Ceftriaxone- amikacin combination therapy versus ceftriaxone monotherapy in the treatment of enteric fever in Bangladesh.

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Abstract:

Background: Typhoid fever is common infectious disease in our country. In the era of antimicrobial resistance combination drug therapy now is the standard of treatment in infectious diseases like TB, HIV, leprosy, malaria and kala-azar. Synergistic action between beta-lactum and aminoglycosides had been shown In-vitro for salmonella but clinical evidence to support these data was sparse. So, this study was designed to compare clinical outcome of enteric fever treated with ceftriaxone alone with ceftriaxone-amikacin combination therapy in our context. ***Methods:*** This was an open-label, Randomized Control Trial (RCT), conducted in the Department of Medicine, Chittagong Medical College & Hospital, Chittagong, from May 2012 to November 2014. Blood culture positive patients were included in this study. They were randomized to allocate either ceftriaxone monotherapy (Group-A) or ceftriaxone and amikacin (Group-B) combination therapy. The dose of ceftriaxone and amikacin were 80mg iv/kg/day (maximum 4gm/day) and 7.5mg iv/kg/dose (maximum 1gm/day) was given according to WHO and Asian Antibiotics guideline. All the patients were followed up 12 hourly till the patients afebrile for 4 consequent follow up. Seven patients dropped out from the study. ***Result:*** Total sixty patients with positive blood culture for S. typhi(83.3%) and S. paratyphi (16.7%) were finally analysed (per-protocol analysis) in this study. There were 35 (58.2%) male and 25(41.8%) female, mean age was mean±SD:29±15.5 years (range 16 to 80 years). The sensitivity of salmonella was to co-amoxiclav (100%), amikacin (95%), ceftriaxone (93%), chloramphenical (81%), azithromycin (73%), ciprofloxacin (50%) and nalidixic acid (45%). Fever was an invariable feature in all patients followed by headache, myalgia and vomiting. Thirty patients treated with ceftriaxone (Group-A) and thirty patients were treated with ceftriaxone and amikacin (Group-B) were finally analysed. All patients were cured clinically and blood culture also negative after 7 days treatment. The mean time (mean±SD) for patients to become afebrile was 8.0±1.5 days for ceftriaxone monotherapy and 7.5±2.0 days for ceftriaxone and amikacin combination therapy (p>.05and 95% CI: 0.83- 1.34). There was no complication and significant adverse drug reaction. ***Conclusion:*** Combination of ceftriaxone and amikacin is not superior to ceftriaxone alone in the treatment of enteric fever.

Key words: Ceftriaxone-Amikacine, Combination Therapy, Monotherapy, Enteric Fever.

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Introduction

Typhoid fever is one of the most common infectious disease in developing countries including Bangladesh. It is the 5th among the top ten diseases in primary and secondary health care level in Bangladesh[1]. The changing spectrum of antibiotic sensitivity is more for salmonella[2]. Fluroquinolones are resistance commonly in Indian subcontinent and UK. Extended-spectrum cephalosporin (ceftriaxone) is useful alternative but has slightly increase treatment failure rate. Another alternative azithtromycin is not validated in severe typhoid fever[3]. Trials of ceftriaxone showed that fever defervescence takes longer and relapses occur in patients treated for shorter duration[4]. Moreover, irrational and in judicial use of Ceftriaxone by health provider is great concern to clinician in our country. In such circumstances, there is a need to find an effective treatment regimen for typhoid

fever. Combination therapy has been used in variety of infectious diseases because of synergy, (i.e., a 14-fold decrease in the MIC of each drug when tested together against a pathogen in vitro) , broadening the spectrum and delay or prevent resistance. The rationale of used of aminoglycoside /b-lactam combinations to get these benefits has been developed from animal studies in the early and mid-1980s[5]. Since then, the practice of using this combination therapy had become very popular for the management of infectious diseases. Evidences support combination therapy in the treatment of infectious disease like, TB, HIV, leprosy and kala-azar. S. typhi is a facultative intracellular pathogen that exists inside the macrophages of typhoid patients and amikacin is less effective in this case[6]. The question of a combination of ceftriaxone/ amikacin confers any benefit in empirical treatment is unsettled for Salmonella. With the availability of new broad-spectrum and highly bactericidal antibiotics, the need to combine beta-lactams (ceftriaxone) with a second agent(amikacin)for the treatment of typhoid fever should be reassessed.

Objectives

A) General objective:

- To compare clinical outcome ceftriaxone and amikacin combination versus ceftriaxone monotherapy in the treatment of enteric fever.

B) Specific objectives:

- To evaluate the effectiveness of cefriaxone and amikacin combination and ceftriaxone alone in the management of enteric fever.
- To determine whether the ceftriaxone and amikacin combination therapy is superior to ceftriaxone monotherapy in the treatment of enteric fever.
- To find out complications or adverse drug reaction of ceftriaxone and amikacin combination therapy.

Patients and Methods

It was open label, randomized, prospective clinical trial and was conducted in the Department of Medicine, Chittagong Medical College and Hospital, Chittagong, Bangladesh, from May 2012 to November 2014.

Inclusion criteria

A patient with documented fever >38°(100.5°F) for at last three days, with microbiologically confirmed by positive blood culture of salmonella.

Exclusion Criteria

- Women with pregnancy.
- Patient had any clinical evidence of renal or neoplastic diseases.
- Patient had known hypersensitivity and resistance to Ceftriaxone or Amikacin.
- Patient who did not give consent for study.

Methods

Written informed consent was obtained from each patient. On admission, the diagnosis of typhoid fever was ascertained clinically by detail history, thorough physical examination. Then collected 10-15 ml of venous blood and sent for culture. The duration and severity of fever, abdominal pain, vomiting, diarrhea and constipation and general well being was recorded. Initial base line other findings also recorded. Blood culture had done on FAN(First Antibiotics Neutralized) Method and Bactec 9200 tube Method. In automated FAN method there was indicator after growing of any salmonella within 2-8 hours.

Study procedures

The dose of ceftriaxone and amikacin were 80mg/kg/day (maximum 4gm/day) and 7.5mg/kg/dose (maximum 1gm/day) respectively were given according to WHO and Asian Antibiotics guideline. Antipyretic (paracetamol, 15mg/kg/dose) was given on demand (axillary temperature >101ºF). Clinical outcomes and any adverse drug reactions were observed in both the groups 12 hourly. Vital signs (pulse, BP, temperature and respiration rate) and a standardized clinical assessment (symptoms /signs list) were monitored accordingly. Patient was considered clinically cured if patients were afebrile for 4 consequent follow up. Thorough out the study there were no such adverse events that might stopped the study. Finally 15 ml blood was sent for culture after 7 days treatment.. All supportive care was provided by Department of Medicine CMCH.

Clinically remission of fever for 4 consequent follows up of 12 hours interval without anti pyretic. Blood culture negative of salmonella after completion of treatment microbiologically. Chi-square and unpaired student t-test was used to compare time of defervescence, improvement in general wellbeing, headache, vomiting and abdominal pain. All patients randomly allocated to either group were included to per-protocol analysed. The level of significance was fixed at 5%.

Result

During the study period, a total of 650 fever cases were screened by protocol. Statistical analysis was done to show difference of treatment outcome between the two groups. There were 30 Patients in each group (Total 60 Patients were enrolled). In group-A 53.3% patients were male; in group-B 63.3% patients were male. Total 58.3% patients were male and 41.7% patients were female. The median age of the patients was 27 years and the youngest and the oldest patients were 16 and 80 years respectively (Table-I). Mode of clinical presentations demonstrates that fever and Myalgia were invariably present in all cases of both Group-A and Group-B, followed by coated tongue (75%), anorexia (70.0%), headache (70.0%), abdominal pain (40.0%), vomiting (51.7%). chi-square test was done. The signs and symptoms which were <20% are rash, cough, constipation, splenomegaly and diarrhoea. The mean body temperature was in group-A 102.9(±3)ºF and group-B 103(±3)º F the range of temperature was101-106ºF. There were no significant different between the groups (Table-II). The patients had history of taking antibiotics before being admitted in the hospital were 46.7%. The common antibiotics were Ciprofloxacin (42.8%), Azithromycin (39.3%) and Ceftriaxone (17.9%). Among the history of antibiotics taken patients 94.0% received single and 6.0% multiple antibiotics. The average duration of treatment with antibiotics was 3.0 ± 2.0 days. In Group-A (83.3%) of the bacteria isolated on blood culture, were S. typhi, and in Group-B, 80%,wasS.typhi in both 81.65% was S. typhi. Sensitivity of salmonella showed to amoxiclav (100%), amikacin (95%) ceftriaxone (93%),nalidixic acid (45%), ciprofloxacin (50%), chloramphenicol (81%) & cotrimoxazole (75%) (Table-IV). Between the study groups, 80% of the patients of Group-A need >1week to subsided fever and in Group-B 73.3% need >1week. The mean defervescence time was in Group-A 8±1.5 days and in Group-B 7.5±2 days the range of fever clearance time was in Group-A 5-12 days and Group-B 6-12 days, student t-test was done there were no significant differents between the arms (Table-V). 75% of major signs and symptoms (general wellbeing, headache and myalgia) took more than one week to improve in both groups. Improvement of general wellbeing and Subsidence of headache and myalgia occurred in Group-A 8(±2), in Group-B 7.5(±2.7). Subsidence of anorexia/nausea, vomiting, abdominal pain and tenderness occurred <1 week. No culture yielded at the end of the treatment and after 28th(enrolled) there were 3.3% culture positive in group-A and 3.3% in group-B. There were no significant different between the groups.

Table - I: Distribution of the age among the study groups (n = 60)

Study Groups	N	mean age (yrs.)	± SD	median age (yrs.)	range	significance.*
Group A	30	31.7	15.2	28	16 – 80	t = 1.308 P = 0.196 NS
Group B	30	27.3	10.7	24	16 – 60	
TOTAL	60	29.5	13.2	27	16 – 80	

* Independent sample t – test. NS = Not Significant (P > 0.05)

Table – II: Distribution of common clinical features among the study groups (with X2 test significance), n=60

Major Signs & Symptoms		STUDY GROUPS				total		X^2 Test Significance
		group A		group B				
		N	%	N	%	N	%	
Fever	Present	30	100.0	30	100.0	60	100.0	–
	Absent	0	0.0	0	0.0	0	0.0	
Headache	Present	20	66.7	22	73.3	42	70.0	$X^2 = 0.884$ $P = 0.347^{NS}$
	Absent	10	33.3	08	26.7	18	30.0	
Myalgia	Present	30	100.0	30	100.0	60	100.0	–
	Absent	0	0.0	0	0.0	0	0.0	
Anorexia/ Nausea	Present	22	73.3	20	66.7	42	70.0	$X^2 = 0.884$ $P = 0.347^{NS}$
	Absent	08	26.7	10	33.3	18	30.0	
Coated Tongue	Present	23	76.7	22	73.3	45	75.0	$X^2 = 0.089$ $P = 0.766^{NS}$
	Absent	7	23.3	8	26.7	15	25.0	
Bradycardia	Present	15	50.0	15	50.0	30	50.0	$X^2 = 1.364$ $P = 0.243^{NS}$
	Absent	15	50.0	15	50.0	30	50.0	
Vomiting	Present	15	50.0	16	53.3	31	51.7	$X^2 = 0.884$ $P = 0.347^{NS}$
	Absent	15	50.0	14	47.7	29	49.3	
Abdominal Tenderness	Present	13	43.3	11	36.7	24	40.0	$X^2 = 0.884$ $P = 0.347^{NS}$
	Absent	17	56.7	19	63.3	26	60.0	
Abdominal Pain	Present	13	43.3	11	36.7	24	40.0	$X^2 = 0.884$ $P = 0.347^{NS}$
	Absent	17	56.7	19	63.3	26	60.0	

*NS = Not Significant (P > 0.05)

Table – III: Distribution of blood culture isolates among the study groups (with X2 test significance)

Blood Culture Isolates	STUDY GROUPS				Total	
	Group A		Group B			
	number	%	number	%	number	%
S. typhi	25	83.3	24	80.0	49	81.65
S. paratyphi	5	16.7	6	20.0	7	19.35
Total	30	100.0	30	100.0	60	100.0

*X^2 value = 1.456. P = 0.228. Not Significant (P > 0.05)

Table – IV: Distribution of antibiotics sensitivity patterns among the study groups (with X2 test significance), n=60.

Antibiotic Sensitivity Pattern		STUDY GROUPS				total		X^2 Test Significance
		group A		group B				
		number	%	number	%	number	%	
Amoxiclav	Sensitive	30	100.0	30	100.0	60	100.0	–
	Resistant	0	0.0	0	0.0	0	0.0	
Amikacin	Sensitive	27	90.0	30	100.0	57	95.0	$X^2 = 3.158$ $P = 0.076^{NS}$
	Resistant	3	10.0	0	0.0	3	5.0	

Ceftriaxone	Sensitive	30	100	28	93.3	56	93.3	$X^2 = 0.000$ $P = 1.000^{NS}$
	Resistant	0	00	2	6.7	4	6.7	
Azithromycin	Sensitive	27	90.0	17	56.7	44	73.3	$X^2 = 8.523$ $P = 0.004^{HS}$
	Resistant	3	10.0	13	43.3	16	26.7	
Ciprofloxacin	Sensitive	15	50.0	15	50.0	30	50.0	$X^2 = 3.391$ $P = 0.183^{NS}$
	Resistant	15	50.0	15	50.0	30	50.0	
	Not Done	3	10.0	0	0.0	3	5.0	
Nalidixic Acid	Sensitive	14	46.7	13	43.3	31	45.0	$X^2 = 0.069$ $P = 0.966^{NS}$
	Resistant	15	50.0	16	53.4	27	51.7	
	Not Done	1	3.3	1	3.3	2	3.3	
Cefixime	Sensitive	11	36.7	19	63.4	30	50.0	$X^2 = 5.042$ $P = 0.080^{NS}$
	Resistant	4	13.3	4	13.3	8	13.3	
	Not Done	15	50.0	7	23.3	22	36.7	
Cotrimoxazole	Sensitive	23	76.4	22	73.3	45	74.9	$X^2 = 1.143$ $P = 0.565^{NS}$
	Resistant	6	20.3	6	20.3	12	20.3	
	Not Done	1	3.3	2	6.4	3	4.8	
Ampicillin	Sensitive	11	36.7	11	36.7	7	36.7	$X^2 = 0.175$ $P = 0.916^{NS}$
	Resistant	4	13.3	3	10.0	22	11.7	
	Not Done	15	50.0	16	53.3	31	51.6	
Chloramphenicol	Sensitive	24	81.0	23	76.4	47	77.2	$X^2 = 1.333$ $P = 0.513^{NS}$
	Resistant	5	16.7	6	20.3	11	18.5	
	Not Done	1	3.3	1	3.3	2	4.3	

Table – V: Subsidence of fever among the study groups (with X2test and t – test significance), n=60.

	Study Group	number	mean	± SD	median	range	
Subsidence of fever (Days)	Group A	30	8.0	1.5	8.0	5 – 12	t = 2.267 P = 0.270 NS
	Group B	30	7.2	2.0	7.0	6 – 12	
	TOTAL	60	7.6	1.5	7.0	5 – 12	

* Independent sample t – test. NS = Significant (P > 0.05)

Discussion

This study was done to evaluate the effect of adding amikacin with ceftriaxone in the treatment of typhoid fever. Total male were 35 (58.2%) and female were 25 (41.8%). This is nearer to the findings by Saha SK et al[7].where 54% were male and 46%were female and Kadhiravan et al[8] But, another study, Mathura et al[9] showed 71% were male and 29% were female and Butler and others also showed similar result that infection rate was slightly higher in male[10]. Mathura and Butler expressed their opinion that greater exposure of male to contaminated food and water outside the home might be region of higher rate of infection among this population. Khan KH et al[11]. reported that 84% typhoid patients are 40 years of age or young adult. In the present study, mean age of group A, was 31.7 (± 15.2) years and among the group-B, mean age was 27.3 (± 10.7) years; which co-relate with the mean age of 26.21 (± 15.64) above studies. So our findings regarding age of typhoid was very nearer to the above findings.

Mode of clinical presentation demonstrates that fever and myalgia were invariably present in all cases of both groups followed by anorexia/nausea (70.0%) where in Group-A was 66.7% and Group-B was 73.3%, headache (70.0%)where in Group-A was73.3% and Group-B 66.7%, abdominal pain (50%) where in Group-A was 56% and Group-B was 44%, vomiting(50%) where in Group-A was 45% and Group-B was 55%. Very few patients (5%) have had diarrhea and cough. Physical examination showed that almost all (100%) of the patients had risen of body temperature (>102ºF) and 75% had coated tongue. Abdominal tenderness, relative bradycardia and were present in 50%

(Group-A was 56% and Group-B was 44%), 45% (Group-A was 40 and group-B was 50%) and 3% of cases respectively. Abdominal distension, delirium and rash were atypical presentations (5%, 3% and 2% cases respectively). These symptoms and signs consistent with Wasfy et al[12]. Near half (46.7%) of the of the patients had taken antibiotics before they admitted in the hospital. Ciprofloxacin was the commonest drug with average duration of treatment with antibiotics being 3.2 ± 2.0 days. Which similar to Wasfy et al[12]. The ratio of S. typhi and paratyphi were about 5:1. Among 60 patients 49(81.65%) patients were S. typhi. And 11(18.35%) were S. paratyphi in which Group-A 25 (83.3%). But it differed from Gosai et al[13] and Pokhrel et al[14] which were 5.3% and 5.4% in Nepal Study. The relative low sensitivity of the blood culture in diagnosing typhoid fever is a common phenomenon. Blood culture is promising of diagnosis for enteric fever in the first week and is very specific, but its sensitivity is poor due to various factors. Sensitivity of cultures can be affected by type of culture medium, length of incubation and variations of bacteraemia. Antibiotic treatment prior to collection of sample inhibits the growth on blood cultures[14] Similar finding were found by Lin and others, where they showed that the S. typhi was recovered from 5.3% of patients with prior antibiotic intake versus 5.8% without prior antibiotics[15]. The sensitivity of blood culture is highest in the first week of the illness and reduces with advancing illness. Overall sensitivity is around 50% but drops considerably with prior antibiotic therapy. Failure to isolate the organism may be caused by several factors which include inadequate laboratory media, the volume of blood taken for culture, the presence of antibiotics and the time of collection. For blood culture it is essential to inoculate media at the time of drawing blood[16]. The highest sensitivity observed in co-amoxyclav (100%) followed by amikacin (95%) and ceftriaxone (93.7%). Third generation cephalosporins have been recommended as an alternative to quinolone treatment in enteric fever and several physicians have claimed good results with them, particularly with ceftriaxone[17]. As consequences of extensive use of ceftriaxone and other third generation cephalosporin, resistance is being reported with increasing frequency all over the world. Another study by Saha and others reported about the highly ceftriaxone resistant strain of S. typhi in Bangladesh[7].Another study from Bangladesh showed that the decreased susceptibility to ciprofloxacin was detected in 24 (18.2%) out of 132 randomly selected strains during 1990 to 200211. Fluoroquinolones, especially ciprofloxacin, have been in use for more than 18 years and have remained an important against S. typhi. Inspite of this, in recent years, several reports have appeared worldwide concerning reduced activity of ciprofloxacin against S. typhi[18]. Resistance to azithromycin and cefixime also emerging, In this study S. typhi was sensitive to azithromycin 73.4% among which Group-A was 90.6% and Group-B 56.2% and Cefixime was 66.1% sensitive among which Group-A was 62.5% and Group-B was 69.7%. Both the drugs are not effective in severe typhoid fever.Cotrimoxazole, ampicillin and chloramphenical were sensitive to S. typhi 73.5% 70.1%, and 81.5% among which no significant different between the groups. There have been some reports of the reemergence of the sensitivity of S. typhi to chloramphenicol and other first line drugs[19]. In this study the range of deffervicence time in Group-A 5-12 and in Group-B 6-12 days respectively. Mean deffervicence time in Group-A 8±1.5 and in Group-B 7.5±2.0. There is no statistically significant different between 2 groups (p>.05:95% CI=.84-1.34). In this study, it is showed that ceftriaxone-amikacine was not superior to ceftriaxone alone, in the treatment of typhoid fever, which remember the clinical reviewed of 58 RCT of Scott T. et al where they proved that amikacincan not killed intracellular pathogen like S. typhi[20] also reviewed 158 articles on Gram negative sepses, have found no benefit on combination ceftriaxone and amikacin therapy. Cochrane reviewed 64 articles of 7586 patients but no benefit of combination therapy[21]. In this study defervecence time was set as 4 consequent follow up of 12 hours interval after normal recorded of temperature without antipyretic so, actual fever free time was 6±1.5 in group-A and 5±1.5 in Group-B. Both ceftriaxone and amikacin had the chance of renal impairment we were in fear for Group-B for renal impairment. Other clinical features like headache, myalgia, were relieved in Group-A 7±1.7 days and in Group-B 7±1.4 days there were no t-test significant between two Groups (p>.05). Although there are theoretical reasons why combination antimicrobial therapy may, in certain patients and situations, be superior to monotherapy for the treatment of infections with S typhi, the clinical data supporting these theories are neither

overwhelming nor defnitive. On the contrary, RCT that have been conducted exclusively demonstrate no difference in clinical outcomes between the two treatment strategies for defnitive management of infections with S.typhi. This suggests that, combination of ceftriaxone-amikacin is not better than ceftriaxone monotherapy in the treatment of typhoid fever.

Conclusion

Ceftriaxone-amikacin could not reduce the defervescence time than ceftriaxone monotherapy significantly and additional observation is the re-emergence of sensitivity of Salmonella typhi to chloramphenicol and cotrimoxazole. This study also generate information that, ensuring the dose, frequency of administration, and duration over which an antibiotic is infused are optimized is likely more important in early recovery from fever than the addition of a second agent. As the re-emergence of sensitivity of older drugs has increased coupled with the increasing prevalence floruquinolone resistance infections, combination therapy may be used with re-emergence sensitive drugs for when actually necessary is vital in the war against antimicrobial resistance.

Limitation of the study

❑ The study was an open label randomized controlled trial, there was no blinding.

❑ The study was done in single centre only. The multicentre study would be more representative.

Recommendation

This study has shown the similar effect of Ceftriaxone-Amikacin combination therapy and Ceftriaxone monotherapy in the treatment of enteric fever, so (i). Ceftriaxone-Amikacin combination therapy has no additional benefit over monotherapy in treatment of typhoid fever. (ii). Increasing resistance to ceftriaxone (10%) coupled with re-emergence of sensitivity of Salmonella typhi to chloramphenicol and cotrimoxazole may be re-evaluated for treatment of typhoid fever.

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