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Original Article

Safety Profile of Intravitreal Injections in the Injection Cabinet: No Cases of Endophthalmitis Seen After 7238 Injections

Gokhan Ozgur,[1] Onur Gokmen[2]

[1]Department of Ophthalmology, Samsun University, Samsun, Türkiye
[2]Department of Ophthalmology, Yuzuncu Yıl University, Van, Türkiye

Abstract

Objectives: The present study evaluates the rate of endophthalmitis in intravitreal injections (IVI) performed in a modular injection cabin that could be easily sited in a closet in an office environment, and the performance tests of the cabin in terms of heating, ventilation, and air conditioning (HVAC).

Methods: The injections were given over approximately 18 months in the cabin and the demographics of the patients were screened retrospectively, and the cabin was subjected to HVAC tests.

Results: A total of 7,238 injections were performed in the defined period, and no cases of endophthalmitis were encountered (0%). The results of the airflow and flow rate, particle count, pressure difference, decontamination time, light, moisture, and heat tests were all found to be above the standard defined by the International Organization for Standardization (ISO).

Conclusion: An injection cabin is a practical modular construction that can be easily sited in any space without the need for special climatization, and provides a sterile and safe environment for IVI.

Keywords: Air conditioning tests, endophthalmitis, heating, ventilation, injection cabinet, intravitreal injection

Introduction

Intravitreal injections (IVI) have developed into a routinely applied treatment method in ophthalmology outpatient and retina clinics for the treatment of diabetic maculopathy, age-related macula degenerations, retinal vein branch occlusions, and choroidal neovascular membranes. IVIs account for a vast proportion of the surgical ophthalmology procedures in many clinics (1).

Although IVI is a frequently applied treatment approach, there are many potential complications, the most feared among them being endophthalmitis (2).

The first step in increasing the safety of IVIs involves the selection of an appropriate environment (3). Some physicians prefer to perform IVIs in an office environment while others prefer sterile operating rooms, and the rates of endophthalmitis among applications performed in different settings are variable (4).

We present here an injection cabin design that supports the practical transformation of an office environment into a new medium in which IVI can be safely performed. The present study evaluates the rate of endophthalmitis in those undergoing IVI in the cabin, and the results of the heating, ventilation, and air conditioning (HVAC) performance tests of the cabin.

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Address for correspondence: Gokhan Ozgur, MD. Department of Ophthalmology, Samsun University, Samsun, Türkiye
Phone: +90 505 238 74 98 **E-mail:** g_ozgur@hotmail.com

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Methods

Patient Population and Study Design

Included in the study were people aged 18 years and above who underwent IVI in the newly designed injection cabin located in the ophthalmology outpatient clinic of Samsun University Hospital between September 1, 2020, and March 14, 2022. The study was approved by the Scientific Investigations Ethics Board of Samsun University Hospital. (GOKA/2021/20/19) and in this study, the authors have adhered to the tenets of the Declaration of Helsinki. Demographic and descriptive data of the participants were obtained retrospectively from the hospital information management system and subjected to a statistical analysis. Furthermore, the installed injection cabin was subjected to HVAC performance tests.

Injection Method

The IVIs were made by ophthalmologists using the injection cabin after gaining the approval of the hospital infection committee for the use of the injection cabin (Number: 36 Date: August 25, 2020). The surgeon performing the IVI and assisting personnel wore masks, surgical caps, and sterile gloves throughout the procedure. A proparacaine 0.5% drop was applied topically to the eye of the patient undergoing the procedure. Subsequently, the eyelids and orbit were cleaned with 10% povidone-iodine and a 5% povidone-iodine solution was applied to the eye, including the conjunctivae and fornices. The patient was draped in a sterile cover and a speculum was applied to the eyelid. The injections were performed at a point approximately 3.5–4 mm away from the limbus using a 30-gauge injector tip, refraining from insertions into the periocular muscles. A cotton sponge was placed on the injection site and pressure was applied to prevent vitreous reflux after the injection. An ophthalmologic ointment containing Bacitracin + Neomycin sulfate was applied to the eye, and the eye was kept closed for 2–3 h. The patients were prescribed a moxifloxacin 0.5% drop to be used q.i.d. for 5 days. Although the use of prophylactic antibiotics after IVI is controversial, due to our very high volume working conditions we prefer to use it (5).

Bevacizumab was used in most of the injections in line with the application protocol of the health authority in this country for the IVI procedure. The Bevacizumab injections were performed after filling multiple syringes from a single vial, maintining the sterility conditions at a high level. Assistance was received by an experienced nurse during the preparation of the drugs and taking them into the injectors, by observing the sterility environment. The ranibizumab and aflibercept used in the study were drawn into the syringe in a single filling from single vials, and the pre-filled form of ranibizumab was applied by attaching a 30 gauge needle to the syringe, while dexamethasone was applied as a preloaded intra ophthalmic implant form.

Technical Properties of the Injection Cabin

The ophthalmological injection cabin is a new concept featuring a modular structure. Its 3 m×2 m dimensions allow IVI procedures to be performed in a safe and sterile setting. It is constructed out of completely antibacterial materials so as to meet the environmental requirements detailed in the quality standards and the current legislation (Figs. 1 and 2). The main skeleton of the cabin is constructed out of 304-grade stainless steel and laminated glass, and all

Figure 1. Inside view of the cabin.

Figure 2. View of the office where the cabin is located.

mountings and apparatus are made of chrome (Fig. 3). This method of assembly supports the modularity of the cabin and allows cabins to be produced to the desired dimensions.

A positive air pressure in the cabin is created by two LAF (laminar airflow) filtration units with G4 and HEPA 14 (high-efficiency particulate air) filters, supporting the attainment of International Organization for Standardization (ISO) level-5 air quality.

Clean air with 99.999% quality positive pressure is provided within the cabin by the two LAF filtration units, measuring 610×1220×250 mm, and a 650 m^3/h capacity filter the air in the environment and transmit the air in positive laminar flow characteristics into the cabin (Total airflow=1270 m^3/h). This allows the air in the environment to be used without the need for a separate air conditioning system. The level of pollution in the HEPA filter is monitored using an analog differential manometer.

HEPA filters can be easily changed without contamination, and are provided in a special impermeable plenum box, having passed the dispersed oil particulate test (HEPA filter impermeability test).

There is a speed level adjustment on the LAF unit to adjust the airflow and to provide the option of running the device when the cabin is empty or during an operation. A special ultraviolet light system that can also be used during operation is provided in the cabin to deactivate any small microorganisms that may pass through the HEPA filter. UV light system is placed between the filter and the cabin ceiling in a way to filter the air coming out of the HEPA filter, and it has no effect on the cabin and the users. The passage of clear air is directed from the lower part and sides of the cabin outside by means of the applied side panel design of the cabin. The assembly was made by leaving 2 cm gaps between the steel frame and the laminated glass. Likewise, the cabin does not sit completely on the floor and there are still 2 cm gaps between the floor and the cabin. Thanks to these cavities: It is ensured that the particles can be swept outside with the continuous positive pressure created in the cabin.

This ensures that both the air in the cabin and the in the room in which the cabin is sited are continuously filtered, and no separate airlock or anterior passage area is required thanks to the continuous positive air pressure produced in the cabin. An automatic door with a hand sensor allows controlled passage into the cabin, preserving the continuity of the positive air pressure, and also to ensure the safety of the operation. Light-emitting diode luminaires with an appropriate lux level have been preferred for lighting, along with an AC (Alternating Current) fan with a maximal 65 dBA sound intensity to ensure the minimum of fan noise in the cabin.

Statistical Analysis

The statistical analysis was conducted using IBM SPSS Statistics (Version 21.0. Armonk, NY: IBM Corp.). Descriptive statistics were used in the study, in which quantitative variables were presented as mean and standard deviation (SD), and qualitative variables as percentages.

Figure 3. Closed state of the cabin.

Results

Involved in the study were 1,833 patients, of which 911 were female (49.7%) and 922 were male (50.3%). The mean age of the participants was 65.23±12.3 years SD (range: 18–95) in females and 64.19±12.0 years SD (range: 18–92) in males. There was no statistically significant difference in age between the male and female participants ($p>0.05$). The total number of injections applied to the participants was 7,238, with injections applied to a single eye and to both eyes in 988 (54%) and 845 (46%) cases, respectively (Table 1). Bevacizumab, aflibercept, ranibizumab, and dexamethasone were applied to 5,847 (81%), 614 (8.5%), 588 (8%), and 189 (2.5%) of the eyes, respectively (Table 2). The diagnosis for the indication of IVI was diabetic macular edema, age-related macula degeneration, retinal vascular obstruction, uveitis, and myopic choroidal neovascularization in 1,015 (55.3%), 472 (25.7%), 301 (16.5%), 28 (1.5%), and 17 (1%), respectively. No endophthalmitis developed in any of the patients who underwent the IVI procedure in the injection cabin (0%).

Table 1. Demographic data of patients

	n (%)
Gender Distribution	
Female	911 (49.7)
Male	922 (50.3)
Age, year±SD	
Female	65.23±12.3
Male	64.19±12.0
Eye	
One Eye	988 (54)
Bilateral	845 (46)
Diagnosis	
Diabetic Macular Eodema	1015 (55.3)
Age-Related Macular Degeneration	472 (25.7)
Retinal Vascular Occlusion	301 (16.5)
Uveitis	28 (1.5)
Myopic Choroidal Neovascularization	17 (1)

IVI: Intravitreal injections. n Patient = 1833; n IVI = 7238.

Table 2. Drugs used for intravitreal injections

Drugs	Numbers (%)	Injection
Bevacizumab	81	584
Aflibercept	8.5	614
Ranibizumab	8	588
Dexametazon	1.5	189

HVAC Performance Tests

HVAC system in the injection cabin was operated at the resting status for 24 h. No one was permitted inside the cabin for at least 2 h before the tests, after which the tests were conducted. The level of pollution in the rough and sensitive filters was checked, and routine cleaning and maintenance of the filters was performed before the test date. The technical staff checked the diffuser for perforations and damage to the airflow laminators. The classification of the clean rooms was performed according to the ISO 14644-1:2015 (13), 14644-2:2015 (14), and 14644-3:2006 (15) standards defined by ISO. The airflow, particle count, difference pressure, decontamination time, light, moisture, and heat test results were evaluated in accordance with these guidelines.

As a result of the tests applied in line with the ASHRE, DIN 1946-4, SKS version-6, IEST-RP-CC034.2, ISO 14644-1, ISO 14644-2, ISO 14644-3, and VDI 2167:2007 standards and technical references:

The average value determined as a result of nine different particle measurements was 194.25 in 0.5 µm/m3 (the required value for ISO Level 5 is 3250). The impermeability value of the HEPA filters was found to be 0.0014 as a result of the impermeability tests performed using a photometer and smoke generator (Reference acceptance criterion <0.010).

The air inside the cabin can be circulated 85 times an hour by the LAF filtration system (value required for ISO Level 7 is ≥15 circulations/hour).

A positive pressure test was performed on the cabin, and the air was measured as flowing to the outside from inside with a +5 Pa. difference, ensuring the inside of the cabin can be kept continuously sterile. The duration of decontamination of the cabin was measured at 4 min (value required for ISO Level 7 is maximum 20 min).

Discussion

IVI, especially intravitreal anti-vascular endothelial growth factor (VEGF) treatment, has become one of the most frequently applied intra-ophthalmic treatment methods over the last 10 years. It today accounts for a significant proportion of current ophthalmology practices, as well as a substantial proportion of outpatient clinic treatments in many medical retinal units (1).

There is a lack of international standards at present governing IVI procedures, and the environment and circumstances required are unclear. IVIs are performed in an office setting in the United States and Canada and are generally performed in the operating room or a sterile room with operating room conditions in European countries (6). The most feared and destructive complication after IVI is endophthalmitis, (7) and it is, therefore, of utmost

importance to clarify the medium and circumstances under which IVIs should be performed.

A total of 134.701 IVIs performed in three European hospitals between 2003 and 2016 were evaluated in a retrospective and multicenter study, and a very low rate of endophthalmitis (only 10 cases) was encountered following these injections, performed using a standard sterile technique in operating rooms with laminar flow (0.0074%) (8).

In another study, all injections were performed under sterile conditions and in an operating room with positive pressure, and no endophthalmitis developed following 20,293 IVI procedures (9). In another study in which 40,011 injections performed in Sweden in the 2004–2012 period were evaluated, and only three cases of endophthalmitis were seen (0.0075%) (10).

These studies detailed above demonstrate that operating room conditions are far safer environments for IVI, although there are studies reporting the contrary. The rate of endophthalmitis seen after IVI's performed under office conditions was found to be lower than in those performed in operating rooms in a retrospective study evaluating 11,710 cases (4).

Endophthalmitis developed in 0.049% (52) of cases in a meta-analysis evaluating 105,536 injections (11). The most commonly isolated organism in the obtained cultures was reported to be streptococcus species, which was present in 41% of the saliva flora of the adult sample, and it was suggested that the infection had occurred through droplet infection (11). Air conditioning and bacterial filtration of the medium in which injections are performed may substantially decrease the contamination of subjects with such pathogens, and consequently, reduce the risk of endophthalmitis.

Pathogens cannot move freely in the air, and so must attach themselves to particles. Sterile environments are classified in terms of the number of particles of 0.1–5 μm dimensions found in 1 mm^3 of air (12). According to the standards by which sterile areas in which surgical operations are performed are measured, which are determined by the health authority in this country, HEPA filters should be used, the direction of airflow should be from a clean area to a dirty area, and with positive pressure, laminar flow should be directed to the area of the surgical operation and a particle count matching the ISO class should be provided (13). The injection cabin presented in the present study has been shown to meet all of these standards.

The mean number of particles in 0.5 $\mu m/m^3$ achieved by a two-stage filter system (G4 and HEPA 14) and by the ultraviolet light used in the cabin was 194.25. This number is 3520 in ISO Level 5 operating rooms. Operating room levels are governed according to ISO 6 and 7 standards in this country, in which the required number of particles is 35,200 (ISO 6) and 352,000 (ISO 7), respectively in 0.5 $\mu m/m^3$ (13).

In addition, surgical fields are kept sterile continuously through the provision of positive laminar flow over the operation area. The entry of outside air into the cabin in the present study is prevented by the positive pressure.

The duration of decontamination is a maximum of 20 min in ISO 7 operating rooms, which can be provided very quickly, in 4 min. The number of air cycles is ≥15 cycles/h in ISO 7 rooms, compared to 85 cycles/h in the cabin (14). The cabin can be quickly prepared due to the short decontamination time and the very high number of cycles, and thus no preliminary preparation is needed before an IVI procedure. The standard durations are adequate for operating rooms, which have a far slower patient turnover, while the numbers reached in the IVI cabin are very high, and this rapid patient turnover is suggested to be very helpful.

Performing IVIs in an office environment offers many advantages, such as savings in time and cost, as well as increased practicality, although concerns have been raised about the sterility of such environments. Using the operating room eliminates concerns about the sterility of the environment, although this approach can be challenging due to the effect on safety of a high traffic of patients into the operating room, not to mention the increased costs and time constraints. We have been using this practical and safe injection cabin, with design registration number 2021 006829 in Turkish patent and trademark Institution, for 1.5 years as a means of overcoming the challenges and limitations mentioned above.

The rate of endophthalmitis among the more than 10,000 IVIs conducted in Arcsterile® cabin was reported as 0%, (15) although the cabin in that study differed from the one in this present study. The arcsterile® cabin has one completely open side which prevents the creation of positive pressure or a controlled passage of air. Furthermore, the system features filters in the side walls, while the laminar flow passes from the sides to the operation field. In another study, the number of particles in the air was found to be substantially decreased when a device providing air filtration by mobile laminar flow was used in a medium in which IVIs were performed, and the risk of endophthalmitis was suggested to be decreased to a great extent due to the decrease of the number of particles on the ocular surface (16). A positive laminar flow filtration system is installed in the cabin used in the present study, and a higher level of air purity than that required by ISO standards is obtained. Subsequently, the risk of contamination is decreased to a minimum through perfect particle filtration, contributing to the safety of IVI procedures.

The rate of endophthalmitis in the provision of anti-VEGF drugs in pre-filled forms has been reported in literature to be almost half the rate recorded from drug applications in which the syringe is filled from a vial (17,18). It has been suggested that the time required to fill the syringe from a vial is removed through the use of pre-filled syringes, and thus the risk of contamination is decreased. In this present study, we encountered no cases of endophthalmitis, despite using bevacizumab drawn into multiple syringes from a vial, and believe that this 0 rate of endophthalmitis can be attributed to the strict adherence to the rules of sterility and the air purity obtained in the cabin.

The main limitation of the present study is the lack of a control group allowing a comparison of the outcomes of patients who underwent injections in the operating room and in the cabin. The reason for this is that the ophthalmology clinic taken out of service during the COVID-19 pandemic and refunctioned as a COVID clinic, and so the ophthalmology clinic containing the injection room was unusable, and the operating room could not be used to full capacity for the same reason. Furthermore, the need for such an injection cabin became clearly as a result of these inadequacies, and the cabin allowed us to manage the process in a very effective manner.

Conclusion

In conclusion, an injection cabin serves as a practical environment in which the necessary safety and sterility are achieved for the IVIs that comprise a vast proportion of daily ophthalmology practice. No additional air conditioning system is required since the air present in the environment is used, and the cabin can be sited easily in the required location, providing a sterile and safe medium for IVIs.

Disclosures

Ethics Committee Approval: The study was approved by the Scientific Investigations Ethics Board of Samsun University Hospital. (GOKA/2021/20/19) and in this study, the authors have adhered to the tenets of the Declaration of Helsinki.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – G.O.; Design – G.O.; Supervision – G.O., O.G.; Data collection and/or processing – G.O., O.G.; Analysis and/or interpretation – O.G.; Literature search – O.G.; Writing – O.G.; Critical reviews – O.G., G.O.

References

1. Amoaku W, Bailey C, Downey L, Gale RP, Ghanchi F, Hamilton R, et al. Providing a safe and effective intravitreal treatment service: Strategies for service delivery. Clin Ophthalmol 2020;14:1315–28. [CrossRef]
2. Fintak DR, Shah GK, Blinder KJ, Regillo CD, Pollack J, Heier JS, et al. Incidence of endophthalmitis related to intravitreal injection of bevacizumab and ranibizumab. Retina 2008;28:1395–9. [CrossRef]
3. Lai TY, Liu S, Das S, Lam DS. Intravitreal injection--technique and safety. Asia Pac J Ophthalmol (Phila) 2015;4:321–8. [CrossRef]
4. Tabandeh H, Boscia F, Sborgia A, Ciracì L, Dayani P, Mariotti C, et al. Endophthalmitis associated with intravitreal injections: Office-based setting and operating room setting. Retina 2014;34:18–23. [CrossRef]
5. Bhatt SS, Stepien KE, Joshi K. Prophylactic antibiotic use after intravitreal injection: Effect on endophthalmitis rate. Retina 2011;31:2032–6. [CrossRef]
6. Lau PE, Jenkins KS, Layton CJ. Current evidence for the prevention of endophthalmitis in anti-VEGF intravitreal injections. J Ophthalmol 2018;2018:8567912. [CrossRef]
7. Fileta JB, Scott IU, Flynn HW Jr. Meta-analysis of infectious endophthalmitis after intravitreal injection of anti-vascular endothelial growth factor agents. Ophthalmic Surg Lasers Imaging Retina 2014;45:143–9. [Crossref]
8. Freiberg FJ, Brynskov T, Munk MR, Sørensen TL, Wolf S, Wirth MA, et al. Low endophthalmitis rates after intravitreal anti-vascular endothelial growth factor injections in an operation room: A retrospective multicenter study. Retina 2017;37:2341–6. [Crossref]
9. Brynskov T, Kemp H, Sørensen TL. No cases of endophthalmitis after 20,293 intravitreal injections in an operating room setting. Retina 2014;34:951–7. [Crossref]
10. Casparis H, Wolfensberger TJ, Becker M, Eich G, Graf N, Ambresin A, et al. Incidence of presumed endophthalmitis after intravitreal injection performed in the operating room: A retrospective multicenter study. Retina 2014;34:12–7. [Crossref]
11. McCannel CA. Meta-analysis of endophthalmitis after intravitreal injection of anti-vascular endothelial growth factor agents: Causative organisms and possible prevention strategies. Retina 2011;31:654–61. [Crossref]
12. Mora M, Mahnert A, Koskinen K, Pausan MR, Oberauner-Wappis L, Krause R, et al. Microorganisms in confined habitats: Microbial monitoring and control of intensive care units, operating rooms, cleanrooms and the international space station. Front Microbiol 2016;7:1573. [Crossref]
13. T.C. Sağlık Bakanlğı Sağlık Hizmetlerinde Kalite Standartlarına (SKS-Hastane V5.R1). Sağlık Hizmetleri Genel Müdürlüğü Sağlıkta Kalite ve Akreditasyon Daire Başkanlığı. 2nd ed. Ankara: Pozitif Matbaa; 2020. p. 232.
14. DIN 1946/4. Ventilation and airconditioning-Part 4: Ventilation in hospitals; 2008.
15. Furino C, Grassi MO, Bini V, Nacucchi A, Boscia F, Reibaldi M, et al. Intravitreal injections in arc sterile setting: Safety profile after more than 10,000 treatments. J Ophthalmol 2020;2020:3680406. [Crossref]
16. Lapid-Gortzak R, Traversari R, van der Linden JW, Lesnik Oberstein SY, Lapid O, Schlingemann RO. Mobile ultra-clean

unidirectional airflow screen reduces air contamination in a simulated setting for intra-vitreal injection. Int Ophthalmol 2017;37:131–7. [Crossref]
17. Storey PP, Tauqeer Z, Yonekawa Y, Todorich B, Wolfe JD, Shah SP, et al. The impact of prefilled syringes on endophthalmitis following intravitreal injection of ranibizumab. Am J Ophthalmol 2019;199:200–8. [Crossref]
18. Baudin F, Benzenine E, Mariet AS, Bron AM, Daien V, Korobelnik JF, et al. Association of acute endophthalmitis with intravitreal injections of corticosteroids or anti-vascular growth factor agents in a nationwide study in France. JAMA Ophthalmol 2018;136:1352–8. [Crossref]