Clinical Outcomes in Acanthamoeba Keratitis Treated with Polyhexamethylene Biguanide as Monotherapy

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Abstract

***Purpose*:** To assess the efficacy of polyhexamethylene biguanide (PHMB) in treating Acanthamoeba keratitis (AK) and also to identify related factors affecting final visual outcome in AK patients treated with PHMB

***Methods*:** In these interventional case series study, 27 eyes of 25 patients with AK received PHMB 0.02% and divided into two groups according to the final visual acuity (VA); VA equal to or greater than $^{20}/_{25}$ and VA less than $^{20}/_{25}$. Two groups were evaluated for the effectiveness of PHMB in treatment of AK.

***Results*:** Before treatment, more than 85% of the eyes had VA of less than $^{20}/_{25}$ whilst after treatment final VA was $^{20}/_{25}$ or better in 66.7% of eyes. VA regressed in 14.8% of the eyes during follow-up and improved or remained the same in more than 85% of eyes. Patients with deep stromal keratitis or a ring infiltrate had more than a 28-fold increase in the odds of a visual outcome worse than $^{20}/_{25}$ [odd ratio (OR), 28.0; 95% CI, 3.3-240.8, p=0.001]. Patients with Initial VA<$^{20}/_{40}$ had a 9-fold increase in the odds of a visual outcome worse than $^{20}/_{25}$ (OR, 8.6; 95% CI, 1.2-59.8, p=0.003). Longer duration of symptoms (≥ 3 weeks) or the medication used prior the first visit were not associated with poorer final VA (p>0.05). Five eyes (18.5%) finally required keratoplasty.

***Conclusion*:** Initial stage of corneal involvement at presentation was the most predictive factor for final visual outcome in AK. Although PHMB, even as monotherapy, is effective in treatment of AK, a remarkable proportion of patients still suffer a final grim visual outcome which requires aggressive treatments.

***Keywords*:** Acanthamoeba Keratitis, Polyhexamethylene Biguanide, Visual Acuity

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Introduction

After the first reported cases of Acanthamoeba keratitis (AK) in 1973,[1,2] there has been a dramatic increase in the incidence rate of this disease in recent decades simultaneous to the growing rate in the number of soft contact lens wearer.[3,4] AK is a rare, but devastating corneal infection which is characterized by severe pain, sometimes disproportionate to the signs that can lead to considerable visual loss and ocular morbidity.[3] There have been several reports about the prevalence and clinical courses of AK in Asia,[4-6] Europe,[7,8] New Zealand,[9] America[10] and Africa.[11-12] A majority of cases with AK are through contact lens wearers[3] with a predominance of soft lenses compared to rigid ones.[3,13]

In recent years, some efficient topical therapeutic agents for AK such as polyhexamethylene biguanide (PHMB) and propamidine isethionate have been reported.[14,15] These new treatments seems to be an appropriate replacement and can prevent reinterventions like keratoplasty that was commonly indicated in the early 1980s.[16] The efficacy of PHMB for AK, particularly as combination therapy has been confirmed by several studies.[17-19] Though there are a limited number of well designed studies with adequate sample size and statistical significant which have investigated the efficacy of PHMB in treating AK as monotherapy. Meanwhile, there is a wide gap in the literature to assess prognostic factors affecting final visual outcome in patients with AK who underwent treatment with PHMB. Some factors such as late presentation,[20-22] corneal disease staging at presentation,[23] and also initial visual acuity (VA)[24] have been suggested to be associated with worse visual outcomes after treatment of AK. This study was designed to assess the efficacy of PHMB as monotherapy in treating AK and also to identify other related factors affecting final visual outcome in patients with AK treated with PHMB.

Methods

Study design, population, inclusion and exclusion criteria

The study protocol was approved by Ethics Committee of Tehran University of Medical Sciences (TUMS). In this interventional study, between April 2009 and April 2010, all consecutive cases with AK presented to Farabi Eye Hospital, Tehran, Iran, were enrolled. An informed consent was obtained from the patients or their parents for children under 18 years prior their enrollment. At entrance, a detailed questionnaire about patients' demographic characteristics and past medical history including age, gender, previous treatments were registered by trained ophthalmology residents. Initial best corrected visual acuity (BCVA) was measured by an optometrist. Then all the patients underwent slit-lamp examination by a the same corneal fellowship (SMR) and were categorized in three stages based on the depth of corneal involvement; stage I was defined as one of the three conditions: (i) epithelial splitting or elevated line; (ii) epithelial irregularity; (iii) pseudodendritis. Anterior stromal infiltration was considered as stage II, and stage III was determined as either deep stromal or ring infiltration.

Confocal biomicroscopy was performed for the patients and in the cases of Acanthamoeba cysts or trophozoite it was considered positive. To confirm Acanthamoeba infection, specimens from patients' cornea or contact lens solutions were sent for microbiologic culture. Those with negative microbiologic culture results but with a history of contact lens wear or specific clinical manifestations suggestive of AK such as keratitis with disproportionate pain, ring or perineural infiltrates were included in the study if their confocal test was positive. Finally, those who were recognized as AK according to the clinical symptoms, ocular examination and results of confocal or microbiologic culture were enrolled in the study. Whenever initial evaluation confirmed other forms of microbial keratitis other than AK, patients were taken apart from the trial. Patients with low vision in the eye without AK or those without compliance during the treatment were excluded. In the cases of drug toxicity in each stage of the protocol, drug was discontinued and patient was switched to other treatments.

Treatment protocol

After diagnosis of AK was established, patients received PHMB 0.02% (Sina Company, Tehran, Iran). In seven referred

patients who showed no response to other anti-Acanthamoeba treatments (six patients treated with propamidine and one had received ketoconazole), previous drugs were discontinued. PHMB 0.02% was commenced for the affected eye for the first two days with the frequency of hourly day and night application; reduced to hourly by day for the next three days and then reduced to each two hours daily. According to the clinical response to the treatment, drug was gradually tapered. In some of the patients specially those with anterior uveitis, topical steroid (Betamethasone 0.1%) was applied to control inflammation. In none of the cases, steroid therapy was applied in the first two weeks and it was discontinued prior to the end of treatment with PHMB in all of them. Patients who showed scleritis symptoms receive oral prednisolone 1 mg/kg. Oral analgesic (Acetaminophen 325 mg) or artificial tear eye drops were prescribed in some patients in order to regress patients' symptoms.

Patients were followed each 2-3 days in the first 10 days after initiation of treatment, then weekly up to the first month and then each 2-4 weeks up to the end of the treatment. In each visit, patients were evaluated for BCVA, associated complications and clinical response of their symptoms and signs to the treatment. These complications were limbitis, persistent epithelial defect, scleritis, anterior uveitis, cataract, glaucoma, eyelash downfall, corneal vascularization and reactivation of the disease after the initial response to the treatment. Treatment was considered successful whenever all primary ocular complaints except visual loss were disappeared and there was no sign of active disease in ocular examination. The end of the treatment was defined as discontinuation of PHMB and all other used drugs based on the disappearance of all symptoms and signs of the disease. All the patients were followed at least six months after the treatment ended.

Primary and secondary outcomes

Primary outcome was final BCVA which was measured by constant optometrist who measured initial one. This value was classified as $\geq {}^{20}/_{25}$ and $< {}^{20}/_{25}$. Secondary outcomes were duration of treatment with PHMB and presence of corneal scar at the end of the treatment. Severity of corneal involvement was quantified as the percentage of corneal surface with scar divided into the total surface of cornea. Corneal images of affected eyes were analyzed using Imege software (version Mac OS 9.0.4, Apple computer, INC.). The need for corneal graft was assessed after six months of treatment. Patients who needed corneal graft were categorized in two groups of optical penetrating keratoplasty and optical lamellar keratoplasty.

Statistical analysis

Results were reported as mean±standard deviation (SD) for quantitative variables and percentages for categorical variables. The groups were compared using the Student's *t*-test for continuous variables and the χ^2 test (or Fisher's exact test if required) for categorical variables. P-values of 0.05 or less were considered statistically significant. All the statistical analyses were performed using SPSS version 13 (SPSS Inc, Chicago, IL, USA) for Windows.

Results

Demographic characteristics, clinical presentation

Table 1 summarizes patients' demographic characteristics and clinical data. In this study 25 consecutive cases (27 eyes; 21 females and 4 males) with documented diagnosis of AK were recruited. Mean age of subjects was 23±6 years (range, 14-36 years). Majority of subjects wore contact lens, and presented with VA of less than ${}^{20}/_{25}$. Patients mostly had previous history of treatment with anti-viral, anti-bactrial, anti-Acanthamoeba, and corticosteroids therapies. One third of subjects presented in the late stage of corneal involvement.

Clinical course

Primary and secondary outcomes have been shown in table 2. After treatment, final VAs were equal or greater than ${}^{20}/_{25}$ in two third of patients. The majority of patients received PHMB associated with corticosteroids which prevented worsening of symptoms, and improved VA in 85% of subjects. Corneal scar was found in around 60% of subjects after treatment. The mean percentage of corneal surface involvement was 13%.

Primary outcomes

Table 3 presents the association between patients' demographic and clinical characteristics and final visual outcome of $<^{20}/_{25}$. Patients with deep stromal keratitis or a ring infiltrate had more than a 28-fold increase in the odds of a visual outcome worse than $^{20}/_{25}$ [odd ratio (OR), 28.0; 95% CI, 3.3-240.8, p=0.001]. The mean final BCVA did not show a significant difference in patients with corneal involvement stages 1 and 2 (0.91±0.3 vs. 0.92±0.15, p=0.97). Patients with stages 1 and 2 of corneal disease had a better BCVA than those with stage 3 of corneal disease (0.91±0.3 and 0.92±0.15 vs. 0.78±0.31, p=0.001, p=0.02, respectively). Patients with Initial VA$<^{20}/_{40}$ had a 9-fold increase in the odds of a visual outcome worse than $^{20}/_{25}$ (OR, 8.6; 95% CI, 1.2-59.8, p=0.003). Longer duration of symptoms (≥3 weeks) or none of the medication used prior the first visit were not associated with poorer final visual outcome (p>0.05).

Secondary outcomes

The percentage of corneal scar in patients with worse initial VA ($\leq^{20}/_{63}$, N=12) was greater than those with better VA ($\geq^{20}/_{25}$, N=4), (22.8±22.1% vs. 4.0±8.3%, p<0.001), and the mean duration of PHMB treatment was also longer (164.7±53.7 days vs. 121.1±44.7 days), however this difference in the duration of treatment was not significant (p=0.4). Likewise, patients with stage 3 of corneal disease at presentation had finally more percentage of corneal scar as compared to patients with stages 1 and 2 (31.2±21.6% vs. 4.0±7.5%, p<0.001), and were under PHMB treatment for a longer duration of time (135±46 days vs. 101±48 days, p=0.1).

Complications

Table 4 lists patients' complications at initial and during follow-up. Five eyes (18.5%) finally required keratoplasty (perforating keratoplasty for three eyes and lamellar keratoplasty for two eyes).

Table 1. Patients' demographic characteristics and clinical data (25 patients, 27 eyes)

Variables	Mean±SD or % (n)
Age (years)	23.1±6.2
Female gender	84.0 (21)
Involved eye	
Right	52.0 (13)
Left	40.0 (10)
Both	8.0 (2)
Lens wear	
Cosmetic contact lens	85.2 (23)
Optical contact lens	11.1 (3)
Positive Confocal biomicroscopy	96.3 (26)
Positive culture microbiology	81.5 (22)
Initial visual acuity	
VA≥20/25	14.8 (4)
20/63<VA<20/25	40.7 (11)
VA≤20/63	44.4 (12)
Duration of symptoms before treatment	
≤3 weeks	63.0 (17)
>3 weeks	37.0 (10)
Previous anti-Acanthamoeba treatment	26.9 (7)
Previous corticosteroids treatment	44.5 (12)
Duration of previous anti-Acanthamoeba Treatment (Days)	19.3±22.4 (range, 5-70)
Duration of previous corticosteroids Treatment (Days)	11.0±9.1 (range, 2-30)
Previous antibacterial use	92.6 (25)
Previous antiviral use	33.3 (9)
Stages of corneal disease	
Stage 1	40.7 (11)
Stage 2	25.9 (7)
Stage 3	33.3 (9)

Stages of corneal disease; Stage I was defined as one of the three conditions: (i) epithelial splitting or elevated line; (ii) epithelial irregularity; (iii) pseudodendritis. Anterior stromal infiltration was considered as stage II, and stage III was determined as either deep stromal or ring infiltration.

Table 2. Primary and secondary outcomes of the study

Outcomes	Mean±SD or % (n)
Final BCVA	
VA≥$^{20}/_{25}$	66.7 (18)
VA<$^{20}/_{25}$	33.3 (9)
Quality of final VA compared to initial VA	
Better	77.8 (21)
Same	7.4 (2)
Worse	14.8 (4)
Duration of treatment with PHMB (days)	112.6±49.3 (range, 40-215)
Duration of treatment with Corticosteroids (days)	74.9±51.1 (range, 17-180)
Required keratoplasty	
Perforating keratoplasty	11.1 (3)
Lamellar keratoplasty	7.4 (2)
Presence of corneal scar	59.5 (16)

BCVA: Best corrected visual acuity, PHMB: Polyhexamethylene biguanide

Table 3. Association between patients' demographic and clinical characteristics and final visual<$^{20}/_{25}$

Variables	OR	Confidence interval	p
Demographic and Clinical factors			
Symptoms duration≥3 weeks prior treatment Vs.<3 weeks	1.6	0.3-8.2	0.57
Stage 3 corneal disease at presentation Vs. stages under 3	28.0	3.3-240.8	0.001
First BCVA≥$^{20}/_{40}$ vs.<$^{20}/_{40}$	8.6	1.2-59.8	0.003
Medication use before treatment			
Steroid use	2.0	0.39-9.9	0.41
Antibiotic use	1.2	0.15-3.6	0.30
Antiviral use	0.45	0.07-2.8	0.39
Anti-Acanthamoeba use	0.74	0.11-4.90	0.75

BCVA: Best corrected visual acuity

Table 4. Patients' complications at initial and during follow-up

Complications	% (n)
Inflammation of limbus	
At initial	22.2 (6)
In continue	59.3 (16)
Corneal scar	59.3 (16)
Uveitis	
At initial	3.7 (1)
In continue	48.1 (13)
Corneal vascularization	33.3 (9)
Persistent epithelial defect	22.2 (6)
Scleritis	18.5 (5)
Eyelash downfall	18.5 (5)
Reactivation	11.1 (3)
Cataract	7.4 (2)
Glaucoma	3.7 (1)

Discussion

AK is a rare, but devastating ocular infection which is mostly associated with grim visual outcomes. In this study a considerable proportion of cases (65.0%) were diagnosed within three weeks subsequently at initiation of symptoms and in early stage of corneal disease (40.2%). Before treatment, more than 85% of all patients had BCVA of less than $^{20}/_{25}$ whilst after treatment protocol finally 66.7% of them achieved final VA of $^{20}/_{25}$ or better. Only

in 14.8% of cases, VA regressed during follow-up and more than 85% of them showed improvement or the VA remained unchanged. These results are considerably higher compared with previous similar studies,[25] and are also comparable with those achieved by other studies used combination therapy.[15,19,26] In a similar setting, Yamazoe et al investigated the final VA in patients with AK who received chlorhexidine gluconate. Their patients were divided into two groups according to the final visual outcomes ($VA \geq {}^{20}/_{25}$ or $< {}^{20}/_{25}$). Similar to our findings, patients with severe corneal disease at initial presented had worse VA at the end.[24] They reported VA at initial examination as the most predictive factor for final visual outcome in patients with AK.[24] Therefore, early diagnosis of patients with a better initial VA would improve the final VA. Applying simultaneous two parallel diagnostic techniques can lead to diagnosis of patients in earlier stages of the disease,[3,23] therefore patient can receive treatment earlier which can affect final visual outcome.[3,27-30] AK diagnosis in our study was based on both microbiologic confirmation of disease and Confocal biomicroscopy leading to a remarkable positive diagnosis rate of 100% with simultaneous objective evidences of disease in ocular examination. Up to our knowledge, the percentage of AK diagnostic confirmation in this series exceeded previous similar studies.[4,23,31]

Duration of symptoms prior to treatment is another factor that can affect initial disease staging or final VA.[23] However symptoms duration is based on the patient's recall, and may not be reliable enough in predicting the final visual results. Since the rate of clinical and anatomical disease progression is individually different and depends upon several factors in the host. Therefore, more objective variables like corneal disease staging at presentation with slit-lamp examination could be more reliable and should be of priority.[23,25] EY et al in a well-designed study of 72 eyes (65 patients) with AK concluded that corneal disease staging at presentation was strongly associated with final visual outcome.[23] The other issue is to identify that corneal involvement stage grading by slit-lamp examination is due to Acanthamoeba infection or the reactive host immune response is causative.

Application of a good diagnostic technique which permits early diagnosis seems to have a critical role in patient's final outcomes. In vivo corneal confocal scan is a rapid noninvasive tool for the diagnosis of acanthamoeba and fungal keratitis with high sensitivity and specificity compared with smear and culture. It may also be helpful in excluding fungal or Acanthamoeba-like structures in cases with negative bacteriologic results and in early bacterial keratitis before clarification of microbiologic results.[32]

Individual characteristics may affect person susceptibility for disease and may affect the outcome of treatment. Our data revealed the predominance of female gender and the young ages among patients with AK. Nearly the whole of our patients (except one) had a history of contact lens wear. Contact lens, especially soft lens, is a known risk factor of AK. However non-contact lens wearers also can present the disease,[33-36] and may even have poorer visual outcome due to the delay in diagnosis.[13,35] Finally, five eyes (18.5%) required keratoplasty (perforating keratoplasty for three eyes and lamellar keratoplasty for two eyes). This rate is relatively greater than previous reports.[15,23,25]

The limitations of our study were low sample size and no control group. Further studies with adequate sample size are required to confirm associations seen in this study. Twelve of 27 eyes (44.5%) received steroids before diagnosis, statistically limiting the ability to examine the effect of steroids on the disease outcome. It was not clear to determine which complication was caused by courses of the disease or was side effect of the drugs. Also patient's satisfaction at the end of the treatment could be added as one of the outcome measures.

Conclusion

Initial stage of corneal involvement at presentation was the most predictive factor for final visual outcome in AK. Although PHMB, even as monotherapy, is effective in treatment of AK, a remarkable proportion of patients still suffer a final grim visual outcome which requires aggressive treatments.

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