COMPARISON OF EFFICACY OF ORAL AZITHROMYCIN WITH INTRAVENOUS CEFTRIAXONE FOR THE TREATMENT OF UNCOMPLICATED ENTERIC FEVER

BUSHRA SAEED, TOOBA RIAZ

ABSTRACT

OBJECTIVE: To determine the efficacy of oral azithromycin and intravenous ceftriaxone for treatment of uncomplicated enteric fever and the frequency of relapse in both groups.

STUDY DESIGN: A randomized controlled trial

PLACE AND DURATION: Study was conducted at Pediatric Medicine Ward and Emergency Department of Sir Ganga Ram Hospital from 1st May 2013 to 31st Oct 2013.

METHODOLOGY: Using Non probability purposive sampling, 100 patients with uncomplicated enteric fever were taken who were fulfilling the inclusion criteria. Patient was randomly divided in 2 groups using random numbers, Group "A" and Group "B", with 50 patients in each group. Group A was given ceftriaxone for 7 days. Group B was given azithromycin once a day for 7 days. A culture was repeated at day 4 of therapy. Both groups were compared for efficacy and relapse.

RESULTS: Efficacy achieved by both the oral azithromycin and intravenous ceftriaxone in treatment of uncomplicated enteric fever was statistically same. However, higher rate of relapse was observed in group treated by intravenous ceftriaxone compared to oral azithromycin.

CONCLUSION: Efficacy achieved by both oral azithromycin and intravenous ceftriaxone in treatment of uncomplicated enteric fever was satisfactory and statistically same. However, higher rate of relapse was observed in group treated by intravenous ceftriaxone compared to oral azithromycin.

KEYWORDS: Typhoid fever, Ceftriaxone, Azithromycin, Children.

INTRODUCTION

Enteric fever (also known as typhoid fever), a systemic infection caused by Salmonella enterica serovars (S. typhi & S. paratyphi) always remains a major public health issue especially in developing countries. According to a study, WHO reported that there are about 21 million cases of typhoid fever in the world and it has swallowed more than six hundred thousand people worldwide. Typhoid fever leads to nearly 22 million cases and 216,500 deaths annually, primarily in Asia, and case fatality rate is 1% to 4%. The prevalence of enteric fever is high in developing countries like Pakistan. Developing nations suffer more from this fatal disease because of increase in population size, growing trend of urbanization, limited availability of safe water for drinking and unsatisfactory systems of health. Enteric fever starts usually 7-14 days after exposure to virulent bacteria S typhi. The most predominant feature of uncomplicated enteric fever is fever which is high grade and gradually increases in intensity over several days. Patients can also have abdominal pain, anorexia, headaches, diarrhea, cough, rose colored spots on neck, chest and abdomen, malaise and hepatosplenomegaly. Unusual presentation of enteric fever could be in form of severe headache that is easily confused with meningitis, lung consolidation, isolated arthralgia, arthritis, dysuria or burning micturition, polyserositis and cholestatic hepatitis. Complications of typhoid fever usually occur in those patients who have not been given adequate treatment in form of antibiotics. Complications are seen in about 1 in 10 patients, which are usually seen in third week of infection. Complications most commonly seen are perforation of bowel and hemorrhages in intestine that can lead to shock, inflammation of pancreas, pneumonia, myocarditis, meningitis, Osteomyelitis, abscesses anywhere in body and rare neurological complications like Guillain Barre syndrome. The gold standard of diagnosis for enteric fever is Bone marrow culture but as it is an invasive procedure the mainstay of diagnosis in 1 week of illness is positive blood culture. The bacterium that causes typhoid fever spreads to humans through fecal oral route and endemic in countries with poor sanitation and lack of availability of clean drinking water. In Pakistan, patients of uncomplicated typhoid fever are given home treatment of 7-14 days. Patients with complications are admitted in hospital. Around 1 in 20 children who are treated for typhoid fever suffer from relapse, in which symptoms reappear. Symptoms usually reappear about a week after the treatment with antibiotics has finished. The relapse is usually milder, but it is recommended to treat the patient with antibiotics. The timely appropriate management of typhoid fever can considerably reduce both morbidity and mortality.

With the development of multidrug resistance (resistance to ampicillin, chloramphenicol, and co-trimoxazole) in enteric fever, ciprofloxacin was introduced as first line therapy.
However strains with decreased susceptibility to ciprofloxacin resulting in treatment failure have been endemic in several countries in Indian subcontinent and High level ciprofloxacin resistance has evolved in Asian countries. Fluoroquinolones then were mostly recommended as drug of choice for the treatment of typhoid fever. But sadly, few strains of S. typhi have developed some resistance to fluoroquinolones so the therapeutics of ciprofloxacin and fluoroquinonones resistant enteric fever narrows down to third & fourth generation Cephalosporins and azithromycin.

One of the members of macrolide group of antibiotics, Azithromycin, is now increasingly used as an alternate drug for treatment of Typhoid fever because of its properties of achieving low intravascular levels, good penetration into the tissues and long half-life. Absorption of this drug from gut is rapid and if used orally it is well tolerated by the body. These properties of Azithromycin make it eligible for once daily dose and a shorter duration of treatment is required.

Considering the hazards of intravenous therapy i.e. transmission of infections, local complications and discomfort to the child, it was worthwhile to compare oral azithromycin with intravenous ceftriaxone in patients with enteric fever. Oral therapy with azithromycin was cost effective, avoids hospital stay and will avoid hazards of intravenous therapy and will also give the benefit of shorter duration of treatment. It is also worthwhile that previous studies have been done using small number of patients so study including increased number of patients should be done.

**METHODOLOGY**

This randomized controlled trial was conducted in Pediatric Medicine Ward and Emergency of Sir Ganga Ram Hospital, Lahore over a period of six months from 1st May 2013 to 31st Oct 2013. Inclusion criteria were age 3 to 12 years, gender: both male and female, history of fever for at least 4 days and blood culture positive for S.typhi or S.paratyphi. Exclusion Criteria were documented hypersensitivity to ceftriaxone or azithromycin (or to any other macrolide), significant underlying illness (e.g. heart disease, asthma requiring chronic medications, or immunodeficiency) documented by previous medical record and those patients who had treatment with in past 4 days with either study medicine or with ampicillin, cotrimoxazole or chloramphenicol.

Patients fulfilling the inclusion criteria, admitted in Pediatric ward of Sir Ganga Ram Hospital through OPD or emergency were enrolled. Informed consent regarding inclusion in study was taken from parents or guardians and risk benefit ratio was discussed. The attendants were ensured that appropriate measures were taken promptly in case of adverse effects. Consent from ethical committee was taken. Patient was randomly divided in 2 groups using random numbers, Group "A" and Group "B", with 50 patients in each group. Group A was given ceftriaxone (75mg/kg/day) X OD for 7 days. Group B was given azithromycin (10mg/kg /day) OD for 7 days. Patients were followed closely with vital records 8 hourly, daily examination for resolution of sign and symptoms. A culture was repeated at day 4 of therapy. Both groups were compared for efficacy and relapse. All this was entered in the Proforma.

**RESULTS**

The mean age of the patients was 6.68±2.77 years for group A and 7.47±2.93 years for group B. The minimum age of patients in group A was 1 year and maximum age was 12 years similarly the minimum age of the patients in group B was 3 years and maximum age was 12 years. (Table-I) Number of patients in different age groups is shown in Table. (Table-II) There were 27(54%) males and 23(46%) females in group A and 27(54%) males and 23(46%) females in group B out of total 100 patients. (Table-II)

There were 43(86%) patients in Ceftriaxone group (A) with efficacy and 7(14%) patients with no efficacy. There were 40(80%) patients in Azithromycin group (B) with efficacy and 10(20%) patients with no efficacy. Efficacy achieved by oral azithromycin as well as intravenous ceftriaxone in treatment of uncomplicated enteric fever was statistically same (p-value= 0.424). (Table-III)

There were 11(22%) patients in Ceftriaxone group (A) with relapse and 39(78%) patients with no relapse. There were 3(6%) patients in Azithromycin group with relapse and 47(94%) patients with no relapse. The rate of relapse was different statistically in both groups (p-value= 0.021) (Table-IV)

**TABLE- I: DESCRIPTIVE STATISTICS FOR AGE IN TREATMENT GROUP (n=100)**

<table>
<thead>
<tr>
<th></th>
<th>Treatment Group</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group-A</td>
<td>Group-B</td>
<td></td>
<td>Total</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td>Mean</td>
<td>6.68</td>
<td>7.47</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>2.77</td>
<td>2.93</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Minimum</td>
<td>1</td>
<td>3</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Maximum</td>
<td>12</td>
<td>12</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

Group-A= Ceftriaxone
Group-B= Azithromycin
Tooba Riaz et al.

TABLE-II: DESCRIPTION OF AGE AND GENDER IN BOTH GROUPS (n=100)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Group A</th>
<th>Group B</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3 years</td>
<td>7(14%)</td>
<td>2(4%)</td>
<td>9</td>
</tr>
<tr>
<td>4-6 years</td>
<td>16(32%)</td>
<td>23(46%)</td>
<td>39</td>
</tr>
<tr>
<td>7-9 years</td>
<td>18(36%)</td>
<td>9(18%)</td>
<td>27</td>
</tr>
<tr>
<td>10-12 years</td>
<td>9(18%)</td>
<td>16(32%)</td>
<td>25</td>
</tr>
<tr>
<td>Total</td>
<td>50(100%)</td>
<td>50(100%)</td>
<td>100</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender</th>
<th>Group A</th>
<th>Group B</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>27(54%)</td>
<td>27(54%)</td>
<td>54</td>
</tr>
<tr>
<td>Female</td>
<td>23(46%)</td>
<td>23(46%)</td>
<td>46</td>
</tr>
<tr>
<td>Total</td>
<td>50(100%)</td>
<td>50(100%)</td>
<td>100</td>
</tr>
</tbody>
</table>

Group-A= Ceftriaxone  
Group-B= Azithromycin

TABLE-III: COMPARISON OF EFFICACY OF BOTH TREATMENT GROUP (n=100)

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Group-A</th>
<th>Group-B</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>43(86%)</td>
<td>40(80%)</td>
<td>83</td>
</tr>
<tr>
<td>No</td>
<td>7(14%)</td>
<td>10(20%)</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>50(100%)</td>
<td>50(100%)</td>
<td>100</td>
</tr>
</tbody>
</table>

Group-A= Ceftriaxone  
Group-B= Azithromycin  
Chi-Square=0.64  
p-value=0.424

TABLE-IV: COMPARISON OF RELAPSE IN BOTH TREATMENT GROUP (n=100)

<table>
<thead>
<tr>
<th>Relapse</th>
<th>Group-A</th>
<th>Group-B</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>11(22%)</td>
<td>3(6%)</td>
<td>14</td>
</tr>
<tr>
<td>No</td>
<td>39(78%)</td>
<td>47(94%)</td>
<td>86</td>
</tr>
<tr>
<td>Total</td>
<td>50(100%)</td>
<td>50(100%)</td>
<td>100</td>
</tr>
</tbody>
</table>

Group-A= Ceftriaxone  
Group-B= Azithromycin  
Chi-Square=5.32  
p-value=0.021

DISCUSSION

Typhoid fever is one of the commonest diseases in children as well as adults. Particularly, in south central and South East Asia, this problem continues to be a major cause of illness and mortality. This is because of high prevalence of poor sanitary system, hazardous food and poor water condition in these countries. Various treatment options are opted for treatment of this problem that mainly constitutes the medications for children. However the efficacy of each drug has its own advantages and disadvantages, and need to be chosen according to individual case. Our study henceforth, focused on the efficacy of oral azithromycin with intravenous ceftriaxone for treatment of uncomplicated enteric fever. Also, the frequency of relapse was studied in both the groups.

In our study, out of total 100 patients, maximum number (39%) was from age group of 4-6years. These results were compatible with a number of international studies in which school going children have been reported to be at more risk of disease. One international study showed the global burden of typhoid and paratyphoid fever in India and found very narrow age ranges with high incidence of disease in under five and school going children. The author of the study has therefore focused on the importance of school vaccination instead of infant vaccination to reduce the incidence of enteric fever.  

Another study showed the most critical age range of children at risk of enteric fever to be 3-10 years, much similar to our study. In Our study Efficacy achieved by oral azithromycin as well as intravenous ceftriaxone in treatment of uncomplicated enteric fever was statistically same (p-value= 0.424). The rate of relapse was different statistically in both groups (p-value= 0.021) and Azithromycin was found to be superior in reducing relapses as compared to Ceftriaxone.

The results in our study were compatible to another similar study which was done in 2011 by Effa EE in which he compared the efficacy of Azithromycin with other antibiotics including Ceftriaxone. He also concluded that Ceftriaxone was similar in curing enteric fever with Azithromycin but Azithromycin significantly reduced the relapse rate as compared to ceftriaxone.  

In a meta-analysis, Triyedi NA studied the safety and efficacy of Azithromycin with other antibiotics including ceftriaxone. He concluded that Ceftriaxone was similar to Azithromycin in preventing clinical failure in enteric fever but Azithromycin was
seen to reduce significantly the chance of relapse with RR 0.1 (95% CI 0.01-0.76). No significant adverse effects were seen in any of the trials. These results were similar to our study but here author has also enforced the importance of large clinical trials in pediatric age group to reach a final conclusion.28 Now a day the biggest concern is the worldwide appearance of multidrug resistant strains. Work is being made to increase our understanding of the molecular pathogenesis. New areas of targets in diagnosis and treatment are being explored by genomic studies. The importance of availability of safe water for drinking, good sanitary measures,37 and immunization in the presence of increasing resistance of antibiotics is cardinal.38 Also the growing importance of Salmonella enterica serotype Paratyphi A in Asia is also a concerning fact.30,32 Large studies should be done for Calculation of the incidence of typhoid fever during preschool and school years so that the optimum age of immunization for public-health programs in developing countries can be estimated. Also, need of the time is to conduct large control based trials to reach a final conclusion regarding treatment of uncomplicated typhoid fever with a safe drug with minimum adverse effects, clinical failure and relapse rate.

CONCLUSION

Efficacy achieved by both the oral azithromycin and intravenous ceftriaxone in treatment of uncomplicated enteric fever was satisfactory and statistically same. However, higher rate of relapse was observed in group treated by intravenous ceftriaxone compared to oral azithromycin.

Contribution of Author:
Bushra Saeed: Conception and design, Collection and assembly of data, Analysis and interpretation of the data, Statistical expertise
Tooba Riaz: Drafting of the article, Critical revision of the article for important intellectual content, Final approval and guarantor of the article

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