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Study to find the indications and adverse reactions in patients receiving intravitreal injections at ophthalmology unit, RVM hospital, Telangana state, India

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Abstract
Introduction: Intravitreal injection of air was first used by Ohm in 1911 for repairing retinal detachments. Intravitreal pharmacotherapy is likely to increase as more and more agents are being developed and tested for a variety of retinal diseases.
Methodology: A hospital based prospective randomised interventional study conducted on patients attending ophthalmology department of RVM Hospital from May 2019 to March 2020, where intravitreal injections of Triamcinolone acetonide (4mg/0.1 ml), Bevacizumab (1.25mg/0.05ml), Ranibizumab (0.5mg/0.05ml), Ganciclovir (2mg/0.1ml) were injected for various vitreoretinal diseases.
Results: The common age group was 46-60 years in this study and the age group of 16-30 were limited in this study. Age-related macular degeneration (AMD) was 148, retinal vein occlusion (RVO) 169, Proliferative Diabetic Retinopathy (PDR) 114 were main indications for intravitreal injection therapy and the least being Coats disease 3, and idiopathic polypoidal choroidal vasculopathy (IPCV) 3. Bevacizumab is the drug which was used excessively in this study as intravitreal injection (57.45%) followed by Ranibizumab (19.66%) and the least being Ganciclovir (10.33%).
Conclusion: Intravitreal injection is a safe and efficient technique. The risk of serious vision threatening complications is very low.

Keywords: Intravitreal, injections, Triamcinolone acetonide Bevacizumab, Ranibizumab, Ganciclovir

Introduction

Intravitreal injection of air was first used by Ohm in 1911 for repairing retinal detachments [1]. For many decades, air/gas and antibiotics were the only agents injected intravitreally. In the last decade, there has been an explosion in the intravitreal pharmacotherapy. Between 1997 and 2000, fewer than 5000 intravitreal injections were performed annually. Thereafter, the annual number of intravitreal injections more than doubled every year through 2006, reaching a high of 812,413 in 2007 [2].

Intravitreal pharmacotherapy is likely to increase as more and more agents are being developed and tested for a variety of retinal diseases. The primary benefit of IVI is that the therapeutic agent is targeted in the eye while minimising systemic absorption. Intravitreal injections have revolutionised the treatment of retinal diseases like diabetic retinopathy [3], neovascular age-related macular degeneration (wet ARMD) [4], retinal vein occlusions (RVOs) [5], neovascular glaucoma [6], retinopathy of prematurity (ROP) [7] and intraocular tumors [8].

Aim & Objectives: To know the different indications and early postoperative complications that can arise after intravitreal injections. Objective is to determine the incidence and outcome of complications associated with the administration of intravitreal injections.

Methodology: A hospital based prospective randomised interventional study conducted on patients attending ophthalmology department of RVM Hospital from May 2019 to March 2020, where intravitreal injections of Triamcinolone acetonide (4mg/0.1 ml), Bevacizumab (1.25mg/0.05ml), Ranibizumab (0.5mg/0.05ml), Ganciclovir (2mg/0.1ml) were injected for various vitreoretinal diseases.

Inclusion Criteria: All patients receiving intravitreal injections of Triamcinolone Acetonide, Bevacizumab, Ranibizumab, antivirals.

Exclusion Criteria: Patients receiving intravitreal antibiotics for endophthalmitis were excluded from this study.

The present study included 590 patients that received intravitreal injections for various vitreoretinal diseases. The patients were followed up on 1st post injection day and at the end of 1 week. Complications related to the procedure and the drugs were noted.

The data was collected based on the study observations and spread over excel sheet and the analysis was done using SPSS 21.0 version.

Informed and written consent was obtained from the study participants prior to the study and institutional ethics committee permission was obtained from RVM Institutional ethics committee.

Results

Table 1: Distribution of study population based on age

Age group	Male	Female	N=590
16-30	28	20	48
31-45	64	52	116
46-60	104	124	228
61-75	96	102	198

The common age group was 46-60 years in this study and the age group of 16-30 were limited in this study

Table 2: Gender wise distribution among the study population

Gender	Number of individuals (%)
Male	292(49.49%)
Female	298(50.50%)
Total	590 (100%)

Female preponderance was observed in this study with 298(50.50%) when compared to males 292 (49.49%).

Table 3: Different indications observed among the study population

Indications	Male	Female	N=590
AMD	56	92	148
RVO	90	79	169
PDR	60	54	114
VH	25	16	41
CMV Retinitis	32	26	58
CME	18	28	46
Coat's disease	3	0	3
Vasculitis	3	1	4
CSR	3	1	4
IPCV	2	1	3
Total	292	298	590

Age-related macular degeneration (AMD) was 148, retinal vein occlusion (RVO) 169, Proliferative Diabetic Retinopathy (PDR) 114 were main indications for intravitreal injection therapy and the least being Coats disease 3, and idiopathic polypoidal choroidal vasculopathy (IPCV) 3.

Table 4: Injections wise distribution among the study population

Injections (Drugs)	No. Of Patients (%)
Bevacizumab	339(57.45%)
Ranibizumab	116(19.66%)
Triamcinolone acetonide	74(12.54%)
Ganciclovir	61(10.33%)
Total	590(100%)

Bevacizumab is the drug which was used excessively in this study as intravitreal injection (57.45%) followed by Ranibizumab (19.66%) and the least being Ganciclovir (10.33%).

Table 5: Distribution rate of immediate complications (1 week) following the intravitreal therapy

Adverse Reactions	No. of Patients	Rate (%)
SCH	184	31.18%
Ocular hypertony (>21 mmHg)	29	4.91%
Anterior uveitis	7	1.18%
Non-infective endophthalmitis	3	0.50%
Infectious endophthalmitis	1	0.16%
Total	224	37.96%

The adverse reactions which are reported in this study were SCH (Sub-conjunctival haemorrhage) which accounts to 31.18% and the least possible reaction was Infectious endopthalmitis 0.16%.

Table 6: Injection wise complication distribution among the study population

	Injections				Total (224)
Compli Cations	Bevacizumab (AVASTIN)	Ranibizumab (LUCENTIS)	Triamcinolone Acetonide (IVTA)	Ganciclovir	
SCH	88(47.8%)	38(20.6%)	52(28.2%)	6(3.2%)	184(100%)
Ocular hypertony	5(17.2%)	1(3.4%)	23(79.3%)	0	29(100%)
Anterior uveitis	5(71.4%)	2(28.5%)	0	0	7(100%)
Non- infective endophthalmitis	1(33.3%)	1(33.3%)	1(33.3%)	0	3(100%)
Infectious endophthalmitis	1(100%)	0	0	0	1(100%)
Total	100(44.6%)	42(18.7%)	76(33.9%)	6(2.6%)	224(100%)

The immediate complications were among 224 individuals and among them the observed complications are high with Bevacizumab which was comparatively more than other three drugs which is 100 (44.6%) and the least observed complications was with Ganciclovir (2.6%)

Discussion

Most of our patients reported pain and foreign body sensation on 1st post injection day which was relieved with topical and systemic NSAIDs. Few patients complained of floaters in the injected eye on the 1st day that relieved within 1-2 days. This could be due to the inadvertent injection of air bubble while injecting the drug. Drug loss due to vitreous reflux leading to conjunctival bleb formation was observed in straight injection technique. Sub-conjunctival haemorrhage is the most common complication (31.18%) observed in this study. It is a minor complication and was mild in most of the cases. In a similar study conducted by Jamrozy Witkowska *et al.* [9], the incidence of subconjunctival haemorrhage was 36% (of 943 eyes) which is near similar to the present study.

Ocular hypertony (>21mmHg) was the 2nd most common complication which was observed in 29 eyes (4.91%). Of these. 23 cases (79.3% of ocular hypertony) resulted after IVTA, in 5 cases after Avastin (17.2% of ocular hypertony) and in 1 case after intravitreal LUCENTIS (3.4% of ocular hypertony). In a study conducted by Angulo Bocco MC *et al.* [10], ocular hypertony was encountered in 7.69% of 2028 injections which is a bit more than the present study, this may be due to more number of cases are studied and reported.

Anterior uveitis was an uncommon complication noticed in our study accounted for 1.18% of the total 7 eyes) all resulted after anti-VEGFs. (avastin-5 eyes and lucentis 2 eyes) Patients presented with congestion of the eye and anterior chamber reaction with blurred vision on the 1st day after injection. All the patients were put on topical steroid drops and cycloplegics and were followed up. AC reaction decreased and eyes were quiet at 1 week with improved visual acuity to pre-injection levels. This observation is near similar to the study conducted by Jamrozy- WItkowska *et al*. [9] where 16 cases (1.7%) of which anti-VEGFs accounted for 81%. In our study, out of 339 bevacizumab injections 5 cases (1.18%) resulted in anterior uveitis which is similar to Mozayan A *et al.* [11] study. On-infective endophthalmitis was observed in 3 cases (0.50%-3/590) following avastin (0.15% - 1/590), lucentis (0.15% - 1/590), IVTA (0.15% - 1/590).Two patients improved with topical corticosteroids and cycloplegics in a week's time. In a study conducted by Davin Johnson BSc *et al.* [12], the incidence of acute intraocular inflammation reported was 1.3% of 693 bevacizumab injections with mean loss of vision 6.1 lines which is near similar when compared to the present study. Joaquin Marticorena *et al.* [13] have reported the incidence of sterile endophthalmitis to be between 0.09-1.1% of intravitreal bevacizumab which falls in the same range as our present study**.** Infective endophthamitis is seen in 1(100%) among the 590 cases with IVTA. In Jamrozy-Witkowska A *et al.* [9] study, the incidence of culture proven endophthalmitis reported was 0.1% (1/943) that occurred after IVTA which is similar to the incidence reported in the current study. The culture revealed Staphylococcus epidermidis. Jonas JB *et al.* [14] study reported 0.04 +/- 0.03% incidence of infectious endophthalmitis after intravitreal bevacizumab (2/5403). Angulo Bocco MC *et al.* [10] reported infectious endophthalmitis in two cases of IVTA with an incidence of 0.1%. These results are comparable to the results of the present study.

Conclusion

Intravitreal injection is a safe and efficient technique. The risk of serious vision threatening complications is very low. This is encouraging, as the frequency of intravitreal injections for treatment of numerous retinal pathologies is likely to continue to rise in the coming years of anti-VEGF era. Though the complication rate is low, all the patients receiving the intravitreal injections should be explained about the possible risks of these injections. Improvements should be achieved to find the optimal angle and location of incision as well as better needles and syringes.

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