Risk of intraocular pressure elevation associated with triamcinolone acetonide administration via different routes in macular edema: a systematic review and network meta-analysis of randomized controlled trials

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Abstract

Aims: Despite their overall favourable safety profile, the intraocular pressure increases after any routes of triamcinolone acetonide application are not rare. We designed a systematic review and network meta-analysis to compare risk of IOP elevation among TA for different routes of administration used by patients diagnosed with macular edema. Methods: We obtained data from the PubMed, MEDLINE, Embase, and Cochrane Library. We performed random-effects model and consistency model network meta-analyses to summarize the evidence. The Bayesian approach was used for direct and indirect comparisons, and the treatments were ranked by the surface under the cumulative ranking curve. The study was registered with PROSPERO, CRD42022366513 Results: Sixteen studies were included in the network meta-analysis. There was a significant difference in IOP between IVTA and STiTA (MD, 1.67 [95% CrI, 0.25, 3.15]) at the 12th week. At the 24th week, compared with the placebo group, IVTA, SCTA and STiTA had statistically significant effect on IOP (MD, 1.35 [95% CrI, 0.23, 2.30], 2.42 [95% CrI, 4.53, 0.19], and 1.31 [95% CrI, 2.49, 0.02]). The probabilities of rankings and SUCRA showed that IVTA and SCTA were generally considered the higher risk of IOP elevation than the other routes of injection therapy. In addition, RITA was shown to be safer. Conclusion: IVTA and SCTA appeared as the least safe routes of injection therapy for ME, which being more prone to increase the risk of IOP elevation. RITA demonstrated a safer profile. However, more high-quality randomized controlled trials will be necessary to further confirm this.

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Conclusion: IVTA and SCTA appeared as the least safe routes of injection therapy for ME, which being more prone to increase the risk of IOP elevation. RITA demonstrated a safer profile. However, more high-quality randomized controlled trials will be necessary to further confirm this.

KEYWORDS

triamcinolone acetonide, macular edema, network meta-analysis, intraocular pressure, Bayesian framework

1 INTRODUCTION

Macular edema (ME) is secondary to many different ocular and systemic disease processes and is defined as the accumulation of intra and/or subretinal fluid in the macular region.[1-2] It can occur in several retinal conditions, such as diabetic retinopathy (DR), agerelated macular degeneration (AMD), retinal vascular disorders, and many other ocular and systemic diseases resulting in visual impairment.[3-4]At present, anti-vascular endothelial growth factor (anti-VEGF) drugs, glucocorticoids, and laser photocoagulation alone or in combination are mostly used to reconstruct the blood-retinal barrier in patients with macular edema in clinical practice.[5-6] In their midst, glucocorticoids have both angiostatic and anti-inflammatory effects, so they have been recommended by guidelines for intravitreal injection or implantation as a second-line therapy for diabetic retinal vein occlusion (RVO) and diabetic macular edema (DME).[7-8] Sometimes glucocorticoids are even a first-line treatment, e.g. patients with high-risk cardiovascular disease, poor compliance, severe edema (>500 mm), patients with pseudolenses, patients scheduled for cataract surgery, and patients with a history of vitrectomy.[8]

Glucocorticoids have long been used in the treatment of macular edema; systemic glucocorticoids are effective but are associated with adverse events, including adrenal insuffciency, Cushing's syndrome, diabetes, cardiovascular disease, osteoporosis, and immunosuppression. Local application of glucocorticoids results in much lower systemic concentrations of the drug and reduces the incidence of adverse events associated with systemic therapy. However, these come with their own set of risks, most commonly an increased risk of cataracts and elevations in intraocular pressure (IOP).[9] In comparison with other glucocorticoids, because triamcinolone acetonide (TA) is a minimally water-soluble steroid in a suspension form, it can maintain a long-term intraocular concentration for an expanded period of time. TA has been reported to be present in the eye for as long as six months after the injection, and it is present in measurable concentrations up to 1.5 years after intravitreal injections of triamcinolone acetonide (IVTA).[10] The incidence of IOP increase after IVTA may be as high as 83.3% in the literature.[11] The most recent meta-analysis indicated that sub-Tenon's capsule injection of TA injection has a comparable effect to the intravitreal injection of TA injection and carries a lower risk of intraocular complications.[12]

At present, there is no comparison of the safety of triamcinolone acetonide in the treatment of macular edema with different routes of administration, and no recommendations are provided. Therefore, we conducted this systematic review and network meta-analysis (NMAs) to comprehensively evaluate and compare the safety of triamcinolone acetonide administration via different routes in patients with macular edema.

2 METHODS

We registered our protocol on PROSPERO (CRD42022366513) and the study adheres to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines for NMAs (Supplementary Table 1).[13]

2.1 Search strategy and eligibility criteria

We comprehensively searched PubMed (up to April 24, 2022), Embase (using the OVID platform: from 1974 to January 2022), MEDLINE (OVID MEDLINE (R):from 1946 to Present), and the Cochrane Library (CENTRAL) from inception to the first quarter of 2022. We searched ClinicalTrials.gov and the reference lists of key reviews and meta-analyses to supplement the identified citations. Searches included terms relating to triamcinolone acetonide, macular edema, and randomized controlled trials (Supplementary Table 2).

2.2 Study selection

Inclusion criteria were defined using the 'Patients, interventions, comparators, outcomes, study designs, timeframe' (PICOST) framework, as follows: 1) Participants: ME Patients, age [?]18; 2) Interventions/Comparisons: Triamcinolone acetonide of different routes of administration, including injection triamcinolone acetonide (IVTA), orbital floor triamcinolone acetonide (OFTA), retrobulbar injections triamcinolone acetonide (RITA), suprachoroidal triamcinolone acetonide (SCTA), Sub-Tenon's infusion of triamcinolone acetonide (STiTA) or placebo; All treatments should be given alone and not in combination with any other routes of administration mentioned for TA in interventions. 3) Outcomes: Intraocular pressure (IOP) change from baseline; 4) Study Design: The language of the published or unpublished randomized controlled trials (RCTs) was limited to English or Chinese. 5) Timeframe: The duration of treatment should be longer than twelve weeks.

The exclusion criteria were as follows: 1) Animal experiments; 2) Including participants with pregnant or lactating woman; 3) Studies published in a language other than English or Chinese; 4) Published as abstract only; 5) Published as duplicate data; 6)Data could not be extracted; 7) Studies under the risk of poor-quality (e.g. retracted, without random sequence generation or allocation concealment).

2.3 Screening process, data extraction

For each eligible study, two independent reviewers (XKL and YJY) independently used EndNote X9 (Clarivate Analytics, Philadelphia, PA, USA) to screen titles and abstracts based on the inclusion and exclusion criteria, and any discrepancies were resolved by discussion with a third reviewer (NS) when necessary. We extracted the data including the baseline on included study characteristics (register number/trial name, year of publication, country or countries, funding, duration), population (disease, sample size by number of eyes, patient demographics), intervention description (route of administration, dose) and outcome (IOP). For IOP, the mean and standard deviation after intervention of each study were extracted.

Quality assessment, the certainty of evidence

Two independent reviewers (XKL and YJY) independently used ROB 2 by RevMan version 6.1 to independently assess the risk of bias of all included studies,[14] and the discrepancies were resolved by discussion with a third reviewer (NS) when necessary. The tool is used to determine the risk of bias in randomized trials, including five types of bias risk: risk of bias arising from the randomization process; risk of bias due to deviations from the intended interventions; risk of bias due to missing outcome data; risk of bias in measurement of the outcome; and risk of bias in selection of the reported result. Each risk of bias evaluation dimension had three classifications: low risk of bias, some concerns, or high risk of bias.

2.5 The certainty of evidence

Two independent reviewers (XKL and YJY) independently used the GRADE approach for network meta-analysis to assess the certainty of the evidence.[15-17] Each outcome had four classifications: high, moderate, low, or very low, based on consideration of the risk of bias, incoherence, inconsistency, indirectness, intransitivity, publication bias, and imprecision. Discrepancies were resolved by discussion with a third reviewer (NS) if necessary.

2.6 Statistical analysis

Treatment nodes included different routes of administration. We drew network plots with the *multinma*package in R (version 4.1.3).[18] We conducted the network meta-analysis using a random-effects model and consistency model. This analysis was performed with the Bayesian framework.[19] We chose mean differences (MD) and 95% credible intervals (CrI) for intraocular pressure. We used the Markov chain Monte Carlo method, which built up four chains, and set 80,000 iterations after an initial burn-in of 20,000 and a thinning of one. We assessed local incoherence and obtained indirect estimates using node splitting models.[20] We calculated the surface under the cumulative ranking curve (SUCRA) to rank different administration routes.[21] SUCRA is a percentage interpreted as the probability of a treatment that is the safest without uncertainty on the outcome, which is equal to 1 or 0 when the treatment is certain to be the best or the worst respectively. We performed multiple sensitivity analyses: 1) exclusion of studies without diabetes mellitus; 2) exclusion of studies with fewer than 20 participants; and 3) exclusion of studies with combined laser therapy. We conducted the above statistical analyses using the *gemtc*package in R (Version 4.1.3).

3 RESULTS

3.1 Characteristics of eligible studies

The literature search flow chart is shown in Figure 1. After screening 1138 articles and registered clinical trials, a total of 16 studies between 2005 and 2022 were included in the meta-analysis according to predetermined criteria, involving 834 eyes (575 patients).[22-37] The main characteristics of the selected studies are collated in Table 1. Among the 16 RCTs, 1 studie was registered and 15 studies were published in English. The diseases involved were diabetic macular edema (11 RCTs), diffuse diabetic macular edema (DDME) (2 RCTs), refractory diabetic macular edema (RDME) (1 RCT), and macular edema associated with branch retinal vein occlusion (BRVO-ME) (2 RCTs). Of the included studies, 13 were two-arm studies and 3 were three-arm studies. Subsequently, we divided interventions into a placebo group and the following 4 groups: IVTA, RITA, SCTA, and STiTA. Fourteen RCTs involved IVTA compared with other routes of TA administration (the retrieved routes of administration contained RITA, SCTA, and STiTA); 6 RCTs compared TA to placebo (the retrieved routes of TA administration contained IVTA, STiTA and RITA); and 3 RCTs both the intervention group and the control group received intravitreal bevacizumab, which was a full-length humanized monoclonal antibody against vascular permeability-associated endothelial growth factor. The baseline characteristics included the overall proportion of men, 52.01%; age, ranging from 39.5 to 76.67 years; and length of follow-up, from 12 to 24 weeks. In addition, none of the trials were funded by pharmaceutical companies.

3.2 Risk of bias of included studies

The overall risk of bias was not high. The key limitations were the lack of information on random methods and the low level of reported blinding of participants because the TA was administered by injection and could not be blinded. The assessment of the risk of bias in the included studies is shown in Figure 2. Of the 16 studies, for selection bias, 4 studies (25%) were at low risk of bias in the randomisation process, 4 studies (25%) were at low risk of bias in deviations from the intended interventions, and 16 trials (100%) were at low risk in missing outcome data. The outcome indicator (IOP) in this analysis was objective and was not influenced by evaluators, so the 16 studies (100%) were at low risk for measurement of the outcome and selection of the reported result. Overall, three studies (19%) had a low risk of bias, thirteen studies (81%) had some concerns of bias, and no trials had a high risk of bias. A quantitative synthesis of the evidence through a network meta-analysis was deemed appropriate given the comparability in study design, outcome measures, patients involved, and inclusion and exclusion criteria. Homogeneity and consistency assumptions were confirmed.

3.3 Results of network meta-analysis

The network plots of each outcome are presented in Figure 3 (A, B and C), presenting the results and

quality of evidence for IOP at the 4^{th} week, the 12^{th} week , and the 24^{th} week of triamcinolone acetonide treatment by different routes of administration. Heterogeneity of the network meta-analysis is also shown in the appendix(Supplementary Figure 1-3).

3.4 IOP

Eighteen RCTs including 834 eyes (575 patients) reported IOP after triamcinolone therapy with different routes of administration. Intervention nodes included in this network meta-analysis were intravitreal injection triamcinolone, retrobulbar injections triamcinolone, sub-Tenon's infusion of triamcinolone, suprachoroidal triamcinolone, and placebo. The GRADE quality for network meta-analysis is shown in Figure 4. Detailed data are shown in the appendix (Supplementary Table 4-6). In pairwise comparisons within the network of these RCTs: at the 4th week, there was no statistically significant effect on IOP between triamcinolone acetonide by different routes of administration and placebo. At the 12th week, there was a significant difference in IOP between IVTA and STiTA (MD, 1.67 [95% CrI, 0.25, 3.15], Figure 4B), whereas other pairwise comparisons were not different from each other. At the 24th week, compared with the placebo group, IVTA, SCTA and STiTA had statistically significant effects on IOP (MD, 1.35 [95% CrI, 0.23, 2.30], 2.42 [95% CrI, 4.53, 0.19], and 1.31 [95% CrI, 2.49, 0.02], Figure 4C).

3.5Rankings and sucra

The rank probabilities of different routes of administration for triamcinolone acetonide and placebo are shown in Figure 5. The rank diagrams show that the probabilities of RITA being the safest routes of administration were 35.50% (the 4th week), 57.80% (the 12th week), and 65.60% (the 24th week). The rank diagrams show that the probabilities of IVTA being among the top safety routes of administration are both 0.00% at the 4th week, the 12th week, and the 24th week. The SUCRA values of triamcinolone acetonide treatment by different routes of administration were RITA (0.7041) > STiTA (0.5865) > PLA (0.5431) > SCTA (0.5149) > IVTA (0.1513) at the 4th week, RITA (0.8029) > STiTA (0.6380) > PLA (0.5973) > SCTA (0.3691) > IVTA (0.0926) at the 12th week, and RITA (0.8726) > PLA (0.8221)> STiTA (0.3704) > IVTA (0.3565) > SCTA (0.0783) at the 24th week. Detailed data are shown in Supplementary Tables 7-9.

3.6 Sensitivity analyses

The sensitivity analyses are presented in Supplementary Tables 10-15. The sensitivity analyses were consistent with the results of the main analysis. The results did not change when the analyses for all interventions on the outcomes excluded studies with non diabetic macular edema, and excluded studies with fewer than 20 eyes.

4DISCUSSION

Treatment choice should not be based only on the effectiveness of the treatment, but also on the management of adverse events and long-term tolerability. This systematic review and network meta-analysis involving 16 studies that enrolled 834 eyes (575 patients) provided moderate certainty evidence, which investigated the safety of triamcinolone acetonide by different routes of administration and placebo treatment for ME. Intraocular pressure was selected as an outcome index for safety evaluation. This paper had comparative data from randomized trials with objective outcome measures that were essential to understand which routes of injection with triamcinolone acetonide offer the optimal balance of efficacy and safety in the management of these patients. The network meta-analysis found that, in early treatment (in 4 weeks), there was no significant difference in the risk of IOP between triamcinolone acetonide by different routes of administration and placebo. Nevertheless, although not statistically significant, our results indicate that RITA is the safest route of injection and IVTA ranked first in the risk of IOP. With the extension of treatment time, IVTA, SCTA and STiTA increased the risk of IOP elevation. This risk did differ significantly between them and placebo. According to the ranking and SUCRA values, it was found that compared to the other routes of injection, the incidence of IOP with RITA was even lower.

Despite several attempts to establish its route of administration, only IVTA has been used as a second-line therapy for DME and RVO by guidelines.[38-40] However, triamcinolone acetonide is not an approved

medication for DME. It has been used off-label. According to the statistical results, IVTA may be associated with a have the higher risk of IOP from 4 to 36 weeks of follow-up. This effect seems to persist even in comparison with placebo or other routes of administration. For instance, a randomized controlled trial showed that the IOP change from baseline was significantly higher in the IVT group than in the STiTA group after injection.[33] Two RCTs found that the addition of IVTA + IVB significantly increased the risk of IOP at the end of the study period compared with IVB.[30,32] From a head-to-head trial, IVTA increased the risk of IOP compared with placebo.[26] Our results are in accordance with previous reports. which are consistent with the comparison of the network meta-analysis. Of note, a meta-analysis of IOP percentage increases from baseline levels indicated that there exists an increase in the IOP measure at its peak 4 weeks after the injection. However, 24 weeks after the injection, the increase in IOP compared to its preoperative level showed a decrease.[41] In summary, our study shows that IOP elevation is a significant side effect of IVTA injection. Careful follow-up of IOP is required after IVTA injections.

Currently, only triamcinolone suspension, released by the FDA in 2021, has been approved for the treatment of macular edema associated with uveitis as a suprachoroidal injection. However, there were few studies related to SCTA administration, and 2 RCTs were finally included according to our inclusion criteria.[22,37] They only reported that regarding IOP elevation both IVTA and SCTA have insignificantly different effects. These data are consistent with those reported by the HULK study and the TYBEE study following CLS-TA injection.[42-43] All of these studies prove that TA injection has a similar effect on IOP either injected intravitreally or in the suprachoroidal space. It is noteworthy that, our network meta-analysis results shed light on the IOP effects of SCTA compared with the placebo group. SCTA had statistically a significant effect on IOP (MD, 2.42 [95% CrI, 4.53, 0.19] at the 24th week. Intriguingly, as suggested by the SUCRA ranking scheme, SCTA was ranked last at the 24th week. IVTA was ranked last at the 4th and 12th weeks.

As suggested by the SUCRA ranking scheme, RITA was consistently ranked first from 4 to 24 weeks, and STiTA was ranked behind RITA. Nonetheless, it is important to note that our network meta-analysis only included two clinical trials using RITA. Thus, the clinical significance may still be limited and unclear. hence, further research is mandatory in this context. Maggio et al found that RITA was proposed, which had the advantage of being associated with fewer side effects when compared with IVTA, including a reduced risk of steroid-induced cataract and IOP rise, and no risk of endophthalmitis and rhegmatogenous retinal detachment.[44] This agreed with our study, we can conclude that RITA/STiTA appear to be valid alternatives to IVTA/SCTA in terms of safety outcome with a lower risk of IOP elevation. In this paper, the safety of RITA has been verified, the balanced use of RITA combined with the therapeutic effect is still required. Grzybowski et al recommend a stepwise therapy: retrobulbar or sub-Tenon's corticosteroids in moderate pseudophakic cystoid macular edema (PCME) and intravitreal corticosteroids in recalcitrant PCME.[45] Moreover, the IOP increases after any routes of triamcinolone acetonide application are not rare, although the temporary interruption of treatment is generally not required.[46]Considering this, careful follow-up of IOP is required after TA administration via different routes therapy.

4.1 Strengths and limitations

Although there is a substantial body of literature reporting the efficacy and safety of intravitreal injection triamcinolone, retrobulbar injections triamcinolone, suprachoroidal triamcinolone, and sub-Tenon's infusion of triamcinolone in the treatment of macular edema, there have been no network meta-analysis comparisons of these four commonly used therapies. The strengths of our review include the most comprehensive synthesis of evidence to date on the saftey of triamcinolone acetonide by different routes of administration therapies for macular edema, including all recent publications. To the best of our knowledge, this is the first network meta-analysis to compare the efficacy of triamcinolone acetonide by different routes of administration for macular edema. In addition, this study has a higher standard, due to accurate experimental types of randomized trials, identifying interventions outside of laser interference, unity of follow-up time. We used state-of-the-art approaches to categorize and present the findings using GRADE frameworks.

Limitations of our review include the limited quality of evidence, which may be caused by the limited number of RCTs. It had further influence on indirect comparisons of some network estimates. This problem would be

resolved with the augmentation of high-quality RCTs. Second, the test results of triamcinolone acetonide by different routes of injection therapy showed that statistical heterogeneity was limited in randomized controlled trials, which provides limited confidence in the findings. The third limitation is that our inclusion criteria for disease were not highly strict. Macular edema from various diseases, such as diabetes and branch retinal vein occlusion were included in our network meta-analysis.The fourth limitation is the small sample size of some RCTs included in the present study. However, The results did not change when sensitivity analyses for all interventions on the outcomes excluded studies with non diabetic macular edema and excluded studies with fewer than 20 eyes.

5. CONCLUSION

In this systematic review and network meta-analysis of studies of patients with macular edema and at least 12 weeks of follow-up, our findings underscore the notion that any TA by different routes of injection therapy compared with placebo did increase IOP risk. RITA is potentially the safest route of injection in macular edema treatment for the risk of IOP. At 4 and 12 weeks of follow-up, the highest risk of IOP was found in IVTA, and at 24 weeks of follow-up, the highest risk became SCTA. This conclusion may help doctors evaluate the balance of pros and cons of various routes of injection and adjust their treatment accordingly. In the future, large-scale trials must be performed to validate the risk identified in the current meta-analysis.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

AUTHORS' CONTRIBUTIONS

KXL and YJY were in charge of study design, data collection and interpretation, the quality assessment of evidence, and manuscript preparation. NS critically reviewed the manuscript and provided revisions. KXL, JX, and LZ were involved in the statistical analysis. NS was involved in data collection, data interpretation, and the quality assessment of evidence.All authors contributed to the article and approved the submitted version.

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COMPETING INTERESTS

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://

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