

Combined effect of Interceed and 5-fluorouracil on delayed adjustable strabismus surgery

Jeong-Min Hwang, Bong Leen Chang

Abstract

Aims/background—To discover a more reliable method of performing delayed suture adjustment as a basis to investigate whether delayed adjustment actually provides more stable results. In order to prevent the formation of postoperative adhesions and delay the time of adjustment, an animal study was performed to determine the combined effect of physical barriers, Viscoat and Interceed, and a pharmacological agent, 5-fluorouracil (5-FU).

Methods—38 rabbit eyes were divided into three groups. After recession of the superior rectus muscle (SRM), 5-FU was applied beneath and over the SRM in group 5-FU. Group I-f had Interceed and 5-FU and group I-fv, Interceed, 5-FU, and Viscoat. Delayed adjustment was performed once on each SRM at 1, 2, and 3 weeks postoperatively. The possible length and the necessary force to adjust as well as the degree of adhesions were recorded.

Results—5-FU delayed the adjustment for up to 1 week after surgery in three out of four eyes. Combined use of Interceed and 5-FU could delay the adjustment for up to 1 week after surgery in three out of five eyes. Addition of Viscoat could delay the adjustment for up to 1 week after surgery in four out of five eyes. Adjustment was possible on only one of four eyes thereafter.

Conclusions—Combined use of Interceed, 5-FU, and Viscoat could delay the adjustment in rabbits until 1 week postoperatively.

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Adjustable strabismus surgery is an effective method of providing the surgeon with one more chance to modify the amount of surgical correction in the immediate postoperative period.^{1,2} However, postoperative alignment may drift with time even after placing the eyes in a suitable position with adjustment.¹⁻⁵ Thus, delayed adjustment may be desirable for better postoperative results,^{6,7} but the postoperative healing process causes adhesions, which inhibit such delayed adjustment.

Delayed adjustments have been attempted by the implantation of silicone, viscoelastic material, Interceed, polyglactin 910 mesh, or polytetrafluoroethylene (PTFE).⁷⁻¹¹ In animal experiments, silicone delayed the adjustment up to 8 weeks,⁸ viscoelastic material and Interceed up to 1 week,^{9,10} and PTFE up to 4 weeks.¹¹ However, the silicone can cause discomfort because of its thickness and rigidity and may trigger

infection, extrusion, or granuloma formation. As a barrier, Interceed (TC7) is a fabric composed of oxidised, regenerated cellulose specifically designed as a surgical adjuvant to reduce the formation of postsurgical adhesions.¹²⁻¹⁴ It is known to be effective in reducing postoperative adhesions.¹²⁻¹⁴ Viscoat is a viscoelastic solution composed of sodium hyaluronate and sodium chondroitin sulphate, and has been reported to be effective for preventing postoperative adhesion formation.^{10,15-18} 5-Fluorouracil (5-FU) is a fluorinated pyrimidine analogue that inhibits fibroblast proliferation by competitive inhibition of thymidylate synthetase. It is an antimetabolite agent with cell cycle specificity, thus relatively less toxic than other antimetabolites.¹⁹⁻²¹ It has been used as an antifibrotic agent in glaucoma surgery.¹⁹⁻²¹

This study was designed to assess the efficacy of Interceed, Viscoat, and 5-FU in delaying adhesion formation and adjustment.

Materials and methods

Nineteen New Zealand white rabbits, weighing 2.0-3.0 kg, underwent 5 mm recession of the superior rectus muscle (SRM) using double armed 6-0 polyglactin 910 (Alcon Surgical Inc, Fort Worth, TX, USA) in rabbit eyes with future adjustment at postoperative 1 week and double armed 5-0 Dacron (Alcon Surgical Inc, Fort Worth, TX, USA) adjustable suspension sutures in others. 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 proxymetacaine (proparacaine) hydrochloride. As a physical barrier, Interceed (TC7, Johnson & Johnson Medical Inc, Arlington, TX, USA) was used in group I-f, and Interceed and Viscoat (Alcon, Fort Worth, TX, USA) in group I-fv. As a pharmacological agent, 5-FU (250 mg/5 ml, Choongwae, Hwasung, Korea) was used in all groups.

PROCEDURES

Preoperative surgical antisepsis with polyvinylpyrrolidone-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 6-0 polyglactin 910 or double armed 5-0 Dacron suture close to the insertion and disinserted from the globe. Two pieces of Weck Cel sponge were soaked in 5-FU (50 mg/ml). One sponge was placed beneath the SRM, and another was laid over it.

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

Group	Time of adjustment (weeks)	Adjustment possible (No of eyes)	Adjustment not possible (No of eyes)	Force (g) Mean (SD)	Length (mm) Mean (SD)
5-FU	1	3	1	51.67 (9.71)	4.00 (0.00)
	2	0	4	*	*
	3	0	4	*	*
I-f	1	3	2	48.33 (23.63)	3.67 (0.58)
	2	1	3	65	2
	3	0	4	*	*
I-fv	1	4	1	36.75 (10.44)	4.50 (0.57)
	2	1	3	75	1.5
	3	0	4	*	*

5-FU = 5-fluorouracil; I-f = Interceed + 5-FU; I-fv = Interceed + 5-FU + Viscoat.

*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)
5-FU	1 week	1 (3) 2 (1)	0 (1) 1 (3)
	2 weeks	1 (1) 2 (3)	1 (3) 2 (1)
	3 weeks	2 (2) 3 (2)	2 (4)
I-f	1 week	1 (3) 2 (2)	1 (3) 2 (2)
	2 weeks	1 (2) 2 (2)	1 (1) 2 (3)
	3 weeks	1 (2) 2 (1) 3 (1)	2 (4)
I-fv	1 week	1 (3) 2 (2)	1 (3) 2 (2)
	2 weeks	1 (1) 2 (2) 3 (1)	1 (1) 2 (3)
	3 weeks	2 (3) 3 (1)	2 (4)

5-FU = 5-fluorouracil; I-f = Interceed + 5-FU; I-fv = Interceed + 5-FU + Viscoat.

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.

Tenon's and conjunctiva were pulled over the upper sponge and they were left undisturbed for 5 minutes. After sponge removal, the eyes were irrigated with 10 ml balanced salt solution to remove any excess 5-FU. An Interceed plate was placed between the sclera and SRM in group I-f and group I-fv. Viscoat was placed around SRM in group I-fv. Finally, the SRM was reattached to the original insertion. A loop handle of 5-0 Dacron 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 drops and dexamethasone ointment were applied topically and 4 mg of gentamicin was injected in the thigh muscle.

DELAYED ADJUSTMENT

The previous conjunctival incision site was reopened by spreading both ends of the tip of curved needle holder. The SRM was adjusted under the same anaesthesia once on each SRM at 1, 2, and 3 weeks postoperatively. A dial tension gauge (DT-50, Teclock, Japan) or push pull gauge (PP-705, 5 g, 500 g, Teclock, Japan) grasped loop handle of the sutures connected to the muscle. The muscle was then moved anteriorly (measured by a Castroviejo caliper) 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 adhesions easily separable with blunt dissection, 2 = mild to moderate adhesions with freely dissectible plane, 3 = moderate to dense adhesion with difficult dissection, and 4 = non-dissectible plane.

HISTOLOGICAL EXAMINATION

The involved tissues were subsequently examined macroscopically and microscopically using haematoxylin and eosin staining. 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 and the force necessary for advancing the muscles were analysed using Wilcoxon rank sum test. The severity of the adhesions were analysed using Mann-Whitney U test.

Results

ADJUSTABILITY

In group 5-FU, adjustment was possible in three out of four eyes 1 week postoperatively. Adjustment thereafter was not possible (Table 1). In group I-f, adjustment was possible in three out of five eyes 1 week postoperatively and in one out of four eyes 2 weeks postoperatively. Adjustment thereafter was not possible (Table 1). In group I-fv, adjustment was possible in four out of five eyes 1 week postoperatively and in one out of four eyes 2 weeks postoperatively. Adjustment thereafter was not possible (Table 1).

LENGTH AND THE FORCE FOR THE ADJUSTMENT

One week postoperatively, the average length and force for the adjustment were 51.67 g and 4.00 mm in group 5-FU, 48.33 g and 3.67 mm in group I-f, and 36.75 g and 4.50 mm in group I-fv, respectively (Table 1). Two weeks postoperatively, the length and force for the adjustment were 65 g and 2.00 mm in only one eye in group I-f, and 75 g and 1.5 mm in group I-fv, respectively (Table 1).

DEGREE OF ADHESIONS BETWEEN SRM AND THE CONJUNCTIVA

In group 5-FU, the degree of adhesions was 1 in three eyes and 2 in one eye 1 week postoperatively, 1 in one eye and 2 in three eyes 2 weeks postoperatively, and 2 in two eyes and 3 in two eyes 3 weeks postoperatively (Table 2). In group I-f, the degree of adhesions was 1 in three eyes and 2 in two eyes 1 week postoperatively, 1 in two eyes and 2 in two eyes 2 weeks postoperatively, and 1 in two eyes, 2 in one eye, and 3 in one eye 3 weeks postoperatively (Table 2). In group I-fv, the degree of adhesions was 1 in three eyes and 2 in two eyes 1 week postop-

eratively, 1 in one eye, 2 in two eyes, and 3 in one eye 2 weeks postoperatively, and 2 in three eyes and 1 in one eye 3 weeks postoperatively (Table 2).

DEGREE OF ADHESIONS BETWEEN SRM AND THE SCLERA

In group 5-FU, the degree of adhesions was 0 in one eye and 1 in three eyes 1 week postoperatively, 1 in three eyes and 2 in one eye 2 weeks postoperatively, and 2 in four eyes 3 weeks postoperatively (Table 2). In group I-f and I-fv, the degree of adhesions was 1 in three eyes and 2 in two eyes 1 week postoperatively, 1 in one eye and 2 in three eyes 2 weeks postoperatively, and 2 in four eyes 3 weeks postoperatively (Table 2).

HISTOLOGICAL EXAMINATION

There was lymphocyte infiltration and some fibrosis around the muscle. Light microscopic examination did not reveal any abnormalities of the sclera or underlying ciliary body.

STATISTICAL ANALYSES

Comparing adjustability at postoperative 1 and 2 weeks, there was no significant difference between three groups ($p=1.00$).

Comparing the length and force for adjustment and the degree of adhesions, there was no difference between group 5-FU and I-f at postoperative week 1 ($p = 0.32$ for the length, $p = 0.51$ for the force) as well as between group 5-FU and I-fv ($p = 0.18$ for the length, $p = 0.08$ for the force) and between group I-f and I-fv ($p = 0.11$ for the length, $p = 0.47$ for the force). Comparing the degree of adhesion between SRM and conjunctiva or sclera, there was no significant difference among three groups at postoperative 1, 2, or 3 weeks ($p > 0.05$).

Discussion

Delayed adjustment may provide better chance for the surgeon to align the eyes,^{6,7} but postoperative adhesions prevent delayed adjustment. For the purpose of delaying adjustment, many kinds of materials have been tested in attempts to prevent reformation of adhesions following strabismus surgery, usually acting as mechanical barriers.⁷⁻¹¹ These materials have included silicone, viscoelastic material, Interceed, polyglactin 910 mesh, and polytetrafluoroethylene.⁷⁻¹¹

Interceed was redesigned Surgicel in order to provide a material that could cover traumatised tissues and act as a barrier to the formation of adhesions. Preclinical studies with Interceed demonstrated that it promoted negligible tissue response, completely absorbed from the peritoneal cavity in less than 28 days, and reduced the extent and severity of post surgical adhesions in standardised animal models.¹³ Although Yaacobi and associates reported that the use of Interceed sleeves significantly increased formation of postoperative adhesions, they speculated that failure of Interceed to prevent postoperative adhesions may have been due to the presence of some blood in the surgical field.¹⁴ To obtain maxi-

mum benefit, it is essential to achieve complete haemostasis before applying Interceed. Viscoat is a viscoelastic substance known to be low immunogenic and anti-inflammatory, and its use in anterior segment eye surgery has been already approved by the Food and Drug Administration.¹⁵⁻¹⁷ Sodium chondroitin sulphate (SCS), one component of Viscoat, was useful for preventing adhesion formation in pelvic surgery in an animal study.¹⁵ Sodium hyaluronate (SH), the other component of Viscoat, is known to decrease inflammation, fibrosis, and scarring.¹⁶⁻¹⁸ In our previous study with balanced salt solution,¹⁰ adjustment was possible in three out of three eyes (100%) 2 days postoperatively, and in two out of four eyes (50%) 4 days postoperatively. Adjustment was then impossible 6 days postoperatively.¹⁰ This represent the control study without any physical barriers. In previous experiment with Viscoat, it could delay the adjustment up to 6 days postoperatively in four out of five eyes.¹⁰ Interceed could delay the adjustment up to 1 week postoperatively in two out of five eyes.⁹ We assume that the additional use of Viscoat or a pharmacological agent would be more helpful for delaying the adjustment. To our knowledge, combined use of a physical barrier and pharmacological agent has never been tried for delaying adjustment.

In terms of the adjustment technique, there may be some question about how to deal with conjunctival adherence to the sclera. Rabbits have little subconjunctival connective tissues, thus the original recession surgery could be performed with little bleeding. Cauterisation was not necessary. It is not difficult to reopen the previous conjunctival incision even at postoperative 3 weeks. We have never used scissors, but have instead used the tip of a curved needle holder to spread the previous incision site. This technique can make it possible to reopen the incision without bleeding.

Intraoperative sponge 5-FU is thought to be a reasonably safe and effective adjunct to trabeculectomy surgery.²¹ In strabismus surgery with rabbits using 5-FU, we did not observe any complications such as non-healing. In glaucoma surgery in rabbits, the mean bleb grading in the 5-FU treated eyes was significantly higher than in the control group on days 3-18.²⁰ We also observed a temporary effect of delaying the adjustment for up to 1 week postoperatively. Adjustment thereafter was not possible (Table 1). In comparison with our previous results with Interceed⁹ or Viscoat,¹⁰ the additional use of 5-FU gave better results than with Interceed or Viscoat alone. In group I-f and I-fv, delayed adjustment was possible in 60% and 80% of rabbit eyes 1 week postoperatively, respectively, and in one out of four eyes 2 weeks postoperatively. Additional use of Viscoat reduced the average force and length for the adjustment, but failed to make any statistically significant difference in group I-fv. In our experience, combined use of Interceed, 5-FU, and Viscoat allows suture adjustment as late as 1 week after the operation in 60% to 80% of the experimental eyes. In conclusion, combined use of Interceed and 5-FU showed

promise as a more reliable means of delaying the formation of adhesions and timing of adjustment in extraocular muscle surgery up to 1 week postoperatively.

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