Open-Label, Randomized Study of Amoxcicillin, Azithromycin,and Cefprozil in Childhood Sinusitis

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ABSTRACT

Aim: There are many antibiotics used in acute sinusitis in paediatric practice. We planned this study to contribute rational antibacterial treatment considering the clinical efficiency, side effects and cost of the treatment.

Materials and methods: Our study was a prospective, randomized and open label study in children. Patients diagnosed as having acute sinusitis based on the major and minor clinical diagnostic criteria were randomized to receive 14 days of amoxicillin (40 mg/kg/day, in 3 doses), 5 days of azithromycin (10 mg/kg/day, single dose for first 3 days and 5 mg/kg/day-single dose for 2 days) and 14 days of cefprozil (30 mg/kg/day, 2 doses).

Results: Of a total of 151 patients who were between the ages of 5 and 14 years (mean: 8.33±2.82 standard error), 50 patients received amoxicillin, 52 azitromycin and 49 cefprozil. At the end of the treatment improvement rates were 72 %, 80.7 %, and 69.3 % respectively ($p>0.05$). The occurrence rates of adverse effects were 8 %, 7 %, and 10 % in these groups respectively ($p> 0.05$).

Conclusion: We emphasize that clinicians should prefer appropriate antibiotics for acute sinusitis in children, in regard to the parameters of low cost, high compliance and minimum adverse effects.

Key words: amoxicillin, azithromycin, cefprozil, children, sinusitis, treatment

INTRODUCTION

Acute sinusitis is a common disease that millions of people suffer from in the world. In United States of America 3 million people are diagnosed with sinusitis in a year. This is the fifth leading cause of outpatient infectious disease. Inaccurate or misdiagnosis of sinusitis leads to many problems in the course of the disease. Resolution of symptoms is delayed, and insufficient antibiotic use may cause chronic sinusitis. In some conditions serious bacterial complications may occur. On the other hand, antibiotic abuse may increase the treatment cost, side effects, and bacterial resistance. So it is important to determine the cost-effective treatment strategies (1).

Werninget al conducted a study in which internal medicine specialists', otorhinolaryngologists', and family practitioners' suggestions for acute sinusitis treatment were examined. In that study otorhinolaryngologists were using more imaging techniques, more drugs than internal medicine specialists and family practitioners (2). Considering that otorhinolaryngologists deal with recurrences and complications more frequently the above mentioned difference can be explanied.

Ultrasonography, computerized tomography, magnetic resonance imaging, anterior rhinoscopy, antral punction and nasal cytology were not included in the study. Because they are expensive, invasive, needs more time and expertise for the first step of health services, it seems that it is not possible to use them in routine practice (1).

In the literature we could not find a comparative study of amoxicillin, azitromycin and cefprozil in childhood sinusitis. When the diagnosis is accurate in childhood sinusitis antibiotic treatment is needed. Kakish et al conducted a study in 249 acute sinusitis patients. They gave antibiotics to 88% of them and did not give any antibiotics to 12% of them. Amoxicillin was the drug of choice in 35.8% of those given antibiotics; 23% azithromycine, 15% cefaclor, 10% TMP-SMX, 8.5% amoxicillin-clavulanic acid, 3.5% ampicillin, 3.5% clarithromycin were the others. At the end of the study on the 10th day they controlled the patients and found a significant difference between the treated and untreated group. The treatment group improved (3). According to the clinical literature data, in acute sinusitis judicious antibiotic treatment is needed in order to prevent the development of complications and chronicity (1).

Nasal cytology does not give any information about the intrasinusoidal bacteriology (4). Anterior

Table-1 Major and minor criteria for diagnosing acute sinusitis

Major criteria	Minor criteria
Pressure or pain on face/head	Headache
Sensation of fullness on face	Halitosis
Nasal congestion	Fatigue
Nasal discharge	Toothache
Hyposmia/anosmia	Cough
Fever	Earache

rhinoscopy needs exact patient compliance and for children this is very difficult. Antral puncture is accepted as the gold standard in literature but it takes long time, is invasive and painful.

Antibiotic prescription for acute sinusitis in outpatient practice, can have a major impact on cure and costs. We performed a prospective open label study to compare effectiveness of the three antibiotics in the treatment and cost of acute sinusitis in childhood.

MATERIALS AND METHODS

Our study was a prospective, randomized and open label study in children. Patients diagnosed as having acute sinusitis based on the major and minor clinical diagnostic criteria were randomized to receive 14 days of amoxicillin (40 mg/kg/day, in 3 doses), 5 days of azithromycin (10 mg/kg/day, single dose for first 3 days and 5 mg/kg/day-single dose for 2 days) and 14 days of cefprozil (30 mg/kg/day, 2 doses).

All the patients included in the study were evaluated by the same doctor (DB). Children having any other disease were not included in the study. History of drug hypersensitivity and/or allergy, any antibiotic use fifteen days before the admission, malignancy, serious heart, liver, kidney or gastrointestinal disease were also criteria for non-inclusion.

Diagnosis of acute sinusitis was made by history and clinical findings. In Table-1, the major and minor criteria used for the diagnosis of acute sinusitis were given (4). According to these, patients having at least two major, or one major and two minor criteria were accepted as acute sinusitis (2). (Tables 2, 3).

Treatment effectiveness of the three antibiotics were evaluated according to the improvement in clinical findings and complaints. (Tables 4, 5).

Table-2 Distribution of the study groups according to complaints at admission*

	I. Group (Amoxicillin) (n:50)	II.Group (Azithromicin) (n:52)	III.Group (Cefprozil) (n:49)	
Fever	41(% 82)	52(%100)	49(%100)	p<0.05
Cough	26(%52)	44(%84.6)	36(%73.5)	p<0.05
Headache	39(%78)	26(%50)	36(%73.5)	p<0.05
Nasal discharge	27 (%54)	30 (%57.7)	28 (%57.4)	p>0.05
Congestion	22 (% 44)	15 (%28.8)	13 (%26.5)	p>0.05
Halitosis	10(% 20)	3(%5.8)	10(%20.4)	p>0.05

**percentages are to be evaluated for the same group*

In our study the most common complaints were fever, cough and headache (Table 2).

Table-3 Distribution of the study groups according to physical examination findings at admission *

	I. Group (Amoxicillin) (n:50)	II.Group (Azithromicin) (n:52)	III.Group (Cefprozil) (n:49)	
Postnasal drainage	50(%100)	52(%100)	49(%100)	p>0.05
Fever	39(%78)	52(%100)	49(%100)	p<0.05
Nasal discharge	27(%54)	16(%30.8)	25(%51)	p<0.05
Halitosis	11(%22)	4(%7.7)	7(%14.3)	p>0.05

**percentages are to be evaluated for the same group*

The most common physical examination findings at the admission were postnasaldrainage and fever. (Table 3).

Table-4 Distribution of the study groups according to complaints and physical examination findings at control *

	I. Group (Amoxicillin) (n:50)	II.Group (Azithromicin) (n:52)	III.Group (Cefprozil) (n:49)	
Fever	%0	%2	%6	p>0.05
Cough	%43	%20	%34	p>0.05
Headache	%25	%42	%26	p>0.05
Nasal discharge	%37	%52	%47	p>0.05
Nasal congestion	%46	%42	%59	p>0.05
Halitosis	%18	%0	%0	p>0.05
Postnasal drainage	%36	%31	%41	p>0.05

**percentages are to be evaluated for the same group*

When we compare the complaints and physical examination finding before and after treatment, there were no statistically significant differences between the groups (p> 0.05). The most persistent finding was nasal congestion in all three groups.

1) "Cure" was defined by disappearance of the two major, or one major and two minor criteria

2) "Partial clinical improvement" was defined by disappearance of one major criteria and/ or any minor criteria.

3) "Failure" was defined by persistence of one major criterion. The failure group was sent to the Outpatient Unit of the Ear-Nose-Throat section.

Patients were asked for the adverse effects in the control examination. (Table 5).

The statistical analysis of this study was done by SPSS 10.0. p values less than 0.05 were accepted as significant.

In the evaluation of the parameters, Student's T test, Chi square and Correlation test was used. The data was given as mean and standard deviation.

RESULTS

A total of 151 patients who were between the ages of 5 and 14 years were included in the study (mean: 8.33±2.82 standard error). In our study 50 of 151 patients received amoxicillin, 52 azithromycin and 49 cefprozil. At the end of the treatment improvement rates were 72 %, 80.7 %, and 69.3 % respectively (p>0.05). (Table 6). The occurrence rates of adverse effects were 8 %, 7 %, and 10 % in these groups respectively (p> 0.05). (Table 5).

Table-5 Distribution of the study groups according to adverse effects

	I. Group (Amoxicillin) (n:50)	II.Group (Azithromicin) (n:52)	III.Group (Cefprozil) (n:49)
Abdominal pain	2	1	1
Nausea	1	3	4
Constipation	1	0	0
Total	%8	%7	%10

Table-6 Distribution of the study groups according to the clinical improvement

	I. Group (Amoxicillin) (n:50)	II.Group (Azithromicin) (n:52)	III.Group (Cefprozil) (n:49)
Clinical improvement	36(%72)	42(%80.7)	34(%69.3)
Failure	14(%28)	10(%19.3)	15(%30.7)
			p>0.05

DISCUSSION

Acute sinusitis is a very common infection in childhood, but its management remains a controversial issue. Cefprozil and azithromicin are acceptable alternatives to amoxicillin in the treatment of sinusitis in children. As stated before, because of the risk of complications and chronicity this study was not designed as placebo controlled. History and physical examination was used for diagnosis. Waters' radiological view and leukocyte count was important for supporting the clinical diagnosis. Ros et al. compared the Waters' view with three dimensional head views and found that Waters' view is sufficient with a sensitivity of 89% and a specifity of 83% in diagnosing acute sinusitis (5). So we used the Waters' view not as a diagnostic tool it to but to evaluate the relationship with the clinical diagnosis.

Engels et al made a meta-analysis in which 6 studies for the diagnosis of acute sinusitis were included. In one part of the meta analysis sinus aspiration ad sinus radiographs were compared. When the positivity of X-rays was defined as the presence of fluid in the sinus and/or opacity and/or mucosal thickening they found out the sensitivity as0.9 and specificity as 0.61 (1). Stewart et al states that in primary care, the physician does not need imaging techniques for diagnosing uncomplicated acute sinusitis (7). In our study there were correlation between Waters' view improvement and general clinical outcome. We have the results which are parallel with the studies suggesting that every imaging technique needs to be evaluated under the light of history and clinical examination (1, 4, and 5).

In our study the most common complaints were fever, cough and headache. Families tend to bring their child when he/she has fever otherwise they wait for recovery. Night cough especially alarms the family. The mean age (8.33 year) of our study group was appropriate for expressing their complaints by themselves.

Williams et al. asked for symptoms of acute sinusitis in a prospective study of 221 adult patients and found out that the most common complaint was fatigue (62%) (8). In our study the most common complaint was fever (95%). Fatigue probably couldn't be expressed by our patients because they are in the childhood age group. Lindbaeck et al. found out that in 357 adult patients clinical diagnosis of sinusitis is generally correct and erythrocyte sedimentation rate, C reactive protein and leukocyte count has a limited value in diagnosis of sinusitis. We also found leukocytosis only in 33.8% of the patients (9). Conrad et al. published a review and determined that childhood sinusitis is caused by S. pneumonia, H. influenza and M. catarrhalis, radiologic examination is unnecessary and the first treatment regimen should be high dose amoxicillin (80-90 mg/kg/day) at least 7 days after the symptom resolution; approximately 10-14 days (10). We used the 14 day standard treatment regimen for amoxicillin since our study population is of a lower socio-economic status.

In a study conducted by Virant, 30-50% of childhood sinusitis patients also have asthma. In these patients aggressive medical or surgical treatments enable

relief of both upper and lower respiratory symptoms in a significant manner. Judicious antibiotic use is also useful for relieving asthma symptoms in these patients (11).

Garbut et al. conducted a comparative study for amoxicillin, amoxicillin-clavulanate, and placebo; and found out no statistically significant difference in treatment effectiveness. This information may make us think that in childhood sinusitis there is no need for antibiotics, but the investigators, used S5 score (congestion, day cough, head or facial pain, colored nasal mucus) (12). They wanted from the parents to score those parameters 0-3. This seems to be a subjective scaling, because parents may exaggerate or minimize the symptoms according to their personality. Williams et al published an article in which 32 studies about adult acute maxillary sinusitis were included. They stated that although recent evidence has been limited, 7-14 days of penicillin or amoxicillin treatment is useful. Additionally they recommended that the balance between the treatment benefit and the adverse effects should be evaluated before prescribing the antibiotic (13). In our study, because we found no statistically significant difference between effectiveness and adverse effects, we may conclude that all the three drugs may be prescribed confidently with respect to this balance. From the three drugs, azithromycin had not only the highest percentage of treatment effectiveness, but also the lowest percentage of adverse effects.

In a meta- analysis (11 studies and 1742 patients), Ioannidis et al studied azithromycin in sinusitis treatment, and found that there were no statistically significant difference between azithromycin and other antibiotics in respect to treatment effectiveness. In that meta- analysis, there were 0.8 % drop outs because of the adverse effects (14). In our study we also didn't find any significant difference between treatment effectiveness of azithromycin and the other drugs, but we had no drop outs because of the adverse effects.

Garcia et al conducted a study in which 78 adult and paediatric patients having acute respiratory system infection were compared for the treatment effectiveness of azithromycin, amoxicillin- clavulanate and cefaclor. They found 97% of azithromycin patients were improved or cured, 85 % of amoxicillin-clavulanate and 84% of cefaclor group accordingly. Azithromycin had statistically significant difference in treatment effectiveness than amoxicilin-clavulonic acid and cefaclor ($p < 0.02$). Adverse effect frequency was 0%; 15%; and 16% accordingly (15). Although antibiotics and the indication of use are not the same, we also found azithromycin as the most efficient one with a percentage of 80.7; but this is not statistically significant. This difference may be caused by the difference between the indications of the antibiotic use (acute respiratory system infection vs. acute sinusitis). The adverse effect ratios were similar in our study. Azithromycin had 7%, amoxicillin had 8%, and cefprozil had 10%.

There are limited studies that investigate the treatment effectiveness of cefprozil in acute sinusitis. In a study conducted by Hedrich et al, it has been shown that in acute otitis media, high dose amoxicillin-clavulanate and cefprozil had equal treatment effectiveness and low adverse effect profile (16).

Arguedas et al, showed similar results in otitis media with effusion, i.e. that cefprozil has an effect equal to amoxicillin-clavulanate, but a lower adverse effect profile (17). Adelglass et al conducted a study in 278 adult patients and compared amoxicillin-clavulanate and cefprozil. They found no significant difference between the treatment effectiveness of the two, but adverse effect frequency is high for amoxicillin-clavulanate (18). We conducted our study in a paediatric age group and found similar results for amoxicillin and cefprozil but cefprozil has more frequent adverse effects than amoxicillin (10% and 8%).

Cassiano determined that short term amoxicillin use (10 days) is as effective as azithromycin use (5 days) in adulthood acute maxillary sinusitis. Short term antibiotic use has advantages in terms of treatment compliance, adverse effect frequency and bacterial resistance (19). Pichichero published a review and stated that short term antibiotic use has similar results with long term use in acute sinusitis (20). We also found out no significant difference between 5 days azithromycin, 14 days amoxicillin and 14 days cefprozil treatment. For childhood sinusitis there is a need for more short term studies.

Brook et al, in one of their reviews listed the indications for referral to an otorhinolaryngologist as treatment failure, immune deficiency, nosocomial infections and disturbance of the general status of the patients (4). In our study we referred the treatment failure group (25.8%) to an otorhinolaryngologist.

Powers, in his study comparing the taste of azithromycin with other antibiotics, concluded that dose interval, treatment duration and the taste of the drug affected the compliance and the clinical outcome. Children preferred azithromycin to cefpodoxime (90% to 52%); and to cefprozil (63% to 33, 1%). Azithromycin is an effective antibiotic, with its taste influencing the compliance and the clinical outcome (21).

At the end of the study "clinical improvement" was evaluated as total (TI), partial (PI) or no improvement (NI) respectively. These figures for amoxicillin were 62%, 10% and 28%, for azithromycin 64%, 17% and 19% and for cefprozil 53%, 17% and 30% respectively.

When total and partial improvements were collectively defined as clinical improvement (CI), the

figures became 72% for amoxicillin, 81% for azithromycine and 69% for cefprozil, the difference of which were not statistically significant.

Adverse effect rates were 8% in the amoxicillin group, 7% in the azithromycine group and 10% in the cefprozil group. These were mild reactions and there was no need to stop the treatment in any patient.

Piccirilo et al found out that first line and second line drugs have similar treatment effectiveness but second line drugs have a nearly two fold cost compared to first line drugs (22).

In our country amoxicillin is the cheapest drug, and azithromycin has two fold and cefprozil has five fold cost. In the paediatric age group sinusitis is a very common disease. Therefore we emphasize that the preference of the cheapest and effective antibiotic is a more realistic and rational treatment policy.

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