Gentamicin Nasal Irrigation in Children with Chronic Rhinosinusitis: A Retrospective Cohort of 38 Patients

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ABSTRACT

Background: Chronic rhinosinusitis is a common problem in patients with allergic rhinitis or antibody deficiency. Topical antibiotic therapy for chronic sinusitis has been shown to improve symptoms and quality of life in adults. The objective of this study was to describe the clinical outcomes after using gentamicin nasal irrigation in children with recalcitrant rhinosinusitis.
Methods: This retrospective cohort was performed in children with chronic rhinosinusitis who received gentamicin nasal irrigation from January 2005 through February 2011. The clinical symptoms, frequency of sinusitis, hospitalization and antibiotic treatment due to rhinosinusitis between pre- and during treatment of gentamicin nasal irrigation were compared.
Results: Thirty-eight patients (23 males) with the mean age of 12.7±1.1 years were recruited. The most common comorbidities were allergic rhinitis and antibody deficiency. After the initiation of gentamicin nasal irrigation, there were significant improvements in nasal congestion, rhinorrhea, itching, post nasal drip, purulent nasal discharge, halitosis, chronic cough, sneezing and anosmia ($p<0.05$). The frequency of sinusitis and the frequency of antibiotic treatment were significantly decreased after the treatment ($p\leq0.001$). Hospitalization due to sinusitis exacerbation and number of intravenous antibiotic infusions also significantly decreased ($p<0.05$). The success rate of treatment was 78.9% (CI 0.64-0.89). There was no reported complication.
Conclusion: This study showed that gentamicin nasal irrigation was useful in the reduction of rhinosinusitis symptoms and hospitalization in children with chronic rhinosinusitis without reported complication.

Keywords: Chronic rhinosinusitis, gentamicin nasal irrigation, children with chronic rhinosinusitis, treatment of chronic rhinosinusitis

Siriraj Med J 2014;66:28-32
E-journal: http://www.sirirajmedj.com

INTRODUCTION

Chronic rhinosinusitis (CRS) is an inflammatory condition involving the paranasal sinuses and the lining of the nasal passages.[1] CRS (with or without nasal polyps) in both adults and children is defined as: presence of two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior /posterior nasal drip): ± facial pain/pressure; ± cough for more than 12 weeks.[1] CRS is strongly correlated with increased morbidity, emotional distress and poor physical and social function.[2,3]

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Received 23 May 2013
Revised 18 July 2013
Accepted 25 July 2013

The microbiology of CRS includes *H. influenzae, S. pneumoniae, M. catarrhalis, coagulase-negative Staphylococci, α-hemolytic Streptococci* and anerobes (*anerobic Streptococci, Bacteroides* and *Fusobacteria*).[4-7] Additional antibiotic therapy and adenoidectomy should be considered before functional endoscopic sinus surgery.[8]

Adjunctive agents are frequently prescribed in addition to systemic antibiotics (ATB) in order to facilitate drainage of retained secretions through sinus ostia into nasal cavity. Isotonic saline nasal irrigation is used for mechanical removal of mucous and also enhancement of mucociliary clearance.[9] Nasal irrigation, performed with a large volume and delivered with low positive pressure, are more effective than saline sprays for the treatment of CRS symptoms.[10] The most frequently recommended medications for treatment of both acute and chronic rhinosinusitis are antibiotics, followed by antihistamines, nasal decongestants, corticosteroids, antitussive, expectorant, and mucolytic agents, respectively.[11] Antihistamines,

intranasal corticosteroids and decongestants have been prescribed to reduce mucosal edema, capillary permeability, and mucus production.[11]

Along with oral and intravenous antimicrobial therapies for the treatment of CRS, topical administration of these agents has become increasingly popular over the past few years. The interest in topical antimicrobial agents is based on their ability to localize delivery to the sinonasal mucosa in order to minimize the systemic side effects seen with systemic antibiotic.[12,13] The previous efficacy study of 4-week, large-particle nebulized topical tobramycin-saline solution in the patients with CRS who were refractory to medical and surgical therapy, showed the improvement of symptoms and objective parameters of CRS.[14] Another study showed that nasal lavage with 0.05% mupirocin was effective and well tolerated in the treatment for post-surgical recalcitrant CRS associated with *Staphylococcus aureus* infection.[15]

Topically administered aminoglycosides such as gentamicin have been introduced since 1983.[16] They may have the positive effect on target organisms that may be resistant to oral antibiotics. Delivering drugs directly to the site of infection may reduce bacterial colonization. The rate and extent of bacteria killed by aminoglycosides are a function of drug concentration or dose dependent, but not time dependent.[17] The antibacterial activity of gentamicin is limited to gram-negative organisms and some Gram-positive cocci including *Staphylococcus aureus.* Gentamicin nasal irrigation has been used in the pediatric allergy clinic at Siriraj Hospital since 2005. A number of the CRS patients were prescribed gentamicin nasal irrigation when their symptoms had not improved after a full course of antibiotics, NSS irrigation and the appropriate treatment of comorbidities. The solution for gentamicin nasal irrigation consisted of gentamicin 8 mg in isotonic saline 80 ml. The patients irrigated each nostril with 20 ml of the solution twice daily. No previous studies have been done to evaluate the efficacy of gentamicin nasal irrigation in CRS children.

The aim of this study was to describe the clinical outcomes after using gentamicin nasal irrigation in children with recalcitrant rhinosinusitis.

MATERIALS AND METHODS

Subjects

This retrospective cohort was performed in children with chronic rhinosinusitis who received gentamicin nasal irrigation. The medical records of children with CRS who received gentamicin nasal irrigation at the pediatric allergy clinic, Siriraj Hospital, from January 2005 to February 2011 were reviewed. Patients were excluded if they used gentamicin nasal irrigation less than 3 months, received azithromycin prophylaxis, intravenous immunoglobulin (IVIG), immunotherapy or underwent surgical intervention within 1 year before or 6 months after starting gentamicin nasal irrigation. The local gentamicin nasal irrigation solution is made by Siriraj Hospital pharmacy in the concentration of 4 mg/mL. Two mL of solution was diluted with NSS to 80 mL. Twenty mL of diluted solution was irrigated to each nostril twice daily. The dose of gentamicin nasal irrigation was 2 mg per each nostril/dose. All of the cases included in the study had used normal saline irrigation for at least 3 months without response before gentamicin nasal irrigation was started. The study was reviewed and approved by the Institutional Review Board of the Faculty of Medicine Siriraj Hospital, Mahidol University (Si.024/2011).

The clinical data included age, sex, weight, height, onset of sinusitis, age of gentamicin usage, comorbidities, and family history of atopy and environmental exposure were recorded. Allergic rhinitis was diagnosed according to modified Allergic Rhinitis and its Impact on Asthma (ARIA).[18] Medications, frequency of sinusitis exacerbation, number of hospitalizations due to sinusitis exacerbation, frequency and duration of ATB usage and number of intravenous ATB usages in the period of at least 6 months before (pre-treatment) and during gentamicin nasal irrigation (during treatment) were recorded as the occurrences per year.

Statistical analysis

Data were analyzed with SPSS 16 program (SPSS Inc, Chicago, Illinois). Comparison between pre and during treatment was calculated by Wilcoxon signed-rank test. Statistical significance was denoted by p-value of less than 0.05.

RESULTS

There were 207 patients who were on gentamicin nasal irrigation at Siriraj Hospital during the 5-year-period. Among them, 120 patients (58%) were classified as chronic rhinosinusitis. Thirty eight patients (18.4%) met the inclusion criteria and were enrolled into this study.

Of 38 enrolled patients, 23 (60.5%) were male and 15 (39.5%) were female. The mean ± SD age was 12.7 ± 1.1 years. The mean age at the onset of sinusitis was 5.8 ± 1.0 years and the mean age when gentamicin nasal irrigation was started was 8.5 ± 1.1 years. The most common comorbidities were allergic rhinitis (n=20, 52.6%) and IgG subclass deficiency (n=20, 52.6%). Family history of atopy was found in 67.6%. Demographic data of the patients has been shown in Table 1.

Intranasal corticosteroid was the most common drug used in the pre-treatment period (n=34, 89.5%) followed by antihistamine (n=27, 71%). There was no significant difference in medications usage between pre- and during gentamicin nasal irrigation treatment as shown in Table 2.

Both purulent nasal discharge and postnasal drip were the most frequent complaints (n=38, 100%) followed by nasal congestion and rhinorrhea (n=37, 97.4%). Severity of rhinosinusitis symptoms were compared between pre- and during gentamicin nasal irrigation treatment as shown in Table 3. During gentamicin nasal irrigation, there were significant improvements in nasal congestion, rhinorrhea, itching, post nasal drip, purulent nasal discharge, halitosis, chronic cough ($p \leq 0.001$), sneezing, headache and anosmia ($p < 0.05$). There were no significant differences in facial pain and fatigue.

The frequency of sinusitis, the frequency of antibiotic usage, duration of antibiotic usage and number of antibiotic usages significantly decreased after the treatment ($p \leq 0.001$). The number of hospitalization and intravenous antibiotic usages also significantly decreased after the treatment ($p<0.05$) as shown in Table 4. The frequency of sinusitis decreased in 30 out of 38 patients, so the success rate of treatment with gentamicin nasal irrigation was 78.9%.

Comparing the groups with and without IgG subclass deficiency, the demographic data, severity of rhinosinusitis, and result of treatment at pre- and during the treatment of gentamicin irrigation were not significantly different. The shortest time of gentamicin nasal irrigation usage was 6 months while the longest time was more than 5 years. The median time of gentamicin nasal irrigation usage was 15 months. Seventy percent of the cases received gentamicin irrigation from 6 to 24 months. None of the cases reported side effects such as nose pain, dry nose, nose bleed, vertigo, headache, hearing defect, renal disorder or other problems.

TABLE 1. Demographic data of patients with chronic rhinosinusitis.

Characters	n (%)
Sex	
Male	23 (60.5)
Female	15 (39.5)
Age (mean±SD, years)	12.7±1.1
Body weight (mean±SD, kg.)	30.5±16.1
Height (mean±SD, cm.)	123.7±17.6
Age of onset of sinusitis (mean±SD, years)	5.8±1.0
Age of gentamicin usage (mean±SD, years)	8.5±1.1
Comorbidities	
Allergic rhinitis	20 (52.6)
IgG subclass deficiency	20 (52.6)
Nonallergic rhinitis	12 (31.6)
Asthma	11 (28.9)
Atopic dermatitis	1 (2.6)
Family history of atopy*	25/37 (67.6)
Maternal atopy	17/37 (45.9)
Parental atopy	5/37 (13.5)
Sibling atopy	10/37 (27.0)
Environmental exposure**	
Pet	10/35 (28.6)
Smoking	6/35 (17.1)

*Number of total cases that had the record of the family history = 37

**Number of total cases that had the record of environmental status = 35

TABLE 2. Comparison of medication usage between pre- and during treatment of gentamicin nasal irrigation.

Medication	Pre-treatment	During-treatment	p-value
Antihistamine	27 (71.1)	27 (71.1)	1.0
Intranasal steroid	34 (89.5)	36 (97.7)	0.5
Antileukotriene	5 (13.2)	5 (13.2)	1.0
Inhale corticosteroid	8 (21.1)	12 (31.6)	0.125
Decongestant	20 (52.6)	16 (42.1)	0.125
Bronchodilator	3 (7.9)	3 (7.9)	1.0

TABLE 3. Comparison of severity of rhinosinusitis symptoms between pre- and during treatment of gentamicin nasal irrigation.

Symptoms (n)	Pre-treatment (n, %)	During treatment (n, %)	p-value
Postnasal drip (38)			<0.001
None	7 (18.4)	18 (47.4)	
Mild	2 (5.3)	11 (28.9)	
Moderate	12 (31.6)	5 (13.2)	
Severe	17 (44.7)	4 (10.5)	
Purulent discharge (38)			<0.001
None	0	11 (28.9)	
Mild	0	13 (34.2)	
Moderate	10 (26.3)	10 (26.3)	
Severe	28 (73.7)	4 (10.5)	
Congestion (37)			<0.001
None	0	7 (18.9)	
Mild	4 (10.8)	22 (59.5)	
Moderate	13 (35.1)	5 (13.5)	
Severe	20 (54.1)	3 (8.1)	
Rhinorrhea (37)			<0.001
None	2 (5.4)	7 (18.9)	
Mild	2 (5.4)	18 (48.6)	
Moderate	11 (29.7)	7 (18.9)	
Severe	22 (59.5)	5 (13.5)	
Sneezing (30)			0.028
None	15 (50)	18 (60)	
Mild	3 (10)	6 (20)	
Moderate	10 (33.3)	6 (20)	
Severe	2 (6.7)	0	
Itching (28)			0.001
None	13 (46.4)	18 (64.3)	
Mild	6/ (21.4)	7 (25)	
Moderate	7 (25)	3/ (10.7)	
Severe	2 (7.1)	0	
Cough (28)			0.003
None	15 (53.6)	20 (71.4)	
Mild	3 (10.7)	4 (14.3)	
Moderate	5 (17.9)	4 (14.3)	
Severe	5 (17.9)	0	
Halitosis (27)			0.001
None	7 (25.9)	11 (40.7)	
Mild	5 (18.5)	11 (40.7)	
Moderate	5 (18.5)	3 (11.1)	
Severe	10 (37)	2 (7.4)	
Headache (24)			0.012
None	18 (75)	19 (79.2)	
Mild	3 (12.5)	5 (20.8)	
Moderate	2 (8.3)	0 (0)	
Severe	1 (4.2)	0 (0)	
Anosmia (22)			0.014
None	15 (68.2)	18 (81.8)	
Mild	3 (13.6)	1 (4.5)	
Moderate	2 (9.1)	3 (13.6)	
Severe	2 (9.1)	0	

TABLE 4. Comparison of sinusitis between pre- and post-treatment of gentamicin nasal irrigation.

Sinusitis	Pre-treatment median (min,max)	Post-treatment median (min,max)	p-value
Frequency of sinusitis (times/year)	3.5 (1.5,>10)	1.5 (0,>10)	< 0.001
Number of hospitalization (times/year)	0 (0,>10)	0 (0,3.5)	0.01
Frequency of ATB* usage (times/year)	3.5 (1.5,>10)	3.5 (0,>10)	< 0.001
Duration of ATB usage (wk/attack)	3.5 (1.5,10)	2.5 (0,5.5)	< 0.001
Number of intravenous ATB usage (times/year)	0 (0,5)	0 (0,1)	0.027

*ATB= Antibiotic

The interview of the patients or the parents (n=22) showed that 40.9% (9 cases) of the interviewed cases were very satisfied and 45.5% (10 cases) were satisfied with gentamicin nasal irrigation. Three cases reported no satisfactory improvement in rhinitis symptoms between pre- and during gentamicin nasal irrigation treatment.

DISCUSSION

This study demonstrated that gentamicin nasal irrigation in CRS patients was useful for adjunctive treatment. Gentamicin nasal irrigation can reduce both frequency of recurrent sinusitis and the usage of antibiotics.

A previous study on the safety profile of systemic absorption of intranasal gentamicin irrigation in healthy volunteers showed that serum level of gentamicin was undetectable when the drug (dissolved in saline without glycocholate) was given in the dose equivalent to 2 mg/kg of body weight.[16] There was another study in 12 patients (age 4 to 74, mean 43 years) with persistent purulent exacerbation of CRS after the use of systemic antibiotics and endoscopic sinus surgery.[19] Endoscopically guided culture showed that the cultured organisms in 10 out of 12 patients were sensitive to gentamicin. All of the patients in that study were treated with gentamicin nasal irrigation (30 cc of 80 mg/L solution) bilaterally twice daily (equivalent to gentamicin 2.4 mg/each nostril/dose with total of 9.6 mg/day). The length of treatment ranged from 3 to 15 weeks (mean 7 weeks). Ten of patients (83%) had detectable post-treatment serum gentamicin levels, with a mean serum level of 0.42 mcg/mL (range 0.3 to 0.7 mcg/mL).[19] Four of 12 patients (33%) had serum gentamicin levels within the normal range for gentamicin trough (0.5 to 2 mcg/mL). None of the patients reported hearing loss or vertigo during the treatment.[19] A previous study on systemic absorption of gentamicin irrigation (consisted of 1.5 ml of gentamicin, 60 mg) during intra-operation of the paranasal sinus showed that serum gentamicin levels were detected in 3 of 20 patients at 30 minutes post-irrigation. The levels were 0.3, 0.3 and 0.4 mg/L. No fluorescein was visualized behind tympanic membrane and no significant hearing loss was observed in any of the patients.[20]

In this study, the dose of gentamicin usage was 2 mg/each nostril/dose which was lower than the doses in the previous studies. All of the patients could tolerate the treatment. However, serum gentamicin level and audiologic testing were not evaluated since this was a retrospective study. Gentamicin nasal irrigation solutions are available in concentrations of 0.08 mg/mL (Wedgewood pharmacy) and 0.16 mg/mL (Wilson's solution gentamicin plus normal saline). Our local gentamicin nasal irrigation solution made by Siriraj Hospital pharmacy is in the concentration of 0.1 mg/mL.

Gentamicin nasal irrigation could relieve rhinosinusitis symptoms such as nasal congestion, rhinorrhea, itching, posterior nasal drip, purulent discharge, halitosis and cough. Facial pain and fatigue were not significantly improved in our study since these symptoms were subjective and some of the children were too young to complain. The study showed that 84.6% of the patients were satisfied with gentamicin nasal irrigation. Normal saline irrigation could relieve some rhinosinusitis symptoms, so the improvement of rhinosinusitis symptoms may be from both gentamicin and normal saline irrigation. However, in this study the result should be from gentamicin nasal irrigation since all of the cases did not respond to normal saline irrigation that had used before administration of gentamicin nasal irrigation. Since the overuse of topical antibiotic may increase bacterial resistance and also selectivity of the bacterial resistance, the use of gentamicin nasal irrigation should be closely observed by physicians. The treatment should be stopped if the symptoms do not improve within 3-6 months. The treatment also should be stopped a few months after the symptoms have improved. The limitations of this study were 1) unblinded, without placebo control and 2) adjustment of intranasal corticosteroid might affect the symptoms. This is the first publication that has reviewed the results of gentamicin nasal irrigation in Thai children with CRS. Since this study is a retrospective study, the further prospective double blind, placebo controlled study should be performed to support the advantage, side effects and the effect on bacterial resistance of gentamicin nasal irrigation usage.

CONCLUSION

Gentamicin nasal irrigation was useful in reduction of rhinosinusitis symptoms and hospitalization in children with chronic rhinosinusitis without reported complications.

ACKNOWLEDGMENTS

This study was supported by Siriraj Research Fund and the National Research University grant from the Commission on Higher Education (CHE) through the Center for Biopharmaceutical Development and Innovative Therapy, Mahidol University, Thailand.

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