Impact of Coronavirus Disease 2019 on Intravitreal Antivascular Endothelial Growth Factor Injection Rates in Nigerians

Abstract

Aim: To quantify the impact of coronavirus disease 2019 (COVID-19) on the rate of intravitreal antivascular endothelial growth factor (VEGF) injections (IVI) in eye hospitals in Nigeria. **Materials and Methods:** A retrospective, observational, comparative study. The IVIs given 12 months before (pre-COVID) and 12 months after the first announcement of the COVID-19 lockdown (COVID) in Nigeria in four hospitals were used as the sample for this study. All eyes were treatment naïve. We determined the total number of all anti-VEGF injections, the number given for each indication, and the number of each type of the three anti-VEGFs given. A comparison of the presenting vision in IVI eyes between the two eras and the visual outcome of the IVI treatment was made. Data were analyzed using the SPSS version 22 to determine statistical significance. **Results:** Male/female ratio, pre-COVID 63.4%/36.6% and COVID 58.6%/41.4% (P = 0.123). Age, pre-COVID 61.3 (SD 12.9) 9–95 years and COVID 57.5 (SD 16.4) 0.15–95 years. There was a 15.3% (81 eyes) reduction in the number of eyes between pre-COVID and COVID eras (528 and 447 eyes, respectively). Likewise, the number of IVIs reduced by 26% (221 IVIs) from 850 pre-COVID to 629 COVID, P = 0.005. A comparison of the proportion of eyes in the four clinic locations between the two eras was not statistically significant (P = 0.148). The commonest indication was proliferative diabetic retinopathy in both eras, 208 versus 178 eyes (323 versus 226 IVIs). Bevacizumab, Ranibizumab, and Aflibercept were given in the following proportions 60.2%, 22.3%, and 17.4% (pre-COVID) versus 60.2%, 31.5%, and 8.3% (COVID), P = 0.000. Presenting visual acuity was >6/60 in 67.4% of eyes (pre-COVID) versus 59.4% of eyes (COVID), P = 0.039. Vision improved in 51.3% of eyes (pre-COVID) versus 47.7% (COVID); there was no significant difference in visual outcome comparing both eras, P = 0.972. **Conclusion:** COVID-19 significantly reduced the number of eyes and IVIs. Eyes had worse presenting visual acuity during the COVID era; however, treatment outcome was comparable between COVID and pre-COVID eras.

Keywords: *Age-related macular degeneration, antivascular endothelial growth factors, COVID-19, intravitreal injections, retinovascular diseases*

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic is a SAR-CoV-2 respiratory infection that spread throughout the regions of the world and resulted in death, hospitalization, and other morbidities. Several measures were instituted by responsible health authorities and organizations worldwide to limit the rapid spread of this viral infection. Hand sanitization, social distancing, and travel bans were some of the measures. However, the strictest of the measures was the "lockdown" of communities, states, and nations. The imposition of the lockdown and travel bans had several direct and indirect effects on the social, economic, and health indices of the communities. The impact of the COVID-19 pandemic has been assessed in several health and socioeconomic indices, including in medical education, vaccination, mental health, and scientific research but to mention a few.

Retinovascular and macular diseases are a frequently encountered cause of vision loss in Nigeria, Africa, and worldwide. Intravitreal antivascular endothelial growth factor (VEGF) injections (IVI) are a first-line treatment option for several retinovascular and macular diseases such as diabetic macular edema (DME), retinal vein occlusion (RVO), and neovascular age-related macular degeneration (nAMD). IVIs are also used in the treatment of polypoidal

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choroidal vasculopathy (PCV), proliferative sickle cell retinopathy (PSCR), proliferative diabetic retinopathy (PDR), and other nonretinovascular diseases. Multidosing of the IVI is required and should be administered monthly when treatment is initiated. Up to three monthly loading doses of IVI are prescribed to treat common retinal diseases. Yang *et al.*[1] investigated the impact of COVID-19 on anti-VEGF injections in China. They reported a 70% decrease in injections and that COVID-related differences in treatment posed a risk of negative impact on IVI treatment visual outcome. Naravane *et al*. similarly reported that IVIs treatment delays had a negative impact on the visual and anatomic outcomes of patients with nAMD and DME.[2]

Therefore, we sought to determine and quantify the impact of COVID-19 restriction and its related effects on IVI use in eye clinics in Nigeria.

Materials and Methods

We performed a retrospective comparative noncontrolled case series using the IVIs given and eyes treated 12 months before (pre-COVID era) and 12 months after the first announcement of the COVID-19 lockdown (COVID era) in Nigeria (lockdown began on March 30, 2020). Consecutive patients attending four eye hospitals in Nigeria were used as the sample for this study. These four eye hospitals were branches of the same hospital group and were in different areas of Nigeria. Two hospitals were in urban areas, and one in semiurban and rural locations. Data were extracted from the patient's case records. We determined the total number of all IVIs, the number of IVIs given for each indication, and the number of each type of the three anti-VEGFs (Bevacizumab-Avastin, Ranibizumab-Lucentis, and Aflibercept-Eylea) administered in the four eye hospitals. Also, we compared the vision at the first presentation and the visual outcome of the IVI treatment between the two eras. To do this, we determined each eye's Snellen visual acuity pretreatment (vision before commencing anti-VEGF treatment) and posttreatment (vision after the last visit). From this, we determined the Snellen line change in visual acuity for each eye treated in the two eras. Change in visual acuity was then categorized as "worse" if pretreatment vision was better than posttreatment, "same" if the posttreatment vision remained the same as pretreatment, and "better" if the posttreatment vision was superior to the pretreatment vision. All study eyes were treated naïve before IVI was commenced.

Ethical approval for this study was sought from the Eye Foundation Hospital Health Research Ethics Committee. A waiver was given since this was a retrospective study and only involved a review of case records. The study was conducted according to the principles of the Declaration of Helsinki.

Data management

Data were analyzed using IBM SPSS version 22.0 (IBM Corp. Armonk, NY, USA). Data were entered into a Google spreadsheet and transferred to SPSS for analysis. Frequencies and percentages were used to summarize categorical variables. Cross-tabulations of variables against study outcomes (injection time and visual outcome) were done. Pearson Chi-square was used to determine the association between study variables. Mann–Whitney *U* test measured the difference between nonparametric variables, and a P value < 0.05 was deemed statistically significant.

Results

The age of study participants was pre-COVID 61.3 (SD 12.9) 9–95 years and COVID 57.5 (SD 16.4) 0.15–95 years. A total of 975 eyes of 788 patients were studied in the two eras (pre-COVID 528 eyes and COVID 447 eyes) [Table 1]. There were 343 right eyes, 258 left eyes, and 374 both eyes. The bilateral cases were counted as right eye and left eye for the purpose of data analysis. The total number of IVIs given during the two eras was 1479, pre-COVID 850 and COVID 629. Details of the number of eyes and the mean number of injections are presented in Table 2.

The indications for the IVIs are categorized in Tables 1 and 2. Proliferative diabetic retinopathy was the most common indication in both pre-COVID and COVID eras, 208 (39.4%) and 178 (39.8%), respectively. There was a statistically significant reduction in the number of eyes that received IVIs by 15.3% (81 eyes) from the pre-COVID to COVID eras $P = 0.001$ (Pearson Chi-Square test) [Table 1]. Similarly, the number of IV anti-VEGF injections given was reduced by 26% (221 IVIs) from 850 pre-COVID to 629 COVID, $P = 0.005$ (Mann–Whitney test) [Table 2].

The proportion of male and female patients was similar between the two eras, $P = 0.123$ (Pearson Chi-Square test) [Table 3].

In most indications, the number of IVI eyes reduced from pre-COVID to COVID, including AMD, CRVO, DME, PDR, PCV, RG, PSCR, DME, and Uveitis. However, the number of eyes increased during COVID in CNVM, BRVO, HRVO, and ROP.

The proportion of eyes that received IVI was not affected by socioeconomic status ($P = 0.148$) (Pearson Chi-Square test), indicated by the clinic's location in urban or rural communities [Table 4]. On the converse, COVID had a significant impact on anti-VEGF injection type given ($P = 0.000$) (Pearson Chi-Square test) between the two eras, "demonstrated by the higher proportion of Lucentis and lower proportion of Eylea administered during the COVID era compared to the Pre-COVID era [Table 5]." Table 5 illustrates the significant difference in the type of anti VEGF injection used between the pre-COVID and COVID eras.

Analysis of the impact of COVID-19 on vision; presenting vision was significantly worse during the COVID era, with a higher rate of vision <6/60 at presentation in 40.6% of

Table 1: Indications for intravitreal antivascular endothelial growth factor injection

Diagnosis	Pre COVID		COVID		*P* value
	N	Eyes (%)	*N*	Eyes (%)	
AMD	31	5.9	25	5.6	0.001
CNVM	18	3.4	19	4.3	
BRVO	41	7.8	46	10.3	
CRVO	42	8.0	30	6.7	
HRVO	5	0.9	6	1.3	
DME	36	6.8	26	5.8	
PDR	208	39.4	178	39.8	
PCV	31	5.9	27	6.0	
RG	40	7.6	36	8.1	
PSCR	21	4.0	11	2.5	
Pterygium	7	1.3	8	1.8	
ROP	0	0.0	15	3.4	
PME	31	5.9	6	1.3	
ERM	4	0.8	3	0.7	
Uveitis	2	0.4	0	0.0	
Others	11	2.1	11	2.5	
Total	528	100	447	100	

AMD: age-related macular degeneration, CNVM: choroidal neovascular membrane, BRVO: branch retinal vein occlusion, CRVO: central retinal vein occlusion, HRVO: hemi retinal vein occlusion, DME: diabetic macular edema, PDR: proliferative diabetic retinopathy, PCV: polypoidal choroidal vasculopathy, PSCR: proliferative sickle cell retinopathy, ROP: retinopathy of prematurity, PME: pseudophakic macular edema, ERM: epiretinal membrane, RG: rubeotic glaucoma

Table 2: Indications, mean, and the total number of anti-VEGF injections for the pre-COVID and COVID eras

Indication	Pre-COVID			COVID		
	Mean no of injs.	Total no of Injs. (*N*)	%	Mean no of injs.	Total no of injs. (*N*)	%
AMD	1.64	51	6	1.88	47	8
CNVM	1.72	31	4	1.68	32	5
BRVO	1.73	71	8	1.78	72	11
CRVO	1.60	67	7	1.67	50	8
HRVO	1.80	9	1	1.33	8	1
DME	1.97	71	8	1.61	42	7
PDR	1.60	323	38	1.26	226	36
PCV	1.51	47	6	1.48	40	7
RUBEOTIC GLAUCOMA	1.57	66	7	1.25	45	7
PSCR	1.52	32	4	1.27	14	2
PTERYGIUM	1	7	1	1	8	1
ROP	0	0	0	1	15	2
PME	1.74	54	6	1.67	10	2
ERM	1	4	1	1.67	5	1
UVEITIS	1.5	3	1	0	0	0
OTHERS	1.27	14	2	1.36	15	2
TOTAL		850			629	

AMD: age-related macular degeneration, CNVM: choroidal neovascular membrane, BRVO: branch retinal vein occlusion, CRVO: central retinal vein occlusion, HRVO: hemi retinal vein occlusion, DME: diabetic macular edema, PDR: proliferative diabetic retinopathy, PCV: polypoidal choroidal vasculopathy, PSCR: proliferative sickle cell retinopathy, ROP: retinopathy of prematurity, PME: pseudophakic macular edema, ERM: epiretinal membrane

COVID eyes versus 32.6% of pre-COVID eyes ($P = 0.039$) (Pearson Chi-Square test) [Table 6]. Despite this, the visual outcome of treatment was not significantly different between the two eras; demonstrated by the proportion of improved/ worse vision, which was 51.3%/18.4% (pre-COVID) and 47.7%/17.2% (COVID) $P = 0.972$.

Discussion

We sort to quantify the impact of COVID-19-related restrictions and its other effects on the number of eyes that received IVIs and the number of IVIs given. We observed a 15.3% reduction in the number of eyes from the pre-COVID

Table 3: Gender distribution Pre-COVID and COVID era

	Male	Female	Total	*P* value
Pre-COVID	335	193	528	0.123
	63.4%	36.6%	100.0%	
COVID	262	185	447	
	58.6%	41.4%	100.0%	
Total	597	378	975	
	61.2%	38.8%	100.0%	

Table 4: Distribution of eyes based on clinic location

	Urban 1		Urban 2		Semi urban		Rural		Total	%	*P* value
	N	%	*N*	%	*N*	%	*N*	%			
Pre-COVID	345	65.3	159	30.1	17	3.2	7	1.3	528	100	0.148
COVID	320	71.6	113	25.3	8	1.8	6	1.3	447	100	

Table 5: Distribution of intravitreal injection type

	Avastin	Lucentis	Eylea	Total	*P* value
Pre-COVID	318	118	92	528	0.000
	60.2%	22.3%	17.4%	100%	
COVID	269	141	37	447	
	60.2%	31.5%	8.3%	100%	
Total (Eyes)	587	259	129	975	
	60.2%	26.6%	13.2%	100%	

Table 6: Presenting Snellen's visual acuity during pre-COVID and COVID eras

Snellen acuity	Pre-COVID		COVID		*P* value
	N	Eyes (%)	*N*	Eyes (%)	
6/6	13	2.5	12	2.8	0.039
6/9	48	9.1	33	7.7	
6/12	41	7.8	28	6.5	
6/18	68	12.9	56	13.0	
6/24	60	11.4	30	7.0	
6/36	55	10.4	58	13.5	
6/60	71	13.5	39	9.0	
CF	92	17.5	87	20.2	
HM	43	8.2	50	11.6	
PL	22	4.2	17	3.9	
NoPL	14	2.7	21	4.9	
	527		431		

CF: counting fingers, HM: hand motion, PL: perception of light, No PL: no perception of light

to the COVID era and a 26% reduction in anti-VEGF injections over the same period.

A pandemic is extremely rare, and the COVID-19 pandemic took the world unawares and ill-prepared. COVID-19 has considerably impacted several indices of our human living and well-being, and the world is yet to recover from its effects. COVID has affected socioeconomic systems, healthcare delivery, and public health indices (including the rate of vaccinations) and also has political implications.[3,4] One of the significant effects of COVID-19 is on health care and the delivery of care to needy patients.[4] It has been suggested that COVID-19 could have a significant negative impact on the rate of vaccinations in countries with poorly developed health systems, resulting in a decrease in the rate of vaccinations and an increase in the occurrence of vaccine-preventable diseases.[3]

The intravitreal anti-VEGF injection is a first-line therapy in the care of several retinovascular and macular diseases. Anti-VEGF injections are also used in the treatment of non-retinovascular diseases. Because this form of therapy often requires frequent dosing, in several cases monthly or bimonthly injections, patients require frequent multiple clinic visits to receive these injections. COVID-19-related restrictions hindered access to eye clinics since, in several countries, provision was not made to cater to those receiving these injections. Also, health systems were strained and, in some instances, overwhelmed, having to deal with the emergency fostered on them by COVID. Because of these and other reasons, several patients receiving anti-VEGF injections could not receive scheduled injections. Postponements and long delays were experienced to receive IVIs.[5,6] There needs to be more information on the impact of COVID-19 on anti-VEGF injections, as experienced in a lower middle-income country with infrastructure deficits and poorly developed health systems.

Our findings of a reduction in the number of eyes receiving IVIs agree with the findings of Wasser *et al.*[7], who also reported a decrease of up to 50% in eyes. Their finding far exceeds our finding of 15.3%. Wasser's higher numbers can be explained by the fact that their study sampled eyes within 4 weeks only during the earlier season of the COVID outbreak when there was more anxiety over COVID and extreme patients' reluctance to attend hospitals. By this time, the effect of the lockdown was more severe. Therefore, COVID's impact at this time was more acutely felt and severe. In another study, Mirghorbani *et al.*[8] reported a 37.6% decrease in the number of patients receiving IVI in COVID period. Sindal *et al.*[9] reported delays in IVIs in their series on the profile of patients, with their commonest indication for IVI being DME in 53.5% of eyes. PDR was the commonest indication in 38% of eyes in our study. Our findings also agree with Sindal's finding of poor presenting vision in treatment naïve eyes. We found that treatment naïve eyes during the COVID era had significantly poorer vision than pre-COVID. This finding can be explained by the delay in clinic access occasioned by COVID restrictions and the slower recovery of clinic attendance. For fear of contracting COVID from hospitals, several patients preferred to stay away from hospitals (including eye hospitals) even after the COVID lockdown was lifted.[10] Another explanation could be the poor financial position of many patients and their families because of the economic decline which trailed COVID. Therefore, several patients who must pay out of pocket could not afford the cost of care.

Though the presenting visual acuity of COVID-era eyes was inferior to that of pre-COVID eyes, it is gratifying to note that the outcome of treatment for COVID eyes was comparable to pre-COVID during the 1-year analysis. This agrees with reports of the final vision of COVID-era eyes being comparable with real-life outcomes reported by Agorogiannis *et al.*,[11] who studied the impact of COVID-19 on patients with CNV treated with IVI. The outcome illustrates the effectiveness of anti-VEGF injections and the ability to improve vision despite delays in initiating therapy. Hurand *et al.*[12] have shown that adherence to IVI guidelines during the pandemic is associated with better vision compared to nonadherence. Therefore, in case of future pandemics, other waves of COVID or similar emergency restrictive situations, the goal must remain to improve compliance and adherence to treatment protocols since delays in timely retinal care result in a supposed short-term negative outcome.[13] This will require legislature by healthcare policy makers, granting waivers and pass to allow patients on IVI access to the hospital during such emergency situations.

Variation has been reported in the vulnerability of various retinovascular diseases to delays in IVIs. Contrary to other reports, Bulut reported that a 6-month delay in treating DME eyes did not negatively affect the vision but recommends no delay in the IVI treatment for RVO and wet AMD.[14] In another report by Douglas *et al.*,[15] who examined the short and long-term effects of delay in IVI, DR, and CRVO eyes were more vulnerable in the short term, whereas, in the long-term, CRVO patients, followed by the wet AMD patients had the least recovery of vision. BRVO patients were found to be less affected by a delay in IVI treatment. This disease-based variability may have affected the outcome in our cases. We did not investigate the extent or degree of COVID delay in general or on individual diseases. But our 1-year post-COVID assessment can be described as long-term. Our study duration gives room for recovery of vision during the COVID era and may also explain the improved vision observed. Furthermore, in our study, the mean number of IVI for BRVO, CRVO, and AMD was higher in the COVID-era eyes [Table 2]; this again may have significantly impacted the improved visual outcome in our COVID-era eyes.

Our study generally reports low compliance to anti-VEGF injections in both the pre-COVID and COVID eras. Table 2 shows that DME had the highest mean number of anti-VEGF injections, 1.97 injections, during the pre-COVID-era, while AMD's 1.88 injections were the highest COVID-era. Both fall short of the recommended three consecutive loading doses prescribed when initiating anti-VEGF treatment. This finding suggests poor compliance with anti-VEGF injections in Nigerian patients. In this study, PDR had the highest contribution of eyes, followed by RVO. This finding differs from other reports on anti-VEGF use from other countries, which reported DME as the commonest indication for anti-VEGF.9 The late presentation of patients living with diabetes for an eye examination, which is a shared experience in lower-income countries, and the absence of screening programs to detect early stages of diabetic retinopathy may explain this finding of more advanced diabetic eye disease. Though macular and retinovascular diseases were the commonest indications for anti-VEGF use, our study also included nonretinovascular indications of anti-VEGF use, including uveitis, ERM, pseudophakic macular edema, and pterygium. We did this to give a holistic presentation of anti-VEGF use. Anti-VEGF has been investigated and used as an adjunct before and after pterygium surgery.[16,17] The anti-VEGF injection is given into the pterygium. Pterygium contributed only 1% in both the COVID and pre-COVID era, having a negligible impact on the study data analyzed. Moreover, having similar numbers of pterygium in both eras would likely cancel out pterygium's overall effect.

Conclusion

IVIs effectively manage several macular, retinovascular, and nonretinovascular diseases, some of which could result in significant loss of vision or blindness if untreated. A drawback of IVI is the need for multiple dosing, which can be challenging since patients must make frequent hospital visits to keep prescribed treatment schedules. In the setting of restrictions to movement and social emergencies, when hospital attendance is impossible, significant loss of vision can occur. Our study quantifies the impact of such restrictions on the number of eyes unable to receive IVI and the reduction in IVI to be 15.3% and 26%, respectively. These figures provide a numerical basis for future planned interventions to provide access for patients in case of another pandemic, lockdown, or similar social emergencies. Such interventions may include granting administrative passes to patients during the lockdown or providing home care administration of IVI.

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Conflicts of interest

There are no conflicts of interest.

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