

Comparative efficacy and safety of B-lactum, nitroimidazole, macrolide and fluoroquinolone in patients of Acute Rhinosinusitis at tertiary-care

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Abstract

Objective: 1) To compare the efficacy of gatifloxacin, azithromycin, amoxicillin plus metronidazole with amoxicillin as positive control for the treatment of Acute Rhinosinusitis (ARS). 2) To monitor adverse drug reaction profile of amoxicillin, metronidazole, azithromycin and gatifloxacin in patients of ARS.

Material & Methods: It was an open randomized trial of comparative efficacy and safety of amoxicillin, amoxicillin with metronidazole, azithromycin and gatifloxacin in patients with ARS. Patients were randomized into four groups as under:- *Group 1* – Patients on oral Amoxicillin 500mg TDS for 10 days. *Group 2* – Patients on oral Amoxicillin 500mg TDS for 10 days plus oral metronidazole 400mg TDS for 10 days. *Group 3* – Patients on oral azithromycin 500mg OD for 5 days. *Group 4* – Patients on oral gatifloxacin 400mg OD for 10 days.

Patients were evaluated for signs and symptoms at day 1, day 7 (for group 3), on day 12 (for group 1,2,4) as primary end points and 28 days after post therapy as secondary end point.

Results: All the four group antimicrobial drugs i.e. amoxicillin, amoxicillin plus metronidazole, azithromycin and gatifloxacin were effective in reducing symptoms of acute sinusitis on Visual analogue scale (VAS) scoring. Azithromycin showed significant improvement radiographically on day 7 ($p < 0.01$) and on day 35 ($p < 0.01$). Gatifloxacin elicited very highly significant improvement radiographically on day 40 ($p < 0.001$) and significant improvement on day 12 ($p < 0.01$) when compared with amoxicillin. Combination of amoxicillin plus metronidazole was more effective than azithromycin in reducing symptoms of acute sinusitis on day 40 ($P < 0.001$ Vs $P < 0.01$). Azithromycin showed significant improvement in radiographic scoring on day 7 ($p < 0.01$) and on day 35 ($p < 0.01$). Amoxicillin plus metronidazole when compared with amoxicillin showed significant improvement in radiographic scoring both on day 12 ($P < 0.05$) and day 40 ($P < 0.001$). Amoxicillin was associated with maximum adverse effects. Metronidazole was associated with metallic taste, whereas azithromycin was associated with least adverse effects.

Conclusion: All the four group of antimicrobial drugs i.e. amoxicillin, amoxicillin plus metronidazole, azithromycin and gatifloxacin were effective in reducing symptoms of acute sinusitis on visual analogue scale scoring. Gatifloxacin was found to be most effective drug both in terms of improvement in signs and symptoms on visual analogue scale and radiographic scoring and was associated with least adverse events in comparison to rest of two drugs under study. Combination of metronidazole with amoxicillin was associated with earliest improvement in radiographic scoring.

Keywords: acute rhinosinusitis (ARS); Gatifloxacin-respiratory fluoroquinolone; metronidazole; amoxicillin; azithromycin.

INTRODUCTION

Rhinosinusitis is a global problem. It is principally an adult disease. It is usually a disease of sino-nasal

obstruction and bacterial trapping. Sinusitis occurring alone is uncommon. It is usually preceded by and occurs in tandem with viral URTI. Sinusitis is an important source of morbidity and loss of income and

may exacerbate chest disease. Sinusitis is considered to be an inherent part of the "common-cold syndrome" and hence the term 'rhino-sinusitis' defines this disease more precisely.^{1,2} In case of combined viral-bacterial infection, the clinical feature of disease reflects its dual nature.² When the sinus ostium is obstructed, the retained secretions may become infected with a variety of pathogens, including viruses, bacteria and fungi.³ There is always a preceding viral upper respiratory infection upon which bacterial infections get superimposed, for which antibiotics are commonly prescribed in 85% to 95% of cases.⁴⁻⁶ In spite of the disease being very common, there is likely possibility of it being often mis-diagnosed. At the same time disease warrants early diagnoses and timely anti-microbial treatment so as to avoid complications of ARS.⁷ The treatment of such a condition is still empirical and quite controversial in terms of anti-bacterial drug of choice, frequency, route and duration of treatment and other adjuvant drugs being used. There is no general consensus among physicians world-wide with regard to drug treatment of this disease. So the present study was envisaged to compare different anti-microbial drugs in treatment of ARS.

MATERIAL AND METHODS

Study design

An open randomized trial of comparative efficacy and safety of amoxicillin, azithromycin and gatifloxacin in patients with ARS.

Subjects: Adults patients presenting in ENT Out-patient Department at Himalayan Institute of Medical Sciences (HIMS), Jolly Grant, Dehradun during the course of one year with a primary diagnosis of clinically and radiologically documented acute sinusitis of less than or equal to 4 weeks duration were enrolled with us. Eligible adults of either sex of at least 18 years of age were enrolled. Use of adjunctive treatment such as antipyretic, phenylephrine nose drops or xylometazoline spray were allowed. The patients were informed about the trial both orally and in writing and their informed consent was obtained.

Inclusion criteria: The study included patients with symptoms lasting for more than 1 week or those with symptoms of severe rhinosinusitis such as: nasal

discharge of any quality, facial pain unrelated to trauma, predominantly unilateral maxillary pain, maxillary toothache or pain when chewing, unilateral pain above and below eyes on bending forward.

Exclusion Criteria: Patients excluded from the study were those with chronic symptoms (> 1month), compromised immune system, previous sinus surgery, co-morbidity (diabetes, heart failure, hepatic diseases, renal disorders, immune deficiency), pregnant / lactating women, use of antibiotics for less than 4 weeks, nasal disorders (nasal polyps), concurrent bronchitis, current episodes of longer than 3 months, known hypersensitivity to penicillins, macrolides or fluoro-quinolones, coagulation disorders, seizure disorder or any condition requiring therapy with major tranquilizers, patients who required nasal or systemic steroids.

STUDY PROTOCOL

Baseline characteristics

Demographic characteristics of patients regarding age, sex, occupation, socio-economic status also taken into account. Relevant medical history taken from patient followed by ENT examination.

Diagnostic criteria

Based on presence of at least 2 major diagnostic factors or 1 major and 2 minor factors as follows⁸

Major factors

- Facial pain or pressure
- Facial congestion or fullness
- Nasal obstruction
- Purulent rhinorrhoea / discoloured postnatal discharge
- Hyposmia or anosmia
- Fever with preceding URTI

Minor factors

- Headache
- Halitosis (foul breath)
- Fatigue

- Dental pain (maxillary toothache)
- Cough

Antimicrobial therapy and assessment

After fulfilling inclusion and exclusion criteria, patients with clinical diagnosis of ARS were recruited to study protocol and randomized into 4 groups (of ten patients each) as under:-

Group 1 – Patients on oral Amoxicillin 500mg three times a day for 10 days.

Group 2 – Patients on oral Amoxicillin 500mg three times a day for 10 days plus oral metronidazole 400mg Three times a day for 10 days

Group 3 – Patients on tablet Azithromycin 500mg once a day for 5 days

Group 4 – Patients on oral Gatifloxacin 400mg once a day for 10 days.

Patients were evaluated for signs and symptoms at day 1, day 7 (for group 3), on day 12 (for group 1, 2, 4) as primary end points and 28 days after post therapy as secondary end point.

Evaluation of Efficacy

Efficacy evaluation included assessment of clinical signs and symptoms, overall clinical response rating and radiographic findings, Water's view⁹ before and after drug treatment as primary end point and after 28 days as secondary end point.

Assessment of clinical signs and symptoms

Clinical signs and symptoms was assessed on admission to study, at the post therapy hospital visit 2 days after end of therapy, and at the post study follow up 28 days after the end of therapy. The clinical signs and symptoms of ARS were recorded with severity of symptoms assessed by Visual analogue scale (VAS). Seven signs / symptoms were given grading as per individual patients on a scale from zero to ten (facial pain, nasal block, purulent rhinorrhoea, post-nasal drip, altered or loss of smell, headache, overall discomfort).

Radiographic findings and assessment

Radiographic studies was done on admission and at

the post therapy hospital visits 2 days after the end of therapy. Radiographic scoring was done with help of radiographic scoring system¹⁰

X-ray sinus findings	Score
Mucous membrane thickening <6mm	1
Mucous membrane thickening >6mm	2
Air-fluid level	2
Mucous membrane thickening <6mm plus air fluid level	3
Mucous membrane thickening >6mm plus air fluid level	4
Complete sinus opacity	6

Radiographic findings was assessed as resolved, improved, worsened or unchanged and their overall radiographic improvement in scoring was assessed before and after treatment.

Evaluation of safety:

Safety evaluation was done simultaneously by monitoring Adverse drug reactions at each visit of the patient in the hospital. Adverse events were graded as- mild: awareness of symptoms but easily tolerated; or moderate: discomfort sufficient to reduce or affect normal daily activity and severe: Causes inability to work / requires hospitalization / results in permanent disability or is life-threatening.

Statistical analysis:

It was done to test the efficacy of the study drug groups by applying student's t-test. All results have been reported according to an Intent-to-treat analysis.

OBSERVATION AND RESULTS

1. Comparison of signs and symptoms on visual analogue scale scoring in patients of acute rhinosinusitis [Table1]

Among the same group on day 1, 7/12 or day 35/40. Paired t-test was applied whereas intergroup comparison on day 7/12 or day 35/40 was done by Unpaired t-test.

Intra-group comparisons

Amoxicillin as positive control in group 1 patients,

produced highly significant fall in values of scoring on visual analogue scale on day 12 ($p<0.001$) and day 40 ($p<0.001$). Combination of amoxicillin with metronidazole in group II patients showed highly significant improvement in symptoms of sinusitis on day 12 ($p<0.001$) and day 40 ($p<0.001$). Azithromycin in Group III patients was effective in significant reduction in symptoms of acute sinusitis in visual analogue scale on day 7 [$P<0.001$] and on day 35 [$P<0.01$]. Gatifloxacin in Group IV patients, was also effective in significant reduction in symptoms on Visual Analogue Scale on day 12 [$P<0.001$] and on day 40 [$P<0.001$].

Thus all the three antimicrobial drugs i.e. Amoxicillin, azithromycin and gatifloxacin were effective in reducing symptoms of acute sinusitis on visual analogue scale [VAS] scoring. When VAS-scoring on day 7 was compared with that of day 35, Azithromycin-group showed very significant improvement in symptoms on VAS [$P<0.001$].

Inter-Group Comparisons

Azithromycin and combination of amoxicillin with metronidazole were equally efficacious as amoxicillin in reducing symptoms of ARS as measured on VAS. Azithromycin was found to be equally efficacious to amoxicillin + metronidazole in controlling symptoms of acute – sinusitis on day 7/12 [$P<0.001$]. Combination of amoxicillin with metronidazole was more effective than azithromycin in reducing symptoms of acute sinusitis on day 40 [$P<0.001$ vs. $P<0.01$]. Amoxicillin with metronidazole was found not to be equally effective as amoxicillin alone in reducing symptoms on VAS on day 12 and day 40 [$P>0.05$]. Combination of azithromycin was found to be equally effective as amoxicillin alone in reducing symptoms on visual analogue scale on day 7 and day 35 [$P>0.05$]. Gatifloxacin was found to be most effective in reducing symptoms on VAS on day 12 [$P<0.02$] and day 40 [$P<0.05$] when compared to amoxicillin.

2. Radiographic improvement in patients of Acute rhinosinusitis as assessed by radiographic scoring [Table 2]

Comparison of Radiographic scoring of sinus X-rays picture in patient of ARS among same group was

done by paired t-test and between different groups by Un-paired t-test.

Intra-group Comparisons

Amoxicillin (Group I) showed significant improvement in radiographic scoring on day 12 ($p<0.05$) and day 40 ($p<0.01$). Combination of amoxicillin with metronidazole (group II) showed highly significant improvement in radiographic scoring on day 12 ($p<0.001$) and day 40 ($p<0.001$). Azithromycin (group III) showed significant improvement in radiographic scoring on day 12 ($p<0.05$) and highly significant improvement on day 40 ($p<0.001$). Gatifloxacin (group IV) showed highly significant improvement in radiographic scoring on day 12 ($p<0.001$) and day 40 ($p<0.001$).

Inter Group Comparisons

Amoxicillin + metronidazole when compared with amoxicillin showed significant improvement in radiographic scoring both on day 12 ($p<0.05$) and 40 ($p<0.01$). Likewise azithromycin showed significant improvement in radiographic improvement on day 7 ($p<0.01$) and on day 35 ($p<0.01$). Gatifloxacin elicited very highly significant improvement radiographically on day 40 ($p<0.001$) and significant improvement on day 12 ($p<0.01$) when compared with amoxicillin

3. Comparison of safety of various antimicrobials by noting adverse drug reactions.[see table 3]

Amoxicillin was associated with maximum adverse reactions like nausea in 80% (mild-3, moderate-5), vomiting in 60% (mild-4, moderate-2), gastric upset in 70% (mild-3, moderate-4), abdominal pain in 70% (mild-4, moderate-3), diarrhoea in all patients, headache in 70% (mild-2, moderate-5), and rash in 60% of patients. Combination of amoxicillin with metronidazole was associated with nausea in 70% (mild-5, moderate-2), vomiting in 50% (mild), gastric upset in 50% (mild-4, moderate-1), headache in 70% (mild-2, moderate-5), dizziness in 40%, insomnia in 50% patients and metallic taste in 90% of patients. Azithromycin, the ketolide was associated with less adverse effects like nausea in 50% of patients (mild-3, moderate-2), vomiting in 30% (mild), gastric upset in 30%, abdominal pain in 20% and Headache in 60% of patients (mild-4, moderate-2). Gatifloxacin, the

newer respiratory fluoroquinolone, was associated with least adverse events in comparison to rest of three drugs under study. The observed adverse events were nausea (30%), mild vomiting (10%) and mild headache in 70% of patients (See table 3).

CONCLUSION

The primary goals of management of acute sinusitis are to eradicate the infection by appropriate systemic anti-microbial treatment, decrease the severity and duration of symptoms, and prevent complications i.e. mucocoele, chronic sinusitis. The appropriate antibiotics therapy should be given for 10-14 days. In present study, Group II patients received metronidazole in combination of amoxicillin, considering anaerobic factors playing a role in causation of acute bacterial sinusitis. Dental infection may precipitate anaerobic infection. Combination therapy showed synergistic effect in significant reduction in symptoms on visual analogue scale on day 12 and day 40. In all 4 groups, individually all the antimicrobial drugs i.e. amoxicillin, combination of amoxicillin with metronidazole, azithromycin and gatifloxacin were effective in reducing symptoms of acute sinusitis or visual analogue scale (VAS) scoring. Gatifloxacin was found to be most effective drug both in terms of improvement in signs and symptoms on visual analogue scale and radiographic scoring. Gatifloxacin, the newer fluoroquinolone, was associated with least adverse events in comparison to rest of three drugs under study. The observed adverse events were mild. Azithromycin, the ketolide was the 2nd safest drug associated with less adverse effects. Convenience of dosing is an additional advantage with gatifloxacin as well as Azithromycin in improving patients compliance. Combination of amoxicillin with metronidazole was more effective than amoxicillin, in hastening earlier resolution of sinusitis radiographically.

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