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The argument for sterile loading of all intravitreal injections and the benefit of replicated results

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Recently two studies from different countries using different datasets reported remarkably similar findings with regards to risk of endophthalmitis after intravitreal injections of anti-vascular endothelial growth factor(anti-VEGF) agents. The first study, published in JAMA Ophthalmology by Baudin and colleagues was conducted using the French national medical-administrative database covering roughly 66 million people from 2012–2015.¹ They found that factory prepared syringes of ranibizumab decreased endophthalmitis compared to office prepared injections(ranibizumab IRR:1.40 & aflibercept IRR=1.46).¹ Less than a month later, we published a second study in the journal Retina using a similar sized U.S. insurance database covering the years 2005–2016, finding that using office-filled ranibizumab and aflibercept increased the odds of endophthalmitis(OR=1.29) compared to sterilely compounded bevacizumab.² Baudin *et al.* also found a similarly increased post-injection risk of endophthalmitis for women compared to men(IRR=1.28) as our paper did(OR=1.30).^{1,2}

The higher rates of endophthalmitis for office-loaded injections compared to pre-packaged agents offer the broadest and most significant policy implication.^{1,2} Pre-loaded syringes became a significant issue in the U.S. in 2015 when a couple of highly publicized epidemics of endophthalmitis were found to be related to poor compounding practices of bevacizumab. To address this, the US Food and Drug Administration proposed to institute “beyond-use-dates” on compounded medications that would have prevented proper sterility testing of the post-compounded product. This in effect would have essentially stopped the use of bevacizumab in the United States. Fortunately, after strong lobbying efforts by the American Academy of Ophthalmology and the American Society of Retina Specialists, this policy was

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never implemented. Part of the rationale used to fight this policy was the suggestion within concurrent reports that when done properly, compounding could actually decrease the rate of endophthalmitis.³ The thought was that by eliminating the in-office transferring of the medication, a potential source of contamination would also be removed and endophthalmitis rates would be reduced. Now that this principle has been demonstrated in not one, but two studies, we can confidently state that sterile-loading of syringes can substantially reduce post-injection endophthalmitis.

Taken together these studies offer a research standard too infrequently obtained, yet provided here: independent, outside replication. While not identical in study design or comparison groups, the ability for two unrelated groups to find similar results with different sets of data argues strongly for the validity of the findings. Moreover, the subtle differences between the studies also inform this discussion. Compounding and pharmaceutical pre-packaging are not identical processes, but both are performed in sterile conditions. Since the reported risk reductions were very similar, it is reasonable to infer that the reduction is not related to the medications themselves, but instead a property of the loading process.

Similarly, one of the drawbacks Baudin *et al.* admitted to within their study was their inability to account for changes in injection techniques over the course of their study. In 2014, an expert panel released an updated intravitreal injections best practices which included discontinuing pre- and post-injection antibiotics, stressing the importance of limiting aerosolized oral bacterial contamination and emphasizing the need for povidone iodine.⁴ As these recommendations have become more broadly utilized, the general consensus is that the overall rate of post-injection endophthalmitis is decreasing.⁵ This is relevant to their study due to the overlap of these trends with the availability of pre-packaged ranibizumab only in the later periods of the study. Fortunately, our study is able to address this issue. First, compounded bevacizumab was the used throughout the time course of our study, and second, we were able to use a much longer observation period 2005–2016. Using this extended window, we were able to show that the rate of post-injection endophthalmitis has as expected, significantly decreased with time. More importantly however, even after accounting for this temporal change, compounded bevacizumab still conferred a protective effect compared to office-loaded syringes.²

Baudin et al. and our studies also found a 29% and 30% increased risk of endophthalmitis in women, respectively.^{1,2} These represent the first reports linking gender to endophthalmitis rates. Interestingly, despite age, gender and race almost uniformly being controlled for in other ophthalmic assessments (even when no demonstrable link exists to do so), gender has often been over-looked with regards to endophthalmitis after intravitreal injections. At a minimum, these results suggest gender should be accounted for in all future studies of post-injection endophthalmitis. While the underlying pathophysiology responsible for this link is only speculative at this point, one possibility is that the higher incidence of dry eye in women may impair any known anti-infective properties of a normal, functioning tear film. If so, improving the peri-procedure tear film may lead to the next stage in lowering endophthalmitis rates.

While not specific to our recent study, Baudin *et al.* also provided confirmatory findings of increased endophthalmitis risk with steroid injections to a different study we previously published.⁶ Yet again, we see that despite replication, new insight was added since the dexamethasone implant comprised the vast majority of their steroid injections, compared to mostly triamcinolone in ours. More importantly, however, these results further demonstrate the need for careful consideration and discussion with patients the increased risk of endophthalmitis steroid injections pose. This is particularly true for macular edema combination therapy, which is a regimen increasingly being argued for, yet not necessarily with the full consideration the increased risks this mode of therapy confers. Laboratory work has already shown that presumably through immune-suppression, steroids reduce the bacterial load required to induce endophthalmitis.⁷ In addition to the increased risk of the steroid injection itself, the residual intraocular steroid may have implications for the risk of any follow up anti-VEGF injections.

Lastly, these studies generally underscore the unique contributions “Big Data” offer. The most “eye-catching” numbers within these studies are the huge amount of injections collected for analysis, however, statistically, the more important number is the amount of endophthalmitis cases. While these are the largest collection of post-injection endophthalmitis cases (444 for Baudin¹, 380 in our study²) to date, these in of themselves are not tremendously large numbers. Since the statistical power of a study is typically driven by the number of outcomes, it is not surprising that it took a study this size to find these results (and why they might not have been discovered sooner). Sample size is frequently the plight of studies assessing rare outcomes or complications, particularly when considering relatively small but clinically meaningful differences. A power calculation shows that for an 80% chance of finding a modest risk ratio of 1.4 when the outcome only occurs 1/4000 injections, a sample size of 400,000 is recommended for *each group*, much larger than any previously published study. Fortunately, both studies were able to collect enough injections and outcomes to offer these new insights.

In conclusion, endophthalmitis is a rare, yet frequently devastating complication of intravitreal injections. Two recent studies have provided several new interesting findings that further our understanding of the risk factors associated with post-injection endophthalmitis.^{1,2} While these findings are novel to many of us, it is possible Genentech suspected this issue would arise as they have already received FDA approval and distributed pre-packaged syringes for both their 0.5mg(October 2016) and 0.3mg(March, 2108) doses of ranibizumab. Together, these studies offer compelling evidence that a policy mandating the sterile packaging of all intravitreal injections needs to be strongly considered.

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