AZITHROMYCIN VERSUS CEFTRIAXONE- WHICH IS BETTER IN UNCOMPLICATED TYPHOID FEVER? A CLINICAL TRIAL IN A TERTIARY CARE HOSPITAL

Vishwanath Machakanur¹, Rohit S²

¹Assistant Professor, Department of Paediatrics, KAHER’s Jawaharlal Nehru Medical College, Belagavi, Karnataka, India.
²Postgraduate Student, Department of Paediatrics, KAHER’s Jawaharlal Nehru Medical College, Belagavi, Karnataka, India.

ABSTRACT

BACKGROUND
Enteric fever has been very common and many times a fatal infective disease found in developing countries and has been known to have increasing resistance to novel drugs. So, there is an urgent need for a simple, therapeutic, cost-effective medicine to treat typhoid fever & to prevent further drug resistance.

METHODS
It is a non-randomized, case-control study done in Paediatrics department of Dr. Prabhakar Kore Hospital & Research centre of KAHER (KLE Academy of Higher Education and Research), attached to J N Medical College, Belagavi, over a period of 18 months from June 2017 to December 2018. The study included 200 children (2-17 years of age) with positive Widal result, uncomplicated-enteric fever; in this cohort, 100 children were treated using (oral, low dose, for short duration of 6 days) Azithromycin and remaining 100 children were treated with (intravenous, 7 days) Ceftriaxone. Each child was assessed clinically every day, & study results were captured as clinical and microbiological cure or failure, at the end of either drug regimens. This descriptive data was statistically analysed in SPSS-20.0 software. The p-value of <0.05 was taken as significant statistically.

RESULTS
Periods required by children for responding to drug therapy and to became afebrile i.e., defervescence were significantly (p=0.000) less with Azithromycin receiving group than ceftriaxone receiving group. 95% of children who received azithromycin showed defervescence by 5th day of regimen but, only 29% of children receiving ceftriaxone attained defervescence by 5th day of regimen. There was no microbiological clearance at 10th day in only one case of ceftriaxone trial-group. Significantly (p=0.027) there was early clinical cure in azithromycin trial group as compared to ceftriaxone trial group. The microbiological cure was not comparable in either groups (p=0.135).

CONCLUSION
At the end we come to the conclusion that oral Azithromycin (10 mg/kg/day, once a day for 6 days) is more efficacious in uncomplicated-typhoid fever management as compared to intravenous ceftriaxone (100 mg/kg/day in 2 divided doses for 7 days) in children and adolescents of 2 to 17 years age group.


BACKGROUND
Enteric fever caused by Salmonella typhi and paratyphi has been a very common and often fatal disease in children of developing countries. There is an incidence of 500 cases/lakh population (0.5%) and a high mortality rate.¹,² As per the World Health Organization at least 12.5 million cases of typhoid are diagnosed worldwide annually.³,⁴

For many decades, chloramphenicol has been drug of choice for enteric fever.⁵ But it is also found that many resistant strains have been emerging recently. Thus, there is need for any other treatment options.⁶ Fluoroquinolone resistant strains of Salmonella typhi have been isolated & documented. Ceftriaxone (A 3⁴ generation cephalosporin) is highly effective in enteric fever; but every time it is supposed to be administered parenterally; hence, considered as lesser ideal treatment option in enteric fever.

Many studies have shown that the azithromycin concentration in neutrophils are more than 100-fold the serum level. It is also recently found that azithromycin given once daily appears to be helpful in treatment of typhoid fever.⁷ If these results are confirmed, in developing countries where in resources are limited, oral azithromycin could be a convenient alternative drug for the treatment of typhoid fever.

Therefore, we hereby provide a simple study for a clinically effective drug in treatment of typhoid fever (Uncomplicated): comparing oral Azithromycin with intravenous Ceftriaxone.

METHODS
A sum of 200 Widal positive uncomplicated typhoid fever children were considered for this study in age group of 2-17 years who were admitted in the pediatriic department of Dr Prabhakar Kore Hospital & Research of KAHER, attached to J. N. Medical College, Belagavi, over a period of 18 months June 2017 to December 2018.
Comparative Outcome of The Study: (Table 2)

- It was observed that there was early clinical cure in cases treated with azithromycin than those with ceftriaxone, also was significant statistically (p=0.027). (Fig 1)
- The bacterial clearance in blood culture on 10th day was defined as microbiological cure, was not much differing in both study groups (p=0.131).
### Table 1. Comparison of Symptoms and Signs Between Azithromycin and Ceftriaxone Receiving Groups

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Azithromycin Day 1 N (%)</th>
<th>Azithromycin Day 3 N (%)</th>
<th>Azithromycin Day 5 N (%)</th>
<th>Azithromycin Day 7 N (%)</th>
<th>Ceftriaxone Day 1 N (%)</th>
<th>Ceftriaxone Day 3 N (%)</th>
<th>Ceftriaxone Day 5 N (%)</th>
<th>Ceftriaxone Day 7 N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>96 (96)</td>
<td>95 (95)</td>
<td>29 (29)</td>
<td>49 (98)</td>
<td>46 (92)</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>60 (60)</td>
<td>74 (74)</td>
<td>100 (100)</td>
<td>100 (100)</td>
<td>100 (100)</td>
<td>100 (100)</td>
<td>100 (100)</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>100 (100)</td>
<td>45 (90)</td>
<td>98 (98)</td>
<td>100 (100)</td>
<td>100 (100)</td>
<td>100 (100)</td>
<td>100 (100)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>78 (78)</td>
<td>42 (84)</td>
<td>100 (100)</td>
<td>100 (100)</td>
<td>100 (100)</td>
<td>100 (100)</td>
<td>100 (100)</td>
<td></td>
</tr>
<tr>
<td>Melena</td>
<td>100 (100)</td>
<td>49 (98)</td>
<td>100 (100)</td>
<td>100 (100)</td>
<td>100 (100)</td>
<td>100 (100)</td>
<td>100 (100)</td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>68 (68)</td>
<td>32 (64)</td>
<td>96 (96)</td>
<td>96 (96)</td>
<td>90 (90)</td>
<td>100 (100)</td>
<td>98 (98)</td>
<td></td>
</tr>
<tr>
<td>Coated tongue</td>
<td>44 (44)</td>
<td>42 (42)</td>
<td>88 (88)</td>
<td>98 (98)</td>
<td>88 (88)</td>
<td>100 (100)</td>
<td>98 (98)</td>
<td></td>
</tr>
<tr>
<td>Abdominal tenderness</td>
<td>100 (100)</td>
<td>86 (86)</td>
<td>100 (100)</td>
<td>100 (100)</td>
<td>100 (100)</td>
<td>100 (100)</td>
<td>100 (100)</td>
<td></td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>54 (54)</td>
<td>57 (57)</td>
<td>82 (82)</td>
<td>98 (98)</td>
<td>84 (84)</td>
<td>100 (100)</td>
<td>94 (94)</td>
<td></td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>28 (28)</td>
<td>48 (48)</td>
<td>70 (70)</td>
<td>98 (98)</td>
<td>80 (80)</td>
<td>100 (100)</td>
<td>98 (98)</td>
<td></td>
</tr>
</tbody>
</table>

### Discussion
This study compares the clinical & microbiological efficacy of oral Azithromycin with Intravenous ceftriaxone in treating children who had uncomplicated typhoid fever in age group of 2 to 17 years, admitted Paediatric department of Dr. Prabhakar Kore Hospital & Research Unit of KAHER, attached to J N Medical College, Belagavi.
The two study groups were not differing in demographic data and chief complaints; were comparable. There was even distribution of severity of symptom in both the study groups, as even observed in other similar studies.\textsuperscript{7,8,9}

The 2 groups (Azithromycin and ceftriaxone receiving) were found comparable in all demographic data, presentation and were not significant statistically. Typhoid severity was equally distributed in both the groups. The complaint of fever in both treatment groups were in days (9-11 days) reported in prior published trials on the treatment of typhoid.\textsuperscript{7,8,9}

In present study, blood culture was done before first antibiotic dose after hospitalisation and second on 10\textsuperscript{th} day of admission irrespective of the clinical outcome. Another similar study by Tribble D et al., practiced blood culture sampling in between the study on 3\textsuperscript{rd} and 7\textsuperscript{th} day.

Our study has persistent bacteraemia (1 out of 5 culture positive) i.e., among ceftriaxone receiving patients 1 out of 5 cultures were still growing salmonella on 10\textsuperscript{th} day of treatment. This finding is not similar to the study of typhoid fever using chloramphenicol and ceftriaxone comparatively, where 3rd day blood cultures for chloramphenicol receiving patients were still positive and those of ceftriaxone receiving patients were cleared (0 out of 28).\textsuperscript{10}

Another very interesting finding we had was there was no correlation between in vitro resistance and in vivo effectiveness against Enteric fever. The possible reason being serum drug levels determine sensitivity/susceptibility tests, but the main drug action of azithromycin is intracellular bactericidal action. Sometimes intracellular azithromycin levels increase to 100 times than of serum levels.\textsuperscript{11,12}

Similar study result was explained by Robert W Frenc k Jr et al. in a study.\textsuperscript{13}

In our study we had documented a Relapse case who was treated with intravenous ceftriaxone. There were no relapses in azithromycin received group. The possible explanation for no relapses in azithromycin received patients is that, the azithromycin concentration being high intracellularly, its secretion in biliary tree and a relatively longer half-life.\textsuperscript{8,14,15}

Another similar trial conducted by Tribble D et al., concluded that the high dose azithromycin for a short duration (20 mg/kg/day, maximum 1000 mg/day, for 5 days) is effective in treating enteric fever of uncomplicated type in children.\textsuperscript{13,15} A trial by Agarwal A et al., in 2000 documented safe and effective therapeutical role of azithromycin (6days short course) in typhoid fever.\textsuperscript{16}

In the current study a low dose Azithromycin is used for a short duration (10 mg/kg/day, OD, for 6 days) the reason being the possible adverse effects of high dose azithromycin. A study done by Saha S K et al., used low dose azithromycin with no comparison with any other drugs; found to be effective in treating enteric fever in children.\textsuperscript{17}

Based on parents’ opinion, frequent need of intravascular access was a reason for non-compliance and oral once a day Azithromycin increased the compliance. Similar observations were quoted in studies of Robert W Frenck Jr et al.\textsuperscript{13,12,17}

A much recent study from Vietnam reported that the decreased duration of azithromycin therapy can be equally effective in treating adult typhoid fever.\textsuperscript{17} This result encouraged us to use low dose, short duration Azithromycin in childhood enteric fevers.

Thus, our study clearly shows that the clinical cure is better in low dose, short duration oral Azithromycin regimen than conventional intravenous ceftriaxone regimen; this observation was significant statistically (p=0.026). But the microbiological-cure was still comparable between two groups (p=0.132). Five more studies showed similarity in clinical and microbiological cures using oral Azithromycin and even there were microbiological-cure rates exceeding 90% without any significant adverse drug reactions or relapses in typhoid fever.\textsuperscript{7,15,16}

CONCLUSIONS
A short course of oral Azithromycin (10 mg/kg/day once a day for 6 days) is more efficacious in treating uncomplicated typhoid fever as compared to intravenous ceftriaxone (100 mg/kg/day in 2 DD for 7 days) in children and adolescents.

Study Limitations
1. In this study, we could not effectively describe the microbiological outcome, because blood culture yield was poor (only 12%); it is very much less than that described in the text books. Prior administration of antibiotics before admission to the study hospital was not addressed, which might have affected the culture results in the study.
2. Further multicentric trials with larger sample-size is recommended.

Acknowledgement
We are thankful to the staff, postgraduates and ethical committee of the department of paediatrics, Dr. Prabhakar Kore Hospital & Research Unit, attached to KAHER’s J N Medical College, Belagavi, for making this research work a success. We are very thankful to the hospital laboratory. We are grateful to all the children & their parents who participated in the study. This study was funded by the authors.

REFERENCES


