Intravitreal Injections during the COVID-19 Outbreak in Northern Italy: An Innovative Approach for a High Quality and Safe Treatment

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Abstract

Background: Intravitreal injection (IVI) is a standard procedure performed in ophthalmology to treat several conditions, and is performed in different settings across countries. The Italian guidelines recommend this intervention is performed in an operating room to minimize the risk of infections, while in other countries, including Canada, USA and the UK, IVIs are performed in the ophthalmologist’s office. The 2020 COVID-19 outbreak caused a dramatic modification in outpatient care. Consequently, non-urgent surgical activities, like IVIs, were subjected to a drastic reduction.

Methods: We conducted observational study which investigated the outcomes of IVIs performed in an ophthalmologist’s office using a mobile laminar flow unit, the Operio mobile (Tou Meditech, Operio®) versus an operating room setting.

Results: Use of the Operio mobile allowed the safety performance of 3838 IVIs during COVID-19 and significantly reduced the waiting time of the first visit. This results in a faster intervention without affecting the technical IVI procedure that remained unchanged comparing the two settings. Specifically, we observed a 26% reduction in operation costs for each IVI performed in the office, which can be translated to a higher impact when considering the total number of IVIs performed over one year.

Conclusion: The use of the Operio mobile in an ophthalmologist’s office provides flexibility to perform IVIs, assuring patient safety, reducing healthcare personnel employment times, and the waiting lists for the patients, increasing the number of surgeries and improving the cost-effectiveness of the procedure.

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Introduction

Intravitreal injection (IVI) is one of the most common procedures performed in ophthalmology. Due to population aging, the number of patients who need this treatment is expected to increase.¹⁻⁴ IVI involves the administration of medications directly into the vitreous cavity of the eye to treat a variety of retinal conditions, which include, among others, neovascular age-related macular degeneration, diabetic macular edema, proliferative diabetic retinopathy, retinal vein occlusion, pathological myopia, and uveitis.⁵ According to a recent report by the Italian Society of Ophthalmology (SOI), 300,000 IVIs are performed annually in Italy to patients suffering from age-related macular degeneration.⁶

The administration of the three mostly used anti-VEGF agents (ranibizumab, bevacizumab and aflibercept) via IVI has shown comparable elevated levels of efficacy and safety in clinical procedure.⁷ However, repeated administrations of the drug(s) are usually needed to achieve disease resolution, meaning that patients require repeated visits to the hospital. IVI can also be accompanied by complications affecting the ocular structures, including endophthalmitis, which lead to loss of vision and a significant risk of enucleation.⁸ Previous studies have estimated risk of infection between 0.03% and 0.2%⁹⁻¹² but, due to the need for frequent procedures, this risk is repetitive and cumulative.
The IVI setting differs across countries, mainly due to their different regulations and reimbursement policies. In Canada and the USA, IVIs are primarily performed in an ophthalmologist’s office. Most clinicians in the UK and the Netherlands perform IVIs in a dedicated cleanroom with high hygiene standards but no air filtration systems. The SOI guidelines recommend performing IVIs in an operating room (OR) to minimize the risk of endophthalmitis especially with the adoption of laminar airflow technologies or filters. This means that the patient must undergo preparation for the procedure and an operating theater must be available, together with a surgeon and team of medical staff. Although interventions in this setting present a safe profile and a good outcome, they are time-consuming and not cost-effective.

On March 11, 2020, the World Health Organization declared the Coronavirus Disease 2019 (COVID-19) outbreak as a pandemic. This resulted in a drastic modification in outpatient care to reduce the chance of spreading the SARS-CoV-2 virus. Outpatient visits were restricted to urgent care, and it was the providers’ responsibility to defer elective and preventive visits. The reduction to the access to eye-care departments caused a dramatic decrease of several ophthalmological procedures, as highlighted by reports of the European COVID-19 Cataract Group (EUROCOVCAT): the number of screening visits, cataract surgeries, corneal donations and transplantations, and pediatric eye-care significantly dropped all over Europe. In particular, cataract interventions were reported to be diminished by 97%, highlighting the need of re-organization of the pathway to assure a safe surgery, avoiding cancelation and delaying of the procedure. Moreover, following the lockdown, in some institutions, 62.8% of patients did not attend routine visits or IVIs, with a potential threat to their health, exposing them to deterioration of visual abilities such as loss of visual acuity in patients with neovascular age-related macular degeneration. This is especially important in children as extended vision loss during development is irreversible.

The North of Italy was the first and most affected area hit by COVID-19 in Europe. The intensive care units (ICUs) became overcrowded, and hospitals had to reorganize to address this situation. Surgical theaters were partially converted into ICUs, with a drastic reduction in elective and non-urgent surgical activities. Also, several ophthalmology departments were converted into COVID-19 units.

Due to their close contact with patients during the several ophthalmological examinations, ophthalmologists are considered a high-risk category for infection by SARS-CoV-2. Indeed, risk of infection among health care professionals has been reported to be threefold higher than the general population, making them a vector for virus spreading. Studies on COVID-19 hypothesized a possible transmission through the eyes when no eye protection was worn because of the presence of the SARS-CoV-2 host receptor ACE 2 on the cornea and conjunctiva. Moreover, SARS-CoV-2 has been found in tears and conjunctival sacs. Although a recent study did not find a clear correlation between eye infection and most severe respiratory symptoms, a specific attention to clinical practice is needed in ophthalmology. Thus, the SOI developed clinical practice guidelines to help ophthalmologists during their procedures, together with an update of the guideline and best practice recommendation for IVIs. Despite these indications, the appropriate methodology to be adopted is still not completely clear, and ophthalmologists are now facing new issues due to the mandatory use of personal protection equipment: an increment in the requests of refractive surgery to get rid of spectacle fogging and the apparent increased of the risk of infections in the post-operative setting, as oral and nasopharyngeal droplets redirect towards the eyes because of the presence of the unsealed upper boarder of the mask.

Some hospitals introduced preventive measures to drastically reduce COVID-19 infection of health professionals’ by combining tests, tracing, and treatment. The adoption of these preventative measures avoided spreading the virus among patients subjected to IVIs, whom are usually older people who exhibit higher mortality and morbidity with COVID-19. Any treatment that was not urgent was postponed and non-demandable operations in surgical rooms were kept COVID-19-free and in service all day long.

The Working Group on Medical Retina of the Netherlands Ophthalmological Society recently underlined that IVIs are non-elective treatments. Thus, delaying or reducing these procedures would expose patients to an increased risk of vision loss, significantly affecting all aspects of patients’ lives. We considered it necessary to achieve a balance between infection control and the provision of ophthalmology services. Given the drastic reduction in available surgical spaces, and the necessity to continue delivering IVIs, we decided to move out of the OR for this crucial activity.

We conducted a preliminary observational study to investigate the outcome of IVIs performed in an ophthalmologist’s office, with the use of the laminar flow equipment Operio mobile (Toul Meditech, Operio®). Here we report the results of performing IVIs in this setting in terms of the number of IVIs performed, complications suffered, time spent by patients in the hospital before and after the procedure, and its cost-effectiveness compared with the use of an OR.

Methods

Patient’s characterization and preparation for the procedure

This study was performed between March and July 2020. Five centers located in the North of Italy and one center
located on one of the major islands participated in the project. The study included patients with neovascular aged-related macular degeneration, diabetic maculopathy, macular edema due to retinal vein occlusion, or myopic choroidal neovascularization, all already indicated to receive IVI with anti-VEGF agents or with a delayed-released steroid. Patients of all ages and gender were considered eligible for the study.

The study was conducted in compliance with ethical standards. The IVI outside of the OR was performed in accordance and under the direction of the chief medical officer. All the patients agreed and signed an informed consent form before the IVI procedure. All the data are registered with the health manager registry. Before administering the IVI, patients were subjected to standard preparation for intraocular surgery, including sterile draping of the surgical field, use of lid speculum and povidone-iodine 10%, irrigation of the surgical field with no post–IVI antibiotic treatment.45,46

**OR setting preparation/office setting preparation**

The IVI procedure in an OR is as follows. The patient arrives in the ophthalmological day surgery where two nurses give the patient povidone-iodine and anesthetic eye drops. One nurse leads the patient to the OR entrance, where a second nurse accompanies the patient to the room where the procedure will take place (travel time: a few minutes). In the OR, a doctor prepares the operating table, the surgeon carries out the IVI, and a nurse passes the material to the surgeon and performs the last instillation of povidone-iodine eye drops. Once the procedure is over, the patient is accompanied outside the room and is ready to leave the hospital.

The IVI procedure in an ophthalmologist’s office is as follows. The patient arrives in the reception room. Two nurses prepare the patient for surgery through the instillation of povidone-iodine and anesthetic eye drops. One nurse accompanies the patient to the office (minimum travel time) where the surgeon prepares the operating table and performs the IVI, while a nurse passes the material to the surgeon and performs the last instillation of povidone-iodine eye drops. Once the procedure is over, the patient is accompanied outside the room and is ready to leave the hospital.

**Operio mobile**

Unlike traditional aeration systems, the Operio mobile provides a horizontal ultraclean laminar airflow directly over the surgical site and sterile instruments, minimizing the presence of bacteria-carrying particles. This system uses a HEPA filter that eliminates particles smaller than 0.3 µm from the air. Its airflow speed of 0.4–0.5 m/s cleans 400 m³/h to 600 m³/h and protects an area up to 120 cm.47 These characteristics guarantee the particle levels necessary to obtain the ISO 5 class value in the OR (UNI EN ISO 14644, UNI EN ISO 11425).

In the OR setting, traditional ventilation systems push the filtered air towards the floor, which is always contaminated, meaning the air rapidly loses its sterility. The use of the Operio mobile permits the preparation of surgical instruments in the area protected by the laminar flow, preserving sterility even during long interventions. At the beginning of the procedure, the flow is directed towards the instrument table and the operating field thereby guaranteeing protection of the surgical wound area.

**Parameter acquisition**

The operators carried out an observational analysis measuring the time of the procedure in both the ophthalmologist’s office and the OR by creating daily procedure reports in a digital form. The cost was assessed by measuring the standard operators’ hourly costs in the two settings and adding the OR’s cost per hour.

All centers were using the Operio mobile, guaranteeing a higher performance standardization.

**Data analysis**

Data analysis was performed using R Statistical Software (R version 4.1.0).48 This is a retrospective observational analysis and data were collected from different centers, as available. To statistically compare the events, a weighted linear regression analysis on aggregated data was applied. This analysis allows to assign a different weight to the measurements. P < 0.05 was considered statistically significant.

**Results**

Overall, 5678 IVIs were performed on 2150 patients with different pathologies (Table 1).

All centers participating in the study had limited their eye-surgical procedures because of the reduction in the

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**Table 1. Demographics of patient population.**

| Parameter | Value |
|-----------|-------|
| Total number of IVIs performed | 5678 |
| Number of patients (male/female) | 2150 (989/1161) |
| Mean patient age (min-max) | 76 (35–90) |
| Patient distribution according to pathology (%) | |
| Neovascular age-related macular degeneration | 68 |
| Diabetic maculopathy | 19 |
| Macular edema due to retinal vein occlusion | 9 |
| Myopic choroidal neovascularization | 4 |
availability of ORs or the shortage of personnel mainly employed in ICUs.
Perceiving the IVI in the ophthalmologist’s office significantly reduced the waiting time of the first visit (51.4 vs 82.8 days, p < 0.001, respectively), while the time patients spent in the clinic for IVI remained comparable between the two settings (30.3 vs 30.2 min, Operio and OR procedure, respectively) (Table 2).

The percentage of reported complications was low (0.0465%) and only one patient developed endophthalmitis with the office-based IVI.

IVIs performed in an office with the support of the Operio mobile were cost-effective (Table 3). Over a 5-h period, the number of IVIs was higher when performed in the office versus the OR setting (40 vs 35, respectively) and the unit cost per IVI was lower (338€ vs 459€, respectively), with a reduction of 26% in the total costs.

**Discussion**

We show here that IVIs performed outside the OR with use of the Operio mobile are safe and represent a valid alternative in emergencies and daily routine clinical practice. The health emergency due to COVID-19 made it necessary to reorganize hospital areas and eventually postpone patients’ treatments to avoid the spread of the virus. IVIs are considered non-elective treatments since delaying or reducing the number of injections exposes patients to an increased risk of vision loss. Thus, despite the significant drop in in-person visits, it was mandatory to allow patients to receive their treatment. However, the lack of ORs shifted IVIs to office spaces using a laminar flow. Following the example of other European countries, daily activity rooms were converted into IVI areas using Operio mobile.

Previous studies have demonstrated that the use of ultraclean air flow close to the operating table prevented the growth of pathogenic bacteria and should be considered as an alternative to ORs to avoid contamination of materials and drugs. Our results show different advantages from using the laminar flow, primarily, a reduction in the waiting time needed to perform the IVI. Although the IVI is a procedure already performed in the office in several countries, in Italy and Southern Europe IVIs are still preferably performed in the OR. Notably, IVIs performed outside the OR did not increase the percentage of infections. Indeed, a review published in 2019 showed that the rate of endophthalmitis occurring after IVIs performed in the office and the OR did not differ (0.027% for each), suggesting that it is safe to perform this procedure in both conditions. Our experience confirmed this finding as we registered a similar percentage of infections with the use of the mobile laminar flow, resulting a recommendable alternative for the procedure outside the OR. Indeed, the manageability of the Operio mobile allows the improvement of the logistic organization within the office that could be re-organized according to the daily needs. In addition, the use of the mobile laminar flow would allow the decentralization of the IVIs, which could be performed locally, closer to patients’ home.

The use of a tool which allows safe IVIs outside the OR is part of the main re-organizational process of ophthalmological procedures – new ethical strategies, triage systems, alternative treatments – necessary to implement access to treatments, guaranteeing patients with retinal pathologies equity of assistance within the appropriated time in health emergency situations. The adoption of new tools and procedures could help avoiding severe consequences for patients, such the potential threat for vision deterioration.

In light of the recent health emergency, it has to be noted that the measures to avoid the spread of SARS-CoV-2 are likely to remain. Hospitals and all sanitary areas will have to keep minimizing patients’ presence to reduce the risk of infection. Patients who require IVIs are usually older and might need an accompanying person. Thus, performing the IVIs in the ophthalmologist’s

**Table 2.** Summary of intravitreal injections (IVIs) performed in an ophthalmologist’s office with the use of the Operio mobile versus in an operating room (OR).

|                         | Office setting with Operio mobile | OR setting |
|-------------------------|----------------------------------|------------|
| Number of IVIs          | 3838                             | 1840       |
| Days to access the first visit, weighted average (min-max) | 51.4*** (15–117) | 82.8 (18–196) |
| Minutes needed for the treatment, weighted average (min-max) | 30.3 (8–46) | 30.2 (20–60) |

***p < 0.001.

**Table 3.** Estimation of number and costs of intravitreal injections (IVIs) over a 5-h working period.

|                         | Operating room | Ophthalmologist’s office |
|-------------------------|----------------|--------------------------|
| **Number of IVIs**      | 35             | 40                       |
| **Personnel cost (€)**  | 725.75         | 490.75                   |
| Setting                 | 6000.00        | 2000.00                  |
| **Drugs§ (€)**          | 8800.00        | 10,440.00                |
| **Custom pack (€)**     | 525.00         | 600.00                   |
| **Total cost (€)**      | 16,050.75      | 13,530.75                |

§Including the costs for Operating Room booking and power.

*average costs for a standard operation procedure, including both on-label and off-label drugs.
office or even outside the hospitals with the Operio mobile is recommended to assure the continuity of the treatment and to reduce waiting time for the starting of the procedure. The time needed to perform the IVI resulted to be similar in the two settings. This highlights the maintenance of the same surgical preparation routine in performing IVI, which is not influenced by the change of setting. In addition, we speculate that a further standardization of the office procedure will result in a reduction of the time spent in the medical center and improvement of patients’ and caregivers’ safety and satisfaction.

Moreover, performing the IVI in an office area leaves the OR available for other surgeries, reducing the waiting list, the number of personnel needed, and the time spent by each health professional to get ready for the procedure. The use of the Operio mobile was also shown to be cost-effective, since we demonstrated that it not only permits an increase in the number of IVIs performed per hour, the associated cost of each IVI was overall 26% cheaper compared with the OR. This reduction can be of an even higher impact when considering the total number of IVIs performed in each center over one year.

Conclusions

Migration of IVIs out of surgical rooms was undertaken in Italy’s selective hospitals as an emergency action pushed by the need to continue sight-saving and non-elective treatments.

The data collected here show that this is not only a safe setting but, also offers a significant improvement in terms of the efficiency of the entire process, with an observed reduction in the time lag between diagnosis and first IVI. The easy handling of the system is appreciable for the possibility to increase the independence of the IVI from both the OR and the office routine, further reducing the time spent in the hospital by patients and caregivers. We stress the importance of delivering a higher number of IVIs in a shorter time from the diagnosis and the importance of having every patient in a dedicated and fluent pipeline with a consequent shorter time of permanence in the treating areas. This is crucial to keep performing as many ophthalmological activities as possible, despite the persistence of the COVID-19 safety procedures.

In conclusion, using the Operio mobile to perform IVIs has different advantages. It can provide greater flexibility in the provision of IVIs, as well as reducing healthcare personnel employment times, and the waiting lists for the first visit. Also, it increases the number of surgeries that could not be performed in a clinical practice area by minimizing the use of the OR. Finally, performing the IVIs in an office setting improves the cost-effectiveness of the procedure and minimizes the costs associated with the use of an OR.

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