European Journal of Ophthalmology / Vol. 15 no. 5, 2005 / pp. 530-535

Comparison of the effectiveness of mitomycin-C and Viscoat on delayed adjustable strabismus surgery in rabbits

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PURPOSE. To determine a way to prevent the formation of adhesions and delay the time of suture adjustment in the course of adjustable strabismus surgery, an animal study was performed to assess and compare the effects of mitomycin C (Mit-C) and viscoelastic material Viscoat (sodium hyaluronate 3% and chondroitin sulphate 4%, Alcon, Fort Worth, TX).
METHODS. Right eyes of 47 rabbits were divided into three groups. After recession of the superior rectus muscle (SRM), Mit-C was administered beneath and over the SRM in Group M (16 eyes), Viscoat was administered beneath and over SRM in Group V (16 eyes), and ringer lactate was administered in Group C (15 eyes). SRM then recessed 5 mm with adjustable strabismus surgery technique. Animals in each group were subdivided into 1 and 2, where 1 = adjustment 1 week postoperatively and 2 = adjustment 3 weeks postoperatively. Delayed adjustment was performed in M_1 group (6 eyes), V_1 group (6 eyes), and C_1 group (7 eyes) after 1 week; in M_2 group (6 eyes), V2 group (6 eyes), and C_2 group (6 eyes) after 3 weeks. Histopathologic examinations were performed for the remaining 10 eyes without suture adjustment at the end of first and third weeks after adjustable strabismus surgery. The possible length and the necessary force to adjust and the degree of adhesions were recorded.
RESULTS. When length and strength of the adjustment, adhesions between muscle and sclera, and adhesions between muscle and conjunctiva were taken into consideration, there was no statistically significant difference among M, V, and C groups at postoperative weeks 1 and 3. The force needed for adjustment in M_1 group was statistically lower than M_2 group.
CONCLUSIONS. The intraoperative use of Mit-C (0.4 mg/mL) may decrease adhesion formation in the early postoperative period, especially in the first week. The intraoperative use of Viscoat was not effective in reducing postoperative adhesions and delaying adjustment. (Eur J Ophthalmol 2005; 15: 530-5)

KEY WORDS. Suture adjustment, Viscoat, Mitomycin C

Accepted: March 23, 2005

INTRODUCTION

Adjustable strabismus surgery is an effective method for the surgeon to modify the position of the eye one more time in the immediate postoperative period (1-3). Even after placing the eyes in a suitable position with adjustable strabismus surgery, alignment of the eyes may change with time (1-6). In such cases, a delayed adjustment may be desirable, which can be prevented by postoperative adhesions (7, 8). Direct tissue trauma, excessive bleeding, multiple operations, reactions to suture materials, and postoperative infections may cause postoperative adhesions, which often hinders the ability to predict surgical results and to perform adjustment after strabismus surgery

1120-6721/530-06$15.00/0

(9). Even using atraumatic and careful surgical techniques, the most effective means of preventing postoperative adhesions, such adhesions may occur in patients at high risk of exaggerated scarring. Therefore, attempts to inhibit the adhesions after strabismus surgery and to delay the adjustment have been made by a variety of mechanical barriers (8-16) and antiproliferative agents (10, 17-20). These materials have included tissue implants such as Amnioplastin, egg membrane, Tenon's capsule, and peritoneum; and plastic implants such as polyester film, polyvinylidene chloride, silicone, and cellulose. However, some of these materials like silicone and plastic implants can cause discomfort because of thickness and rigidity and cause infections, extrusion, or granuloma formation (8, 21-24).

Viscoelastic material Viscoat (sodium hyaluronate 3% and chondroitin sulphate 4%, Alcon, Fort Worth, TX) is known to be low immunogenic and anti-inflammatory and to decrease inflammation, fibrosis, and scarring (14, 15, 25). Mitomycin C (Mit-C) is an antineoplastic agent that already has an established role in ophthalmology, especially in trabeculectomy to reduce postoperative scarring and increase bleb survival (26, 27). It also has been used in restrictive strabismus to reduce postoperative adhesions with encouraging results in experimental studies and clinical trials (20, 28). This study was conducted to further assess and compare the efficacy of Mit-C and Viscoat in delaying adhesion formation and adjustment.

MATERIALS AND METHODS

Procedures

A total of 47 New Zealand white rabbits weighing approximately 2500 to 3000 g were selected for the study. The care and handling of the rabbits were in accordance with the Association for Research in Vision and Ophthalmology Resolution on the Use of Animals in Research and the policies in the Guidelines for the Care and the Use of Laboratory Animals (National Institute of Health publication No 85-23, as revised in 1985). Each rabbit was anesthetized with a mixture of ketamine hydrochloride, 30 mg/kg, and xylazine hydrochloride, 5 to 10 mg/kg, intramuscularly and topical anesthesia with proxymetacaine hydrochloride. Surgical antisepsis with polyvinylprolidone-iodine was applied to the eyelids before each operation. 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 SRM was then placed on a double armed 5-0 Dacron suture close to the insertion site and disinserted from the globe. An antiproliferative agent Mit-C and physical barriers, Viscoat and ringer lactate solution, were used for experimental groups, Groups M and V; and control group, Group C.

Mit-C was applied to 15 eyes, Viscoat to 15 eyes, and ringer lactate to 16 eyes. Two pieces of eye sponge were soaked in Mit-C (0.4 mg/mL). Sponges were placed beneath and over the SRM. Tenon's and conjunctiva were pulled over the upper sponge and they were left undisturbed for 5 minutes.

The eyes were irrigated with 10 mL ringer lactate to remove any excess Mit-C. In Group V, 0.2 mL Viscoat was applied around SRM; ringer lactate (about 10 mL) was applied around SRM in Group C. Then, the SRM was reattached to the original insertion. SRM then recessed 5 mm with adjustable strabismus surgery technique. A loop handle of 5-0 Dacron suture was made for suture adjustment.

The edges of the conjunctival peritomy were closed with interrupted 8-0 polyglactin sutures. Fusidic acid and corticosteroid ointment were applied topically and 2 mg of gentamicin was injected in the thigh muscle at the end of each procedure.

Animals in each group were subdivided into 1 and 2, where 1 = adjustment 1 week postoperatively and 2 = adjustment 3 weeks postoperatively.

Delayed adjustment

The conjunctival incision site was reopened. The SRM was adjusted using the same anesthesia once on each SRM at 1 week in M_1 group (6 eyes), V_1 group (6 eyes), and C_1 group (5 eyes), and 3 weeks postoperatively in M_2 group (6 eyes), V_2 group (6 eyes), and C_2 group (7 eyes). A push pull gauge (Pesola 300 g, Swiss) 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.

Evaluation of adhesions

At the time of adjustment, the adhesions among the muscle, sclera, and the conjunctiva were evaluated and recorded. The severity of the adhesions was scored on a continuous scale according to Hwang and Chang (10)

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.

Histologic examination

The involved tissues (muscles, conjunctiva, sclera) were examined macroscopically and microscopically using hematoxylin and eosin staining for the remaining 10 eyes (V_1=2 eyes, M_1=2 eyes, C_1=1 eye, V_2=2 eyes, M_2=2 eyes, C_2=1 eye) without suture adjustment at the end of the first and third weeks after adjustable strabismus surgery. Masson's trichrome staining was also performed to evaluate the degree of fibrous proliferation.

Statistical evaluation

The differences between control group and experimental groups in length of advancement and the force necessary for advancing the muscles and the severity of the adhesions between conjunctiva/muscle and sclera/muscle were analyzed using Kruskal Wallis test. The differences in these parameters between first and third weeks in each group were analyzed using Mann-Whitney U test.

RESULTS

Length and the force for the adjustment

One week postoperatively, the average length and the force for the adjustment were 53.16±8.89 SE g and 2.54±0.64 SD mm in Group M_1; 112.33±24.04 SE g and 1.87±0.80 SD mm in Group V_1; and 101.28±22.58 SE g and 2.28±0.75 SD mm in Group C_1. Three weeks postoperatively, the average length and the force for the adjustment were 90.00±10.03 SE g and 2.70±1.01 SD mm in Group M_2; 121.33±11.49 SE g and 1.91±0.53 SD mm in Group V_2; and 124.66±24.31 SE g and 1.95±0.53 SD mm in Group C_2 (Tab. I).

Comparing the length and force for adjustment, there was no difference among Groups M_1, V_1, and C_1 at postoperative week 1 (p=0.81, p=0.310 respectively), as well as between Groups M_2, V_2, and C_2 at postoperative week 3 (p=0.232, p=0.406, respectively). Comparing the force for adjustment, there was a statistically significant difference between M_1 and M_2 (p=0.025).

Degree of adhesions between SRM and the conjunctiva

The averages of adhesions were 2.50±0.83 SD in Group M_1; 2.66±0.81 SD in Group V_1; and 2.71±1.11 SD in Group C_1 1 week postoperatively (Tab. II). The averages of adhesions were 3.16±0.75 SD in Group M_2; 3.33±0.81 SD in Group V_2; and 3.66±0..51 SD in Group C_2 3 weeks postoperatively (Tab. II). Comparing the degree of adhesion between SRM and conjunctiva, there was no significant difference among three groups at postoperative 1 and 3 weeks (p>0.05).

Degree of adhesions between SRM and the sclera

The averages of adhesions were 3.50±0.54 SD in Group M_1; 3.66±0.51 SD in Group V_1; and 3.71±0.48 SD in Group C_1 1 week postoperatively (Tab. II). The averages of adhesions were 3.16±0.75 SD in Group M_2; 3.83±0.40 SD in Group V_2; and 3.33±0.51 SD in Group C_2 3 weeks postoperatively (Tab. II). Comparing the degree of adhesion

TABLE I - THE TRACTIONAL FORCE AND LENGTH FOR THE ADJUSTMENT

Subgroup	Time (week)	Eyes (number)	Length, mm, mean±SD	Force, g, mean±SE
M_1	1	6	2.54±0.64	53.16±8.89
M_2	3	6	2.70±1.01	90.00±10.03
V_1	1	6	1.87±0.80	112.33±24.04
V_2	3	6	1.91±0.64	121.33±11.49
C_1	1	5	2.28±0.75	101.28±22.58
C_2	3	7	1.95±0.53	124.66±24.31

SD = Standard deviation; SE = Standard error

between SRM and sclera, there was no significant difference among the three groups at postoperative 1 and 3 weeks ($p>0.05$).

Histopathologic examinations

Histologic examination by light microscopy revealed foreign body reaction and inflammation around suture materials. 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. The histopathology revealed no evidence of any tissue toxicity in the experimental and control eyes.

DISCUSSION

Adhesions following strabismus surgery often affect the postoperative outcome and make adjustment difficult postoperatively (9). Mit-C is an antineoplastic agent that already has an established role in ophthalmology, especially in trabeculectomy, to reduce postoperative scarring and increase bleb survival (26, 27). It also has been used in restrictive strabismus to reduce postoperative adhesions with encouraging results in experimental studies and clinical trials (19, 28) and to reduce recurrence of pterygium following excision (29). Sodium chondroitin sulphate and sodium hyaluronate are members of the family of biochemical compounds referred to as glycosaminoglycans. The adhesion-preventing properties of sodium chondroitin sulphate are based upon its ability to coat epithelial surfaces and its double negative charge, which enables it to adhere strongly to tissue surfaces separated by supplying repelling negative charges (25). Sodium hyaluronate has the ability to separate collagen matrices physically and to delay the arrival and inhibit the function of inflammatory mediators. It has been used since 1987 to reduce the adhesions of eye muscles to the sclera and to facilitate the employment of postoperative adjustable suture for strabismus surgery, known to be low immunogenic and anti-inflammatory and to decrease inflammation, fibrosis, and scarring (14, 15, 25, 30).

In this study, we investigated and compared the adjustment delaying effects of the viscoelastic substance composed of both sodium chondroitin sulphate and sodium hyaluronate, and antimetabolic agent, Mit-C. We could perform adjustment to all eyes in postoperative weeks 1 and 3. Comparing the length and force for adjustment, degree of adhesion between SRM and conjunctiva and sclera, there was no difference among Groups M, V, and C at postoperative weeks 1 and 3. The force needed for adjustment in M_1 group was statistically lower than M_2 group. We concluded that Mit-C decreases adhesion formation in the early postoperative period, especially in the first week. This is in accordance with the studies by Cruz and Matkovich (28), Oh et al (31), and Mahindrakar et al (32) in which the amount of postoperative adhesions was less but not completely absent following intraoperative application of Mit-C. Mit-C applied for 5 minutes intraoperatively in the concentration of 0.2 mg/mL was reported to be effective in delaying adhesion but did not completely eliminate the problem of postoperative fibrosis (31). Mit-C applied for 5 minutes intraoperatively in the concentration of 0.5 mg/mL was reported to be effective in decreasing the amount of fibroblast growth factor and it was suggested that Mit-C may help to prevent postoperative adhesion formation (33). In this study, we applied Mit-C in the concentration of 0.4 mg/mL. The aspect and the nature of the conjunctivas in the mitomycin groups during adjustments were not different from the other groups. Also, no difference among the groups was observed with regard to clinical evaluation of adhesion formation and

TABLE II - DEGREE OF ADHESIONS IN EACH GROUP

Subgroup	Time (week)	Eyes (number)	SRM/conjunctiva (SD)	SRM/sclera (SD)
M_1	1	6	3.50±0.54	2.50±0.83
M_2	3	6	3.16±0.75	3.16±0.75
V_1	1	6	3.66±0.51	2.66±0.81
V_2	3	6	3.83±0.40	3.33±0.81
C_1	1	5	3.71±0.48	2.71±1.11
C_2	3	7	3.33±0.51	3.66±0.51

SD = Standard deviation; SRM = Superior rectus muscle

histologic examination of the conjunctiva and involved other tissues. We concluded that Mit-C may delay adhesion formation in the early postoperative period applied in this concentration and duration without causing toxic complications.

Minguini et al (34) reported that the intraoperative use of Mit-C (0.4 mg/mL) was not effective in controlling the postoperative inflammatory response in rabbit eyes 7 weeks after extraocular muscle surgery when they compared their study and control groups histologically. We also could not observe any histologic differences between our groups in early and late postoperative periods.

Previously, alone or combined usage of Viscoat were reported to be effective in delaying adjustment at postoperative week 1. The additional use of 5-FU with Interceed or Viscoat were reported to be more effective in reducing postoperative adhesion than usage of Interceed or Viscoat alone. Additional use of Viscoat with an antineoplastic agent 5-FU and Interceed was reported to reduce average force and length of adjustment and delay adjustment 1 week postoperatively in 60 to 80% of rabbit eyes (10, 14). In our present study we could not observe any difference in these parameters when we compared Viscoat with controls and Mit-C usage.

In the present study, we preferred to use nonabsorbable suture 5-0 Dacron. Both absorbable and nonabsorbable sutures have been used in experimental studies of adjustable suture strabismus surgery. In a recent animal model of scar remodeling after strabismus surgery, the use of nonabsorbable sutures was associated with shorter and thicker scars. The use of nonabsorbable sutures in the repair procedures of previously overcorrected patients reduced the recurrence rate compared to the use of absorbable sutures (35).

In this experimental study, Viscoat could not reduce the force and length of adjustment and delay adjustment in adjustable strabismus surgery. Mit-C applied for 5 minutes intraoperatively in the concentration of 0.4 mg/mL reduced the force needed for adjustment in the early postoperative period and was clinically well tolerated. We suggest that the delaying effect of Mit-C in adjustable strabismus surgery can be augmented by combining with other drugs and materials.

The authors have no proprietary interest in any aspect of the article.

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