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Incidence, Risk Factors and Outcomes of Endophthalmitis Following Intravitreal Dexamethasone Implant in a Tertiary Eye Unit

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Abstract

Aim: Review of current literature regarding infection rates following intravitreal dexamethasone implant shows very little real-world data to date. Comparisons with infection rates following anti-VEGF or triamcinolone injections may not be clinically useful due to differing procedures and localised drug effects. We report the first direct clinical data on endophthalmitis rates following intravitreal dexamethasone implants in a tertiary eye unit in the UK.

Methods: Retrospective study of electronic patient records of all endophthalmitis cases between March 2010 and March 2018, with identification of dexamethasone-related cases. Review of treatment given, visual outcomes and possible risk factors.

Results: From 947 documented injections, 3 endophthalmitis cases were identified, giving a post-operative endophthalmitis rate of 0.32%.

Conclusion: Our data show a higher rate than previously published. Discussion of the cases reveals one case in a previously vitrectomised eye with post-operative wound leak. This may represent a risk factor for infection, but small numbers currently prevent useful statistical analysis. We discuss modifications to the protocol in our unit based on our experiences and available evidence.

Keywords: Endophthalmitis; Intravitreal steroid; Retinal vascular disease

Introduction

Intravitreal steroid is by no means a new treatment, and there is record of use of triamcinolone and dexamethasone as far back as the 1970s [1]. Intravitreal dexamethasone implants are a newer incarnation of steroid delivery, with a patented slow-release preparation being approved for use by the US Food and Drugs Authority in 2009 [2], and the European Medicines Agency in 2010 [3]. Since then, many thousands of injections have been performed world-wide, and the scope for use has spread to include retinal vein occlusion, diabetic macular oedema, and uveitis. The original licensing reports were largely based on the Geneva study [4], in which 1830 injections were performed, but no cases of endophthalmitis were reported. Whilst this is undoubtably a positive attribute of the drug preparation, it leaves clinicians with very little guidance as to consenting patients for procedural risks, and also as to audit standards within clinical practice. As a comparison, we have large amounts of data regarding anti-vascular endothelial growth factor (anti-VEGF) injections, with infection rates in the region of 0.025% [5] to 0.05% [6]. However, anti-VEGF agents are commonly administered with 30-gauge needles, leaving small scleral wounds that are predominantly self-sealing. The applicator for dexamethasone implants is a proprietary device using a 22-gauge needle, and cannot be interchanged with other needles. The technique recommended for use involves a stepped scleral incision [7], in order to ensure sealing of a wound that is potentially much larger than with anti-VEGF agents. With the two scleral wounds being so different, comparison of infection rates between the differing procedures is not clinically useful. Triamcinolone is a crystalline preparation, so typically a 27-gauge needle may be used [8], which sits between the other two gauges. However, intravitreal preparations of triamcinolone are largely unavailable outside of the USA, and excipients in the intra-articular preparations used elsewhere have been thought to increase risk of a sterile inflammatory endophthalmitis [9]. Bearing this in mind, we cannot use triamcinolone endophthalmitis rates for an accurate comparison either.

Recent data was published by Stem et al. [10], which reported medical insurance billing data from the USA, and extrapolated infection rates following dexamethasone implants. The data includes co-injection with anti-VEGF agents, giving a range of possible incidence between 0.06% and 0.14%. Whilst this is a useful guide for clinicians, to our knowledge, there has been no published dataset to date coming directly from clinical units regarding the post-operative endophthalmitis rates following intravitreal dexamethasone implant.

Subjects and Methods

This was a retrospective study of all patients between 1st March 2010 and 1st March 2018 at Southampton Eye Unit. This is a tertiary referral centre on the south coast of England, which runs a specialised intravitreal injection unit for medical retina patients, as well as ophthalmic operating theatres with access to vitreoretinal services. Data from both settings were reviewed.

Data were collected from the electronic patient record system to find all cases of post-operative endophthalmitis. Patient records were evaluated to determine causative surgery and identify dexamethasone implant-related cases. This was compared to total numbers of dexamethasone implant injections performed to determine incidence rate. Cases were also analysed to determine pre-existing risk factors, management of infection, and final visual outcome. Following one endophthalmitis case in a previously vitrectomised eye, all dexamethasone injections within the time period were audited to determine the number of previously vitrectomised eyes undergoing the procedure.

Results

We found documentation for 947 intravitreal dexamethasone implants over the period studied, with indications of retinal vein occlusion, diabetic macular oedema and non-infectious uveitis. There was a total of three cases treated for endophthalmitis (Table 1), giving an incidence rate of 0.37%.

Case	Age	Indication for Dex	Diabetes	Other risk factors	Days to presentation
1	77	BRVO	No	None	6
2	90	CRVO	No	Age	4
3	43	CRVO	No	Previous vitrectomy	33
BRVO- Branch retinal vein occlusion, CRVO- Central retinal vein occlusion, Dex- Dexamethasone implant					

Table 1: Demographics

All of the precipitating dexamethasone injections were performed in-house, with no referred cases from outside units. Each procedure was performed trained medical professionals to local protocol involving povidone iodine, use of lid speculum, use of injector face-mask, and subconjunctival anaesthesia. Two cases reported procedural difficulties, the first with problematic entry of the needle into the sclera, and the second with patient movement. The third case was in a previously vitrectomised eye, and re-presented the day following dexamethasone injection with hypotony and wound leak, requiring suturing of the entry wound.

Of the 947 dexamethasone injections performed, 84 eyes (8.8%) had previously undergone pars plana vitrectomy in our unit. Due to the limitations of the electronic record system, this is likely to be lower than the true figure, due to patients having undergone vitrectomy in other units, without record in our patient notes.

All cases of infection were triaged through the unit's eye casualty and managed in the eye ward and surgical theatres (Table 2.) Two cases received initial vitreous 'tap-and-inject' as per the local protocol, whilst one case received par plana vitrectomy with removal of implant and intravitreal antibiotics as primary management. Antibiotic choice for post-operative endophthalmitis was guided by local microbiology recommendation for intravitreal vancomycin 1 mg in 0.1 ml as Gram-positive organism cover, and ceftazidime 2.25 mg in 0.1 ml as Gram-negative cover.

Case	Intravitreal Rx	Topical Rx	Systemic Rx	Vitrectomy
1	1 mg vancomycin, 2.25 mg ceftazidime	Chloramphenicol	None	Yes 23 g (primary treatment)
2	1 mg vancomycin, 2.25 mg ceftazidime	Ofloxacin	Ciprofloxacin	Yes 23 g
3	1 mg vancomycin, 2.25 mg ceftazidime	Ofloxacin, cefuroxime	None	Yes 23 g

Table 2: Treatment

Systemic treatment was varied, with one of the three cases receiving oral ciprofloxacin, whilst the others did not. The duration of treatment was not specified in the documentation.

All three cases provided microbiological growth from the vitreous biopsy; all three grew coagulase-negative Staphylococcal species (Table 3.) Antibiotic sensitivities were available for two of the isolates, with chloramphenicol resistance found in the first case.

Case	AC isolate	Vit. isolate	Sensitivities
1	None	Coagulase-negative Staph.	Resistant- chloramphenicol. Sensitive- ciprofloxacin, flucloxacillin, fusidic acid, gentamicin
2	None	Coagulase-negative Staph.	Not available
3	None	Coagulase-negative Staph.	Sensitive: chloramphenicol, vancomycin, linezolid
AC: Anterior chamber, Vit: Vitreous			

Table 3: Microbiology

Two of the three cases showed deterioration of the final visual acuity as compared to pre-procedure level, in keeping with severe intraocular infection (Table 4.) Case 1 conversely showed an improvement in final visual acuity, and was also the only case to receive par plana vitrectomy as an initial procedure as opposed to 'tap-and-inject.'

Discussion

Our rate of post intravitreal dexamethasone endophthalmitis of 0.32% was higher than previous reports. Stem's group recently published data from medical insurance claims in the USA, which included 3593 injections, some from centres which co-injected with anti-VEGF injections during the same surgical session as dexamethasone. Unfortunately, this mixture of data prevents accurate interpretation of the rate, as it is possible that a proportion of the

infections were caused by the anti-VEGF injection as opposed to the dexamethasone. Two of the infected cases were dexamethasone-only injections, with three other cases (one culture-negative) in mixed injections. If it is assumed that the anti-VEGF was responsible in the co-injections, a rate of 0.06% is given. If it is assumed that the dexamethasone was responsible for all the infection cases, a rate of 0.14% is given; without being able to filter the causative injection, we are left with a range between the two figures. The lower end is therefore comparable to published infection rates for anti-VEGF mono-injections, whilst the upper end is closer to our rate. If the higher endophthalmitis rate from Stem's group is compared to our rate, there is no statistically significant difference. This is likely due to the small numbers involved with incidence of endophthalmitis.

Case	Pre-op VA	Presenting VA	Final VA	Detachment	Phthisis	Enucleation
1	0.52	0.8	0.36	No	No	No
2	0.48	1.02	1.08	No	No	No
3	0.52	1.08	HM	Yes	No	No

Table 4: Outcomes (LogMar acuity)

The higher rate of endophthalmitis seen after steroid implant compared to anti-VEGF is possibly due to a number of factors. Dexamethasone implant requires a thicker gauge of needle, leading to larger scleral wounds, and possibly 'Vitreous wick syndrome' as described in endophthalmitis following vitrectomy [11]. Diagnosis of early-stage endophthalmitis may be challenging as steroids may mask some of the early symptoms of pain or signs of low grade inflammation due to local immunosuppression. Additionally, the localised immunosuppression may prevent innate elimination of pathogens, leading to a higher rate of infection [11]. As previously mentioned, intra-articular triamcinolone preparations may be used where licensed intra-ocular preparations are not available, so a number of the triamcinolone-related endophthalmitis cases without identifiable microbiological isolates may be a reaction to excipients rather than true infection. Likewise, the same effect may possibly apply to the sustained-release intraocular preparations, and indeed the recent review by Goel [12] looked at five reported cases after dexamethasone, with three of the five not growing any microbiological isolate. It is therefore very difficult to unpick the effect of immunosuppression versus inflammatory response to steroid excipients.

The stepped incision technique used for dexamethasone implant is different to the perpendicular entry used in anti-VEGF, and based on our data; the implementation of this may play a role in risk of infection. With high-volume injection lists being mainly composed of anti-VEGF cases, the switch to steroid injection may prove a challenge for injector. In all three of our cases, there were procedural difficulties recorded.

Eyes with previous vitrectomy are theoretically at a higher risk of procedural difficulties and hypotony. This could be from localised conjunctival scarring necessitating more force and manipulation, or thinner sclera from previous surgical procedures causing making water-tight wound closure less likely. Unfortunately, the data available from our study does not give enough statistical power to calculate a meaningful relative risk in the case of post-vitrectomy eyes, so further study is required in this area. Anecdotal notation from the cases observed raises concern toward this possibly being a risk factor, so in our unit protocol has been modified until further evidence is available: all post vitrectomy cases are now performed by senior staff in eye operating theatres as opposed to injection suite. Based on our experiences, units performing intravitreal dexamethasone implants in post-vitrectomy eyes should consider precautionary measures as deemed appropriate. Further and more robust studies are required to provide more statistically meaningful data on infection rate following dexamethasone implant and whether previous vitrectomy plays any role on this.

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