

ijo

Indian Journal of Ophthalmology



official journal of
ALL INDIA OPHTHALMOLOGICAL SOCIETY

ISSN : 0301-4738
Vol 66, Issue 2, February 2018



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Transcleral approach for closing retinal tears using DuraSeal™ hydrogel sealant

Tilda Barliya¹, Shai Sandalon², Ron Ofri², Tami Livnat^{1,3,4}, Dov Weinberger^{1,3,5}

Purpose: The aim of this study was to evaluate an innovative approach for closing retinal tears using DuraSeal™ (DS) hydrogel sealant in a rabbit model. **Methods:** Retinal detachment with a small tear was performed on 20 New Zealand rabbits. Thereafter, rabbits were divided into two groups; the experimental group received a transscleral injection of 0.1 ml DS into the subretinal space whereas the control group received sham injection of saline. Eyes were clinically evaluated using indirect ophthalmoscopy, retinal function was recorded in ten rabbits by electroretinography and the sealant's toxicity was evaluated histopathologically. **Results:** We found that the DS hydrogel was easily injected transsclerally into the subretinal space of the detached retinas with no major complications. Retinal reattachment was seen in both groups within 2 weeks with no toxicity to the sensory retina. There were no significant differences in retinal function between groups. **Conclusion:** Subretinal injection of hydrogel through a transscleral route is easy to perform and may open a new avenue in the treatment of retinal detachment. However, the efficacy of the DS as a tamponade for sealing retinal tear is yet to be definite. Long-term clinical, functional, and toxicological studies are needed to evaluate its full potential for clinical applications.

Key words: DuraSeal hydrogel sealant, retinal detachment, retinal tear, transcleral approach

Rhegmatogenous retinal detachment (RRD) is a serious condition in which the retina is detached from the underlying retinal pigment epithelium (RPE), and if left untreated it can lead to vision loss and blindness. In the course of the disease, vitreous traction, trauma, or injury to the eye may cause a small tear or a break in the retina allowing vitreous fluids to accumulate in the subretinal space and thus lead to its detachment.^[1,2] Therefore, closure of the retinal hole and reattachment of the retina are the primary aims of treatment. Several gold-standard approaches are available to treat retinal holes, including laser, cryotherapy, sclera buckle, gas, and silicon oil; however, they all have disadvantages due to their high invasiveness, potential cellular toxicity, and complications leading to cataract formation and glaucoma.^[3,4] In view of the limitations associated with these surgical techniques, development of a safe and efficacious treatment with minimal toxicity and invasiveness which takes into consideration the anatomical and physiological constraints of the eye remains challenging.

In recent years, the need to improve the treatment of retinal detachment envisioned a logical alternative in the form of a biocompatible and biodegradable sealant to close the retinal breaks. Some intraocular adhesive glues, including

cianoacrylate, fibrin glue, and others have been used to patch retinal breaks in experimental retinal detachment models and in clinical cases yet, each glue has limitations and is not an ideal treatment for closing retinal breaks. Recently, adhesive and liquid hydrogels are potential tissue sealants since they are hydrophilic, flexible, and biodegradable, and therefore, they have been evaluated for their efficacy in closing retinal breaks with minimal toxicity.^[5-8] Campbell *et al.* reported DuraSeal™ (DS) sealant to have the fastest reaction time, highest strength, and moderate water uptake among the tested sealants.^[9] This hydrogel was later evaluated by Sueda *et al.*^[7] as treatment for closing retinal breaks. In spite of the promising advantages of the hydrogel, the authors encountered a low success rate, mainly due to technical problems in the mixing of the liquid glue and side effects associated with its intraocular application. This, in turn, led us to develop a different strategy for closing retinal holes using this DS hydrogel delivered through a transscleral route as discussed by Gupta *et al.* and Patel *et al.*^[10,11]

Developing a new delivery approach which takes into consideration the anatomical and physiological constraints of the eye, as well as the chemical properties of the hydrogel, should be further explored and we believe that transscleral delivery may offer a potential new route using DS hydrogel for tissue repair.

¹Laboratory of Eye Research, Felsenstein Medical Research Center (FMRC), Rabin Medical Center, Petah Tikva, ²Koret School of Veterinary Medicine, The R. H. Smith Faculty of Agriculture, Food and Environment, The Hebrew University of Jerusalem, Rehovot, ³Division of Ophthalmology, Rabin Medical Center, Beilinson Campus, Petah Tikva, ⁴The Israeli National Hemophilia Center, Sheba Medical Center, Tel Hashomer, ⁵Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

Correspondence to: Dr. Tilda Barliya, Felsenstein Medical Research Center, Rabin Medical Center, Laboratory of Eye Research, Beilinson Campus, Petach Tikva 49100, Israel. E-mail: tildabarliya@gmail.com

Manuscript received: 27.08.17; **Revision accepted:** 27.10.17

Access this article online

Website:

www.ijo.in

DOI:

10.4103/ijo.IJO_758_17

Quick Response Code:



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Cite this article as: Barliya T, Sandalon S, Ofri R, Livnat T, Weinberger D. Transcleral approach for closing retinal tears using DuraSeal™ hydrogel sealant. Indian J Ophthalmol 2018;66:238-43.

In this study, we evaluated the efficacy of DS hydrogel sealant in closing retinal holes and explored a transcleral approach as a new paradigm in retinal reattachment surgeries.

Methods

Surgery to induce rhegmatogenous retinal detachment

Twenty New Zealand albino rabbits (Harlan Biotech Israel Ltd., Jerusalem, Israel) weighing 1.5–1.7 kg were used in this study. Animals were handled according to the recommendations of the ARVO statement for the Use of Animals in Ophthalmic and Visual Research and the hospital's Institutional Animal Care and Use Committee.

All procedures were carried out in the right eyes with sterile techniques under a surgical microscope. Animals were anesthetized by intramuscular (IM) ketamine hydrochloride (35 mg/kg), and xylazine (5 mg/kg). Pupils were dilated with topical 0.5% phenylephrine hydrochloride, 0.5% tropicamide, and 1% atropine. Conjunctival peritomy and sclerotomy of 180° (from 0800 to 1400 h) were carried out at the corneoscleral limbus, and a two-port vitrectomy was performed. An infusion port was made 1 mm posterior to the sclerocorneal limbus in the inferotemporal quadrant using a small gauge stiletto (Accurus Surgical System 25-gauge; Alcon, TX, USA), and a 25G infusion cannula that delivered a balanced salt solution (BSS; Alcon Japan) was then inserted into the trocar cannula.

The second port, created in the same manner, was used for inserting a vitreous cutter into the superotemporal quadrant. Subsequently, we performed a core vitrectomy, and retinal detachment was made approximately 2–3 DD from the optic nerve by injecting 0.1 ml BSS under the retina using a 25G-soft-tip needle (Alcon, TX, USA). The same 25G-soft-tip needle was used to create a small tear in the retina.

Hydrogel and its delivery

DS dura sealant system (Covidien Mansfield, MA, US) is a biodegradable and biocompatible hydrogel, Food and Drug Administration-approved for cranial and spinal dura surgeries.^[12] It can adhere strongly to moist tissue. This hydrogel is composed of two synthetic liquids – a polyethylene glycol (PEG) solution with a gel-like texture (>90% water), and an amine component, which acts as a precursor. The PEG is a nontoxic, water-soluble chemical that increases biocompatibility. On mixing of the two components, polymerization occurs

within 20 s without generating heat, leading to the formation of a solid, flexible, and adherent hydrogel layer. The hydrogel swells as it absorbs fluid from its surroundings. In reality in the eye, the polymerization process was instant.

Immediately after the detachment was performed, rabbits were divided into two groups, 12 in the experimental group and 8 in the control group. Since the hydrogel was used as a surrogate for subretinal tamponade, more animals were allocated to the experimental group. In this group, a total volume of 0.1 ml of the PEG and the amine component (0.05 ml each) were injected under direct visualization into the subretinal space through the sclera of the right eye of each treated rabbit. Since the detachment was induced in the peripheral retina closer to the limbus, there was no need to induce globe prolapse. The injection was conducted in two steps, with the PEG (containing a blue tracer) injected first to allow good visualization, immediately followed by the injection of the clear amine solution, thus enabling the mixing of the two liquids and formation of the gel. The tip of the needle was inserted into the globe tangentially (bevel-away-from-sclera so that when the needle was in the subretinal space of the previously induced retinal detachment, the bevel was away from the retina). In the control group, 0.1 ml of BSS was injected transsclerally into the subretinal space of the right eye of the rabbit. In both groups, the left eyes were left untouched as internal controls. All operated eyes were treated with 5% chloramphenicol ointment at the end of this procedure.

An illustration of the injection procedure is shown in Fig. 1.

Clinical examination of the fundus was conducted using an indirect ophthalmoscope (Vantage Plus Digital Indirect Ophthalmoscope®, Keeler Ltd., Windsor, UK) and performed on the 1st, 3rd, 7th, 14th, and 21st postoperative days. Operated eyes were monitored for the presence of a detachment and a retinal tear, as well as other potential ocular complications.

Electroretinography

Electroretinographies (ERGs) were recorded on ten rabbits (5/group) a week before, and 7 and 20 days after surgery. Following overnight dark adaptation, the rabbits were anesthetized with an IM injection of ketamine (60 mg/kg) and xylazine (8 mg/kg) and pupils were dilated with 0.5% tropicamide at least 8 min before the beginning of the ERG session. Subcutaneous needles at the base of the left ear and

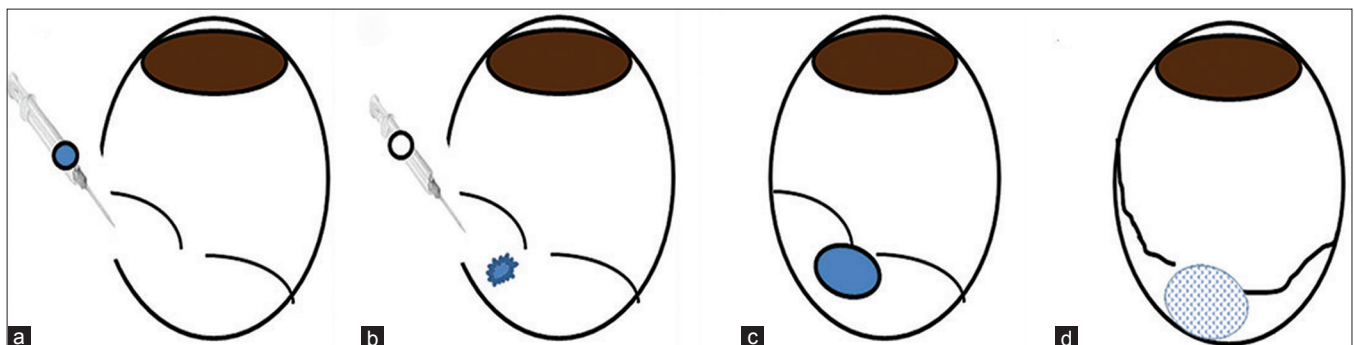


Figure 1: Illustration of transscleral delivery of DuraSeal™ hydrogel for closure of a previously induced retinal break and detachment. (a) Transscleral injection of DuraSeal™ polyethylene glycol solution to the subretinal space, (b) Transscleral injection of the amine solution, (c) The two components of the hydrogel mix and polymerize, (d) The hydrogel swells as it absorbs water from its surroundings. The hydrogel forms a subretinal tamponade and closes the retinal tear

at the lateral canthus of the recorded eye served as ground and reference electrodes, respectively. After application of topical anesthesia (oxybuprocaine 0.4%) and conductance medium (hydroxymethyl cellulose 1.4%), a jet corneal active electrode was placed. Impedance was kept below 2 k Ω . The operated eye was recorded first. Recordings were conducted using an integrated system (HM_sERG, Ocuscience, NV, USA) with band-pass filter of 0.3–300 Hz. Flash stimuli and background adapting light were delivered unilaterally with a “miniganzfeld” dome placed about 3 cm from the recorded eye. The rabbit was positioned in lateral recumbency on a pillow, thus preventing light exposure of the unrecorded eye. Responses to the standard protocol of the International Society for Clinical Electrophysiology of Vision [Table 1] were recorded.

a- and b-wave amplitudes were measured from baseline to the first trough and from that trough to the next positive peak, respectively.

Electroretinography statistical analysis

Since the same individual rabbits were repeatedly recorded throughout the study, ANOVA with repeated measures was used. Within-Subjects ANOVA was used where the two different conditions were the day of recording and flash luminance. The group effect was measured both within subjects (i.e., as the interaction between recording day and group) and between subjects. Error bars and “ \pm ” indicate standard deviation.

Histology

At the end of a 3-week follow-up, animals were euthanized with an overdose of pentobarbital (Vetmarket, Shoham, Israel) and both eyes were enucleated for histological evaluation. Eyes were fixed in 4% Formalin for 24 h, dehydrated by increasing sucrose gradient and cryopreserved in OCT. Serial 10 μ m cryosections were stained with H and E (American MasterTech Scientific[®], Lodi, CA, USA) and examined by light microscopy (Olympus Optical Co., Tokyo, Japan).

Results

Clinical findings

To explore the surgical approach, RRD was created in 20 rabbits as described and transscleral injections of either saline or DS hydrogel were performed. The area of the detachment

was dramatically reduced 3 days posttreatment and absorbed by the 14th day, in both groups regardless to the treatment. In 2/12 rabbits in the experimental group, the eyes became hypotonic following induction of RRD, thus making it difficult to inject the hydrogel. However, once the pressure in the eyes was restored, transscleral injection of the hydrogel was easily feasible. In addition, these two eyes had minor and local hemorrhage immediately after the detachment procedure, which resolved between 1 and 3 weeks postoperatively [Fig. 2]. Furthermore, two eyes in each group developed a fibrotic membrane within 14 days postoperatively, thus hindering our ability to perform additional follow-up examinations of the fundus.

Electroretinography

ERG was used to study retinal function in ten saline-treated and ten DS-treated rabbits. Fig. 3 shows the a-[Fig. 3a] and b-[Fig. 3b] wave amplitudes of intact (i.e., the contralateral, not operated eyes) and retinal detachment eyes before surgery and at 7 and 20 days postsurgery. The time-dependent changes in the a-wave amplitudes of operated eyes were found to be significant [Fig. 3a, ANOVA of repeated measures, $P < 0.05$] yet these changes were similar across hydrogel and saline treatment groups. Dark and light-adapted b-wave amplitudes remained unaffected regardless of treatment group [Fig. 3b, ANOVA with repeated measures, $P > 0.30$]. Although an interesting reduction in a sub b-wave was noted in both groups (manuscript in review).

Histology

We examined the retinas for pathological changes that might be associated with the transscleral approach and for potential toxicity of DS. Histological analysis performed 21 days after RD

Table 1: Electroretinography protocol sequence. The interval between consecutive steps was 2 s except for 30 s between steps 2 and 3

Step	Flash intensity (cd*s/m ²)	Number of flashes averaged	Interval between flashes (s)
1	0.01	10	2
2	3	4	10
3	10	4	20
4	Light adaptation: 30 cd/m ² for 10 min		
5	3	32	0.5
6	10	32	0.5
7	3	128	0.032 (flicker)
8	10	128	0.032 (flicker)

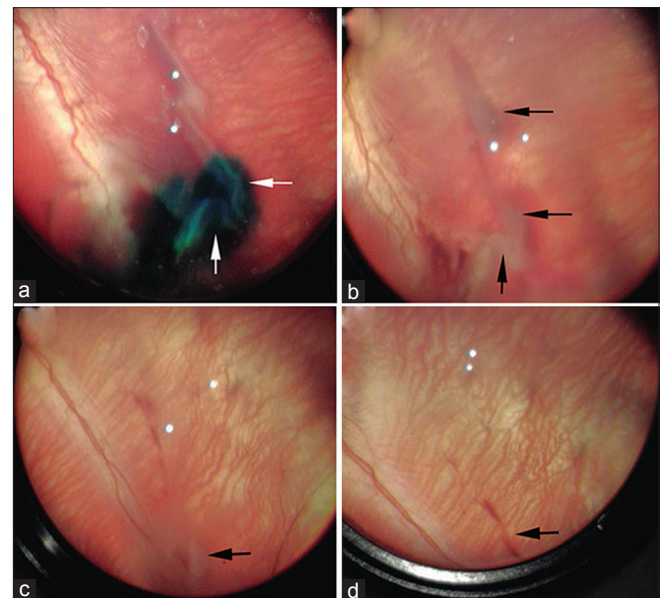


Figure 2: Three-week follow-up of a representative DuraSeal[™] hydrogel-treated eye. (a) A detachment with DuraSeal[™] localized to a small area under the retina (dark blue, white arrows). A major reduction in the size of the detachment was seen 3-days postsurgery (b), which almost completely cleared 14 days postoperatively (c), a small area of detachment is visible (c black arrow). By the end of the third week, however, there is no sign of a detachment nor a retinal tear (d). A local scar was observed (white arrow)

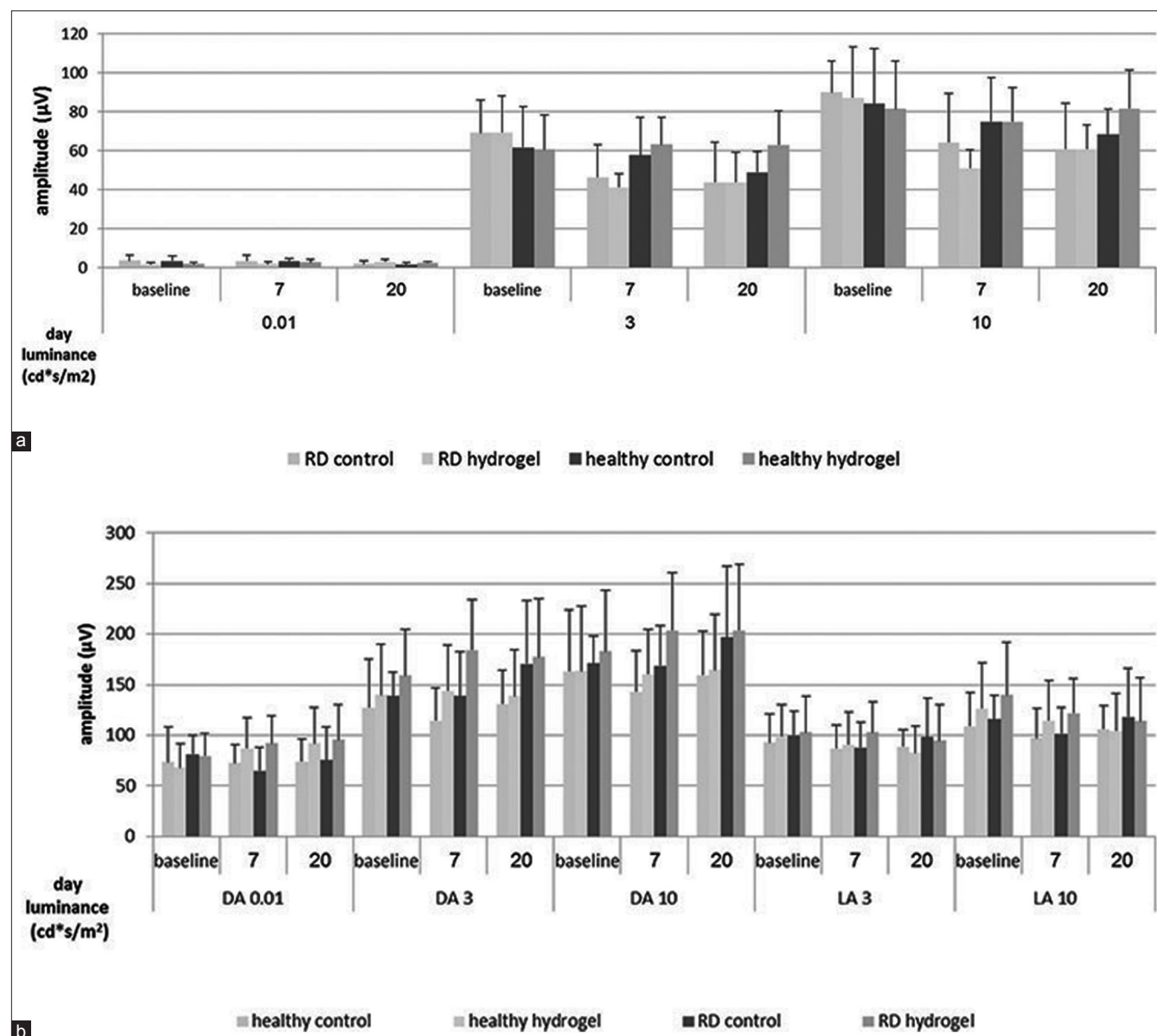


Figure 3: Electrorretinography analysis of saline- and DuraSeal™-treated eyes. electroretinography was recorded at baseline, 7- and 20-days postsurgery. Mean \pm standard deviation amplitudes of the a-(a) and b-waves (b) are illustrated. No differences were found between intact and operated eyes in any parameter tested

revealed minor changes in the detached retinas of all operated eyes, regardless of the treatment group, including edema and vacuolar degeneration, mostly in the inner nuclear layer and ganglion cell layer. No major histopathological differences were observed between eyes of the two groups. In addition, no major cellular alternations were seen in the experimental eyes compared to the saline-treated eyes [Fig. 4].

Discussion

Closure of retinal tears is a crucial step in the management and treatment of retinal detachment. Surgical techniques such as scleral buckling, laser, cryopexy, and vitrectomy are widely-used approaches to treat RRD by attaching the edge of the tear to the RPE. However, every technique has disadvantages and failure to close the break may result in formation of preretinal membrane, proliferative vitreoretinopathy, and RRD.

In the past few decades, tissue adhesives have been evaluated for closure of retinal tears including cyanoacrylate,^[13-19] fibrin glue,^[20,21] mussel glue,^[22] transforming growth factor beta^[23] and m-Gelatin.^[24] Results have been disappointing, mostly due to fast polymerization rate, low strength of adherence, or toxicity. The ideal intraocular adhesive should have biocompatibility, biodegradability, nontoxicity, good strength of adhesion, and long-term effect and should be easily delivered. Synthetic adhesives and liquid hydrogels fit these requirements and proved to be superior to previously tested adhesives, mainly due to their hydrophilic nature, biocompatibility, and safety. Sefrafil[®] and DS have been recently evaluated^[6-9] for their potential use as intraocular adhesives to patch retinal breaks and have been found to be nontoxic, nonimmunogenic, and biocompatible.^[6,7] We were considerably interested in the DS liquid hydrogel due to its water-uptake ability, which is a

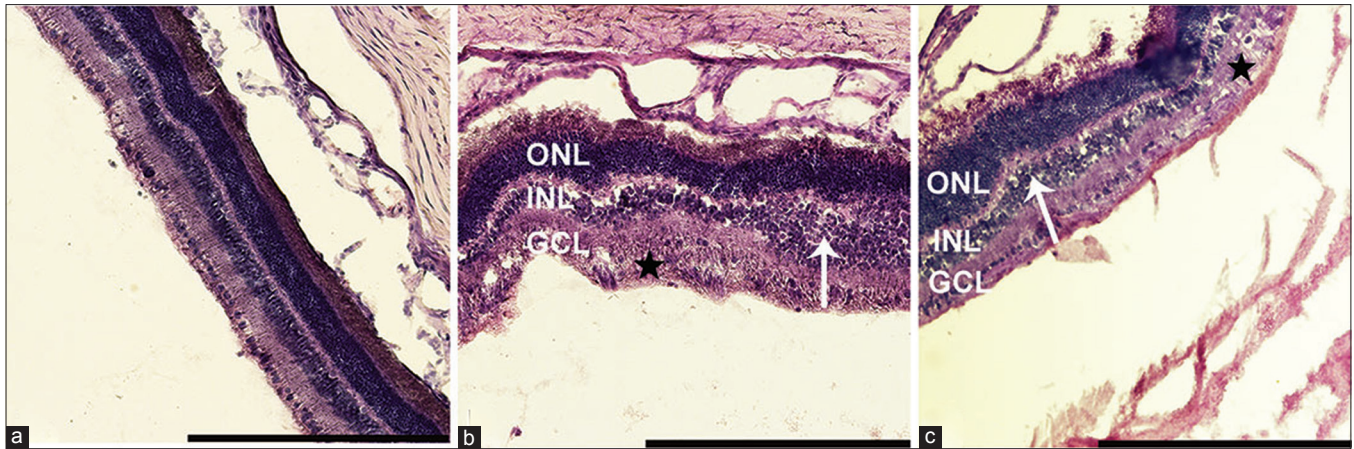


Figure 4: Histological comparison of control untreated, saline-and DuraSeal™-treated eyes. Control unoperated eyes exhibit a normal morphology (a). Edema and vacuolar degeneration were observed around the site of retinal detachment, mostly in the inner nuclear (white arrows) and ganglion cell (asterisk) layers of both saline-treated (b) and DuraSeal™-treated (c) detached retinas. No differences were seen between saline-treated (b) and DuraSeal™-treated (c) eyes. Scale bar 100 μ m

beneficial feature due to the pathophysiology of RRD. Since the course of RRD includes vitreous liquefaction, tearing of the retinal membrane and fluid inflow into the subretinal space, we hypothesized that the DS hydrogel is a good candidate for water absorption, reduction of subretinal fluid volume, and the formation of a tamponade to seal and flat out the retina. However, both Seprafilm and DS suffered from technical difficulties associated with delivery, which limited their full potential, and thus, there is a need to develop a new delivery method that would improve their outcome.

In our experimental setup, it was hard to evaluate the full potential of DS in closing retinal breaks due to the spontaneous absorption of the retinal detachment that was seen in the control group. Therefore, the efficacy of the DS has not been proven in this specific experimental study, and while the transscleral approach may be feasible, it was not easy to use. Indeed, many rabbit models for RRD use injection of hyaluronic acid solutions into the subretinal space to lift up the retina and ensure a longer duration of the detachment. We, however, wished to prevent any potential interactions between the hyaluronic acid and DS components that could have adversely affected the polymerization of the hydrogel and which may have led to failure of the study. However, our decision to induce RRD with saline became a two-edged sword, resulting in relatively fast, spontaneous absorption of the detachment without retinal pathologies, thus making it difficult to compare the two groups and evaluate the full potential of this adhesive. The feline eye serves as a good animal model for retinal detachment/reattachment surgeries, and recently, Wassmer *et al.*^[25] developed a potentially more suitable surgical technique for the detachment in the feline model and should be taken into consideration when designing future experiments. While the spontaneous absorption in our study posed some limitations for the evaluation of the full potential of the hydrogel and only the safety can be stated, the rabbit eye is anatomically similar to the human eye^[1] and therefore serves as a good model for the surgical techniques, in specific the transscleral delivery approach.

On another note, creation of a more bullous RD may not necessarily serve as a better model for RD as it induced an

intraocular pressure and prevented a good outreach to the retinal tear (data not shown).

Histological analyses revealed minor pathological changes, including edema and vacuolar degeneration in the inner nuclear and ganglion cell layers of both DS- and saline-treated groups. As these changes were observed in both groups, we speculate that these changes may be due to retinal remodeling associated with the detachment.^[2,26-28] Whether histological artifacts are present due to a technical procedure, it seems to equally exist in detached and DS-treated groups. It is important to note that no significant functional or pathological differences were observed between the groups [Fig. 3 and 4] and no sign of toxicity was seen in the DS group [Fig. 4]. The hydrogel, therefore, seems to be biocompatible to the eye, thought its potential to serve as a sealant in tissue repair in the clinic should be further evaluated using prolonged toxicological studies.

In this study, we assessed a new, transscleral delivery method that takes into consideration the anatomical and physiological constraints of the eye, the different aspects of retinal detachment, and the chemical properties of the hydrogel. We exploited the feasibility of the transscleral route while exploring the potential use of DS hydrogel to close retinal breaks. We found the transscleral approach for hydrogel injections to be feasible but moderately easy, safe, with minimal toxicity and reproducible.

It is important to note that while transvitreal approach is a gold standard in many ocular surgeries, it may not be suitable for the polymerization of adhesive sealants, such as DS, due to the gas of air-filled in the operated eyes which are used to prevent hypotony.

Although being relatively feasible approach in our setup, in the clinical setting the transscleral approach might be more suitable for RRDs without vitreous traction with tears allocated, especially in the upper half of the retina. The approach might therefore be proper for very selected RRDs.

Conclusion

Based on our observations, we believe that a transscleral delivery of an adhesive tamponade may be safe in the treatment

of retinal detachment. However, further studies, with a more appropriate experimental animal model, are needed to evaluate the efficacy of DS hydrogel in closing retinal tears.

Acknowledgment

The authors would like to thank Dr. Tamar Kadar for her assistance with the histological analysis.

Financial support and sponsorship

This study was financially supported by a grant from the Claire and Amedee Maratier Institute for the Study of Blindness and Visual Disorders, Sackler Faculty of Medicine, Tel-Aviv University.

Conflicts of interest

There are no conflicts of interest.

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