LITERATURE REVIEW

Current Therapy of Diabetic Macular Edema Bevacizumab, Triamcinolone Acetonide, and Laser Photocoagulation

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ABSTRACT

Background: Diabetic macular edema (DME) is the main cause of visual impairment in diabetic retinopathy (DR). Current gold standard therapy of DME is macular laser photocoagulation (MPC). Growing evidences have shown benefits of intravitreal anti-VEGF agents (i.e bevacizumab) and intravitreal corticosteroids (i.e triamcinolone acetonide).
Aim: To compare the visual acuity (VA) improvement of patients with DME, treated with intravitreal bevacizumab (IVB), a combination of IVB and intravitreal triamcinolone (IVB/IVT), and MPC.
Method: A comprehensive PubMed® and Cochrane® databases search was conducted on May 4th, 2017 using appropriate keywords (diabetic macular edema, bevacizumab, triamcinolone, and laser photocoagulation using their MeSH terms). Studies were filtered using inclusion criterions (clinical trials, RCT, meta-analysis, systematic review, English, humans, and publication within 10 years)
Results: Three studies (2 systematic reviews and 1 RCT) were found suitable. From these results, all studies showed favoring effects of IVB when compared to IVB/IVT combination and MPC in short term period (up to 6 months). However, there was no significant improvement of VA beyond this period in all groups.
Conclusion: IVB appears to be superior to IVB/IVT and MPC in improving VA during 6 months follow-up period. Future systematic reviews and meta-analysis are required on the effect of IVB and MPC combination in cases of DME.

Keywords : diabetic macular edema, intravitreal anti-VEGF, intravitreal corticosteroids, treatment, macular laser photocoagulation, bevacizumab, triamcinolon acetonide

Southeast Asia is facing an increasing burden of non-communicable diseases. One of the diseases that cost enormous financial and social burden is DM. Approximately 2.1% of deaths in Southeast Asia is caused by DM and its related complications.[1] Data in Indonesia shows that DM affects 4.8% of the population and is responsible for 3% of death in the country. One of the most devastating complications of DM is diabetic retinopathy (DR). DR affects approximately 30% of DM patients of productive age. Data in Indonesia showed varied prevalence of DR, from 17.2% -

42.6% leading to lower quality of life and loss of productivity.[2]

The main cause of visual impairment in DR is DME. DME is caused by the leakage of blood-retinal barrier (BRB) due to hyperglycemia. BRB disruption or so-called breakdown occurs due to loss of pericytes, loss of cell to cell junctions, and thickening of the basement membrane. This will lead to extravasation of fluid into the extracellular space thus formation of DME. These effects are usually mediated by VEGF which triggers neovascularization, triggers phosphorylation of proteins in the tight junction thus increasing permeability and triggers release of matrix metalloproteinases (MMPs) thus bridging the thickening of the basement membrane.[3]

Inflammation also plays role in pathogenesis of visual impairment in DME by triggering retinal leukostasis. Inflammation leads to release of cytokines, prostaglandins, leukostasis, and accumulation of macrophages. Increased leukostasis in DR leads to impaired endothelial function, retinal blood supply, and vascular permeability.[3]

The current gold standard of therapy in cases of DME is macular laser photocoagulation (MPC). However, studies have shown promising results of intravitreal anti-VEGF and intravitreal corticosteroids in cases of DME. Bevacizumab is one of the anti-VEGF drugs that is widely used as an *off-label* treatment for DME. Thus, this evidence-based case report would like to review the effectiveness of intravitreal anti-VEGF agent (bevacizumab/IVB), a combination of IVB and intravitreal corticosteroids (triamcinolone acetonide/IVT), and laser photocoagulation in the treatment of DME with the improvement of visual acuity as the primary outcome.

METHODS

A comprehensive search via Pubmed® and Cochrane® database were conducted using search terms "diabetic macular edema", "bevacizumab", "triamcinolone", "laser photocoagulation", and their MeSH terms on May 4th, 2017. Results obtained were filtered by type of study (clinical trials, randomized controlled trials (RCT), systematic review, and meta-analysis), time of publication (10 years), language (English), and subjects (human). Further screening on titles and abstracts were performed to include relevant studies to our clinical question. From these selected articles, further full-text analysis was carried out. The process of the database search is as presented in Fig 1.

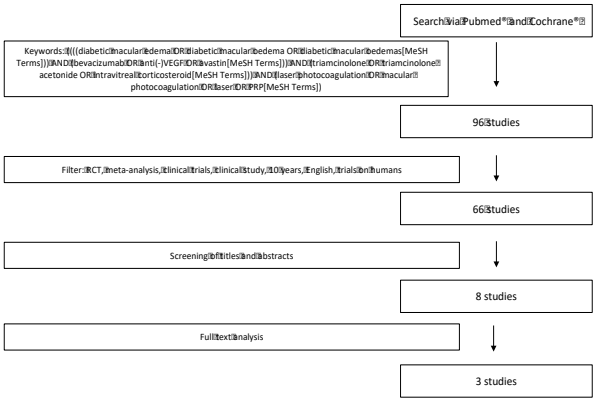

Fig 1. Search flowchart conducted on May 4th, 2017

Studies obtained were appraised using tools from the Center of Evidence-Based Medicine, University of Oxford for systematic review and randomized controlled trials. [4]

RESULTS

Search results

From the search results filtered with inclusion criteria and passed the screening of titles and abstracts, 8 studies were found. From these 8 studies, there are few studies excluded from our appraisal and analysis.

The studies which are dismissed along with the reasons are presented in Table 1.

Table 1. Reasons for exclusion of studies from full-text analysis

Author	Title	Reasons for Exclusion
Soheilian, *et al*. (2007)[5]	Intravitreal bevacizumab (Avastin) injection alone or combined with triamcinolone versus macular photocoagulation as primary treatment of diabetic macular edema	Has already been included in the systematic review
Faghihi, *et al*. (2008)[6]	Intravitreal bevacizumab versus combined bevacizumab-triamcinolone versus macular laser photocoagulation in diabetic macular edema	Has already been included in the systematic review
Soehilian,*et al*. (2009)[7]	Randomised trial of intravitreal bevacizumab alone or combined with triamcinolone versus macular photocoagulation in diabetic macular edema	Has already been included in the systematic review
Jusufbegovic, *et al*. (2015)[8]	Evolution of controlling diabetic retinopathy: changing trends in the management of diabetic macular edema at a single institution over the past decade	Analysis was not performed based on treatment groups.
Adelman, *et al*. (2015)[9]	Strategy for the management of diabetic macular edema: the European Vitreo-Retinal Society Macular Edema Study	No comparison between IVB, IVB/IVT, and MPC

Seven studies were obtained and full-text analysis was carried out. From these studies, 1 RCT and 2 systematic reviews.

Quality of studies

Studies used were appraised using tools from Oxford's Center for Evidence-Based Medicine based on the type of the study as presented in Table 2 and 3.

Table 2. Validity and Relevance Assessment of The Systematic Reviews Included

Articles	Year	Validity						Level of Evidence
		PICO	Appropriate Searching	Relevant Study Included	Quality Assessment of Trials	Heterogeneity	Result Presentation & Forest Plot	
Yilmaz, *et al*[10]	2010	+	+	+	+	-	+	1
Goyal, *et al*.[11]	2010	+	+	+	+	+	+	1

* + : yes - : no ? : not stated

Table 3. Validity and Relevance Assessment of the Therapy Studies Included

Article	Year	Type of Study	Validity						Importance		Applicability
			Randomisation	Group Similarity	Treatment Similarity	Intention to Treat	Blinding	Small lost to follow-up	Treatment effect	Narrow CI	
Soheilian, *et al*.[12]	2012	RCT	+	+	+	+	+	no	Not applicable	+	+

+ : done. - : not done ? : not mentioned

Table 4. Summary of Studies Used

Author	Primary Endpoint	Result	Summary
Soheilian, *et al.*[12]	Improvement in best corrected visual acuity and central macular thickness	1. Three-arm randomized controlled trials (1.25 mg IVB, 1.25 mg/2 mg IVB/IVT, MPC) 2. Loss to follow-up: 24.7% eyes and 24.8% patients with total of 113 eyes completed 24 months follow-up. 3. VA improvement was significant (p=0.002) on the 6th month follow-up analysis with favouring results towards IVB. IVB group had the best VA improvement compared to others. There was no significant changes observed in the 12th and 24th months 4. CMT decline was significantly found in IVB group on 12th and 24th months (p=0.002 and p=0.036) but not followed by VA improvement. 5. Complications occurred: cataract (mostly in IVB/IVT group), vitreous hemorrhage, and ocular hypertension. 6. Limitations: poor injection interval (12 weeks)	The study shows favouring results towards IVB use in comparison to other two groups. Changes in VA was significant in 6th month use of IVB but were not significant in the long term follow-up. CMT changes were observed in the use of IVB. There was no additional benefit in the usage of IVT.
Goyal, *et al.*[11]	VA and CMT in patients with DME at 6, 12, 24 weeks	1. Four RCTs were included for analysis with the total 484 eyes. One study did not use IVT and one study did not use MPC. Therefore, only 2 RCTs fulfilled inclusion criteria of this study. Follow-up period were 6th and 12th weeks. 2. In terms of CMT, forest plot showed favouring effects towards IVB compared to controls at 6th (-48.2 um CI -86.2 to 10.2, Q test p-value =0.01), 12th (-22.3 um, CI -57.9 um to 13.3 um,Q test p =0.03, statistic p-value not significant) , and 24th weeks (-186.75 – 51.4 um, Q test p<0001, statistic p-value not significant) 3. VA, when compared to controls, statistically improved in 6 weeks favouring IVB (-0,13 logMAR CI -0.23 to -0.02 Q-test p-value=0.001), 12 weeks was not significant although favouring IVB (-0.10 logMAR, CI -0.26 to 0.07 Q-test p-value <0.001), 24 weeks was statistically significant favouring IVB but not heteregenous (-0.191 logMAR, CI -0.28 to -0.10, Q test p-value = 0.29) 4. IVB/IVT did not show any additional benefit when compared to IVB in terms of BCVA and CMT 5. Complications: anterior chamber reactions (in IVB and IVB/IVT group), raised IOP (IVT group), endophthalmitis 6. Limitations: small number of trials and significant heterogeneity	IVB is beneficial when compared to MPC and IVB/IVT in short term (6 weeks) follow-up period but not for longer follow-ups.

Yilmaz, *et al.*[10]	VA and CMT at 6th and 12th-week timepoint	1. Four RCTs were included in the analysis which all studied minimal 3 interventions (IVB, IVT/IVB, MPC) but only 3 RCTs fulfilled inclusion criteria with a total of 336 patients with 383 eyes. 2. In the 6th week follow-up period, IVB was showing superiority when compared to MPC (-0.09 CI -0.15 to -0.02, p=0.01) and IVB/IVT (-0.07, CI -0.14 to 0.00, p=0.05). Similar result was shown in 12th weeks but not significant 3. CMT was decreased in IVB group compared to MPC (-30.36 um, CI -52.21 to -6.60 p=0.01) but not significant when compared to IVB/IVT (p=0.11). In 12th weeks, there was no significant difference found between groups. 4. Adverse events include endophthalmitis, mild anterior chamber reaction, and ocular hypertension.	IVB was superior in compared to two other interventions in the short-term follow-up period. However, authors still recommend MPC as the first line treatment

DISCUSSION

DME is the main cause of visual impairment of DR. If not treated, this will lead to blindness which causes extreme social and financial burden, especially in developing countries such as Indonesia.

Current gold standard therapy of DME is MPC. Growing evidences, such as studies by RISE, RIDE, BOLT and RESOLVE studies have shown the safety and efficacy of anti-VEGF agents.[13,14,15] From the selection of anti-VEFG agents, bevacizumab has shown increasing popularity and seems to be superior in terms of cost analysis.

This report includes 3 studies with 2 systematic reviews (level of evidence 1) and 1 randomised controlled trials (level of evidence 2). All studies were appraised by authors and have shown good qualities. However, there are few limitations of the studies included such as small sample size per intervention group (all less than 100 participants) and the heterogeneity of the population by Goyal, *et al.*[11] From these studies, the DRCN study was excluded from our analysis as this study did not use a combination of IVB and IVT.[17] A study conducted by Ahmadieh, *et al.* also did not fulfill our inclusion criteria as they did not use MPC as treatment.[18] These studies also did not mention any interval dosing or use, if any, of MPC. Hence, we propose further additional information to be disclosed for future studies and appraisal.

These reports showed a consistent result of VA improvement in short term follow-up period of IVB use with varied follow-up period (maximum of 6 months). However, this effect seemed to deteriorate over long-term follow-up period as shown as study by Soehilian in the 2 year follow-up period.[12] The study by Soehilian, however, had high number of loss to follow-up, which might influence their result.

All the studies show a consistent result of ineffectiveness IVT use which did not show any additional improvement when compared to other two groups. Instead, studies show few cases of complications in the IVB/IVT group such as increase of IOP and one case of cataract.[10-12] An author discussed that this may be the reason of poor VA improvement when compared to other groups.[12] However, we seem to disagree on this as for the number of complications and increased IOP is seemed to be small when compared to the total sample size thus additional of IVT to the therapy regimen may not be beneficial. Another study by Sutter, *et al.* showed conflicting result to our study as they found improvement of BCVA post-injection of 4 mg IVT when compared to placebo.[19] An author proposed that this may due to the certain degree of macular ischemia.[20] Appropriate dosing of IVT should also be explored further as small dose (such as 2 mg

used in our studies) may not produce beneficial effect but higher dose seem to produce more cases of ocular hypertension.[20]

A study of cost-effective analysis showed that use of laser and anti-VEGF combination therapy produced better quality-adjusted life-years (QALY) when compared to other monotherapy and other combination therapy. Laser and anti-VEGF combination was also proven to be more effective in terms of cost. [21] At the lower cost of ranibizumab, bevacizumab had also been proven to be superior in terms of cost and QALY. However, Pershing, *et al*. seemed to point out questions on its safety regarding systemic absorption.[21]

Future studies need to be conducted to to provide optimal dosing and intervals as well as looking at the effects of MPC and IVB combination.

We also included studies written in English only thus might affect our literature search. Studies available on this matter seem to originate mostly from Iran as bevacizumab may not be legal to be used in cases of DME in several countries, including the US.

CONCLUSION

IVB appears to be superior to IVB/IVT and MPC in improving VA during first 6 months follow-up period. Addition of IVT to the treatment of DME may not provide additional benefit. Future systematic reviews and meta-analysis are required on the effect of IVB and MPC combination in cases of DME.

Ethics and consent to participate

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. The local ethics committee ruled that no formal ethics approval was required in this particular case report.

Acknowledgments

This study received no specific grant from any funding agency or institution. The authors would like to express gratitude to Surya Husadha Hospital Nusa Dua, Badung, Bali, Indonesia for the willingness to provide the patient for the case report.

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