

Adjuvant Therapies for Diabetic Retinopathy Patients Undergoing Cataract Surgery: a Summary of Current Evidence

Katarakt Cerrahisi Uygulanan Diyabetik Retinopati Hastalarındaki Adjuvan Tedavi Yöntemleri: Mevcut Kanıtların Özeti

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ABSTRACT

Aim of this study, review the current evidence on cataract surgery in patients with diabetic retinopathy (DRP) and effect of adjunctive treatment modalities. A standardized PubMed search was performed and the articles with the highest level of evidence on each clinical scenario or treatment modality were selected for the purpose of this review. The progression of diabetic retinopathy or the risk of developing of macular edema was not reported to increase after phacoemulsification cataract surgery. In patients with preexisting diabetic macular edema, cataract surgery was shown to increase macular edema. Adjunctive treatment with intraoperative intravitreal administration of anti-VEGF agents (bevacizumab, ranibizumab) or steroids (triamcinolone, dexamethasone implant) was shown to prevent worsening of diabetic macular edema. Current evidence indicated that an adjunctive treatment is only needed in cases with preexisting diabetic macular edema when performing cataract surgery in diabetic retinopathy patients. While only intravitreal treatment modalities showed improvement in macular edema in such cases, there is no study available comparing the efficacy or safety of the above-mentioned treatment options when administered simultaneously with cataract surgery.

Key Words: Bevacizumab, cataract surgery in diabetic patients, diabetic macular edema, intravitreal steroids, ranibizumab.

ÖZ

Bu çalışmanın amacı, diyabetik retinopati (DRP) olan hastalarda katarakt cerrahisi üzerine mevcut kanıtları ve yardımcı tedavi yöntemlerinin etkisini gözden geçirmektir. Standart bir PubMed araştırması yapılmıştır ve bu klinik senaryo ya da tedavi şekli hakkında en üst düzeyde bilgi bulunan makaleler seçilmiştir. Fakoemülsifikasyon katarakt cerrahisi sonrası diyabetik retinopatinin ilerlemesi veya makula ödemi gelişme riskinin artmadığı bildirilmiştir. Daha önceden diyabetik makula ödemi olan hastalarda katarakt cerrahisinin mevcut makula ödeminin arttırdığı gösterilmiştir. İntraoperatif intravitreal anti-VEGF ajanlar (bevacizumab, ranibizumab) veya steroidlerin (triamsinolon, deksametazon implant) uygulanmasının, diyabetik maküler ödemin kötüleşmesini önlediği gösterilmiştir. Mevcut kanıtlar, diyabetik retinopati hastalarda katarakt ameliyatı yaparken sadece daha önceden diyabetik makula ödemi olan hastalarda yardımcı tedavinin gerekli olduğunu göstermiştir. Bu gibi durumlarda sadece intravitreal tedavi yöntemleri makula ödeminde düzelmeye rağmen, katarakt ameliyatı ile eşzamanlı olarak uygulandığında, yukarıda belirtilen tedavi seçeneklerinin etkililiğini veya güvenliğini karşılaştıran bir çalışma yoktur.

Anahtar Kelimeler: Bevasizumab, diyabetik hastalarda katarakt cerrahisi, diyabetik maküler ödem, intravitreal steroidler, ranibizumab.

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INTRODUCTION

Development of cataract is a common condition in the age group of diabetic retinopathy patients. Diabetes by itself also increases development of cataract.¹ Therefore, we often need to do cataract surgery to patients with coexisting diabetic retinopathy (with or without diabetic macular edema) in our daily clinical practice. We also know that cataract surgery exerts trauma to the eye and includes implantation of a foreign body, therefore cataract surgery by itself has the potential to induce ocular inflammation. Whether this inflammation increases progression of diabetic retinopathy adversely or not, has been a subject of debate for many years.^{2,3} The aim of this article is to review current evidence on cataract surgery and diabetic retinopathy relationship and try to clarify whether an adjunctive treatment is needed, if needed when and where.

We did a PubMed search with the terms “diabetic retinopathy and cataract surgery”, “diabetic cataract surgery and bevacizumab”, “diabetic cataract surgery and ranibizumab”, “diabetic cataract surgery and triamcinolone”. We selected and read the studies that were relevant to the subject. We only included data from articles presenting the highest level of evidence on a subject. When randomized controlled trial data was present on a subject, we did not include case series or retrospective surveys on the same subject, but when such level of evidence did not exist such as in the use of ranibizumab in cataract surgery patients with diabetic macular edema, we also accepted data from case series.

Uncomplicated phacoemulsification cataract surgery does not increase the progression of non-proliferative diabetic retinopathy. In patients with diabetes, who do not have macular edema, adjunctive treatments are not necessary during or before cataract surgery. In patients with diabetic macular edema, intravitreal injection of a medication used in diabetic macular edema (bevacizumab, ranibizumab, triamcinolone acetonide or dexamethasone implant) has been shown to prevent worsening of macular edema after cataract surgery.

CATARACT SURGERY AND PROGRESSION OF DIABETIC RETINOPATHY

The earlier studies on cataract surgery and diabetic retinopathy development suggested that cataract surgery increased the progression of diabetic retinopathy. Jaffe et al. reported that extracapsular cataract surgery with intraocular lens (IOL) implantation increased the progression of non-proliferative diabetic retinopathy (NP-DRP) compared to the unoperated fellow eyes of the same subjects.⁴ Henriksen et al. did a similar study in a group of patients with NP-DRP and proliferative DRP (PDRP) and found that the progression of DRP was not significantly different between the operated and unoperated eyes of the patients.⁵ In this study both ex-

tracapsular lens extraction and phacoemulsification accompanied with IOL implantation techniques were used.

Recent studies with phacoemulsification cataract surgery suggest that cataract surgery does not increase the rate of DRP progression, although there are some old reports with conflicting results. This difference between the results of the earlier studies and current data probably results from advancements in the techniques of cataract surgery and consequently a lesser induction of postoperative inflammation. Similar studies by Kepler et al., Squirel et al. and Romero-Aroca et al.⁶⁻⁸ assessed acceleration of diabetic retinopathy following uncomplicated phacoemulsification cataract surgery and found that progression of DRP was similar in both operated and unoperated eyes of the patients. On the other hand, in a recent paired eye comparison study, Hong et al. suggested that phacoemulsification cataract surgery may increase the progression of diabetic retinopathy (OR=2.21, 95% CI: 0.85–5.71), but this increase in progression in smaller compared to earlier studies with intracapsular and extracapsular lens extraction techniques.⁹ However, in that study the observed difference is not statistically significant, as the CI included values under and above 1.0, similar to the previous reports above. A summary of these studies is presented at Table 1.

Another question about cataract surgery in patients with diabetes was whether the risk of macular edema increases after cataract surgery. Three important studies in patients with symmetrical NP-DRP indicate that the risk of developing clinically significant macular edema was not increased in diabetic patients who did not have macular edema preoperatively.⁶⁻⁸ Degenring et al. and Biro et al. did similar studies to compare central macular thickness (CMT) with optical coherence tomography (OCT) in cataract surgery patients with diabetes and healthy controls.^{10,11} Both studies found that the risk of developing macular edema after cataract surgery was not significantly different between diabetic patients and healthy controls. In a recent study, Brito et al. compared macular and subfoveal choroidal OCT changes in a mixed diabetic retinopathy group and control subjects. In that study, foveal thickness increased at postoperative 1st week and 1st month in both control group and diabetic retinopathy patients, except for the ones who received bevacizumab injection for preexisting clinical significant macular edema (CSME). But none of the groups had a significant increase in subfoveal choroidal thickness. The authors hypothesized that the edema observed in foveal thickness was associated with surgical inflammation, but there was no disruption at the inner blood-retinal barrier and diabetic choroidal angiopathy.¹² These studies support the idea that modern cataract surgery techniques do not increase the progression of diabetic retinopathy.

Table 1. Cataract surgery and progression of diabetic retinopathy.				
Author – year	Country	N, follow- up period	Design	Result
Krepler et al. 2002	Australia	n=50, 1 year	Prospective observational study, paired eye comparison, mild-moderate NP-DRP	No additional risk for DRP progression and development of CSME
Squirrel et al. 2002	UK	n=50, 1 year	Prospective observational study, paired eye comparison, symmetrical NP-DRP	No additional risk for DRP progression and development of CSME
Romero-Aroca et al. 2006	Spain	n=132, 11+/-1.7 months	Prospective observational study, paired eye comparison, DM±NPDRP (symmetrical)	No additional risk for DRP progression and development of CSME
Hong et al. 2009	Australia	n=45, 12 months	Prospective observational study, paired eye comparison, just DM	OR=2.21 (95% CI, 0.85–5.71)
Degenring et al. 2006	Germany	DM n=24, HC n=84, 1 month	Prospective observational study, DRP vs.HC	Risk of developing ME is not changed (OCT study)
Biro et al. 2010	Hungary	DM n=18, HC n=53, 2 months	Prospective observational study, mild-moderate NPDRP vs.HC	Risk of developing ME is not changed (OCT study)
These studies indicate that risk of DRP progression and developing macular edema remain unchanged after phacoemulsification cataract surgery. (DRP: diabetic retinopathy, HC: healthy controls, ME: macular edema, CSME: Clinically significant macular edema, OCT: Optical coherence tomography)				

ADJUVANT TREATMENTS BEFORE CATARACT SURGERY

An important question about cataract surgery in these cases was whether a prophylactic treatment or completion of the DRP treatment before cataract surgery does any contribution to the long term final visual acuity of the diabetic patients. Suto et al. did a prospective study on the timing of panretinal photocoagulation (PRP) in DRP patients undergoing cataract surgery.¹³ The patients in this study did not have macular edema at the beginning of the study, if present macular edema was treated before the study. The first group received PRP three months before cataract surgery and the second group had first cataract surgery followed by PRP. Both groups of patients had similar final visual acuities at postoperative one year follow up, but PRP-first group had a higher aqueous flare until postoperative three months and this group was twice likely to develop macular edema postoperatively. The authors explained that inflammation induced by PRP was probably the reason why the PRP-first group had a higher risk of developing macular edema. They also suggested that treating patients with topical steroid for a longer period of time after PRP may be useful to reduce inflammation.

There are two important studies on the use of steroids in DRP patients undergoing cataract surgery. Kim et al. studied

the use of intraoperative subtenon injection of triamcinolone acetonide (STTA) in patients with mild/moderate DRP.¹⁴ In this study, they found that at postoperative one month visual acuity (VA) was better and CMT was thinner in the eyes that received intraoperative STTA compared to the eyes with phacoemulsification cataract surgery alone. But at 6th month, the VA and CMT were not significantly different between the two groups. Ahmedabadi et al. did a randomized controlled study on the use of intravitreal triamcinolone acetonide (IVTA) in patients with moderate DRP.¹⁵ They found that there was not any statistically significant difference in VA and CMT between the phaco + IVTA and phaco only groups, while intraocular pressure was significantly higher in the phaco + IVTA group. In four of twenty-three cases among the phaco only group, the development of CME was observed while none of the patients in the phaco + IVTA developed CME, but this difference was not statistically significant. (p=0.056) In a recent pilot randomized controlled study, Agarwal et al. randomized 18 eyes with diabetic cataract to phaco + dexamethasone implant group and phaco group. The authors found that there was no statistically significant difference in intraocular pressure and CMT between the two groups at postoperative 24th week. However, the change in the CMT and the gain of VA (ETDRS letters) was significantly different in favor of the dexamethasone implant group.¹⁶

Antibodies to neutralize vascular endothelial growth factor (VEGF) are commonly used in the treatment of diabetic macular edema. There are also some studies on the prophylactic use of anti-VEGFs before cataract surgery. Fard et al. studied the effect of 1.25mg intravitreal (IV) bevacizumab in a randomized controlled study (RCT) among patients with DRP.¹⁷ They found that CMT was higher in the phaco only group compared to phaco+1.25mg IV-bevacizumab group at postoperative first month, but at postoperative 6th month the VA and CMT was not significantly different between the two groups. Cheema et al. also studied the effect of intravitreal injection of 1.25 mg bevacizumab in a group of DRP patients with and without CSME¹⁸. They found that there was no significant difference between the two groups in VA and CMT at postoperative 6th month, but the progression of DRP was significantly reduced in the bevacizumab group at postoperative 6th month. Udaondo et al. performed a RCT with ranibizumab to observe the changes in CMT after cataract surgery¹⁹. They found that CMT and incidence of CME was decreased in the phaco + IV-ranibizumab group compared to phaco only group. But in this study long term results and visual acuity data is missing. The question whether the 6th month results between two groups would still have a significant difference or not remains unknown in this study. Chae et al. evaluated cataract surgery with ranibizumab or placebo injection in NP-DRP patients without macular edema²⁰. In this prospective RCT, they found that CMT and occurrence rate of CSME between the two groups was only significantly different at postoperative 1st month, and remained insignificant in the postoperative 3rd and 6th month visits, while total macular volume was significantly less in the ranibizumab group in each postoperative visit and mean BCVA was only significantly different at postoperative 6th month (p=0.046). This evidence is also controversial, as we mostly use CMT and BCVA in our routine clinical practice for follow-up of these patients rather than total macular volume. The current evidence supports the idea that we can not modify a risk which is not increased, with a prophylactic treatment.

ADJUVANT TREATMENTS IN PATIENTS WITH DIABETIC MACULAR EDEMA

The treatment of cataract patients with diabetic macular edema is different from patients with other NP-DRP patients, as macular edema by itself requires an intervention. The most commonly used treatment modality for DME are anti-VEGF agents. Lanzagorta-Aresti et al. did a RCT to answer whether intraoperative intravitreal injection of 1.25 mg bevacizumab improves ME, in moderate DRP patients with diffuse macular edema.²¹ They found that phaco + IV bevacizumab group had a better visual acuity compared to phaco + IV BSS injection group and CMT in the bevacizumab group did

not change significantly, but CMT in the sham group has increased in the postoperative 3rd and 6th months. Takamura et al. also did a similar RCT on patients with diabetic macular edema.²² They also found that phaco + 1.25 mg bevacizumab group had a better VA compared to phaco only group and CMT in the bevacizumab group was significantly reduced at postoperative 3rd month while CMT in the phaco only group was increased. Chen et al. has also reported a retrospective study where they treated DRP patients with CSME either with phaco + 2.5 mg bevacizumab or phaco only.²³ They have observed that CMT was decreased at postoperative 3rd month in the bevacizumab group, while CMT did not change in the phaco only group and BCVA was increased in both groups.

There is only one case series on the use of ranibizumab in diabetic macular edema. Rauen et al. performed cataract surgery to patients with macular edema refractory to laser treatment and used intravitreal 0.5mg ranibizumab for adjuvant treatment.²⁴ They have observed that BCVA had significantly increased, while CMT did not change significantly at postoperative 12th week. The lack of CMT reduction in this study may also be related to altered macular anatomy or severity of the cases rather than the anti-VEGF used in treatment, as these cases are not comparable to the cases in the above mentioned RCTs. There is a case series on the use of anti-VEGF and steroid combination therapy in cataract patients with diabetic macular edema refractory to laser treatment. Akinci et al. did cataract surgery combined with intravitreal 1.25 mg bevacizumab and 2 mg triamcinolone acetonide treatment and observed that BCVA of the patients increased and CMT of the patients were decreased at postoperative 3rd months of the treatment.²⁵ Sze et al. recently reported a case series with patients who underwent combined phacoemulsification and intravitreal dexamethasone implant. Twelve of these patients had diabetic macular edema and in these cases both visual acuity and CMT improved after treatment with median follow-up of 11.5 months.²⁶ Summary of related studies is presented at Table 2.

CONCLUSION

Diabetic patients are under increased risk of developing cataracts. The progression of diabetic retinopathy or development of macular edema has not been shown to increase after phacoemulsification cataract surgery. On the other hand, in patients with preexisting diabetic macular edema cataract surgery tends to increase diabetic macular edema. Adjuvantive treatment with intraoperative intravitreal bevacizumab/ranibizumab, triamcinolone or intravitreal dexamethasone implant has been shown to prevent worsening of diabetic macular edema and in some studies it has also been shown to ameliorate macular edema. There is no study on the use

Table 2. Adjuvant treatment modalities in cataract surgery patients with diabetic macular edema.				
Author – year	Country	N, follow- up period	Design	Result
Lanzagorta-Aresti et al. 2009	Italy	N=26, 6 months	Pilot randomized controlled trial. Phaco + IV bevacizumab vs. phaco + IV BSS	Visual acuity was better and macular thickness was thinner in the bevacizumab group.
Takamura et al. 2009	Japan	N=42, 3 months	Prospective, randomized, masked cohort study. Phaco + IV bevacizumab vs. phaco only	Visual acuity was better and macular thickness was thinner in the bevacizumab group
Chen et al. 2009	China	N=29, 12 weeks	Retrospective cohort, Phaco + IV bevacizumab vs. phaco only	Visual acuity was better and macular thickness was thinner in the bevacizumab group
Rauen et al. 2012	Brazil	N=11, 12 weeks	Prospective case series, Phaco + IV ranibizumab in patients with DME refractory to laser	Visual acuity improved significantly, no significant change was observed in macular thickness.
Akinci et al. 2011	Turkey	N=22, 3 months	Retrospective case series, Phaco + IV Bevacizumab + IV TA in patients with DME refractory to laser	Both visual acuity and macular thickness improved after treatment.
Sze et al. 2014	Hong Kong	N=12, 11.5 months	Retrospective case series, Phaco + IV Dexamethasone implant in patients with DME	Both visual acuity and macular thickness improved after treatment.

These studies summarized the adjuvant treatment modalities in cataract surgery patients with diabetic macular edema (DME: diabetic macular edema, IV: intravitreal)

of pegaptanib and aflibercept during cataract surgery of diabetic patients. There is also no data on whether these intravitreal injections increase the risk of endophthalmitis in these patients and the sample sizes of the current studies are not enough to provide such information. We do not have a study comparing the efficacy of different treatment modalities (bevacizumab, ranibizumab and triamcinolone acetonide) applied during cataract surgery of patients with diabetic macular edema.

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