

EXTENDED REPORT

Use of polyurethane with sustained release dexamethasone in delayed adjustable strabismus surgery

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Aim: To determine the effect of polyurethane film with sustained release dexamethasone (SRD) in delayed adjustable strabismus surgery.

Methods: A prospective, masked observer, controlled study was performed in rabbits. Thirty four rabbit eyes were divided into three groups. After recession of the superior rectus muscle (SRM), polyurethane film with or without SRD, or balanced salt solution was applied beneath and over SRM in the polyurethane-dexamethasone group (group P-D), polyurethane group (group P), and the control group (group C), respectively. Delayed adjustment was performed once on each SRM at 4 and 6 weeks postoperatively by a masked observer. The possible length to adjust and the necessary force required for the adjustment, as well as the degree of any adhesions, were also evaluated.

Results: In the control group, adjustment was impossible in all of the eyes at 4 and 6 weeks postoperatively. In group P-D, adjustment was possible in 11 out of 11 eyes (11/11) 4 weeks postoperatively and in 10/11 eyes 6 weeks postoperatively. In group P, adjustment was possible in 9/11 eyes 4 weeks postoperatively and in 10/12 eyes 6 weeks postoperatively.

Conclusions: Use of polyurethane film with and without SRD could delay adjustment in most eyes for up to 6 weeks postoperatively. Polyurethane is helpful for delaying adjustment in rabbit eyes until 6 weeks postoperatively without the need for frequent topical instillation of steroids.

Since Jampolsky's description and modifications in 1975,¹ adjustable suture strabismus surgery has become an effective method to adjust the binocular alignment in the immediate postoperative period.² However, binocular alignment may drift over time even after placing the eyes in a suitable position with adjustable strabismus surgery.³ Therefore, delayed adjustment may be desirable for better postoperative results.^{4,5} However, the postoperative healing process causes adhesions, which inhibit such delayed adjustment.

Delayed adjustment has been attempted by the implantation of physical barriers such as silicone,^{5,6} viscoelastic material,⁷ Interceed,⁸ polyglactin 910 mesh,⁸ poly(tetrafluoroethylene),⁹ antiproliferative agents such as mitomycin C,¹⁰ 5-fluorouracil,^{11,12} and combinations of the various physical barriers and antiproliferative agents.^{11,12} In animal experiments, adjustment could be delayed by using silicone for up to 11 days in humans⁵ and up to 8 weeks in rabbits.⁶ However, silicone can cause discomfort because of its thickness and rigidity, and may trigger infection, extrusion, or granuloma formation. As a barrier, poly(tetrafluoroethylene) has been proved to delay adjustment for up to 4 weeks with some advantages over other physical barriers.⁹

However, with every barrier, frequent instillation of anti-inflammatory agent was necessary.

A system that would slowly release steroids at sustained therapeutic concentrations over several days or weeks would obviate the requirement of multiple instillations. Polymeric drug delivery system, in which drug moieties are covalently linked to polymeric matrices, can be released at the site of action very slowly.¹³ It could provide longer duration of drug activity, optimal rate of drug delivery, and minimal dosage for therapeutic response at the local site by a preferential localisation in the body, thus maximising the beneficial response as well as minimising the undesirable adverse effects. Among the polymers, segmented polyurethanes are very popular as an intravascular device,¹⁴ urethral stents,¹⁵

intraocular lenses and keratoprotheses,¹⁶ and for meniscal reconstruction,¹⁷ and cartilage and bone repair^{18,19} because of their excellent mechanical properties, high elongation capacity, blood compatibility, and good biocompatibility.^{20–22} A local drug delivery device used in this research is designed to control the release of dexamethasone from polyurethane films for a period of 50 days. In this experimental study, we used this polyurethane film as a barrier. It had not been previously used as a physical barrier for delaying the adjustment after adjustable strabismus surgery. In addition, we evaluated the effectiveness of using sustained released dexamethasone with the polyurethane film for the prevention of postoperative adhesions.

Polyurethane is originally an alternative elastomer that is unrelated to PLGAs (poly(lactide-co-glycolide)). However, many kinds of polyurethanes, generally called segmented polyurethanes composed of various kinds of hard and soft segments have been synthesised. Polyurethanes with poly(oxyethylene), poly(oxypropylene), and poly(oxytetramethylene) as the soft segments, and with both hydrophilic and hydrophobic segments were made. A drug delivery polyurethane which consisted of a copolymer of lactide and glycolide (poly(lactide coglycolide)) was developed by two of the authors (SYJ and MHJ) and used in this study. Control matrixes consisted of the polymer without the drug. In this experimental study, we used this polyurethane film as a barrier. We evaluated the effectiveness of using sustained released dexamethasone with the polyurethane film for the prevention of postoperative adhesions, thus allowing delay of adjustment after strabismus surgery.

MATERIALS AND METHODS

Thirty four New Zealand white rabbits, weighing 2.0–3.0 kg, underwent 5 mm recession of the both superior rectus

Abbreviations: SRD, sustained release dexamethasone; SRM, superior rectus muscle

muscle (SRM) using double armed 5–0 polyester suture in rabbit eyes with future adjustment at postoperative 4 weeks and 6 weeks.

Polyurethane film with sustained release dexamethasone was used as a physical barrier in group P-D, and polyurethane without dexamethasone was used in group P. In group C, no physical barrier was used. Sixty eight SRMs of 34 New Zealand white rabbits were grouped in group C (16 muscles including eight for 4 week examination and eight for 6 weeks), group P (27 muscles including 13 for 4 weeks examination and 14 for 6 weeks), and group P-D (25 muscles, 12 for 4 week examination and 13 for 6 weeks). The operator (KJH) imposed the number on the 68 SRMs, and decided which group a muscle belonged to by lot.

Preparation of polyurethane film

The dexamethasone sustained released polyurethane film was cast by two of the authors (SYJ and MHJ) as previously reported.²¹ Dexamethasone 21-sodium phosphate, 20 mg, was completely dissolved in 3.5 ml dimethylacetamide, and 1.6 g of polyurethane was then added to the solution and dissolved for 24 hours. For group P, only polyurethane was dissolved in dimethylacetamide. The prepared solution was cast on the glass mould. The dexamethasone impregnated polyurethane film was formed by the evaporation of solvent for 48 hours at 60°C and 48 hours in a vacuum. The resulting polyurethane film was irradiated with ultraviolet rays for sterilisation. The *in vitro* release of dexamethasone from polyurethane film was performed in a phosphate buffered saline solution (pH 7.4) at 37°C. The concentration of dexamethasone in the released medium was determined by ultraviolet spectrometry at 238 nm. The dexamethasone was released at 37.59 µg/cm² on first day, and then at 1.469 µg/cm²/day for 50 days.

Procedures

General anaesthesia was achieved intramuscularly with 30–45 mg/kg of ketamine hydrochloride and 5–10 mg/kg of xylazine hydrochloride and topical anaesthesia with oxybutyprocaine (proparacaine) hydrochloride (Alcaine, Alcon-Couvreur, Belgium). The procedure of muscle recession with/without physical barrier was done by JHK.

Preoperative surgical antisepsis with poly(vinylpyrrolidone)-iodine to the eyelids was performed. A limbal peritomy was performed from 10 to 2 o'clock. The SRM was isolated on a Jameson hook and intermuscular connections were dissected. The superior oblique tendon was disinserted and allowed to retract from the surgical field. The SRM was then placed on a double armed 5–0 Ethibond suture close to the insertion and disinserted from the globe. Two separate sheets (12×15 mm) of polyurethane film with sustained release dexamethasone were placed between sclera and SRM, and between conjunctiva and SRM in group P-D (26 eyes), polyurethane film without dexamethasone in group P (26 eyes) and balanced salt solution (Ca 1 ml) in the group C (15

eyes). Finally, the SRM was recessed 5 mm and reattached to the original insertion using a hang back suture technique. A bucket handle suture was made for the future traction. The edges of the conjunctival peritomy were approximated with interrupted 8–0 polyglactin sutures. At the end of each procedure, ofloxacin eye ointment was applied topically and 4 mg of gentamicin was injected in the thigh muscle.

Delayed adjustment

The procedure of delayed adjustment was done by JMH. In a masked, random fashion, the SRM was adjusted under the same anaesthesia once on each SRM at 4 and 6 weeks postoperatively in group P-D, group P, and group C. At the time of adjustment, polyurethane was visible and was removed before the adjustment. A dial tension gauge (DT-50, Teclock, Japan) in which force on the muscle was rather precisely controlled by the turning of a dial and mechanical pulling of a strain gauge by hand was not involved in the measurement grasped bucket handle of the sutures connected to the muscle. The muscle was then moved anteriorly (measured by a Castroviejo calliper) as much as possible with the force needed to do so registered on the gauge. The length and force for adjustment were recorded and adjustment completed.

Evaluation of adhesions

At the time of adjustment, the adhesions between the muscle, sclera, and conjunctiva were evaluated and recorded. The adhesions were classified as SRM/C (superior rectus muscle/conjunctiva) or SRM/S (superior rectus muscle/sclera) when located above or below the SRM, respectively. The severity of the adhesions was scored from 0 to 4, where: 0 = no adhesion, 1 = filmy adhesion easily separable with blunt dissection, 2 = mild to moderate adhesion with freely dissectible plane, 3 = moderate to dense adhesion with difficult dissection, and 4 = non-dissectible plane. The animals were sacrificed after the delayed suture adjustment with 10 ml intravenous injection of sodium pentothal.

Postmortem histological examination

The involved tissues of each eye in each group were subsequently examined macroscopically and microscopically using haematoxylin and eosin staining after sacrifice. We performed histopathological study to evaluate adhesions among sclera, SRM, and conjunctiva. Masson's trichrome staining was also performed to evaluate the degree of fibrous proliferation.

Statistical analyses

A statistical analysis was performed to ascertain any differences in the adjustability between the two groups using Fisher's exact test. The length of advancement, the force necessary for advancing the muscles and the severity of the adhesions were analysed using Mann-Whitney test. Statistical significance was determined at a *p* level of 0.05.

Table 1 Number of adjustable eyes and tractional force and length for the adjustment

Group	Time of adjustment	Possible adjustment (No of eyes)	Adjustment not possible (No of eyes)	Force Mean (SD)	Length Mean (SD)
C	4 weeks	0	5	*	*
	6 weeks	0	6	*	*
P	4 weeks	9	2	35.27 (19.60) g	2.86 (1.60) mm
	6 weeks	10	2	39.17 (20.37) g	2.79 (1.53) mm
P-D	4 weeks	11	0	35.00 (7.44) g	3.72 (0.98) mm
	6 weeks	10	1	37.82 (16.43) g	3.16 (1.39) mm

C: control; P: polyurethane; P-D: polyurethane+dexamethasone.

*Impossible to move the muscle because of adhesion.

Table 2 Degree of adhesions in each group

Group	Time	M/C* Grade (no of eyes)	M/S† Grade (no of eyes)
C	4 weeks	1 (1) 2 (3) 3 (1)	1 (2) 2 (2) 3 (1)
	6 weeks	1 (2) 2 (2) 3 (1) 4 (1)	2 (1) 3 (3) 4 (2)
P	4 weeks	1 (12)	1 (8) 2 (3)
	6 weeks	1 (10) 2 (2)	1 (7) 2 (4) 3 (1)
P-D	4 weeks	0 (2) 1 (8) 2 (1)	0 (2) 1 (9)
	6 weeks	1 (9) 2 (2)	1 (8) 2 (3)

C: control; P: polyurethane; P-D: polyurethane+dexamethasone.

*M/C: between superior rectus muscle and conjunctiva.

†M/S: between superior rectus muscle and sclera.

0: no adhesion ; 1: filmy adhesions easily separable with blunt dissection; 2: mild to moderate adhesions with freely dissectible plane; 3: moderate to dense adhesions with difficult dissection; 4: non-dissectible plane.

RESULTS

During the follow up period before adjustment, two eyes of group C and one eye of group P and group P-D respectively were lost as a result of death of the rabbits. Two eyes of group C (15%) and group P-D (8%) respectively and three eyes of group P (12%) were lost because of infection. One superior rectus muscle was lost during the procedure.

Adjustability

In group P-D, adjustment was possible in 11 out of 11 eyes 4 weeks postoperatively, and in 10 out of 11 eyes 6 weeks postoperatively. In group P, adjustment was possible in nine out of 11 eyes 4 weeks postoperatively, and in 10 out of 12 eyes 6 weeks postoperatively. In group C, adjustment was impossible in five out of five eyes 4 weeks postoperatively and six out of six eyes 6 weeks postoperatively (table 1).

When comparing the adjustability at 4 weeks postoperatively, there was a significant difference between group P and the control group ($p = 0.003$), as well as between group P-D and the control group ($p < 0.001$). When comparing the adjustability at 6 weeks postoperatively, there was also a significant difference between group P and the control group ($p = 0.001$), as well as between group P-D and the control group ($p < 0.001$). There was no significant difference in the adjustability between group P and group P-D at 4 weeks postoperatively ($p = 0.147$) or 6 weeks postoperatively ($p = 0.598$).

The amount and the force for the adjustment

In group P-D, the average amount and force for the adjustment (advancement) were 2.73 mm and 35.00 g 4 weeks postoperatively and 3.48 mm and 41.60 g 6 weeks postoperatively. In group P, the average amount and force were 3.48 mm and 43.10 g 4 weeks postoperatively and 3.35 mm and 47.00 g 6 weeks postoperatively (table 1).

When comparing the amount and force necessary for adjustment, there was no difference between group P and group P-D at 4 or 6 weeks postoperatively ($p > 0.05$).

The degree of adhesions between SRM and the conjunctiva

In group P-D, the degree of adhesion was 0 in two eyes, 1 in eight eyes, and 2 in one eye 4 weeks postoperatively, and 1 in nine eyes and 2 in two eyes 6 weeks postoperatively. In group P, the degree of adhesion was 1 in 11 eyes 4 weeks postoperatively and 1 in 10 eyes and 2 in two eyes 6 weeks postoperatively. In group C, the degree of adhesion was 1 in one eye, 2 in three eyes, and 3 in one eye 4 weeks postoperatively, and 1 in two eyes, 2 in two eyes, 3 in one eye, and 4 in one eye 6 weeks postoperatively (table 2).

There was a significant difference in the degree of adhesion between the SRM and the conjunctiva at 4 weeks postoperatively between group P and the control group ($p = 0.006$), as well as between group P-D and the control group ($p = 0.031$). There was also a significant difference between group P and the control group in the degree of adhesion at 6 weeks postoperatively ($p = 0.009$), as well as between group P-D and the control group ($p = 0.033$). However, when comparing the degree of adhesion between the SRM and the conjunctiva, there was no difference between group P and group P-D at 4 or 6 weeks postoperatively ($p > 0.05$).

The degree of adhesions between SRM and the sclera

In group P-D, the degree of adhesion was 0 in two eyes, and 1 in nine eyes 4 weeks postoperatively and 1 in eight eyes and 2 in three eyes 6 weeks postoperatively. In group P, the degree of adhesion was 1 in eight eyes and 2 in three eyes 4 weeks postoperatively and 1 in seven eyes, 2 in four eyes, and 3 in one eye 6 weeks postoperatively. In group C, the degree of adhesion was 1 in two eyes, 2 in two eyes, and 3 in one eye 4 weeks postoperatively and 2 in one eye, 3 in three eyes, and 4 in two eyes 6 weeks postoperatively (table 2).

There was no significant difference in the degree of adhesion between the SRM and the sclera at 4 weeks postoperatively between group P and the control group ($p = 0.163$). There was a significant difference in the degree

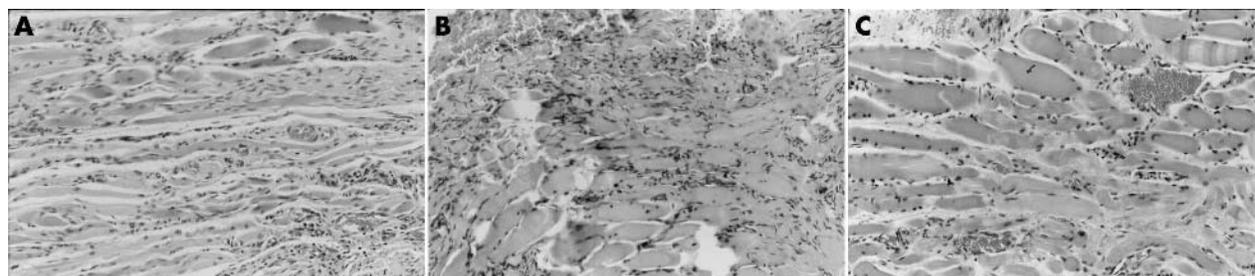


Figure 1 Light microscopic findings (haematoxylin and eosin, original magnification $\times 200$) of the superior rectus muscle of rabbits at postoperative 4 weeks: (A) control group, (B) polyurethane group, (C) polyurethane-dexamethasone group.

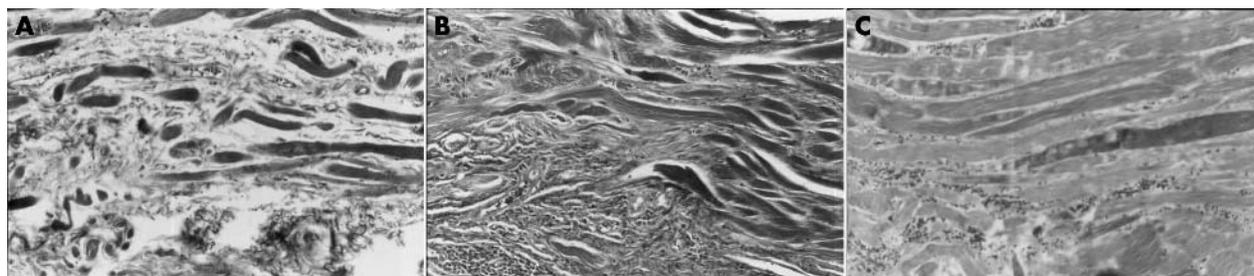


Figure 2 Light microscopic findings (Masson Trichrome, original magnification $\times 200$) of the superior rectus muscle of rabbits at postoperative 6 weeks: (A) control group, (B) polyurethane group, (C) polyurethane-dexamethasone group.

of adhesion between the SRM and the sclera at 4 weeks postoperatively between group P-D and the control group ($p = 0.011$). There was also a significant difference between group P and the control group in the degree of adhesion at 6 weeks postoperatively ($p = 0.002$), as well as between group P-D and the control group ($p = 0.011$). When comparing the degree of adhesion between the SRM and the sclera, there was no significant difference between the group P and the group P-D at postoperative 4 weeks ($p = 0.051$) and at 6 weeks ($p = 0.417$).

Histological examination

Histological examination showed inflammation and some fibrosis around muscle. Inflammatory reaction and fibrosis were least prominent in group P-D compared to those in the control group or in the group P (figs 1, 2).

DISCUSSION

Polyurethane is relatively biocompatible, transparent, colourless, and autoclavable. In the field of ophthalmology, a polyurethane keratoprosthesis was well tolerated by rabbit eyes even 1 year after implantation. Unlike poly(methylmethacrylate) (PMMA), polyurethane is autoclavable; thus, it has been suggested as a potential material for intraocular lenses and keratoprostheses.¹⁶ Because of these encouraging results, we believed that polyurethane could be safely used as an extraocular physical barrier to adhesion formation. There have been no previous reports on the use of this material for delayed adjustable strabismus surgery. The ideal drug release devices for our purpose should fulfil the following criteria.²² Firstly, the device should provide a sustained and relatively uniform therapeutic concentration of the drug in a reliable and predictable fashion over an adequate period of time. Secondly, the device should be easily implantable or injectable, but must remain stable and non-migratory within the eye. Thirdly, the device should have a long shelf life, and it should be easy to handle and sterilise. Finally, there should be no toxic effects from sustained exposure to the drug. Because it is necessary for us to re-open the conjunctival incision and to adjust the sutures, the device does not need to be biodegradable, unlike other intraocular devices. None of the sustained delivery systems introduced to date have fulfilled all of these criteria. In this study, polyurethane film of 0.1 mm thickness was used. Because it was very thin, the polyurethane film could be well tolerated without discomfort. However, such thin film is difficult to manipulate because it rolls up and sticks together easily. Perhaps a film that is slightly thicker would be easier to manage without causing too much discomfort.

Delayed adjustment may provide a better chance for the surgeon to align the eyes,^{4,5} but postoperative adhesions can prevent delayed adjustment. Our previous data suggested that poly(tetrafluoroethylene) alone could allow adjustment to be delayed for up to 4 weeks after surgery in 40% of the

experimental eyes,⁹ and that the combined use of poly(tetrafluoroethylene) and 5-fluorouracil, or the addition of Viscoat, could allow adjustment to be delayed for up to 4 weeks after surgery in 80% of the experimental eyes.¹² This study showed better results using polyurethane film without the necessity for frequent instillation of topical steroids. In group P-D, adjustment was possible in 11 out of 11 eyes 4 weeks postoperatively and in 10 out of 11 eyes 6 weeks postoperatively. Even though there was no statistically significant difference, adjustment was possible in more eyes in group P-D than in group P. In addition, the degree of adhesion between the SRM and the sclera was slightly lower in groups P-D than groups P at 4 weeks postoperatively. These results demonstrated that polyurethane with sustained release dexamethasone could effectively prevent the development of adhesion after strabismus surgery in this rabbit model.

In terms of the adjustment technique, there may be some question as to the best method for dealing with conjunctival adherence to the sclera. Rabbits have little subconjunctival connective tissue, thus the original recession surgery could be performed with substantially no bleeding. Cauterisation was not necessary. It was not that difficult to reopen the previous conjunctival incision, even at 6 weeks postoperatively. We have rarely needed to use scissors for this, and instead have used the fine tip of a curved needle holder to reopen the previous incision site. This technique made it possible to reopen the incision without bleeding. Even in humans, it is not difficult to remove a physical barrier and the adjustment procedure was not that different either with or without a physical barrier.

Delaying adjustment might give the surgeon a better picture of where a given patient's motility will stabilise. In humans, Hwang suggested that delayed adjustable strabismus surgery was possible with the clinical use of a thin poly(tetrafluoroethylene) plate.²³ Shokida and colleagues suggested that delayed adjustment surgery using silicone sheet showed better results for patients with exotropia and re-operated cases than immediate adjustment.²⁴ The result of this study suggests that polyurethane with steroid could also delay adjustment even without frequent postoperative instillation of anti-inflammatory drugs.

In summary, a new drug delivery system for the extraocular sustained release of dexamethasone from the polyurethane film has been presented. Polyurethane is helpful for delaying adjustment in rabbit eyes until 6 weeks postoperatively without the need for frequent topical instillation of steroids.

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The authors have no proprietary interest in any of the materials used in this study

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