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In vivo study comparing an X-shaped polymethylmethacrylate and a cylindrical collagen implant for deep sclerectomy

THESE

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par

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In vivo study comparing an X-shaped polymethylmethacrylate and a cylindrical collagen implant for deep sclerectomy

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Résumé

Il s'agit de comparer in vivo la sécurité et l'efficacité d'un implant en polyméthylméthacrylate (PMMA) avec un implant standard en collagène dans la sclérectomie profonde (SP) sur une durée de six mois. La population étudiée comprend vingt lapins, chaque lapin étant randomisé pour une SP avec implant en PMMA dans un œil et implant de collagène dans l'autre œil.

Plusieurs éléments ont été pris en compte dans la comparaison :

- la mesure de la pression intraoculaire
- l'évolution de l'espace de drainage intrascléral et de la bulle de filtration sous-conjonctivale, suivie par ultrasonographie biomicroscopique (UBM)
- la croissance de nouveaux vaisseaux de drainage sous-conjonctivaux, croissance quantifiée par angiographie du segment antérieur à la fluorescéine combinée au vert d'indocyanine
- la facilité à l'écoulement de l'humeur aqueuse (C), mesurée à six mois par cannulation-perfusion de la chambre antérieur
- la sclère au site de SP, histologiquement comparée à la sclère native opposée à 180°, également à six mois

La pression intraoculaire moyenne préopératoire à une, quatre, douze et 24 semaines postopératoires est comparable dans les deux groupes ($P>0.1$). L'UBM montre une régression légèrement plus rapide (statistiquement non significative) de la bulle de filtration sous-conjonctivale et la persistance d'un espace de drainage intrascléral dans le groupe PMMA ($P>0.05$). De nouveaux vaisseaux de drainage sont observés à un mois de la chirurgie ; à six mois, ces vaisseaux sont plus nombreux dans le groupe PMMA, tant sur l'analyse angiographique que sur l'analyse histologique ($P>0.05$). La facilité moyenne à l'écoulement de l'humeur aqueuse est significativement plus élevées à six mois dans les deux groupes par rapport aux valeurs préopératoires ($P>0.05$), sans qu'il n'y ait de différence entre les deux implants ($0.24 \pm 0.06 \mu l/min/mmHg$ [PMMA] et 0.23 ± 0.07 $\mu l/min/mmHg$ [implant en collagène]) ($P = 0.39$).

Cette étude a pu démontrer que la sclérectomie profonde avec implant en collagène ou en PMMA donne des résultats similaires en terme de diminution de l'IOP et d'augmentation de la facilité à l'écoulement de l'humeur aqueuse, sans différence sur le plan des réactions inflammatoires post-intervention.

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Original Article

In vivo study comparing an X-shaped polymethylmethacrylate and a cylindrical collagen implant for deep sclerectomy

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Abstract

Background: Study *in vivo* characteristics of a polymethylmethacrylate (PMMA) implant compared to the standard cylindrical collagen implant for deep sclerectomy (DS).

Design: Six-month comparative study.

Samples: Twenty eyes of ten rabbits.

Methods: Eyes were randomized to have DS with PMMA implant in one eye and collagen implant in the opposite eye. The growth of the new subconjunctival drainage vessels was assessed by combined fluorescein and indocyanin green anterior segment angiography; intrascleral and subconjunctival blebs were imaged by ultrasound biomicroscopy (UBM). At six months, outflow facility (C) was measured by anterior chamber perfusion and portions of one side of the DS were compared to portions on the 180° opposite side and native sclera on histology.

Results: The mean IOP preoperatively and at one, four, twelve, and twenty-four weeks was comparable in both groups ($P > 0.1$). UBM showed a statistically insignificant quicker regression of the subconjunctival bleb as well as a durable intrascleral lake in the PMMA group ($P > 0.05$). New drainage vessels were initially observed one month after surgery; they were more numerous in the PMMA group on angiographic and histological findings at 6 months ($P < 0.05$). The mean C increased significantly after surgery compared to preoperative values ($P < 0.05$) and no difference was observed between the implants (0.24 ± 0.06 µl/min/mmHg [PMMA] and 0.23 ± 0.07 µl/min/mmHg [collagen implant]) ($P = 0.39$).

Conclusions: Deep sclerectomy performed with PMMA or collagen implants showed similar IOP lowering effects, outflow facility increase, and degree of inflammatory reaction.

Key words: collagen implant, deep sclerectomy, glaucoma, PMMA implant, rabbits.

Introduction

Deep sclerectomy (DS) is a non-perforating filtration procedure used for the surgical treatment of open-angle glaucoma.[1] Intrascleral space maintaining devices are used to diminish the risk of scleral fibrosis and to enhance the flow from the anterior chamber to the subconjunctival space by avoiding the collapse of the newly created intrascleral space.[2] The implants may differ in material, size, shape, design, consistency, water content and rate of absorption.

An X-shaped implant made of non-absorbable polymethylmethacrylate (PMMA), was designed by one of the study authors (AM) to enhance the intrascleral outflow. PMMA is a well-tolerated prosthetic material used for more than 50 years in ophthalmic surgery, mostly in cataract surgery.[3] In addition, the PMMA implant is less costly than the collagen implant. Our group has previously shown that the X-shaped PMMA implant has similar success and

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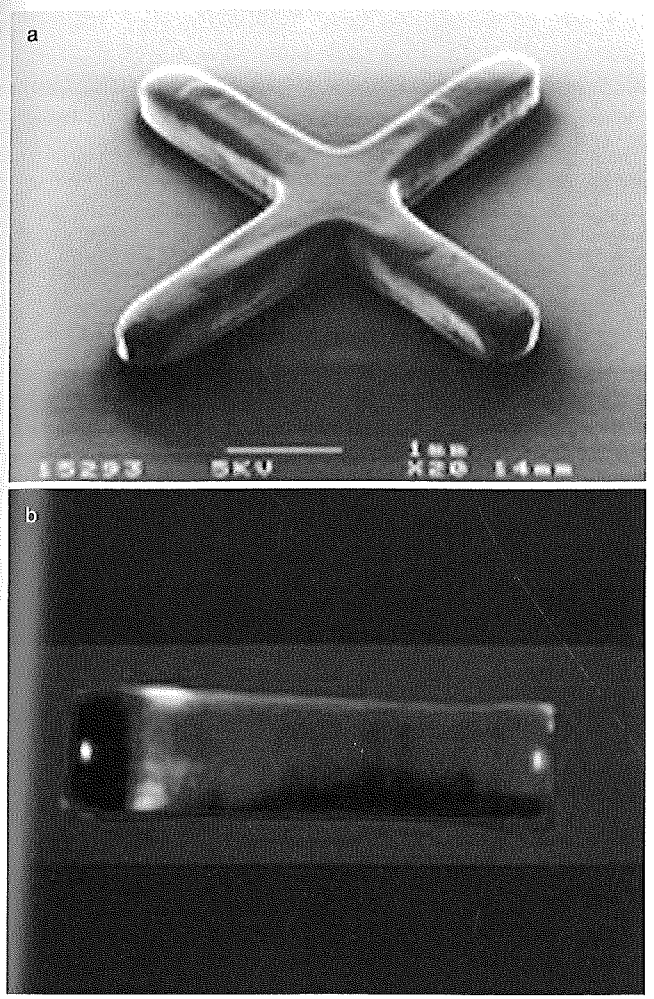

Figure 1. Light microscopy views of: (a) non-absorbable X-shaped polymethylmethacrylate implant; (b) cylindrical absorbable collagen implant.

complication rates in patients with uncontrolled open-angle glaucoma.[4] To enable careful study of *in vivo* changes related to the PMMA implant, we designed a laboratory study using a rabbit model of glaucoma surgery to document the angiographic, ultrasound biomicroscopy (UBM) and outflow facility of the PMMA implant compared with the cylindrical collagen implant.[5]

METHODS

The glaucoma space maintainers

The cross-shaped PMMA (HOMDEC SA, Belmont, Switzerland) was developed at the glaucoma unit of the Jules Gonin Eye Hospital, University of Lausanne, Switzerland. It is a rigid, non-absorbable implant. The cross-shaped drainage device measures 4.0×4.0 mm, with a total length of arm of 5.4 mm and has a thickness of 0.5 mm (Fig. 1a). The commercially available cylindrical collagen implant drainage device (Aqua-Flow, Staar Surgical AG, Nidau, Switzerland) measures $1.0 \times 1.0 \times 4.4$ mm and is placed radially in the centre of the DS dissection and secured with a single 10-0 nylon suture to the thin remnant scleral layer, posterior to Schlemm's canal (Fig. 1b). The implant is processed from lyophilized porcine scleral collagen that has been sterilized by radiation. The collagen implant swells with aqueous and tissue fluid once it is placed in the eye, is absorbed within 6–9 months after surgery and then replaced by a younger, more porous collagen meshwork that sustains the exit pathway.

Study protocol

The entire procedure, care and treatment of the rabbits were in accordance with the Cantonal Veterinary Service of Lausanne, Switzerland, and the ARVO statement for the use of animals in ophthalmic research (http://www.arvo.org/AboutArvo/animalst.asp#Recommended%20References).

All experiments were performed under general anaesthesia by an intramuscular injection of a 37.5 mg/kg ketamine and a 5.0 mg/kg xylazine solution. After appropriate acclimatizing, 10 pigmented female rabbits (2.0–3.0 kg) underwent DS on both eyes by the same experienced surgeon (SR). A superior rectus muscle suture was placed. The conjunctiva and Tenon's capsule were opened in the upper fornix, and the sclera was exposed. A limbus-based 5×5 mm scleral flap, with a thickness of one-third of the sclera (300 μm), was created. To be able to reach the Descemet's membrane later in the dissection, the superficial scleral flap had to be cut first anteriorly into the clear cornea. A second deep scleral flap measuring 4×4 mm was then dissected. The horizontal dissection was performed starting posteriorly and moving anteriorly using a crescent blade. Near the limbus the Schlemm's canal was automatically unroofed. The dissection was continued anteriorly using a blunt spatula or a sponge to find the natural cleavage plan between the Descemet's membrane and the corneal stroma. When the Descemet's membrane had been exposed for 1 mm, the second scleral flap was excised. One eye randomly received a cross-shaped PMMA implant; the other one received a cylindrical collagen implant. After putting the implant in place, the superficial scleral flap was repositioned over the implant and secured with two single 10-0 nylon sutures; the knots were buried inside the flap. The conjunctiva and Tenon's capsule were then closed with a running 8-0 polyglactin (Vicryl) suture.

The intraocular pressure (IOP) (the mean of five consecutive readings) was recorded weekly during the first month and then every second week thereaf-

ter for 5 months. IOP was measured by the same person (AC) who was unaware of which implant had been placed in which eye of each rabbit. This was to avoid interpersonal differences using a TONO-Pen-XL tonometer (Mentor, Norwell, MA, USA).[6] Recordings were performed between 11:00 AM and 3:00 PM to limit the effects of diurnal variation. The presence of an intrascleral lake and a subconjunctival blebs at 1, 3 and 6 months after DS was assessed by UBM by the main investigator (AC). The images shown in this article were obtained with a human setting commercial UBM (Humphrey Instruments, Inc., San Leandro, CA, USA) and a standard 50 MHz transducer. A non-disposable hard plastic eye cup measuring 18 mm diameter was inserted between the lids, and methylcellulose was the coupling agent. Multiple cross-sections of images were taken of the anterior segment and the bleb, from the limbus to its posterior extent. The image that displays maximum bleb height was used for measurement. The bleb height was measured with calipers provided in the system software. The growth of new intrascleral drainage vessels was assessed by simultaneous indocyanin green and fluorescein anterior segment angiography 1, 3 and 6 months after surgery as we described it previously.[7] After general anaesthesia, 0.2 mL of a solution of 0.1 mL (1 mg/mL) of fluoresceine and 0.1 mL (1 mg/mL) of indocyanin green were injected into the interior chamber although limbal paracenthesis. Several sequences pictures of the surgical site were taken with a digital camera (TRC50IA, Nidek, Tokyo, Japan). Following the procedures eyes were treated for seven days with a daily drop of Dexamethasone and Chloramphenicol (Spersadex C, Ciba Vision, Bülach, Switzerland). The number of drainage vessels (encompassed in an area delineated by a virtual line drawn 2 mm parallel to the limbus and extending from the lateral edge of the superior rectus muscle down to the upper edge of lateral rectus muscle) was counted.

Six months after surgery, outflow facility (C) was measured using the technique of anterior chamber perfusion under constant pressure.[8–10] Under microscopic control, the eyes were pressurized with a needle-guided silicon catheter introduced through the corneal limbus into the anterior chamber, 180° away from the surgical site. The catheter was connected via a polyethylene tubing to a micro-syringe pump (type SP 200i, WPI, Sarasota, FL, USA) allowing various flow rate ranging from 0.2 mL/h to 426 mL/h. The catheter-syringe unit was then connected to a water manometer and an electronic pressure transducer (WPI, Sarasota, FL, USA). Pressure measurements were monitored by a pressure monitor (Ape BP-1, WPI, Sarasota, FL, USA) and printed on a chart recorder (Type L200 E, Linseis GmbH, Selb, Germany). The IOP could be increased or lowered by adjusting the height of the water manometer. The pressure system was adjusted at the lowest pressure at which a flow was detectable. IOP was then increased by 10 mmHg increments to a maximum 40 mmHg. At each pressure level, the infusion flow was adjusted to maintain the IOP constant, which corresponded to the outflow of the eye minus the aqueous produced by the ciliary body. The infusion flows were then plotted against IOP and a regression line was computed. The slope of the curve represents the outflow facility. The outflow facility (C) was calculated using the Goldmann equation:

$$C = \Delta I / \Delta \mathrm{IOP}$$

$\Delta I = (I2 - I1)$, where $I1$ and $I2$ are successive inflow rates (μL/min)

$\Delta \mathrm{IOP} = (P2 - P1)$, where $P1$ and $P2$ represent IOP at $I1$ and $I2$, respectively (mmHg)

The mean outflow facility of each implant group was then compared with the mean physiological outflow facility of about 0.15 ± 0.02 μL/min/mmHg.[10] At the end of the outflow facility measurement, a 50 mg/mL cationic ferritin solution (horse spleen ferritin, MW = 800 000, Biochemica, Fluka Chemie, Buchs, Switzerland) was injected through the catheter into the anterior chamber. While maintaining the IOP at about 40 mmHg, the ferritin was allowed to diffuse into the trabecular meshwork and the new drainage vessels for 15 min. The eyes were then immediately enucleated after an intracardiac injection of a 65 mg/mL sodium pentobarbital solution and fixed in a 4% formaldehyde solution. Histological sections of the entire eye (radial cut) were performed and stained using haematoxylin–eosin (HE) and Prussian blue dye, which reacts with ferritin-marked tissues. The aqueous drainages vessels were identified by their blue colour caused by the reaction between ferritin and Prussian blue.[10] Light microscopy at an original magnification ×100 was used to observe the mean number of new aqueous drainage vessels in the sclera, the inflammatory response and scarring process around the implant. The mean number of drainage vessel from five consecutive sections at the surgical site was compared with five consecutive sections on non-operated region 180° opposite from surgery site.

Statistical analysis

The data are presented as the mean ± standard deviation (SD). Comparisons of the means were performed using the Wilcoxon rank sum test between eye and Kruskal–Walllis test for different time point

measurement. A difference was considered statistically significant when $P < 0.05$.

Results

No perforation of the trabeculo-Descemet's membrane (TDM) occurred in any of the surgical procedures. All experiments were well tolerated by each animal throughout the entire study. None of the eyes presented clinically significant postoperative anterior chamber inflammation. One eye developed a small anterior chamber fibrin filament (inferior to 1 mm), which resolved spontaneously following the angiography at the third month. All corneas stayed clear, there was no case of corneal oedema, and no endophthalmitis was observed. Comprehensive results are presented in Tables 1–4.

Intraocular pressure

The mean IOP follow up is depicted in Figure 2b. For the PMMA implant group, the mean IOP significantly decreased from a preoperative value of 13.3 ± 0.8 mmHg to a postoperative value of 9.3 ± 1.5 mmHg at 1 week (reduction of 4.0 ± 1.4 mmHg [30.0%]; $P < 0.05$), 9.6 ± 0.5 mmHg at 1 month ($P < 0.05$), 11.7 ± 1.2 at 3 months ($P < 0.05$) and 12.1 ± 0.9 mmHg at 6 months (reduction of 1.2 ± 0.8 mmHg or 9.0%; $P < 0.05$). In the cylindrical collagen implant group, the mean IOP significantly changed from a preoperative value of 13.4 ± 0.8 mmHg to a postoperative value of 8.8 ± 0.8 mmHg 1 week after surgery, thus representing a reduction of 4.6 ± 0.8 mmHg (34, 3%) ($P < 0.05$). At 1 month, the postoperative IOP was 9.5 ± 0.5 mmHg ($P < 0.05$), at 3 months 11.7 ± 1.1 mmHg ($P < 0.05$) and at 6 months 12.0 ± 0.9 mmHg, showing a reduction of 1.4 ± 0.9 mmHg (10.4%) ($P < 0.05$). The differences in the IOP drop at 1 week, 1, 3 and 6 months after surgery were not statistically significant between the two groups (Table 1).

UBM analysis

The non-resorbable PMMA implants were easily identified postoperatively and during the entire follow up (Fig. 2). No evidences of structural modification or displacement of the implant were noted. The size of the collagen implants decreased progressively over time. After 6 months, the collagen implants were no longer visible. Instead, the degraded implants left a visible void in the intrascleral space. Subconjunctival filtration blebs were present at the surgical site in all eyes of both groups at 1, 3 and 6 months postoperatively. There was a tendency for faster regression of the subconjunctival bleb's height over time in the PMMA group (P = NS) (Table 2). TDM was well delineated between the anterior chamber and the intrascleral space. The intrascleral space, between the posterior part of the trabeculum and the anterior portion of the implant, was noticeable in both groups at all times. A suprachoroidal effusion was observed under the sclerectomy site in five eyes (50%) with PMMA implant and in three eyes (30%) with the collagen device ($P < 0.05$). However, no case of retinal detachment was observed.

Angiography

One month after surgery, collagen implants were seen as a hypofluorescent mass within the scleral bed. At 3 months, the implants were no longer identifiable following complete biodegradation. The non-resorbable PMMA implants remained plainly visible over time, their contour being well

Table 1. Time-course changes in IOP reduction from baseline IOP

IOP reductions (mmHg and %) from baseline IOP	1 week	1 month	3 months	6 months
Collagen implant	4.6 ± 0.8 (34.3%)	3.9 ± 0.5 (29.1%)	1.7 ± 1.0 (12.6%)	1.4 ± 0.9 (10.4%)
PMMA implant	4.0 ± 1.4 (30.0%)	3.7 ± 0.5 (27.8%)	1.6 ± 1.2 (12%)	1.2 ± 0.8 (9.0%)
Wilcoxon rank sum test (P)	0.13	0.19	0.25	0.14

IOP, intraocular pressure; PMMA, polymethylmethacrylate.

Table 2. Maximum subconjunctival bleb's height over time (cm)

Subconjunctival thickness (cm) ± standard deviation	1 month	3 months	6 months
Collagen implant	0.20 ± 0.06	0.19 ± 0.09	0.20 ± 0.06
Polymethylmethacrylate implant	0.22 ± 0.05	0.18 ± 0.05	0.15 ± 0.06
Wilcoxon rank sum test (P)	0.57	0.69	0.09

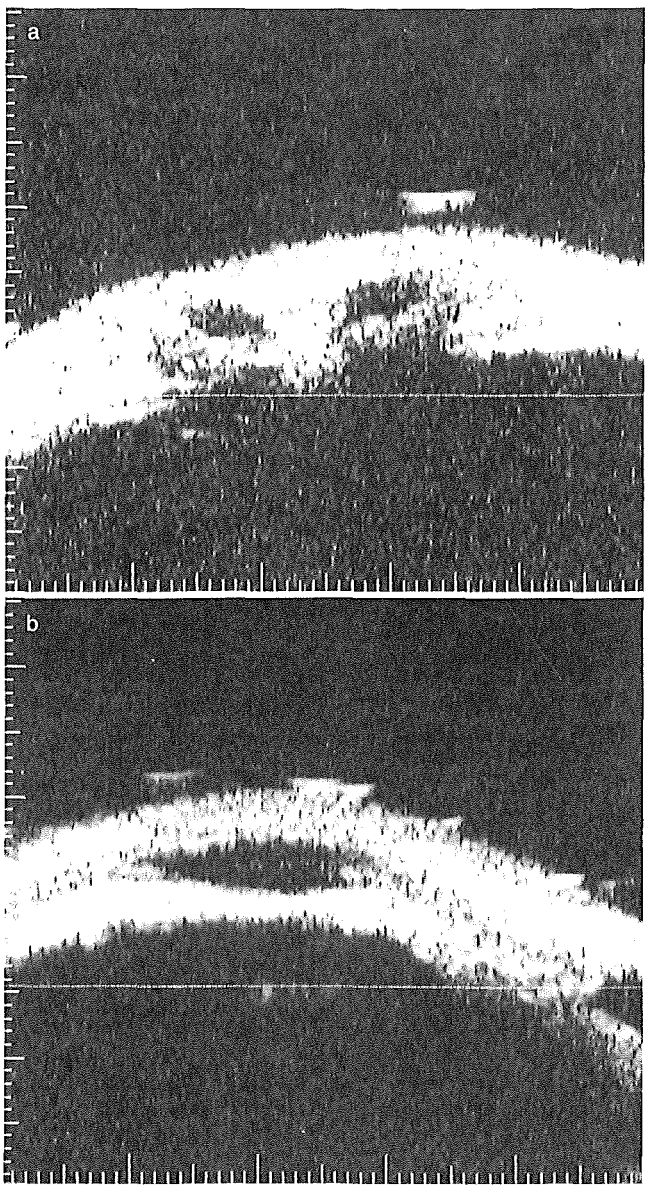

Figure 2. Ultrasound biomicroscopy images showing: (a) transversal view of the X-shaped polymethylmethacrylate implant (i); (b) radial view of subconjunctival bleb (sb).

delineated by fluorescein. The modified aqueous drainage pathway was easily visualized. The filtration bleb and the surrounding new aqueous subconjunctival draining vessels were clearly visible on angiography 1 month after surgery for both types of implant. A progressive growth of these vessels around the filtration site was clearly observed at 3 and 6 months (Fig. 3). In both groups, marked proliferation of new drainage vessels was observed between the first and the third postoperative month. However, no statistical differences were observed between the two groups (Table 3). The angiographic results were interpreted, and any indication of which implant had been used were masked.

Outflow facility

Six months after surgery, the mean outflow facility was 0.24 ± 0.06 μL/min/mmHg for the PMMA and 0.23 ± 0.07 μL/min/mmHg for the collagen group. The mean outflow facility for both groups significantly dropped from the physiological value ($P < 0.05$). The differences in the mean outflow facility drop after surgery were not statistically significant between the two groups ($P = 0.32$).

Histological examinations

In both groups, light microscopy at 6 months after surgery revealed presence of more drainage vessels (Figure 4a and b) in the sclera adjacent to the dissections site compare with the opposite limbal sclera. In the PMMA group, there were 3.7 ± 0.8 new drainage vessels per viewing area compared with 2.0 ± 0.7 in the collagen implant group. The difference was considered significant ($P < 0.05$) (Table 4).

In the collagen group, the intrascleral space was lined with spindle cells. In the PMMA group, the X-shaped device was well identified and lined up with a higher number of spindle cells.

No evidence of inflammatory reaction on the surgical site was seen for either implant type.

Discussion

The X-shaped implant made of synthetic non-absorbable PMMA was designed to enhance the intrascleral outflow. Being non-absorbable with good biocompatibility, the implant's role is to maintain a permanent patent intrascleral lake and prevent adhesions between the superficial scleral flap and the trabecular meshwork, leading to a better IOP control. The implant is also supposed to stabilize and provide additional support to the thin TDM. Free areas between the limbs of the X-shaped implant should also act as an aqueous reservoir. The collagen implant has been the primary implant used in DS surgery. Its advantages are complete resorption, leaving a large subconjunctival bleb. It is made of porcine collagen and carries a potential risk of animal transmitted disease.

During the entire follow up, the IOP-lowering effect of the DS with PMMA implant was similar to DS with a collagen implant. The maximal lowering effect was observed shortly after surgery and during the first postoperative 3 months for both groups. The fact that IOP was lowered to the same extent in both groups throughout the 6-month period indicates that the efficacy of DS in reducing the IOP with either implant is comparable. This was also confirmed with the outflow facility results showing a significant and equivalent increase for both types of implant.

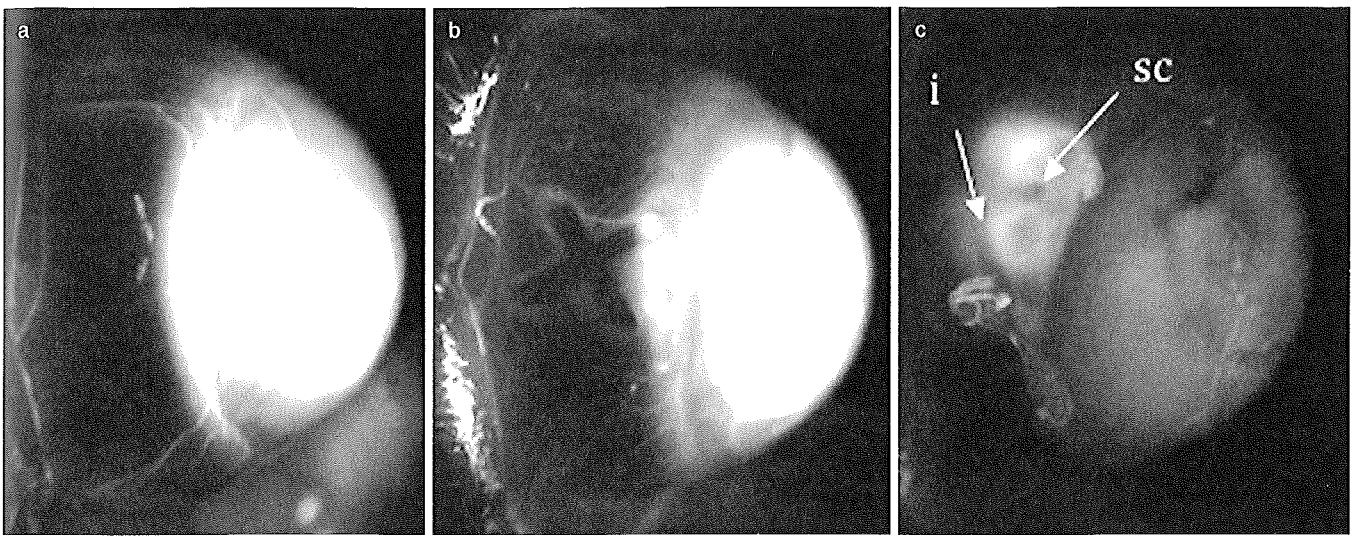

Figure 3. Anterior segment angiographies: (a) preoperative; (b) X-shaped implant (i) and new vessels at 6 months post surgery; (c) X-shaped implant and subconjunctival filtration bleb (sc) in late phase.

Table 3. Angiography

Mean number of new outflow vessels	1 months	3 months	6 months
Collagen implant	0.8 ± 0.6	1.9 ± 1.7	2.8 ± 1.4
Polymethylmethacrylate implant	1.3 ± 0.5	2.6 ± 1.1	3.1 ± 1.1
Wilcoxon rank sum test (*P*)	0.36	0.25	0.29

Mean number of new subconjunctival outflow vessels over time.

Table 4. Histology

Mean number of new outflow vessels	6 months	
	Collagen implant	PMMA implant
Surgical site	3.6 ± 0.7	5.1 ± 0.8
180° unoperated site	1.6 ± 0.5	1.4 ± 0.5
Absolute new vessels	2.0 ± 0.7	3.7 ± 0.8
Wilcoxon rank sum test (*P*)	$P < 0.05$	

Mean number of new scleral outflow vessels at 6 months. PMMA, polymethylmethacrylate.

Anterior segment angiography images allowed an easy visualization of the subconjunctival aqueous draining pathway. Proliferation of new drainage vessels was observed around the operated tissues with both implant types. The subconjunctival proliferation rate, as well as the IOP-lowering effect, were more important during the first 3 months, and there was no significant difference between the groups during the entire follow up. This would support the role played by such vessels in draining aqueous and

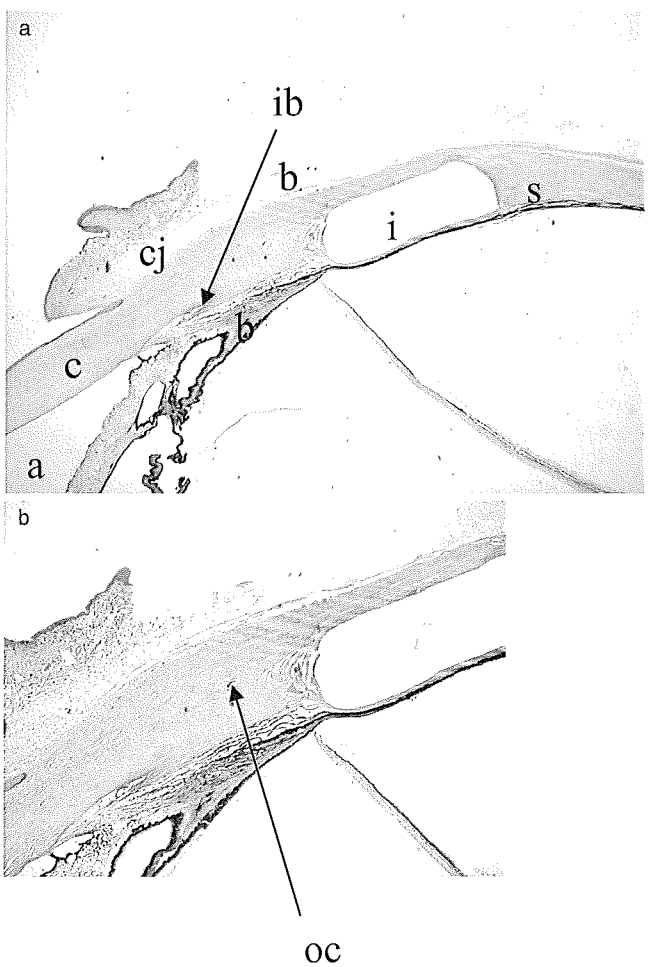

Figure 4. Light microscopy of the operated site (a) and (b): anterior chamber (a), ciliary body (cb), cornea (c), conjunctiva (cj), X-shaped implant (i), intrascleral bleb (ib), outflow vessels (oc) and sclera (s).

controlling the IOP level. It is worth mentioning that the number of scleral drainage vessels, as observed on histological sections at 6 months, was more significant in the PMMA group. This finding suggests that the PMMA device may potentially trigger a longer vasoproliferative response than the collagen implant. This could be explained by the permanent presence of the device compared with the degraded short-life collagen.

In both groups, subconjunctival and intrascleral filtration blebs were equally identified on UBM in all eyes. However, the slower reduction in the height of the subconjunctival bleb observed in the collagen implant group may indicate a slightly more developed filtering bleb than in the PMMA group. We also observed the presence of choroidal effusion in half of the PMMA eyes and less than a third in collagen eyes. These observations may support the hypothesis that the aqueous outflow draining into the suprachoroidal space through a surgically thinned sclera might be higher in the PMMA group. For reasons that remain to be clarified, this phenomenon was not associated with a significantly lower IOP, possibly as a consequence of a slight increase in the aqueous production counterbalancing the higher outflow. Based on histology, the PMMA device was as well tolerated as the collagen device and no severe inflammatory reactions were observed on the surgical site. However, the number of spindle cells lining on the scleral filtration space and fibrosis around the surgical site was more significant in the PMMA group. It is possible that the long-term effect of having an inert material may lead to a foreign body reaction triggering a mild and locally marked scarring and tissue remodelling response. One observable difference was noted in the PMMA group: an increase in the intrascleral outflow with a shallower subconjunctival bleb was observed in the PMMA group.

In this *in vivo* study, we demonstrated in through a rabbit model that the implant is well tolerated. A possible limitation of the present study might be unknown factors that led to a low IOP-lowering response (about 1.5 points or 10% in either surgery) in the rabbits' eyes. However, one explanation would be that these eyes did not profit from the same postoperative management (i.e. Nd:YAG gonioponcture for fibrosis of the TDM, etc.) as human eyes. A randomized controlled trial comparing the same two implants in 60 human eyes showed a similar safety profile and a good success rate in both groups (42% of PMMA patients and 44% of collagen patients achieved an IOP of 21 mmHg or less without medication).[5]

In conclusion, the non-absorbable X-shaped PMMA implant compares favourably to the collagen implant in a rabbit model. The presence of new intrascleral drainage vessels and the onset of suprachoroidal effusion support the concept that the intrascleral bleb filtration is one of the main outflow mechanisms for the PMMA implant. The PMMA implant might be a good and more affordable alternative to the standard collagen implant in decreasing the complications and discomfort related to large subconjunctival blebs. The use of the PMMA implant on a larger scale could also contribute to lower the potential risks related to the use of porcine collagen in terms of transmitting animal-carried diseases.

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