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CLINICAL EVALUATION OF SHIGELDYSENT AND CIPROFLOXACIN IN THE TREATMENT OF *SHIGELLOSIS*

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ABSTRACT

Objective: A comparative randomized controlled clinical trial was undertaken to evaluate the effectiveness of herbal coded formulation "ShigelDysent" in comparison with Ciprofloxacin for the treatment of *Shigellosis* in order to establish an appropriate safe and effective traditional medicine for *Shigellosis*. **Methods:** Two hundred and fifty patients were enrolled in the study and divided into two groups according to treatment regimen. Ciprofloxacin was given to 125 patients (Control Group) as a control drug and ShigelDysent was prescribed to 125 (Test Group). Stool culture was examined before and after treatment. **Results:** Test drug (ShigelDysent) was found to be more effective in controlling *Shigella* dysentery by eradicating more *Shigella* species, as 75% of *Shigella* colonies were absent in test group as compared to control in which 59% of *Shigella* colonies were absent after treatment. **Conclusion:** ShigelDysent has been found to be more effective in comparison with Ciprofloxacin for the treatment of *Shigellosis*. There were no side effects associated with the treatment by ShigelDysent and this is found to have good acceptability by all treated patients.

KEYWORDS: *Shigellosis,* traditional medicine, efficacy, ShigelDysent, Ciprofloxacin.

INTRODUCTION

Shigellosis is the infection of the colon caused by *Shigella* species which includes *Shigella dysenteriae*, *Shigella sonnei*, *Shigella flexneri* and *Shigella boydii* [1]. These are Gram-negative small, immotile bacilli that cause infection leading to diarrhea and dysentery affecting approximately 164.7 million episodes globally per year. *Shigellosis* is mostly found in the children of developing countries (99%) and considered a major factor of death (69%) in these countries according to a recent report by WHO [2,3]. Clinical manifestation by this infection may be asymptomatic but in severe cases, it includes diarrhea with or without mucus, abdominal pain, fever and tenesmus. Intestinal perforation, toxic mega colon, enteropathy, arthralgia, sepsis, electrolyte imbalance, convulsion and nervous disturbances are the major complications as a result of this infectious disease and leading to death in more severe cases [4,5]. Patients with *Shigella* infection are given specific antimicrobial therapy and several studies have indicated that effective antibiotic treatment rapidly rids off the patient's intestine from *Shigella* organisms and decreases the manifestations of clinical illness [6]. The sulphonamides were once the most extensively used antimicrobial agents in the treatment of *Shigellosis*. Nevertheless, sulphonamide-resistant strains of *Shigella* have been reported and this drug is no longer used in the treatment of this disease. Resistance of *Shigella spp.* to tetracycline and chloramphenicol has also increased; and neither of them are now used in the treatment of *Shigellosis* [7, 8]. Ampicillin has been claimed to be a safe and highly effective drug and has often been used as the drug of choice in *Shigella* diarrhoea. Significant proportion of *Shigella* strains have been found resistant to ampicillin [9]. It is apparent that a search for new antimicrobial agents in the treatment of *Shigellosis* is necessary. Co-trimoxazole (Trimethoprim-sulphamethoxazole) has been found to be very effective in growth inhibition of most *Shigella* strains *in vitro* and some recent studies have claimed its therapeutic value in the treatment of the disease [10,11]. *Shigella* isolates have also been found to be highly sensitive to furazolidone *in vitro*. The use of furazolidone in some hospitals is based on the *in vitro* sensitivities of many *Shigella* isolates to the drug [12].

There is a great need to find some alternate therapy for the treatment of *Shigellosis* in order to overcome the overwhelming problem of antimicrobial resistance of the current regimens. Therefore a multi-herb formulation "ShigelDysent" was designed which comprises of different medicinal plants possessing antibacterial activity. The purpose of this study was to compare Ciprofloxacin with ShigelDysent in the treatment of *Shigellosis*.

MATERIALS AND METHODS

A randomized comparative controlled clinical trial was conducted in Mother Care Hospital, Shifa-ul-Mulk Memorial Hospital Karachi Pakistan, at Pehlwan Goth, Safora Goth and Patel Para from April 2010 to August 2011 with the clinical symptoms of acute gastroenteritis. All patients were randomly assigned either Ciprofloxacin or ShigelDysent. Before specific therapy was started, rectal swabs were obtained and immediately inoculated on to MacConkey and S.S. agar plates. Antimicrobial therapy was started without awaiting the results of stool cultures. Patients were withdrawn from the study if their stool cultures did not confirm the diagnosis of *Shigellosis*. Clinical evaluation of the disease and also rectal swab cultures were made on before and after treatment for seven days.

Ciprofloxacin was given in capsule form (500 mg capsule twice a day); ShigelDysent capsule 500 mg containing *Myrtus communis* L. (Fruit of Hub-ul-Aas powder) 150mg, *Aegle marmelos* L. (Fruit of Belgiri powder) 100mg, *Polygonum bistorta* L. (Bikh Anjibar powder) 75mg, *Phyllanthus emblica* L. (Fruit of Aamla powder) 75mg, *Holarrhena antidysenterica* L. (Maroor phalli powder) 50mg and *Citrus aurantifolia* L. (Post Turang powder) 50mg was prescribed twice a day.

Two hundred and fifty *Shigellosis* patients completed the three scheduled visits. One twenty five patients were treated with Ciprofloxacin and one twenty five were treated with ShigelDysent capsules. These patients are characterized in terms of age, duration of frequency of stools before therapy.

Frequency of stools is the indication of duration of diarrheal days. In this study we noted the days the patient had suffered the diarrheal dysentery before and after the treatment started. Afterwards the frequency of stool outcome that is for how long the dysentery persists (in the form of number of days) after the intervention of drugs is recorded so as to evaluate the efficacy of the control and test drugs.

Frequency of stools outcome was divided into days for complete recovery from duration of dysentery. Frequency in number of patients and cumulative percent was also calculated.

Ethical issues and clinical trial approval

Study was conducted under the rules of Ethical Committee (EC) of Shifa-Ul-Mulk Memorial Hospital, Faculty of Eastern Medicine, Hamdard University Karachi, Pakistan. Study design

and protocols were presented to the board members of Ethical Committee (EC) and Board of Advance Studies and Research (BASR) for their clearance and permission before the start of clinical trial.

Diagnostic technique and outcome measures

Stool culture was performed at baseline and after treatment. Eligible patients were interviewed and their physical examination, including weight and height was performed. A questionnaire regarding demographic data (name, age, sex, etc.), as well as about the presence of other illnesses or habits (smoking, alcohol, etc.), was filled up before the start of treatment. Clinically improved patients represented as a patient having no fever and regaining a well-formed stool without blood or mucus. The number of stools a day became fewer than three.

It indicated occurrence of number of stools per day in participants of both groups before and after the treatment so as to prove the efficacy of control and test drugs. Number of stools were graded as 3, 5, 6, 8 stools per day whereas the number of stool outcome was given the scale as none, >5 and <5 in number.

Treatment outcome represented the complete recovery of the illness from all the signs and symptoms in terms of days. Treatment outcome in both test and control groups were compared in the form of quick response to the drugs. The level of decline or severity of the symptoms was recorded after the treatment between test and control groups applying test of significance (*p* value). Clinical treatment failure represents the days that take more than 10 days to cure all the symptoms, persistent dysentery and presence of colonies

Statistical analysis

Patient's characteristic data was expressed as mean ± standard deviation (SD). Statistical analysis was performed using SPSS for Windows and Microsoft excels. A *p* -value of less than 5% was considered significant.

RESULTS

Prevalence of Shigellosis

A total of 250 patients with gastroenteritis were treated in this study. *Shigella spp*. were isolated as *Shigella sonnei* that was found in 96 (38%) cases, *Shigella flexneri* in 74 (29%) cases, *Shigella boydii* in 30 (12%) cases whereas in one of the areas "Patel Para" we found

50 (20%) cases of *Salmonella* spp. effecting gastro-intestinal tract of these patients. The study groups were comparable in regard to the following characteristics. The highest number of cases 40 (16%) of *Shigella sonnei* was found in age interval of 30-35 years, highest number 33 (13%) of *Shigella flexneri* was found in 41-45 years of age group whereas for *Shigella boydii* the highest cases 28 (11%) was in age interval of 36-40 years. For *Salmonella* spp. the highest number of cases 45 (18%) was found in age group of 25-29 years.

Antibacterial response of the therapies

The bacteriological responses to the treatment are listed in Table 1. Stool culture is an important tool for identification of organism in the specimen. Stool culture report has been categorized for *Shigella sonnei, Shigella flexneri, Shigella boydii and Salmonella* spp., number of species have been calculated with cumulative percent in either group. Significant *Shigella* colonies were present in 5% of patients treated with ShigelDysent while 21% in Ciprofloxacin treated group. Patients that had no *Shigella bacilli* in their stools after treatment and had negative *Shigella* stool cultures after 7-10 days of treatment were 75% in case of ShigelDysent and 59 % in Ciprofloxacin treated group. Of the 125 patients given Ciprofloxacin patients that got cure in 7 days (49), 9 days (29), 10 days (13), 11 days (18) and 12 days (16). In case of ShigelDysent patients that got cure in 7 days (56), 9 days (34), 10 days (21), 11 days (11) and after 12 days (3) as given in Table 2.

Table 1: Stool culture outcome

Stool Culture Follow Up	Test Group	Control Group	*p* value
Salmonella Absent	7%	9%	0.0063
Significant *Salmonella* colonies	2%	5%	
Significant *Shigella* colonies	5%	21%	
TFTC *Salmonella spp.*	10%	6%	
Shigella absent	75%	59%	
Total	**125**	**125**	

Table 2: Representation of treatment outcome in both groups

	Test Group Frequency			Control Group Frequency		
No. of days	**Patients Frequency**	**Percent**	**Cumulative Percent**	**Patients Frequency**	**Percent**	**Cumulative Percent**
7days	56	45	45	49	39	39
9days	34	27	72	29	23	62
10days	21	17	89	13	10	73
11days	11	9	98	18	14	87
12days	3	2	100	16	13	100
Total	**125**	**100**		**125**	**100**	

DISCUSSION

The clinical illness of *Shigella* infection may vary from mild and self-limiting to severe and fatal. In most cases symptoms generally decrease spontaneously in three to seven days. The results of this study indicated that ShigelDysent is not only efficacious from a bacteriological standpoint but that it statistically significantly reduces the duration of clinical illness when compared with Ciprofloxacin. The poor response to non-absorbable antimicrobial agents in *Shigellosis* patients may be due to the fact that *Shigella* bacilli have the ability to invade the sub-mucosa of the intestine during the course of the illness, so that the antimicrobial agents are unable to act on the intracellular micro-organisms [13]. The *in vitro* study indicated that most but not all of the isolates were sensitive to trimethoprim. Nevertheless, alternative treatment supports the suppression of many diseased conditions very effectively and may become helpful in becoming a substitute for rising antibiotic resistance. Analysis authenticated that Cotrimoxazole as well as Ampicillin are not considered to be the cure of bacillary dysentery. Until 2004, Nalidixic acid was advocated via WHO as the drug of choice for the treatment of *Bacillary dysentery*, afterwards it was substituted with ciprofloxacin. In China and Bangladesh Nalidixic acid absolute resistance was obvious that evidently diminished the worth of the drug eventually in both countries. By now 6% of *Shigella flexneri* strains are ciprofloxacin resistance in China [14]. Emergence of alternative drugs for *Shigella* spp. might be of great assistance to *Bacillary dysentery* events that have been monitored in this study. Considering the wide use of antibiotics in the community, where antimicrobials are available without prescription, it is believed that a sharp increase in the number of resistant *Shigella* strains might be expected. In this regard it will be extremely important to observe the sensitivity of *Shigella* bacilli and to look for a new agent for the treatment of this disease.

Test drug is more effective in controlling *Shigella* dysentery by eradication of *Shigella* species, because 75% of *Shigella* colonies were absent in test group as compared to control in which 59% of *Shigella* colonies were absent. This eradication of *Shigella* by herbal coded "ShigelDysent" may be due to the fact that medicinal plants included in this formulation are *Phyllanthus emblica, Aegle marmelos, Holerrhena antidysenterica, Myrtus communis, Polygonum bistorta* and *Citrus aurantifolia* possessing remarkable ethno-botanical and scientific evidences for the treatment of dysentery. These plants have anti-febrile, anti-atherogenic, adaptogenic, gastro-protective, wound healing, analgesic, anti-diarrheal, hepato-

protective, nephro-protective, neuro-protective, antioxidant, antibacterial, antifungal, anti-inflammatory, free radical scavenging and antioxidant as well as chemo-preventive qualities. Variations in prevalence of different species of *Shigella* have been recorded in different areas of Karachi, Pakistan which may be due to different water and sanitary conditions in these areas. *Shigella sonnei* was the most frequently isolated spp; 96 cases in Pahlwan Goth and in Safora Goth were found whereas *Shigella flexneri* 74 cases except in Patel Para where *Salmonella* was most common in 50 cases**.** *Shigella boydii* was infrequently isolated from 30 cases. In each of the three study sites *Shigella sonnei* was more frequently isolated from age group of 30-35 years. In contrast, *Shigella flexneri* was more frequently isolated from age group of 41-45 years.

The present study also highlights that *Shigellosis* can be manifested independent of age and sex. The clinical findings reveal that patients were suffering from dysentery comprising of blood and mucus, in addition with abdominal cramps/pain, tenesmus, nausea and anorexia. Few cases of dehydration were also seen, although there was no major complication observed.

CONCLUSION

ShigelDysent has been found to be more effective ($p<0.05$) in comparison with Ciprofloxacin for the treatment of Bacillary dysentery (*Shigellosis*). There were no side effects associated with the treatment by ShigelDysent and this is found to have good acceptability by all treated patients as compared to Ciprofloxacin. However, further clinical trials on larger scale and studies pertaining to mechanism of ShigelDysent are required before prescribing it as an alternate therapy against *Shigellosis*.

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Conflict of interest

Authors declare no conflict of interest.

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