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ORIGINAL ARTICLE

A randomized controlled trial of 5-day regimen of azithromycin and a 10-day regimen of co-amoxiclav for treatment of acute sinusitis

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ABSTRACT

Background: Acute sinusitis constitutes a significant portion of health service utilization globally both in- and out-patient as well as emergency department visits, with 83% resulting in a prescription for an antibiotic. This study compared the efficacy of a 5-day regimen of azithromycin (a macrolid antibiotic) with a 10-day regimen of co-amoxiclav (combination of an aminopenicillin with a betalactamase inhibitor) for the treatment of acute sinusitis.

Patients and methods: A total of 76 subjects with acute sinusitis were randomly assigned in two groups, azithromycin (n=40) and co-amoxiclav (n=36). One group received azithromycin, 500mg in the first day and 250mg for 4 days and the other group received co-amoxiclav 625mg, 3 times a day for 10 days. Patients were visited 4 times during the study (baseline, phone call, end of treatment, end of study) and regression/progression of their symptoms and their response to the treatment was evaluated.

Results: There was no significant difference between the two groups' demographic and clinical presentations. Duration of regression of the symptoms in the azithromycin group was significantly shorter than the co-amoxiclav group (7.6 days versus 10.6, p=0.03). Clinical success rate at end of the study was 80% for azithromycin and 66.7% for co-amoxiclav (p=0.025). Clinical success rates among females in both groups seemed to be higher than males, but this difference was not statistically significant (p=0.13).

Conclusion: Results revealed that azithromycin regimen is more efficient, has less side effects, and required shorter treatment period. Patients were able to tolerate the medications better with a higher compliance and less economic cost than co-amoxiclav regimen.

Keywords: *Acute sinusitis, Azithromycin, Co-Amoxiclav.*
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INTRODUCTION

Acute sinusitis constitutes a significant portion of health service utilization globally both in- and out-patient as well as emergency department visits, with 83% resulting in a prescription for an antibiotic (1). The distinction between viral and bacterial sinus infection is difficult to make in the primary care setting, and symptoms of acute bacterial sinusitis (ABS) usually resolve without intervention. Therefore, several recent publications

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have questioned the benefit of antibiotic treatment of ABS in a physician practice setting (2-4). However, the signs and symptoms of sinusitis can have a significant impact on a patient's quality of life and productivity (5-7), and these outcomes may be improved with earlier symptom resolution.

Recent recommendations for clinical trials of acute sinusitis highlight the importance of symptom resolution as an indicator of treatment efficacy (8,9). Draft guidance from the US Food and Drug Administration on the design of future clinical trials of ABS recommends that the primary efficacy end point reflect outcomes that are clinically important to patients. An end point of time to clinical success, defined as the period from the start of study drug administration to complete relief of symptoms, should be used in this setting (9). However, few antibiotic trials have compared treatments using patient-reported symptom resolution as an end point. One review of antibiotic therapy suggested that antibiotics improve symptom resolution in patients with suspected bacterial disease (10), whereas a more recent meta-analysis of placebo-controlled trials reported that antibiotics have a minimal impact for most patients who receive them in clinical practice (4). A recent small, prospective, randomized trial failed to find improvement in symptom resolution rates between amoxicillin and placebo (3).

A post hoc analysis from a phase III clinical trial showed that significantly more patients receiving a single, 2-g dose of azithromycin extended release had complete resolution of 3 of 4 cardinal symptoms of sinusitis than patients who received levofloxacin 500 mg once daily at a study visit 3 to 5 days after randomization (32.6% vs 23.4%, p = 0.018) (11,12). These findings have not been tested prospectively.

The objective of this study is to compare the efficacy of a 5-day regimen of azithromycin (a macrolid antibiotic) with a 10-day regimen of co-amoxiclav (combination of an aminopenicillin with a betalactamase inhibitor) for the treatment of acute sinusitis.

PATIENTS and METHODS

This is a single blind randomized clinical trial, comparing azithromycin and co-amoxiclav for the treatment of acute sinusitis in terms of efficacy and symptoms relief. Study subjects were randomly selected from the patients arriving in Niayesh Clinic in Shahryar, Tehran, Iran. Any subject who entered the study was provided with a written informed consent prior to any study-related procedure performed.

The following inclusion criteria were applied at baseline: outpatients, both genders, 18 years or older with a diagnosis of acute sinusitis of maxillary sinus. Acute sinusitis was diagnosed with clinical symptoms of post nasal discharge and facial pain and tenderness in maxillary sinus area for at least 7 and at last 28 days. Meanwhile, the following exclusion criteria were considered: allergy to any penicillin or macrolid antibiotic, history of taking systemic antibiotic for at least 24 hours in 2 weeks before entering the study, history of chronic sinusitis (described as, sinusitis, 3 or more times during the past 6 months), history of sinus surgery except for diagnostic proposes or taking systemic antihistamines (13).

Subjects were randomly assigned in two groups of 5-day azithromycin regimen and 10-day co-amoxiclav regimen. Therefore, the first group was treated with 250mg capsule of azithromycin (ZIMEXIR® manufactured by Exir Company), 500mg single dose on the first day and 250mg single dose for the next 4 days. The second group was offered 625mg coated tablet of co-amoxiclav, 3 times a day for 10 days.

Each subject was visited 4 times by a physician at baseline (visit 1), phone call (visit 2), end of treatment (visit 3), and at the end of study (visit 4). At baseline visit after written informed consent was obtained, the investigators reviewed inclusion and

exclusion criteria. If the inclusion criteria were met, the investigators collected demographic, medical history, and drug and non-drug therapy information. We also performed a targeted physical exam, clinically assessed signs and symptoms of acute sinusitis and recorded vital signs. At the second visit, on day 4th, investigators collected information about progression or regression of acute sinusitis symptoms by phone calls. At the end of treatment (visit 3) as well as the end of study (visit 4), a physician evaluated the clinical response to the therapy by examining acute sinusitis signs, symptoms and vital signs.

Efficacy was measured by clinical success rates based on the global assessment of the clinical presentation of the subject made by the investigator at the end of treatment and end of study. Cure was defined as "resolution of signs and symptoms of acute sinusitis to the level that existed prior to the occurrence of the acute illness and without requirement of antibiotics (other than study drugs) given for treatment of sinusitis". Improvement (applicable only at end of treatment) was defined as "partial but not complete resolution of the signs and symptoms of acute sinusitis and no requirement for additional antibiotic use". Failure was defined as "persistence of one or more signs or symptoms of acute sinusitis or appearance of new signs or symptoms and/or change in antibiotic therapy".

RESULTS

A total of 76 subjects with acute bacterial sinusitis were randomly selected and assigned in two groups: azithromycin (n=40) and co-amoxiclav (n=36). Sinus pain/tenderness and unilateral facial swelling were found to be the most common symptoms and presented in all patients. Headache, fever and toothache were other presenting symptoms in our subjects. Signs and symptoms of patients in both groups were more or less similar (figure 1). It should be noted that symptoms and signs prevalence and duration of symptoms before treatment were similar in both therapy groups. Subjects also had similar age distribution.

Figure 2 shows the average symptoms and signs relief duration (treatment period) which was 7.6 days for azithromycin and 10.6 days for co-amoxiclav therapy group. Duration of symptoms regression in azithromycin group was significantly shorter than co-amoxiclav group (p=0.03). Clinical success rate at the end of the study (day 30th) was 80% for azithromycin and 66.7% for co-amoxiclav (p=0.025), however, these figures were 75.5% 58.3% at the end of treatment (day 10th) (p=0.02). Clinical success rates among females in both groups seemed to be higher than males, but this difference was not statistically significant (p=0.13).

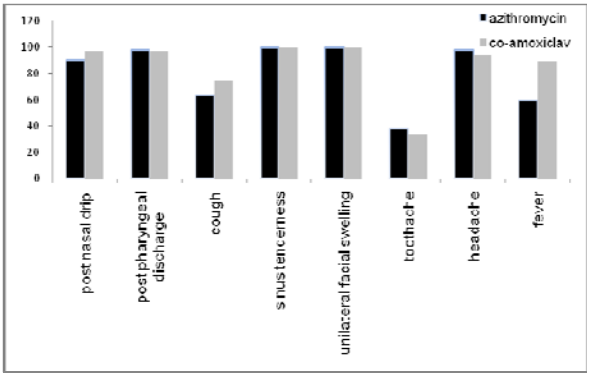

Figure 1. Signs and symptoms of patients with acute sinusitis in azithromycin and co-amoxiclav group

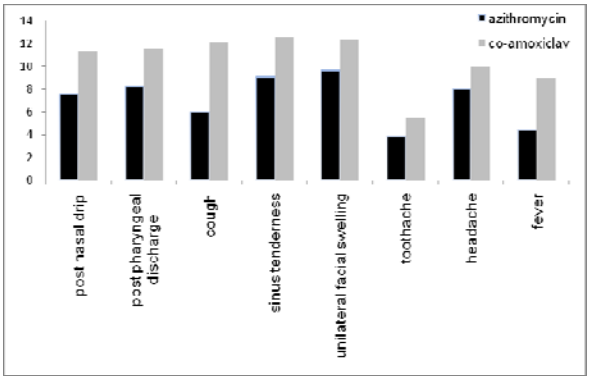

Figure 2. Average symptoms and signs relief duration (treatment period, days) in azithromycin and co-amoxiclav group

DISCUSSION

This study compared azithromycin (500mg single dose in the first day followed by 250mg single dose for the next 4 days) with co-amoxiclav regimen (625mg, thrice daily for 10 days) for the treatment of acute sinusitis. Our findings showed that the clinical success rate at the end of study was significantly higher among azithromycin-treated subjects (p=0.025). Furthermore, clinical success rate in both groups was higher among females than males, but the difference did not reach a statistically significant level, which could be in part explained by small sample size.

This study also showed that the duration of symptoms and signs relief in azithromycin group was 33.1% shorter than co-amoxiclav group (p=0.03), hence, further therapies would not be indicated for symptom relief (i.e., anti-inflammatory or anti-congestive agents). Our findings revealed shorter treatment period and fewer dose of azithromycin. Additionally, azithromycin can be used in patients who may have allergy to the penicillin family. It should be noted that a single dose of azithromycin may increase patient compliance and lower the incidence of side effects.

This study faced a number of limitations. Diagnosis of acute sinusitis was purely based on clinical signs and symptoms which may be associated with biased results. The ideal diagnostic criteria included diagnostic imaging as well as bacteriological investigations. Meanwhile, it was not possible to eliminate those patients who had viral infections and/or allergic rhinitis which do not require antibiotic treatment. All these may have introduced selection bias in this study, therefore, the findings of this study must be interpreted with caution.

Totally, findings of this study showed that azithromycin may be more efficient, have less side effects, and required shorter treatment period. Patients were able to tolerate the medications better with a higher compliance and less economic cost than co-amoxiclav.

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