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ARTICLE

Post-injection endophthalmitis rates with reduced povidone-iodine prophylaxis in patients with self-reported iodine sensitivity

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Abstract

Background Our objectives were (1) to report the post-injection endophthalmitis rate over 18 months, and (2) to determine any difference in the incidence of endophthalmitis in patients treated with reduced or no 5% povidone-iodine (PI) due to self-reported PI sensitivity.

Methods We performed a retrospective cohort study of all patients who received intravitreal injections (IVIs) from January 1st, 2018 to June 26th, 2019. Information on patients' age, gender visual acuities, the number of injections, drug administered, self-reported iodine sensitivity and injection protocols were obtained from electronic and paper records. For endophthalmitis cases, vitreous culture results and treatment were also noted. Patients were divided into three cohorts based on the injection protocol used for statistical analysis.

Results During the study period 22,046 IVIs were administered to 3332 eyes of 2709 patients. Intolerance to PI was reported by 2.4% of patients. The incidence of endophthalmitis was 0.02% (4/21,185) with the standard 5% PI protocol, 0.78% (6/769) with a reduced PI protocol involving fewer drops of 5% PI and chlorohexidine 0.05% for periorbital skin cleansing, and 1.09% (1/92) without any PI use. Receiving the standard PI protocol was associated with significantly lower rates of endophthalmitis compared to both the reduced PI and no PI protocols ($p < 0.0001$).

Conclusions Patients who opt for less or no PI use are likely at significantly increased risk of developing post-IVI endophthalmitis. It is imperative to educate, counsel and consent these patients accordingly while exploring alternative antiseptic solutions.

Introduction

The use of intravitreal injections (IVIs) as a mainstay of treatment for a multitude of ophthalmic conditions has exponentially increased over the past decades [1]. At present, IVI is the most commonly performed intraocular procedure in the UK and globally with an estimated 5.9 million injections administered in the US in 2016 [2]. While the efficacy of IVI for conditions such as age-related macular degeneration, diabetic macular oedema and retinal vein occlusions is well established, periprocedural injection protocols vary widely [3]. Variations in practice include in the setting of administration, use of face masks, lid speculum versus disposable injection devices as well as the timing and strength of topical antiseptic solutions [3, 4]. Despite these differences in clinical practice, a review of the published literature found the reported incidence of potentially sight-threatening post-IVI endophthalmitis to be relatively consistent across the world [5]. Periocular and topical povidone-iodine (PI) remains the most effective and widely used antiseptic agent to reduce the risk of endophthalmitis during intraocular procedures including IVIs [4–6]. Hydrophilic povidone allows free iodine to penetrate cytoplasmic membranes and oxidises vital cell molecules and organelles and exert its broad antimicrobial spectrum and bactericidal properties [7]. PI has also been shown to be effective against bacterial virulence factors such as endotoxins, exotoxins and cytokines [8]. Its antimicrobial efficacy appears to be linked to both exposure time and

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concentration [9]. In ophthalmology, 5–10% PI solution remains the gold standard for procedural antiseptic prophylaxis choice due to its affordability, ready availability and wide spectrum of action [4, 6]. However, even as a diluted formulation, PI can cause corneal irritation with signs of tear film and ocular surface abnormalities leading to discomfort for patients, particularly following repeated use [10]. Increasingly, patients report sensitivities to topical PI use, particularly following repeated applications [10]. While true allergy to topical PI is exceedingly rare [11, 12], individuals who experience PI-induced ocular surface toxicity, may opt for IVI without the use of perioperative PI to avoid the resulting corneal irritation and discomfort. The limited published data on the risk of endophthalmitis without PI use suggests that the incidence is significantly greater than with the use of PI or aqueous chlorhexidine [13, 14]. In the era of patient choice, the ophthalmologist may increasingly face the clinical dilemma of whether to withhold IVI or to administer injections with less or no PI in patients with self-reported PI sensitivities [11]. In this context, we set out to report the post-injection endophthalmitis rate in our department over 18 months and to determine any difference in the incidence of endophthalmitis in patients with self-reported PI sensitivity who requested a reduced PI protocol involving fewer drops of 5% PI or a protocol in which PI was entirely foregone.

Methods and materials

Study period

The study period covered 18 months from 1st January 2018 to 26th June 2019.

Inclusion criteria

All patients receiving therapeutic IVI for any indication at the Gloucestershire Hospital NHS trust were initially included in the study. The trust operates across two sites (Cheltenham General Hospital and Gloucester Royal Hospital), serving a population of ~1 million people across Gloucestershire and a portion of Worcestershire.

Exclusion criteria

Patients who underwent IVI were excluded from the study if any of the following criteria were met: administered under general anaesthesia, administered in combination with a surgical procedure or the patient was diagnosed with endogenous or postoperative endophthalmitis.

Data collection

The total number of IVIs administered during the study period (1st January 2018–26th June 2019), clinical and demographic patient data were obtained using electronic medical records (Medisoft Limited, Leeds, UK). Information on iodine sensitivities and the use of PI were identified from electronic and paper medical records. Electronic patient records for all cases of endophthalmitis during the study period were reviewed. For each case of post-IVI endophthalmitis, microbial culture and sensitivity patterns based on vitreous taps, visual acuity before, at diagnosis, and following treatment were reviewed electronically. Visual acuity documented as counting fingers or hand movement was converted to LogMAR values to enable quantitative analysis (counting fingers = 1.98, hand movement = 2.28) [15]. Light perception was not converted and is reported alongside the LogMAR values.

Injection protocols

Trained clinical staff administered IVIs according to the agreed departmental injection protocol in an outpatient setting at both hospital sites. Injectors wore surgical masks, a disposable apron and sterile gloves during the injection procedure. All IVIs included in this study were performed under topical anaesthesia with either single-use oxybuprocaine hydrochloride 0.4% or tetracaine hydrochloride 0.5% drops (Bausch & Lomb, UK). The standard departmental PI protocol consisted of two drops of 5% PI instilled 3 min before injection, followed by cleansing of the periorbital skin with 10% PI and a further drop of 5% PI 1–2 min before the injection. One drop of chloramphenicol 0.5% (Bausch & Lomb, UK) was administered after the injection.

The reduced PI protocol involved one drop of 5% PI 3 min before the injection, followed by cleansing of the periorbital skin with cutaneous 0.05% w/v chlorhexidine gluconate containing cocamidopropyl betaine as a detergent (Sterets Unisept, Medlock Medical Ltd, UK). After the injection, a forniceal washout was performed with sterile normal saline 0.9% solution and one drop of chloramphenicol 0.5% was administered.

When the patient refused all PI use, the periorbital skin was cleaned with chlorhexidine 0.05% and post-injection topical chloramphenicol 0.5% was administered. No topical antiseptic agent was used in these cases, as aqueous chlorhexidine was unavailable. Single-use lubricating carbomer eye drops (Viscotears Single Dose Unit 2.0 mg/g Eye Gel, Alcon) was administered after the injection.

All patients were encouraged to follow the standard PI protocol and were counselled on a potentially higher risk of sight-threatening endophthalmitis with less or no PI use.

Table 1 Demographics of the intravitreal injection treatment population by antiseptic protocol used.

	Total	Standard PI	Reduced PI	No PI
Injections, *n* (% total)	22,046	21,185 (96.09%)	769 (3.49%)	92 (0.42%)
Patients, *n* (eyes)	2709 (3332)	2644 (3240)	58 (81)	7 (11)
Injections per eye, *n* (±SD)	6.6 (±3.8)	6.54 (±3.79)	9.49 (±3.41)	8.55 (±3.34)
Female, % of injections	58.9%	57.83%	84.14%	90.22%
Mean age, years (±SD)	78.5 (±11.3)	78.58 (±11.3)	75.82 (±9.6)	76.14 (±8.4)

PI povidone-iodine, *SD* standard deviation.

Results

Demographics

During the study period, a total of 22,046 IVIs were administered to 3332 eyes of 2709 patients (Table 1). The mean age of patients was 78.5 years ±11.3 (mean ± SD) with a slight female preponderance (58.9% females). Patients received an average of 8.14 injections (6.62 injections per eye) with aflibercept (47%) and ranibizumab (46%) making up the majority of administered therapeutic agents.

PI sensitivity

A reduced PI protocol was requested by 58 (2.14%) of patients and 7 (0.26%) requested no PI use (Table 1). Patients requesting either reduced PI protocol or no PI were more likely to receive a larger number of injections during the study period compared to those opting for the normal PI protocol (8.01 ± 5.56 for normal PI, 13.45 ± 7.13 for reduced/no PI; $p < 0.0001$). As a result, these two groups made up 3.91% of all injections given during the study period. Patients opting for a reduced PI protocol and no PI were overwhelmingly female at 84.14% and 90.22%, respectively. Dry eye syndrome was noted in three patients (42.86%) who requested no PI prophylaxis.

Endophthalmitis

Endophthalmitis developed in 11 patients, or 1 in 2000 injections (0.05%), during the study period (Table 2). The incidence of endophthalmitis in patients treated with the standard PI protocol was 1 in 5000 injections (0.02%). By contrast, the risk of endophthalmitis was 1 in 128 (0.78%) and 1 in 92 injections (1.09%) in patients receiving reduced PI and no PI prophylaxis, respectively. While the difference in endophthalmitis rates in IVIs given with standard PI protocol and those with reduced ($p < 0.0001$) or no PI protocol ($p < 0.0001$) was statistically significant, no significant difference in the incidence between the reduced PI protocol and no PI use was demonstrated ($p = 0.95$).

The mean number of injections received during the study period was higher in patients who developed endophthalmitis compared to those who did not (11.91 ± 8.50 vs. 8.12 ± 5.64; $p = 0.013$). Table 3 summarises the clinical and demographic characteristics of each case. Endophthalmitis developed following administration of aflibercept in five cases and ranibizumab in six cases. The mean time from the last injection to the presentation was 5.18 (±3.6) days (range 2–14 days). The mean reduction in visual acuity (LogMAR) following treatment for endophthalmitis was 0.06 for the standard PI protocol group with one patient's vision being reduced to light perception only. For the reduced PI protocol group, the mean reduction was 0.49 and for the no iodine group it was 0.2 with neither group involving a case of reduction to light perception only.

Vitreous samples were obtained in all but one case of endophthalmitis. Seven cases of culture-positive endophthalmitis were confirmed with the causative organisms being coagulase-negative staphylococci ($n = 4$) and *Staphylococcus epidermidis* ($n = 3$). The three remaining cases were culture-negative.

All cases of endophthalmitis were treated with intravitreal ceftazidime (2.25 mg/0.1 ml) and vancomycin (1 mg/0.1 ml) on the day of diagnosis. Two patients also underwent a pars plana vitrectomy.

Discussion

This is the first large UK study to report rates of post-injection endophthalmitis rates in patients opting for reduced or no PI prophylaxis. Internationally, reported rates of post-injection endophthalmitis broadly vary from 0.02 to 0.09% [3, 16]. These data are in keeping with our rates of 0.05% for the entire cohort and 0.02% among the subset of injections administered with standard 5% PI prophylaxis. By contrast, data on post-IVI endophthalmitis rates administered with less or no prophylactic topical PI remains limited. Table 4 summarises the only three studies with published endophthalmitis rates in patients with self-reported iodine allergies or sensitivities. One of the studies did not provide the total number of injections administered without PIs, therefore not allowing for the

Table 2 Summary of endophthalmitis cases by antiseptic protocol.

	Total	Standard PI	Reduced PI	No PI
Endophthalmitis cases, *n* (%)	11 (0.05%)	4 (0.02%)	6 (0.78%)	1 (1.09%)
Mean age at presentation, years (±SD)	78.47 (±11.28)	76.25 (±7.04)	80.67 (±4.23)	69
Mean time to presentation, days (±SD, range)	5.18 (±3.43, 2–14)	3.75 (±0.05, 2–5)	4.67 (±0.47, 3–10)	14 (±1.46, 14)
Culture-positive cases, *n*	7	2	4	1
LogMAR visual acuity prior to endophthalmitis (±SD, LP)	0.54 (±0.32)	0.57 (±0.01, 0)	0.54 (±0.06, 0)	0.38 (±0.04, 0)
LogMAR visual acuity at diagnosis (±SD, LP)	2.06 (±0.38)	2.2 (±0.03, 0)	2.16 (±0.17, 1)	1 (±0.10, 0)
LogMAR visual acuity after treatment (±SD, LP)	0.87 (±0.67)	0.63 (±0.01, 1)	1.03 (±0.12, 0)	0.58 (±0.06, 0)
Overall reduction in LogMAR visual acuity (±SD, LP)	0.36 (±0.37, 1)	0.06 (1)	0.49 (0)	0.2 (0)
Vitrectomy performed, *n*	2	1	1	0

PI povidone-iodine, *SD* standard deviation, *LP* light perception.

calculation of the true incidence rate [17]. Results from a clinical trial with only a small number ($n = 13$) of IVIs given without PI place the incidence of endophthalmitis at 16% [13], while real-life data from 319 IVIs suggest a much lower rate of 0.31% [14]. This large variation in endophthalmitis incidence is not surprising considering the relatively small number of injections administered without PI in both studies and the lack of other published data. In our study, 92 IVIs were administered entirely without PI. One case of endophthalmitis occurred in this cohort, resulting in an incidence rate of 1.1%. While the incidence falls within the range reported [13, 14], the total number of injections was too small to allow further meaningful statistical analysis. When combining data for patients who opted for less and no prophylactic topical PI ($n = 861$), the incidence of post-injection endophthalmitis was 0.8% or 1 in 125 injections. This equates to a 40-fold increase compared to injections given with the standard PI protocol (odds ratio [OR] = 43.4; 95% CI 12.7–148.6; $p < 0.0001$).

The prevalence of self-reported PI sensitivity in our study was 2.4%. Notably, a significantly higher rate (15.9%) has been reported by Peden et al. [14]. Both studies are retrospective and relied on self-reported symptoms rather than an objective assessment of the cornea for signs of toxicity. In the absence of further data, the true prevalence of PI sensitivity remains unknown. Despite the lack of reliable prevalence figures, PI is well recognised as a cause of corneal irritation and toxicity [7, 11]. In vitro studies have shown a demonstrable effect of PI on the corneal epithelium, stroma and endothelium even at dilute concentrations [18, 19]. Clinically, this explains the symptoms of ocular pain, hyperaemia and epiphora that some patients experience following administration of topical PI [10]. Considering the impact of these symptoms on patients and their willingness to receive further topical 5% PI as antimicrobial prophylaxis, alternative antiseptic protocols and solutions have been evaluated with variable results [20–22]. Repeated application of more dilute PI (0.25–1%) has been shown to effectively lower bacterial load in the conjunctival fornices and anterior chamber in vitro, and reduce the incidence of endophthalmitis in vivo [20]. Similarly, Peden et al. suggest that PI at concentrations between 0.625 and 2.5% may be effective against post-IVI endophthalmitis with an incidence of 0.02% [14]. However, a clinical study randomising patients to either 1 or 5% PI found that a greater reduction in bacterial colonies with the higher PI concentration [23]. Our results suggest that a single-drop application of 5% PI three minutes before the IVI may not provide adequate antimicrobial prophylaxis compared to a protocol involving repeated application.

Also, even at concentrations as low as 1% repeated or prolonged application of PI can cause corneal irritation and dry eye symptoms [24]. Our data suggest that patients with self-reported sensitivity to PI received comparatively more IVIs which may have sensitised their corneas with time. Therefore, simply reducing the amount or concentration of preoperative PI may not be acceptable for patients with self-reported sensitivity to iodine.

While symptoms of PI-induced corneal irritation may be partially managed with prophylactic and therapeutic lubricants [5], substitute antiseptics have been explored. Chlorhexidine gluconate, in particular, has shown promise as an alternative agent to PI with comparable efficacy [21, 22]. Moderately strong evidence supports the use and efficacy of chlorhexidine-based solutions over those containing PI as antiseptic skin preparation to reduce surgical site infections [25, 26]. Alcohol-based chlorhexidine acts by disrupting microbial cell membranes and denaturing proteins with excellent efficacy against Gram-positive and Gram-negative organisms [27]. An alcohol-based solution is, however, not suitable for ophthalmic use due to the potential for significant ocular toxicity [22, 28–31]. Aqueous chlorhexidine also functions as a membrane disruptor. While less effective than alcohol-based chlorhexidine, the aqueous formulation still has good coverage against Gram-positive and Gram-negative

Table 3 Patient characteristics and clinical information of all exogenous endophthalmitis cases following intravitreal injections at Gloucestershire NHS Foundation Trust between January 1st, 2018, and June 26th, 2019.

Case	Age at diagnosis; Gender	Povidone-iodine protocol	Anti-VEGF agent	Number of previous injections	Time from last injection to presentation	Organism	VA before endophthalmitis	Final documented VA
1	79 years; Female	Standard PI	Ranibizumab	22	5 days	No growth	0.48 logMAR	0.5 logMAR
2	75 years; Female	Reduced PI	Aflibercept	21	3 days	*S. epidermidis*	0.36 logMAR	0.84 logMAR
3	80 years; Female	Reduced PI	Ranibizumab	25	4 days	No growth	0.06 logMAR	0.2 logMAR
4	87 years; Female	Reduced PI	Ranibizumab	8	5 days	*S. epidermidis*	0.4 logMAR	0.6 logMAR
5	78 years; Male	Reduced PI	Aflibercept	12	10 days	No growth	0.26 logMAR	0.26 logMAR
6	82 years; Female	Standard PI	Ranibizumab	24	4 days	*S. epidermidis*	0.6 logMAR	0.9 logMAR
7	84 years; Female	Reduced PI	Ranibizumab	12	3 days	Coagulase-negative staphylococcus	0.96 logMAR	CF
8	66 years; Male	Standard PI	Aflibercept	4	2 days	Coagulase-negative staphylococcus	0.4 logMAR	0.5 logMAR
9	69 years; Male	No PI	Aflibercept	28	14 days	Coagulase-negative staphylococcus	0.38 logMAR	0.58 logMAR
10	79 years; Female	Standard PI	Aflibercept	12	4 days	No culture taken	0.8 logMAR	PL
11	79 years; Male	Reduced PI	Ranibizumab	8	3 days	Coagulase-negative staphylococcus	1.2 logMAR	HM

PI povidone-iodine.

bacteria [27, 32]. Unlike alcohol-based chlorhexidine gluconate or PI, it does not readily cause corneal damage or irritation and is generally well tolerated by patients [21, 22]. However, cases of chlorhexidine keratitis [33, 34], as well as true allergy and anaphylaxis to chlorhexidine [35, 36], have been described in the literature. It also requires a longer time to exert its antimicrobial effect and has a narrower spectrum of activity than PI, potentially enhancing bacterial resistance patterns [22, 37–39]. While current national and international consensus guidelines on antiseptic prophylaxis advocate the use of 5% PI [4, 12, 16, 40], low concentration aqueous chlorhexidine is considered a potential alternative to PI-based solutions for ophthalmic procedures in patients with self-reported sensitivity to PI [21, 22]. An Australian multi-centre retrospective cohort study of 40,535 injections performed using solely aqueous chlorhexidine 0.05 and 0.1% reported an endophthalmitis incidence of 0.0074% [21]. However, several questions around the efficacy and safety of prophylactic chlorhexidine remain. As the authors highlight, the contact time for chlorhexidine is likely significantly longer than that of PI with the optimal contact time yet to be established. They also acknowledge the need to determine the most effective concentration of chlorhexidine [21]. In its patient information leaflet, Moorfields Eye Hospital notes a tenfold increase in post-injection endophthalmitis risk with the use of chlorhexidine compared to PI [41]. This information is based on unpublished clinical data from a 2-year review of endophthalmitis rates at Moorfields Eye Hospital which revealed an incidence of 1 in 5000 (0.018%) with PI use versus 1 in 350 (0.25%) with chlorhexidine [42]. However, other studies have demonstrated safe and effective use of aqueous chlorhexidine for ocular irrigation at concentrations of 0.05 and 0.1% [21, 22, 32]. Based on this evidence, the Royal College of Ophthalmologists advises in its guidance on IVIs that aqueous chlorhexidine 0.1% may be used in patients with PI sensitivity [40]. However, at present, a licensed aqueous chlorhexidine 0.05 or 0.1% solution for ocular irrigation does not exist in the UK. All commercially available formulations contain detergents or surfactants such as cocamidopropyl betaine (Medlock), octoxinol-8 (Pfizer) or glacial acetic acid (Baxter) which exhibit concentration-dependent corneal irritation or toxicity [21, 43–45]. Consequently, manufacturers of chlorhexidine gluconate and chlorhexidine acetate, including Pfizer and Baxter used by Merani et al. [21], caution against its use on the ocular surface [43, 45].

While our unit did not have access to aqueous chlorhexidine licensed for ocular use, the periorbital skin was carefully cleansed with detergent-containing chlorhexidine 0.05% in patients requesting no PI use. Discussion with a

Table 4 Summary of all published studies on endophthalmitis rate following intravitreal injection without topical PI administration.

Reference	Study design	Total number of injections	Injections without PI use (eyes)	Endophthalmitis rate	Endopthalmitis rate with PI use	Endophthalmitis rate without PI use
[13]	Retrospective multi-centre cohort study in clinical trial patients	28,786	13 (3)	0.031% (9/28 786)	0.024% (7/28 773)	16% (2/13)
[14]	Retrospective, single-centre cohort study	35,060	319	0.039% (14/35 060)	0.037% (13/34 741)	0.314% (1/319)
[17]	Retrospective, multi-centre case series	63,745	Unclear	0.019% (12/137,45)		Unable to calculate incidence rate; 5 cases in patients in patients receiving a total of 53 injections without PI

regional retinal group led to the consensus decision against the off-license use of detergent-containing chlorhexidine gluconate (Sterets Unisept, Medlock) on the ocular surface as it has been known to cause corneal toxicity and, therefore, can induce ocular discomfort and irritation similar to PI in these patients. Every patient with PI sensitivity was strongly encouraged to opt for the standard or, at a minimum, the reduced PI protocol. In cases where patients refused the use of PI, a clinical decision was made to administer an IVI. The increased risk of endophthalmitis was weighed against a potentially irreversible reduction in vision as a result of omitting intravitreal anti-VEGF. Authors of previous studies noted a similar clinical dilemma which led to them performing a limited number of IVIs without PI prophylaxis at patients' requests [13, 14, 17].

The lack of data on the efficacy of alternative antiseptic protocols and associated endophthalmitis rates means that it is difficult to provide patient-specific risk ratios when obtaining informed consent. This study was conceived to obtain a better understanding of these risks and improve the informed consent process for patients refusing PI prophylaxis. In other areas of clinical practice, large data collections via electronic medical records have enabled ophthalmologists to provide patients with reasonably accurate, individualised outcome predictions including the risk of complications for cataract surgery [46, 47]. Future work should focus on collecting similar data on patient characteristics, clinical factors as well as injection protocols to better analyse risk factors for the development of post-IVI endophthalmitis. This information can be utilised to risk-stratify patients and personalise the consenting process.

Limitations of this study include its retrospective single-centre design. Patient factors such as acute or chronic blepharitis were not recorded but may have a confounding effect on the risk of post-IVI endophthalmitis. Additionally, the reliance on patient-reported sensitivity to PI means that the true prevalence may have been higher. Patients may also have requested a reduced or no PI protocol during the injection without this having been documented in the medical records. Thus, caution should be taken when interpreting the results and applying them more broadly in different healthcare settings. Finally, endophthalmitis, fortunately, remains a rare complication of intravitreal therapy. The low incidence rate makes it difficult to identify and adjust for potential confounders without inadvertently over or underestimating their effects.

In conclusion, we present the largest UK study on post-IVI endophthalmitis rate in patients with reduced and no PI prophylaxis. Our data add to the emerging evidence that patients with self-reported iodine sensitivity are at significantly increased risk of endophthalmitis. Our results suggest that the incidence may be up to 40 times greater in patients who opt for a reduced PI protocol or no PI use. Further large, prospective studies are needed to optimise injection protocols for patients with PI sensitivity and provide more tailored risk profiles for the development of post-IVI endophthalmitis.

Summary

What was known before

- Topical 5% povidone-iodine (PI) is the gold standard antiseptic agent for the prevention of post-IVI endophthalmitis.
- PI-induced corneal irritation and toxicity are directly related to its concentration and length of administration, resulting in self-reported sensitivity to PI in a subset of patients receiving intravitreal injections.

What this study adds

- A reduced single-drop application of 5% PI or no PI use is associated with a significantly increased risk of post-IVI endophthalmitis (1 in 125 injections) compared to repeated 5% PI applications (1 in 5000 injections).
- Quantifying this risk can facilitate patient education and counselling, and enable a more informed, patient-specific consenting process to take place.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Consent and ethical approval This retrospective clinical study was registered with the Trust's audit department and ethical approval was not required.

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