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Original Article

Intravitreal injection of Conbercept combined with micropulse laser therapy enhances clinical efficacy in patients with diabetic macular edema

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Abstract: Purpose: To analyze the clinical efficacy of intravitreal injection of Conbercept (IVC) combined with micropulse laser (MPL) therapy in the treatment of diabetic macular edema (DME). Methods: In this retrospective study, we selected 64 DME patients who visited the First People's Hospital of Yunnan Province between February 2019 and February 2021 for analysis. Based on different intervention methods, 31 cases treated with IVC were included as a control group (the Con group) and 33 cases with IVC + MPL combination therapy were in a research group (the Res group). Data on curative effects, injection frequency, pre- and post-treatment best corrected visual acuity (BCVA) and central macular thickness (CMT), visual field gray value, 30° visual field average light threshold sensitivity, and mean visual field defect (VFD) were collected for inter-group comparisons. Further, Cox multivariate regression analysis was performed to identify factors affecting the curative efficacy of DME patients. Results: Compared with the Con group, the Res group had a higher total response rate and a lower injection frequency. In addition, higher BCVA and lower CMT were determined in the Res after 6 months of treatment. Moreover, Res group exhibited statistically lower visual field gray value and mean VFD, as well as higher 30° visual field average light threshold sensitivity than the Con at 1 month postoperatively. All the above differences were statistically significant. According to the Cox multivariate regression analysis, treatment modality was the influencing factor for the efficacy of DME patients. Conclusions: IVC + MPL have better clinical efficacy than IVC alone for DME. The combined modality can improve patients' visual quality, inhibit DME, and reduce medication frequency.

Keywords: Diabetic macular edema, Conbercept, micropulse laser, clinical efficacy

Introduction

Diabetes mellitus (DM) is a high-incidence metabolic disorder featuring absolute deficiency of insulin and insulin resistance [1]. Nowadays, people's unhealthy lifestyles are making DM more influential on a global scale, with statistics indicating more than 451 million sufferers [2]. It is predicted that this figure will rise to approximately 700 million in 2045, making it one of the the fastest growing and global health challenges in the 21st century [3]. Hyperglycemia in DM patients can induce a number of concurrent symptoms, including macular edema (ME) [4]. The pathogenesis of ME is complex, but among various risk factors, poor blood glucose control has been well demonstrated to increase the risk of ME [5]. Diabetic macular edema (DME) has been claimed as the most common cause of vision loss in both type 1 and type 2 DM patients [6]. Currently, laser photocoagulation, vitrectomy and anti-vascular endothelial growth factor injection are commonly used to treat DME, but with unstable curative effects [7]. Thus, an effective treatment scheme is urgently needed to minimize the harm of DME. This study used intravitreal injection of Conbercept (IVC) combined with micropulse laser (MPL) as the breakthrough point to find a better therapeutic method for the treatment of DME, which has positive significance for the clinical rehabilitation of such patients.

For the treatment of DME, drugs (e.g., Conbercept and Paclitaxel) have been shown to

play an important role in the clinical front line [8], of which Conbercept is an anti-vascular endothelial growth factor (VEGF) drug [9]. The increase in VEGF level is known to cause the rise of the patient's retinal vascular wall permeability, adversely influencing the rehabilitation [10]. Conbercept is indicated to be safe and effective in the treatment of ME secondary to central retinal vein occlusion, but it is still limited in clinical treatment of DME due to some deficiencies [11]. Micropulses, defined as laser pulses in the microsecond range, are safe because they limit the spread of heat to adjacent retinal layers [12, 13]. In a comparative analysis of laser therapy by Al-Barki et al. [14], the micro-pulse system was suggested to produce better results than the short-pulse system. In this study, we compared the clinical efficacy of IVC plus MPL with that of IVC alone in DME, so as to verify the clinical advantages of the combination therapy and provide some reference for the treatment optimization of DME patients.

Materials and methods

General information

This retrospective study collected 64 DME patients who visited the First People's Hospital of Yunnan Province between February 2019 and February 2021. Based on differences in intervention methods, 31 cases treated with IVC were set as a control group (the Con group) and 33 cases with IVC + MPL as a research group (the Res group).

The general data were similar between the two groups, suggesting clinical comparability (P>0.05). The First People's Hospital of Yunnan Province Ethics Committee has approved this research protocol, and all subjects signed informed consent before enrollment.

Patient enrollment and exclusion criteria

Subjects were enrolled based on the following criteria: Patients who met DME diagnostic criteria [15]; patients with monocular disease and without any fundus treatment; patients whoes optical coherence tomography (OCT) results showed ME, macular center thickening, but no scarring or tissue hyperplasia; patients with good compliance including active cooperation during the followed-up.

On the contrary, patients who met any of the following were excluded: Patients with conjunctivitis, keratitis, uveitis or other inflammations; patients with cataract, retinal vein occlusion, glaucoma or other ocular organic diseases; patients with keratopathy, lens opacity or vitreous opacity that seriously affect fundus observation; patients with severe heart, lung or kidney dysfunction.

Therapeutic regimens

After admission, all patients underwent medical history inquiry and general examinations such as blood glucose and blood pressure measurements. Tobramycin Eye Drops (Jiangsu Hanchen Pharmaceutical Co. Ltd., H20083324) were used for 3 days before treatment, and conjunctival sac flushing was performed before IVC. Subsequently, the Con received IVC treatment, and the Res received IVC + MPL therapy, with the specific treatment methods described as follows.

IVC: The patient was placed in a supine position, and the pupil of the affected eye was fully dilated. After surface anesthesia and skin preparation, the surgical film strips were applied, the eyelid was opened, and the conjunctival sac was rinsed with tobramycin dilution. Then the needle was inserted 3.5-4.0 mm behind the limbus, through which 0.05 mL of Conbercept (Chengdu Kanghong Biotechnology Co. Ltd., S20130012) was injected into the vitreous cavity. After needle withdrawal, the operated eye was compressed with Q-tips for a moment and then wrapped. Patients were re-examined once a month after IVC, and the decision about re-injection was made according to their specific condition.

MPL: The French Quantel 577Y micropulse laser (Shanghai Hanfei Medical Equipment Co. Ltd.) was used for therapy, with an operating load of 15%, a wavelength of 577 nm, a spot diameter of 100 μm, an interval time of 1 ms and a working time of 0.17 ms. First, the threshold energy was measured outside the macula, and the power was then gradually increased. Using double laser power and triple exposure time, laser photocoagulation was performed at a range of 1 PD beyond the central fovea of the macula.

Table 1. Baseline data of 64 DME patients

Classification	Control group (n=31)	Research group (n=33)	χ^2/t	P
Sex (male/female)	17/14	20/13	0.218	0.641
Age (years old)	57.13±7.63	59.88±8.06	1.400	0.167
Disease course (years)	10.39±1.15	10.61±1.25	0.731	0.467
cc (kg/m^2)	23.90±1.27	23.48±1.03	1.457	0.150
Affected eye (left/right)	16/15	18/15	0.055	0.814
Intraocular pressure (mmHg)	15.84±4.78	16.18±4.57	0.291	0.772
Type of diabetes (I/II)	6/25	9/24	0.558	0.455
Smoking (yes/no)	10/21	8/25	0.508	0.476
Drinking (yes/no)	11/20	10/23	0.195	0.659

Note: DME, Diabetic Macular Edema; BMI, Body Mass Index.

Patients in the Res group were treated with MPL photocoagulation only once. Both patient cohorts were followed up for 6 months.

Analysis indexes

(1) *Therapeutic efficacy:* Evaluation criteria [16]: significant improvement of ME, increase of best corrected visual acuity (BCVA) by ≥2 lines, and significant reduction of leakage area were considered as marked response; relieved ME, increase of BCVA by ≥1 line, and improvement of leakage area were deemed to response; no obvious change in ME, no change or decrease in BCVA, and unaltered leakage area were considered as non-response. The overall response rate was calculated as (marked response + response) cases/total number of cases.

(2) *Injection frequency:* The average number of injections of both patient cohorts within 6 months was observed and recorded.

(3) *Pre- and post-treatment BCVA and central macular thickness (CMT):* We used the international standard visual acuity chart and OCT to measure the BCVA (converted to LogMAR) and CMT of patients before and 6 months after treatment.

(4) *Visual field parameters:* Humphrey perimetry was used to measure and record the post-treatment visual field gray value, average light threshold sensitivity of 30° field of view (FoV), and mean visual field defect (VFD).

Statistical analysis

SPSS 23.0 was used to statistically process the data in this study, and P<0.05 was used to indicate a significant difference. Counted data (denoted by number of cases/percentage [n/%]) and measured data (represented by mean ± SEM) were compared between groups using the χ^2 test and the independent sample t test, respectively. Finally, Cox multivariate regression analysis was carried out to analyze the factors affecting the efficacy of DME patients.

Results

Baseline data of 64 DME patients

We divided the 64 DME patients into two groups and compared their baseline data (**Table 1**). The results determined no statistical significance in sex, age, disease course, body mass index (BMI), location of the affected eye, intraocular pressure, type of diabetes, smoking or drinking between groups (P>0.05).

Therapeutic efficacy in 64 DME patients

We compared and evaluated curative efficacy between patients who received the two treatment methods (**Table 2**). The total response rate of treatment was higher in the Res group than in the Con group (90.91% vs. 67.74%, P<0.05).

Injection frequency in 64 DME patients

The injection frequency of both patient cohorts within six months after treatment was recorded to assess the degree of injection dependence under the two regimens (**Figure 1**). The data revealed statistically fewer times of injections in the Res group compared with that in Con group (P<0.05).

Table 2. Therapeutic efficacy in 64 DME patients

Classification	Control group (n=31)	Research group (n=33)	χ^2	P
Marked response	12 (38.71)	19 (57.58)	-	-
Response	9 (29.03)	11 (33.33)	-	-
Non-response	10 (32.26)	3 (9.09)	-	-
Total response rate (%)	21 (67.74)	30 (90.91)	5.300	0.021

Note: DME, Diabetic Macular Edema.

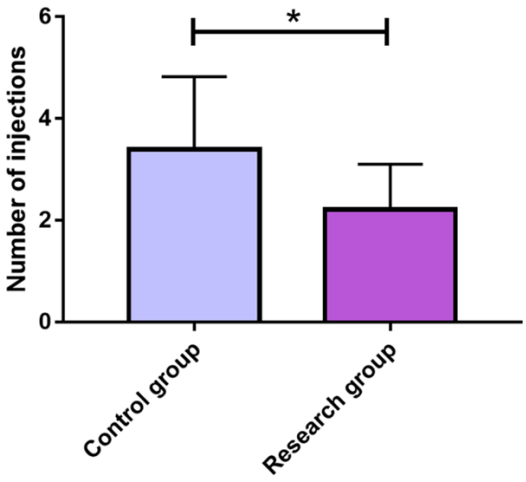

Figure 1. Injection frequency in 64 patients with DME. *P<0.05. DME, Diabetic Macular Edema.

BCVA and CMT in 64 DME patients

BCVA and CMT of both cohorts were tested to further analyze the clinical efficacy of the two treatments (**Figure 2**). No statistical inter-group differences were found in pre-treatment BCVA and CMT (P>0.05). However, there were significant changes after treatment, with elevated BCVA and decreased CMT in both cohorts. Further, compared to the Con group, BCVA was higher and CMT was lower in the Res group (P<0.05).

Visual field parameters of 64 DME patients

We tested three visual field-related parameters (visual field gray value, average light threshold sensitivity for 30° FoV and mean VFD) in the two groups, so as to evaluate the effect of the two treatments on the visual quality of DME patients (**Figure 3**). Compared to those in the Con group, the visual field gray value and mean VFD of the Res group were significantly lower, while the average light threshold sensitivity for 30° FoV was significantly higher (P<0.05).

Cox multivariate regression analysis of factors affecting efficacy in DME patients

According to the Cox multivariate regression analysis (**Table 3**), sex, age, course of disease, BMI, location of the affected eye, intraocular pressure, type of diabetes, smoking or drinking were not significantly correlated with the efficacy of DME patients (P>0.05), but the treatment modality was (P<0.05).

Discussion

Diabetic macular edema (DME), a multifactorial complex disease driven by inflammation, hypertonicity,, and angiogenesis, can occur at any stage of diabetic retinopathy [17]. Long-term poor blood sugar control can cause damage to the small blood vessels in the eyes, allowing fluid to seep into the retina. As the disease progresses, extracellular fluid accumulates in the macula, eventually leading to macular swelling [18, 19]. DME can cause blurred vision and increase the risk of irreversible vision loss [20]. In recent years, a rising prevalence of DME has been witnessed. According to statistics, the global prevalence of DME in type 1 and type 2 DM is about 11.4% in European countries, while it is as high as 45.3% in North American countries, posing a severe challenge to global healthcare [21]. Therefore, this clinical study based on DME is significant to the vision rehabilitation and quality of life of patients.

Sixty-four patients with DME were included in this study, and based on the intervention methods, they were assigned to the Con and the Res groups treated with IVC alone and IVC + MPL, respectively. The results revealed a statistically higher total response rate in the Res than in the Con (90.91% vs. 67.74%), suggesting the ability of IVC + MPL to improve the curative efficacy in DME patients. This may be attributed to the positive effect of MPL on the biological processes in the retina of DME patients, thus play-

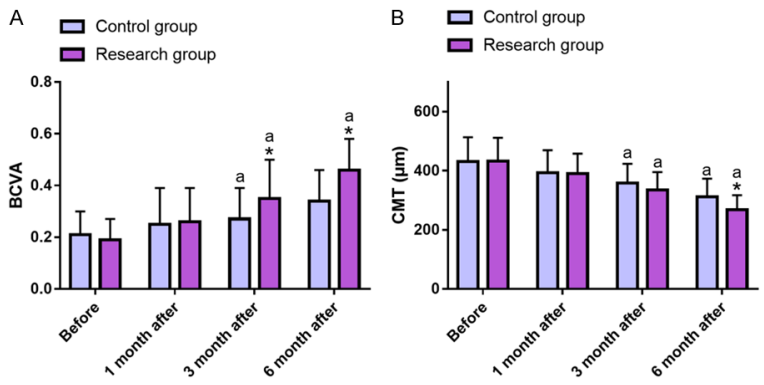

Figure 2. BCVA and CMT of 64 DME patients. A. The research group had statistically increased BCVA at 3 and 6 months after initial treatment, higher than in the control group. B. The research group had statistically reduced CMT at 3 and 6 months after initial treatment. The CMT at 6 months after initial treatment was lower in the research group than in the control group. Note: *P<0.05 vs. control group; a P<0.05 vs. before treatment within the group. BCVA, Best Corrected Visual Acuity; CMT, Central Macular Thickness; DME, Diabetic Macular Edema.

ing a role in repairing the blood-retinal barrier in the body [22]. However, MPL therapy may cause damage to photoreceptors and capillaries, resulting in temporary vision loss and increased retinal thickness and other adverse events in patients, as well as reduced therapeutic effect over time, so it is often combined with anti-VEGF drugs [23]. As an anti-VEGF drug, IVC used in this study has the advantages of multiple targets, strong affinity and long action time. IVC can inhibit the formation of neovascularization by reducing VEGF expression in the vitreous cavity of DME patients and inhibit exudation, edema, and inflammation related to macular vascular leakage, thus further improving the visual quality of patients [24]. Also, we recorded BCVA and CMT in both groups, and found higher BCVA and lower CMT in the Res group compared to the Con group after treatment. The significant inter-group difference in CMT in this study indicates that the combined therapy has a better inhibitory effect on ME. While the difference in BCVA suggests that the combination therapy used in the Res group plays a significantly more positive role on patients' vision than IVC alone, which is consistent with the results of Qiao et al. [25] in a randomized controlled trial on MPL for DME. To further determine the effect of the combined therapy on patients' visual field, we recorded the visual field gray value, the average light threshold sensitivity of 30° FoV and the mean VFD of patients. After comparative analysis, we found a markedly lower gray value and mean VFD while higher average light threshold sensitivity of 30° FoV in the Res group compared to the Con group. The average light threshold sensitivity can reflect the sensitivity of patients' visual field to light. According to previous literature, the average light sensitivity of the general population decreases linearly with the increase of age and eccentricity, while for DME patients, this value reduces with the aggravation of the disease [26]. From our research findings, IVC + MPL are more advantageous in restoring visual field quality. This may be due to the higher safety of MPL, which can prevent the formation of retinal scarring and tissue damage as it cannot induce protein coagulation [27]. There is a positive correlation between tissue damage and VFD of patients, so the mean VFD of patients treated with MPL was lower and the visual field recovery quality was better. In addition, we recorded drug injection frequency in patients, and found that the times of drug injections in the Res group were significantly fewer during the 6 months of treatment, indicating that the combined treatment can reduce drug use in DME patients. The observation of Bıçak et al. [28] indicated that MPL after initial loading doses reduced the need for anti-VEGF injections, similar to our findings. Finally, we conducted an in-depth analysis of the influencing factors of efficacy in DME patients by Cox multivariate regression analysis, and the results identified that the treatment modality was a significant factor affecting the efficacy, further confirming the efficacy of IVC + MPL in the treatment of DME.

The innovation of this study lies in the comprehensive evaluation of IVC + MPL in the treatment of DME from a multi-dimensional perspective, including efficacy, infusion frequency, BCVA, CMT, and visual field related indexes, confirming both the effectiveness and significance of the combination therapy (with lower injection frequency) for DME and the outstand-

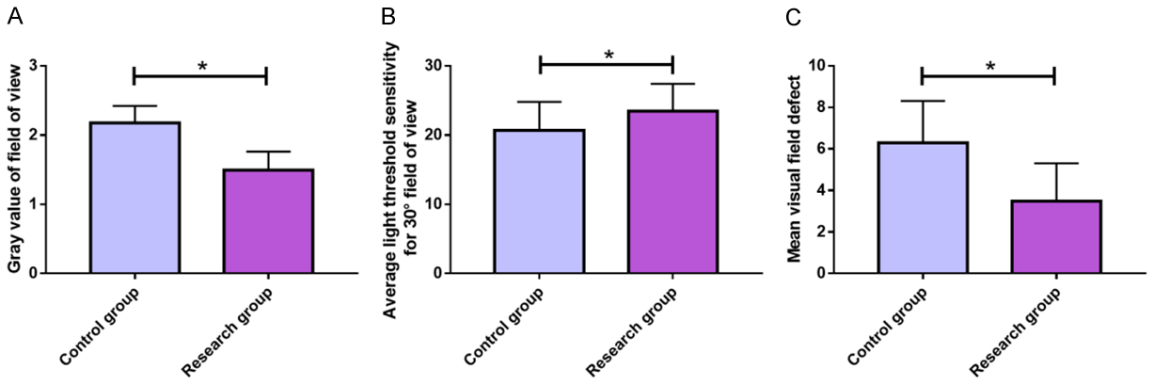

Figure 3. Visual field parameters of 64 patients with DME. A. The research group showed a statistically lower gray value of field of view than the control group did. B. The research group exhibited a statistically higher average light threshold sensitivity for 30° field of view than the control group did. C. The research group had a statistically lower mean visual field defect than the control group did. Note: *P<0.05. DME, Diabetic Macular Edema.

Table 3. Cox multivariate regression analysis of factors affecting the efficacy in patients with DME

Factor	B	SE	Wald	P	Exp (B)	95% CI
Sex	-0.361	0.659	0.300	0.584	0.697	0.192-2.535
Age (years old)	-0.050	0.042	1.413	0.235	0.951	0.875-1.033
Disease course (years)	-0.116	0.248	0.217	0.641	0.891	0.548-1.449
BMI (kg/m^2)	0.309	0.241	1.650	0.199	1.363	0.850-2.185
Affected eye	-0.054	0.665	0.007	0.936	0.948	0.257-3.491
Intraocular pressure (mmHg)	-0.097	0.056	2.977	0.084	0.908	0.813-1.013
Type of diabetes (I/II)	0.636	0.728	0.762	0.383	1.888	0.453-7.872
Smoking	0.061	0.648	0.009	0.924	1.063	0.299-3.788
Drinking	-0.402	0.712	0.319	0.572	0.669	0.166-2.702
Treatment modality	1.332	0.659	4.090	0.043	3.790	1.042-13.785

Note: DME, Diabetic Macular Edema; BMI, Body Mass Index.

ing contribution of this therapy to the improvement of visual quality and the reduction of ME.

Conclusion

To sum up, for DME, IVC + MPL render remarkable clinical benefits, which not only improve the visual quality of patients and inhibit ME, but also greatly reduce the number of injections, with promising clinical application potential and a value for clinical promotion. Our findings provide not only new insight into the application of IVC + MPL in the treatment of DME, but also novel options and clinical guidance for the treatment optimization of DME patients. Still, this study has some limitations that need further improvement. First, this is a small-sample study with possible information collection bias, so it is necessary to increase the sample size to improve the accuracy of the experimental results. Second, basic research has not yet been done, and further mining of the potential molecular mechanism will help to reveal the therapeutic mechanism of IVC + MPL in DME. We will constantly improve the research in the future to overcome the above limitations.

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Disclosure of conflict of interest

None.

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