Ocular Biocompatibility of Nitinol Intraocular Clips

Jeffrey L. Olson, Raul Velez-Montoya, and Michael Erlanger

PURPOSE. To evaluate the tolerance and biocompatibility of a preformed nitinol intraocular clip in an animal model after anterior segment surgery.

METHODS. Yucatan mini-pigs were used. A 30-gauge prototype injector was used to attach a shape memory nitinol clip to the iris of five pigs. Another five eyes received conventional polypropylene suture with a modified Seipsler slip knot. The authors compared the surgical time of each technique. All eyes underwent standard full-field electroretinogram at baseline and 8 weeks after surgery. The animals were euthanized and eyes collected for histologic analysis after 70 days (10 weeks) post-surgery. The corneal thickness, corneal endothelial cell counts, specular microscopy parameters, retina cell counts, and electroretinogram parameters were compared between the groups. A two sample *t*-test for means and a *P* value of 0.05 were used for assessing statistical differences between measurements.

RESULTS. The injection of the nitinol clip was 15 times faster than conventional suturing. There were no statistical differences between the groups for corneal thickness, endothelial cell counts, specular microscopy parameters, retina cell counts, and electroretinogram measurements.

CONCLUSIONS. The nitinol clip prototype is well tolerated and showed no evidence of toxicity in the short-term. The injectable delivery system was faster and technically less challenging than conventional suture techniques. (*Invest Ophthalmol Vis Sci.* 2012;53:354–360) DOI:10.1167/iovs.11-8496

Current advanced ophthalmic microsurgical techniques involve a wide range of specialized equipment and skills. The trend in ophthalmic surgery has been an evolution toward minimally invasive surgery, with smaller and smaller incisions allowing faster recovery times, less inflammation, decreased infection risk, and reduced discomfort after surgery.^{1–4} The standard incision size (2–3 mm) for cataract extraction several years ago now seems large compared with the current trend to construct incisions of 1.7 mm.^{4–6} This trend holds true for vitreoretinal surgery as well. The standard 20-gauge vitrectomy probe has gradually been supplanted by 23- and 25-gauge instrumentation, with a decrease in sclerotomy size from 0.89 mm in diameter to 0.5 mm.^{7,8} Indeed, still smaller instruments are currently under evaluation and they are expected to be introduced in the clinical practice in the near future.^{9,10}

The progression to microincisions and microinstrumentation, along with a space-confined surgical setting encountered

during intraocular procedures demands a high level of training and expertise. This is especially true for working within the anterior chamber of the eye, which has a volume of approximately 165.5 μ L.^{11,12} This small space makes certain maneuvers such as suture fixation of posterior chamber intraocular lenses (IOLs) and iris reconstruction difficult.¹³ These techniques are time-consuming, and the longer surgical time increases the risk of infection, inflammation, and light microscope-induced phototoxicity.¹⁴

In response to this need, this project details the use of a small-gauge, shape memory alloy clip designed to replace anterior segment suturing. The clips are comprised of nitinol, a biocompatible, nonferromagnetic metal alloy, which is widely used in many medical fields including but not limited to cardiovascular surgery, neurosurgery, orthopedics, and orthodontics, because of its unique physical properties of shape memory and superelasticity.¹⁵ Recent studies have demonstrated that the use of nitinol clips for coronary anastomoses and the repair of mitral valve insufficiency are well tolerated and have excellent physiological outcomes, equivalent to traditional suture-based repair.¹⁶ The special properties of the nitinol clips are exploited in endoscopic and robotic surgery where the surgical environment is also space-limited.¹⁷

The aim of this study is to evaluate the short term tolerance and biocompatibility of a pre-formed nitinol clip, specially designed for joining intraocular structures. The clip is injected through a hollow bore 30-gauge needle delivery system, in an animal model of anterior segment surgery. Measurements were then made between the nitinol clip group and a control group which received standard 10 to 0 polypropylene intraocular suture tied using the modified Seipsler technique.¹⁸ Specific areas of investigation included corneal thickness by corneal optic coherent tomography (OCT), specular microscopy cell counts, specular microscopy parameters, electroretinogram (ERG), and histopathological analysis of the corneal endothelium and retinal layers.

METHODS

The study was reviewed and approved by the University of Colorado Institutional Animal Care and Use Committee. All procedures were performed according to the ARVO statement for the use of animals in ophthalmic and visual research. The study was conducted at the University of Colorado facilities and was funded by the Colorado BioScience Discovery Grant.

During surgery, a 30-gauge prototype injector was used to attach the nitinol clips to the iris. All procedures were performed by a single surgeon (ME). The injector was designed based on a conventional syringe configuration, which allows a rapid, directed, and one-handed injection of the nitinol clip. The device was engineered to enter tissue through a 30-gauge needle, with either a straight or curved configuration at its distal end. The shape memory nitinol clip is housed within the lumen of the needle, and is deployed by depressing the plunger of the device (Fig. 1). When the two tissues to be joined have been penetrated by the 30-gauge needle, the device is activated by depressing the plunger. This pushes an injection rod through the lumen of the needle that houses the preloaded, straightened nitinol clip. During deployment, the shape

From the Department of Ophthalmology, University of Colorado Health and Science Center, Rocky Mountain Lions Eye Institute, University of Colorado School of Medicine, Aurora, Colorado.

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Corresponding author: Jeffrey L. Olson, 1675 Aurora Court, Aurora, CO 80204; jeffrey.olson@ucdenver.edu.

FIGURE 1. (A) Plastic prototype of the syringe-based injector. The nitinol wire plunger and clip are housed within the lumen of the needle. (B) Deployment mechanism of the nitinol clip.

memory property of the nitinol causes the clip to return to its closed, circular conformation. At the same time, the surgeon slowly retracts the injector, leaving the clip in place. For this study the clips were set to a 0.5 mm circular diameter.

Yucatan minipigs were used, five eyes receiving the nitinol clip and five eyes receiving conventional 10 to 0 polypropylene (Prolene; Ethicon, Johnson and Johnson, San Angelo, TX) suture with the modified Seipser slip knot. Both the clips and the suture were placed in the mid-peripheral iris. All animals underwent anterior segment ophthalmic surgery to compare the nitinol clip with conventional suture, for surgical time and biocompatibility. Both maneuvers, the Seipser knot placement and the nitinol clip deployment, were timed to compare the difficulty of the techniques. The biocompatibility end points were corneal thickness as measured by corneal OCT, corneal cell counts by specular microscopy, specular microscopy parameters, corneal endothelial staining, ERG, and retinal histology. Pigs 1 to 3 each received a single intraocular nitinol clip, pig 4 received four clips, and pig 5 received nine clips.

After general anesthesia was induced, a full-field baseline ERG was done in all eyes using a stimulator (CMG S-1 Mini Ganzfeld; LKC Technologies, Gaithersburg, MD) and a recorder (EPIC-4000; LKC Technologies). Both eyes were dilated with tropicamide 1% and phenylephrine 1%. A standard protocol was followed, with 30 minutes of dark adap-

tation prior to scotopic phase of the ERG, followed by a 10-minute light adaptation before the photopic assessment. After the ERG was complete the eyes were prepped with topical povidone iodine (10%) and covered with sterile surgical drapes.¹⁹ A sterile wire eyelid speculum was placed and two standard 1 mm paracenteses were created with a side-port blade. In five of the eyes the prototype injector was used to place a nitinol clip in the mid-peripheral iris. In the five other eyes, standard iris sutures were placed using a 10 to 0 polypropylene (Prolene) suture with the modified Seipser technique. In both the nitinol clip and conventional suture eyes the anterior chamber was stabilized with a viscoelastic device. After the surgery and after the viscoelastic device was washed from the anterior chamber, topical instillation of analgesics (diclofenac 0.1%) and antibiotics (tobramycin ointment 3.0 g) were given as single doses (Fig. 2).

The nitinol clips and the sutures were left in place for 70 days (10 weeks). The animals were examined daily for the first week and then weekly thereafter. All animals underwent a repeat electroretinogram at 8 weeks. The animals were then euthanized by barbiturate overdose and the eyes enucleated for further analysis.

Immediately after enucleation, a corneal OCT (Carl Zeiss Meditec, Dublin, CA) was performed. Then the corneas were harvested and placed in a corneal viewing chamber filled with a corneal storage medium (Optisol; Bausch & Lomb, Rochester, NY) where they were

FIGURE 2. Enucleated eye which shows the nitinol clip (*white arrow*) in the peripheral iris; properly placed and secured.

examined with specular microscopy (Konan Medical, Irvine, CA). Then the corneas were fixed and processed for histologic examination of the corneal endothelium. A double staining technique using trypan blue and alizarin red dye was used. Fixation of the stain was achieved with 2.48% glutaraldehyde in sodium cacodylate buffer (osmolality 301 mOsm/kg, pH 7.2). An 8-mm donor corneal pouch (Sharp Point Inc., Reading, PA) was used to obtain the dual stained central corneas.²⁰

Tissue from the posterior pole of the eyes were preserved in paraffin, cut in sections of 10 μm , and placed on glass slides. The sections were deparaffinized, rehydrated, and stained with hematoxylin and eosin for retina histologic analysis.

The double stained central corneal endothelium was viewed through an automated microscope (Leica DM750; Leica Microsystems Inc., Buffalo Grove, IL) manipulated by a controller (J2-2000; Clemex Technologies Inc., Guimond Longueuil, Canada) and equipped with 20 $\times$ /0.70 objective. Digital images were captured by a camera (Qicam Fast 1394; QImaging, Surrey, Canada) mounted on the top of the microscope. Three images were obtained per slide (10 slides, 30 images). The images were stored as JPEG files and analyzed with a computer-assisted image program (Image-Pro Plus 5.1; Media Cybernetics, Silver Spring, MD). The image intensities were equalized using the automatic tool of the software and an automatic bright object count was used for assessing the number of objects in the image. Then a watershed split and a cluster analysis were made for a more accurate count.^{21,22}

A total of 10 slides per each animal eye (100 slides) of the posterior pole were analyzed and their image captured and stored in the same way as described above. Three images per slide (two from the periphery and one from the area centralis) were processed with the same computer-assisted image program. An area of interest was cropped manually in each image, to analyze separately the outer nuclear layer (ONL), the inner nuclear layer (INL), and the ganglion cell layer (GCL). The images were equalized and an automatic object count was done using the following color saturations: red, 120–130; green, 45–75; and blue, 120–130. Then a watershed split and a cluster analysis were made for a more accurate count.²²

Statistical analyses were made using spreadsheet software (Excel 2007; Microsoft Corp., Redmond, WA). A two-sample *t*-test for means of two paired samples was used and a *P* value of < 0.05 was considered to be statistically significant.

RESULTS

Seventy days after surgery, none of the study or control eyes showed signs of inflammation, infection, or cataract formation on ophthalmologic examination. The histologic examination showed no signs of inflammation.

Corneal Thickness

Using the automatic measurement of the corneal thickness from the software of the anterior chamber OCT device, the corneal thickness was assessed at the center, 1.5 mm, 3.0 mm, and 4.0 mm from the corneal center (Fig. 3). The means $\pm$ standard deviations of the measurements are summarized in Table 1. The overall mean corneal thickness in the study group was $663.95 \pm 12.2 \mu\text{m}$ and in the control group: $668.51 \pm 45.18 \mu\text{m}$. The *P* values are summarized in Table 1. There were no statistical differences between the study and control eyes.

Specular Microscopy

The software of the device estimated the endothelial cell count, their volume (maximum and minimum), and the number of hexagonal shapes. The means $\pm$ standard deviations of the measurements are summarized in Table 1. There was no statistical difference between the study and control eyes. The *P* values are summarized in Table 1.

Computer-Assisted Cell Counts

A total of 15 images per group were analyzed for endothelial cell count. After averaging all images, the mean endothelial cell count in the nitinol clip group was 2290.52 ± 615.7 cells. In the suture group: 2326.65 ± 1005.05 cells (Fig. 4A). There was no statistical difference between groups (*P* = 0.8).

A total of 150 images per group (100 from the retina periphery and 50 from the area centralis) were analyzed for differences in the cell counts of the ONL, INL, and GCL. After averaging all images, the total cell counts of the ONL were: nitinol clip group, 671.5 ± 30.8 cells; and control group: 657.9 ± 52.8 cells. The total cell counts of the INL were: nitinol clip group, 331.7 ± 7.44 cells; control group, $298.35 \pm$

FIGURE 3. Anterior chamber optical coherence tomography. (A) Nitinol clip properly placed in the peripheral iris (*white arrow*). (B) Measurement of the corneal thickness by OCT in the same eye.

54.9 cells. The total cell counts of the GCL were: nitinol clip group, 81.7 ± 12.1 cells; control group, 75.43 ± 17.93 cells (Fig. 4B). There was no statistical difference between groups ($P > 0.5$ in all three groups).

Electroretinogram

The ERG measurements (mean $\pm$ SD) are summarized in Table 2. There were no statistical differences between baseline and follow-up measurements in either group for any of the five steps of the ERG protocol. The P values are summarized in Table 2.

Surgical Time

In the control eye the mean surgical time from corneal incision to completion of the modified Seipsler slip knot was 19 minutes and 38 seconds. The overall mean surgical time from corneal incision to clip fixation for the nitinol group was 1 minute and 18 seconds. The nitinol clip delivery system was nearly 15 times faster to deploy than conventional suturing with no qualitative differences in mechanical stress testing. Only six procedures were timed for this measurement (three per group).

DISCUSSION

The McCannel and Seipsler knots allow surgeons to place sutures in the tight confines of the anterior segment of the eye.^{23,24} While these techniques have been invaluable in allowing iris fixation of IOLs and iris repair, suturing in the closed chamber eye is both time consuming and difficult.²⁵ The injectable shape memory suture described in this report allows these procedures to be done quickly and easily, and marks a departure from conventional intraocular suture techniques. In the present study we describe the short-term biocompatibility of a nitinol clip specifically designed for joining intraocular structures. The clip was engineered to simplify the techniques and shorten the surgical time of intraocular suturing. Our study demonstrated that the placement of the clip in the iris did not have any adverse effects on the eye, specifically the corneal endothelium and retina. The corneal thickness, corneal endothelial cell count and morphology, cellular layers of the retina, and electroretinogram were statistically similar to the control eyes receiving polypropylene (Prolene) suture. Further, the surgical time was significantly faster for the deployment of the shape memory clip.

TABLE 1. Comparative Chart of the Anterior Chamber Measurements

Measurement	Nitinol Clip (μm)	Polypropylene (Prolene) Suture (μm)	P
<i>ACOCT</i>			
Center	656.47 $\pm$ 8.91	684.52 $\pm$ 51.22	0.6
1.5 mm	647.50 $\pm$ 12.12	645.85 $\pm$ 39.9	0.8
3.0 mm	682.43 $\pm$ 5.76	671.83 $\pm$ 64.02	0.9
4.0 mm	669.40 $\pm$ 12.56	671.87 $\pm$ 28.8	0.5
Measurement	Nitinol Clip	Polypropylene (Prolene) Suture	P
<i>SM</i>			
CD	4131.80 $\pm$ 130.93 cells/mm ²	4127.60 $\pm$ 258.63 cells/mm ²	0.9
CV	32.4 $\pm$ 2.3	32.8 $\pm$ 2.17	0.8
Maximum	529.40 $\pm$ 42.62	509.20 $\pm$ 35.23	0.4
Minimum	84.20 $\pm$ 8.81	76.00 $\pm$ 20.38	0.4
6A	48.40 $\pm$ 4.16	49.60 $\pm$ 4.28	0.7

There were no statistical significant differences between groups. Mean corneal thickness values are shown. The lower part of the table compares the SM parameters between both groups. 6A, hexagonality index; ACOCT, anterior chamber optical coherent tomography; CD, cell density; CV, coefficient of variation; SM, specular microscopy.

Surgical options to correct aphakia or to treat patients without adequate capsular support include anterior chamber IOL, a scleral-fixated IOL or an iris-fixated IOL.^{26,27} Anterior chamber IOL is the simplest surgical procedure to correct aphakia; however despite its open-loop modern design, they are commonly associated with complications such as corneal endothelial loss leading to corneal decompensation, iris sphincter erosion, glaucoma, chronic inflammation, and hyphema.²⁷ Some eyes may require a pupilloplasty to support an anterior chamber intraocular lens.²⁸ Suturing an IOL offers a more anatomically correct final position, by placing the IOL nearer to the nodal pole of the eye.²⁹ Nevertheless, either scleral or iris-fixated IOL techniques have potential disadvantages. Although severe late complications like retinal detachment, choroidal effusion, and hemorrhage have been described with both techniques, their incidence is quite low.¹³ The more frequent complications are IOL decentration, tilting, slippage, and subluxation.³⁰ These late complications usually occur 2 to 5 years after the implantation, and are often related to suture slippage or failure.^{13,29,30} Further, the amount of time required to tie a suture knot in the anterior segment of the eye can take

an experienced surgeon 15 minutes or more. In comparison, the device and clip discussed in these experiments can be deployed in approximately 1 minute in an in vivo surgical setting.

There is no consensus about why the intraocular sutures fail in the long-term. Theories about suture biodegradation, ultra-violet light photodegradation, erosion of the knot, and rupture or cutting by the sharp edge of the positioning hole have been theorized.²⁹ Experts in the field have urged the development of new suture materials and techniques to avoid such complications. This is especially relevant for iris-fixated IOLs, in where clinicopathological studies have demonstrated that IOL haptics are frequently situated outside the ciliary sulcus, therefore proper long-term positioning relies largely on the integrity of the fixation sutures.²⁹

The potential use of clips for intraocular fixation has been suggested before. Tzu et al.³¹ used titanium clips for vascular repair and cardiovascular procedures (AnastoClip VCS, LeMaitre Vascular Inc., Burlington, MA) to clip an intraocular lens to the iris. However, the device used in their study was not designed for its intraocular use, and could only be used with an

FIGURE 4. Histology. (A) Corneal endothelium sample from a study eye with normal characteristics. (B) Retina from the same eye. There are no structural changes in any of the retinal layers.

TABLE 2. Comparative Chart of the Mean Values of the Electroretinogram between Groups

	Nitinol Clip Group			Suture (Control) Group			Nitinol Clip Group vs. Control
	Baseline	8-Week Follow-Up	P	Baseline	8-Week Follow-Up	P	8-Week Follow-Up, P Value
Dark Adapted							
Rod response							
b-Wave amplitude	12.42 ± 15.69	14.32 ± 18.03	0.8	8.52 ± 8.93	3.20 ± 15.25	0.6	0.3
Maximal combined response							
a-Wave amplitude	-17.36 ± 17.87	-7.80 ± 3.92	0.3	-7.08 ± 6.08	-15.98 ± 21.53	0.4	0.4
a-Wave latency	13.40 ± 3.21	12.20 ± 0.84	0.3	10.80 ± 3.70	10.20 ± 2.68	0.7	0.1
b-Wave amplitude	80.20 ± 47.78	58.80 ± 32.80	0.4	45.78 ± 18.27	73.10 ± 74.08	0.5	0.6
b-Wave latency	34.40 ± 8.56	35.80 ± 7.85	0.7	43.20 ± 12.40	36.40 ± 10.678	0.2	0.8
Oscillatory potentials	70.02 ± 72.48	58.90 ± 54.32	0.6	19.56 ± 45.39	55.38 ± 34.94	0.8	0.8
Light Adapted							
Single flash							
a-Wave amplitude	-6.82 ± 19.20	-2.82 ± 3.69	0.5	-8.42 ± 4.86	-4.24 ± 5.50	0.3	0.6
a-Wave latency	8.40 ± 2.33	8.10 ± 1.82	0.8	20.30 ± 24.77	9.40 ± 3.85	0.3	0.5
b-Wave amplitude	45.56 ± 34.32	17.34 ± 11.81	0.1	19.44 ± 16.91	24.18 ± 6.73	0.6	0.1
b-Wave latency	28.20 ± 2.86	31.20 ± 10.18	0.5	72.80 ± 24.08	29.60 ± 10.31	0.3	0.8
Flicker (30 Hz)							
Amplitude	61.28 ± 33.43	29.86 ± 23.66	0.2	40.74 ± 37.36	43.90 ± 35.21	0.9	0.5
Implicit time	29.60 ± 4.92	21.50 ± 12.91	0.2	27.80 ± 18.01	19.20 ± 10.77	0.4	0.7

There were no statistical significant differences between groups.

“open sky” approach, involving the removal of the central cornea as during penetrating keratoplasty. The cartridge was very wide (3 mm) and each clip measures 0.9 mm in width. Our 30-gauge device allows a closed chamber approach through microincisions, making it more suitable for ophthalmological surgeries.

The clip used in this study is composed of nitinol, which is a metal alloy which has become widely used across many medical fields. Because it is a nickel-based alloy, there are concerns about the dissolution of nickel ions in the body and the possibility of inducing allergic, toxic, and carcinogenic effects.^{32–34}

Nonetheless, modern manufacturing methods allow minimizing the risk by using surface coatings and surface modifications to improve biocompatibility.³⁵ The major concern with a nitinol intraocular implant is corrosion.³⁶ There are several methods to prevent this from occurring and involve forming a stable protective layer over the nitinol. This may be accomplished by chemical or electrochemical polishing, surface laser treatment, ion implantation titanium, or adding bioactive surfaces such as plasma fibronectin.^{36,37} One of the most efficient ways to stabilize the alloy is by thermally oxidizing the material, to create a solid layer of titanium oxide TiO₂ on the surface.^{38,39} This can be accomplished by simple autoclaving, which was done for the implants used in this study. Studies have shown that this effect can be further augmented by surface passivation with electropolishing.³⁸

Nitinol's superelasticity and shape memory make it useful for adjoining tissue. The long-term effectiveness of a nitinol clip for vascular anastomosis and arteriotomy repair has been demonstrated in several studies and its biocompatibility validated. The healing and pathologic response in such cases has been proven to be very well tolerated, as the clips were fully covered with an endothelial layer, had minimal inflammatory response, and an absence of tissue necrosis. Furthermore, the tensile strength of the alloy is 38 times the tensile strength of comparable polypropylene (Prolene) or 10-0 nylon suture.^{16,17}

The study has a few limitations that we would like to address. The small number of animals in the study affects the

variability of the results. The absence of baseline measurements of specular microscopy and anterior chamber OCT diminishes our capability of analysis of changes over time. However, the study does evaluate the effect of nitinol compared with 10-0 polypropylene (Prolene) suture as a control.

In summary, our study demonstrated that nitinol is well tolerated in the eye and showed no toxicity in the short-term, even in eyes injected with multiple clips. Seventy days after the initial surgery, the animals exhibited no anatomic or physiologic changes in the cornea or retina. Additional studies are under way to further characterize the surgical utility and biocompatibility of shape memory alloy clips in ophthalmic surgery.

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