SCIENTIFIC REPORT

Effects of intravitreal triamcinolone acetonide injection with and without preservative

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Aims: To evaluate the effects of intravitreal injection of preservative-free triamcinolone acetonide (PFTA) and TA containing preservative (KE).

Methods: A retrospective review was conducted of 646 intravitreal 4 mg/0.1 ml steroid injections in 471 eyes. A total of 577 intravitreal injections of PFTA and 69 injections of KE were administered in non-randomised eyes. No supernatant removal from KE was performed. Non-infectious endophthalmitis was defined as pseudohypopyon/hypopyon with or without an inflammatory reaction that regressed after steroid eye drop instillation. Ocular hypertension was defined as more than 23 mm Hg with Goldman applanation tonometry. Patients were followed and examined 1, 7 and 28 days, and 3, 4, 6 and 12 months after injection and annually thereafter. Statistical analysis was performed using Fisher's exact test and X^2 test. p Values <0.05 were considered significant.

Results: Both groups did not differ in demographics ($p>0.05$). Follow-up ranged from 6 to 57 months (mean 13, SD 7.5). Ocular hypertension was present in 127 eyes (20%), but both groups did not differ significantly ($p=0.167$). Four eyes (3.15%) required trabeculectomy. Non-infectious endophthalmitis developed in 12 eyes (1.9%) and varied significantly in both groups ($p=0.005$). One eye developed bacterial endophthalmitis (0.15%).

Conclusions: Non-infectious endophthalmitis was observed significantly more often after KE injections (7.3%) than after PFTA injections (1.2%) ($p<0.05$). An inflammatory reaction was more clinically relevant in the KE group than in the PFTA group.

Intravitreal injection of triamcinolone acetonide (TA) has commonly been administered worldwide to treat macular oedema from many causes.[1–7]

The prolonged duration of action of TA in eyes is related to its crystalline formulation, which is insoluble.[1] However, hypopyon or pseudohypopyon, intraocular inflammation, or all of these (non-infectious endophthalmitis) may develop after intravitreal injection of TA.[1 3–9] It is often difficult to distinguish hypopyon from pseudohypopyon; the latter clinical finding probably occurs as a result of deposition of crystals in the anterior chamber and is currently observed a few hours after intravitreal injection.[1 7 9] The development of infectious endophthalmitis after intravitreal steroid injection is usually associated with fewer symptoms than endophthalmitis secondary to cataract extraction and trauma, probably due to steroid inhibition of the inflammatory process, which may delay the correct diagnosis.[1 7 9]

The pathomechanisms of non-infectious endophthalmitis are unknown. A toxic sterile reaction is believed to occur,[9] probably due to the preservative vehicle in commercially available forms of TA.[1 5] However, other studies have suggested that non-infectious endophthalmitis after TA injection is related to inflammation induced by migration of macrophages caused by its crystals.[1 9] The rate of non-infectious endophthalmitis (pseudoendophthalmitis or sterile endophthalmitis) after intravitreal injection of TA was 1.6% in a series of 441 injections.[9]

We retrospectively evaluated the safety of intravitreal injections of triamcinolone acetonide containing preservative (KE) and of preservative-free triamcinolone acetonide (PFTA).

METHODS

A retrospective chart review from the Department of Ophthalmology, Vision Institute, Federal University of São Paulo, was performed from January 2002 to March 2006. Six hundred and forty-six intravitreal steroid injections were administered in 467 consecutive and non-randomised eyes of 471 patients to treat different diseases. A total of 577 intravitreal injections of PFTA and 69 injections of KE were administered. All injections of intravitreal steroids (4 mg/0.1 ml) were performed under topical anaesthesia. The procedures were performed by three vitreoretinal specialists following this method:

Pre-injection conjunctival instillation of topical 5% povidone was followed by intravitreal TA (Triamcinolone Ophthalmos, Ophthalmos Laboratories, São Paulo, Brazil) or KE (Kenalog, Bristol-Myers Squibb, Princeton, NJ, USA) injections performed after a sterile drape was placed, anterior chamber paracentesis performed and 0.1 ml aqueous humour removed. These procedures were performed in the operating room and were followed by conjunctival instillation of a combination of dexamethasone 0.1% and ciprofloxacin 0.3% for 7 days six times daily.

The corticosteroids were then injected through the inferotemporal pars plana 4.0 mm posterior to the limbus in phakic eyes and 3.0 mm posterior to the limbus in pseudophakic eyes using a 27-gauge needle.

The dose of 40 mg/ml of the corticosteroid was used in each group. No attempt was made to isolate the supernatant from the crystals of the steroid in the KE group.

The patients were followed and examined 1, 7 and 28 days and 3, 4, 6 and 12 months after injection and annually thereafter. A complete ophthalmologic examination was performed at each visit. Eyes with hypopyon or vitreous debris after injection were examined and followed after appropriate treatment. Intraocular pressure (IOP) measurement was performed using Goldman applanation tonometry in all eyes; IOP elevation greater than 23 mmHg by three consecutive measurements was considered as ocular hypertension.

Abbreviations: IOP, intraocular pressure; KE, triamcinolone acetonide containing preservative; PFTA, preservative-free triamcinolone acetonide; TA, triamcinolone acetonide

Only eyes with a minimum follow-up of 6 months were evaluated and cataract progression was not analysed in this retrospective study.

Non-infectious endophthalmitis was defined as pseudohypopyon or hypopyon with or without an inflammatory reaction that regressed after maintaining the conjunctival instillation of a combination of dexamethasone 0.1% and ciprofloxacin 0.3% for 7–14 additional days. Infectious endophthalmitis was suspected clinically by a decrease in vision, redness and pain, and confirmed by culture-proven growth of bacteria or fungus.

Statistical analysis was performed using Fisher's exact test for non-infectious endophthalmitis and X^2 test for IOP. p Values below 0.05 were considered statistically significant.

RESULTS

From all 471 patients submitted to intravitreal triamcinolone injection, 263 (56%) were men and 208 (44%) were women. Patients' age ranged from 22 to 89 years (mean 69, SD 10.35). One hundred and thirty-two (29.93%) patients were under treatment for diabetes. There were no differences between the two groups regarding gender, age and diabetic status. The main indications for such treatment were macular oedema following: Irvine-Gass syndrome (27.86%), diabetic retinopathy (25.38%), branch retinal vein occlusion (23.83%), central retinal vein occlusion (21.70%) and retinitis pigmentosa (1.23%).

Follow-up ranged from 6 to 57 months (13, SD 7.5) after the injections. The main postoperative abnormalities observed were high IOP (19.8%), non-infectious endophthalmitis (1.9%) and culture-proven endophthalmitis (0.15%) (table 1).

Non-infectious endophthalmitis

Non-infectious endophthalmitis developed in 12 eyes (1.9%) after 646 intravitreal steroid injections.

Two patterns of non-infectious endophthalmitis were observed. In the first, 7 (1.2%) of the 577 injections of PFTA resulted in pseudohypopyon without ocular pain and conjunctival redness but with minimum vitreous reaction. In the second pattern, 5 (7.3%) of the 69 injections of triamcinolone containing preservative developed hypopyon and had clinical findings of a mild painful and red eye. The difference in the non-infectious endophthalmitis rates between the two groups (1.2% from preservative-free TA group vs 7.3% from KE group) was statistically significant ($p = 0.005$) (table 1).

Culture-proven endophthalmitis

Of the 646 intravitreal injections, 1 eye (0.15%) of the KE group developed culture-proven bacterial endophthalmitis (table 1). Needle aspiration followed by Gram staining disclosed leucocytes and gram-positive cocci. Culture showed *Staphylococcus epidermidis*. The eye was managed by two intravitreal injections of vancomycin 1.0 mg/0.1 ml and ceftazidime 2.25 mg/0.1 ml; the final visual acuity was 20/200.

High intraocular pressure

One hundred and twenty-eight eyes (19.8%) after all 646 injections had high IOP (average 28 mm Hg, SD 4 mm Hg) including all measurements of IOP >23 mm Hg. A postoperative IOP elevation occurred in 19.1% of eyes after PFTA injections and 26.1% of eyes after KE injections. The difference did not reach statistical significance ($p = 0.167$) (table 2).

Of the 128 eyes with high IOP, 4 eyes (3.15%) required trabeculectomy to control the IOP (2 after intravitreal KE and 2 after intravitreal PFTA injections).

DISCUSSION

In the current study, 69 intravitreal injections of KE and 577 intravitreal injections of a PFTA were administered. Twelve (1.9%) of the intravitreal steroid injections caused non-infectious endophthalmitis, with significant difference between the groups ($p = 0.005$). We hypothesised the higher rate of of pseudo-endophthalmitis in the KE group than the PFTA group was related to the benzyl alcohol in the formulation of the KE molecule.

Injection of KE and PFTA resulted in two different patterns of presumed non-infectious endophthalmitis. All procedures that resulted in presumed non-infectious endophthalmitis with minimal inflammatory reaction (early pseudohypopyon formation) were related to the preservative-free TA injections (table 1). However, all procedures that resulted in presumed non-infectious endophthalmitis with a more severe inflammatory reaction (hypopyon reaction) were related to the KE injections (table 1).

Experimental studies using rabbit as the retinal toxicity model, showed that the commercial form of TA (Kenalog), and vehicle of KE alone were non-toxic to the rabbit retina, based on clinical and morphological data.[10 11] More recently, Lang and colleagues showed in 32 eyes that intravitreal KE was non-toxic to human retina, based on electrophysiology analysis, although no data regarding non-infectious endophthalmitis were presented.[8]

A recent study also reported that 1.6% of patients who underwent intravitreal injection of Kenalog (Brystol-Myers, USA) developed non-infectious endophthalmitis,[9] a lower rate than with the current study (7.3%) of KE cases of non-infectious endophthalmitis (table 2). KE contains 0.99% benzyl alcohol, 0.75% carboxymethylcellulose and 0.04% polysorbate

Table 1 Findings after intravitreal triamcinolone injection with and without preservative

Diagnosis	Bacterial endophthalmitis	Presumed non-infectious endophthalmitis (more severe inflammation)	Presumed non-infectious endophthalmitis (minimal inflammation)
Clinical findings	Painless loss of vision and hypopyon only a few days after injection. Delayed diagnosis	Painful loss of vision and mild red eye, hypopyon due to inflammatory reaction a few days after injection	Pseudohypopyon formation sooner (a few hours after injection) probably due to migration of crystals to the anterior chamber
PFTA injection (577) 89.32%	0	0	7 (1.2%)
KE injection (69) 10.68%	1	5 (7.3%)	0
Total injections (646) 100%	Total endophthalmitis 1 (0.15%)	Total non-infectious endophthalmitis with or without inflammatory reaction 12 (1.9%) Fisher's exact test (7.3%×1.2%; p=0.005)	

PFTA, preservative-free triamcinolone acetonide; KE, triamcinolone containing preservative.

Table 2 Intraocular pressure elevation after intravitreal triamcinolone injection with and without preservative

Intraocular pressure (IOP) elevation (>23 mmHg)	Group		
	PFTA injection (%)	KE injection (%)	Total (%)
Positive	110 (19.1)	18 (26.1)	128 (19.8)
Negative	467 (80.9)	51 (73.9)	518 (80.2)
Total	577 (100)	69 (100)	646 (100)
X^2 test	p=0.167		

PFTA, preservative-free triamcinolone acetonide; KE, triamcinolone containing preservative.

80.[1 9] PFTA contains sodium chloride, monobasic and dibasic sodium phosphate, 0.04% polysorbate 80, water for injection, and no benzyl alcohol (Ophthalmos Laboratories, Sao Paulo, Brazil, written communication, July 2006). These chemicals may be a potential stimuli for the inflammatory reaction within the eye or even increase the inflammatory reaction that also may be initially induced by the TA crystals.[12–14] It is unknown if preservative benzyl alcohol may influence the aggregation properties of crystals or even cause a more important inflammatory reaction.[12–14]

The eyes that developed pseudohypopyon and a minimal inflammatory reaction had all received a preservative-free TA injection. In these eyes, the pseudohypopyon was observed within the first day after injection in most patients, which suggests that the mechanism of pseudohypopyon formation is related to the migration of steroid crystals to the anterior chamber.

Only one case (0.15%) of infectious endophthalmitis developed after 646 intravitreal injections. There was no evidence that this finding was related to the type of steroid used (TA or KE) (table 1) and may be coincidental although it followed the KE injection. The incidence of infectious endophthalmitis after intravitreal TA has been reported to be 0.45% after 440 intravitreal injections.[1 9 15–17] We believe that preoperative use of a sterile drape and pre-injection use of topical povidone as well as frequent postoperative instillation of antibiotic eye drops should be performed to minimise these complications.

The patient with bacterial endophthalmitis presented with an atypical clinical picture 5 days after intravitreal TA injection, characterised by slow onset and painless loss of vision, which is similar to a previous report.[9] This patient required two intravitreal injections of antibiotics to control the infection.

Care must be taken by clinicians to differentiate infectious from non-infectious endophthalmitis and to be aware of the variability in the clinical presentation. Failure to differentiate these entities may result in unnecessary invasive treatments.

In summary, this preliminary study suggests that preservative-free TA is safer than TA containing preservatives for intravitreal use regarding the occurrence and intensity of secondary inflammatory reactions and the severe adverse events are very rare with both formulations. This should be considered before selecting intravitreal TA for injection into human eyes.

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