Macular translocation: histopathologic findings in swine eyes

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PURPOSE. *Macular translocation has been proposed as an alternative technique in the treatment of some cases of choroidal neovascularization. The purpose of the paper is to report the histopathologic findings in the retina of swine eyes undergone macular translocation.*
METHODS. *Ten eyes of ten Yucatan pigs underwent posterior pars plana vitrectomy and scleral imbrication to achieve macular translocation. Mattress sutures were preplaced at the equator of the eyes. After a pars plana vitrectomy, balanced saline solution was injected under the temporal retina to produce a retinal detachment. Scleral imbrication was achieved by tightening the mattress sutures. An air-fluid exchange was performed and the eye was filled with sulfur hexafluoride 18%. The eyes were enucleated 2, 4, 8 and 12 weeks after surgery and analyzed under light and electron microscopy.*
RESULTS. *Macular translocation was achieved in all cases. The major findings consist of a minimal decrease in the number of photoreceptors outer segments; also a change in the morphology was noted. This included some degree of loss of vertical alignment and an increase in the interphotoreceptor space. There was a recovery in the morphology of the photoreceptors over time.*
CONCLUSIONS. *Minimal changes in the photoreceptors and retinal pigment epithelium are observed when macular translocation is performed with recovery of these changes over time. Scleral imbrication is an effective technique to achieve translocation of the fovea.*
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KEY WORDS. *Choroid, Histopathology, Macula, Neovascularization, Surgery, Translocation, Treatment*

INTRODUCTION

Choroidal Neovascularization (CNV) is a major cause of severe visual loss in the United States and developed countries (1). The condition is a common complication in the course of Age-Related Macular Degeneration (AMD). This disease affects the elderly and is becoming more common as the number of individuals over the age of 65 increases. The two most common treatments for choroidal neovascularization are photocoagulation and surgical removal of the neovascular network. Neovascularization involves the area above the choroid and despite the relative success of laser photocoagulation for classic, well defined, extrafoveal regions of subretinal neovascularization (2, 3), irreversible damage to the foveal photoreceptors may occur in cases involving subfoveal location, resulting in an increased rate of central visual loss (4, 5). Unfortunately, the majority of lesions occurring in AMD are either occult or subfoveal in nature (6, 7),

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and while the Macular Photocoagulation Study (MPS) has shown long term benefits when treating selected cases with laser surgery, eyes with poorly defined or subfoveal choroidal neovascularization have a poor visual prognosis, resulting in legal blindness in most of the cases (2, 5, 8). The principal problem in most of the current treatments is the direct or secondary damage of the photoreceptors. In laser surgery, the destruction of the network under the retina by photocoagulation causes irreversible damage to the photoreceptors in the treated area. Removing subretinal tissue in macular surgery also includes the removal of pigment epithelium that secondarily causes damage to the outer retina (9,10). In order to maintain a viable retina, an innovative method was developed to relocate the foveal photoreceptors away from the network and onto a healthy or less damaged RPE: macular translocation.

Macular translocation has been proposed as a promising surgical technique for the preservation and restoration of visual function (11-17). The goal of the technique is to relocate the foveal photoreceptors away from the neovascular network and to place them onto healthy or less damaged retinal pigment epithelium (RPE).

This technique has undergone various modifications, and successful results in visual outcomes have been reported (12,13). These results suggest an anatomic and functional integrity of the photoreceptors when moved from its original RPE.

In 1993, Machemer and Steinhorst (11,12) reported performing foveal relocation. In their technique, the retina was completely detached and cut free with a 360° peripheral retinotomy at the ora serrata. The retina was reattached following rotation around the optic nerve; however, a poor outcome was obtained because of the high rate of development of PVR due to the size of the retinotomy.

Ninomiya and Tano (13) modified the size of the retinotomy to make it less than 180°.

The macula was rotated upward or downward, resulting in a radial fold that extended from the optic nerve head to the superior or inferior edge of the retinotomy, respectively. Using this procedure, a post-operative visual acuity of 20/20 was reported. But once again, manifestations of PVR were present.

After that, de Juan developed the method of scleral shortening to achieve foveal translocation (16,17). In one study that he conducted (17), a patient having undergone translocation by this method achieved a postoperative visual acuity of 20/30. The technique involved superotemporal or inferotemporal scleral resection and shortening as described in the report. Despite some secondary effects on the globe such as induced corneal astigmatism and torsional strabismus, the visual outcomes were promising. One of the advantages of this technique is the absence of a large retinotomy, decreasing the risk for development of PVR.

More recently a combined macular translocation and surgical excision of the membrane has been reported with good results (18). Furthermore, combined macular translocation and extraocular muscle surgery has been described (19). The technique described in this article has the advantage of reducing the risk of perforation to the globe since no scleral resection is performed.

The purpose of this article is to describe the histologic findings using light and electron microscopy in pig eyes undergoing macular translocation with the technique of scleral imbrication.

METHODS

All procedures were performed following the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. Ten female 6-month-old Yucatan pigs weighing 13.5 to 16.7 kg were used for the project. Foveal translocation was performed on each of the right eyes, and the left eyes were used as a control. All of the pigs were placed under general anesthesia after an initial intramuscular injection of acepromazine (0.2 mg/kg), atropine (0.05 mg/kg), and ketamine (22 mg/kg) and an intravenous injection of bruprenex (0.05 mg/kg - 0.1 mg/kg). One gram of cefazolin sodium, USP was given the day of surgery. The pupils were dilated with topical phenylephrine 10%, atropine 1%, and tropicamide 1%.

Surgical technique

In order to provide a better view of the surgical field, a lateral canthotomy followed by a 360° peritomy were performed. The rectus muscles were then isolated and hooked with 2-0 silk sutures, allowing rotation of the eye and exposure of the posterior sclera. The method
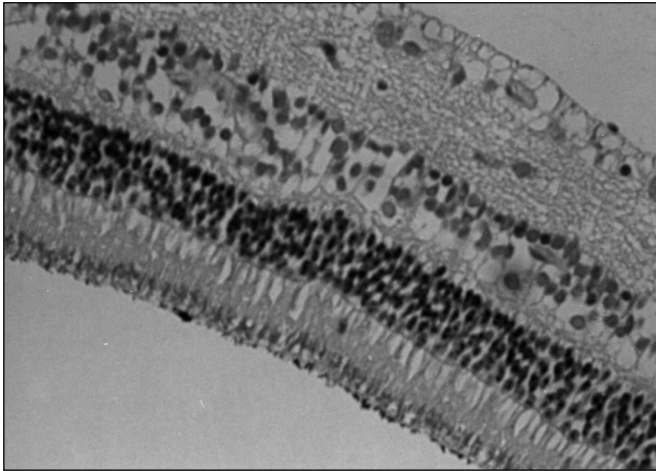
Fig. 1 - *Light microscopy of the area of translocation 8 weeks after surgery, (outer and inner layers of the retina). The morphology of the inner retina is preserved (HE 400x).*

used to achieve the translocation of the macula consists on pars plana vitrectomy and scleral imbrication.

First, five Nylon mattress sutures were placed for 130° in the superotemporal quadrant at the equator of the pig eye. The sutures were pre-placed but not tied. A conventional three-port pars plana posterior vitrectomy was performed, placing the infusion cannula 2 mm posterior to the limbus in the inferotemporal quadrant. Two sclerotomies were made 2 mm posterior to the limbus using a 20ga MVR blade in the superonasal and superotemporal quadrants. First, a central vitrectomy followed by the removal of the posterior cortical vitreous was performed. After that, the retina (the temporal retina) was detached internally by injecting saline solution in the subretinal space with a 32ga cannula. We used three injection sites: inferior, superior and temporal to the macula. Once we achieved retinal detachment of the temporal retina, the preplaced sutures were then tied, creating a fold in the sclera. Finally, an air-fluid exchange was performed and sulfur hexafluoride (18%) was injected into the vitreous cavity. Post-operatively, atropine was administered twice a day and prednisolone, polimyxin, and neosporin four times a day for 2 weeks.

Histopathologic study

The pigs were followed every week after surgery with indirect ophthalmoscopy to assess retinal attachment. The animals were then euthanized with KCl (3 cc) and
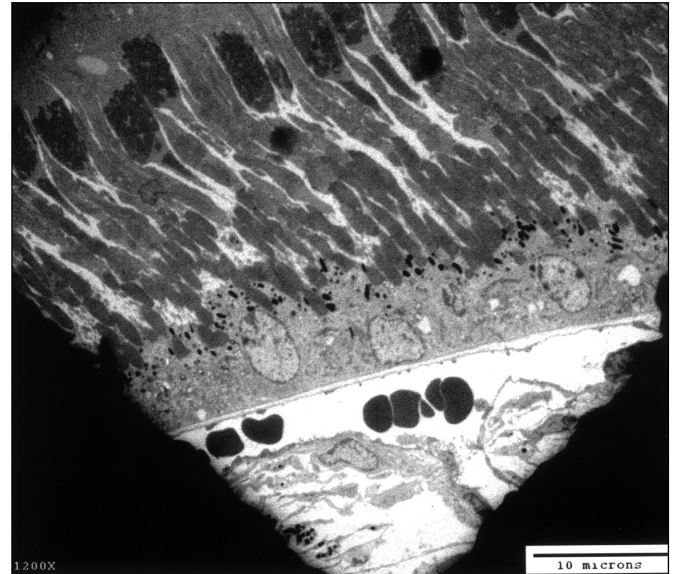

Fig. 2 - *Electron micrograph of the control eye. Normal photoreceptor RPE complex showing the alignment of the outer segments and the morphology of the RPE (1200x).*
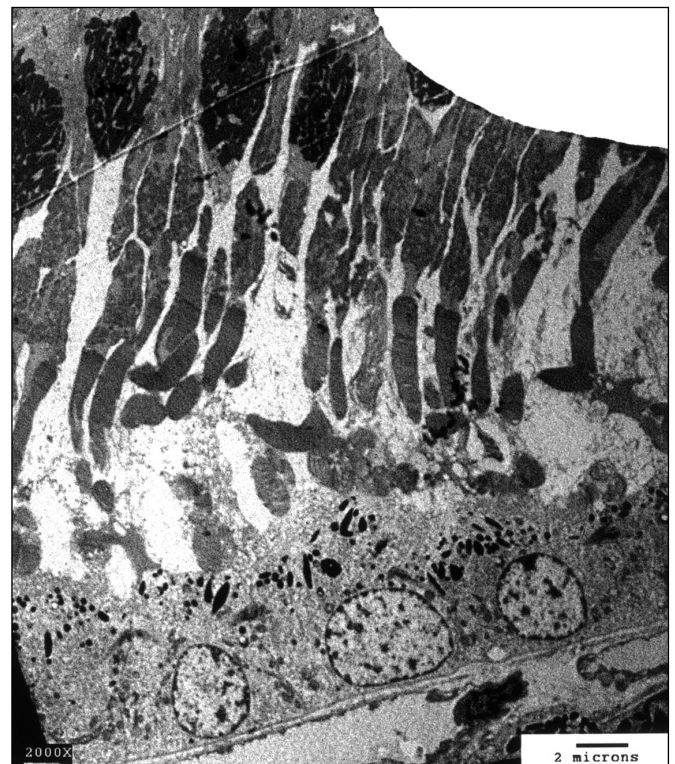

Fig. 3 - *Electron micrograph of the area of translocation 2 weeks post-operatively. Note the minimum decrease in the photoreceptor number, an increase in the interphotoreceptor space and the loss of the alignment of the outer segments in this area. (2000x).*
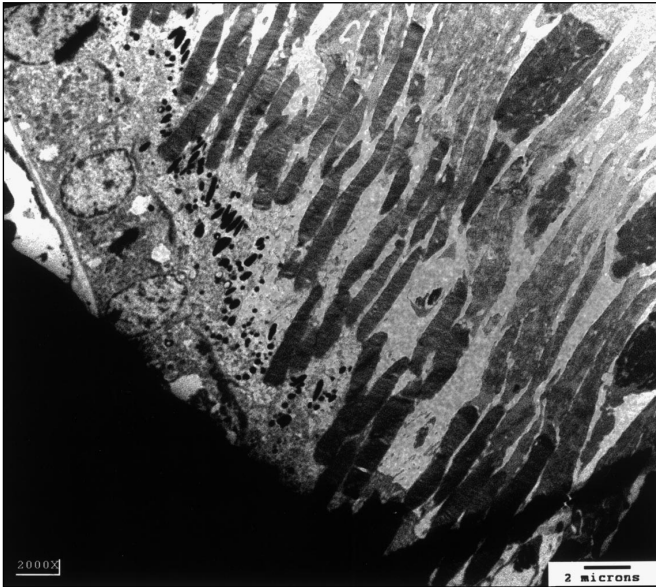
Fig. 4 - *Electron micrograph of the area of translocation 8 weeks post-operatively. No significant cell migration or proliferation were found (2000x).*
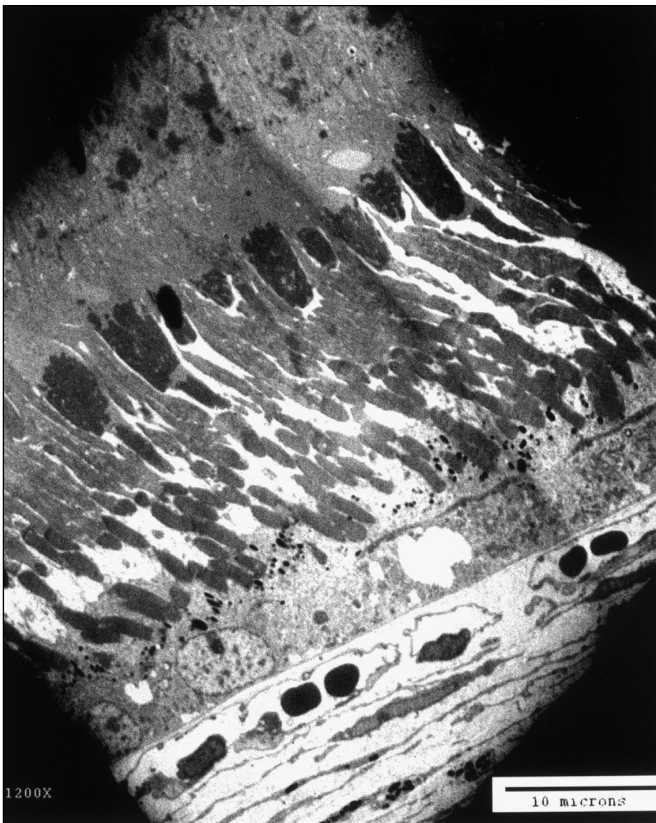

Fig. 5 - *Electron micrograph of the area of translocation 8 weeks post-operatively. A re-establishment of the morphology in the outer retina is observed (2000x).*

enucleated 2 weeks (4 pigs), 4 weeks (2 pigs), 8 weeks (2 pigs), and 12 weeks (2 pigs) after surgery. Globes were analyzed using light and electron microscopy.

For light microscopy, a coronal cut was made after enucleation at the limbus of each globe, and the specimens were placed in a 10% neutral buffered formalin fixative for 24 hours.

The tissues were then embedded in paraffin and cut by a microtome at 2 µ thickness. Sections were mounted onto slides and stained with hematoxylin and eosin.

For electron microscopy, a coronal cut was made, removing the anterior segment to allow the fixative to penetrate the vitreous cavity. Samples were placed in 2% cacodylate glutaraldehyde overnight and post-fixed in 2% osmium tetroxide. Sections 0.5 micron thick were cut and stained with toluidine blue. Finally, 70 nm thin sections were cut and double stained with uranyle acetate and lead citrate. Samples were analyzed under a JEOL JEM 1210 EM equipped with digital imaging.

One of the 10 pigs developed postoperative proliferative vitreo-retinopathy (PVR) and retinal detachment during follow-up. Macular translocation was achieved in all cases, with the macula moved inferiorly about half disc diameter. On gross examination of the globe, a scleral fold covered by retina could be identified superotemporally to the macula.

Histopathologic findings

The major changes observed under light and electron microscopy were found on the outer layers of the retina, and the morphology of the internal retina was preserved (Fig. 1). When compared to the control eye (Fig. 2), the changes in the photoreceptor outer segments consist of a minimum decrease in number in some parts of the area of translocation as well as an increase in the interphotoreceptor space. A minimal change in the morphology was noted, including some degree of loss of vertical alignment; this was especially noted at 2 weeks post-operatively (Fig. 3).

The normal morphology of the retinal pigment epithelium was preserved, including the interdigitations with the photoreceptor outer segments. We did not find migration or proliferation of cells in the subretinal space or within the retina (Fig. 4). Over time, a recovery of the alignment of the photoreceptors with a

decrease in the interphotoreceptor space and reestablishment of the photoreceptor-RPE interface was noted (Fig. 5); the morphology of the RPE-photoreceptor complex and photoreceptor outer segments were normal at 12 weeks.

No changes were found in the choroid; the structure of the vessels was normal in the area of the scleral fold.

DISCUSSION

Age related macular degeneration is the leading cause of severe, irreversible, central visual loss among adults aged 65 years and older in the United States and developed countries (1, 20). Although the atrophic form is more common, the exudative form is responsible for severe visual loss in up to 90% of patients (21). The management of the disease has produced disappointing results. Laser photocoagulation is the only treatment proven by a controlled study to be beneficial; but the long-term visual outcomes are only slightly better than those resulting from the natural course of the disease in most of the cases (2, 5, 8, 22, 23). Many alternative methods have been used in the management of the disease: radiation therapy, retinal pigment epithelium transplantation and subretinal surgery for the removal of the neovascular membrane.

Unfortunately, the visual outcomes are still lacking and investigations of these procedures and others continue (24-31).

The clinical results and visual outcomes in macular translocation surgery performed in patients with AMD, suggest that the RPE-photoreceptor complex is functional after moving the photoreceptors to a different location. The results of this study demonstrate a minimal change in the RPE-photoreceptor complex, with no change in the internal layers of the retina and choroid.

In a previous report (16), translocation of the macula was performed in the rabbit eye. In a brief description of the histopathologic study they noted mild morphologic damage to the outer retinal layers and a normal morphology for the inner layers. Some retinal pigment epithelium cell proliferation and multi-layering were evident. It is important to note that the study was performed in the rabbit, which lacks capillaries in the neural retina. We used the pig eye for our study because its vascularity more closely resembles the human retina. As opposed to the study in rabbits, we did not find any proliferation of RPE or other cell types. Due to the presence of capillaries in the neural retina in the pig, a better recovery of the photoreceptor-RPE complex is expected in this species. The availability of vascularized retina may explain this difference.

We observed a minimal decrease in the number of the photoreceptor outer segments in some areas; this could be explained by mechanical damage during the injection of fluid to detach the retina. We also observed minimal damage to the outer retinal layers with improvement and recovery after a period of time. In published data of experimental retinal detachment and reattachment (32-34) changes in the outer layers of the retina, specially in the photoreceptors and RPE have been described, these changes increase with the time of detachment; however, once the retina is reattached there is some recovery from these changes. The degree of recovery basically depends upon the time of reattachment. In macular translocation surgery, the retina is detached for a very short time so the changes in the outer layers are expected to be minimal as we demonstrated.

The results also support the idea that foveal photoreceptors can be placed on a non-specific RPE location with a recovery of anatomy and function.

The technique of scleral imbrication appears to be an effective and safe method to achieve translocation of the macula.

Macular translocation is still a procedure under investigation and is not indicated in all cases of choroidal neovascularization, however the clinical and histologic results suggest that this procedure can have a role in the treatment of CNV.

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