A problem! Now a solution?

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Diplopia after cataract surgery

Ophthalmologists are, and should be, proud of the advances in cataract surgery and aphakic correction that have occurred over the past two decades. Today, cataract surgery is considered one of the most successful surgical procedures performed throughout the world. The resulting quality of vision is usually excellent and the complication rate reasonably low. One post-operative complication, diplopia, has been a subject of intense scrutiny of late.¹⁻⁶ Although multiple causes of diplopia after cataract surgery have been described, most recent studies have emphasised the problem of extraocular muscle toxicity resulting from direct injection with a local anaesthetic at the time of surgery.¹⁻⁶ Han *et al*⁷ reported a series of patients with postoperative diplopia after cataract surgery. The authors concluded that 50% of the cases were associated with either direct trauma or anaesthetic myotoxicity to the extraocular muscles. It is noteworthy that they emphasised that overactions of the injured muscles were much more common than underactions. The only other major cause of persistent diplopia after cataract surgery in this study was sensory strabismus (32%).

Conventional local anaesthetics such as bupivacaine cause considerable myotoxicity and neurotoxicity.⁸ This has been studied extensively in skeletal muscle, but to a lesser degree in extraocular muscle.⁹ After the injection of bupivacaine into skeletal muscle, there is a dramatic degeneration of muscle fibres accompanied by a moderate inflammatory response.^{10,11} Subsequently, satellite cells are activated to myoblasts and take part in a brisk regeneration process. Localised muscle hypertrophy results in the area of the original anaesthetic injection.¹² A similar sequence of events has been documented in the extraocular muscle of rats injected with metivacaine.¹³ The ultrastructure of regeneration of extraocular muscle fibres differs little from the regeneration of skeletal muscle fibres under these circumstances.

The issue of myotoxicity related to local anaesthetics has been recognised by ophthalmologists for two decades.⁹ Many experts in strabismus have invoked

it to explain cases of post-cataract surgery diplopia, especially those with a primary vertical deviation.^{1-7,14,15} However, the usual hypothesis has been that injection of a local anaesthetic directly into an extraocular muscle results in almost immediate paresis, followed by contracture and restriction of the injured muscle.^{1-3,5,6,15,16} Focal thickening of the involved extraocular muscle can be seen on magnetic resonance imaging scans and has usually been attributed to segmental contracture and fibrosis.^{1,2,16} However, not all authors agree that fibrosis and contracture is the ultimate outcome of extraocular muscle injury by local anaesthetics.⁴ An alternative hypothesis is that the injection of local anaesthesia causes muscle degeneration, followed by functionally relevant hypertrophy of the affected muscle. This, in turn, results in overaction and strengthening of the previous injured muscle. Scott *et al*, (see page xxx) in this issue of the journal, suggest that this explanation is not only reasonable but also likely. Moreover, they emphasise that the alternative hypothesis that invokes secondary fibrosis and scarring as a fundamental process in the repair of the injured muscle has not yet been documented in any animal studies.¹⁸ This alternative hypothesis by Scott *et al* to explain the events surrounding the myotoxicity of extraocular muscles is in itself thought-provoking and exciting. However, they have taken the idea one step further. They report treating a patient who had had previous strabismus surgery but who presented with a persistent 14-prism dioptre esotropia. They chose to treat this patient by injecting the right lateral rectus muscle with bupivacaine 0.75%, thus inducing paresis of the right lateral rectus for 7 days. This, however, was followed by a period of improvement in lateral rectus function, and the elimination of the diplopia 33 days after treatment. Alignment remained normal at an additional evaluation 54 days after treatment. Magnetic resonance imaging showed a focal increase in the size of the injected right lateral rectus of 58% in the posterior area, with less change in the anterior portion of the right lateral rectus muscle.

The authors suggest that physiological strengthening of the right lateral rectus muscle as a result of the hypertrophy induced by the local anaesthetic injury provided an effective treatment for the small-angle esotropia in this patient. Although this is a single case, with only short-term follow-up, it is a remarkable report. If further studies confirm these findings, therapeutic strengthening of extraocular muscles in the management of strabismus may become a reality.

Many questions remain. Animal studies and future human trials will be necessary. Ultimately, local anaesthetic injections may not be necessary to induce this change. Many questions surrounding the report of Scott *et al* can be raised. However, the fundamental observations of this case are noteworthy and truly ground-breaking. The authors and other investigators should be encouraged to study the possible therapeutic use of local anaesthetic injections into extraocular muscle for the treatment of some forms of strabismus.

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Intravitreal Avastin

Intravitreal Avastin for choroidal neovascularisation in pathological myopia: the controversy continues

P J Rosenfeld

Intravitreal Avastin provides an opportunity to prevent visual acuity loss particularly in non-Western countries

In this issue, Yamamoto *et al*¹ and Sakaguchi *et al*² (see pages 157 and 161) are the first to report the use of intravitreal Avastin (bevacizumab; Genentech, Roche) for the treatment of subfoveal choroidal neovascularisation (CNV) secondary to pathological myopia. The use of intravitreal Avastin in this disease is a natural extension of the previous work with intravitreal Avastin in neovascular age related macular degeneration (AMD). Last year, Michels *et al*³ reported on systemic Avastin for the treatment of neovascular AMD in nine patients followed over 3 months, and this cohort was subsequently expanded to 18 patients followed over 6 months.⁴ During these 6 months, the authors observed a rapid and sustained improvement in visual acuity and anatomical outcomes. Following the report of these initial observations, a much smaller dose of Avastin was injected intravitreally in a patient with CNV from AMD and a patient with macular oedema from a central retinal vein occlusion.⁵⁻⁶ The anatomical improvements were rapid and appeared very similar to the results observed after the systemic infusion of Avastin. Since these two case reports were published, numerous publications have supported the *in vitro* and *in vivo* safety of intravitreal Avastin,⁷⁻¹⁵ and several retrospective reviews and one prospective study have reported impressive improvements in visual acuity, angiographic and optical coherence tomography (OCT) outcomes in patients with neovascular AMD and macular oedema.¹⁶⁻²⁰ Case reports have also shown dramatic improvements after administering intravitreal Avastin in eyes with proliferative diabetic retinopathy, neovascular glaucoma and cystoid macular oedema.²¹⁻²⁶

The same progression of events is now taking place in the use of Avastin for CNV secondary to pathological myopia. Last year, Nguyen *et al*²⁷ reported on the use of systemic Avastin for the treatment of subfoveal CNV secondary to pathological myopia in two patients. As with neovascular AMD, there was a reduction in angiographic leakage and OCT central retinal thickness after treatment in three eyes. These anatomical improvements were associated with visual acuity improvements in two of the three eyes. This report provided the first evidence that vascular endothelial growth factor-A played an important part in promoting CNV in pathological myopia. By inhibiting vascular endothelial growth factor-A with systemic Avastin, Nguyen *et al*²⁷ observed visual acuity and anatomical improvements that were not typical for normal disease progression. As the growth of CNV and the accompanying vision loss in neovascular pathological myopia are often not as predictable or severe as with CNV in AMD, the observed improvements in these patients were temporally related to the systemic infusion of Avastin and were unlikely to be the result of chance alone. Similar results have now been achieved after the intravitreal injection of Avastin.

Yamamoto *et al* report on a retrospective case series of 11 eyes from 9 patients injected with intravitreal Avastin. All patients were treated as part of their routine clinical care at the New England Eye Center (Boston, Massachusetts, USA). Of these 11 eyes, 5 eyes were previously treated with verteporfin photodynamic therapy (PDT). All eyes were followed by visual acuity, fluorescein angiography and OCT. As with systemic Avastin, intravitreal

Avastin resulted in both visual acuity and anatomical improvements that were temporally related to the treatment. With a mean follow-up of only 153 days, no conclusions are possible regarding the long-term benefits of intravitreal Avastin, but the short-term results appear promising. The average visual acuity improved 3.5-fold and the average OCT central foveal thickness measurement decreased by 103 µm. Overall, 10 of the 11 eyes showed improvement in visual acuity and 4 of the 5 eyes previously treated with PDT showed improvement as well. Only 3 of the 11 eyes received two injections each and the remaining 8 eyes received just one injection each, suggesting that frequent injections with Avastin may not be necessary.

Sakaguchi *et al* report on a prospective case series of 8 eyes from 8 patients injected with intravitreal Avastin. With a mean follow-up of only 4.4 months (range 3 to 7), the short term results once again appear very promising. Average visual acuity improved with 6 patients (75%) improving 2 or more lines. The mean OCT central foveal thickness measurement decreased by 43 microns. Only 3 of the 8 eyes received two injections each while the remaining 5 eyes received just one injection each once again suggesting that frequent injections with Avastin may not be necessary.

As no ocular or systemic adverse events were reported, there remains a theoretical risk that these eyes may be more susceptible to retinal tears and detachment after an intravitreal injection. It is impossible to draw any conclusions about safety from so few patients with such short follow-up, but these preliminary results do suggest that an eye with pathological myopia can tolerate an injection.

As with any retrospective review that examines a small number of patients with variable follow-up, there are many limitations that preclude generalisation of these results to all patients with neovascular pathological myopia. There is sure to be controversy as to whether it was ethical to use off-label intravitreal Avastin as primary treatment when PDT was approved and was available for the treatment of these patients. However, for those patients who were losing vision despite receiving PDT, the non-surgical options were limited. Treatment options included additional PDT, subtenons or intravitreal steroid, enrolment in the ongoing systemic Avastin study,²⁷ or the use of off-label intravitreal Avastin or Macugen (pegaptanib sodium;