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REVIEW

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Endophthalmitis following intravitreal anti-vascular endothelial growth factor (VEGF) injection: a comprehensive review

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Abstract

The purpose of this review is to report and summarize previously reported studies and assess many of the individual steps of the intravitreal injection procedure's possible effect on the prevention of endophthalmitis. The pooled endophthalmitis rate from 20 large retrospective case series of anti-VEGF injections was 144/510,396 (0.028%; 1/3,544). Injections may be performed in an office-based location or in an operating room (OR) and low rates of endophthalmitis can be achieved in either location with careful attention to asepsis. Pre- or post-injection topical antibiotics have not been shown to be effective, and could select for more virulent microorganisms. Povidone-iodine prior to injection is accepted as the gold-standard antiseptic agent, but *aqueous* chlorhexidine may be an alternative. Antisepsis before and after gel or subconjunctival anesthetic is suggested. The preponderance of Streptococcal infections after intravitreal injection is discussed, including the possible role of aerosolization, which can be minimized by using face masks or maintaining silence. As with other invasive procedures in medicine, the use of sterile gloves, following adequate hand antisepsis, may be considered. Control of the eyelashes and lid margin is required to avoid contamination of the needle, but this can be achieved with or without a speculum. Techniques to minimize vitreous reflux have not been shown to reduce the risk of endophthalmitis. Same day bilateral injections should be performed as two separate procedures, preferably using drug from different lots, especially when using compounded drugs.

Keywords: Endophthalmitis, Intravitreal injection, Anti-VEGF, *Streptococcus*, Masks, Antisepsis, Povidone-Iodine, Chlorhexidine, Antibiotics, Speculum

Introduction

Intravitreal injection (IVI) is the most commonly performed ophthalmic procedure. In the USA, the number of injections performed has increased exponentially, from 4,215 injections in 2001 to 82,994 in 2004, to 812,413 in 2007, to 1.27 million in 2009 and to 2.5 million injections in 2011 [1, 2]. Similar increases have been observed in Canada and the United Kingdom [3, 4].

Infectious endophthalmitis (IE) secondary to IVI is a potentially devastating complication. It can be difficult to distinguish infectious endophthalmitis from "sterile" or non-infectious endophthalmitis. For the purpose of this review, IE refers to endophthalmitis that is clinically suspected to be infectious, and treated as such with a vitreous tap and injection of antibiotics and/or vitrectomy surgery.

Bacteria are most likely inoculated into the vitreous cavity at the time of injection, or much less likely gain access later through the needle tract [5, 6]. The potential sources of bacteria include the patient's ocular or periocular surfaces, aerosolized bacteria, or contamination of the needle, instruments, drug or drug vial [7].

Two meta-analyses including both retrospective series and clinical trials have calculated the pooled rate of endophthalmitis after anti-VEGF injections. McCannel found a rate of 52/105,536 injections (0.049%; 1 in 2030) [8] and more recently, Fileta et al. [9] calculated a rate of 197/350,535 (0.056%; 1 in 1,779). As patients typically receive ongoing intravitreal therapy, the per-patient risk

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of endophthalmitis is significantly higher than the per-injection risk.

The rate of needle contamination after IVI has been reported as between 0.36 and 18%, which is significantly higher than the incidence of endophthalmitis after IVI [5, 7, 10]. The threshold inoculum size required to develop endophthalmitis is related to the type of bacteria and their virulence, intraocular immune mechanisms and anatomical characteristics of the vitreous [11, 12]. Animal studies have shown that a smaller number of bacterial colony-forming units are required to induce endophthalmitis when injected into the vitreous compared to when they are injected into the anterior chamber [13]. Endophthalmitis following intravitreal injection often presents earlier than after cataract surgery [14, 15].

The purpose of this review is to estimate the rate of endophthalmitis after intravitreal injection and to examine each step of the injection procedure that may influence the risk of endophthalmitis. To be able to prove that a particular measure reduces the risk of endophthalmitis would need huge numbers of patients in a randomized controlled trial, given that endophthalmitis is a relatively rare outcome. There is thus no Level 1 evidence for any preventative measure to reduce the incidence of endophthalmitis after intravitreal injection. As a result, this review largely summarizes retrospective papers, with their inherent biases.

Methods

A systematic literature search of the Medline database from 1996 to December 2014 was performed through Ovid, using search terms relevant to each section. Further literature was sourced from the reference lists of retrieved publications.

To estimate the per-injection rate of endophthalmitis after anti-VEGF injection, retrospective case series with at least 10,000 such injections were included. Studies that did not report a breakdown of the drugs used were excluded to avoid including triamcinolone and other injections in this calculation. Questionnaire-based and population-based studies were excluded given the incomplete data. Clinical trials were excluded as they may not reflect real-world practice, with more stringent requirements regarding injection technique often included in the protocols.

Results

Twenty retrospective case series meeting the inclusion criteria were identified. Details of the injection procedure and associated aseptic measures used in each series are summarized in the Table 1. Where data were missing, the corresponding author for each study was contacted by email. Only two authors were not contactable.

We identified 144 cases of endophthalmitis from 510,396 anti-VEGF injections which equates to a pooled endophthalmitis rate of 0.028% or 1 in 3,544 injections [16–33].

Review

Location—office vs operating room (OR)

In the 2013 American Society of Retinal Specialists (ASRS) Preferences and Trends (PAT) Survey, over 98% of USA-based specialists reported performing injections in an office setting, compared with only 47% of international specialists [34]. In Germany and other parts of Europe, more injections are performed in the operating room (OR) [35, 36].

It has been [29] suggested that an advantage of the OR location is the superior air circulation systems. However, the ESCRS endophthalmitis study group was not able to find a relationship between the number of air changes per hour and the incidence of endophthalmitis after cataract surgery when they compared locations with minimal airflow, 20 air changes per hour and ultraclean air systems using laminar flow principles [37, 38].

Pooling the results of three OR-based injection series, the endophthalmitis rate was just 6/78,506 (0.0076% or 1 in 13,084) [19, 23, 25]. Common to these studies was the careful attention to asepsis with the use of sterile gloves, face masks, and drapes which were not used in most other office-based series (see Table 1). A notable exception is Shimada et al's series with no cases of endophthalmitis out of 15,144 injections where similar strict aseptic measures were followed in an office setting [27].

Abell et al. [29] reported an endophthalmitis rate of 4/3,376 (0.12%) for office-based injections compared with 0/8,873 (0%) for OR-based injections. In this non-randomized series, patients with private health insurance were treated in the OR while those without insurance were treated in the office. The difference in endophthalmitis rates may be a reflection of socioeconomic or other factors [39]. Tabendeh et al. [30] reported an endophthalmitis rate of 3/8,210 (0.037%) anti-VEGF injections in the office compared with 2/3,047 in the operating room (0.066%), in another non-randomised study that was not powered to be able to detect a difference. Compared with office-based injections, there was no apparent benefit to an OR environment in this small study.

Although there is no doubt that the OR has many advantages, there are logistical hurdles that make access to OR facilities difficult for many patients, and the OR location

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Table 1 Endophthalmitis following intravitreal anti-VEGF injection—retrospective cases series with at least 10,000 injection

Period and location	Authors	n = injections	Rate of clinically suspected IE	Pre-injection antibiotics	Post injection antibiotics	Mask	Drape	Conjunctival povidone-iodine concentration	Anaesthetic agents used	Sterile lid speculum	Gloves	Location
1 Jan 2009 to 1 Oct 2012 Single-centre, USA	Storey et al. [16] (PIE study group) Ophthal 2013	117,171	**Overall** 44/117,171 (0.038%; 1/2,663) **By Agent** Rani: 24/71,791 (0.033%; 1/2,991) Bev: 20/44,007 (0.045%;1/2,200) Aflib: 0/1,373	Variable	Variable	No*	No	5%	Drops Subconj (rarely)	Variable	Nil*	Office
1 Jan 2005 to 31 Dec 2010 Single-centre (multi-site), USA	Moshfeghi et al. [17] Retina 2011	60,322	**Overall** 12/60,322 (0.020%; 1/5,027) **By Agent** Rani: 5/18,607 (0.027%; 1/3,721) Bev: 7/39,700 (0.018%; 1/5,671) Peg: 0/2,015	No	Variable	No*	No	5%	Drops	Yes	Non-sterile	Office
1 Jan 2007 to 31 Dec 2011 Single-centre, USA	Chaudhary et al. [18] Retina 2013	49,002	**Overall** 17/49,002 (0.035%; 1 in 2,882) **By Agent** Rani: 2/20,297 (0.0099%;1/10,149) Bev: 15/28,705 (0.052%;1/1,914)	Yes	Yes	No	No	5%	Drops Gel Subconj	Yes	Nil or non-sterile	Office
2004 to 2012 Multicentre, Switzerland	Casparis et al. [19] Retina 2014	40,011	**Overall** 3/40,011 (0.0075%;1 in 13,337) **By Agent** Rani: 3/36,398 (0.0082%, 1/12,133) Bev: 0/3,518 Aflib:0/89 Peg: 0/6	No	Variable (yes in one hospital, no in the other)	Yes	Yes (adhesive)	5–10%	Drops	Yes	Sterile	OR
1 Aug 2006 to 31 Jul 2007 Multi-centre, USA	Klein et al. [20] Ophthal 2009	30,736	**Overall** 15/30,736 (0.049%; 1/2,049) **By Agent** Rani: 10/22,579 (0.044%; 1/2,258) Bev: 5/8,039 (0.062%; 1/1,608) Peg: 0/128	Variable	?	?	?	5–10%	?	Variable: used in 14 of the 15 cases with endophthalmitis	?	Office

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Table 1 continued

Period and location	Authors	n = injections	Rate of clinically suspected IE	Pre-injection antibiotics	Post injection antibiotics	Mask	Drape	Conjunctival povidone-iodine concentration	Anaesthetic agents used	Sterile lid speculum	Gloves	Location
July 2000 to July 2010 Single-centre (multi-site), USA	Chen et al. [21] Retina 2011	29,995	**Overall** 11/29,995 (0.037%; 1/2,727) **By Agent** Rani: 8/22,336 (0.036%; 1/2,792) Bev: 3/6,675 (0.045%; 1/2,225) Peg: 0/984	Yes	Yes	No*	No*	5–10%	Drops Gel Subconj	Yes	Non-sterile*	Office
1 Jun 2005 to 7 Aug 2007 Multicentre, USA	Fintak et al. [22] Retina 2008	26,905	**Overall** 6/26,905 (0.022%; 1/4,484) **By Agent** Rani: 3/14,320 (0.021%; 1/4,773) Bev: 3/12,585 (0.024%; 1/4,195)	No*	Variable (used in all the cases of endophthalmitis)	No*	No*	5–10%	Drops Gel Subconj	Variable (used in all the cases of endophthalmitis) Fingers to spread the eyelids in a minority	Nil*	Office
March 2007 to May 2013 Single-centre, Denmark	Brynskov et al. [23] Retina 2014	20,293	**Overall** 0/20,293 **By Agent** Rani: 0/20,024 Aflib: 0/269	No	Variable	Yes	Yes (adhesive)	5%	Drops	Yes	Sterile	OR
1 Aug 1997 to 31 Oct 2012 Single-centre, USA	Bhavsar and Sandler [24] Retina 2015	17,666	**Overall** 1/17,666 (0.0057%, 1/17,666) **By Agent** Rani: 0/1,669 Bev: 1/15,479 (0.0065%, 1/15,479) Aflib: 0/148 Peg: 0/370	No	No	No	No	5% (before and after injection)	Drops	Yes	Non-sterile	Office
Jan 2005 to end July 2012 Single-centre, Germany	Nentwich et al. [25] Retina 2014	18,202	**Overall** 3/18,202 (0.016%; 1/6,067) **By Agent** Rani: 1/10,097 (0.010%, 1/10,097) Bev: 2/7,865 (0.025%;1/3,932) Peg: 0/240	No	Yes	Yes	Yes (non-adhesive)*	1%	Drops	Yes	Sterile	OR

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Table 1 continued

Period and location	Authors	n = injections	Rate of clinically suspected IE	Pre-injection antibiotics	Post injection antibiotics	Mask	Drape	Conjunctival povidone-iodine concentration	Anaesthetic agents used	Sterile lid speculum	Gloves	Location
Jan 2007 to May 2012 Multicentre, India	Mithal et al. [26] BJO 2013	15,925	**Overall** 8/15,925 (0.050%;1/1,991) **By Agent** Rani: 1/705 (0.14%; 1/705) Bev: 7/15,035 (0.044%;1/2,275) Peg: 0/185	No*	Yes*	Yes*	Variable	2.5%*	Drops*	Yes*	Sterile*	Office*
July 2009 to July 2012 Single-centre, Japan	Shimada et al. [27] Graefes 2013	15,144	**Overall** 0/15,144 **By Agent** Rani: 0/13,750 Bev: 0/846 Peg: 0/548	Yes	Yes	Yes	Yes (adhesive)	0.25% (before and after injection)	Drops + Sub-conj	Yes	Yes	Office
Jan 2005 to Aug 2010 Multi-centre, Canada	Cheung et al. [28] Ophthal 2012	14,960	**Overall** 7/14,960 (0.047%; 1/2,137) **By Agent** Rani: 3/9,453 (0.032%; 1/3,151) Bev: 4/5,386 (0.074%; 1/1,347). Peg: 0/121	Variable	Variable	No*	No	10%	Drops Gel	Yes	Nil*	Office
Mar 2006 to Mar 2012 Multi-centre (single-surgeon), Australia	Abell et al. [29] BJO 2012	12,249	**Overall** 4/12,249 (0.033%; 1/3,062) **By Agent** Rani: 3/10,574 (0.028%; 1/3,525)* Bev: 1/1,675 (0.060%; 1/1,675)*	No	Variable (used until 2011)*	Yes	Yes (non-adhesive)*	10%	Drops + Gel*	Yes	Sterile	Office = 4/3,376 OR = 0/8,873
Jan 2009 to Dec 2011 Multi-centre, USA and Italy	Tabandeh et al. [30] Retina 2014	11,257	**Overall** 5/11,257 **By Agent** Rani: 3/2,724 (0.11%; 1/908) Bev: 2/8,533 (0.023%; 1/4,267)	Yes in OR No in office	Yes	Yes in OR No in office	Yes in OR No in office	5%	Drops Subconj	Yes	Sterile in OR Non-sterile in office	Office = 3/8,647 OR = 2/3,063

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