Efficacy and safety of retrobulbar amphotericin B injection in invasive fungal rhinosinusitis with orbital invasion patients*

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Abstract

Background: At present, there is no consensus for optimal orbital infection management in invasive fungal rhinosinusitis patients. This is the first retrospective cohort study aimed to determine efficacy and side effects of the retrobulbar amphotericin B injection for orbital management in invasive fungal rhinosinusitis patients.

Methodology: A retrospective chart review was conducted from 2005 to 2020. Thirty-six patients (forty-two orbits) diagnosed with invasive fungal rhinosinusitis with orbital invasion, treated with or without retrobulbar amphotericin B injection, were included in the study.

Results: There were a total of 36 patients in the study, 12 patients received retrobulbar amphotericin B injection and 24 did not. There was no significant difference in orbital exenteration and death between two groups. Visual acuity change at the 3rd month was significantly better in the exposure group. There was a significant difference in the overall clinical outcome at 3rd month and 12th month. There was no report of severe side effects in all patients.

Conclusions: Retrobulbar amphotericin B injection showed significant efficacy in stabilizing or even improving visual acuity without any side effects. This procedure should be considered as adjunctive treatment.

Key words: invasive fungal rhinosinusitis, chronic rhinosinusitis, retrobulbar amphotericin injection, orbital infection

Introduction

Rationale

Invasive fungal rhinosinusitis is an aggressive and invasive condition that causes significant tissue destruction with a resultant morbidity and mortality rate (40% - 80%)[1,2]. The infection often extends from the paranasal sinuses into the orbit and intracranial space. At present, there is no consensus on optimal management for orbital infection [3]. Eradication of the infection requires local control of the disease. Standard therapy includes systemic treatment with antifungal agent, aggressive orbital debridement and possible orbital exenteration. The most challenging decision remains to be whether or not to exenterate the patient [4].

Recently, there have been reports of alternative treatment modalities intended to improve the orbit's local control and possibly spare the need for exenteration. These include local administration of antifungal agents, conservative debridement with irrigation of orbital tissue and hyperbaric oxygen (HBO) [2,4]. Since there are still no proven benefits of orbital exenteration over conservative procedures [5], initiation of this treatment with the latter choice is reasonable.

Amphotericin B is a broad-spectrum antifungal agent that leads to fungal cell death by binding to fungal cell membrane components (ergosterol) and causes ion leakage. Many physicians use local administrations in the form of intraarticular, intrapleural, intranasal and retrobulbar injections.

To date, only 8 cases from case reports and case series have documented the use of transcutaneous retrobulbar amphoteri-

cin B injection. The results show that visual acuity was stabilized or improved in every case and only one patient died from the disease one month after the treatment [6].
Although previous studies have been carried out, evidence for retrobulbar amphotericin B injection is still lacking. Therefore, this study aims to demonstrate the efficacy of transcutaneous retrobulbar amphotericin B injection as orbital management in invasive fungal rhinosinusitis with orbital involvement as well as to observe its possible side effects.

Review of literature

Fungal rhinosinusitis is classified based on both duration of symptoms and histology. Chronologically, the disease can be acute (symptom duration < one month) or chronic (symptom duration > three months). Histologically, the disease can be non-invasive or invasive [6].
Acute and chronic invasive fungal rhinosinusitis are life-threatening conditions, most commonly caused by fungi within the genera *Aspergillus*, *Rhizopus* and *Mucor*. The acute form is seen almost exclusively in the immunocompromised host. Standard treatment includes 1) appropriate systemic antifungal therapy, 2) Repeated endoscopic surgical debridement of necrotic sinonasal tissue, and 3) reversal of the immunocompromised status [3,6,10].
For the management of orbital infection, there are no standard guidelines. In practice, choices of treatment include 1) appropriate systemic antifungal treatment, 2) local therapy for the orbit from conservative management such as local administration of antifungal agents, conservative debridement with irrigation of orbital tissue and hyperbaric oxygen (HBO) to an aggressive method, which is orbital exenteration. Since there is no data to support that outcomes from orbital exenteration better than conservative treatment, it is reasonable to choose the latter option. There are three local antifungal application methods reported in the literature: transcutaneous retrobulbar, transnasal, and retaining catheter.
Cahill et al. [2] reports the first successful palliative treatment of an Aspergillus fumigatus orbital mass in a patient with acquired immunodeficiency syndrome by direct injection of amphotericin B into the abscess cavity.
Colon et al. [3] published a literature review for cases of sino-orbital fungal infection treated with local administration of amphotericin B. At that time, there were only 5 case reports and 1 case series of 12 patients [7-9]. Of these, 2 cases were treated with retrobulbar amphotericin B injection. Most cases established a consistent dose of 3.5 mg/ml (range, 1–4 mg/ml) with a volume of 1 ml per injection. The frequency was not well defined, with some reports describing retrobulbar injection frequencies of 2 to 3 times per day while others reported injecting only every 48 to 72 hours. The result showed stability or improvement of VA (visual acuity) in all cases; only one case died from disease 1month after treatment. They conclude that retrobulbar Amphotericin B injection may be a useful adjunct to hyperbaric oxygen and parenteral antifungals to control sino-orbital fungal infections. More research is also needed to establish the most appropriate dosing, frequency, and duration of treatment.
Hirabayashi et al. [5] presented an excellent clearance of orbital mucormycosis with retrobulbar amphotericin B injections.
Kalin et al. [6] reviewed six cases to-date that documented the use of transcutaneous retrobulbar amphotericin B injection and reported the stabilization or improvement of visual acuity in every patient.
However, Brodie et al. [1] reported orbital compartment syndrome, a severe side effect following retrobulbar injection of amphotericin B. Other possible complications include globe perforation, optic nerve injury and retrobulbar hemorrhage.
Even though there is still no standard dose, approach or frequency of administration, outcomes from the retrobulbar amphotericin B injection are quite promising as visual acuity was stabilized or improved in all 8 cases from prior reports (6). Further study with a higher level of evidence is still needed to prove the benefits of this procedure.

Objectives

To determine the efficacy and safety of transcutaneous retrobulbar amphotericin B injection to decrease orbital exenteration rate, decrease mortality rate, and stabilize visual acuity without serious side effects.

Utility

This paper will be the first analytic studies (retrospective cohort) to investigate the efficacy and safety of retrobulbar amphotericin B injection which is a conservative option for the treatment of invasive fungal rhinosinusitis with orbital invasion patients.

Materials and methods

This study is a retrospective cohort study. Inclusion criteria were 1) Patients over 15 years of age diagnosed as invasive fungal rhinosinusitis with orbital involvement confirmed diagnosis with the histopathologic report and treated with or without retrobulbar amphotericin B injection, in King Chulalongkorn Memorial Hospital from 1st January 2005 to 30th September 2020, 2) Orbital invasion was diagnosed by clinical orbital involvement or imaging study with or without histological confirmation.
Exclusion criteria were 1) Incomplete data collection (no data of outcomes of interest or possible confounding factors), 2) Loss to follow up before three months after diagnosis.

Data collection

A chart review was conducted by using ICD 10 searching and review of all inclusion and exclusion criteria. All patients who met the criteria were included in the study. The primary outcome was

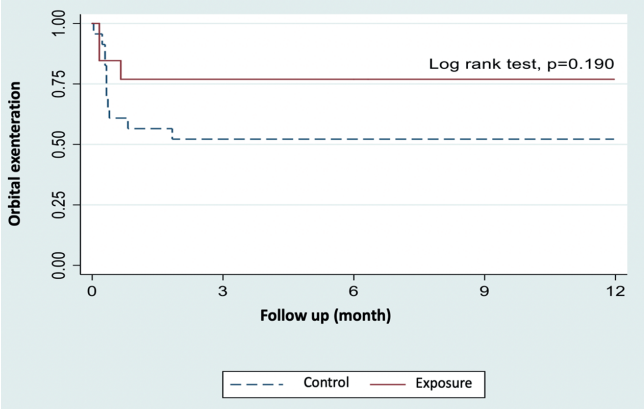

Figure 1. Kaplan-Meier curve and Log-rank test for orbital exenteration. No significant difference between the two groups.

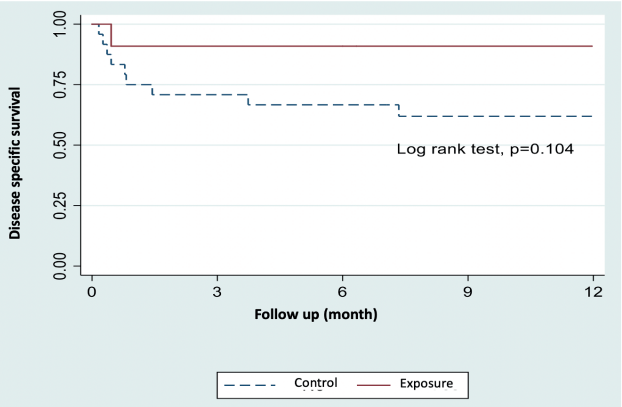

Figure 2. Kaplan-Meier curve and Log-rank test for disease-specific survival at I year. No significant difference in disease-specific survival between the two groups.

orbital exenteration recorded as time from diagnosis, undergoing tissue biopsy and receiving systemic antifungal therapy, to the exenteration date.

Secondary outcomes included 1) death from invasive fungal rhinosinusitis recorded as time from diagnosis to date that the patient passed away, 2) visual acuity change that was recorded as worse or not from diagnostic date to the first week, third month and twelfth month, 3) overall clinical outcome which was recorded as worsening if a patient was exenterated or dead from the disease at the third and twelfth month, and 4) serious side effects from the intervention such as globe perforation, optic nerve injury, retrobulbar hemorrhage or orbital compartment syndrome.

The following variables were also collected: age, gender, immunocompromised status, disease extension as intracranial involvement, a fungal pathogen, other standard treatments including systemic antifungal agent (type, duration), surgical debridement of sinonasal tissue, reversal of immunocompromised status and orbital surgical management apart from the intervention.

Statistical analysis

For statistical analysis, STATA version 15.0 was used. Survival analysis for orbital exenteration and disease-specific survival were conducted using the Log-rank test and Cox proportional hazard model. Visual acuity change (worsened or not) and overall clinical outcome were analysed using Pearson's Chi-square test. The authors also analysed baseline characteristics and possible confounding with Pearson's Chi-square test and independent t-test to seek for any significant differences between groups. Statistical significance was considered at p-value < 0.05.

Dosage and duration protocol of retrobulbar amphotericin B

During the study period, physicians used the "Department of Ophthalmology and Otolaryngology, King Chulalongkorn Memorial Hospital protocol": Amphotericin B 50 mg/vial was mixed with sterile water 10 ml for a concentration of 5mg/ml Amphotericin B then 1ml was mixed with sterile water 4 ml for a 1mg/ml solution. Physicians injected the 1 ml Amphotericin B via transcutaneous retrobulbar route, every other day for two weeks, then every week for two months. The amphotericin B injection method was carried out using a round-tipped retrobulbar needle number 25, length 1.5 inches. First, ensuring that the patient's eye was in primary gaze, palpating the inferior orbital rim while gently pushing up on the globe. The needle is inserted just above the rim at the lateral third of the eyelid. The needle is advanced, bevel up, parallel to the orbital floor. After 1 cm when the needle has passed the equator, it is redirected to about 30° superonasal, and advanced for an additional 2.5 cm. After ensuring no blood return from aspiration, no resistance and no globe rotation, 1 ml (1mg/ml) of amphotericin B is slowly injected. Mild pressure is applied after removing the needle to prevent hemorrhage and to increase the diffusion of the agent.

Ethics

Accession to patient records and research conduction were approved by the Institutional review board (IRB) of Faculty of Medicine, Chulalongkorn University. IRB No.703/63

Results

Between 1st January 2005 to 30th September 2020, there were 36 patients (42 orbits) diagnosed with invasive fungal rhinosinusitis with orbital involvement. There were 12 patients (13 orbits) in the exposure group who received retrobulbar amphotericin B injection and 24 patients (29 orbits) in the control group did not. The more recent patients have received retrobulbar injections with historical control. Every patient was evaluated by an otolaryngologist, ophthalmologist and infectious disease subspecialist at King Chulalongkorn Memorial Hospital (patient's baseline characteristics, disease extension, fungal pathogen and

Table 1. Demographic data and patient characteristics.

Baseline characteristic	Control (n=29)	Retrobulbar Amphotericin B (n=13)	p-value
Age range, (mean ± SD)	15-86 (58±15)	38-81 (59±20)	0.887
Gender (n,%)			
Male	16(55.2)	7(53.8)	0.936
Female	13(44.8)	6(46.2)	0.936
Underlying (n,%)			
unknown	2(6.9)	0	0.332
DM	21(72.4)	10 (76.9)	0.759
Hematologic malignancy	3(10.3)	1(7.7)	0.787
HIV	1(3.4)	1(7.7)	0.551
Others	2(6.9)	2(15)	0.386
Intracranial extension (n,%)			
Yes	12(41.4)	9(69)	0.095
No	17(58.6)	4(31)	0.095
Fungal pathogen (n,%)			
Mucormycosis	10(34.5)	7(54)	0.237
Aspergillus spp.	19(65.5)	5(38.4)	0.101
mixed	0	1(7.6)	0.131
Orbit surgical intervention (n,%)			
No	26(90)	10(76.9)	0.276
Orbital decompression	1(3)	1(7.7)	0.551
Conservative debridement	2(7)	2(15.4)	0.386
Immune reconstitution (n,%)			
Yes	2(7)	2(15.4)	0.386
No	27(93)	11(84.6)	0.386

Independent t test and Chi-square test.

therapeutic management other than the retrobulbar amphotericin B are shown in table1). There was no significant difference between exposure and control group. All patients received proper systemic antifungal therapy and sinonasal surgical debridement according to their disease severity and clinical response.

Primary outcome

Orbital exenteration

Of 42 orbits, 29 in the control and 13 in the exposure group, six orbits belonged to patients who died before exenteration, therefore, were not included in the analysis. 11 of 23 orbits were exenterated in the control group compared with 3 of 13 orbits in the exposure group. All patients were exenterated within the first month, except one patient in the control group. Calculated survival probabilities at 3rd month were 52% (95%CI 31-70%) and 77% (95%CI 44-92%) in the control and exposure groups, respectively. From the survival analysis displayed as Kaplan-Meier curve using Log-rank test(Figure 1), there was no significant difference in orbital exenteration between both groups, p=0.19.

Secondary outcomes

1) Visual acuity change

Visual acuity change was recorded at the first week, third month and twelfth month as worsening or stable to improved, compared to pretreatment. One patient in the control group (2orbits) died before the 1st week, so it was not included in the analysis. Using Pearson's Chi-square, of 40 orbits, 27 in the control and 13 in the exposure group, there was no significant difference in VA change at the first week, p=0.748. At the 3rd month, 76.9% (10/13) of patient's orbit in the retrobulbar amphotericin B injected group achieved stable or improved VA compared to 39.1% (9/23) in the control group with a statistically significant difference, p=0.029 RR1.97(95% CI1.09-3.55). There is missing data of 4 orbits in the control group because patients died before three months. There was no significant difference in VA change at the twelfth month between the two groups, p=0.225. Two patients in the control group had worsened VA during the 3rd to 12th months compared to one patient in the exposure group. There were four more patients missing data at the 12thmonth in each group due to loss of follow-up; of these three orbits had worsened VA in the control group, but all four orbits in the exposure group had stable or improved VA at the 3rd month.

2) Death from invasive fungal rhinosinusitis

A total of 36 patients, 9 of 24 in the control group, and 1 of 12 in the exposure group, died from the disease. By the 3rd month, most patients died (7 from control, 1 from exposure group) with survival probability of 71% (95%CI 48-85%) and 91% (95%CI 51-99%) in the control and exposure group, respectively. From the survival analysis using the Log-rank test (Figure 2), there is no significant difference between the two groups, p=0.104. Using the Cox Proportional hazards model, HR was 0.21(95%CI 0.026-1.66) for death in the exposure group compared to the control group.

3) Side effects

There were no serious side effects reported after retrobulbar amphotericin B injection in the exposure group.

4) Overall clinical outcome

Overall clinical outcome was defined as worsening when the patient required orbital exenteration or were deceased at 3rd and 12th months. Using Pearson's Chi-square for the total of 36 patients, there was a significant difference in Overall clinical deterioration between both groups at the 3rd month, p= 0.0094,

Table 2. Visual acuity change from Pretreatment at first, third and twelfth month.

VA change from pretreatment	1st week		3 month		12 month	
	Retrobulbar injection	No	Retrobulbar injection	No	Retrobulbar injection	No
worse	4 (30.8%)	7 (25.9%)	3 (23.1%)	14 (60.9%)	4 (44.4%)	13 (68.4%)
Stable or improved	9 (69.2%)	20 (74.1%)	10 (76.9%)	9 (39.1%)	5 (55.6%)	6 (31.6%)
p-value	0.748		0.029*		0.225	

Pearson's Chi-square test, * $p < 0.05$.

Table 3. Overall clinical deterioration defined as the patient was dead or exenterated at third and twelfth month.

		Retrobulbar AmB injection		p-value
		Yes (n=12)	No (n=24)	
Overall clinical deterioration 3 month	no	10 (83%)	9 (37.5%)	0.0094*
	yes	2 (17%)	15 (62.5%)	
		Retrobulbar AmB injection		p-value
		Yes (n=9)	No (n=23)	
Overall clinical deterioration 12 month	no	7 (78%)	8 (35%)	0.0284*
	yes	2 (22%)	15 (65%)	

Pearson's Chi-square test, * $p < 0.05$.

RR 0.27 (95% CI=0.073-0.98) and at the 12th month p=0.0284 RR 0.34 (95% CI=0.097-1.199).

Discussion

Baseline characteristics, other standard treatments including systemic antifungal agent (type, duration) and surgical procedure between study groups, were no differences between study groups.

The results from this study showed no significant differences in the primary outcome of orbital exenteration between patients who received transcutaneous retrobulbar amphotericin B compared to the control group and death from invasive fungal rhinosinusitis. The findings may be explained by the study being underpowered to demonstrate any significant differences for survival analysis. However, this sample size was adequate for categorical data analysis. There was a significant difference in the secondary outcome of worsening of visual acuity in the control group at the 3rd month. Due to loss to follow-up in worse VA patients in the control group, there were no significant differences at the twelfth month between groups. Overall clinical outcome worsened when a patient died or required orbital exenteration. There was a significant difference between the two groups at the 3rd and 12th months but there was also low accuracy from the small sample size. No side effects occurred in any of the patients in both groups.

This work is the first retrospective cohort study that compared the efficacy and side effects of transcutaneous retrobulbar amphotericin B injection to control group. From our results, retrobulbar amphotericin B injection has achieved this objective to stabilize or even improve the visual acuity, which is supported by findings from a previous case report and case series from Colon et al. [3] and Kalin et al. [6]. Although the result is still not significant for orbital exenteration due to the limited sample size, it is quite promising to find that this procedure can improve the outcome. Although it may not be possible to report that only the effect from retrobulbar amphotericin B injection alone can improve patient survival rate, it could be an integral part of the proper management process to help control the source of infection and prevent a patient from death. Our results also failed to exhibit this effect; however, further study should take this matter into account. This study has proven the safety of this procedure in all 13 orbits.

A limitation of this study is the small sample size, even though we included all patients that were consistent with the study protocol. Four patients in the control group and three patients in the exposure group were lost to follow up before one year and 2 patients in the exposure group were followed up but there was no available VA data at the 12th month. Potential confounding factors were the protocol of retrobulbar amphotericin B injection used during the earlier study time in which the protocol

had just established and data was still recorded on paper with some visits and there was no mention of injection detail. With the retrospective study design, we were unable to control the exact date that patients received the retrobulbar amphotericin B injection from the diagnostic date, which counts as the start of the study. However, all of the patients had orbital involvement at their presentation and started to receive retrobulbar amphotericin B injections not more than 2 days after their biopsies. Data collection of visual acuity was first planned to use the Log-MAR scale, but because of severe orbital involvement, almost all data was recorded as "no light perception" or "light projection" so, we changed the data collection method as progression of VA which is a categorical data and prone to be more subjective.

Further research is still needed to prove the efficacy of retrobulbar amphotericin B injection with a larger sample size and a higher level of evidence to answer the therapeutic research question. Besides patient characteristics of infected orbital severity that will benefit from the procedure, data for appropriate dose and frequency of injection is still needed.

Conclusion

Retrobulbar amphotericin B injection showed significant efficacy in stabilizing or even improving visual acuity without any side effects. This procedure should be considered as conservative treatment for invasive fungal rhinosinusitis patients with orbital invasion prior to more aggressive treatment such as orbital exenteration. A study with a larger sample size and higher quality of evidence is still needed to support these findings.

Authorship contribution

PA: Data collection, Data analysis and interpretation, Drafting the article, Final approval of the version to be published. PS: Conception or design of the work, Data collection. SA, KS, SC: Final approval of the version to be published. JK: Conception or design of the work, Data collection, Data analysis and interpretation, Drafting the article, Critical revision of the article, Final approval of the version to be published.

Conflict of interest

No conflict of interest.

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