PUBLIC HEALTH RESEARCH

Costs and Effectiveness of Ciprofloxacin and Ceftriaxone in Treatment of Typhoid Fever in Children in Thailand

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ABSTRACT

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Introduction The burden of typhoid fever remains high in impoverished settings, and increasing antibiotic resistance is making treatment costly. The purposes of this study were: to compare the costs and the effectiveness of typhoid programs between oral and injection treatments in pediatric patients at Songkhla Hospital.

Methods This study was an incidence-based cost-of-illness analysis from providers' perspective. Micro-costing approach was employed for calculating patient-specific data. The study was conducted in Songkhla Hospital in the southern part of Thailand from 2009 to 2010. The total number of the cases was 78. Patients taking antibiotics for 48 hours, and those suspected of having complicated typhoid fever like peritonitis, ileus, toxic encephalopathy were excluded. We collected and reviewed medical records. In all provisionally selected children, blood was drawn for complete blood count, widal test and blood culture. The statistics used in data analysis were descriptive statistics and the cost-effectiveness of typhoid treatment with the two methods was compared using independent t-test.

Results The results of the study revealed that the average cost of typhoid treatment with oral Ciprofloxacin calculated with DRG was 3,301.88 baht which was lower than that of injection Ceftriaxone treatment calculated with DRG (3,615.05 baht). When the operation costs were considered, the results of the study remained the same, i.e. the treatment cost of typhoid with oral Ciprofloxacin was two times lower than that with injection Ceftriaxone. The average cost of the oral treatment was 2,844.45 baht, and that of the injection treatment was 5,303.19 baht. Regarding the effectiveness of typhoid treatment with Ciprofloxacin measured from the time the fever was reduced, it was found that the body temperature of the two methods of treatment were used was not significantly different ($p<.05$). The patients on oral medications had a fever for an average of 3.36 days while those on injection treatment had a fever for an average of 3.76 days. However, the lengths of stay (LOS) of the two groups of patients were significantly different.

Conclusions The results of this study showed that the cost-effectiveness of oral treatment was better than injection. Bedside, the patient and caregiver spent less time when oral treatment was administered than when injection treatment was used. Therefore, the direct cost for treatment was reduced and the indirect cost as a result from LOS was also reduced. Above all, the patient did not get pain from injection while the effectiveness of fever reduction was not different.

Keywords Costs -Effectiveness -Ciprofloxacin - Ceftriaxone -Typhoid Fever -Children

INTRODUCTION

Typhoid fever (TF) has been an important health problem in many parts of the world. Typhoid fever is a major cause of morbidity and mortality with an estimated global incidence of 21.6 million cases[1]. In developing countries, its annual incidence ranges from 12 to 622/100□000 persons. *Salmonella enterica* serovar Typhi (*S*. Typhi) is responsible for the majority of cases followed by *S. enterica* serovar Paratyphi A (*S.* Paratyphi A) that causes 20% of the cases[2-4]. In Thailand, TF is occasionally endemic in temporary shelters along the Burmese border and usually the Multidrug-Resistant Salmonella Typhiz (MRD). In the southern part of Thailand, TF endemics began during 2009-2011 and it has been continuously found in Songkhla Province where TF is most prevalent among the five lower southern provinces [5-7]. There are published reports that cefixime a third generation of oral cephaplosporin is effective in treating typhoid fever and well practiced in typhoid fever[8,9,10,11].

Oral ciprofloxacin fluroquinolone group is widely used in pediatric infectious diseases and mostly similar to cephaplosporin in its pharmacological and antimicrobial properties but cheaper than cephaplosporin[12-18]. Now, there are no published controlled studies evaluating oral ciprofloxacin and intravenous ceftriaxone in typhoid fever. We, therefore, undertook the study where we prospectively health economics evaluated the medical costs and effectiveness of oral ciprofloxacin and intravenous ceftriaxone therapy for children sign from used blood culture as the standard for comparison or confirmed typhoid fever and compare with that of intravenous ceftriaxone with a hypothesis that oral ciprofloxacin is effective in treating typhoid fever. We opted for ceftriaxone because, firstly, there are reports that ceftriaxone is more effective for typhoid fever in children[19] and the costs are likely to be lower than cefotaxime. Secondly, cefotaxime needs to be injected 3-4 times a day while ceftriaxone is administered only 1-2 times a day. This study was an attempt to estimate the cost and effectiveness of typhoid programs between oral and injection in pediatric patients at Songkhla Hospital. We, therefore, undertook this a study where we prospectively evaluated the cost and clinical effectiveness of oral therapy and intravenous ceftriaxone therapy for children is effective, safe and cheaper oral option for treatment of typhoid fever in children.

Definition of Term

Costs of treatment refer to expenses in treatment of typhoid fever with ciprofloxacin and intravenous ceftriaxone calculated using operational costs (laboratory cost, pharmacy cost, routine service cost).

Diagnosis-related group (DRG) is used to determine how much money health care providers will be given to cover future procedures and services, primarily for inpatient care.

Effectiveness refers to the results of treatment of typhoid fever with ciprofloxacin and intravenous ceftriaxone; in this study, clinical effectiveness and the lengths of stay (LOS) were measured.

METHODS

The study was conducted in Songkhla Hospital in the southern part of Thailand from November 2009 to February 2010. Children between 1 year to 14 years with clinical feature suspected of typhoid fever were assessed for eligibility (proved by blood culture positive for Salmonella Typhi (Hemoculture for Salmonella Typhi using Mac Conkey agar, sensitivity tests using the disc diffusion method, stool cultures using selective media agar plates). The total number of cases was 78. Patients taking antibiotics for 48 hours, and being suspected of complicated typhoid fever and toxic encephalopathy were excluded. We collected and reviewed medical records.

In all provisionally selected children, blood was drawn for a complete blood count, widal test and blood culture. However, only culture confirmed typhoid fever was finally enrolled for RCT. Children were enrolled in the study after approval of the ethical review committee of the hospital. Eligible children were allotted double blind RCT to received oral ciprofloxacin (15-20 mg/kg/day divided every 12 hours for the experimental group or EG) and intravenous ceftriaxone (70-100 mg/kg/day divided every 12 hours for the control group or CG). Simple Randomization technique was done using a table sampling.

After being discharged, the patients were given appointments to come to the OPD for follow-ups: one week after the discharge to check their clinical wellbeing and whether they had completely taken medications prescribed for them, and then 6-8 weeks after that for rectal swab cultures. Clinical defervescence was defined as temperature below 37.8^0C for at least 24 hours without antipyretic. A satisfactory clinical response or clinical effectiveness was defined as complete resolution of all presenting symptoms and signs, clinical failure were defined as persisting fever more than 7 days[20]. Hence, types of cost for this study were the following: 1) Laboratory cost consisting of practical laboratory investigations. 2) Pharmacy cost equaled acquisition drug cost plus drug-dispensing cost. 3) Routine service cost was the sum of outpatient and inpatient service. 4) Total cost or total treatment cost consisting of all costs mentioned above (points 1, 2, and 3). For this study, resources used by the hospitals and service

outputs were collected from the official records of the two hospitals. The hospital-related data were collected for the 2009-2010 financial year. Descriptive statistics were used.

RESULTS

In this study, 78 children were assessed for suspected typhoid fever (oral ciprofloxacin = 11, intravenous ceftriaxone = 67). The sample size for oral cases was small because when children were sick and admitted, most of them were not ready to take the medicine orally as it was bitter; however, it was necessary to give them immediate treatment, and therefore, injections were given for their safety. This is why the number of the oral cases was limited. The two groups showed similar clinical responses with similar defervescence in days (oral ciprofloxacin (OC) vs intravenous ceftriaxone (IC) and similar clinical cure with only one clinical failure in each group on subsequent blood culture. No relationship was found between pretreatment febrile illness in days and clinical cure (r= .0023, p=0.71) and no significant relationship was found between nutritional status and days required defervescence (r= 0.042, p=0.66) (Table 1).

Table 1: Comparison of baseline characteristics, clinical and bacteriological responses in the two sample groups

Baseline characteristics	Oral ciprofloxacin (OC) (n=11)	Intravenous ceftriaxone (IC) (n=67)
Age in years	7.5±2.58	7.63±2.88
Male:Female	3:8	25:22
Initial temperature	39.59±2.30	39.60±2.11
Deferverscence in days	3.36±1.8	3.76±.18
Bacteriological cure	11/11(100%)	67/67(100%)

No significant side effects were observed during the course of therapy in the two (Results of significance for deferverscence in days between oral ciprofloxacin and intravenous ceftriaxone was p=0.29 and results of significance for clinical cure between oral ciprofloxacin and intravenous ceftriaxone was p=.70 (Table 2).

Table 2: Comparison of baseline complete blood count (CBC) between oral ciprofloxacin and intravenous ceftriaxone

Clinical data	Oral ciprofloxacin	Intravenous ceftriaxone	t-value	p-value
HCT	36.74+.82	35.29+.42	1.33	.18
WBC	7045.45+500.43	7132.09+2517.89	-.11	.91
LYMP	26.87+3.78	31.76+1.44	-1.26	.21
PMN	65.75+4.07	60.31+1.68	1.22	.21
PLT	230909.09+22713.81	180480.00+9143.35	2.09	.06

Treatment cost for this study was obtained by multiplying the unit cost of medical services and quantity of the services used. The two groups included in this study were quite different due to treatment costs based on actual situation (base case). When the treatment costs were compared between the two methods, it was found that the average operational costs of treatment using oral ciprofloxacin was 2,844.45 baht which was lower than that using intravenous ceftriaxone, for which the average costs was 5303.19 baht. And on comparing the expenses calculated with DRG. Diagnosis-related group (DRG) is used to determine how much money health care providers will be given to cover future procedures and services, primarily for inpatient care. It was found that the average costs of treatment using oral ciprofloxazine was 3,301.88 baht which was lower than that of treatment using intravenous ceftriaxone which was 3,615.05 baht (Table 4).

Table 3: Comparison of costs between oral ciprofloxacin and intravenous ceftriaxone

Type of antibiotics used in treatment	Operational costs		DRG	
	Mean	SD.	Mean	SD.
Oral ciprofloxacin	2,844.45	587.02	3,301.88	190.35
Intravenous ceftriaxone	5,303.19	381.04	3,615.05	1522.94

From Table 3, when effectiveness of the two methods of treatment for typhoid fever was compared, it was found that oral ciprofloxacin was significantly more effective in terms of length of stay (p=.00) but in terms of clinical effectiveness, the difference was not statistically significant .

Table 4: Comparison of effective variables (body temperature and length of stay or LOS) between oral ciprofloxacin and intravenous ceftriaxone

Effective variables	Oral ciprofloxacin	Intravenous ceftriaxone	t-value	p-value
Body temperature	37.04+.18	36.91+.18	.79	.43
Length of stay	3.36+.45	3.76+.28	-3.68	.00

The treatment results revealed a 100% clinical cure, neither clinical failure nor microbiological failure was found (after the complete treatment, rectal swab culture was carried out during the 6^{th} -8^{th} week and no Salmonella Typhi was found). Clinical relapses and chronic carriers were not found. The fever clearance time of the group using ciprofloxazin was 3.36 days and that of the initial intravenous ceftriaxone was 3.76 days, so the difference was not statistically significant. However, the LOS for the oral group was shorter than that for the group that had initial intravenous ceftriaxone, 1.73 days and 4.39 days, respectively, and the difference was thus statistically significant.

DISCUSSION

While comparing the treatment cost between treatments, it was found that the oral ciprofloxacin had lower than that of the intravenous ceftriaxone, This was because during treatment, it was found that the children could take the oral medication very well; their temperature was lower, and some of them recovered quickly and their parents wanted to take them home. Therefore, follow-ups at home were used and as a result, the LOS was different. As routine service cost (at outpatient and inpatient departments) contribute 80 % of the total cost, a longer duration of stay of child led to higher treatment cost for them compared to the treatments. There are reports that ceftriaxone is more effective for typhoid fever in children and the costs are likely to be lower than cefotaxime[19]. A study in urban slums of Deli in 1996 found that A study in the urban slums of Delhi in 1996 found that the average direct cost of blood culture-con-firmed typhoid, blood culture-confirmed paraty-phoid, and clinical typhoid wan Rs 277, Rs 74, and Rs 432 respectively. These costs were converted into Us dollar in 2004 rate, and the same stood at US$ 12.14, 7.63, and 18.94 respectively[20-21]. The present study also calculated the average treatment cost of blood culture-confirmed typhoid, blood culture-confirmed paratyphoid, and Widal test-postitive cases. However, the sample size of the subgroups was too small to present the means separately. Hence, the average treatment cost was reported, and it was US$94.80 and US$176 .77 (oral ciprofloxacin = 2,844.45 bath and intravenous ceftriaxone = 5,303.19 bath) which was quite different to the average treatment cost found in the study in Thailand. Both DRG were nearly equal to the costs associated with two treatments. Diagnosis-related group (DRG) is used to determine how much money health care providers will be given to cover future procedures and services, primarily for inpatient care[22].

In addition, in this study, neither adverse events nor side effects of the two drugs were found; only the bitter taste of ciprofloxazone that made it difficult for patients to take it orally and as a result they vomited (Ciprofloxazone was made into syrup for small children). We tried to select drugs that are effective for complete cure and with no chronic carriers in order to prevent the spread of the disease. Therefore, we chose to use ciprofloxacin and ceftriaxone as our drugs of choice for treatment of typhoid fever that was endemic at that time. We used oral ciprofloxacin 15-20 mg/kg/day bid 14 day (the regimen recommended by the manufacturers) or started with initial intravenous ceftriaxone 70 -100 mg/kg/day twice a day until the fever decreased or clinical well being was seen (increasing appetite, and looking well). Then the drug was changed to oral ciprofloxacin 15-20 mg/kg/day bid 14 days, too. We administered the drug for 14 days because we wanted a complete cure so that there would be no relapse and chronic carrier[23-25]. We chose to use ceftriaxone because firstly, it is more effective for treatment of typhoid fever in children than cefotaxime, and secondly, cefotaxime needs to be injected 3 - 4 times a day while ceftriaxone could be administered only 1-2 times a day[26].

Salmonella Typhoid is an intercellular organism. Therefore, factors influencing the efficacy of antibiotics in decreasing the relapse rate include bacteriostatic effectiveness, the ability to penetrate the intracellular environment and the appropriate dose with appropriate duration of therapy[23]. Fluorquinolones[24]and third generation cephalosporins have a better profile in this. It was also found that ciprofloxacin could reduce fever faster than ceftriaxone[26]. Adverse effects of ciprofloxacin on cartilage and growth in humans have not been clearly reporte[14, 27] and we, consequently, decided to use it because the drug

has clinical cure and is without chronic carriers. It was found that the effectiveness of both groups of medicine was not different; all the patients were completely cured; had no relapses and no chronic carriers but the medical costs were significantly different. The costs can be even higher taking into account the expenses of the caregiver, his/her absence from work, etc. This is because during treatment, it was found that the children could take the oral medication very well; their temperature was lower, and some of them recovered quickly and their parents wanted to take them home. Therefore, follow-ups at home were used and as a result, the LOS was different. Last, the treatment that could get rid of a carrier stage could help control the disease[28, 29]. Public health officers were asked followed up the cases on the phone and found that the patients did not vomit after taking the medicine orally. The officers also monitored if the patients received the medication according to the prescription; whether there were anything problems such as nausea, diarrhea, rashes, or fever. If there were any problems, parents could bring the children to see the doctor immediately.

CONCLUSIONS

From the study results, we concluded that oral ciprofloxacin is effective. Our study suggests oral ciprofloxacin is safer and cheaper than the oral option for treatment of typhoid fever in children. Effective typhoid fever measures in this study, as in other areas in the topics, require integration of intensive health education as a public health tool, provision and access to safe water supply and adequate strengthening of health systems.

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