

Effect of mitomycin C on the optic nerve in rabbits

Holger Mietz, Thomas C Prager, Craig Schweitzer, James Patrinely, James R Valenzuela, Ramon L Font

Abstract

Aim—To prevent scarring after surgical optic nerve sheath decompression, it has been suggested that treating the area of fenestration with mitomycin C (MMC) might be effective. An animal model was used to test whether this toxic substance may cause optic neuropathy.

Methods—The optic nerves of 15 rabbits were exposed to balanced salt solution (BSS) or mitomycin C (MMC) in a concentration of 0.2 or 0.5 mg/ml. The unoperated fellow eyes and the eyes that received BSS served as controls. Steady state visual evoked potentials (VEPs) at 40, 50, and 60 Hz were recorded before and 4 weeks after surgery. The nerves were examined by light and electron microscopy after 5 weeks.

Results—VEPs in all non-operated eyes and eyes treated with BSS before and 4 weeks after surgery demonstrated responses at all three stimulus frequencies tested. Eyes operated with MMC had extinguished responses for one, two, or all the different temporal frequencies after 4 weeks with marked reduction in VEP amplitude. Eyes operated with MMC at a concentration of 0.5 mg/ml had significantly more reduced VEP responses than those where MMC 0.2 mg/ml was used. On histopathological examination, special stains for myelin and axons showed normal axons and myelin. On electron microscopy, no distinct abnormalities were seen among nerves operated with MMC and controls.

Conclusion—The data from this study suggest that in rabbits, the application of MMC to the optic nerve has a dose dependent toxic effect in the short term postsurgical follow up period. While a functional alteration could be demonstrated reproducibly by steady state VEPs, the extent was not obvious on histopathological examination of the nerves.

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introduced more than 100 years ago.^{1,2} The most frequent and important clinical indication for ONSD is in pseudotumour cerebri, a disease defined by increased intracerebral pressure, papilloedema, reduction of central visual acuity and/or visual fields in the absence of abnormalities of the cerebral fluid or on cranial imaging studies.³ The visual deficits may be incompletely reversible after longstanding disease, and unilateral or bilateral blindness may ultimately occur.⁴ Diseases in which ONSD is carried out less frequently or are still controversial include chronic papilloedema, papilloedema caused by non-resectable brain tumours, postdecompression blindness, post-injection subarachnoid haemorrhage of the optic nerve, acute retinal necrosis syndrome, central retinal vein occlusion, non-arteritic ischaemic optic neuropathy, glaucoma, and others.^{1,5,6} The specific underlying disease may change the surgical risk. The optic nerve sheath is swollen to some degree in pseudotumour cerebri and perineural haemorrhages, which facilitates incisions or excisions of dura mater and makes surgical trauma to the nerves less likely.

Complications of the surgical procedure include transient double vision, which may persist in a few patients, corneal dellen formation, traumatic optic neuropathy, acute retinal artery occlusion, third and sixth nerve palsies, and transient atonic pupils.^{1,7} A failure rate of up to 35% has been reported,⁸ so that a second or third surgical decompression of the same sheath is required to maintain stable visual function.⁹ Surgical failures of the procedure may be related to scarring of the nerve sheath by proliferation of epidural fibroblasts at the site of the incisions or fenestration.⁸

Based on experience with antifibroblastic agents in glaucoma surgery, the use of mitomycin C (MMC) was advocated to decrease the incidence of fibrotic obstruction of the fenestration site.^{10,11}

It has been shown that MMC is effective in suppressing fibroblast proliferation both in vitro and in vivo.¹²⁻¹⁶ However, severe side effects have been reported including delay of angiogenesis, toxicity to the ciliary epithelium, as well as to the autonomic nerves of the ciliary

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The surgical technique of optic nerve sheath fenestration or decompression (ONSD) was

body, and scleral and conjunctival fibroblasts.¹⁷⁻²¹

Given the toxicity to other ocular tissues, we sought to determine the effects of MMC on the optic nerve. In patients with papilloedema undergoing ONSD, there are multiple confounding factors influencing visual acuity and visual evoked potentials (VEPs), so that the detection of possible additional neural damage caused by MMC is hindered. Therefore, we have chosen a rabbit model to determine the incidence of optic neuropathy following application of MMC.

Materials and methods

We used 15 female New Zealand White rabbits weighing 2.0 to 2.5 kg. The protocol was approved by the local review committee of the institution and complied with the ARVO (Association for Research in Vision and Ophthalmology; Bethesda, MD, USA) statement for the use of animals in research.

SURGICAL TECHNIQUE

Anaesthesia and sedation were introduced by intramuscular injections of ketamine hydrochloride (25 mg/kg) and xylazine hydrochloride (5 mg/kg). The animals were randomly divided into three groups (see Table 1). Surgery was performed on left eyes only. A lateral canthotomy was performed and the conjunctiva incised at the superior fornix. The superior rectus muscle was dissected with a thermal cauter; then, the eye was rotated inferonasally, and the soft tissue surrounding the posterior aspect of the globe dissected superotemporally, until the optic nerve became visible. A 4 × 4 × 1 mm portion of a dry sponge (Surgicot Comp, NC, USA; composed of cellulose and cotton fibre) was placed next to the distal portion of the optic nerve and soaked with 0.1 ml balanced salt solution (BSS) (group 1), MMC 0.2 mg/ml (group 2), or MMC 0.5 mg/ml (group 3) (Fig 1). The sponges remained in place for 5 minutes. Mitomycin C (Medac, Hamburg, Germany) was freshly prepared immediately before surgery by dissolving of 2 mg MMC in either 10 ml or 4 ml BSS. After removal of the sponges, the whole area was carefully irrigated with 10 ml BSS. The optic nerve itself was not incised or touched with any surgical instruments, nor were excisions of the nerve sheath performed. The conjunctiva was closed with an 8-0 Vicryl suture, and the canthotomy was repaired with an 8-0 silk suture. Ointment containing both antibiotics and steroids (Maxitrol; Alcon Laboratories Inc, Fort Worth, TX, USA) was placed into the upper cul de sac. The animals were monitored daily for possible wound complications or orbital infections.

Table 1 Treatment of the optic nerves of 15 rabbits divided into three groups

Group, surgery	Eyes (n)	Treatment	Concentration (mg/ml)
Unoperated fellow eyes (right eyes)	15	—	—
1 (left eyes)	5	BSS	—
2 (left eyes)	5	MMC	0.2
3 (left eyes)	5	MMC	0.5

BSS = balanced salt solution; MMC = mitomycin C.

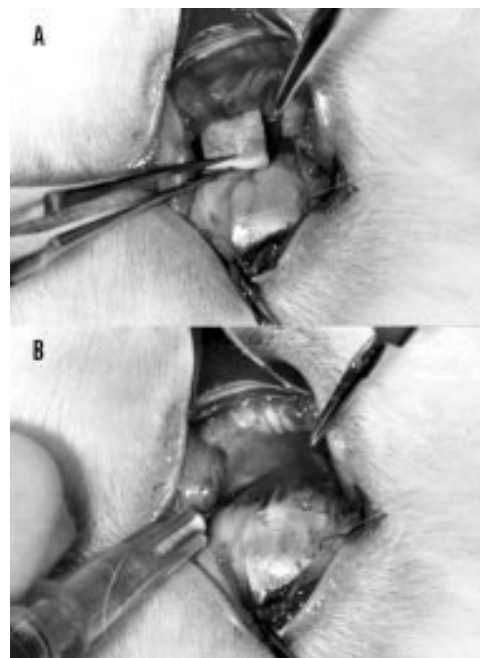


Figure 1 (A) The globe is rotated inferonasally, and a 4 × 4 × 1 mm portion of a dry sponge is placed through the superotemporal incision next to the optic nerve. A lateral canthotomy had been performed earlier. (B) The sponge in the orbit (not visible) is soaked with 0.1 ml of either BSS or MMC.

ELECTROPHYSIOLOGY

Steady state VEPs were performed without sedation and without dilatation of the pupil using a Nicolet Compact Four electrodiagnostic system (Madison, WI, USA). A Grass PS22 photostimulator was used with frequencies of 40, 50, and 60 Hz. The distance of the strobe from the rabbits was 0.6 metre. Gold plated EEG surface electrodes were placed midline on the forehead for reference, occipital for signal detection, and above the right mandible as a ground signal. VEPs were recorded separately for left (surgical) and right (control) eyes while the other eye was patched. For baseline VEPs, the responses of VEP from five randomly chosen rabbits were recorded before surgery. VEPs were recorded in all animals after 4 weeks.

STATISTICAL EVALUATION

The mean amplitudes were determined from at least five consecutive amplitude measurements. For data analysis, the logarithm of the amplitudes was determined and the left/right ratios calculated. To compare the mean left/right ratios among the different groups we used the Student's *t* test for unpaired observations. A significant difference was assumed for correlations smaller than 0.05.

For statistical purposes, an extinguished response was assumed to have an amplitude of 0.01 μV, so that these responses could be included into the analysis. The presence of a regular response was determined by the number and amplitude of the peaks and their latency when compared with the unoperated fellow eye and the responses before surgery (Fig 1). Responses were evaluated by an experienced electrophysiologist who was unaware which was the treated eye.

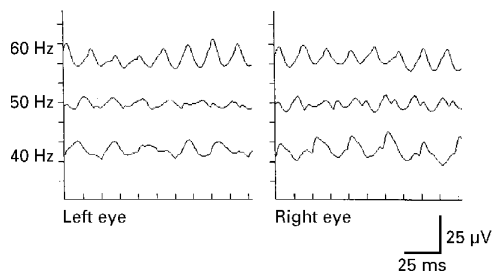


Figure 2 Example of typical VEP response at baseline. Steady state VEPs were performed at 40, 50, and 60 Hz stimulation and recorded separately for right and left eyes.

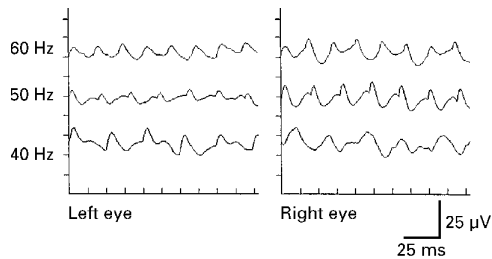


Figure 3 Typical VEP response from a rabbit in which the left eye was operated with BSS. Responses at all frequencies tested are present. On average, the amplitudes are not different compared with baseline.

PATHOLOGY

The animals were killed 4 weeks after surgery by intravenous injection of 1.0 ml of T61 (Hoechst, Germany). Immediately thereafter the complete eyes with 5 mm of adjacent optic nerve were excised. Special care was taken to avoid tissue damage. The nerves were separated about 0.5 mm posterior from the globes using a razor blade, and the globes were placed into 10% buffered formaldehyde. Two optic nerves from each of the three groups were fixed in glutaraldehyde, buffered at pH 7.2, for electron microscopic examination. The remaining optic nerves were fixed in buffered formaldehyde. For comparison, five randomly selected unoperated control eyes and nerves were also

excised, and two of these nerves were prepared for electron microscopy.

For light microscopy, routine embedding and sectioning techniques were used, including embedding in paraffin and preparation of sections of 5 μ m thickness. Stains performed included haematoxylin and eosin, Luxol fast blue as a special stain for myelin, and Sevier-Munger as a special stain for axons.

For electron microscopy, the specimens were processed routinely and embedded in plastic. Semithin sections were stained with toluidine blue, and ultrathin sections were stained with uranyl acetate and lead citrate and examined with an electron microscope.

Results

All animals were healthy during the preoperative and postoperative period. No conjunctival dehiscences or orbital infections occurred, and there was no need for any additional topical or systemic treatment.

ELECTROPHYSIOLOGY

The VEP responses were evaluated as previously described. All control eyes (preoperative and unoperated right eyes) demonstrated no change after 4 weeks as well as all eyes operated with BSS (group 1). Responses for all three frequencies were present and symmetrical between eyes (Figs 2, 3).

Because the amplitudes of the responses at 40, 50, and 60 Hz were variable among animals, the logarithms from the averaged amplitudes for each frequency and eye were determined and the left/right ratios calculated. The results are shown in Table 2. For the baseline amplitudes, there was no difference between left and right eyes (ratio = 0.99). For the controls operated with BSS, the average left/right ratio was 0.83 and not statistically different from baseline ($p < 0.06$, t test). Eyes treated with MMC at a concentration of 0.2 and 0.5 mg/ml had a significantly smaller amplitude in the operated eyes as demonstrated by the mean left/right ratios of 0.51 and 0.28, respectively (ratios smaller than 1.0 express smaller amplitudes in left eyes) (t test: $p < 0.001$ and $p < 0.0001$, respectively). The difference in the amplitudes between eyes receiving MMC at a concentration of 0.2 compared with 0.5 mg/ml was also significant ($p < 0.049$; t test).

All animals whose nerves were treated with MMC at a concentration of 0.2 mg/ml had abnormal responses (Table 3). In three eyes, one response was extinguished, and in two eyes, two responses were extinguished. These results were significantly different from the unoperated eyes and from the eyes treated with BSS ($p < 0.0001$; t test).

In those nerves treated with MMC at a concentration of 0.5 mg/ml, no animal demonstrated normal responses at all three frequencies. In four cases, two of the three responses were extinguished, and in the remaining case all three responses were extinguished. These results also were statistically significantly different from the unoperated eyes and from the eyes treated with BSS (t test: $p < 0.0001$). The

Table 2 Normalised data of steady state visual evoked potentials (VEPs) recorded from right and left eyes separately from rabbits after different treatment during surgery. Stimulation frequencies were 40, 50, and 60 Hz. The left/right ratios of the logarithms of the average amplitudes are shown

Group, treatment	Frequency (Hz)			Mean	Difference compared with baseline; p value
	40	50	60		
Baseline before surgery	0.97	1.04	0.96	0.991	—
1 BSS	0.91	0.75	0.83	0.830	<0.0600
2 MMC 0.2	0.64	0.53	0.35	0.506	<0.0010
3 MMC 0.5	0.36	0.37	0.12	0.284	<0.0001

BSS = balanced salt solution; MMC = mitomycin C; p value = Student's t test; non-paired.

Table 3 Results of visual evoked potential (VEP) testing in 15 rabbits, 10 of which received mitomycin C to the optic nerve sheath on one side without sheath fenestration. Steady state VEPs were performed at 40, 50, and 60 Hz for each eye (3 sets)

Group, treatment (see Table 1)	Eyes (n)	Responses present				p Value
		3/3	2/3	1/3	0/3	
Baseline before surgery	5	5	0	0	0	—
Unoperated fellow eyes	15	15	0	0	0	1.0
1 BSS	5	5	0	0	0	1.0
2 MMC 0.2	5	0	3	2	0	0.0001
3 MMC 0.5	5	0	0	4	1	0.0001

BSS = balanced salt solution; MMC = mitomycin C.

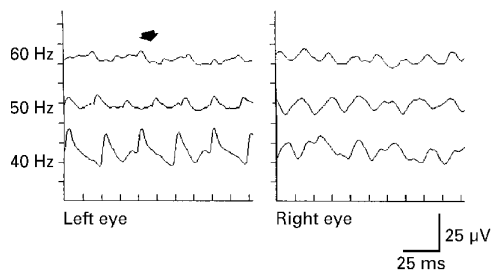


Figure 4 Example of typical VEP response from a rabbit in which the left eye was operated with MMC at a concentration of 0.2 mg/ml. One response (arrow) is extinguished. The amplitudes were reduced compared with baseline.

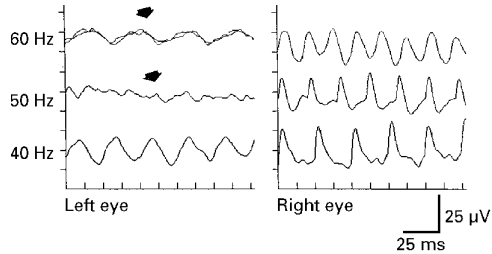


Figure 5 Typical VEP response from a rabbit in which the left eye was operated with MMC at a concentration of 0.5 mg/ml. Two responses (arrows) are extinguished. The amplitudes were reduced on the treated side compared with baseline and rabbits operated with BSS and MMC 0.2 mg/ml.

results were significantly different from those eyes operated with a concentration of 0.2 mg/ml MMC (t test: $p < 0.035$); therefore, the decline in VEP amplitude occurred in a dose dependent manner—higher concentrations produced a higher rate of extinguished responses (Figs 4, 5).

PATHOLOGY

Light microscopic examination of cross sections from all nerves failed to reveal abnormalities. With the special stains used specifically to stain myelin and axons, a normal, homogeneous distribution of myelin throughout the nerves was present (Fig 6). The axons were not altered in size or number, the central vessels were intact and the pial septa were of normal thickness. On electron microscopic examination, the myelin sheaths were intact and the axons arranged in a regular fashion (Figs 7, 8). The astrocytes appeared normal. The small and large vessels present had a regular appearance with a smooth, thin basement membrane. The collagen distribution surrounding the vessels and in the pial septa did not show unanimous differences among treated and control nerves. Sections from all eyes including the pupillary-optic nerve plane (PO sections) were examined with light microscopy. No abnormalities, especially of the retina, were noted.

Discussion

The first report on ONSD originated in the nineteenth century² and the procedure was used to relieve pressure from the optic nerve for such diseases as papilloedema, increased intracranial pressure, and neuroretinitis. The

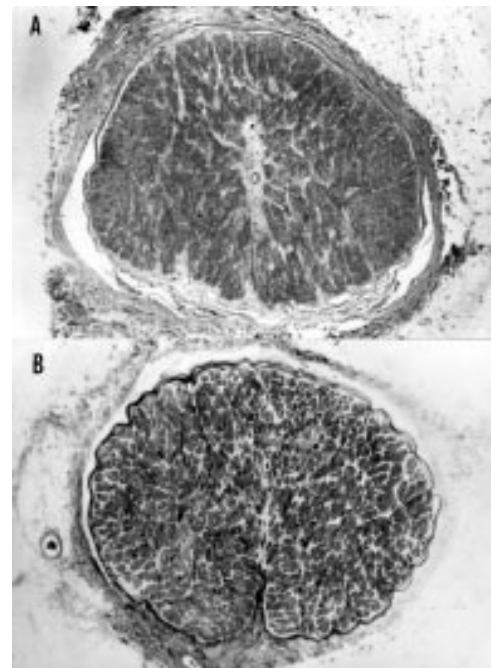


Figure 6 (A) Low power view of a cross section of optic nerve from a rabbit treated with MMC at a concentration of 0.5 mg/ml. The myelin within the nerve bundles is intact. No areas of gliosis are observed. Scattered vacuoles are present as a fixation artefact (Luxol fast blue, magnification $\times 9$). (B) Low power view of a cross section of optic nerve from a rabbit treated with MMC with a concentration of 0.2 mg/ml. There is a normal population of axons within the nerve bundles which are demarcated by thin pial septa (Sevier-Munger, magnification $\times 9$).

indications for this surgical procedure have not changed over the past 100 years, and recently possible beneficial effects using this technique have also been evaluated for other diseases such as non-ischaemic optic neuropathy, glaucoma, and others.^{5, 6} However, the main and most frequent clinical indication is still pseudotumour cerebri. In this disease, it has been reported that clinical results are equivalent to cerebrospinal fluid shunting procedures. The surgical procedure of ONSD is less difficult with fewer complications than the shunt device.²²

The mechanism by which the ONSD actually works is not fully understood. Seiff and Shah²³ developed a model simulating fluid spaces of the cerebrum and optic nerve sheaths and were able to show that increased intracranial pressure is transmitted to the optic nerve sheaths. Further, release of fluid from the nerve sheaths can decrease intracranial pressure and unilateral surgery effectively relieves intracranial pressure on both optic nerves.

In a clinical setting, Brouman *et al*²⁴ demonstrated improvement in patients with pseudotumour cerebri after ONSD, but subarachnoid injection of contrast failed to demonstrate flow from the optic nerve into the orbit. Keltner *et al*²⁵ studied the site of surgery histopathologically in one case of increased intracranial pressure caused by a glioblastoma. Thirty nine days after surgery, the subdural and subarachnoid spaces were intact, and at the site of sheath decompression, a defect of the dura was still present with loose fibrous tis-

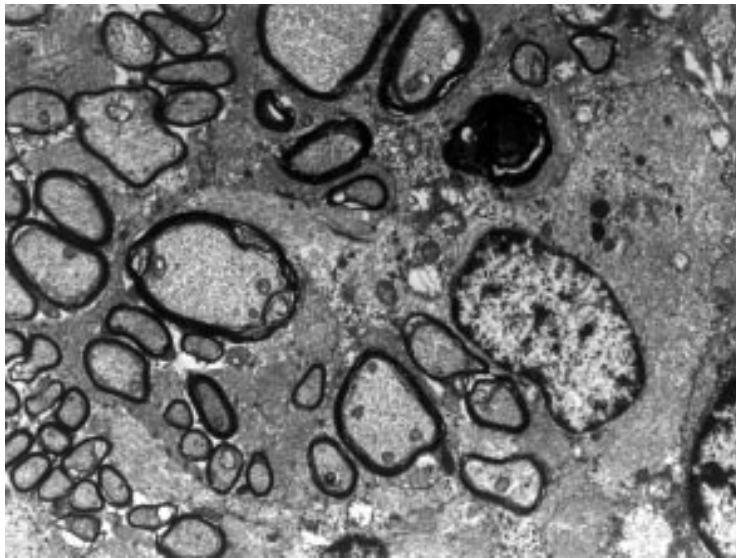


Figure 7 Electron micrograph of a portion of cross section of the optic nerve from a control operated with BSS. The nerve fibres and the myelin sheaths are intact (magnification $\times 3450$).

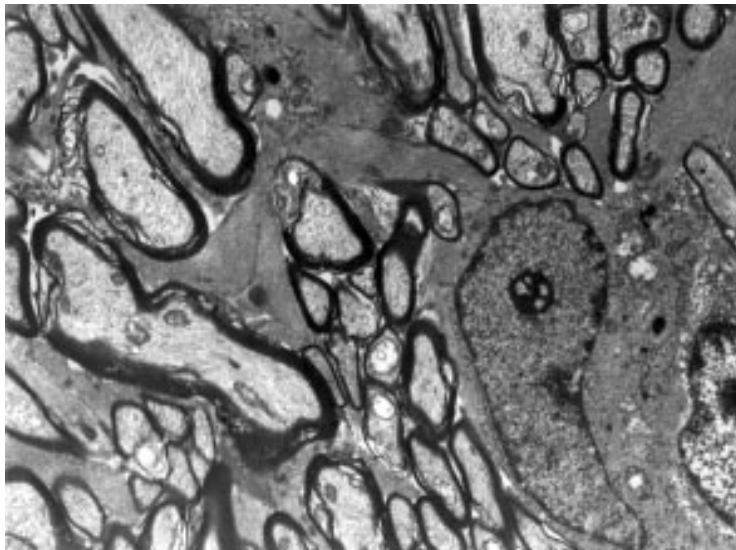


Figure 8 Electron micrograph from a portion of a cross section of a nerve from an animal operated with MMC at a concentration of 0.2 mg/ml. The tissue was sampled 4 weeks after surgery. Although the myelin sheaths appear somewhat irregular, the nerves are still intact. No distinct pathological changes are present (magnification $\times 3450$).

sue bridging the gap creating a fistula. Tsai *et al*²⁶ examined histopathologically both optic nerves from a patient 14 days after ONSD and observed no fistula, but fibroblasts located at the site of fenestration, suggesting that the cerebrospinal fluid filtered through this tissue rather than a filtering bleb.

Hamed *et al*²⁷ studied two patients by echography and one patient by magnetic resonance imaging following successful ONSD and found cyst-like structures at the site of surgery that appeared to be connected to the nerve sheaths. The authors speculated that a filtration area was produced by the surgery and that the pressure was released by egress of fluid through this area. Spoor *et al*⁸ injected dye intrathecally and showed a connection from the subarachnoid space to orbital pseudocysts after ONSD. They concluded that leakage of fluid with creation of a cyst was related to

improved vision in six patients followed up for 20 to 37 months.

Several different surgical approaches for ONSD have been investigated. While the medial approach is probably most frequently used,²⁸ a lateral approach with or without orbitotomy has also been described.³ The types of incisions of the nerve sheath also vary: while some surgeons actually fenestrate the sheath and excise tissue,²⁸ others prefer to incise the nerve sheath many times.²⁹ Recently, MMC has been used adjunctively to reduce the degree of scarring at the site of surgery¹⁰ and to facilitate repeat surgery, if necessary.¹¹ Changes of visual function were compared by evaluation of preoperative and postoperative central visual acuity and visual field testing. In addition, haemodynamic factors were also evaluated.³⁰ No electrophysiological tests were performed.

Gellrich *et al*³¹ performed optic nerve sheath fenestrations in rats and found a 10% decrease of retinal ganglion cells when compared with unoperated control eyes after 30 days. Ellis *et al*³² performed ONSD in guinea pigs who received MMC (0.3 mg/ml). They examined the nerves after 3 weeks by electron microscopy and found no additional damage to MMC treated nerves when compared with controls operated without MMC.

The results of our VEP studies should be interpreted with caution. Little is known about steady state VEPs in rabbits, although the technique of testing of the critical fusion frequency is well established.³³⁻³⁶ It is unclear which specific neurons generate the signals detected, or how the responses correlate to visual acuities. However, we performed our testing strictly comparing treated with unoperated control eyes with each animal acting as its own control. We feel confident, therefore, that the changes in VEP responses reflect actual functional damage.

The results demonstrate no surgical effect on the normalised amplitudes for eyes that received BSS (control). A significantly reduced amplitude was found in eyes receiving either concentration of MMC. Interestingly, the amplitudes decreased in a dose dependent manner such that the higher concentration of MMC evoked smaller amplitudes. Given the relatively small sample size of five animals in each group, this difference suggests a marked toxic effect of MMC.

In a second VEP evaluation we determined the presence or absence of VEPs and whether the latency was similar in both right and left eyes. Since evoked potentials at 40, 50, and 60 Hz were readily detectable before surgery, in unoperated fellow eyes and in eyes treated with BSS, a decrease or absence of a VEP response in postsurgical eyes should reflect a functional deficit of the optic nerve. Again, only eyes that received MMC had abnormal responses.

Our finding that no alterations of the nerves were seen by light and electron microscopic examination is in accordance with previous studies performed on guinea pigs.^{11, 32} It may be that such histopathological changes would be present after longer time intervals between surgery and examination, since in all studies done

so far the interval was no longer than 5 weeks. The results of this study, however, present the first evidence that MMC does have a toxic effect on the optic nerve. The magnitude of this effect was probably small in this experiment but still significant, and may be larger in cases when MMC is applied to already compromised nerves, which is usually the case when ONSD are performed in clinical settings.

Furthermore, our results emphasise the discrepancy between electrophysiological and histopathological examination of optic nerves, in that subtle neuropathies may well be present and detectable by electrophysiological testing, but not by histopathology. This finding may be important for future studies to evaluate optic neuropathies.

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