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Therapeutic Effects of Combination Therapy and Photobiomodulation Therapy on Retinal Regeneration

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Abstract

Introduction: Many systemic and ocular diseases cause macular edema (ME). Macular edema is seen in two primary forms; the first is diffuse thickening of the macula, and the other is a macula with a distinct petaloid (cloverleaf) appearance called cystoid macular edema. Macular edema has a known role in the reduction of visual equity, and many options have been proposed for the reversal of this condition.

Methods: Articles on the effects of macular laser grid photocoagulation on diabetic macular edema (DME) or cystoid macular edema published between 2000 and 2022 were collected from PubMed, Google Scholar, and Web of Science. The following keywords were used for the search: "macular laser photocoagulation", "macular edema", "cystoid macular edema", "intravitreal pharmacotherapies", and "antivascular endothelial growth factor". Two hundred nineteen articles were found in google scholar and 165 articles in PubMed, and a total of 58 articles were included in the study after applying the exclusion criteria.

Results: We investigated the effects of various lasers photocoagulation such as Focal and/or grid macular laser, subthreshold micropulse laser (SMPL), as well as intravitreal pharmacotherapies with triamcinolone acetonide, and fluocinolone, and extended released intraocular implants such as Ozurdex, Retisert, Iluvien, and anti-vascular endothelial growth factors such as bevacizumab (Avastin), Eyela, and Lucentis. Corticosteroids were more effective than lasers, although some researchers have found that lasers and combined lasers and corticosteroids are more effective. In addition, some studies have shown that the frequency and concentrations of intravitreal pharmacotherapies are effective in increasing visual outcomes.

Conclusion: The results of the studies showed that the combined intravitreal corticosteroids are much more effective in improving visual acuity (VA) than a single corticosteroid, and the low concentration of the drug is safer. Still, corticosteroids have side effects such as increased intraocular pressure and glaucoma. Therefore, combining the medication with a laser is much more reasonable than each alone. Also, the subthreshold photocoagulation laser (670 nm) is better at reducing the central macular thickness (CMT) and improving VA than the micro pulse yellow laser and pan-retinal photocoagulation (PRP).

Keywords: Macular laser grid photocoagulation; Cystoid macular edema; Diabetic macular edema; Intravitreal pharmacotherapies.

Introduction

Some neurodegenerative disorders such as Parkinson's can cause damage to the central nervous system (CNS). Other disease including Covid-19 also has a destructive effect on different parts of the cerebral cortex.[1,2] Metabolic diseases can affect the peripheral nerve system and damage sensory structures. Given the critical part of the retina in the visual process, it is essential to

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pay attention to metabolic diseases and their effects. In diabetic patients, the leading cause of blindness is diabetic macular edema (DME); the retinal blood barrier is broken, and plasma and lipids leak into the macula. When the thickness of the fovea increases, the patient experiences a marked reduction in visual acuity (VA). There are inner and outer layers in the retinal blood barrier. Endothelial cells in the retinal vessel wall have tight junctions and form the inner layer. The outer layer is formed by the tight junctions between retinal pigment epithelial cells at their apical side. The first visible sign of DME is deep red spots (hemorrhage 15 to 60 μm in diameter) with saccular protrusions in the capillary wall and hard exudates from the microaneurysm. In clinically significant macular edema, increased retinal thickness occurs within the macular center (500 to 3000 μm), and concentrated exudates arise at a distance of 500 μm of the macular center.[3] Several factors are involved in the pathophysiology of DME, including increased vascular endothelial growth factor levels, decreased tight junction in endothelial cell proteins, and increased inflammatory factors such as prostaglandins and interleukins.[3] Cystoid macular edema occurs due to the hyperpermeability of macular capillaries in the retina, and collections of exudate accumulate as a polycystic expansion in the extracellular space.[4] The factors leading to cystoid macular edema disease include eye inflammation, diabetes, retinal vein occlusion, pars planitis, cataract surgical operation, laser approaches, and radiation retinopathy.[5] Multiple therapeutic options are used to treat macular edema, such as laser grid photocoagulation therapy, intravitreal pharmacotherapies, and pars plana vitrectomy with internal limiting membrane (PPV-ILM). They can be applied as monotherapy or combination therapy.

Laser Grid Photocoagulation Therapy

The use of photobiomodulation therapy has recently been considered in many diseases by stimulating cell migration and proliferation towards the damaged tissue and controlling inflammation, which will eventually cure the disease.[6] Macular laser photocoagulation in grid or focal type is seen as an essential treatment for DME research has shown that it can improve vision in some patients and reduce blindness by up to 50%. Several prospective and randomized studies have shown that the subthreshold micropulse laser (SMPL) is less invasive than the conventional macular laser because it uses lower irradiating energy.[7-11] In grid lasers, the need for oxygen is reduced by the destruction of retinal photoreceptors, while specific microaneurysms responsible for macular edema are targeted in the focal laser.[12,13] A study showed that in two patients after pars plana vitrectomy, barricade laser therapy around the macular hole could lead to the elimination of macular cystoid edema within 1 to 3 months.[14] In DME trials, the results of primary VA and central macular thickness (CMT) are consistent. Still, a study shows that blood glucose control by measuring hemoglobin A1c levels can effectively control diabetes in diabetic patients with macular edema.[15] The use of a red-subthreshold micropulse laser (670 nm) has been more successful in reducing central retinal thickness (CRT) thickness compared to yellow SMPL (577 nm).[16] Factors affecting threshold energy include cataract surgery, vitrectomy, and CMT.[17]

A study also showed that the 4-mg triamcinolone acetonide intravitreal injection (TA), which is more effective than grid *laser photocoagulation* (GLP), could improve VA and reduce CMT in clinical trials. This study performed laser grid photocoagulation after three months, and the mean follow-up was nine months.[18] A study also examined photocoagulation function three weeks after TA injection in diffuse DME. After triamcinolone injection, VA and CMT were measured at three weeks, three months, and six months. Macular laser coagulation effectively improved VA and CMT. They were found significant at three weeks but no longer effective at three or six months.[19] The group in 1984 showed that VA increased in people with macular edema due to branch retinal vein occlusion (BRVO) and VA (20/40 less).[20] To evaluate secondary stable macular edema caused by BRVO, a study using the subthreshold micropulse diode laser evaluated two factors of VA and CMT after six months. CMT decreased after 3 and 6 months but did not change significantly. Reductions of VA ≤ 20/40 were exhibited at 6 and 12 months. This study showed an effective treatment in patients with macular edema due to BRVO.[21] Likewise, a study showed that subthreshold photocoagulation reduced CMT in patients after six months but had no significant changes in macular sensitivity and mean best-corrected visual acuity (BCVA).[22] The second most common disease in retinal arteries is retinal vein occlusion. Thrombus in an obstructed retinal vein increases intravascular hydrostatic pressure, leading to secondary macular edema and vision loss.[23,24] A study showed that photocoagulation in patients with branch vein occlusion or macular vein occlusion had contractile effects on occluded veins, but no change in vessel diameter was observed. Venous contraction indicates success in laser function.[24] Another study showed that the subliminal effect of the micropulse yellow laser for one session on patients with cystoid macular edema due to retinitis pigmentosa improved BCVA and CMT one year after the first treatment session. Still, in BCVA, it was not statistically significant.[25] A study also showed no clinically significant differences in OCT thickness or VA using panretinal photocoagulation (PRP) in one session compared to 4 sessions on macular edema.[26]

Intravitreal Pharmacotherapies

In 65% of patients, a significant improvement in vision

is observed with GLP, but sometimes the results are not satisfactory. In 2001, the intravitreal injection of corticosteroids was tested as an alternative to laser photocoagulation. Numerous studies have used intravitreal pharmacotherapies such as intravitreal corticosteroid and antivascular endothelial growth factor (VEGF) injections as adjunctive or alternative therapies in macular edema secondary to BRVO. By inhibiting VEGF permeability and reducing inflammatory mediators, corticosteroids, including triamcinolone acetonide, fluocinolone, Bevacizumab, and dexamethasone, have been successful in curing macular edema.[27-29] However, the side effects of corticosteroids include increased intraocular pressure, which can lead to glaucoma.[30,31]

Antivascular Endothelial Growth Factor

In 2006, it was found that VEGF plays an essential role in retinal neovascularization and DME. Therefore, the researchers used anti-VEGF for intravitreal injection. VEGF intravitreal levels increase significantly after BRVO, and vascular permeability increases following the destruction of the retinal blood barrier, resulting in macular edema.[32] Results of a study showed that the visual outcome after intravitreal corticosteroid injection is better compared to intravitreal anti-VEGF monotherapy.[33]

Triamcinolone

A study also reported a 3-year outcome of patients receiving intravitreal triamcinolone (IVT) (1 and 4 mg) compared to the focal/grid laser. This study showed that between 2 years (initial result time) and three years, more success in increasing VA was observed in IVT compared to the focal/grid laser.[34] Another study also showed that the use of triamcinolone (1 mg) in patients with secondary macular edema to CRVO had better safety characteristics than triamcinolone (4 mg).[35] A study showed that in patients with diffuse diabetic macular edema (DDME), the injection of IVT (20 mg) for six months was able to temporarily improve VA.[36] In some patients with non-ischemic CRVO, the intravitreal injection of triamcinolone was also shown to be effective in treating CRVO,[37,38] and its 25-mg injection in patients with DDME had a significant effect on VA. and intraocular pressure with a 6-month follow-up.[39] A 4-month follow-up study in CME patients also found that triamcinolone could improve VA and CMT but suggested a follow-up period of the population.[40] A study showed that the low-dose intravitreal injection (2 mg) of triamcinolone was safe and effective in patients with pseudophakic cystoid macular edema.[41] A research study showed that in patients with DME, the injection of triamcinolone in a posterior subtenon was equally effective and safer than intravitreal injection.[42]

Bevacizumab

Bevacizumab, previously used as an anticancer drug, is currently used as an intravitreal injection for DME A study showed that in a patient with macular edema due to ischemic central retinal obstruction, three injections of bevacizumab within one month were more effective when used three months after diagnosis.[43] A report of 2-year outcomes from a study showed that after using bevacizumab for one year, the mean change in BCVA was at least 15 and 10, and the mean reduction in CMT was 146 μm compared to the micropulse laser trabeculoplasty with 118 μm.[44]

Aflibercept

The Food and Drug Administration (FDA) does not yet approve aflibercept as a VEGF inhibitor. A study showed that VA and macular thickness improved by using both aflibercept and bevacizumab in patients with macular edema due to perfused BRVO for 12 months.[45] However, some researchers have observed the effects of increased intraocular pressure. To compare aflibercept and bevacizumab to identify which one had the superior effect, treatment with intravitreal bevacizumab (IVB) acted like aflibercept in VA after six months.[46]

Others

A study showed that BCVA improvement after administration of 700 μg and 350 μg dexamethasone in patients with DME was 33% and 21.1%, respectively.[47] The study also showed a reduction in retinal hard exudates after the intravitreal injection of ranibizumab in patients with secondary macular cystoid edema to diabetic retinopathy or BRVO compared with untreated patients.[48] Another study showed that change in VA was not associated with the frequency of treatment with ranibizumab during the 12-month follow-up, but this treatment could reduce central subfield thickness.[49]

Combination Therapies

A study showed that combination therapy with IVB and macular laser photocoagulation had fewer effects on BCVA than IVB monotherapy.[50] Another study showed that cataracts and secondary glaucoma were more effective in IVT + GLP compared to the combined effect of IVB + GLP. Still, both treatments were effective in the treatment of macular edema due to branch retinal vascular occlusion.[51] A study also showed more success in improving vision with aflibercept injection compared to bevacizumab and ranibizumab in DME at one year. Still, when VA was less, there was no difference in the results between the groups.[52] One study found that the improvement in VA in dexamethasone + ranibizumab treatment at 24 weeks was not different from that of ranibizumab. The dexamethasone + ranibizumab group observed increased intraocular pressure and eye drops.[53] A study also showed intravitreal aflibercept could improve vision after macular laser photocoagulation in patients with DME.[54] In the treatment of DME, during the long-

term follow-up, using the grid laser and ranibizumab therapy was effective.[55] The combined effect of the yellow laser and SMLP photocoagulation with intravitreal ranibizumab showed that it could improve VA and central retinal thickness. Still, no significant difference was observed in the two groups (ranibizumab + subthreshold laser and ranibizumab).[56] Aflibercept treatment with a 16-week interval from the grid laser is promising for two years.[57]

Pars Plana Vitrectomy With Internal Limiting Membrane

Several studies have found that visual enhancement with vitrectomy and ILM peels is more successful than other treatments such as anti-VEGF injection and threshold or subthreshold grid lasers).[58-60]

Conclusion

In improving VA, the comparison of drugs showed that intravitreal corticosteroid injection is more effective than intravitreal anti-VEGF monotherapy, and triamcinolone (1 mg) is safer and more successful than triamcinolone at higher concentrations. Moreover, combining two drugs has a more substantial effect than a single drug. If we want to compare the effect of drugs with the effect of lasers, the combined effect of triamcinolone + GLP was much more effective than IVB + GLP in the treatment of macular edema. Subthreshold photocoagulation reduced OCT and improved VA compared to the micropulse yellow laser and PRP. Although corticosteroids have side effects such as increased intraocular pressure and glaucoma, the combined effects of corticosteroids with the SMPL (670 nm) are effective in increasing VA and CMT.

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Conflict of Interests

The authors declare that they have no conflict of interest.

Ethical Considerations

All protocols were confirmed by the Ethics Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.RETECH.REC.1400.008).

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