Safety Profile of Intravitreal Triamcinolone Acetonide

J. BAATH,1 A. L. ELLS,2,3 A. CRICHTON,1 A. KHERANI,2 and R. G. WILLIAMS2

ABSTRACT

Background: There is currently a widespread use of intravitreal triamcinolone acetonide (IVTA) for age-related macular degeneration, diabetic macular edema, cystoid macular edema secondary to retinal vein occlusions, and uveitis. The aim of this investigation was to assess the rates of various complications associated with this treatment and to determine which factors are associated with the development of these complications.

Methods: A retrospective interventional case series of all patients from one retina specialist undergoing IVTA was conducted in a clinical setting from 2002 to 2005. All disease entities were included. Patients were followed for a mean of 9.5 months after receiving 4 mg (0.1 mL) of nonfiltered triamcinolone acetonide (TA). All complications associated with the injection procedure or with the TA were noted.

Results: Two hundred and twenty-three (223) eyes of 192 patients received a total of 336 IVTA injections between 2002 and 2005. The mean age was 73.3 years and mean follow-up was 9.5 months. A single injection was performed in 144 eyes (64.6%); 2 IVTAs in 55 eyes (24.7%); 3 IVTAs in 16 eyes (7.2%), and 3.6% of eyes had more than 3 injections at a minimal interval of 3 months. The only immediate complication was a single injection (0.3%) associated with a temporary occlusion of the central retinal artery, which opened immediately following anterior paracentesis. Late complications included endophthalmitis in 1 of 336 (0.3%) injections and a steroid response requiring glaucoma medication in 60 of 192 patients (31.3%). In patients with preexisting glaucoma, 58.8% required additional glaucoma medication. Glaucoma-filtering surgery was required in 2 of 192 patients (1.0%).

Conclusions: In the study center, the IVTA is extremely safe in patients without a history of glaucoma. However, patients with preexisting glaucoma with progressive optic neuropathy must be treated with great caution.

INTRODUCTION

A N INCREASING AGE DEMOGRAPHIC and increasing incidence of diabetes in most developed nations make inflammatory, edematous, and neovascular disorders of the retina, such as diabetic macular edema (DME), and exudative age-related macular degeneration (ARMD) common clinical encounters. Recently, intravitreal triamcinolone acetonide (IVTA) has gained widespread use for ARMD, DME, branch retinal vein occlusion (BRVO), central retinal vein occlusion (CRVO), and uveitis, based on the results of several retrospective and some prospective randomized trials that have demonstrated good efficacy for each of these conditions.1–9 In the United

1Undergraduate Medicine, University of Toronto, Toronto, Ontario, Canada.
2Faculty of Medicine/Ophthalmology, University of Calgary, Calgary, Alberta, Canada.
3Calgary Retina Consultants, Calgary, Alberta, Canada.
States and Canada, triamcinolone acetonide (TA) is approved for use in an intra-articular fashion for the management of arthritis. IVTA is currently an off-label therapy, as TA has yet to receive Food and Drug Administration or Health Canada approval for ocular use.

Although effective, IVTA has several reported complications. Immediate postinjection complications include retinal detachment, vitreous hemorrhage, and a collection of triamcinolone crystals, resulting in the formation of a pseudohypopyon.\(^\text{10,11}\) The development of central retinal artery occlusion (CRAO) has also been reported and this requires immediate anterior chamber paracentesis.\(^\text{12}\) Complications developing later in the follow-up or associated with multiple injections have included sterile and non-sterile endophthalmitis, pseudoendophthalmitis, cataract progression, and steroid-induced glaucoma.\(^\text{11,13,14}\)

Although a few large studies have been presented, the majority of the literature concerning the safety of this promising new treatment has consisted of studies with relatively small injection sample sizes. The aim of this study was to further investigate the safety profile of IVTA using a large sample of injections and to determine which factors were associated with the development of complications.

**METHODS**

This retrospective interventional case series included all patients undergoing IVTA injections in a private clinical setting from a retina specialist at the Calgary Retina Consultants in Calgary, Alberta, Canada. This study had institutional review board approval and a total of 192 patients who received IVTA between 2002 and 2005 inclusive were included in the study. All disease entities were included.

Each patient was given a description of the benefits and risks of the IVTA injection and signed an informed consent form, which indicated their understanding and acceptance of these risks. All IVTA injections were administered by one retina specialist (A.K.) on the day of the consent. Preoperative antibiotics and 10% betadine were applied to the conjunctiva, lids, and lashes 10 min prior to the procedure. A subconjunctival injection of 0.3 mL of 1% lidocaine was performed 3 mm from the limbus in the super-temporal quadrant. As vortexing can introduce air bubbles that interfere with the accuracy of the drug dose delivered upon injection, the TA suspension was mixed manually prior to injection. Using a sterile technique, a 30-gauge needle with 4 mg (0.1 mL) of unfiltered TA (Sterile Triamcinolone Acetonide; Cytex Pharmaceuticals Inc., Halifax, Nova Scotia, Canada) was injected 3.5 mm posterior to the limbus into the midvitreous cavity. The inactive ingredients in every 1 mL (40 mg) vial of TA suspension used were 6.6 mg sodium chloride, 0.9% benzyl alcohol, 0.75% carboxymethylcellulose sodium and 0.04% polysorbate 80. Unfiltered TA was selected in order to deliver a standard dose to the eye, as filtering often results in variable drug dosages.\(^\text{15}\) Although evidence establishing 4 mg as the most optimal dose is limited, this dose was selected because it is currently in widespread usage and is the dose used in many of the clinical reports published to date.\(^\text{4,7,10,14,16–20}\)

Postoperatively, indirect ophthalmoscopy was used to examine the optic nerve for arterial pulsation, to ensure the correct placement of the steroid, and to rule out immediate complications, such as vitreous hemorrhage and retinal detachment. An intraocular pressure (IOP) measurement was taken within 5 min of the procedure. An anterior chamber paracentesis and tap was performed, if deemed necessary. Ofloxacin or gatifloxacin were prescribed postoperatively QID for 3 days as a prophylaxis against bacteria, which could potentially be introduced into the eye during the injection procedure. Eyes receiving multiple injections were given injections at a minimum interval of 3 months.

Patients were followed regularly for the development of complications associated with the treatment, and IOP was checked at intervals of 1, 6, and 12 weeks, with an extended follow-up for those with complications or multiple injections. IOP was measured at each visit and its magnitude recorded in the chart. Medication to control elevated pressure was also carefully documented in all charts. The rate of long-term IOP complications was measured by noting changes in IOP following the IVTA injection and by noting the implementation of new glaucoma medications or filtering surgery to reduce the steroid-induced IOE elevation. In our analysis, we used the occurrence of elevated IOP requiring medication (IRM) as a treatment-related complication. Patients already taking glaucoma medication before
injection were deemed to have suffered an IRM complication if IOP rose after injection resulting in the need for altered or increased medication.

A statistical analysis was carried out using GraphPad InStat version 3.00 for Windows (GraphPad Software; San Diego, CA). When analyzing whether the occurrence of a complication was associated with a particular exposure, we created a contingency table and tested for significance, using a χ² test with a two-sided P-value. An odds ratio (OR) with an associated 95% confidence interval (CI) was also calculated for each significant result. A Student t test was employed when comparing pre- and post-operative values of IOP. For both tests, a result was considered statistically significant if a P-value < 0.05 was obtained.

RESULTS

A total of 223 eyes of 192 patients were enrolled in the study, and a total of 336 injections were administered. Among the 223 eyes, 144 (64.6%) had 1 injection, 55 eyes (24.7%) had 2 injections, 16 eyes (7.2%) had 3 injections, 6 eyes (2.7%) had 4 injections, and 2 eyes (0.9%) had 5 injections each. The mean age of the 192 study participants was 73.3 years (standard deviation [SD], 14.0). The study participants were given IVTA for a variety of disease entities, including 59 (30.7%) for DME, 68 (35.4%) for exudative ARMD, 26 (13.5%) for CRVO with CME, 27 (14.1%) for BRVO with CME, 4 (2.1%) for hemivein occlusion with CME, and 8 (4.2%) for CME from posterior uveitis.

Many of the patients had significant comorbidities, including 75 (39.1%) with diabetes mellitus, 90 (46.9%) with hypertension, 35 (18.2%) with documented coronary artery disease, 36 (18.8%) with arthritis, and 22 (11.5%) with dyslipidemia. Among the 336 injections, patients were phakic in 198 (58.9%), pseudophakic in 137 (40.8%), and aphakic in 1 (0.3%). Also, 70 (20.8%) of the injections were given with concurrent focal laser treatment, 8 (2.4%) with concurrent panretinal photocoagulation (PRP), and 96 (28.6%) with concurrent photodynamic therapy (PDT; Table 1).

Patient follow-up averaged 9.5 months (SD, 7.5) in length. There were no cases of immediate retinal detachment, vitreous hemorrhage, or pseudohypopyon. Among the 336 injections, IOP measured at 5 min after the injection was ≥3 mmHg higher than the preinjection IOP for 110 (32.7%) injections. Immediate postoperative IOP measurements averaged 25.2 mmHg (SD, 6.2), with a mean rise of 7.6 mmHg (SD, 6.2) from preoperative IOP levels, representing an IOP rise of 43.2% within 5 min of injection. This rise was deemed to be statistically significant when the re-

Table 1. Characteristics Associated with the Patients, Eyes, and Treatments

<table>
<thead>
<tr>
<th>Patients (N = 192)</th>
<th>Eyes (N = 223)</th>
<th>IVTA injections (N = 336)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>Number of injections</td>
<td>Lens status</td>
</tr>
<tr>
<td>(73.3 years)</td>
<td>144 eyes (64.6%)</td>
<td>Phakic 198 (58.9%)</td>
</tr>
<tr>
<td>(SD 14.0 years)</td>
<td>55 eyes (24.7%)</td>
<td>Pseudophakic 137 (40.8%)</td>
</tr>
<tr>
<td></td>
<td>16 eyes (7.2%)</td>
<td>Aphakic 1 (0.3%)</td>
</tr>
<tr>
<td></td>
<td>6 eyes (2.7%)</td>
<td>Concurrent treatments</td>
</tr>
<tr>
<td></td>
<td>2 eyes (0.9%)</td>
<td>Focal 70 (20.8%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PRP 8 (2.4%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PDT 96 (28.6%)</td>
</tr>
<tr>
<td>Diagnoses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic macular edema</td>
<td>59 (30.7%)</td>
<td></td>
</tr>
<tr>
<td>Exudative ARMD</td>
<td>68 (35.4%)</td>
<td></td>
</tr>
<tr>
<td>CRVO + CME</td>
<td>26 (13.5%)</td>
<td></td>
</tr>
<tr>
<td>BRVO + CME</td>
<td>27 (14.1%)</td>
<td></td>
</tr>
<tr>
<td>HRVO + CME</td>
<td>4 (2.1%)</td>
<td></td>
</tr>
<tr>
<td>Uveitis + CME</td>
<td>8 (4.2%)</td>
<td></td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>75 (39.1%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>90 (46.9%)</td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>35 (18.2%)</td>
<td></td>
</tr>
<tr>
<td>Arthritis</td>
<td>36 (18.8%)</td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>22 (11.5%)</td>
<td></td>
</tr>
<tr>
<td>Mean Follow-up</td>
<td>9.5 months (SD, 7.5)</td>
<td></td>
</tr>
</tbody>
</table>

ARMD, age-related macular degeneration; CRVO, central retinal vein occlusion; BRVO, branch retinal vein occlusion; HRVO, hemiretinal vein occlusion; CME, cystoid macular edema; PRP, Panretinal photocoagulation; PDT, photodynamic therapy.
sults were analyzed using a paired Student $t$ test ($p < 0.0001$). There was 1 (0.3%) injection that caused occlusion of the central retinal artery, requiring an immediate anterior chamber paracentesis.

Several complications that occurred later in the follow-up were also noted. Although 12 of the 223 study eyes (5.4%) had cataract progression requiring extraction, the nature of the study design and age-related cataract progression made it difficult to attribute these findings with the IVTA injection. There was 1 injection (0.3%) that led to the development of endophthalmitis. This occurred in an eye diagnosed with ARMD with choroidal neovascularization, and this was treated concurrently with PDT and IVTA. Cultures revealed the presence of coagulase negative staphylococcus, and visual acuity in the eye fell from 20/100 to light perception following the development of endophthalmitis. The eye was treated with intracocular antibiotics and vitrectomy, resulting in an improvement in the infection, although visual acuity did not improve beyond counting fingers. There were no cases of pseudoendophthalmitis.

The most frequent complication of the IVTA injection was the development of a rise in IOP during follow-up. Baseline IOP prior to injection in the 336 injections averaged 17.6 mmHg (SD, 3.4). At the 1-week follow-up, this average rose ($p < 0.0001$) to 19.8 mmHg (SD, 5.1) and remained elevated ($p < 0.0001$) at the 12-week follow-up when IOP, averaged 19.1 mmHg (SD, 4.4; Fig. 1).

Analysis for the 223 study eyes revealed a change in IOP, from a baseline of 17.4 mmHg (SD, 3.4) prior to the first injection to 17.7 mmHg (SD, 5.3) at the latest follow-up. A paired Student $t$ test revealed that this difference was not statistically significant ($P = 0.48$). Of the 192 patients, 47 (24.4%) developed IOP requiring medication (IRM) during a follow-up of their first injection. In addition to this, 13 patients developed IRM on subsequent injections. Thus, 60 study participants developed IRM, for an overall rate of 31.3%. Among the 192 study participants, 34 had a documented history of primary open-angle glaucoma (POAG) prior to IVTA injection and 20 (58.8%) of these patients developed IRM. This is in comparison to the 158 non-POAG patients, 40 (25.3%) of whom developed IRM. Using a $\chi^2$ test, patients with POAG were found to be more likely to develop IRM with an OR of 4.2 (95% CI, 1.9–9.1).

$\chi^2$ testing was also used to investigate whether the development of IRM was associated with other factors, such as age or an immediate postinjection IOP spike. Among the 110 injections resulting in an IOP rise of $\geq 3$ mmHg within 5 min of injection, 27 (24.5%) developed IRM during a subsequent follow-up for that injection. This was comparable to a rate of 21.2% for those injections, with an IOP change $< 3$ mmHg. A $\chi^2$ test revealed no statistically significant difference between these two rates ($P = 0.59$).

To determine whether age was a factor in the development of IRM, the participants were split
into 2 groups, based on whether their age was above or below the median age for the entire group. Among the 60 patients that developed IRM, 29 (48.3%) were above the median age for all 192 patients and 51 (51.7%) were below the median age. $\chi^2$ testing did not find a significant difference in the rate of development of IRM between the 2 age groups ($P = 0.88$).

Finally, there were 2 (1.0%) patients that required filtration surgery to control their IVTA-induced rise in IOP, and 1 of these patients had a previous documented history of POAG.

**DISCUSSION**

IVTA has been shown to be an effective treatment for numerous retinal disorders. Several mechanisms of action have been proposed, including a decrease in levels of vascular endothelial growth factor (VEGF) and improved blood-retinal barrier function. Complications associated with IVTA include immediate complications such as retinal detachment, vitreous hemorrhage, pseudohypopyon resulting from a collection of triamcinolone crystals, and central retinal artery occlusion requiring immediate anterior chamber paracentesis.

Endophthalmitis has been reported as a rare, but serious, side-effect of this procedure, and there have also been reports of a similar entity, namely, pseudoendophthalmitis. An immediate postinjection rise in IOP has also been reported, as has the development of long-term IOP elevation, requiring medication or filtering surgery. Finally, steroid-induced cataract progression is another commonly cited complication of IVTA use.

Our study had no cases of vitreous hemorrhage or retinal detachment and only one case of temporary central retinal artery occlusion. Other studies have found these complications to be quite rare, with individual studies usually reporting no more than one or two of each complication within their study sample. One study found that retinal detachments occurred only in patients previously treated for retinal breaks. Our study findings confirmed the rarity of these potentially serious complications.

Another reported serious complication, endophthalmitis, occurred after 1 (0.3%) of the injections in our study. Endophthalmitis, in both a sterile and nonsterile form, has been reported to be a complication of IVTA in numerous studies. Although studies with small sample sizes have often reported no cases of endophthalmitis, larger studies have reported rates as high as 0.9%. The occurrence of infectious endophthalmitis is associated with numerous predisposing factors, such as external ocular infection and poor sterile technique. The patient who developed endophthalmitis in our study suffered from diabetes mellitus, another known predisposing factor. Infectious endophthalmitis is associated with significant long-term loss of visual acuity, often down to the level of light perception, as demonstrated by the outcome of our patient and as reported by other investigators. Despite treatment with intraocular antibiotics and pars plana vitrectomy, visual outcomes in these patients are often dismal.

Sterile endophthalmitis, or pseudohypopyon, is thought to represent a dispersion of TA crystals in the anterior chamber and, although it did not occur in our study, a large retrospective study by Moshfeghi and coworkers reported a rate of 0.8%. All studies have concluded that pseudohypopyon does not result in significant ocular morbidity and can be managed with close observation to rule out progressive intraocular inflammation caused by early endophthalmitis. Similarly, pseudoendophthalmitis, defined as anterior chamber cellular reaction without red eye or pain, is an endophthalmitis-like entity that has been observed in numerous studies and has resolved without specific treatment in all cases.

We did not encounter this entity in our study.

The progression of cataract formation after an IVTA injection has been noted in several studies. A prospective, randomized, placebo-controlled study by Gillies and colleagues found a significant correlation between IOP elevation and the progression of posterior subcapsular cataract but not with the progression of nuclear cataract. Other studies have confirmed the finding of cataract progression, and the published rates of cataract progression owing to IVTA injection range from 3.8% to 6.6%. Jonas and coauthors reported that cataract surgery after a single or multiple IVTA injection(s) did not have a significantly different safety or efficacy profile, indicating that this complication can be managed effectively.

In our study, the retrospective study design made it difficult to quantify cataract progression, but we noted the number of eyes that proceeded to cataract extraction surgery during follow-up after an IVTA injection. The rate of
SAFETY PROFILE OF INTRAVITREAL TA


cataract progression requiring extraction in our study was 5.4%. Though this analysis was limited, the relative agreement with the rates of cataract progression in other studies indicates that these previous findings are not challenged by our results.

Steroid-induced IOP elevation is another commonly cited complication of IVTA injection. Dwinger and coworkers reported that IOP was significantly higher 10 min after injection, as compared to the preinjection baseline. In our study, we found that patients experienced a significant immediate postoperative spike in IOP, which averaged 7.6 mmHg in magnitude. However, this postoperative spike was not correlated with a long-term rise in IOP requiring medication. This indicates that this spike should not be worrisome unless it reaches significantly high levels. Follow-up over the 12 weeks after an injection revealed a statistically significant rise in IOP that was sustained over the 12 weeks. However, over total follow-up for all eyes, including those that received multiple injections, there was no statistically significant difference between the baseline IOP and IOP at latest follow-up. This indicates that the rise in IOP is well managed, in most cases, through IOP-lowering interventions. We found that 31.3% of our patients developed IOP elevation that needed to be treated with medication. The vast majority of these cases were well controlled with medication, but 2 (1.0%) patients required filtering surgery to lower their IOP. This is in keeping with other studies, which have reported IOP elevation rates ranging from 20.0% to 40.0% and filtration surgery rates of 1.0%. A study by Gillies and colleagues found that 28.0% of patients required glaucoma medication, a rate which is in strong agreement with our results.17

In two studies, Jonas and coauthors have presented findings that IOP elevation was significantly correlated with a younger age. Although glaucoma medications were more frequently required in younger individuals in our study, this difference was not statistically significant. Thus, our results cannot confirm the findings of Jonas and coauthors, and this point may need further investigation in future studies.

In our study, IOP elevation requiring glaucoma medication was significantly more likely to occur in patients with a previously documented history of POAG prior to an IVTA injection. A study by Rhee and coworkers reported that a preinjection IOP of greater than 16 mmHg resulted in a significantly higher risk for a postinjection IOP elevation of greater than 5 mmHg. Ozkiris and Erkilic also reported a higher rate of postinjection IOP elevation among patients with a preinjection diagnosis of POAG.11

CONCLUSIONS

In conclusion, intravitreal injections of TA represent a very safe treatment option for numerous retinal vascular and inflammatory disorders. Most serious complications associated with the IVTA injection are rare, and cataract progression can be safely and effectively treated. IOP elevation is the most significant and frequent complication of IVTA injections and necessitates a close follow-up of all patients, with special caution reserved for patients with a preinjection history of POAG.

REFERENCES


Received: October 25, 2006
Accepted: February 8, 2007

Reprint Requests: Dr. Dana Ells
Calgary Retina Consultants
103, 49 Richard Way, S.W.
Calgary, Alberta T3E 7M8
Canada

E-mail: anna.ells@calgaryhealthregion.ca