Original Articles

COMPARATIVE EFFICACY OF FURAZOLIDONE AND NALIDIXIC ACID IN THE EMPIRICAL TREATMENT OF ACUTE INVASIVE DIARRHEA: RANDOMIZED CLINICAL TRIAL

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ABSTRACT

Efficacy of furazolidone and nalidixic acid was compared in a randomized trial involving 72 children with acute invasive diarrhea. Thirty six children received furazolidone (7.5 mg/kg/day) and 36 children received nalidixic acid (55 mg/kg/day). Clinical characteristics of the two treatment groups were comparable on admission. Of these, 34 children in furazolidone treated group and 29 children in nalidixic acid treated group completed the full course of treatment and were analyzed finally for clinical efficacy. Clinical cure was observed in 29(85.3%) children treated with furazolidone and 29(100.0%) children treated with nalidixic acid. Nalidixic acid treated group had statistically significantly higher cure rate (p=0.039) as compared to fuazolidone treated group. However, 85% cure rate in furazolidone treated group may be potentially useful for the treatment of acute invasive diarrhea becuase of decreasing efficacy of nalidixic acid against shigellosis in many countries.

Key words: *Furazolidone, Nalidixic acid, Acute invasive diarrhea, Shigella.*

Frequent passage of loose stool with macroscopic presence of blood is indicative of acute invasive diarrhea and it may be assumed that the patient is suffering from shigellosis who lives in an endemic area in the developing countries(l). Shigellosis continues to be a major cause of bacterial diarrhea in the world. About 20% of the hospitalized diarrhea patients have shigellosis world wide(2). Since 1969, several epidemics of shigellosis have been reported from different corners of the globe(3) including India(4,5). Following the epidemic of shigellosis in West Bengal in 1984, Calcutta metropolis and suburbs have become an endemic zone for shigellosis(6,7). Clinicians are often compelled to use antimicrobial agent(s) to treat acute invasive diarrhea (shigellosis) patients empirically. World Health Organization

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(WHO) has also recommended that patients suffering from blood and mucus diarrhea should be considered as having shigellosis and be treated with an appropriate antimicrobial agent according to the susceptibility pattern of the circulating strains of *Shigella* prevailing in the region(l). An *in vitro* study conducted at Calcutta, showed that the recently isolated strains of *Shigella* are resistant to commonly used drugs like tetracycline, ampicillin, trimethoprimsulphamethoxazole, chloramphenicol and kanamycin but are highly susceptible to nalidixic acid, newer quinolones and furazolidone(6-8). Clinical usefulness of nalidixic acid and newer, quinolones has been well documented for the acute invasive diarrheas, particularly shigellosis(9,10). However, furazolidone has rarely been evaluated clinically(ll,12).

The search for less expensive as well as non-toxic regimen prompted us to evaluate further the efficacy of furazolidone for treating acute invasive diarrhea (shigellosis) in children in actual clinical situations.

Material and Methods

Children of both sexes aged up to 5 years admitted to Dr. B.C. Roy Memorial Hospital for Children, Calcutta, during the period between December, 1992 and July, 1993 with a clinical diagnosis of dysentery were included in the study. Dysentery was diagnosed in patients who had frequency of loose stool more than 3 times per day and the stool was intimately mixed with blood and mucus and was also associated with symptoms like fever, abdominal pain and tenesmus. Patients who did not receive any drug before hospitalization or received drugs known to have no effect on dysentery *(i.e.,* non-absorbable sulpha, metronidazole, oral streptomycin or penicillin) were included in the study. Other inclusion criterias were: the patient should have more than ten bowel motions during last 24 hours and duration of diarrhea should be less than 3 days. Those patients who received the antimicrobial agents at home which were known to be effective against shigellosis or who had other obvious systemic illness requiring use of other antimicrobials *(e.g.,* pneumonia, renal failure) were excluded from the study. The study protocol was explained to the parents before hospitalization and their verbal consent was obtained before treatment begun.

After selection (on day 1), a complete history was obtained from either patients or their parents. A thorough physical examination was done and findings were recorded in a predesigned form. Patients were weighed to the nearest 100 g and were allocated to different "weight for age" nutritional groups according to Indian Academy of Pediatrics using Harvard Standard weight(13). Patients were randomized in two treatment groups mentioned below in accordance with a random number table, using permuted block of block length 8. Sealed envelopes were used for treatment allocation. The study group received furazolidone (7.5 mg/kg/day in 4 divided doses) and control group received nalidixic acid (55 mg/kg/day in 4 divided doses). Patients received either drug orally for 5 days. Patients were followed up daily during treatment period until the end of the hospital stay. One of the investigators, who had no knowledge of the drug administered, monitored the clinical response (daily records of body temperature, frequency of stool, presence of blood in the stool, anorexia, abdominal pain and other adverse effects that could be attributed to the drugs). The efficacy of antimicrobial agent was judged by the patients clinical response on

day 5. Clinical response referred to the alteration in the clinical signs and symptoms of the patients of two treatment groups. The treatment was considered effective if the study patient recovered (no blood in stool, no fever, stool semisolid with frequency less than 3 times for last 24 hours or no stool for last 18 hours) on day 5. Though follow up data were collected daily, only the data on day 3 and day 5 were analyzed because these patients were admitted to the hospital on request for close observation and better follow up. Otherwise, these patients were usually treated at the Outpatients, Department and were followed up on alternate days if they did not develop any complication meanwhile. Data analysis on day 3 and day 5 was very much similar to the follow up made on Outpatients, Department. Treatment failure was considered if patients developed complications such as toxic megacolon, paralytic ileus, hemolytic uremic syndrome or any systemic illness requiring deviated course for intended treatment. Treatment failure was also defined as deterioration or no imporvement in clinical parameters *(e.g.,* fever, presence of blood and mucus in stool or frequency of stool on day 5). Some of the patients were assessed as improving (no fever, presence of scanty blood in stool, stool frequency reduced but still more than 3 times during the last 24 hours) or not improving (no change in fever, blood in stool and frequency of stool) on day 3. During hospital stay, older children received full hospital diet and feeding schedule of the younger children were continued. Study patients who recovered and did not develop complications were discharged from the hospital after completion of 5 days of drug therapy. Treatment failure patients were treated with standard treatment of the hospital for shigellosis which includes use of nalidixic acid or fluoroquinolones (only when not responding to nalidixic acid) for 5 days and discharged on recovery. Patients were considered drop-outs if they did not complete the full course of treatment. A direct smear of admission stool sample was examined microscopically in high power field (HPF) for fecal leucocyte counts.

The Chi-square and the Fisher's exact test were applied to compare the differences in cure rate.

Results

A total of 72 children were selected for the study and were randomized into 2 treatment groups. Of these, 36 children in each group received either furazolidone or nalidixic acid. Baseline clinical and laboratory characteristics of two groups were comparable at the time of admission with regard to age, body weight, preadmission duration of diarrhea and other presenting features *(Table I).* Two patients in furazolidone treated group and 7 patients in nalidixic acid treated group dropped out. Finally, 34 patients in furazolidone treated group and 29 patients in nalidixic acid treated group were analyzed for their outcome variables. *Table II* shows the clinical status of the patients in two groups. On day 3, cure was observed in 20(58.8%) children treated with furazolidone and in 25(86.2%) children treated with nalidixic acid. On day 3, cure rate in nalidixic acid group was statistically significantly high (p=.034). Finally, on day 5, 29(85.3%) children in furazolidone group and 29(100.0%) children in nalidixic acid group recovered. Trend of high statistical significance in cure rate (p=0.039) was also observed in nalidixic acid group on day 5.

Discussion

Physicians of developing countries have to treat acute invasive diarrhea patients on

TABLE *I-Baseline Characteristics of Children with Acute Invasive Diarrhea*

Parameters	Furazolidone group (n=36)	Nalidixic acid group (n=36)
Mean (±SD) age (mo)	15.7±8.0	15.2±8.6
Sex		
Male	16	19
Female	20	17
Mean (kg) body weight (±SD)	7.7±2.7	7.5±2.7
Weight for age % (median)		
51-60	5(13.9)	6(16.7)
61-70	9(25.0)	8(22.2)
71-80	10(27.8)	10(27.8)
>80	12(33.3)	12(33.3)
Mean (±SD) duration of diarrhea before inclusion. hours	S7.2±17.S	57.7±19.4
Mean (±SD) frequency of stools in last 24 hours	15.1±3.9	15.3±3.1
Fever [>38.5ºC. No (%)]	32(88.9)	33(91.7)
Abdominal pain [No.(%)]	34(94.4)	33(91.7)
Tenesmus [No. (%))	32(88.9)	34(94.4)
Anorexia [No. (%)]	30(83.3)	29(80.5)
Mean (±SD) fecalleucocytes/HPF	73.8±18.0	68.1 ±19.1

the basis of clinical diagnosis as most of the countries do not have their laboratory facilities for identification of enteropathogens. The empirical treatment of acute invasive diarrhea with antimicrobial(s) has also been recommended by World Health Organization 1). Selection of antimicrobial agent in the empirical treatment of invasive diarrheas should be based on the knowledge of isolation rate of enteropathogens and their susceptibility pattern(l). In Calcutta, rate of isolation of *Shigella* species is very high and they are mainly responsible for acute invasive diarrheas(6,7). The management of acute invasive diarrhea caused by *Shigella* has become complicated particularly in children as circulating strains of *Shigella* are resistant to commonly used antimicrobials(6-8). Tetracycline, ampicillin and trimetboprim-sulphamethoxazole had shown clinical benefit against sensitive *Shigella* strains in the past. Unfortunately, plasmid mediated resistant strains of *Shigella* have spread widely in this country(5-7) as well as in many other countries(3) negating the effectiveness of these

TABLE II-*Clinical Status of the Patients on Day* 3 *and Day 5*

	Furazolidone group (n=34) No. (%)	Nalidixic acid group (n=29) No. (%)	p value
On day 3			
Cured	20(58.8)	25(86.2)	Cure *vs* others
Improving	10(29.4)	3(10.3)	p = 0.034
Not improving	4(11.8)	1(3.4)	
0n day 5			
Total cured	29(85.3)	29(100.0)	Fisher's exact test
Total failure	5(14.7)	0	p = 0.039

drugs. With the appearance of *Shigella* resistant to tetracycline, ampicillin and trimethoprim-sulphamethoxazole, nalidixc acid has become the first line of therapy for shigellosis in many areas. However, resistance of *Shigella* strains to nalidixic acid has already been reported in many countries including India(14,15). Presently *in vitro* and *in vivo* studies show that newer quinolones are highly effective against multi-resistant strains of *Shigella(1).* However, newer quinolones are not yet recommended for routine treatment of shigellosis in children for fear of potential cartilage toxicity reported in animals(16). In search of alternative antimicrobial therapy, investigators have looked at furazolidone because of its excellent *in vitro* activity against *Shigella(6,8).*

The present report is purely based on clinical observations. Stool samples of the study patients were not processed to detect enteropathogens inspite of having screening facilities. It was intended to mimic the situation just as primary or subsidiary level hospitals. Furthermore, the study was designed to test the empirical treatment of acute invasive diarrhea patients and therefore presence of pathogens was not an inclusion criteria. Presence of gross blood in stool, high fecal leucocyte counts and associated other symptoms like fever, abdominal pain and tcnesmus constituted a good clue that the study patients were infected with bacterial enteroinvasive enteropathogen particularly *Shigella.* In this study, patients of both the groups had over 50 fecal leucocytes per high power field (mean ±SD; 73.8±18.0 and 68.1±19.1 in patients of furazolidone and nalidixic acid treatment groups, respectively). This high fecal leucocyte counts are predictive of infection with *Shigella.* Present findings of microscopical examination of stool for leucocyte counts also corroborates the observation of other report that if fecal leucocyte counts exceeds 50 per high power field, a patient is likely to suffer from invasive diarrhea particularly shigellosis(17). The present study showed that cure was achieved in 29(85.3%) of 34 furazolidone recipients and in 29(100.0%) of 29 nalidixic acid recipients. Nalidixic acid was statistically significantly more effective than furazolidone for empirical treatment of invasive diarrhea. However,

85% cure rate in furazolidone treated patients may be useful as furazolidone has many other special characteristics of an ideal drug for treating acute invasive diarrhea: it is cheap, can be administered orally, is appropriate for use in all age groups, is free from severe side effects and also does not change the intestinal microflora(18). It has also been reported that despite its use for last 30 years, significant resistance to the drug has not appeared in any part of the world(19). Until now, there has been only limited clinical experience in the use of furazolidone in the empirical treatment of invasive diarrhea. One study from Mexico showed that furazolidone was more effective than ampicillin, cure was achieved in 97.4% of patients in furazolidone treated group as compared to 65.7% of patients in ampicillin treated group(12). Another study also conducted in Mexico showed that 87.8% of the patients in the furazolidone treated group and 82.7% patients in trimethoprim-sulphamethoxazole treated group achieved clinical cure and no differences in clinical cure rates between the two treatment groups were observed(11). Drop-outs of 9 children from the study (2 in furazolidone and 7 in nalidixic acid treated groups) was high. However, this could be explained that inspite of repeated request parents of those dropout patients refused to keep their children in hospital after 2 days as all of them were in recovery state.

Our study shows that furazolidone is effective in the empirical treatment of acute invasive diarrhea, particularly in this *Shigella* endemic area and it may be potentially more useful in future because of decreasing efficacy of nalidixic acid in shigellosis in many countries including India.

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