Original Article

Endophthamitis Post Intravitreal Injections

A Study on Incidence of Endophthamitis Post Intravitreal Injections in Southern Punjab Rural Population

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ABSTRACT

Objective: To evaluate the incidence of endophthalmitis post intravitreal injection in rural population of southern Punjab (Multan District) of anti-vascular endothelial growth factor.
Study Design: Observational / descriptive study
Place and Duration of Study: This study was conducted at Multan Medical and Dental College, Multan between January 2014and December 2015.
Materials and Methods: Addresses on National Identity Cards were used to enroll the patients who are residing out of multan municipal area. Patient's medical records were maintained to identify the incidence of endophthalmitis. Patients presenting with post operative endophthalmitis between January 2014 till December 2015 were included in the study. All IVIs were performed by single surgeon using standard sterile technique in operation theatre settings. None of the patients were prescribed with preoperative topical or systemic antibiotics. Postoperatively all patients had a QDS dose of topical ofloxacin.
Results: A total of 416 intravitreal injections were performedduring the study period. All patients had bevacizumab as intravitreal anti vascular growth factor (Anti-VEGF).Out of total patients there were two cases of endophthalmitis. This led to an incidence of 0.48%,(95% confidence interval: 0.0026-0.0220%). These two cases had intravitreal specimens which were later found to be culture negative.
Conclusion: The risk of post intravitreal Anti-VEGF in rural southern Punjab was found to be higher than quoted national and international standards though we had a small patient group which demands a similar study with larger sample size.

Key Words: Endophthalmitis, Intravitreal Injections, Bevacizumab.

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INTRODUCTION

There has been an increasing role of Intravitreal injections of Anti-VEGF in current ophthalmic practice.[1,2] It has become the main stay of treatment forwet age related macular degeneration and diabetic macular oedema. [2] Intravitreal injections are given in office as well as operating room settings. At some facilities there are dedicated rooms reserved as it has become a very frequent procedure in ophthalmic practices. Inernational protocols do not point toward a standard settings for the procedure. [3]

There has been no study published so far from our region which take into account the local socioeconomic factors, hygienic conditions and our rural practice leading to an increased incidence of devastating complication as endophthalmitis.

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Endophthalmitis is not the only complication ophthalmologists come across post intravitreal antibiotic injections. Other complications already documented in the literature include retinal detatchment, vitreous haemorrhage and iatrogenic lenticular trauma.[4] However the risk of mentioned complications is relatively low and if managed appropriately can lead to a satisfactory visual outcome.[4,5] Mentioned statement, though greatly differs for devastating complication as endophthalmitis. In contrast to other intraocular surgeries, intravitreal injections appears to be associated with more virulent organisms.[6]Streptococcal strains of organisms appears to be most frequently associated with post injection endophthalmitis. These patients tend to have worse visual outcomes as reported in literature.[7]

There has been multiple large trials published so far looking at the safetly of IVI and associated complications. The international documented incidence is relatively low as compared what has been found in our study. The risk of endophthalmitis in published trials range from 1 in 1500 to 1 in 5500 injections. [5,7,8]

Endophthalmitis as mentioned earlier is the most dreadful complication ophthalmologist comes across. [9]

There has been a lot of controversy regarding the best evidence based practice for intravitreal injections to minimize this risk. [9]In our country, taking into account

the resources, procedure is performed in operation theatres as well as in physician's offices. The use of sterile environment may reduce the incidence of endophthalmitis. It is equally important to conduct such study in our rural population as they comprise the largest group of patients and majority belong to a low income group. In order to test the above mentioned assumption a prospective clinical trial was conducted at Eye Unit, Multan Medical and Dental College. This study also looked at the role of pre and post injection topical antibiotics.

MATERIALS AND METHODS

A prospective study, including the rural population presenting to eye out door at Multan Medical and Dental College, Multan was carried out between January 2014 till December 2015. All patients included in the study had an informed consent of their recruitment prior to intravitreal injections. As this study specifically focused on the rural population which makes approximately 90% of the total out patients, their addresses were confirmed from national identity cards.

All patients had intravitreal bevacizumab as anti vascular endothelial growth factor. Entries were made in hospital register and cross checked prior to compilation of results. Hospital theatre register was used to identify patients presenting and being treated for endophthalmitis. Endophthalmitis was defined as patients presenting with intraocular inflammation and treated with intravitreal antibiotics post vitreous tap following intravitreal injections. Patients who had other intraocular procedures e.g. phacoemulsification, vitrectomy though very few, were excluded from the study. Patients presenting to outdoor clinics with endophthalmitis resulting from treatment elsewhere were also excluded from the study.

All patients had the standard dose of bevacizumab (1.25 mg/0.05 mL) provided by a single local supplier. Source of injections were certified compounding pharmacies based in Lahore. All injections were administered under the sterile conditions in operating theatre. Surgeon used mask, sterile gloves, theatre gowns and had surgical scrub prior to the procedure. Patients had topical anaesthetic drops (Alcaine manufactured by Alcon) preoperatively for local anaesthesia. Injections were administered using standard prefilled insulin syringes with 30 gauge needles on them. Prefilled syringes however, as provided by the local supplier were non sterile as is the common practice in our country. All patients had a thorough cleaning of periocular tissue and lids using 5-10% povidone iodine. Same drops were instilled in the eyes to be operated for two to three minutes in order to achieve the maximum possible sterility.Patients had a self-adhesive surgical drape covering periocular tissue, nose and part of face prior to the procedure. Patients had a sterile speculum inserted followed by the intravitreal injection. Injections were performed in the inferotemporal quadrant. Needle was inserted 3.5mm from the limbus for phakic and 3.5mm for pseudophakic and aphakic patients. Following the procedure, speculum was removed and patients had a single drop of ofloxacin eye drops combined with a single drop of povidone iodine solution. All patients had a sterile eye pad and were instructed to remove it 2-3 hours post procedure. No topical antibiotics were used preoperatively. All patients were prescribed with topical ofloxacin eye drops. Clear written instructions in native language were provided to them for the use of topical antibiotic drops to be used four times a day for five days in the operated eye, starting on the same day following eye pad removal. Data was thoroughly analyzed by the biostatistician using the Wilson score method.

RESULTS

A total of 416 intravitreal injections were given of anti-vascular endothelial growth factor. All patients (100%) had the standard dose of bevacizumab. There were two documented cases (0.48%) of endophthalmitis,(95% confidence interval: 0.0026-0.0220%). There were no comparative groups as standard protocols were followed for all the procedures and all patients had same drug. Two patients presenting with endophthalmitis had a vitreous tap followed by intravitreal injections, though they were found to be culture negative. Both patients had three ports parsplana vitrectomy afterwards but they ended up losing any functional vision due to severity of the complication.

Case 1 (HAD): A 67 year-old man with diagnosed diabetic macular oedema on clinical assessment and optical coherence tomography had intravitreal bevacizumab. Central macular thickness at the time of presentation was 458 microns. This was his third injection in the same eye. He presented a day later with severe pain and loss of vision in the same eye. On examination his visual acuity at timeof presentation had reduced to counting fingers from 6/36. There was anterior chamber hypopyon with hazy view of fundus. Patient had a vitreous tap with intravitreal injections of vancomycin 1.0mg and ceftazidime 0.4mg as per protocol. Vitreous culture failed to grow any organisms. Patient was prescribed a topical combination of tobramycin and dexamethasone, ofloxacin and oral prednisolone following intravitreal antibiotics. He had three ports parsplana vitrectomy with silicone oil 48 hours after initial presentation as there were no clinical signs of improvement. Unfortunately he ended up with a visual acuity of hand movements. He is still being followed up in the out patients.

Case 2 (ZB): A 58-year-old woman with diabetic macular oedema and proliferative diabetic retinopathy presented three days after receiving intravitreal bevacizumab injection. She had a history of poorly

controlled diabetes. Best corrected visual acuity had dropped to hand movements in this particular case. Clinical findings were consistent with acute endophthalmitis. She had the vitreous tap with intravitreal vancomycin and ceftazidime as per protocol. Cultures failed to grow any pathogen. Day after her vision improved to 6/60, which again declined to hand movements four days post intravitreal antibiotics. She had a three ports pars plana vitrectomy with resulting visual acuity of hand movements. She was lost to follow up afterwards.

DISCUSSION

This is a prospective study of 416 intravitreal injections and a very first of its kind to include the rural population of southern Punjab. This prospective analysis was performed to compare the incidence of most devastating complication i.e. endophthalmitis with what has been documented in international trials. It has confirmed the fact that incidence was found to be relatively higher in southern Punjab rural population despite of following standard accepted protocols for the administration of intravitreal antibiotics. Study did not had a comparative group due to its patient pool hence it is not possible to compare the difference between urban and rural population. Moreover no direct comparison was done between administration of injections in operating theatre or outdoor clinics.The higher incidence of endophthalmitis can be explained with the relatively smaller sample size.

One of the largest study published so far looking at the incidence of endophthalmitis post intravitreal injection was the meta analysis by McCannet et al.[6] This analysis included prospective as well as retrospective data. There were 52 reported cases of endophthalmitis post 105,536 injections administered in out patient clinics. The incidence rate was found to be 0.049% per injection (95% CI: 0.038-0.065%. This analysis excluded all the studies done outside of United States. Only studies with proven cases of endophthalmitis which had a vitreous tap were included. Comparing McCannet study with ours, we had a significantly higher incidence. Author will like to mention that it is difficult to provide any direct comparison of this study with any meta analysis performed in the western world. We have to take into account the rural southern Punjab population with their general health conditions, hygiene level, psychological considerations, poverty, literacy rate, socio-economic factors and spiritual/cultural values and beliefs. These factors can have a great influence on post-operative practices which may lead to a less than favorable outcomes and a higher incidence of post-operative complications. These factors are clear limitation when we compare our cohort with international meta analysis.

Another recent study published by Abell RG et al,[10] comparing incidence of endophthalmitis post intravitreal injections performed between operation theatre and outpatient rooms. A statistically higher incidence of endophthalmitis was noticed in procedures performed in out patient clinics. Although incidence quoted i.e. 0.12% (4 in 3,376 IVI) is significantly less than our study. Author again will like to highlight a cohort size almost ten times larger than what we had as the critical limiting factor. According to recommendation of this study procedure should be carried out in sterile operating room environment.

Author is of the view that systemic disease control is of vital importance in preventing post procedural complications. Both of our patients who developed endophthalmitis despite following strict procedural protocols had poorly controlled diabetes with raised HbA1C levels. Endophthalmitis though a rare but no doubted vision limiting condition can be prevented with improved systemic status, hygiene level and better understanding of prescribed post-operative medications.[11,12] Author also finds it interesting to conduct a similar study comparing outpatient and operating room incidence for endophthalmitis. By following international reported incidence the rate of endophthalmitis in clinic settings can presumably be significantly high. This however, is author's personal observation and can only be confirmed with a randomized, prospective study. A direct comparison between our study and incidence reported by Brencher et al and McCannel[3,6] will require a minimum of 5000 procedures. This will incur significant increase in the cost and human resources and is beyond author's institutional capacity.

Endophthalmitis results from direct inoculation of pathogen at the time of procedure or immediately afterwards. [11,12] Hypothetically this can be minimized by following international documented standards. This includes reducing the load of pathogen in conjunctival sac by using povodine iodine and giving it optimum time to work. [11,13] This also includes the use of sterile operating facility, sterile instruments, surgical drape, following standard technique for drug administration and use of post operative topical antibiotics. [6] Author find it very interesting to have a higher incidence despite of following all the standard, documented protocols. [13] Nevertheless, in our society there might be some other factors which play their role in final outcome and needs to be identified. Author supports the international recommended standards devised for this procedure. One important recommendation to be made from our results is use of preoperative topical antibiotic drops for atleast a period of three days. This hypothetically will play a significant role in achieving optimum sterility of conjunctival sac and hence will minimize the incidence of endophthalmitis. Author will also recommend for a prospective study comparing mentioned groups to prove his hypothesis. We have to take into account the fact that there are published

studies against the use of preoperative topical antibiotics. The main concern, being increased in the resistance against pathogens post antibiotic use.[14] Difference however as reported by Moss JM and Roger DL is not statistically different and hence no recommendations can be made on these bases.[12,15]

Taking into account other associated factors leading to endophthalmitis are respiratory droplets and needle contamination. Risk from respiratory droplets how ever, in this study is not considered to be significant. [16] Surgical masks was used by the surgeon during all procedure with sterile drapes being placed on patient minimizing this particular risk factor. Moreover, vitreous tap failed to grow any pathogen associated with airborne contamination.

Rate of needle contamination has been reported from 0.36% to 18%. [17,18] Author will like to point out the fact that in our study injections were transported in non sterile condition as this is the common practice in the country. Lack of local pharmacies, equipped to prepare the injection under sterile condition lead to a transport source 350 km north of the city. This incurs a significant time delay which can greatly effect the sterility of the product. Another important consideration is that bevacizumab syringes are recapped following preparation. This again is against internationally recommended standard for maintaining sterility and contamination free product.[19,20]This study's main limitation is it's sample size. Author will like to recommend further studies especially focused on country's rural population with larger sample size. Author will also like to recommend for a national metanalysis based on local published studies and audits.

CONCLUSION

In this study we have found a higher incidence of endophthalmitis in our rural population as compared to the standard internationally accepted figures. Author will like to register his reservation on our current national practices and recommends a robust change in order to reduce the incidence of endophthalmitis.Author will also like to recommend for a national metanalysis based on local published studies and audits.

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Elman MJ, Qin H, Aiello LP, et al; Diabetic Retinopathy Clinical Research Network. Intravitreal ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: three-year randomized trial results. Ophthalmol 2012;119:2312-2318.
2. Campochiaro PA, Brown DM, Awh CC, et al. Sustained benefits from ranibizumab for macular edema following central retinal vein occlusion: twelve month outcomes of a phase III study. Ophthalmol 2011;118:2041-2049.
3. Brechner RJ, Rosenfeld PJ, Babish JD, Caplan S. Pharmacotherapy for neovascular age-related macular degeneration: an analysis of the 100% 2008 medicare free-for-service part B claims file. Am J Ophthalmol 2011;151:887-895.
4. Michels S, Becker M, Wachtlin J, Binder S. The intravitreal injection: variations in regulations, cost and reimbursement in Europe, Spektrum der Augenheikude 2012;26:2-6.
5. Endophthalmitis Vitrectomy study Group. Results of the Endophthalmitis Vitrectomy Study. A randomized trial of immediate vitrectomy and of intravenous antibiotics for the treatment of postoperative bacterial endophthalmitis. Arch Ophthalmol 1995; 113:1479-1496.
6. McCannel CA. Meta-analysis of endophthalmitis after intravitreal injection of anti-vascular endothelial growth factor agents. Retina 2011; 31:654-661.
7. Rosenfeld PJ, Brown DM, Heier JS, et al. MARINA study Group. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006;355:1419-1431.
8. Brown DM, Kaiser PK, Michels M, et al. ANCHOR study Group. Anibizumab versus verteportin for neovascular age-related macular degeneration. N Engl J Med 2006;355:1432-1444.
9. Green-Simms AE, Ekdawi NS, Bakri SJ. Survey of intravitreal injection techniques among retinal specialists in the United States. Am J Ophthalmol 2011;151:329-332.
10. Abell RG, Kerr NM, Allen P, Vote BJ. Intravitreal injections: is there benefit for a theatre setting? Br J Ophthalmol 2012;96:1474-1478.
11. Safar A, Dellimore MC. The effect of povidone iodine flush versus drops on conjunctival colonization before intravitreal injections. Int Ophthalmol 2007;27:307-312.
12. Moss JM, Sanislo SR. Ta CN. A prospective randomized evaluation of topical gatifloxacin on conjunctival flora in patients undergoin intravitreal injections. Ophthalmol 2009;116:1498-1501.
13. Alabiad CR, Miller D, SehiffmanjC, Davis JL. Antimicrobial resistance profiles of ocular and nasal flora in patientsundergoind intravitreal injections. Am J Ophthalmol 2011;152:999-1004.
14. Kim SJ, Toma HS. Antimicrobial resistance and ophthalmic anitbiotics: 1-year results of a longitudinal controlled study of patients

undergoing intravitreal injections. Arch Ophthalmol 2011;129:1180-1188.

15. Rogers DL, Chheda l, Ford C, et al. the effect of surgical preparation technique on the bacterial load of surgical needles and suture material used during strabismus surgery. J AAPOS 2011;15:230-233.
16. de Caro JJ, Ta CN, Ho HK, et al. Bacterial contamination of ocular surface and needles in patients undergoing intravitreal injections. Retina 2008;28:877-883.
17. Nentwich m, Yactayo-Miranda Y, Weimann S, et al. Bacterial contamination of needle points after intravitreal injection. Eur J Ophthalmol 2009;19: 268-271.
18. Stewart JM, Srivastava SK, Fung AE, et al. Bacterial contamination of needles used for intravitreal injections; a prospective, multicenter study. OculImmunol Inflamm 2011;19:32-38.
19. Speaker MG, Milch FA, Shah MK, Eisner W, Kreiswirth BN. Role of external bacterial flora in the pathogenesis of acute postoperative endophthalmitis. Ophthalmol 1991;98(5)639–650.
20. Nentwich M, Ta CN, Kreutzer TC, et al. Incidence of postoperative endophthalmitis from 1990 to 2009 using povidone-iodine but no intracameral antibiotics at a single academic institution. J Cataract Refractive Surg 2015;41(1)58–66.