Comparative Efficacy and Safety of Various Anti-Microbials in Patients of Acute Rhinosinusitis at Tertiary-Care Hospital in Uttarakhand (UK)

Vivek Sharma · R. K. Saxena · Shalini Sharma ·
Geetanjali Sharma · D. C. Dhasmana ·
K. C. Mishra

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Abstract To compare the efficacy of gatifloxacin, azithromycin with amoxicillin as positive control for the treatment of Acute rhinosinusitis (ARS). To monitor adverse drug reaction profile of amoxicillin, azithromycin and gatifloxacin in patient of ARS. An open randomized trial of comparative efficacy and safety of amoxicillin, azithromycin and gatifloxacin in patients with ARS. Patients were randomized into three groups as under: group 1: patients on oral amoxicillin 500 mg TDS for 10 days; group 2: patients on oral azithromycin 500 mg OD for 5 days; group 3: patients on oral gatifloxacin 400 mg OD for 10 days. Patients were evaluated for signs and symptoms at day 1, day 7 (for group 2), on day 12 (for group 1, 3) as primary end points and 28 days after post therapy as secondary end point. All the three antimicrobial drugs i.e., amoxicillin, azithromycin and gatifloxacin were effective in reducing symptoms of acute sinusitis on visual analogue scale 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. Azithromycin, the ketolide was associated with lesser adverse effects as compared to amoxicillin. All the three antimicrobial drugs i.e., amoxicillin, 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.

Keywords Acute rhinosinusitis (ARS) · Gatifloxacin-respiratory fluoroquinolone, ketolide-azithromycin · Aminopenicillin-amoxicillin

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 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 which gets superimposed by bacterial infections, for which

V. Sharma (✉)
Department of Pharmacology, PGIMS, Rohtak, India
e-mail: vs_doctor@yahoo.com

R. K. Saxena
Department of ENT, HIMS, Dehradun, India

S. Sharma
Department of Physiology, HIMS, Dehradun, India

G. Sharma
Department of Physiology, PGIMS, Rohtak, India

D. C. Dhasmana · K. C. Mishra
Department of Pharmacology, HIMS, Dehradun, India

antibiotics are commonly prescribed in 85–95% of cases [4–6]. In spite of 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.

Materials and Methods

Study Design

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

Subjects

Adults patients presenting in ENT OPD at HIMS, Jolly Grant, Dehradun during the course of 1 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

With symptoms lasting for more than 1 week or those with severe rhinosinusitis symptoms

1. Nasal discharge of any quality.
2. Facial pain unrelated to trauma.
3. Predominantly unilateral maxillary pain.
4. Maxillary toothache or pain when chewing.
5. Unilateral pain above and below eyes on bending forward.

Exclusion Criteria

1. Patient with chronic symptoms (>1 month).
2. Immuno compromised patient.
3. Patient with previous sinus surgery.

4. Patient with antibiotic use within past 1 week.
5. Co-morbidity (diabetes, heart failure, immune deficiency).
6. Pregnancy/breast-feeding.
7. In take of antibiotics for less than 4 weeks.
8. Other nasal disorders (nasal polyps).
9. Concurrent bronchitis, current episodes of longer than 3 months.
10. Known hypersensitivity to penicillins, macrolides, fluoroquinolones.
11. Hepatic, renal or immunological disorders.
12. Coagulation disorders.
13. Seizure disorder or any condition requiring therapy with major tranquilizers.
14. 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 two major diagnostic factors or one major and two minor factors as follows [8].

Major factors:

- Facial pain or pressure.
- Facial congestion or fullness.
- Nasal obstruction.
- Purulent rhinorrhoea/discoloured postnasal 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 over a period of 1 year (2005), patients were recruited to study protocol and randomized into three groups (of ten patients each) as under:

- Group 1: Patients on oral amoxicillin 500 mg TDS for 10 days.
- Group 2: Patients on oral azithromycin 500 mg OD for 5 days.
- Group 3: Patients on oral gatifloxacin 400 mg OD for 10 days.

Patients were evaluated for signs and symptoms at day 1, day 7 (for group 2), on day 12 (for group 1, 3) 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 view [9] 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 was recorded with severity of symptoms assessed by Visual analogue scale (VAS) (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 system [10].

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

Table 1 Comparison of visual analogue scale scoring in patients of acute rhinosinusitis among the same group on day 1, 7/12 or day 35/40 as well as intergroup comparison on day 7/12 or day 35/40

Groups	Day 1	Day 7/12	Day 35/40
Group I (Mean $\pm$ SE)	33.5 $\pm$ 2.20	15.6 $\pm$ 1.88***	7.2 $\pm$ 2.01***
Group II (Mean $\pm$ SE)	29.3 $\pm$ 2.99	10 $\pm$ 1.81***	3.9 $\pm$ 1.23**
Group III (Mean $\pm$ SE)	37.9 $\pm$ 2.94	8.1 $\pm$ 1.95*** [€]	1.8 $\pm$ 0.66*** [¥]

Baseline comparisons

$P < 0.05$ versus corresponding day 1 value

* $P < 0.05$ versus corresponding day 1 value of group 1

** $P < 0.01$ versus corresponding day 1 value

*** $P < 0.01$ versus corresponding day 1 value

[€] $P < 0.02$ versus corresponding day 12 value of group 1

[¥] $P < 0.05$ versus corresponding day 40 value of group 1

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 sign and symptoms but easily tolerated; or moderate: discomfort sufficient to reduce or affect normal daily activity and or 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 (see Table 1).

Observation and Results

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 ($P < 0.001$). Azithromycin in group II 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 III patients, was also effective in significant reduction in symptoms on visual analogue scale on day 12 ($P < 0.001$) and on day 40 ($P < 0.001$).

Inter-Group Comparisons

Combination of azithromycin was found to be equally effective as amoxicillin alone in reducing symptoms on

Table 2 Comparison of Axelssons radiographic scoring by sinus X-rays in patients of acute rhinosinusitis among same groups on day 1 with day 7/12 or day 35/40 as well as intergroup comparison on day 7/12 or day 35/40

Groups	Day 1	Day 7/12	Day 35/40
Group I (Mean $\pm$ SE)	4.3 $\pm$ 0.396	3 $\pm$ 0.395*	2.4 $\pm$ 0.267**
Group II (Mean $\pm$ SE)	3.5 $\pm$ 0.48	1.7 $\pm$ 0.30**,©	1.3 $\pm$ 0.15***,£
Group III (Mean $\pm$ SE)	4 $\pm$ 0.495	1.4 $\pm$ 0.22***,Ω	1.2 $\pm$ 0.134***,†

Baseline comparisons

 $P < 0.05$ versus corresponding day 1 value** $P < 0.01$ versus corresponding day 1 value*** $P < 0.001$ versus corresponding day 1 value $P > 0.05$ in all groups© $P < 0.05$ versus corresponding day 7 value of group 1£ $P < 0.01$ versus corresponding day 35 value of group 1Ω $P < 0.01$ versus corresponding day 12 value of group 1† $P < 0.001$ versus corresponding day 40 value of group 1

visual analogue scale on day 7 and day 35 ($P > 0.05$). Gatifloxacin was found to be most effective in reducing symptoms on visual analogue scale on day 12 ($P < 0.02$) and day 40 ($P < 0.05$) when compared to amoxicillin (see Table 2).

Fig. 1 X-ray maxillary sinus-waters view (Group 1) **Fig. 2** X-ray maxillary sinus-waters view (Group 2)

Radiographic Improvement in Patients of Acute Rhinosinusitis as Assessed by Radiographic Scoring

Intra-Group Comparisons

Amoxicillin (group I) showed significant improvement in radiographic scoring on day 12 ($P < 0.05$) and day 40 ($P < 0.01$). Azithromycin (group II) showed significant improvement in radiographic scoring on day 12 ($P < 0.05$) and highly significant improvement on day 40 ($P < 0.001$). Gatifloxacin (group III) showed highly significant improvement in radiographic scoring on day 12 ($P < 0.001$) and day 40 ($P < 0.001$) (see Figs. 1, 2 and 3).

Inter-Group Comparisons

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 (see Table 3).

Discussion

The primary goals of management of acute sinusitis are to eradicate the infection by appropriate systemic anti-

Fig. 3 X-ray maxillary sinus-waters view (Group 3) **Table 3** Comparison of safety of various antimicrobials by noting adverse drug reactions

ADR	Amoxicillin No. of patients	Severity	Azithromycin No. of patients	Severity	Gatifloxacin No. of patients	Severity
GIT						
Nausea	8/10	Mild-3 Mod-5	5/10	Mild-3 Mod-2	3/10	Mild-3
Vomiting	6/10	Mild-4 Mod-2	3/10	Mild-3	1/10	Mild-1
Gastric-upset	7/10	Mild-3 Mod-4	3/10	Mild-3	–	–
Abdominal pain	7/10	Mild-4 Mod-3	2/10	Mild-2	–	–
Diarrhoea	10/10	Mild-2 Mod-8	–	–	–	–
CNS						
Headache	7/10	Mild-2 Mod-5	6/10	Mild-4 Mod-2	7/10	Mild-7
Dizziness	–	–	–	–	–	–
Insomnia	–	–	–	–	–	–
Hallucination	–	–	–	–	–	–
Delirium	–	–	–	–	–	–
Seizure	–	–	–	–	–	–
Skin						
Photosensitivity reactions						
Rash	6/10	Mild-6	–	–	–	–
Exfoliative dermatitis	–	–	–	–	–	–
Renal	Nil					
Liver	Nil					
Genitourinary system	Nil					
Blood investigations	No significant changes observed in TLC and DLC in comparison to baseline values					

Mod moderate

microbial treatment, decrease the severity and duration of symptoms, and prevent complications i.e., mucocoele, chronic sinusitis. 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.

Summary and Conclusions

In all three groups, individually all the antimicrobial drugs i.e., amoxicillin, 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. It 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 second safest drug associated with less adverse effects. Convenience of dosing is an additional advantage with gatifloxacin as well as azithromycin in improving patients compliance. Although, present study came with the conclusion that gatifloxacin is the drug of choice in acute rhinosinusitis. But further studies are still required in present scenario owing to prevalent nature of disease and perhaps because of smaller sample size.

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