

# Update on Surgical Approaches to Neovascular Age-related Macular Degeneration

## Yaşa Bağlı Maküla Dejenerasyonuna Cerrahi Yaklaşımda Yenilikler

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### ABSTRACT

Age-related macular degeneration (AMD) is the leading cause of vision loss in people 50 years of age or older in the developed world. Neovascular AMD (NVAMD) is the less prevalent type (15%), but responsible for 90% of cases of severe central vision loss. Over the years, many pharmacological and surgical treatments have been developed for NVAMD, among which anti-VEGF treatments are the current standard of care.

Regarding surgical techniques; firstly 'Submacular surgery with surgical removal of choroidal neovascularisation (CNV)' was found to be beneficial especially for hemorrhagic lesions. Secondly, 'Macular Translocation' came into use especially for cases with the damaged retinal pigment epithelium (RPE). Specifically full macular translocation was preferred. Another option is 'RPE Transplantation' which involves autologous transplantation, resulting in improved vision at the beginning. However, recovery is not persistent and there is still a risk of NVAMD. Besides, immunological reactions and rejection possibility are important limiting factors.

'Submacular Hemorrhage Displacement' is another approach, useful in cases complicated by massive submacular hemorrhage. Lastly, the 'GEM study' is an ongoing study regarding gene therapy in NVAMD and involves subretinal placement of lentiviral vector designed to inhibit the effects of both endostatin and angiostatin.

Although intravitreal anti-VEGF injections are the current standard of care, surgical techniques should also be kept in our armamentarium especially for cases complicated by submacular hemorrhage or large AMD lesions, and those that fail to respond or stop responding to anti-VEGF treatment.

**Key Words:** Age-related macular degeneration, neovascular, submacular surgery, translocation, submacular hemorrhage.

### ÖZ

Yaşa bağlı maküla dejenerasyonu (YBMD), gelişmiş ülkelerde 50 yaş ve üzeri popülasyonda görme kaybının önemli bir nedenidir. YBMD'nin bir alt tipi olan Neovasküler YMD ise daha nadir (%15) bir grubu oluşturmakla birlikte, ciddi santral görme kayıplarının %90'undan sorumludur. Yıllar içerisinde, Neovasküler YBMD tedavisine yönelik pek çok farmakolojik tedavi ve cerrahi yöntem geliştirilmiştir. Bunlar arasında anti-VEGF enjeksiyonları şu an için altın standart tedavi seçeneğidir. Cerrahi teknikler ele alındığında; ilk olarak koroidal neovaskülarizasyonun cerrahi çıkarılmasını kapsayan submaküler cerrahi yöntemleri hemorajik lezyonlar için, görme keskinliğindeki azalmanın önlenmesi açısından faydalı bulunmuştur. İkinci olarak, maküler translokasyon, özellikle retina pigment epiteli (RPE) hasarlı olan vakalarda kullanılmaya başlanmıştır. Başka bir seçenek olarak RPE transplantasyonu, olog transplantasyon olup, başlangıçta görmeye iyileşme sağlamıştır. Ancak düzelleme daimi olmayıp, neovasküler YMD riskini de taşımaya devam etmektedir. İmmunolojik reaksiyonlar ve rejeksiyon ihtimali de kısıtlayıcı faktörlerdir. Submaküler hemoraji boşaltılması ise diğer bir yaklaşım olup, masif submaküler hemoraji olgularında uygulanmaktadır. Son olarak, GEM çalışması, halen devam etmekte olan ve neovasküler YBMD hastalarını kapsayan bir gen tedavisi çalışmasıdır. Endostatin ve angiostatinin etkilerini inhibe etmek üzere tasarlanmış bir lentiviral vektörün subretinal alana yerleştirilmesini ele almaktadır.

İntravitreal anti-VEGF enjeksiyonları şu an için altın standart tedavi yaklaşımı olmasına rağmen; cerrahi tedavi yöntemleri de özellikle submaküler hemorajisi olan, YBMD lezyonları geniş olan ya da anti-VEGF tedaviye yanıtız vakalarda akılda tutulmalıdır.

**Anahtar Kelimeler:** Yaşa bağlı maküla dejenerasyonu, neovasküler, submaküler cerrahi, translokasyon, submaküler hemoraji.

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## INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of vision loss in people 50 years of age or older in the developed world.<sup>1</sup> The two types of macular degeneration are non-neovascular (“dry” form) and neovascular (“wet” form). The non-neovascular form (NNVAMD) is responsible for 85% of patients with AMD, and has a milder course unless it is in the type of ‘Geographic Atrophy (GA)’ which may lead to severe vision loss. Neovascular AMD (NVAMD) (15%) is less prevalent but responsible for 90% of cases of severe central vision loss.<sup>2</sup>

Over the years, many pharmacological and surgical treatment options have been developed for NVAMD. These are thermal laser photocoagulation, Photodynamic therapy with verteporfin and various surgical techniques involving submacular surgery, full or limited macular translocation, retinal pigment epithelium (RPE) transplantation and submacular hemorrhage displacement.

Recently, intravitreal vascular endothelial growth factor (VEGF) inhibitors became the gold standard in the management of most patients with NVAMD.<sup>3</sup> However, there is no effective treatment for GA as yet and micronutrient supplementation (vitamin-C, vitamin-E, beta-carotene) is the only option that is recommended in the prevention of disease progression.<sup>4</sup>

Anti-VEGF treatments are the current standard of care in NVAMD patients, and superior to surgical approaches. However, surgical approaches should still be kept in our armamentarium especially for AMD cases complicated by submacular hemorrhage, patients with large lesions of AMD, and patients who fail to respond or stop responding to anti-VEGF treatment.<sup>5</sup>

## SURGICAL APPROACHES

### Submacular Surgery with Surgical Removal of CNV

Vitreoretinal surgical approach was first used in reaching subretinal space and management of two important complications of choroidal neovascularisation (CNV) like submacular hemorrhage and fibrous scarring by Eugene de Juan and Robert Machemer in 1988.<sup>6</sup> In 1992, Matthew Thomas first described the submacular surgical technique in the removal of CNV. His study involved 58 patients having a preoperative mean vision 20/426 of which 33 had CNV due to AMD and 22 of these 33 patients underwent surgery. However, there were also patients in whom CNV was disconnected without removal (7 of 22) and CNV removal resulted in retinal pigment epithelium (RPE) transplant (4 of 22).

Assessment of vision directly after surgery revealed improvement of vision by 2 or more lines in 32% of the patients, stable vision within 1 line from baseline in 32% and deterioration of vision by 2 or more lines in 36% of patients. In the 68% of patients that did not improve, complications like irreversible tissue loss, scarring, retinal detachment (RD), proliferative vitreoretinopathy (PVR) and cataract were reported. The recurrence rate of CNV was 36%.<sup>7</sup>

Later, the Submacular Surgery Trial (SST) Research Group carried out several randomized control studies. Their initial study in 2000 was about the comparison of submacular surgery with laser photocoagulation. It was concluded that submacular surgery was not preferable to laser photocoagulation in their study group.<sup>8</sup> However, since it involved only 70 patients even with recurrent and previously treated CNV patients, their results were not statistically significant. In 2004, another randomized control trial was performed involving comparison of submacular surgery with observation alone, both in patients with new subfoveal CNV (group N) and in predominantly hemorrhagic CNV patients (group B) secondary to AMD. In this study, the main outcome was defined a priori as either improvement of BCVA or VA no more than 1 line worse than baseline. In terms of the primary outcome, results were similar in surgery and observation alone in both group N and group B. Specifically for group B, surgery did reduce the risk of severe VA loss as compared to observation. Quality of Life (QoL) assessment revealed that the surgery made no difference in a group B while favored a better QoL in group N. However, the surgery group had had more complications in both groups, higher percentage of cataract and higher recurrence rate at first but led to less recurrence by the end of the two-year follow-up. In the end, they concluded that although surgery maintained a smaller lesion during follow-up, it could not be recommended for the patients who met their inclusion criteria.<sup>9-12</sup>

In 2007, Falkner et al., published a comprehensive meta-analysis regarding submacular surgical surgery for NVAMD and evaluation of the results with SST. They evaluated data in the literature between 1992 and 2004. The primary outcome was the proportion of patients with 2 or more lines of improvement in VA and the proportion of 2 or more lines of deterioration in VA after surgery. They determined complication percentage as a secondary outcome. According to their study, patients with mean preoperative BCVA of 20/250 improved to mean final vision of 20/200. The percentages of patients with improvement of 2 or more lines and of deterioration of 2 or more lines were 28% and 25%, respectively; on the other hand, the recurrence and complication rates were 22% and 50%, respectively.

Their results seem to be more reliable but are greatly different than those of SST. However, it should be noted that better results could be primarily due to the predominance of studies with low level of evidence, the operation center in which visual outcome had been noted, or the selected population.<sup>13</sup>

### Macular Translocation

In patients with severely damaged RPE (Bruch's membrane and choroid complex), creating a new foveal complex onto a new, healthy RPE could be helpful in restoring visual functions. For this reason, Robert Machemer and Ulrich Steinhorst defined 'Macular Translocation (MT)' technique in three cases with massive submacular hemorrhage for the first time 1993. Although, their first case had improved VA from 20/200 to 20/80 in 5 months, the other two cases developed PVR with low vision.<sup>14</sup>

In 1996, Yoshihiko Ninomiya et al., reported a modification in technique which involved a smaller degree of retinal flap and less rotation, to show their effect on a decreased complication rate in three cases. The VA of the patients improved initially but epiretinal membrane proliferation, retinal detachment (RD) and neovascular glaucoma were seen as complications.<sup>15</sup> Eugene de Juan et al.,<sup>16</sup> defined 'limited MT (LMT)', a technique without large retinotomy in 1998 and reported a large series of 102 eyes in 2000. In their study, eighty-six (84.3%) of 102 eyes completed one-year follow-up. Percentages of patients achieving a VA better than 20/100 were 33% and 49% at 3 and 6 months, respectively. In addition, 37% and 48% of the study group experienced two or more lines of improvement on VA testing at 3 and 6 months, respectively. By the end of 6 months 16% of 102 eyes had greater than 6 lines of visual improvement. They also noted that good baseline vision, achieving the desired amount of macular translocation (62% in their study) and recurrent choroidal neovascularization at baseline were associated with better VA at 3 and 6 months. However, poor preoperative vision and the development of complications (9 cases of RD etc.) were associated with worse vision at 3 and 6 months.<sup>17</sup>

In 2001, Toth et al., investigated the effects of evolutions in instrumentation used in surgery, changes in anesthesia, and improved wide-field imaging systems on outcomes and complications of Full MT (FMT). They reported that shorter surgical time, less retinotomy requirement for RD induction and less postoperative RD cases with better VA were observed in the renovated group.<sup>18</sup> In 2009, a study involving two-year results of a randomized prospective controlled pilot clinical trial comparing FMT with PDT in 50 NVAMD patients came from Gelisken and Bartz-Schmidt et al. Their results suggested that FMT could stabilize BCVA and improve near VA (NVA) over a period of

two years in patients with subfoveal classic CNV secondary to NVAMD, whereas a decrease of BCVA and NVA was found in the PDT group. Contrast sensitivity (CS) did not differ between FMT and PDT. A significant increase of vision-related quality of life (VRQOL) scores was found in the FMT group but not in the PDT group.<sup>19-20</sup>

In 2010, long-term outcomes of FMT in NVAMD were evaluated by L. Da Cruz et al., with a three-year retrospective analysis. They found that 25% of this cohort maintained a three-line gain in VA at three years after macular translocation with close postoperative monitoring and early treatment of delayed complications (recurrent CNV, idiopathic macular edema, macular hole or macular pucker).<sup>21</sup>

Recovery of the sensory retina after FMT and its relation with preoperative measures like macular sensitivity, distance and near visual acuity, reading speed, contrast sensitivity, color vision, and National Eye Institute Visual Function Questionnaire-25 composite quality-of-life (QOL) scores were recently investigated by Toth et al.,<sup>22</sup> They found preoperative macular sensitivity to be independent of surgical outcome. Correlation between the preoperative median retinal sensitivity score and preoperative measures of visual function and vision-related QOL was generally poor, excepting modest correlation between contrast sensitivity and color vision. However, correlation between postoperative median retinal sensitivity score and postoperative measures of visual function and vision-related QOL was uniformly modest, and the change in median retinal sensitivity score correlated modestly with the change in most measures of visual function and QOL.<sup>23</sup>

### RPE Transplantation

RPE transplantation is based on the idea of maintaining a well-functioning RPE that favors restored and well-preserved visual functions. In this regard, although first studies investigated allogenic RPE transplantation, they easily led to several complications due to both the foreign tissue itself and the immunosuppression used for avoiding rejection.<sup>5</sup> In 1991, Peyman et al., transplanted autologous and homologous healthy RPE into the subfoveal space in two eyes with submacular scar secondary to AMD. The eye receiving autologous transplant had improved from 'counting fingers' to 20/400 with fixation over the transplanted RPE cells at 14 months follow-up. However, homologous transplant resulted in no improvement in VA after 10 months and the patient had a fine subretinal membrane without CNV.<sup>24</sup> In 2000, Thumann et al., reported transplantation of autologous iris pigment epithelial cells into the subretinal space to substitute RPE in addition to removal of subretinal fibrovascular membranes.

There was no evidence of any immunologic reaction during the entire follow-up. Their results involved 20 patients that all tolerated surgery well and followed-up for 6-11 months after surgery. Among them, 5 patients improved 3 or more lines in vision, 13 patients remained stable within  $\pm 2$  lines, and 2 patients had reduced visual acuity of 6 lines. In the group, 3 patients developed complications including RD, PVR, and macular pucker.<sup>25</sup>

In 2002, Binder et al., investigated autologous RPE transplantation in eyes with subfoveal NVAMD using the RPE cell suspension technique. 14 eyes were followed-up for 12-24 months. 57% had improvement by 2 or more lines in VA while only in one eye (7%) VA decreased by more than two lines. Since they did not report significant complications in their study group, it was hypothesized that healthy RPE transplantation may prevent CNV recurrence. Later, Falkner et al. also reported with a small randomized clinical trial comparing the RPE-choroid sheet vs. RPE suspension technique that these 2 approaches were comparable among the 14 patients and none showed CNV recurrence after 24 months of follow-up.<sup>26</sup>

In 2005, Mac Laren et al., reviewed the 5-6 year results of their previous studies and suggested that in spite of survival of RPE choroidal grafts in the subfoveal space for at least 5 years, the visual function recovery was not permanent. It could be the result of chronic photoreceptor apoptosis either initiated by surgery or the disease process itself.<sup>27</sup> Later, in a prospective interventional cohort study they had 12 patients who had undergone RPE transplantation after submacular removal of CNV. Successful viable grafts were seen in 11 patients as determined by RPE autofluorescence and choroidal reperfusion. Although it was noted that autologous RPE transplantation could in principle restore vision in neovascular AMD, the surgical complication rate was still high.

Operative complications occurred in 8 patients, including retinal detachment (RD) in 5 patients and hemorrhage affecting the graft in 4 patients. For future investigations they emphasized the possibility of gene therapies, since there is a disadvantage of autologous RPE transplants in terms of containing the same genetic information that may have led to AMD manifestation.<sup>28</sup>

### Submacular Hemorrhage Displacement

Massive submacular hemorrhage is a rare but advanced complication of NVAMD. The resulting visual outcome is obviously poorer than NVAMD alone. Anticoagulation or coagulopathies are also precipitating factors in addition to CNV in this regard.<sup>29-30</sup>

It seems to be more likely that this group of patients may get more benefit from surgical interventions.

Up to date, several surgical approaches have been investigated including simple pneumatic displacement,<sup>31-32</sup> pneumatic displacement with intravitreal Tissue Plasminogen Activator (tPA),<sup>33-35</sup> vitrectomy with subretinal tPA injection and gas tamponade,<sup>36,37</sup> and vitrectomy and retinotomy with mechanical clot evacuation.<sup>9-38,39</sup> In a non-randomized cohort study including patients that had undergone surgery within 72 hours of diagnosis as subretinal hemorrhage (SRH) by Ibanez and Grand et al. in 1995, mechanical clot extraction and tPA assisted lysis and drainage of SRH was compared. Although it was not statistically significant; their results favored the latter technique which had a better VA outcome. For all patients in the study, they noted 21% of the patients improved, and 24% of the patients deteriorated in vision by 2 or more lines.<sup>38</sup> When compared to the outcomes of SRH patients with no treatment applied, it was suggested that either surgical approach is significantly better in spite of the complication (RD, PVR) rate and the trauma risk to the retina.<sup>34</sup>

Later, Heriot et al. defined an intravitreal injection of tPA and expansile gas (SF6 or C3F8) as a less complicated in-office procedure and emphasized the better response in first 3 days of SRH.<sup>40</sup> However, there is still uncertainty in effectiveness of intravitreal injections of tPA regarding its access to subretinal space.<sup>41</sup> In 2010 Hillenkamp et al., compared intravitreal vs. subretinal injections of tPA and gas following pars plana vitrectomy (PPV). It was statistically significant that subretinal injection favors better outcome regarding removal of SRH. However, a higher risk of complication was noted and visual outcomes were not significantly better in the latter group.<sup>42</sup>

In 2007, Falkner et al., identified 264 cases from 16 studies regarding various techniques in the management of SRH. In their analysis, mean preoperative VA of 20/500 improved to mean final VA of 20/182; by using the logistic regression model, 62% of patients had an improvement in their VA by 2 or more lines while 13% deteriorated by 2 or more lines with a statistically significant difference. The overall recurrence of CNV was 16% and complications were observed in 37% of the patients. It is also emphasized that surgical approach was most beneficial in the SRH group since it showed a significant improvement rate and the lowest complication rate of the surgical modalities reviewed above.<sup>13</sup> Although, the SRH group was similar to the hemorrhagic (group B) group of the SST trial which had not as positive results as in this meta-analysis, the difference could be due to the extent of hemorrhage in the patients involved in the SST trial. As indicated, larger SRH area and poorer preoperative VA have more tendency to get benefit from surgery in the era of anti-VEGF treatment.

Unlike the long term outcomes of RPE transplants, the long term results of especially thick SRH displacement are particularly good.<sup>5</sup> Recent studies are based on subsequent administration of anti-VEGF and tPA in the surgical treatment of SRH. In 2009, Shah et al. hypothesized that submacular injection of ranibizumab in addition to tPA after vitrectomy with pneumatic displacement of massive SRH may be a more beneficial strategy in visual outcome of patients with massive SRH.<sup>43</sup> In 2010, Guthoff et al. compared injection of bevacizumab subsequent to intravitreal tPA and gas administration (12 eyes) vs. tPA and gas injection (26 eyes) alone in a retrospective, non-randomized consecutive case series. Anti-VEGF therapy was followed as a standard of care in all patients. Their results suggested that the former group has significantly better results in terms of mean BCVA and percentage of stabilized or improved BCVA.<sup>44</sup>

### GEM Study

There is an ongoing study in the Wilmer Eye Institute, Johns Hopkins University (JHU) by Campochiaro et al. regarding gene therapy in NVAMD. It is an open label, dose escalation study of RetinoStat® which is a non-replicating, recombinant lentiviral vector derived from the genome of the non-primate lentivirus called Equine Infectious Anemia Virus (EIAV). It is designed to inhibit the effects of both endostatin and angiostatin that have roles in angiogenesis and neovascularisation in the pathogenesis of CNV in AMD, on a long term basis. It is known that over expression of VEGF and neovascularisation in NVAMD is part of a chronic process that requires a sustained treatment protocol.

Currently, the NVAMD standard of care anti-VEGF therapy can control the disease progress only by repeated treatment procedures. This gene therapy, RetinoStat®, can stay up to 16 months after its subretinal injection and should be able to achieve sustained suppression of disease progress. Importantly, this lentiviral gene product acts on endostatin and angiostatin levels of only pathological blood vessels unlike anti-VEGF therapies and physiological and quiescent vasculature is not affected.

RetinoStat® also preferentially targets RPE cells that have an indispensable role in vision.<sup>45-48</sup> As a result of animal studies that have previously tested this lentiviral vector, it has to be applied into the subretinal space following vitrectomy in human beings.<sup>49-50</sup> Results will enable us to define effectiveness of therapy, possible adverse events, safety and feasibility of procedure.

Also, the data from this study will facilitate appropriately powered efficacy studies in a phase II/III clinical development program.

### CONCLUSION

Regarding all submacular surgery techniques, there are a similar number of patients in the deteriorated group as in the improved group. Both recurrences and complication rates are also significantly higher. Hemorrhagic lesions have more tendency to get benefit from surgery, since further deterioration in VA is prevented. However, there is no difference in patients with new lesions in terms of VA and the only advantage is better QoL. Therefore, unlike new lesions in which anti-VEGF therapy has a significant role as a standard of care, surgery should be kept in our armamentarium in advanced cases.

In case of macular translocation, it seems that LMT favors better VA since there is less rotation and no retinotomy. Studies involving FMT are also promising. FMT could be preferred to PDT in terms of better VA; however, it should be noted that it is mostly dependent on personal variations like preoperative VA, previous CNV etc. Nevertheless, surgical complications are the most limiting factors for this surgical group, too. Regarding RPE transplantation, it is important to note that transplantation of autologous RPE that has the same genetic information as the patients' tissue itself still carries the risk of NVAMD. Although it seems to improve vision at the beginning, the recovery is not persistent. There is a complication risk in this group, too. By the evolution of gene therapy, as promised similarly in GEM study, it would be possible to have transplants of genetically corrected RPE. This could lead to better results in vision and less recurrence

Since SRH is the advanced course of NVAMD; anti-VEGF therapy as a standard of care is less effective and utilization of surgery is obviously more prominent as compared to other patient groups. Although there is again a significant complication and recurrence risk, long-term results have proven that patients who have SRH get more benefit from surgery especially with a larger area of SRH. It has also been shown that surgery is better than observation alone; therefore it is better to intervene in SRH cases.

Anti-VEGF treatments are still keep the standard of care. The ANCHOR and MARINA trials involving intravitreal Ranibizumab injection disclosed superior results than PDT in terms of maintenance and improvement of vision and showed surgery to be the less commonly indicated treatment modality. However, these trials involved only patients with vision of 20/40-20/320 that indicate a relatively better vision.<sup>51-52</sup> Therefore, surgical approaches may have a more important role in maintenance and even in improvement of vision in people with worse visual functions.

Although all surgical approaches seem to have a high complication and recurrence risk, they may be a viable option for patients who have advanced complications and especially macular hemorrhage, unresponsive large lesions of NVAMD or those that fail to respond or stop responding to anti-VEGF treatment.<sup>5</sup> Gene therapy is a distinct area of research. As in the GEM study, sustained inhibition of neovascularization may be achieved. In the future, it may be possible to create genetically normal components of the disease process and their transplantation may lead to restored visual functions.

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