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ORIGINAL ARTICLE

A comparing study of clarithromycin XL with co-amoxiclav for treatment of chronic sinusitis; a clinical trial

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ABSTRACT

Background: Chronic sinusitis is one of the most common medical problems affecting 30 million people in USA annually. In the present study, we compared the efficacy and safety of clarithromycin XL and co-amoxiclav on clinical and CT scan findings of patients suffering from chronic sinusitis.

Patients and methods: In this clinical trial, a total of 59 subjects (37 males and 22 females, mean age 28 years) with clinical symptoms and CT scan findings of chronic sinusitis were assigned randomly in two groups and treated with clarithromycin XL or co–amoxiclav.

Results: Clinical success rates were similar at the end of therapy period, however, subjects receiving clarithromycin XL showed better CT scan findings when compared with co-amoxiclav-treated subjects (53% versus 29%). Gastrointestinal discomfort was the most frequent treatment–related adverse effects in both groups (NS).

Conclusion: Results revealed that clarithromycin XL and co-amoxiclav have similar efficacy when considered for treatment of chronic sinusitis.

Keywords: *Chronic sinusitis, Clarithromycin, Co-amoxiclav.*
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INTRODUCTION

Chronic sinusitis is a condition in which persistent inflammation has developed in sinus that usually occurs after a period of acute sinusitis. Commonly, chronic sinusitis is associated with symptoms such as nasal congestion, facial pain, coughing, headache, and post nasal discharge (PND), which last more than 3 months or 12 weeks (1). Some references have reported fatigue in these patients (2,3). A correct function of the mucocilliary system (conduction of particles) guarantees sinus health. Nose and sinus surface is covered by stratified epithelium and pseudoculmonar cells which have cilia. Goblet cells which secret mucous and serous producing glands create a mucous blanket in which superficial layer is made of mucous and deeper layer is made of serous. Epithelial cilia move over 1000 times per second, conduct this mucous blanket to the sinus orifice so that particles enter into nasopharynx. Any changes in function of cilia or quality of mucous blanket or sinus orifice lead to sinusitis. For example, stop of cilliary movement by cystic fibrosis disease or cigarette smoking or closure of sinus orifice by an anatomic problem like severe

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septal deviation can induce sinusitis. Size of sinus orifice is an important factor in pathogenesis of sinusitis. Complete or partial obstruction of sinus orifice leads to secretion retention, PH decrease, and PO_2 decline within sinus. These will provide a suitable condition for bacterial growth. Both bacterial growth and retention of secretions cause inflammation in mucus layer (1-4). In European countries, about 5-15% and in the United States 12% of general population (about 30000000 people) suffer from chronic sinusitis. Chronic sinusitis is not a life-threatening disease, although, because it is near to orbit and brain, it can cause serious problem. For example, about 75% of orbital infections and 3.7-10% of brain abscess are due to chronic sinusitis (1,4). Bacteria cause chronic sinusitis include anaerobic coccies, *Haemophilus influenza*e, Bacteroids spp., *Staphylococcus aurous*, Streptococcus spp. and *Moraxella catharrealis* (1,3-5).

Laboratory studies include culture of nasal discharge by cotton swab or sampling from sinus discharge by sinus endoscope. Now, sinus CT scan is the best imaging study which is in coronal sections and 4 mm cuts. It clearly shows sinus anatomy and also presence of pathologies such as opacity, mucosal swelling, and air-fluid level. Complications of chronic sinusitis are adenoiditis, otitis media, dacryocystitis (1,4), orbital cellulites, periorbital abscess, cavernous sinus thrombosis, meningitis, epidural abscess, subdural abscess, brain abscess, osteomyelitis and mucocele (3,4).

Treatment of chronic sinusitis has 3 parts: Control or stop of bacterial growth, lessening of mucosal swelling, and fluid flux into sinus (1,2,6). Since preparing a culture from sinus secretion by sinus endoscope is painful and also expensive, treatment is usually empiric and regarding to previous studies of the pathogens. Antibiotics which are used are: co-trimoxazole, co-amoxiclav, cefixime, erythromycin, and clarithromycin that are usually prescribed for 3-4 weeks with additional supportive therapies (1-6).

Clarithromycin XL is a macrolide and a derivation of erythromycin. It has effect on *Haemophilus influenzae, Moraxella catharrealis*, *Streptococcus pneumonia*, and *Helicobacter pylori*. In addition to antimicrobial effect, it has an important role in immune system modulation, decrease of cytokine and interleukin, hence, suppress of inflammation (7-9). Its extended release (XL) form is more effective than its common form and has less adverse effect (10,11). Its use in pregnancy, lactation, neonates under 6 months, and individual with allergic reaction or old patients should be with caution. Its clearance is both by kidney and liver. It has oral suspension, extended release tablet and common tablet. Dosage for adults is 250-500 mg q12 hour and its adverse effects include diarrhea, taste change, nausea, vomiting, hearing loss and allergic reaction (9,12,13).

Co–amoxiclav is a kind of penicillin that has B-lactamas inhibitor. It is a combination of amoxicillin and clavulanic acid and has effect on *Moraxella catharrealis* and *Haemophilus influenza*e. It has oral suspension, 375 and 625 mg tablets and chewable tablet. It should take with caution in these cases: history of drug hypersensitivity, heart failure, pregnancy and lactation. Its clearance is both by renal and hepatic system. Dosage in adults is 625 mg q8 hour (14).

In the present study, we compared the efficacy and safety of clarithromycin XL and co-amoxiclav on clinical and CT scan findings of patients suffering from chronic sinusitis.

PATIENTS and METHODS

In this clinical trial, patients with clinical symptoms of chronic sinusitis (headache, rhinorrhea, coughing, PND, feeling of facial fullness, and nasal congestion) whose symptoms last more than 12 weeks, were enrolled.

Then, ENT or infectious disease specialist visited the patient and ordered paranasal sinus coronal CT without contrast in 3mm cuts. Subjects

with at least one of these findings in their CT reports were included: sinus opacity, air-fluid level or thickening of mucus layer.

Sinus opacity remission was described by decrease or disappearance of the opacity. Mucosal swelling is a mucosal thickness of more than 3mm and its remission was described by lessening the thickness less than 3 mm.

The following exclusion criteria were applied at baseline: history of allergy to penicillin or macrolide, pregnancy, lactation, age of <8 or >65 years and patients with nasal septal deviation, polyp or conchal hypertrophy in CT scan.

Patients were randomly assigned in two groups: First group received pseudoephedrine tablet, bromhexine tablet, beclomethasone spray, and 500mg clarithromycin XL tablet/day for 3 weeks. Second group received the same, however, instead of clarithromycin XL they received co–amoxiclav 625 mg q8 hour for 3 weeks.

Patient's compliance was evaluated by regular visits. Efficacy of drug was evaluated by its clinical success. Indeed, patients were evaluated for clinical symptoms and signs, including nasal congestion, facial pain, and postnasal discharge on days 7, 17, 21, 28, 42 and 56. Adverse effects were noticed in all patients. Follow up paranasal sinus CT scan was obtained 8 weeks after the therapy commencement and finally data were analyzed by chi square test using SPSS software (version 11.5, SPSS Inc., USA). Significance level was set at $p<0.05$.

RESULTS

A total of 59 patients with chronic sinusitis were enrolled in the study, among which 29 were treated with co-amoxiclav and 30 with clarithromycin XL added to treatment with pseudoephedrine tablet, bromhexine tablet and beclomethasone nasal spray. Table 1 represents some demographic data and shows no statistically significant differences between the two groups.

Table 1. Demographic characteristics of patients with chronic sinusitis receiving either co-amoxiclav or clarithromycin XL

Characteristic	Co-amoxiclav	Clarithromycin XL
Number of patients	29	30
Sex		
Female	12 (41.4)	10(23.3)
Male	17 (58.6)	20(66.7)
Age (yrs)	27.9±10.5	29.7±11.4
Weight (kg)	68.8±9.4	64.9±10.2
Previous antibiotic therapy	12	10

Clinical outcome: All of 59 patients assigned to treatment were judged clinically evaluable, they received therapy for 8 weeks and completed follow-up visits and reassessed at the end of treatment clinically and radiographically by coronal paranasal sinus CT scan. Clinical outcome (improvement, no change, worsen) for each symptom were assessed after treatment in each group and compared with each other (table 2). There were no statistically significant differences in clinical improvement of symptoms between two groups and both treatments were effective.

CT scan findings: Each patient assessed radiographically with coronal paranasal sinus CT scan before and after treatment and opacity, mucosal thickening and air/fluid level where assessed (table 3). Radiographic improvement was defined as clearing or reduction in opacity, mucosal thickening and air/fluid level in at least 2 paranasal sinuses. Radiographic improvement was noted in both groups especially in clarithromycin XL when compared to co-amoxiclav group (53.8% versus 29.6%).

Adverse effects: The most common adverse effects were diarrhea in co-amoxiclav (10.3%) and anorexia in clarithromycin XL group (10%). Other side effects were as follow: skin rash, fever, vertigo, and disequilibrium in co-amoxiclav group (each in one patient), and abdominal pain, nausea, hypertension, and palpitation (each in one patient) and diarrhea, skin rash and right upper quadrant tenderness (each in 2 patients) in clarithromycin

group. Nevertheless the differences did not reach a statistically significant level.

Table 2. Clinical outcome of patients with chronic sinusitis receiving either co-amoxiclav or clarithromycin XL

Symptom	Groups		P
	Co-amoxiclav	Clarithromycin	
PND			
Improvement No	12(40.7)	14(46.7)	0.802
change	14(48.1)	14(46.7)	
Worsen	3(11.2)	2(6.7)	
Headache			
Improvement No	12(40.7)	15(50)	0.626
change	15(55.6)	13(43.3)	
Worsen	2(3.7)	2(6.7)	
Cough			
Improvement No	14(48.1)	12(40)	0.626
change	11(37)	15(50)	
Worsen	4(14.9)	3(10)	
Rhinorrhea			
Improvement	14(48.1)	13(43.3)	0.502
No change	14(48.1)	17(56.7)	
Worsen	1(3.8)	0	
Epistaxis			
Improvement	5(14.8)	3(10)	0.473
No change	23(81.5)	27(90)	
Worsen	1(3.7)	0	
Facial pain or pressure			
Improvement	16(55.6)	17(56.7)	0.995
No change	12(40.7)	12(40)	
Worsen	1(3.7)	1(3.3)	
Nasal congestion			
Improvement	23(81.5)	19(63.4)	0.255
No change	6(18.5)	10(33.3)	
Worsen	0	1(3.3)	

Table 3. Coronal paranasal sinus CT scan findings of patients with chronic sinusitis receiving either co-amoxiclav (Group A) or clarithromycin XL (group B) before and after treatment

CT scan findings	A (%)		B (%)	
	Before	After	Before	After
Sinus opacity				
Maxillary	26(86)	12(40)	24(80)	9(30)
Ethmoidal	8(26)	0	10(33.3)	1(3.3)
Frontal	4(13)	0	2(6.6)	0
Sphenoidal	2(6)	0	2(6.6)	0
Sinus mucosal thickening				
Maxillary	19(63)	11(36)	16(33.3)	14(46.6)
Ethmoidal	7(23)	1(3)	6(20)	0
Frontal	4(13)	1(3)	1(3.3)	0
Sphenoidal	2(6)	0	0	0
Sinus air-fluid level				
Maxillary	16(53)	6(20)	10(33.3)	5(16.6)
Ethmoidal	1(3)	0	2(6.6)	2(6.6)

DISCUSSION

This study revealed that clarithromycin XL for 3 weeks and co-amoxiclav for 3 weeks had no difference in clinical response for treatment of chronic bacterial sinusitis. Although both were effective, CT scan results were better in clarithromycin group.

In a study by Gotfried, 25 patients whose sinusitis was confirmed both clinically and radiographically received 500mg clarithromycin bid for 2 weeks. One and two weeks following the therapy, reevaluation showed less headache, facial pain and PND. Their findings were in accordance with ours (16).

Prior investigators studied the efficacy of macrolide on decrease of interleukin 8 and clinical symptoms in patients who had symptoms (rhinorrhea, nasal congestion, PND, smelling loss and facial pain) for more than one year (7,8,15) and concluded that 400mg clarithromycin daily for 8-12 weeks is associated with IL-8 decrease. Meanwhile, polyp size was reduced.

In another study, the efficacy of 400mg clarithromycin bid for 8-12 weeks was evaluated among 45 patients. They finally suggested that clinical symptoms remission had a direct association with duration of therapy. Indeed, after 2,4,8 and 12 weeks, the remission was 4%, 48%, 63% and 73%, respectively, however, after 12 weeks nasal discharge viscosity in 64%, rhinorrhea in 56%, PND in 62%, and nasal congestion in 51% were decreased (17). Their findings are more or less in agreement with ours.

The most common adverse effects were diarrhea in co-amoxiclav (10.3%) and anorexia in clarithromycin XL group (10%). In a study conducted by Henry et al, abdominal pain (1.6%) and oral taste change (0.8%) were reported more common among clarithromycin users (18), however, in another study the following adverse effects were reported among patients who received clarithromycin: diarrhea, nausea, headache, and confusion (19).

In conclusion, although in our study clarithromycin had better effect on CT scan findings remission than co-amoxiclav (53% vs. 29%), there were no significant difference between 2 drugs. Therefore, therapeutic effect of co-amoxiclav and clarithromycin are the same for treatment of chronic sinusitis. However, with respect to the increased resistant strain of helicobacter-pylori (H-pylori) to clarithromycin, and higher cost of clarithromycin, clarithromycin is not preferable to co-amoxiclav and treatment of chronic sinusitis can be achieved by co-amoxiclav.

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