Anatomic and Functional Outcomes Following Treatment of Acute Endophthalmitis: 7 Year Experience of the Central Region of Portugal

Resultados Funcionais e Anatómicos Após Tratamento de Endoftalmite Aguda: Experiência de 7 Anos da Região Centro de Portugal

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ABSTRACT

INTRODUCTION: Endophthalmitis is a rare but possibly catastrophic intraocular infection, potentially leading to blindness in the affected eye. The purpose of this study was to evaluate the outcomes of acute exogenous endophthalmitis, inferring on the role of *pars plana* vitrectomy (PPV) in the management of these patients, as well as to study the possible prognostic impact of different baseline and treatment related variables.

MATERIAL AND METHODS: Retrospective observational study including patients that underwent antibiotic intraocular injection with/without PPV for the treatment of acute exogenous endophthalmitis at the Department of Ophthalmology of Centro Hospitalar e Universitário de Coimbra, between 2016 and 2022. Minimum follow-up time was 6 months. Demographic and clinical data were recorded and analyzed. Best corrected visual acuity (BCVA) was converted into logarithm of the minimum angle of resolution (LogMAR) for comparison purposes.

RESULTS: A total of 83 eyes of 83 patients (55.42% male) were included. Median age was 77 years (66-82). The two major causes of endophthalmitis were cataract surgery (48.15%) and intravitreal injections (45.68%). Median BCVA at presentation was 2.28 LogMAR (1.98-2.70; equivalent to hand motion). There was a significant improvement in BCVA at the last follow-up (p<0.001), with a median final BCVA of 0.80 LogMAR (0.20-2.28; equivalent to 20/125 Snellen). Almost all patients (98.80%) were treated with intravitreal antibiotic injections (IVIs) and 73.49% of patients were submitted to PPV. The final BCVA was significantly worse in the combined IVI and PPV when compared to the IVI alone group (p=0.026), however there were no significant differences in the variation of BCVA before and after treatment between these two groups (p=0.860). The most frequent complications were retinal detachment (13.3%) and need for evisceration (8.4%).

CONCLUSION: Although acute endophthalmitis represents a serious condition with possible catastrophic outcomes and poor visual prognosis, we found significant improvement in BCVA after appropriate treatment. Despite including one of the highest numbers of patients

in recent single-center studies of this kind, it was not possible to confidently demonstrate superiority of the general use of PPV in the management of acute endophthalmitis in our study.

KEYWORDS: Anti-Bacterial Agents; Endophthalmitis/drug therapy; Endophthalmitis/surgery; Intravitreal Injections; Vitrectomy.

RESUMO

INTRODUÇÃO: A endoftalmite é uma infeção intraocular rara mas possivelmente catastrófica, podendo levar a cegueira do olho afetado. O objetivo deste estudo foi avaliar os outcomes após endoftalmite aguda exógena, inferindo sobre o papel da vitrectomia via *pars plana* (PPV) na abordagem destes doentes, bem como estudar o possível impacto prognóstico de diferentes variáveis de base e relacionadas com o tratamento.

MATERIAL E MÉTODOS: Estudo observacional retrospetivo que incluiu doentes submetidos a injeção intraocular de antibióticos com/sem PPV para tratamento de endoftalmite aguda exógena no Serviço de Oftalmologia do Centro Hospitalar e Universitário de Coimbra, entre 2016 e 2022. O tempo de seguimento mínimo foi de 6 meses. Dados demográficos e clínicos foram registados e analisados. A melhor acuidade visual corrigida (BCVA) foi convertida para logaritmo do ângulo mínimo de resolução (LogMAR) para efeitos comparativos.

RESULTADOS: Foram incluídos 83 olhos de 83 doentes (55,42% do sexo masculino). A idade mediana foi 77 anos (66-82). As duas causas principais de endoftalmite foram cirurgia de catarata (48,15%) e injeções intravítreas (45,68%). A BCVA mediana à apresentação foi 2,28 LogMAR (1,98-2,70; equivalente a vultos). Houve uma melhoria significativa na BCVA no último *follow-up* (p<0,001), com uma BCVA final mediana de 0,80 LogMAR (0,20-2,28; equivalente a 20/125 Snellen). Quase todos os doentes (98,80%) foram tratados com injeções intravítreas de antibiótico (IVI) e 73,49% dos doentes foram submetidos a PPV. A BCVA final foi significativamente pior no grupo que realizou IVI e PPV combinadas, em comparação com o grupo que realizou apenas IVI (p=0,026). Contudo, não houve diferenças significativas na variação de BCVA antes e depois do tratamento entre estes dois grupos (p=0,860). As complicações mais frequentes foram descolamento de retina (13,3%) e necessidade de evisceração (8,4%).

CONCLUSÃO: Embora a endoftalmite aguda represente uma doença grave com possíveis resultados catastróficos e mau prognóstico visual, verificámos uma melhoria significativa na acuidade visual após tratamento. Apesar de incluir uma das maiores amostras de casos de endoftalmite em estudos recentes num único centro, não foi possível demonstrar com confiança a superioridade da utilização generalizada da PPV no tratamento de endoftalmite aguda no nosso estudo.

PALAVRAS-CHAVE: Antibacterianos; Endoftalmite/cirurgia; Endoftalmite/tratamento farmacológico; Injeções Intravítreas; Vitrectomia.

INTRODUCTION

Endophthalmitis is an intraocular infection of bacterial, fungal or, seldom, parasitic etiology. This infection is usually originated by an exogenous cause, but may exceptionally arise endogenously through the hematogenous spread of the microorganisms.[1]

Exogenous endophthalmitis account for more than 90% of reported cases and usually follow ocular procedures, resulting from intraocular surgery or intravitreal injections. They may also be of traumatic origin or associated with infectious keratitis or scleritis.[2-4] This condition can be classified, regarding its presentation, as acute, when its onset lies within the first 6 weeks following the event identified as the origin of the infection, or chronic, when beyond this time frame.[5] The present study will address acute exogenous endophthalmitis (AEE), with the exception of those originating from infectious keratitis or scleritis.

The incidence of this pathology reported in the literature varies considerably, usually between 0.02% and 0.54% depending on the leading cause. However, AEE is more frequent when following penetrating trauma, with its incidence rising up to 18% after traumatic events of this nature.[6-10]

In the management of this condition, intravitreal antibiotics are the standard of care. Moreover, *pars plana* vitrectomy (PPV) alongside antibiotic intravitreal injection (IVI) is recommended as "gold standard" by The European Society for Cataract & Refractive Surgeons (ESCRS), whenever a vitreoretinal surgeon and operating room are available.[1] However, this broader use of PPV is not favored by all clinicians and evidence in recent studies is conflicting.

Centro Hospitalar e Universitário de Coimbra is the most differentiated healthcare facility in the center region of Portugal, which has a population of around 2 million inhabitants, and includes a general emergency department open 24 hours a day. Its Integrated Ophthalmology Responsibility Center has the most differentiated vitreoretinal department in the region, which is why it receives practically every case of endophthalmitis diagnosed in hospitals in this region. For this reason, our casuistry adequately reflects the reality of this pathology in Portugal's central region.

Since AEE represents an ophthalmological emergency, often resulting in irreversible blindness of the affected eye, it is of utmost importance to optimize the approach to this pathology in order to safeguard the patient's quality of life. Thus, this study aims to evaluate the anatomical and functional treatment outcomes of AEE, establishing a comparison between the two most relevant treatment procedures (antibiotic intraocular injection with or without PPV) and further inferring on other pre-treatment, treatment-related and post-treatment factors related to the final outcomes of the patients.

MATERIAL AND METHODS

STUDY DESIGN

A retrospective observational study was carried out at the Ophthalmology Department of Centro Hospitalar e Universitário de Coimbra, which included patients who underwent antibiotic intraocular injections with/without PPV for the treatment of AEE, between January 2016 and June 2022, with a minimum follow-up of 6 months. The patients were selected, consecutively, from a pre-existing database that contained the clinical information necessary to carry out the study, introduced by the doctors who operated and/or followed them. This study was submitted and approved by the local ethics committee.

STUDY POPULATION

All patients undergoing treatment for AEE preceded by an invasive intraocular procedure or open ocular trauma, with a minimum follow-up of 6 months, were included. All patients diagnosed with endogenous endophthalmitis or endophthalmitis originated from infectious keratitis or scleritis were excluded. Those who developed symptoms more than 6 weeks after the originating event (chronic endophthalmitis) were also excluded.

DATA COLLECTION

The data analyzed included age, sex, laterality, symptoms at time of presentation, etiology, date of the invasive procedure (surgery or intraocular injection)/open ocular trauma and time elapsed between this date and the symptoms' onset, date of diagnosis, date of tap biopsy for microbial culture, sample used for microbiological culture (vitreous humor/aqueous humor/both), result of the microbial culture, date of administration of each treatment (PPV and intraocularly injected, systemic, topical and subconjunctival antibiotics), antibiotics administered, best corrected visual acuity (BCVA) at presentation and at the last follow-up, follow-up duration, number of intraocular injections and PPVs performed and intra- or post-operative complications.

Best corrected visual acuities that had been recorded in Snellen chart measures were converted into logarithm of the minimum angle of resolution (LogMAR) values for statistical analysis. For comparison purposes, counting fingers (CF), hand motion (HM), light perception (LP) and no light perception records were substituted with 1.98, 2.28, 2.70 and 3.00 LogMAR, respectively, as described in previous studies.[11,12]

STATISTICAL ANALYSIS

A descriptive analysis of the collected data was carried out using summary measures such as median and interquartile range in non-normally distributed variables and proportions in categorical and binary variables. Additionally, as the studied variables were not normally distributed, non-parametric testing was used for the study of pre- and intraoperative predictors. When Spearman correlation tests were used, r-value indicates the Spearman's correlation coefficient. The data was analyzed using IBM SPSS statistical software version 29.0 (Armonk, NY: IBM Corp), and a P value lower than 0.05 was considered significant.

RESULTS

This study included 83 eyes from 83 patients, 46 male (55.42%). The right eye was affected in 51.81% of cases and the median age was 77 years (66-82). The median follow-up period was 12 months (6-34).

The median BCVA at presentation was 2.28 LogMAR [1.98-2.70; equivalent to HM]. There was a significant improvement in BCVA at the last follow-up (p<0.001), with a median improvement of -0.50 LogMAR (-1.68-0.00) and median final BCVA of 0.80 LogMAR [0.20-2.28; Snellen equivalent (SE): 20/125].

An improvement in BCVA between presentation and the last last follow-up was found in 71.08% of patients. Visual acuity was maintained in 9.64% of cases and 19.28% of patients presented with worse final BCVA than BCVA at time of diagnosis.

PRE-TREATMENT FACTORS

The major factor related to final BCVA results was the visual acuity recorded at presentation, as results showed a strong correlation between worse presenting visions and worse visual outcomes (r = 0.684, p<0.001).

The vast majority of cases of endophthalmitis included were related to intraocular procedures, in 97.59% of patients, with only 2.41% of cases being related with penetrating ocular trauma. Cataract surgery was the most frequent causing procedure, responsible for 48.15% of cases, followed by intravitreal injections in 45.68% of patients. We also included 3 cases following trabeculectomy (3.61% of all procedure related AEEs), one case following vitrectomy (1.20%) and one case following Descemet stripping endothelial keratoplasty (DSAEK) (1.20%).

The most prevalent symptoms at time of presentation were blurred vision/decreased visual acuity (80.72%), eye pain (55.42%) and conjunctival hyperemia (30.12%).

Median symptom onset time was 4 days (2-10) following intraocular procedure or trauma. Symptom onset time was the same between IVI-related cases and cataract surgery-related AEEs, with a median flare-up time of 4 days for both groups. This time period had no significant association with baseline or post-treatment BCVA (p=0.115 and p=0.935, respectively), nor in the BCVA variation (p=0.072).

The great majority of patients started treatment on the day of presentation/diagnosis (median: 0 days; 0-0).

The median interval from symptom onset to intraocular antibiotic injection was 2 days (0-3) and for PPV it was 4 days (2-6). Briefness in treatment initiation from the time of symptom onset was not significantly associated with a better post-treatment visual acuity (p=0.366) or higher visual acuity gains (p=0.242), nor was it related with the number of cases resulting in evisceration (p=0.748).

Median BCVA at presentation and at the last follow-up according to causing event are represented in Table 1. There was no significant difference between the different groups in the BCVA at presentation (p=0.310), BCVA at follow-up (p=0.179) or variation of BCVA (p=0.979).

Microbiology

Collected culture samples varied among patients, with an aqueous sample being collected in 43.94% of cases, a vitreous sample in 34.85% and both aqueous and vitreous samples in 21.21%.

Positive results were obtained in 28.79% of reported cultures, and rate of positivity was not significantly correlated with the type of collected sample (p=0.975). Culture positivity also had no significant correlation with time to symptom onset (p=0.727), however it was associated with worse baseline (p=0.040) and final (p=0.080) BCVA.

All positive cultures were bacterial, with no fungi being detected. Only one case isolated more than one bacteria (positive for 2 different gram-positive bacteria). Gram-positive bacteria were shown in 89.47% of positive cultures, with *Staphylococcus epidermidis* accounting for 40% of all identified bacteria. *Enterococcus faecalis* (20%), *Staphylococcus aureus* (15%) *Streptococcus oralis* (5%), *Staphylococcus haemolyticus* (5%) and *Bacillus cereus* (5%) were the other gram-positive bacteria detected. Only 2 cultures were positive for gram-negative bacteria, representing 10.53% of all positive cultures. The two bacteria identified were *Pseudomonas aeruginosa* and *Haemophilus influenzae*, one for each patient.

Different growth mediums were used, with chocolate-agar and blood-agar mediums being used in all cases before April 2021, with a positivity rate of 23.08%, and brain-heart infusion being used from April 2021 to June 2022, with a positivity rate of 37.04%. Sabouraud-agar was used for fungi culture. The increase in positivity rates between the first and second mediums was not statistically significant (p=0.218).

TREATMENT-RELATED FACTORS

Antibiotic intravitreal injections were administered in 82/83 patients (since one patient was approached with simultaneous PPV and silicone oil tamponade for intra-operative retinal detachment, with injection of cefuroxime only in the anterior chamber). Both ceftazidime 2.25 mg/0.1 mL and vancomycin 1 mg/0.1 mL were injected in the majority of cases (98.78%), and 1 patient was submitted to vancomycin 1 mg/0.1 mL injection alone due to severe cephalosporin allergy. Following positive culture and antimicrobial susceptibility testing, one patient had cefazoline 2 mg/0.1 mL injected after 2 previous injections of ceftazidime and vancomycin, to better fit the microbiologic sensibility.

Cefuroxime was injected (1.0 mg/0.1 mL) in the anterior chamber of 2 patients. In one of them, this was the only antibiotic injection administered, since the patient was submitted to simultaneous PPV with silicone oil tamponade for intra-operative retinal detachment (RD).

Table 1. Best corrected visual acuity according to etiology of endophthalmitis.

	Cataract surgery (n=39)	Intravitreal injection (n=37)	Trabeculectomy (n=3)	PPV (n=1)	DSAEK (n=1)	Penetrating trauma (n=2)
Initial BCVA[a] (LogMAR) (SE)	2.28 (1.98-2.70) (HM)	2.28 (1.98-2.70) (HM)	2.70 (2.28-2.70) (LP)	2.28 (HM)	1.98 (CF)	1.02 (20/200)
Final BCVA[a] (LogMAR) (SE)	1.00 (0.40-2.28) (20/50)	0.40 (0.10-2.49) (20/50)	2.28 (1.98-2.28) (HM)	1.98 (CF)	0.52 (20/63)	0.05 (20/25)

[a] Data is expressed using median and interquartile range (Q1/Q3).

BCVA – best corrected visual acuity; CF – counting fingers; DSAEK – Descemet's stripping automated endothelial keratoplasty; HM – hand motion; LogMAR – logarithm of the minimum angle of resolution; LP – light perception; PPV – *pars plana* vitrectomy; SE – Snellen equivalent.

Considering the simultaneous injection of ceftazidime and vancomycin as only "one injection", the median number of intraocular injections of antibiotic was 1 (1-2), with 54.21% having received one injection, 38.55% two injections and 7.23% three injections. For cases that required more than one intraocular antibiotic injection, the median interval between injections was 2 days (2-3). The number of injections each patient was submitted to did not significantly correlate to post-treatment BCVA (p=0.259) nor to the variation of BCVA (p=0.211).

Patients submitted to PPV accounted for 73.49% of all cases, while antibiotic intraocular injections without vitrectomy were conducted in 26.51% of cases. Most patients required only one PPV, while 2 patients required two or more PPVs.

The improvement in visual acuity between presentation and last follow-up was significant both in the group of patients submitted to intraocular injections alone (p=0.010) and in the patients submitted to injections and PPV combined (p<0.001).

Recorded visual acuities and the comparison between the two treatment groups is represented in Table 2. The final BCVA was significantly worse in the combined IVI and PPV group when compared to the IVI alone group (p=0.026). However, there were no significant differences in the variation of VA before and after treatment (p=0.860), nor in the baseline BCVA (p=0.075) between these two groups.

Combined IVI and PPV treatment managed similar results as injection-only regarding BCVA variation in patient subgroups with presenting BCVA under 1.00 LogMAR (SE: 20/200) (p=0.475), 1.98 LogMAR (CF) (P=0.358), 2.28 LogMAR (HM) (p=0.840) and 2.70 LogMAR (LP) (p=0.376).

From the group of patients who were treated with PPV, 72.13% (44/61) had intraocular antibiotics administered as the first treatment, prior to the PPV, and 27.87% (17/61) were submitted to PPV combined with intraocular antibiotic injection as a first approach. In cases where antibiotic injection preceded PPV, PPV was conducted on a median of 2 days after injection (2-3).

Systemic antibiotics were administered in 97.59% of patients, topical antibiotics in 91.57% and subconjunctival antibiotics in 15.66%. The different antibiotics used are summarized in Table 3.

Table 3. Systemic, topical and subconjunctival antibiotics administered.

Antibiotic	Total (%)
Systemic (n=81)	
Ciprofloxacin	41 (50.62)
Ceftazidime	29 (35.80)
Ceftriaxone	19 (23.46)
Levofloxacin	4 (4.94)
Trimethoprim/Sulfamethoxazole	2 (2.47)
Cefazoline	1 (1.23)
Amoxicillin	1 (1.23)
Topical (n=76)	
Ceftazidime	58 (76.32)
Vancomycin	55 (73.37)
Ofloxacin	22 (28.95)
Tobramycin	8 (10.53)
Oxytetracycline	6 (7.89)
Trimethoprim/Sulfamethoxazole	1 (13.16)
Subconjunctival (n=13)	
Gentamycin	12 (92.31)
Cefuroxime	1 (7.69)

POST-TREATMENT FACTORS

Post-treatment complications included retinal detachment (13.3%), need for evisceration (8.4%), macular oedema (3.6%), corneal decompensation (2.4%), and glaucoma (2.4%). One patient also developed toxic keratitis related to the topical antibiotics administered.

The cataract surgery group was responsible for 66.67% (16/24) of all complications, accounting for 6 RDs, 4 eviscerations, 3 macular oedemas, 2 corneal decompensations and 2 glaucoma cases. The IVI group was responsible for 33.33% of cases with post-treatment complications (5 RDs and 4 eviscerations, with one patient having both complications). The difference between the two groups was not statistically significant (p=0.069).

All RDs occurred in PPV-treated endophthalmitis, in which 6/11 RDs were found intraoperatively and 5/11 took

Table 2. Comparison of visual acuity results for patients treated with intravitreal antibiotics alone versus intravitreal injections combined with *pars plana* vitrectomy.

	IVI alone (n=22)	IVI + PPV (n=61)	*p*-value
Initial BCVA[a] (LogMAR) (SE)	1.98 (0.81/2.70) (CF)	2.28 (1.98/2.70) (HM)	0.075
Final BCVA[a] (LogMAR) (SE)	0.25 (0.04/2.46) (20/40)	1.30 (0.35/2.28) (20/400)	**0.026**
BCVA Variation[a] (LogMAR) (SE)	-0.18 (-1.91/0.01)	-0.72 (-1.58/-0.05)	0.860

[a] Data is expressed using median and interquartile range (Q1/Q3).

BCVA – best corrected visual acuity; LogMAR – logarithm of the minimum angle of resolution; CF – counting fingers; HM – hand motion; IVI – intravitreal antibiotic injection; PPV – *pars plana* vitrectomy; SE – Snellen equivalent.

place after the surgery. The need for evisceration was higher in the PPV and IVI combined group (6.65%), when compared with the IVI alone group (13.64%), but this relation was not statistically significant (*P*=0.306).

DISCUSSION

Acute endophthalmitis is a rare but possibly catastrophic disease, potentially leading to irreversible blindness. This condition is in upward surge, as ever greater incidence rates have been described.[13] Amongst other causes, this surge is mainly due to the increase in both intravitreal injections, the most frequent invasive procedure in ophthalmology practice in current times, and cataract surgeries throughout the world.[14,15]

Addressing this issue is of utmost importance to effectively reduce the impact of endophthalmitis, so prophylactic measures must be held. Safety protocols for IVI procedures must include the use of sterile gloves, drapes and eyelid specula, as well as surgical-masks or a no-talking policy during procedures. Antiseptic application of topical povidone-iodine should prevail over topical antibiotics, as only povidone-iodine has shown to decrease the risk of endophthalmitis following IVIs and further avoids the financial costs and possible risk of increasing antibiotic resistance rates associated with topical antibiotic usage.[1,16-19]

For intraocular surgery procedures, topical povidone-iodine (or, alternatively, chlorhexidine) is also the standard of prophylactic care and should be applied to the cornea, conjunctival sac and periocular skin for a minimum of three minutes prior to surgery. It is also important to address the operating theatre's design, which should include standardized systems with separate clean and dirty circuits for all personnel and equipment involved in each surgery. Proper filtration of the operating theatre's airflow is required, and all operating theatres should be under positive pressure. Doors should be kept closed during procedures. All instruments for surgery should be sterile, single-use instruments should be preferred and sterilization protocols should be followed.[1]

Studying the treatment strategies for acute endophthalmitis in our population and assessing visual outcomes is key to provide the best possible approach to every patient.

This study represents the first national study of this kind, including a high number of patients when compared to other single-center retrospective studies, and including recent data which reflects modern developments in prophylactic protocols for intraocular procedures and minimal incision PPV techniques for AEE's treatment.[20-25]

Current acute endophthalmitis treatment finds its foundations in the advent of intravitreal antibiotic injections.[26,27] Their importance has been undisputed and these are now widely used to achieve better outcomes in acute endophthalmitis patients.[28,29]

The Endophthalmitis Vitrectomy Study (EVS) represents an important landmark in endophthalmitis treatment research. This major multicenter randomized clinical trial, published in 1995, established a comparison between vitreous tapping and injecting and vitrectomy treatment strategies, recommending the second only when patients had LP vision or worse at presentation.[16]

With the improvement in PPV technique over recent years, with smaller incisions, better cutting rates and duty cycle performance, and enhanced visualization techniques, this procedure has since been used more frequently than intraocular injections alone and has been recommended as "gold standard" by the European Society for Cataract & Refractive Surgeons (ESCRS).[1,30-31] In fact, an argument can be made that PPV may help to reduce infection load, clear vitreous opacification, and obtain better sampling for microbiology examination, bringing enhanced value to AEE treatment.[25,32]

Possible gains obtained by generalized use of PPV are still debatable, as recent studies which include modern PPV techniques struggle to confidently conclude its better results. Some smaller single-center retrospective studies have concluded in favor of PPV as the primary treatment for AAEs, but major studies failed to assert its superiority when compared to antibiotic IVI alone.[21,22,24,33,34] In the absence of major prospective studies including modern PPV techniques, retrospective studies like ours add significant value to better understand PPV's role in the treatment of endophthalmitis.

In our study, the final visual acuity results were similar to those described in literature, and the improvement in visual acuity in both groups (injections alone or injections and PPV combined) was significant.[13,20,22,23] As previously described by Crosby NJ *et al*, the fact that visual acuity results did not follow a normal distribution pattern can be seen as an advantage, as the use of non-parametric testing allows for the analysis of visual acuity gains to not be influenced by the absolute value of the LogMAR values assigned to the very low visual acuities, which are often inaccurate.[24]

The variation between pre- and post-treatment visual acuities was similar between the two groups, leading us to believe that IVI and PPV combined was not inferior to injection alone.

Both the need and timing for vitrectomy are difficult to assess, but this treatment strategy is often chosen in patients with more severe disease.[17] This may constitute a bias that can misguide the interpretation of our results, as poorer prognoses were to be expected from patients in which PPV was conducted. Prognosis factors related to endophthalmitis are vast, however the most relevant predictor has been shown to be visual acuity at time of presentation.[35]

As there was a significant difference in final BCVA between the two groups, with the combined IVI and PPV patients showing worse visual outcomes than the IVI alone group, the similar variation in BCVA between both groups strengthens our view that PPV may have been performed in more severe cases, leading to similar visual gains in patients with worse prognosis that the ones treated without PPV.

In our study, patients submitted to IVI and PPV combined had worse presenting BCVAs than those submitted to IVI alone, however this difference did not reach statistical

significance (P=0.075). This would most likely be overcome with the inclusion of a larger population, as made possible by multicenter studies. Nevertheless, our study failed to assert PPV's superiority in patient subgroups with worse presenting visual acuities, as visual acuity gains were similar to those obtained with injections alone. These results are in line with most major studies in this field.

We believe future larger, multicentric studies, to which single-center studies like ours may contribute, are key to more solid and updated recommendations regarding use of PPV in endophthalmitis patients.

It was not possible to study the impact of briefness in treatment initiation on visual outcomes because the great majority of patients started treatment on the day of presentation. However, literature indicates initiating treatment as soon as endophthalmitis is suspected is of extreme importance considering this disease's devastating consequences.[36,37] This is portrayed in the results obtained by Januschowski K *et al* in a study published in 2020 in which all patients were treated within 6 hours of presentation.[23]

When PPV procedure requisites are not available, antibiotic IVI injection is key and must be conducted even when a definitive microbiologic diagnosis is not available. Antibiotic injection procedures can take place almost universally at every hospital facility and should be conducted before the patient's rerouting to more centralized facilities like ours.

Systemic antibiotics are recommended in the ESCRS guidelines.[1] The pharmacokinetic principals behind this lie on the fact that systemic antibiotics can favor intraocular accumulation of injected antibiotics and expand their effect, since without systemic antibiotic administration almost complete removal from the intraocular space is to be expected after 24 hours.[38] On the other hand, blood-retinal barriers make it difficult for systemic antibiotics to penetrate into the tissues of the eye, and intraocular antibiotic levels are never comparable to those obtained by IVIs. This may be the reason why systemic antibiotics are not generally supported by past endophthalmitis studies.[39]

In the EVS, the study design used different drugs systemically and intravitreally, thus not contributing towards maintaining effective antibiotic levels within the eye.[1,16] In our study, this limitation was also present, as in only 51.58% of the patients who received systemic antibiotics, one of these antibiotics was the same as one of those injected intravitreally. Since the percentage of the patients included in our study who received systemic antibiotics was just shy of 100%, we were not able to infer on their impact on visual acuity gains.

Adjunctive subconjunctival and topical antibiotic administration are usually used at discretion of the surgeon. Benefit of topical antibiotics is debatable and, as they were used in over 90% of our patients, we were also not able to demonstrate their positive impact on visual outcomes.[19]

Major causing microorganisms may vary depending on geographical factors and endophthalmitis type, but our microbial findings are in line with past studies, reporting coagulase-negative Staphylococci as the most commonly identified organism.[1,40-42] This is to be expected since they are part of the typical ocular surface flora.

Even though Gram-positive bacteria are most commonly associated with acute endophthalmitis, Gram-negative infections (in particular Pseudomonas aeruginosa infections) may occur and have been associated with poorer visual outcomes, reaffirming the need for a broad specter antibiotic coverage when treating this condition.[6,43] Antibiotic injection agents and dosages used in our patient population were in line with those recommended in previous studies, and the broad spectrum antibiotic coverage proved effective, as only one case required change in the intravitreal antibiotic plan, with injection of cefazolin following antibiotic resistance evidence in the antimicrobial susceptibility testing regarding an *Haemophilus influenzae* infection.[1,44]

Culture positivity rates (28.79%) found were lower than the ones described in previous studies, usually between 55 and 75%.[40,41,45,46] Our rates may have been artificially lower due earlier treatment initiation, leaving less time for bacterial colonies to grow to detectable levels. Notably, in our study, culture positivity showed a significant association with worse BCVA both before and after treatment, probably due to the same principle, meaning appropriate cultures were easier to obtain in cases with more severe intraocular septic environment.

In an effort to increase culture sensitivity, a growth medium update was introduced in April 2021 which managed positivity rates of 37.04%. In fact, similar positivity rates were presented in a study by Peng KL *et al* published in 2021, in which symptom onset and treatment initiation intervals were close to the ones registered in our study.[13]

The inclusion of molecular biology examination of the collected samples, using the polymerase chain reaction technique, is not currently available at the Ophthalmology Responsibility Center for this purpose, but may further improve microbiological identification rates.

This study's limitations are related to the sample size, characteristics of single-center studies, and to its retrospective, nonrandomized study design. The data collection process is another limitation to be considered, since our study had some missing data which may affect the quality of the results.

Despite these limitations, our study will add to current knowledge on acute endophthalmitis treatment. This is the first study to be completed on a national level, but similar studies are already underway in another four central hospital facilities. Therefore, via a multicentric study, a nationwide sample that adequately reflects acute endophthalmitis cases in Portugal will be obtained in the near future. These collaborative efforts will allow us to better evaluate the management and incidence of complications resulting from this condition in the whole country.

Further studies, namely prospective, randomized controlled trials are warranted to continue the search for the best approach possible to improve outcomes for these patients.

CONCLUSION

Even though acute endophthalmitis represents a serious condition with possible catastrophic outcomes and poor visual prognosis, we found an improvement in BCVA after treatment in over 70% of patients.

This is one of the largest series of endophthalmitis cases reported by a single center in recent years. Although this single study was not sufficient to confidently demonstrate superiority of the general use of PPV in the management of these patients, our results will be included in large multicentric Portuguese study which will more adequately reflect acute endophthalmitis management in our country, as well as continue the search for the best approach possible to improve outcomes for these patients.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO:

RF and MA: Data collection, data analysis, writing
TC: Data analysis
MR and JF: Reviewing the scientific content of the article
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RF e MA: Recolha de dados, análise de dados, escrita
TC: Análise de dados
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