EXTENDED REPORT

Adal-1 bioadhesive for sutureless recession muscle surgery: a clinical trial

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Aims: To evaluate the efficacy and biotolerance of the Adal-1 adhesive for muscle sealing in strabismus surgery.

Methods: 27 eyes were included in the study: 17 in the control group and 10 in the study group. Surgery was performed on the recession of the horizontal rectus muscles. In the control group the muscle was joined to the sclera by a Vicryl 7/0 suture. In the study group, the Adal-1 adhesive was used instead. The efficacy of the sealing of the muscle to the sclera and the biotolerance of the surrounding tissues were evaluated.

Results: The muscular recession in the control group was 8.17 (SD 2.38) with displacement of the sealing point of 0.02 (1.7) mm. In the group sealed with adhesive, the muscular recession was 9.09 (3.08) and the displacement was 0.15 (1.56) mm, with no significant differences between the techniques ($p < 0.05$). The inflammation of the surrounding tissues in the immediate postoperative period was greater with the suture technique ($p > 0.05$), but there were no differences in the other postoperative periods (Mann-Whitney U test).

Conclusion: Adal-1 was an effective and safe alternative to sutures in muscle recession for strabismus surgery in this study.

Strabismus surgery requires suture for the recession or resection of the extraocular muscles of the eye. Several types of suture materials have been used in strabismus surgery such as silk, Dexon, Vicryl, and nylon, each with limitations. One of the most severe complications of the suture technique are scleral perforations, which may be caused by the needles used in the procedures, because of the difficult technique in which the points of suture are occasionally placed retroequatorially.¹ The possibility of intolerance to these materials or induction of granulomas caused by foreign body reaction exists and has been reported.² Research into new substances and materials to be used as an alternative to sutures is not new.³ Adhesives have been used in ophthalmic surgery and in particular in strabismus surgery, with both biological^{4–5} and synthetic adhesives.^{6–8} In these applications, the adhesives fulfil their goal. However, despite producing effective sealing, the synthetic adhesives, such as the cyanoacrylates, showed reticulation thus causing a highly rigid polymerised product of considerable strength, but at the same time, were fragile. In addition, erosion, ulceration, and areas of necrosis in surrounding (or adjacent) tissues may occur. These synthetic adhesives are not well tolerated by patients and cause complications such as giant papillary conjunctivitis, granulomatous keratitis, cataracts, and retinal toxicity.⁸ On the other hand, the biological adhesives, such as fibrinogen, have a softer texture, reduce patient discomfort, and are therefore better tolerated. However, there is a possibility of potential viral contamination.⁹ They also have little tensile strength,^{4 10–12} and are not suitable for strabismological surgery, where muscular traction is important. Bioadhesives have proved to be very rapid and efficient sealing agents for conjunctival surgery.¹⁰ They produce minimal eyeball inflammation and offer maximum flexibility with minimal rigidity at the site of union.

Adal-1 is a synthetic adhesive with a cyanoacrylic base. It has structural modifications and additives that provide the mixture with greater flexibility, reduce its rigidity without the loss of tensile strength, and improve tolerance of the

surrounding tissues to the product.^{5 11 13 14} The purpose of this study is to evaluate the efficacy and biotolerance of the Adal-1 adhesive as an alternative to sutures in recession horizontal rectus muscle surgery.

MATERIAL AND METHODS

Following the ethics committee and Spanish Ministry of Health approval, we started an observational, consecutive, prospective randomised clinical trial. In all, 27 eyes were included in the study, with 14 male and 13 female patients with a mean age of 27 years (range 18–76 years). Only one eye and one muscle of each patient was operated. In all cases, informed consent was obtained. Inclusion criteria included patients that required strabismus surgery for the horizontal rectus muscle recession. Fourteen recession surgeries were carried out in the medial rectus and 13 in the lateral rectus muscle.

Material

The study eyes were divided into two groups.

Group I (control group)

The technique within this group was muscle sutured to the sclera with polyglactin 7/0 (Vicryl, Ethicon, Brussels, Belgium) and then suture using the hangback technique^{15 16} (17 eyes).

Group II

The technique within this group was muscle sealed to the sclera using Adal-1 adhesive (10 eyes).

Adal-1 adhesive is a two part adhesive that consists of a mixture of ethyl cyanoacrylate and ethyl carboxyacrylate (fig 1). Ethyl cyanoacrylate was synthesised in three consecutive stages: (1) Knoevenagel reaction between ethyl cyanoacetate and p-formaldehyde in the presence of piperidinium chloride as a base catalyst, (2) depolymerisation by heating with a flame under low pressure, and (3) purification by low pressure distillation.

Figure 1 Adal-1 bioadhesive formula.

Ethyl carboxyacrylate is obtained by acid hydrolysis of ethyl cyanoacrylate.

The new Adal-1 adhesive formulation contains a new acrylic derivative, ethyl carboxyacrylate, which acts as a plastifer improving flexibility and producing less exothermal reaction and reduced toxicity. Polymerisation is relatively short, it provides good immediate adhesion to eye tissues, and the adhesive mixture is not as stiff as ethyl cyanoacrylate.¹⁴

The adhesive mixture should be prepared within 1 hour of application onto the tissues. If this time is exceeded, the adhesive properties of the product may be modified with a resulting reduction in adhesive capacity and in the strength of tissue sealing.

For preservation, it is important to keep the two acrylic compounds in separate containers, out of light, free from humidity and, ideally, in a temperature range of between 5°C and 15°C.

Surgical technique

Following peribulbar anaesthesia with a 5 ml mixture of bupivacaine 0.75% and lidocaine 2%, a conjunctival dissection was carried out with Wescott scissors (Moria, France) and muscular capture was performed with a rectus muscle hook (Moria). Following calculation for recession measurement, the recession of the muscle was carried out with recession of the Tenon layer. Given that this procedure was experimental, and in order to guard against inadvertent loss of the muscle, we devised a technique that utilised a “safety handle.” This safety procedure was carried out to avoid muscular retraction to the muscular cone, where recapture would be very difficult or even impossible, in case the adhesive did not achieve sufficient sealing. This safety handle was 10 mm longer than the corresponding retroinsertion to be performed and was created with polyglactin 7/0 (Vicryl) suture at the edge of the muscle, and was sutured to the sclera (hangback technique)^{15 16} (fig 2).

In order to attach the rectus muscle to the sclera, we carefully dried the scleral area and one drop of the Adal-1 adhesive was applied to both the sclera and the tip of the sectioned muscle with a 25 gauge cannula (Steriseal, UK) (fig 2). The two parts were then joined and pressed against each other for approximately 30 seconds until the start of the prepolymerisation was observed and minimal residue appeared around the side of the muscle when the adhesive was pressed (fig 3). At the site of the junction of the muscle to the sclera, one nylon 10/0 stitch (Alcon, Fort Worth, TX, USA) was placed in the centre of the end of the muscle and could be seen through the conjunctiva.

In the suture group the corresponding retroinsertion was performed with polyglactin 7/0 suture at the edge of the muscle, and was sutured to the sclera (hangback technique), without a safety handle. At the site of the junction of the muscle to sclera, in the centre of the muscle, one nylon 10/0 stitch was placed and the distance of the nylon suture knot to limbus was intraoperatively measured by callipers (Asico, AE-1500 Germany) (fig 4).

We evaluated muscle sealing to the sclera and also the presence of muscular displacement from the initial sealing area. We measured this distance in all postoperative visits. The presence of conjunctival ulceration caused by the

Figure 2 Sealing the muscle to the sclera with Adal-1 bioadhesive showing the safety handle.

Figure 3 The muscle sealed to the sclera with Adal-1 bioadhesive.

Figure 4 Intraoperative and postoperative measurement of the distance from the sealed muscle to the limbus. The arrow indicates the nylon reference suture.

polymerised spicules of the adhesive, and inflammation (conjunctival injection, oedema, erosion, and secretion) were observed on all visits (table 1). Fundus ophthalmoscopy was carried out to ascertain the presence of areas of retinal whitening or scleral burns and/or needle perforation. The eyes were followed up for 3 months after the procedure.

In the immediate postoperative period, 1% dexamethasone drops were applied three times a day for 15 days. Ocular

Table 1 Inflammatory index

	1–3 days	1 month	3 months
Group 1			
Sutured	100%	100%	100%
Not sutured	–	–	–
displaced	6 (35.2%)	6 (35.2%)	6 (35.2%)
Conjunctival injection			
Abs-mild	0%	5 (29.4%)	14 (86.1%)
Mild-mod	3 (17.6%)	10 (58.8%)	2 (11.8%)
Mod-sev	14 (82.4%)	2 (11.8%)	0 (0%)
Conjunctival oedema			
Abs-mild	9 (52.9 %)	10 (58.8%)	17 (100%)
Mild-mod	6 (40%)	5 (29.4%)	0 (0%)
Mod-sev	2 (11.8%)	2 (11.8%)	0 (0%)
Ulceration	No	No	No
Secretion	No	No	No
Complications	No	3 granulomas (17.5%)	3 granulomas (17.5%)
Group 2			
Adal-1	1–3 days	1 month	3 months
Sealed	100%	100%	100%
Not sealed	–	–	–
Displaced	4 (40%)	4 (40%)	4 (40%)
Conjunctival injection			
Abs-mild	0%	4 (40%)	9 (90%)
Mild-mod	5 (50%)	4 (40%)	0 (0%)
Mod-sev	5 (50%)	2 (20%)	1 (10%)
Conjunctival oedema			
Abs-mild	3 (30%)	9 (90%)	9 (90%)
Mild-mod	4 (40%)	1 (10%)	1 (10%)
Mod-sev	3 (30%)	(0%)	(0%)
Secretion	No	Mucus	Mucus
Ulceration	No	No	No
Discomfort	Mild-moderate	Mild 2 (20%)	Mild (20%)
Complications		Granuloma 2 (20%)	Granuloma 2 (20%)

surface inflammation was graded according to an ocular surface inflammatory index previously published by Alió *et al.*¹⁷ Values for this index were obtained at 1–3 days, 1 month, and 3 months after the procedure. The clinical follow up was evaluated by an independent observer who applied the bioadhesives or performed the suture in the strabismus surgery.

The results were analysed using SPSS 10.1 non-parametric Mann-Whitney U test. Statistical significance was considered when $p \leq 0.05$. A normal distribution test was carried out in each group. In order to measure relevance, the Mann-Whitney statistics and the related confidence interval (CI) were used to compare different groups. A two sided 95% CI was chosen in this study design.

RESULTS

In group I, 17 eyes (11 medial rectus and six lateral rectus) were included. The mean muscular recession was 8.17 (2.38) mm ranging between 5.5 mm and 13 mm. In group II, a total of 10 eyes were included (three cases of medial rectus surgery and seven cases of lateral rectus surgery). The mean muscle recession in this group was 9.9 (3.08) mm, ranging between 5 mm and 14 mm.

The clinical findings in group I (Vicryl 7/0 sutures) showed a mean displacement of 0.02 (SD 1.7) mm (5 mm less than desired and 2 mm more than desired) from the nylon 10/0 suture (Alcon, Forth Worth, TX, USA) that was used as a reference. In all cases, the operated muscles were correctly attached to the sclera by Vicryl suture. No eyes showed suture breaking.

The degree of inflammation was evaluated in the immediate postoperative period, at 1–3 days, 1 month, and 2 months. In group I, the complications included the appearance of a granuloma caused by the suture in three cases (17.6%), one in the nasal sector and two in the temporal sector. In the three cases of granuloma, the patients

reported a significant degree of discomfort during the postoperative period (table 1).

In group II (Adal-1 tissue adhesive), in 100% of the muscles, the adhesive was effective in fixing the muscles to sclera in the desired position. There was a mean displacement from the reference nylon suture of 0.15 (1.56) mm. The range was from 2 mm less than desired to 2.5 mm more than desired. Two cases of granuloma were observed. These were caused by the protrusion of the Vicryl safety suture and not by foreign body sensation and there were no cases of pain (table 1).

The degree of displacement of the muscles between the two groups was not statistically significant, $p = 0.459$ (Mann-Whitney U test).

There were no statistically significant differences between the groups regarding the degree of inflammation, which is more likely to be as a result of the surgery than to the sealing technique or the sealing of the muscle to the sclera. There were differences in the immediate postoperative period, with a greater degree of conjunctival irritation in the control group ($p = 0.040$), at 1 month ($p = 0.868$) and at 3 months ($p = 0.089$). There were no statistically significant differences between the two groups in the other inflammatory parameters studied (oedema, secretion, ulceration) during the periods studied. There were no cases of scleral perforation, whitening, or scleral or retinal burn in the Adal adhesive group.

DISCUSSION

Strabismus surgery is one of the most frequent surgeries that takes place in the paediatric age group. In most eyes, the surgical technique includes muscle resection/recession together with suturing of the muscle(s) usually with reabsorbable sutures. The use of sutures in strabismus surgery results in complications related to the suture material itself.^{1,2} In cases in which the shortening and thus the

Figure 5 Granuloma: protrusion of safety handle of Vicryl suture in the bioadhesive group.

traction (fibrosis, restriction etc) is large, tearing of the sclera may occur (caused by the needles and suture). Complications that may arise from the use of sutures as a result of difficult access in cases of retroequatorial recession, or the possibility of scleral perforations or retinal tears^{1 2} may be reduced or avoided with the use of Adal-1 for muscular sealing.

Tissue adhesives have been used previously in ocular surgery.³⁻⁷ One of the problems with using the adhesive is that it can slide over the curvature of the ocular globe towards the muscular cone and adhere to the surrounding tissues. This problem was solved by including additives in the adhesive mixture to give it higher viscosity so that the drop applied with the 25 gauge cannula (Steriseal, UK) flows through the tip of the needle and can be applied to the muscular bulk and pressed for 30 seconds with greater safety. A slight muscular traction is performed with Adson forceps to verify that the adhesive reaction has started.

It was observed during the resection that the two cases of granuloma in the Adal-1 group were not caused by the adhesive, but by the safety suture. In these cases a tissue overgrowth was found around part of the suture (fig 5).

Another point is the negative displacement (5 mm less than desired) of the eyes. The suture handle sometimes folds up and does not reach the desired distance (the total length of the extended handle), so the muscle does not reach sufficient length and is ineffective. This can also be occasionally caused by the locoregional anaesthetic preventing correct eye movement in the immediate postoperative period. In other experimental studies we observed that if the tensile strength of the muscle was very high, the suture may break in some cases and in others muscle fibres may tear causing a longer recession than desired.¹² However, in the cases in which we have re-operated, we have observed that the nylon suture reference stitch was in the same position as previously placed. Displacement in the adhesive group is less than with the hangback technique.

There were no statistically significant differences between the degree of inflammation in the two groups studied. The inflammation can be attributed more to the strabismus surgery than to the suture technique or muscle sealing. In this study, we have not found toxicity associated with the adhesive substances^{7 8 18 19} or ulcerations caused by the excessive hardness of the spicules of the polymerised adhesive.²⁰ The adhesive was applied under the muscular bulk, and as a result neither the spicules nor the pressure of the lid when blinking caused conjunctival perforation.²⁰ The absence of statistically significant differences between the two groups proves the efficacy of the sealing technique using the Adal-1 adhesive.

Neither anterior nor posterior scleral whitening was observed, confirming the minimal degree of exothermal reaction produced by the adhesive mixture. Adal-1 was previously tested on an animal model.⁵ In addition, a small amount of the adhesive was applied in the procedures.¹⁰

Efficacy was 100% in both groups and in all cases of intraoperative sealing. The muscle-sclera junction created with Adal-1 was able to withstand greater or equal tensile strength (for different ocular movements) than sutures.^{5 12} A minimum contact time between the adhesive and the muscle-sclera junction was necessary to imitate prepolymerisation for it to be effective.

A second surgery was required in three eyes of the bioadhesive group as a result of undercorrection. Fibrosis, muscle structural changes, or an alteration of the surrounding tissues were not observed when the conjunctiva was retracted to start the surgery. Muscle dissection was easy and no remnants of the polymerised adhesive were seen 3 months after the initial surgery, confirming the total macroscopic absorption of the adhesive.^{10 13 19 21}

This is the first study carried out on humans and confirms the good results of the previous experimental studies on animal models,^{5 13} such as its good biotolerance in the surrounding tissues and minimal tissue toxicity,¹⁹ proving that Adal-1 adhesive is an effective and safe alternative to suture in strabismus surgery. Moreover, it facilitates the surgical technique of recession surgery and shortens surgical time. Tissue adhesives can also be used in cases of intolerance to suture materials. Further studies are needed to ascertain the effectiveness of the new bioadhesive in muscle resection strabismus surgery.

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