



Impact of COVID-19 on the Management of Diabetic Retinopathy

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i60B34798

Open Peer Review History:

This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: <https://www.sdiarticle5.com/review-history/79930>

Review Article

Received 15 November 2021

Accepted 20 December 2021

Published 23 December 2021

ABSTRACT

Diabetic retinopathy (DR) is one of the most common causes of vision loss in people across the world. COVID-19 Despite the fact that early diagnosis and management guidelines for DR have considerably lowered burden of disease, 19 disease outbreak limitations have had an impact on actual world clinical management in the care of DR patients. This research includes the most latest treatment guidelines and outcomes for DR in the context of the outbreak.

When contrasted to equivalent instants of time in 2019, intravitreal doses for DR have declined dramatically globally during the outbreak, spanning from around 30 percent to around 100percent reduction. After a substantial amount of time, several research on operational findings demonstrate a loss in visual acuity.

In the treatment of DR, changing practice methods have led to lower intravitreal doses and cumulative loss of vision acuity during follow-up. It will be vital to continue reviewing practise guidelines as more COVID mutations arise.

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Keywords: Diabetic retinopathy; coronavirus outbreak; intravitreal injections; treatment; impact of COVID-19.

1. INTRODUCTION

As of April 2021, the coronavirus disease 2019 (COVID-19) outbreak had resulted to enormous comorbidity and deaths around the world, with around 133,552,774 confirmed cases and approximately 894,295 deaths [1]. COVID-19 can cause a variety of symptoms, including SARS-CoV-2 (severe acute respiratory syndrome coronavirus) [2]. The angiotensin-converting enzyme 2 (ACE2) receptor is responsible for these symptoms. The effects of the pandemic are beginning to show themselves in public health, particularly in the therapy and results of long-lasting diseases like Diabetic Retinopathy (DR). DR is reported in approximately one-third of diabetics and is among the most crucial reasons of visual loss around the globe [3,4]. In addition, regardless of the fact that yearly diagnostic tests are recommended, about a triad of diabetic individuals don't follow these guidelines [5]. Frequent DR diagnosing and management has been observed to avoid serious loss of visual acuity while also being budget-friendly [6,7].

Outpatient appointment attendance has been impacted by COVID-19 spread management strategies such as social estrangement and effective utilisation of close protection equipments, along with patient worries during the pandemic [8,9]. The National Patient and Procedure Volume Tracker (Strata Decision Technology, L.L.C., Chicago, IL) looked at over two million patient interactions in the United States and found a decrease in routine checkups across all specialisations, along with an 81 percent decrease in ophthalmology routine care in March to April 2020 in contrast to the corresponding time in the year 2019 [10]. Retina offices lost almost seventy one percent of the total attendance [10]. Because ocular care is primarily reliant on specialised imaging equipment that isn't generally accessible outside of the offices of ophthalmologists, the switch to tele-ophthalmology visits were restricted compared to other specialities [11]. DR testing was also routinely delayed throughout this outbreak, particularly in communities where COVID-19 infection was prevalent [12]. Diabetic eye exams, for instance, fell from approximately 1,145 visits in the six weeks before disease outbreak clinical practisemodifications to just 59 in the first six weeks after they were adopted at

the Wilmer Eye Institute [13]. The American Academy of Ophthalmology and Vision Academy Steering Committee's revised guidelines for DR management and treatment, patient preferences of eye clinic visits during the global epidemic, changes in intravitreal injection frequency, and the resulting changes in conclusions such as vision acuity will be the subject of this article.

2. TREATMENT GUIDELINES FOR DIABETIC RETINOPATHY DURING THE PANDEMIC

Old-age individuals with systemic morbidities, like diabetes mellitus demanding intravitreal medications, are more vulnerable to developing fatal COVID-19 disease [14]. The American Academy of Ophthalmology urged that "all doctors immediately halt delivering any therapy other than essential or critical care" after the COVID-19 outbreak hit the United States on March 18, 2020. Since then, the AAO has amended its guidelines to address concerns about COVID-19 exposures during routine medical examinations and elective procedures. These recommendations include Coronavirus 19 Reverse Transcriptase-PCR lab tests and suitable PPE for operation theater, as well as pro-clinic testing for COVID-19 signs, public estrangement in enclosed areas, repeated sanitization, slit lamp boundaries and breath masks, and face enclosures for patients and clinicians during treatment sessions [15]. The application of all these guidelines at several institutes in the United States and abroad is dictated in a report by Li et al. [16]. According to AAO recommendations, individuals suffering DR who regularly receive medications should consult their specialists for therapy [15].

The Vision Academy's Steering Committee, a global organisation of more than eighty retina consultants endorsed by Bayer, has also presented relevant instructions for anti-vascular endothelial growth factor (VEGF) intravitreal medications for neovascular age-related macular degeneration (nAMD), diabetic macular oedema (DME), and retinal vein occlusions (RVO) [17]. DME and proliferative diabetic retinopathy (PDR), the two most prevalent causes of loss of visual acuity in diabetics, are commonly treated with anti-VEGF intravitreal injections.

The Vision Academy's Steering Committee suggested that anti-VEGF regimens be

streamlined to limit exposure risk, that treatment be prioritised for high-risk patients of lifelong sight loss, and that prescription medicines not be changed until there was an obvious sense of uncertainty. Deferring anti-VEGF medications for confirmed DME suffering individuals and re-check every four months were criteria for DR in the initial phases of the outbreak [17]. Nonetheless, prolonged therapy for serious non-proliferative diabetic retinopathy (NPDR) and progressive PDR wasn't preferred because of the chances of loss of vision. The committee advised individuals with a recent diagnosis of DME to wait six months before starting treatment. The Visual Academy's Steering Council released updated recommendations in 2021 as the outbreak progressed, including providing care with DME and significant vision problems, minimizing therapy delays of more than 4 to 6 months, and re-checking cases within two to three months [18].

3. IMPACT ON PRACTICE PATTERNS IN THE REAL WORLD

The standards developed by ocular specialists and retina specialists to eliminate the possibility of Coronavirus contamination in diabetic retinopathy individuals led to major alterations in clinical practise norms. Patient-related concerns, notably over COVID-19 contamination, also contributed to the pandemic's lack of follow-up. In reality, a study published at 2 tertiary ophthalmology care centres in the United States (Emory Ophthalmology Center in Atlanta, GA, and W.K. Kellogg Ocular Center in Ann Arbor, MI) found that 47 percent of people with nAMD or DR who were expected to deliver a dose between March 13 and May 6, 2020 and those who replied to the research study were averagely to far more worried regarding visual impairment from skipped intravitreal medications throughout the disease outbreak. Panic of contamination, on the other hand, was linked to a fourfold greater risk of individuals decline to follow-up [8]. A retrospective study of patient medical data with nAMD, DME, and RVO who required medications within the first 4 weeks of disease outbreak quarantine in the UK (March 23 to April 17, 2020) found a 67 percent absentees rate [19]. During the pandemic, adjustments in protocols and patient-related factors had a considerable impact on clinic volume, as well as fewer intravitreal injections.

A multiple center cross-sectional study encompassing seventeen facilities in the United

States examined customer information for vitreoretinal therapies from January 1, 2019 to May 21, 2020, producing a total of 526,536 methods [20]. The weekly mean intravitreal doses for every facility for all purposes were considerably lesser in April 2020 in contrast to April 2019. From April 6 to April 12 had seen the sharpest decline in intravitreal injections (about 38.6% decrease). When compared to the same period in 2019, variations in per week intravitreal doses counts were not important anymore by the finish of May 2020. In a series of studies concentrating on 3 COVID-19 most widespread locations in the United States (New York, Boston, and Miami) from March 16 to May 8, 2020, the reduction in intravitreal doses spanned from 30 - 64 percent [21].

During the outbreak, similar variations in practisepatterns were noticed all around the world. In comparison to the same time period in 2019, a regional medical facility in Italy that postponed DME management for as much as 30 to 40 days saw a 91.7 percent decrease in intravitreal medications for nAMD, DME, and RVO together [22]. 40 intravitreal injections were delivered throughout the outbreak shutdown, contrasted to 483 doses over the equal duration of time in 2019. Patients with DME appeared to be disproportionately impacted. During the peak of the pandemic in March and May 2020, 75 percent (n = 30/40) and 15 percent (n = 6/40) of doses for nAMD and DME, accordingly, were provided [22]. In comparison, 46.4 percent (n = 224/483) and 43.5 percent (n = 210/483) of intravitreal doses were provided for nAMD and DME, accordingly, at the same period a year ago [22]. In the nationwide shutdown from March 8th to March 31st, 2020, there was an 81 percent drop in intravitreal medications at the Policlinico Hospital in Milan, Italy [23]. Between March 10 and May 9, 2020, a retrospective study of ophthalmology operations in 39 academic facilities in Italy found an approximately 50% decrease in intravitreal injections for each and every cause [24].

Several trials in other countries have reported 50 to 70% reduction of follow-up rates for intravitreal injections, which is possibly due to the various exposure hazards and COVID-19 related health promotion programs in the specific localities [25,26]. When ambulatory clinic limitations come into place on January 21, 2020, the number of intravitreal injections at the Medical University First Hospital Department of Ophthalmology, China decreased by seventy percent in contrast

to the exactly similar period of time in 2019 [25]. Furthermore, 82 percent of individuals had a 4.5-month or longer wait for treatment. Intravitreal injections declined by nearly 50% at the ShaareZedek Medical Centre, Israel during March 15th to April 14th, 2020, comparatively to expected doses computed from reported doses over the previous four years [26]. All the parameters for anti-VEGF doses were covered in this study.

Intravitreal injections have also been studied during the unlocking phase following virus outbreak-related lockdown in several trials. The quantity of intravitreal injections delivered didn't fully recover, despite the fact that the fall in clinical volume was not as significant. During the "new normal" of operations at the Bascom Palmer Eye University, United States from June 18th to August 7th, 2020, there was a 10 percent decline in intravitreal medications in contrast to the same period of time in 2019 [27]. Likewise, in the month after lockdown (May 11–June 7, 2020), there was an 11.5 percent reduction in noticed intravitreal anti-VEGF doses in contrast to scheduled doses (deduced from the previous 2 years) [28]. Skipped intravitreal doses during quarantine were not reciprocated for upon unlocking, according to these investigations.

Clinic closures, resource limitations, travel cutbacks, a shortage of public transportation, and patient worries all participated to a decline in intravitreal doses [24,25,29]. Anti-VEGF medication was more likely to be adhered to by young patients and those with bad vision accommodations in the other eye [23,30]. In recent months, multiple researches have studied the influence of prolonged management on functional and anatomical consequences in individuals with DR as a response of fewer routine check-ups and intravitreal doses.

4. IMPACT OF DELAYED CARE ON VISUAL OUTCOMES

Treatment delay had a variable effect on BCVA in individuals with DR, according to retrospective research in contrast to the best corrected visual acuity (BCVA) prior and later the Coronavirus outbreak. The influence of prolonged therapy on visual loss has been documented by several institutions. In a retrospective survey of individuals administered with intravitreal medications at the Cole Ophthalmology University in the United States from March 14 - May 4, 2020, individuals with DME and/or PDR whose consultations were postponed ended up

losing 3.48 1.95 ETDRS letters in contrast to the individuals who managed to complete their scheduled consultations (attained 2.71 1.75 ETDRS letters, $p = 0.0203$) [30]. For all individuals who missed appointments, the average wait time was 5.34 weeks. Delay in therapy for individuals with nAMD, DME, or RVO led in more bad BCVA at follow-up in a retrospective study of individuals administered with anti-VEGF medications at the Institute of Minnesota Eye Clinic and the Retina Center, Minneapolis between March 28th, 2020 and September 30th, 2020. Individuals whose doses were postponed had a reduction in eyesight from logMAR 0.544 (Snellen 20/70) pre-shutdown to logMAR 0.722 (Snellen 20/105) at follow-up ($p = 0.06$) in the DME subgroup. Individuals who didn't have their injections prolonged, on the other hand, didn't have a statistically noticeable loss of vision ($p = 0.40$) [31]. In individuals with DME, delaying anti-VEGF medications led to a rise in mean central subfield thickness from 341 to 447 μm ($p = 0.007$).

Other countries have reported similar variations in BCVA as a result of delayed therapy. For individuals suffering with DME, nAMD, and RVO, the length of conventional management intrusions was 5.3 0.8 in months, and the BCVA reduced from logMAR 0.57 0.23 (Snellen 20/74) prior management intrusions to logMAR 0.98 0.41 (Snellen 20/191) after coming back to the Medical University First Hospital Department of Ophthalmology, China [25]. On the return visit, 66.7 percent of individuals suffering from DME lost three or more BCVA lines. Longer treatment interruption was linked to lower BCVA in both Pearson's correlation analysis and multivariate analysis. Anti-VEGF therapy prolongation led to lower visual loss in all individuals receiving intravitreal medications, involving those suffering from DME, according to research conducted at University of Science and Technology, Jordan [32]. During lockdown, the standard delay was 6.21.4 weeks [32]. The need for 3 or more injections prior to the follow-up visit, as well as prolonged intravitreal medications of more than 2 months during the COVID-19 shutdown, were adverse prognostic features for ocular function in individuals with DME at the follow-up consultations, according to a retrospective observational study conducted at Jordan University Hospital from April 20-July 1, 2020 [33-42]. In this study, the average injection delay was 60.97 (24.35) days.

Several other groups, on the other hand, found no difference in functional outcomes as a result

of treatment delays. Using standards identical to the 2021 modified Vision Academy guidelines, the Tanta University Hospitals Ophthalmology Department, Egypt found no significant variation in BCVA following delayed management [34]. Regardless of prolonged therapy delay of 19.1 10.6 weeks, the Aravind Ocular Hospital in India found no difference in BCVA prior and later to delayed DME therapy [29]. The retroactive character of these research, that is vulnerable to selection biases, limited them all. This accounts for the varying findings and different degrees of BCVA effect from postponed anti-VEGF therapy. Population-based researches are needed to completely assess the impact of COVID-19 on DR associated morbidity.

5. CONCLUSION

COVID-19 has wreaked havoc all around the world and had a significant influence on clinical care. COVID-19, in particular for DR, has resulted in fewer routine visits and anti-VEGF doses, which has likely impacted individual's visual outcomes, while the findings isn't definite. More rigorous population-based surveys are required to completely investigate the affect of Coronavirus on DR associated findings and if the related adverse consequences are irreversible. Furthermore, a multiple center study evaluating outbreak-related alterations in retinal treatments and operations found a reduction in laser treatments, vitrectomies for retinal detachment restoration, and vitrectomies for more purposes. The influence of the virus outbreak on PDR-specific laser operations and vitrectomies will require more research.

The outbreak of COVID-19 has also pointed out the importance of tele-medicine in diabetic retinopathy diagnosis and management. Individual self screening, which has been found to be successful utilising the Near Card and the Alleye Programme, could potentially enhance clinic visit and intravitreal injection priority processes. Furthermore, telescreening with Fundus Photography and artificial intelligence-based diabetic retinopathy categorization have shown good specificity and sensitivity in detecting diabetic retinopathy . Moreover, using portable OCT equipment to monitor patients with DME at home would certainly be advantageous. Enormous tele-ophthalmology initiatives, when integrated with artificial intelligence technology and at-home surveillance systems, will assist diabetic retinopathy individuals by enhancing

access to medical facility, especially in the aspect of the Coronavirus outbreak.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
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