

LITERATURE REVIEW: EFFECTIVENESS OF STEROID IMPLANT AS THERAPY FOR MACULAR EDEMA IN RETINAL VEIN OCCULSION

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ABSTRAK

Implan deksametason intravitreal merupakan implan steroid yang dapat terurai secara alamiah yang merupakan pendekatan farmakoterapi terbaru yang disetujui Food and Drug Administration (FDA) Amerika Serikat sebagai pengobatan okultasi atau penyumbatan vena retina yang disertai edema makula, terapi ini diharapkan dapat mengurangi resiko kehilangan penglihatan dan mempercepat penyembuhan. Penelitian ini menggunakan strategi literature review yang ditelaah dari beberapa sumber seperti PubMed, ScienceDirect, dan Google Scholar dengan pemilihan artikel yang diterbitkan tahun 2015 sampai dengan tahun 2021. Pencarian di database dilakukan dengan menggunakan kata kunci seperti deksametason, implan, intravitreal, efektifitas, Edema Makula, Kortikosteroid, keamanan, visus, oklusi vena retina, retinal vein occlusion, RVO. Hasil analisis berbagai literatur menyimpulkan penderita edema makula pada okultasi vena retina yang diberi terapi steroid intravitreal memberikan efek yang baik, efektif dan aman mengurangi resiko kehilangan penglihatan dan efek samping yang pada sebagian besar kasus dapat dikendalikan secara medis seperti kenaikan tekanan intraocular dan pembentukan katarak. Bagi orang-orang yang beresiko mengalami okultasi vena retina, penting untuk melakukan pencegahan seperti mengontrol tekanan darah dan kolesterol.

Kata Kunci: *Implan steroid, edema makuler, oklusi Vena Retinal*

ABSTRACT

The incidence of dysmenorrhea in Indonesia has reached 64.5%, based on a survey conducted at one school in Garut Regency, as many as 60-70% of female students experienced primary dysmenorrhea. This study aimed to determine the relationship between the age of menarche, menstrual cycle, family history, physical activity, frequency of fast food consumption, and history of exposure to cigarette smoke with the incidence of primary dysmenorrhea. The method in this research uses cross-sectional with a total sample of 176 samples determined using stratified random sampling by determining probability using probability proportional to size then tested univariately and bivariately using Chi Square with $\alpha = 0.05$. The results of the study showed that factors associated with the incidence of primary dysmenorrhea included age at menarche, family history, frequency of fast food consumption, physical activity, and history of exposure to cigarette smoke. Meanwhile, the menstrual cycle is not related to the incidence of primary dysmenorrhea. Suggestions that researchers can give include students being more careful and aware of themselves to prevent primary dysmenorrhea.

Keywords: *Steroid implant, macular edema, retinal vein occlusion*

INTRODUCTION

The intravitreal dexamethasone implant is a biodegradable steroid implant which is the newest pharmacotherapy approach approved by the United States Food and Drug Administration (FDA) as a treatment for occultation or retinal vein blockage accompanied by macular edema. This therapy is expected to reduce the risk of vision loss and speed up healing.

The definition of Retinal Vein Blockage or Occlusion (RVO) by (Ilyas, 2010) itself is a condition where there is a blockage in the retinal vein, either in the central part or in the branches, which results in vascularization disorders in the eyeball, so that sufferers will complain of sudden

blindness. Generally, vision or visual acuity can return to function, but the complications of macular edema and glaucoma that occur simultaneously can result in a poor prognosis for the patient (Vaughan et.al, 2010). Macular edema is the main cause of decreased vision in retinal vein occlusion. Immediate initiation of treatment in this condition is associated with better visual outcomes (1).

In the United States, most patients with central retinal vein occlusion are male and older than 65 years. Most cases are unilateral occlusion, and approximately 6-14% of cases are bilateral occlusion. A study in Taiwan in 2008 noted variations in certain seasons. Branch retinal vein occlusion occurs three times more often than central retinal vein occlusion. Men and women are equally matched with the patient's age being between 60 and 70 years (2).

Meanwhile, research with a large population reported that the incidence of patients aged over 40 years who experienced retinal vein occlusion reached 2.14 cases per 1000 people in that population. Meanwhile, in patients over 64 years of age, the incidence reached 5.36 cases per 1000 people (3). In Australia, the prevalence of retinal vein occlusion ranges from 0.7% in patients aged 49-60 years, to 4.6% in patients over 80 years (McIntosh et al, 2010). Local causes of retinal vein occlusion are trauma, glaucoma, and lesions of orbital structures. This local cause remains very rare in branch retinal vein occlusion. It is necessary to suspect the presence of toxoplasmosis, Behçet syndrome, ocular sarcoidosis, and microaneurysm if these are seen in branch retinal vein occlusion (4).

Systemic processes can cause retinal vein occlusion, including hypertension, atherosclerosis, diabetes mellitus, glaucoma, aging, fasting, hypercholesterolemia, hyperhomocysteinemia, SLE, sarcoidosis, tuberculosis, syphilis, protein C resistance (factor V Leiden), protein C deficiency and S, antiphospholipid antibody disease, multiple myeloma, cryoglobulinemia, leukemia, lymphoma, Waldenstrom macroglobulinemia, polycythemia vera, and sickle cell disease (2).

Treatment is aimed at finding the cause of retinal vein occlusion and treating it, administering anticoagulation if the cause is known, photocoagulation of the retinal area experiencing hypoxia, administering corticosteroids if the blockage is caused by phlebitis (aspirin/dipyridamole), administering anti-glaucoma drugs, Radial Optic Neurotomy, Retinal endovascular surgery (REVS) (5).

The intravitreal dexamethasone implant (DEX implant; Ozurdex; Allergan, Inc., Irvine, CA) is a biodegradable steroid implant used in the treatment of retinal vein occlusion accompanied by macular edema. The DEX implant can release dexamethasone 2 slowly into the vitreous over 6 months (6). Although the intravitreal DEX implant has been approved by the United States Food and Drug Administration (FDA) as a treatment for intravitreal macular edema due to retinal vein occlusion, how effective it is compared to its safety needs to be discussed further in this literature review study.

METHOD

This research used a literature review strategy from national and international journals which were reviewed from several sources such as PubMed, ScienceDirect, and Google Scholar with the selection of articles published from 2015 to 2021, a total of 7 articles were reviewed.

A search in the database was carried out using keywords such as “dexamethasone”, “implant”, “intravitreal”, “effectiveness”, “Macular Edema”, “Corticosteroid”, “safety”, “virus”, “retinal vein occlusion”, “retinal vein occlusion”, “RVO”.

At the start of the database search using inclusion criteria, namely journals, and articles that researched and evaluated the effectiveness, advantages, and side effects of Intravitreal Steroid Implant treatment in Macular Edema Therapy for retinal vein blockage or Retinal Vein Occlusion. Then use the exclusion criteria by looking at the publication time in the 2015 - 2021 range.

In the final stage, an assessment is carried out by deleting journals that have the same title and author, incomplete text, and verifying the research results.

RESULTS AND DISCUSSION

Literature Review of the analysis of 7 articles shows that the intravitreal dexamethasone implant administration demonstrates a positive effect in the treatment of macular edema, including a reduction in central retinal thickness and an improvement in corrected visual acuity. Here is the discussion and analysis based on the review of articles.

Table 1. Results of a Literature Review of Effectiveness of Steroid Implant as Therapy for Macular Edema in Retinal Vein Occlusion

No	Author and Year	Title and Aim	Method	Results and Conclusions
1	Lam et.al, 2015 (Kanada) (7)	- Title: Real World assessment of intravitreal dexamethasone implant in patients with macular edema - Objective: To evaluate functional and anatomical improvements in patients with macular edema associated with retinal disease (Diabetes Mellitus, Central Retinal Vein Occlusion)	- Retrospective Cohort Study - Sample: 120 people with macular edema due to various etiologies - Instruments: Snellen Chart, Medical Records, Tonometry, ophthalmoscope	Single-dose intravitreal DEX implants or in combination with pharmacotherapy or other invasive procedures produce functional and anatomical improvements in chronic macular edema associated with retinal disease
2	Bakri SJ et.al, 2016 (8)	Title: Evaluation of multiple	-Retrospective Study - Sample: 31 patients	This study suggests that repeated intravitreal

No	Author and Year	Title and Aim	Method	Results and Conclusions
		dexamethasone intravitreal implants in patients with macular edema associated with retinal vein occlusion Objective: To evaluate patients treated with intravitreal DEX implants in patients with macular edema caused by RVO	- Instruments: Snellen Chart, Medical Records, Tonometry, ophthalmoscope	DEX injections, if necessary, for macular edema associated with RVO are feasible. Patients should be monitored and treated for ocular hypertension and cataract development post-therapy
3	Michalska MK et.al, 2016 (Katowice) (9)	-Title: Evaluation of the effectiveness and safety of glucocorticoids intravitreal implant therapy in macular edema due to retinal vein occlusion -Aim: To evaluate the impact of intravitreal dexamethasone implant administration on macular morphology and visual function of eyes with macular edema secondary to retinal vein occlusion	- Prospective Analysis Study - Sample: 36 patients treated with intravitreal dexamethasone implant injection for persistent macular edema - Instruments: Snellen chart, medical record, tonometry, ophthalmoscope	Intravitreal dexamethasone implant is safe, well tolerated, and likely to lead to rapid morphological and functional improvement of the macula and accelerated visual rehabilitation in patients with macular edema due to retinal vein occlusion
4	Korobelnik JF et.al, 2016 (Louvre) (10)	-Title: Two-year prospective, multicenter study of the use of dexamethasone intravitreal implant for treatment of macular edema secondary to retinal vein occlusion in the clinical setting in France -Aim: to evaluate the usage pattern, effectiveness, and	-Multicenter, longitudinal, observational Prospective Study - Sample: 375 patients - Instruments: Snellen Chart, Tonometry, Medical records, ophthalmoscope	There were changes in visual acuity with changes in BVCA parameters in patients treated with dexamethasone implants

No	Author and Year	Title and Aim	Method	Results and Conclusions
		long-term safety of intravitreal dexamethasone implants in treating macular edema secondary to central retinal vein occlusion		
5	Garweg JG and Zandi S, 2016 (11)	-Title: Retinal vein occlusion and the use of a dexamethasone intravitreal implant in its treatment - Objective: To evaluate clinical experience with Intravitreal dexamethasone implants to establish a clinically based therapeutic regimen	-Prospective Study - Sample: 30 patients - Instruments: Snellen Chart, Medical records, Tonometry, ophthalmoscope	This study concluded that in patients with chronic macular edema unresponsive to repeated anti-VEGF therapy, very satisfactory results were achieved after treatment with an intravitreal dexamethasone implant. However, these results were achieved at the expense of side effects usually associated with steroids, including in as many as 20% of patients treated with Ozurdex®, increased IOP and cataract formation, all of which could be controlled medically in the majority of cases.
6	Eter N et,al, 2017 (Jerman) (12)	Title: Dexamethasone intravitreal implant in retinal vein occlusion: real-life data from prospective multicenter clinical trial Objective: To evaluate the relationship between the duration of macular edema associated with retinal vein occlusion and the achievement of visual benefits in patients receiving intravitreal dexamethasone implants in real-world clinical practice.	-Multicenter prospective observational study - Sample: 573 patients - Instruments: Snellen Chart, Tonometry, Medical records, ophthalmoscope	dexamethasone implant is effective in improving BCVA and reducing central retinal thickness in patients with BRVO and CRVO in real-world clinical practice. The greatest BCVA at 6 months post-therapy occurred in patients with early-onset macular edema, thus confirming the benefits of early treatment. The DEX implant was well tolerated and had an acceptable safety profile for patients

No	Author and Year	Title and Aim	Method	Results and Conclusions
7	Ni Putu Ayu et,al, 2020 (Indonesia) (13)	-Title: Central Retinal Vein Occlusion: A Literature Review -Aim: Detailed discussion of Retinal Vein Occlusion as well as early diagnosis and management	-Literature review - Analysis of 55 journals	anti-VEGF and corticosteroid implants that have been clinically proven to treat CRVO-associated macular edema. Both anti-VEGF injections and intravitreal corticosteroids require repeated injections, but until now the optimal time in which repeat therapy should be carried out has not been found.

A retrospective cohort study on patients with macular edema due to retinal diseases was conducted at an eye clinic in Canada. Best-corrected visual acuity (BCVA), central retinal thickness (CRT), intraocular pressure (IOP), glaucoma and cataract surgeries, and safety data were measured from patients' medical records during a 3-month follow-up period after intravitreal DEX implantation. The study included 120 eyes with macular edema of various etiologies on the retina, including diabetes mellitus (n = 34), retinal vein occlusion (RVO, n = 30; branch in 19 and central in 11), and uveitis (n = 23). The patients had an average age of 60.9 years, and 73.3% of eyes had macular edema for 12 months prior to intravitreal DEX implantation. The mean initial BCVA was 0.63 ± 0.03 logMAR (20/86 on the Snellen chart), and the mean CRT was 474.4 ± 18.2 μ m. The mean number of DEX implant injections was 1.7 ± 0.1 in all eyes; 44.2% of eyes had repeated DEX implant injections (reinjection intervals of 2.3-4.9 months). The largest mean BCVA improvement occurred in eyes with uveitis (3.3 ± 0.6 , $P < 0.0001$), followed by RVO (1.3 ± 0.5 , $P < 0.01$) and DME (0.7 ± 0.5 , $P < 0.05$). Significant CRT reductions were observed: -255.6 ± 43.6 μ m for uveitis, -190.9 ± 23.5 μ m for diabetes, and -160.7 ± 39.6 μ m for RVO ($P < 0.0001$ for all cohorts). A 10 mmHg increase in IOP occurred in 20.6%, 24.1%, and 22.7% of patients with diabetes, RVO, and uveitis, respectively. IOP-lowering medications were administered in 29.4%, 16.7%, and 8.7% of patients with diabetes, RVO, and uveitis, respectively. Glaucoma surgery was performed on 1.7% of all eyes, and cataract surgery on 29.8% of all phakic eyes receiving intravitreal DEX implants. In conclusion, a single-dose intravitreal DEX implant or combination with other pharmacotherapy or invasive procedures resulted in functional and anatomical improvements in chronic macular edema associated with retinal diseases (7).

A retrospective study evaluated patients treated with intravitreal DEX implants for macular edema caused by RVO. Each patient underwent ophthalmologic examinations, optical coherence tomography (OCT), and follow-up at intervals of 4 to 6 weeks. Outcome parameters measured included best-corrected visual acuity (BCVA), intraocular pressure (IOP), central macular thickness on OCT, OCT fluid resolution, and treatments needed for IOP elevation and cataracts. The study's results showed that 31 patients received 82 DEX injections, with 19 patients receiving ≥ 2 injections,

12 patients receiving ≥ 3 injections, 10 patients receiving ≥ 4 injections, 6 patients receiving ≥ 5 injections, and 4 patients receiving ≥ 6 intravitreal DEX injections. All patients were followed up for a minimum of 12 weeks, with an average follow-up duration of 344.94 days. A total of 14 patients (45%) experienced ocular hypertension (≥ 22 mmHg), and 40% of phakic patients required cataract surgery. The average interval for OCT fluid resolution was 52 days (range, 28-245; SD, ± 8), and the average interval for repeat therapy was 119 days (range, 42-309; SD, ± 9). No patients required glaucoma surgery or developed endophthalmitis. The conclusion of this study suggests that repeated intravitreal DEX injections, when necessary, for RVO-associated macular edema can be performed. Patients should be monitored and treated for ocular hypertension and the development of cataracts following therapy (8).

A prospective analysis study was conducted at the Department of Ophthalmology at the University of Ophthalmology and Oncology in Katowice, involving 36 patients (17 females and 19 males) aged 28-77 years (mean age 58 ± 15 years). These patients were treated with intravitreal dexamethasone implant injections for persistent macular edema. The studied group included 16 patients with central retinal vein occlusion (16 eyes) and 20 patients with branch retinal vein occlusion (20 eyes). The objective of this study was to evaluate the impact of intravitreal dexamethasone implant (Ozurdex) administration on macular morphology and visual function in eyes with macular edema (ME) secondary to retinal vein occlusion (RVO).

The effectiveness of therapy was assessed by measuring best-corrected visual acuity (BCVA) and central retinal thickness (CRT). Safety parameters were evaluated based on intraocular pressure side effects and corneal endothelial cell density. The study revealed a significant increase in BCVA after the first, second, and third months of therapy. At 6 months post-therapy, BCVA decreased, although not significantly compared to the values obtained at the third month. Two months after intravitreal dexamethasone implantation, the CRT value was 338 ± 163 μm , which was significantly lower than before therapy. Between the third and sixth months post-therapy, there was a non-significant increase in CRT compared to the thickness observed at the second month. Two months after therapy, there was an increase in intraocular pressure (IOP) in 36% of patients, with further decreases during the last 6 months of follow-up post-therapy. Throughout the treatment, there were no significant differences in corneal endothelial cell density between branch and central retinal vein occlusions. In conclusion, intravitreal dexamethasone implants are safe and well-tolerated, and they provide improvements in visual acuity and macular thickness in patients with macular edema secondary to retinal vein occlusion and tend to lead to rapid improvement in the morphological and functional aspects of the macula and accelerate visual rehabilitation in patients with macular edema due to retinal vein occlusion (9).

A prospective multicenter longitudinal observational study (LOUVRE) conducted over 24 months to evaluate the usage patterns, effectiveness, and long-term safety of intravitreal dexamethasone implant (DEX implant) in treating macular edema secondary to central retinal vein occlusion (BRVO, CRVO) in clinical practice in France. Researchers consecutively enrolled adult patients with macular edema following retinal vein occlusion (RVO) treated with DEX implants at the outset. Re-treatment with DEX implants and other RVO treatments was administered according to the physician's discretion. The measured parameters included changes in best-corrected visual acuity (BCVA) from the beginning of therapy to 6 months post-therapy. Other measured parameters included changes in BCVA, intraocular pressure (IOP), side effects, and RVO treatments administered up to 24 months. The analysis results showed that a total of 375 patients (53.9% BRVO, 46.1% CRVO) received an average of 2.6 DEX implant injections over 2 years, with a mean injection interval of 6.6 months. The average BCVA change from baseline was 5.1 (19.0) letters at 6 months ($p < 0.001$) and 4.6 (22.3) letters at 24 months ($p < 0.001$) post-therapy. During the study, 208 patients (55.5%) received treatments other than DEX implants for RVO, typically laser therapy or ranibizumab therapy, with the first use of other therapies occurring on average at 8.7 months. The average change in BCVA at 6 months of therapy was 5.5 letters ($p < 0.001$, $N = 254$) in patients receiving only DEX implants and 4.2 letters ($p = 0.006$, $N = 121$) in patients who received additional RVO treatment during the first 6 months. At 24 months, the average change in BCVA from baseline was +20.7 letters in patients treated with DEX implants alone ($p < 0.001$) (10).

An analysis of published studies on the clinical experience with intravitreal dexamethasone implant (Ozurdex®) was conducted with the aim of establishing a clinically based therapeutic regimen. This analysis included studies involving a minimum of 15 patients with a prospective design or a minimum of 30 patients with a retrospective design, with a follow-up period of at least 6 months, and at least 2 intravitreal Ozurdex® injections in each eye. The study's results indicated that in the majority of eyes, satisfactory outcomes were achieved with injection intervals between 3 and 5 months. Initial evidence suggests similar effectiveness compared to anti-VEGF therapy as a first-line treatment. Safety issues related to the long-term and repeated use of Ozurdex® were not found in clinical application: its implantation was not associated with a sustained increase in intraocular pressure (IOP) over time or with the number of injections administered. The study concluded that in patients with chronic macular edema unresponsive to repeated anti-VEGF therapy, treatment with intravitreal dexamethasone implant can yield highly satisfactory results. However, these results were obtained with the occurrence of side effects typically associated with steroids, including a 20% incidence of increased IOP and cataract formation in patients treated with Ozurdex®, all of which can be medically managed in most cases (11).

A prospective observational multicenter study conducted over 6 months at 70 locations in Germany included patients diagnosed with macular edema due to branch or central retinal vein occlusion (BRVO, CRVO) who received DEX implants. The study aimed to evaluate the relationship between the duration of macular edema associated with retinal vein occlusion (RVO) and achieving visual gains in patients receiving intravitreal dexamethasone implant (DEX implant) in real-world clinical practice. It also aimed to determine the patterns of DEX implant use, its effectiveness, and safety in treating retinal vein occlusion patients in clinical practice. Follow-up and evaluations were conducted in accordance with standard clinical practices. Repeated DEX implant administrations and the use of other RVO therapies were at the discretion of the treating physicians. The primary endpoint was the mean change in best-corrected visual acuity (BCVA) from baseline at week 12. The analysis population consisted of 573 patients (64% BRVO, 36% CRVO). Patients received an average of 1.17 DEX implant treatments during the study period; 84.3% received a single DEX implant, and 19.9% received additional RVO management. Among patients with BCVA analyzed at baseline and at week 12 post-therapy (n = 351), the mean change from baseline BCVA at week 12 was -0.16 ETDRS letters (p <0.001), and 33.9% of patients gained at least 3 lines of BCVA from baseline. The mean changes from baseline BCVA at week 12 were +9.5, +7.3, and +5.4 ETDRS letters in patients with macular edema durations of <90 days, 90-180 days, and >180 days, respectively. Improvement in BCVA up to week 24 and a decrease in central retinal thickness were observed in BRVO and CRVO patients. The most common adverse event was increased intraocular pressure, with no incisional glaucoma surgeries performed. The study's conclusion is that dexamethasone implants are effective in improving BCVA and reducing central retinal thickness in patients with BRVO and CRVO in real-world clinical practice. The greatest BCVA improvement over 6 months post-therapy occurred in patients with early-onset macular edema, confirming the benefits of early management. DEX implants are well-tolerated and have an acceptable safety profile for patients (12).

Based on a literature review of 55 journals, the management of CRVO has seen rapid advancements with the introduction of various new modalities, including anti-VEGF and corticosteroid implants, which have clinically proven efficacy in treating macular edema associated with CRVO. Both intravitreal anti-VEGF and corticosteroid injections require repeated administrations, but as of now, there is no optimal time interval established for when re-treatment should be performed. Further research is still needed, particularly to determine the optimal treatment intervals, thereby minimizing the burden, cost, and injection-related risks (13).

CONCLUSION AND SUGGESTIONS

Analysis of various medical literature from 7 articles shows that intravitreal steroid implant therapy (dexamethasone) is effective and has a favorable long-term safety profile in reducing the risk of blindness, accelerating healing, and improving visual acuity in eyes experiencing macular edema

due to RVO as assessed based on a decrease in retinal thickness. central and improved corrected visual acuity.

This therapy is well tolerated and tends to accelerate macular morphological and functional improvement as well as visual rehabilitation. This therapy also provides satisfactory results in patients who are unresponsive to repeated anti-VEGF therapy. Common side effects of therapy include increased IOP and cataract formation, all of which can be controlled medically in the majority of cases. It is recommended to prevent risk factors for blockage and immediately see a doctor if your vision suddenly becomes blurry without pain or red eyes. For people who are at risk of experiencing retinal vein occlusion, it is important to take precautions such as controlling blood pressure and cholesterol.

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