone provides benefits in early reduction of inflammation but no changes in visual acuity in the setting of exogenous endophthalmitis.^[18] Thus, these controversial results necessitate a systematic review of current literature to determine if the clinical use of intravitreal dexamethasone has any potential benefits in the treatment of patients with acute bacterial endophthalmitis. To address this question, our meta-analysis demonstrated that patients treated with dexamethasone did not have better visual outcomes.

To the best of our knowledge, currently, there is only one existing meta-analysis evaluating the effects of adjunctive steroids in the setting of acute endophthalmitis conducted by Kim *et al.* (2017).^[19] The authors of Kim *et al.*'s (2017) review concluded that the available evidence was insufficient to suggest the effectiveness of adjunctive dexamethasone.^[19] Notable differences between Kim *et al.*'s (2017) and our current meta-analysis include 1) exclusion of Albrecht

et al. (2011) BCVA study due to grouped visual outcomes and inability to calculate mean final visual acuity with standard deviation; 2) exclusion of Das *et al.* (1999) study due to lack of final visual acuities (functional success was recorded if visual acuity was at least 6/120); 3) inclusion of Manning *et al.* (2018) randomized study; and 4) inclusion of retrospective studies (Eifrig *et al.* 2003, Miller *et al.* 2004).^[9,11,12,18-20] In addition, in our meta-analysis, we analyzed randomized studies alone versus all studies combined (randomized and retrospective). The former approach reduces the risk of bias, whereas the latter approach has a larger sample size with increased power of the analysis. However, both approaches yielded a similar outcome, where there was no statistical difference in visual outcome after supplementation of intravitreal dexamethasone. Lastly, our meta-analysis includes subgroup analysis of PPV patients, demonstrating no visual benefit from dexamethasone supplementation. Indeed, a similar conclusion was drawn by Das *et al.* (1999) randomized study, where dexamethasone supplementation did not affect the final visual outcome in patients with bacterial endophthalmitis treated with vitrectomy and intravitreal antibiotics.^[18] However, this study was excluded from our meta-analysis due to the lack of mean and standard deviation data for the visual acuity.

It is worth noting that there is growing discussion among the retina community regarding a change in practice patterns and treating endophthalmitis with early vitrectomy. A recently published study by Soliman *et al.* (2019)^[21] explored international practice patterns for acute endophthalmitis secondary to intraocular surgery or intravitreal injections. In this retrospective study, a total of 57 retina specialists from 28 countries took part, totaling 253 cases of acute endophthalmitis. They concluded that as a practice pattern, early PPV within 1 week of presentation was performed frequently (74.3%) regardless of the presenting visual acuity. A follow-up study by this group then analyzed the visual outcomes of patients receiving intravitreal antibiotics alone versus early PPV.^[22] Their final conclusion was that visual outcomes were similar between the two groups. The most common gauges used were 23-G (63%), followed by 25 and 20-G vitrectors (23.5% and 13.4%, respectively). Although this was a necessary study exploring outcomes of endophthalmitis with smaller gauge vitrectors and modernized vitrectomy systems, this research provided evidence that early vitrectomy does not provide better visual outcomes. We believe this published report by Soliman *et al.* (2021) is proof that we may need other avenues to more successfully treat endophthalmitis patients.^[22]

Conclusion

Our meta-analysis demonstrates that intravitreal dexamethasone does not provide additional visual benefits to endophthalmitis patients. Nevertheless, considering a relatively small number of patients included in the selected studies, larger randomized studies are needed to further clarify the role of steroids in the treatment of acute bacterial endophthalmitis.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: Characteristics of excluded studies and reason for exclusion

First Author, Year	Location, Type of Study	Reason for Exclusion
Conrady <i>et al.</i> , ^[23] 2020	USA, Retrospective Analysis	Nearly all patients (>90%) received intravitreal dexamethasone, and authors do not distinguish data from patients who did and did not receive dexamethasone. Additionally, 19% of patients received oral steroids
Yannuzzi <i>et al.</i> , ^[24] 2017	USA, Retrospective case series	Does not stratify visual outcomes between subjects who received intravitreal dexamethasone and those who did not.
Jackson <i>et al.</i> , ^[25] 2014	United Kingdom, Systematic Review	Includes endogenous endophthalmitis
Lindstedt <i>et al.</i> , ^[26] 2014	Netherlands, Randomized controlled trial	Does not stratify results between subjects who received dexamethasone vs no dexamethasone
Jacobs <i>et al.</i> , ^[27] 2012	USA, Retrospective case series	Includes chronic endophthalmitis due to bleb-associated endophthalmitis (BAE).
Albrecht <i>et al.</i> , ^[20] 2011	UK, Randomized controlled trial	Reports visual acuities as grouped visual outcomes or as lines of improvement. Unable to calculate the mean visual acuities with standard deviation from the provided data.
Hall <i>et al.</i> , ^[17] 2008	USA, Retrospective case series	Some subjects received oral steroids, does not stratify results based on whether or not patients received oral steroids.
Rehak <i>et al.</i> , ^[28] 2007	Germany, Retrospective analysis	All pts received intravitreal dexamethasone and some received systemic steroids. All also underwent vitrectomy
Yoder <i>et al.</i> , ^[29] 2004	USA, Retrospective case series	69% of cases (11/16) were delayed onset.
Shah <i>et al.</i> , ^[30] 2000	USA, Retrospective comparative trial	Does not provide standard deviation of visual acuities between the dexamethasone and no dexamethasone groups.
Majji <i>et al.</i> , ^[31] 1999	India, Retrospective analysis	Study includes fungal endophthalmitis only
Das <i>et al.</i> , ^[18] 1999	India, Prospective randomized trial	Does not provide mean visual acuity with standard deviation. Defines functional success as visual acuity of at least 6/120.