Journal of the Egyptian Society of Parasitology, Vol.43, No.2, August 2013

J. Egypt. Soc. Parasitol., 43(2), 2013: 463 – 470

COMPARATIVE STUDY BETWEEN THE EFFECT OF NITAZOXANIDE AND PAROMOMYCINE IN TREATMENT OF CRYPTOSPORIDIOSIS IN HOSPITALIZED CHILDREN

BY

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Abstract

Ninety children infected with *Cryptosporidium parvum* attending Al-Azhar University Teaching Hospital (Assuit) were chosen (60 males & 30 females) with age range from 6 months to ten years. The patients were divided into two groups of 45 patients for each (G1 & G2). All patients suffered from chronic diarrhea for more than fifteen days. Cross-matched 45 children suffering from chronic diarrhea were used as a control group (G3). Stool samples were collected and examined for detection of *Cryptosporidium* oocysts using Sheather's sugar and Modified Ziehl-Nelseen stain techniques. The first group (G1) received Nitazoxanide (100 mg and 200 mg every 12 hours for 3 days for children aged 6 months to 3 years and children aged 4 to 10 years respectively), G2 received Paromomycin (25mg/kg/day for 2 weeks). Third group received placebo. Significant improvement and shortening of the duration of diarrhea occur in G1; of 45 patients received Nitazoxanide 39 cases showed complete clinical and laboratory cure (86.6 %), 5 cases showed clinical improvement with reduction in the number of oocysts and 1 case showed no cure. In G2 of 45 cases received Paromomycin 31 cases showed complete cure (68.8 %), 8 cases showed clinical improvement with reduction of oocysts number and 6 cases were not cured. Nitazoxanide proved highly effective than Paromomycin in cryptosporidiosis.

Keywords: Cryptosporidiuosis, Marasmus, Kwashiorkor, Nitazoxanide, Paromomycin

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Introduction

Cryptosporidium parvum is an enteric protozoan parasite of medical and veterinary significance. Dissemination of environmentally resistant oocysts in surface water plays an important role in the epidemiology of cryptosporidiosis (Smith *et al*, 2007). This parasite is an endemic zoonotic coccidian parasite highly prevalent in many of the developing countries (Alles *et al*, 1995). It is an obligate intracellular extracytoplasmic protozoan parasite that is a major

cause of diarrheal illness worldwide and responsible for up to 20% of childhood diarrhea (Mosier and Oberst, 2000). *Cryptosporidium* primarily infects the distal small intestine. Immunocompetent hosts control and eliminate the infection, which typically causes acute, self-limited watery diarrhea lasting 5 to 10 days. Globally, *Cryptosporidium* infection continues to be a significant health problem where it is recognized as an important cause of diarrhea in both immunocompromised and immunocompetent people (William *et al*, 2007). In developing countries persistent diarrhea is the leading cause of death in children younger than five years of age, where it accounts for 30 to 50 percent of those deaths (William *et al*, 2007). However, in patients with defects in cellular immune responses (as AIDS, malnutrition, or defects in CD40-CD154 system), *Cryptosporidium* frequently causes persistent or chronic diarrhea and may also involve the biliary tract (Hunter and Nichols, 2002). In malnourished children, persistent diarrhea is associated with increased susceptibility to recurrent diarrheal episodes, which can lead to death or chronic nutritional and cognitive sequelae (Guerrant *et al*, 1999). The malnutrition, immunosuppression, small age and an increase in the preceding diarrhea burdens are all risk factors for the development of persistent diarrhea (Ochoa *et al*, 2004). Persistent diarrhea seriously affects nutritional status, growth, and intellectual function. Meeting these challenges is profoundly important mainly in developing countries. Aggressive treatment of infectious diarrhea is required in severely immunocompromised children (Huang and White, 2006). Management strategies included rehydration, adequate diet, micronutrient suplementation, and antimicrobials (Ochoa *et al*, 2004). Hundred compounds have been tested both in vitro and in animal models. The United States Food and Drug Administration recently approved the use of Nitazoxanide for treatment of diarrhea caused by *Giardia* or *Cryptosporidium* spp., has a broad spectrum of activity against many other gastrointestinal pathogens, including bacteria, roundworms, flatworms, and flukes (Bobak, 2006). Paromomycin is an aminoglycoside that has shown variable positive results when given orally for cryptosporidiosis. This study aimed to compare the efficacy of Nitazoxanide and Paromomycin in the treatment of cryptosporidiosis in children.

Patients, Materials and Methods

This study was carried out from August 2012 to February 2013. Ninety children infected with *Cryptosporidium parvum* attending Al-Azhar University Teaching Hospital (Assuit) were chosen (60 males & 30 females) with age range from 6 months to ten years. Parents of the children were informed about the nature of the test and written consent was taken from each. Children suffered from malnutrition, marasmus of various degrees, marasmic-kwashiorkor, and failure to thrive. Other causes of persistent diarrhea and concurrent medications were excluded. Sheets were filled out on each patient included age, sex, residence, weight loss, abdominal pain and diarrhea (type, onset,

course and duration). Stool samples were collected in clean dry containers and examined for *Cryptosporidium* oocysts using Sheather's floatation and modified Ziehl-Nelseen stain techniques (Garcia, 2007). Oocysts counting were done before and after treatment initiation (El Shazly *et al*, 2007). The patients were divided into two groups of 45 (30 male & 15 female) for G1 & G2. Cross matched 45 patients suffering from chronic diarrhea other than cryptosporidiosis were used as a control group (G3). G1 received Nitazoxanide as 100mg every 12 hours for 3 days for children aged few months to 3 years and 200mg every 12 hours for children aged 4 to 10 years respectively. G2 received Paromomycin (25mg/ kg/day for 2 weeks). The oral rehydration solution according to the degree of dehydration and plentiful fluids was given. Also, Zinc acetate 20 mg once daily for 14 days was given to improve the mucosal lining of intestine and to avoid diarrhea serious complications.

Statistical analysis: Data were computerized and analyzed by Chi-square test Comparing Nitazoxanide and Paromomycin effect was done according to enhancement of general condition, diarrhea eradication or reduction or complete oocysts eradication.

Results

The results are shown in tables (1, 2, 3 & 4) and figures (1, 2, 3 & 4).

Table 1: Personal characters of studied groups

Personal characters	G I (n= 45)		GII (n= 45)		GIII (n= 45)		P-value
	No.	%	No.	%	No.	%	
Age:							
< 2 years	11	24.4	13	28.9	13	28.9	0.810
2 - < 4 years	9	20.0	5	11.1	6	13.3	
≥ 4 years	25	55.6	27	60.0	26	57.8	
Sex:							
Male	30	66.7	30	66.7	30	66.7	1.000
Female	15	33.3	15	33.3	15	33.3	
Residence:							
Rural	21	46.7	20	44.4	23	51.1	0.812
Urban	24	53.3	25	55.6	22	48.9	

Table 2: General condition of the studied patients in three groups

Items	G I (n= 45)		GII (n= 45)		GIII (n= 45)	
	No.	%	No.	%	No.	%
Marasmus	14	31.1	14	31.1	14	31.1
Kwashiorkor	2	4.4	2	4.4	2	4.4
Marasmic- Kwashiorkor	1	2.2	2	4.4	1	2.2
Failure to thrive	28	62.2	27	60.0	28	62.2

Table 3: Duration of diarrhea /day in groups

	GI (n= 45)	GII (n= 45)	G III (n= 45)
Mean ± SD	18.40 ± 3.77	19.09 ± 5.44	19.36 ± 4.21
Range	15 – 30	14 – 33	15 – 31
P-value	0.588		

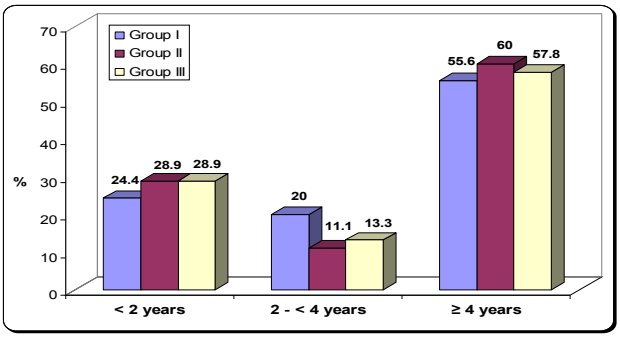

Figure 1: Personal characters of studied groups**.**

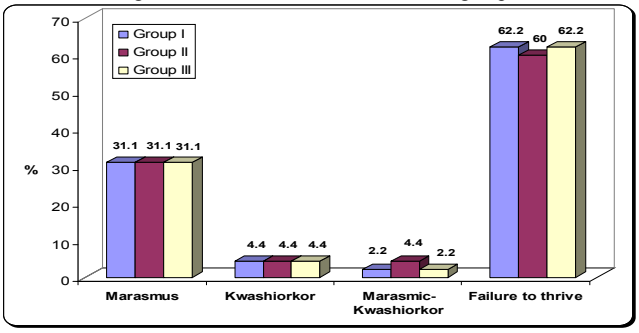

Figure 2: General condition of three groups.

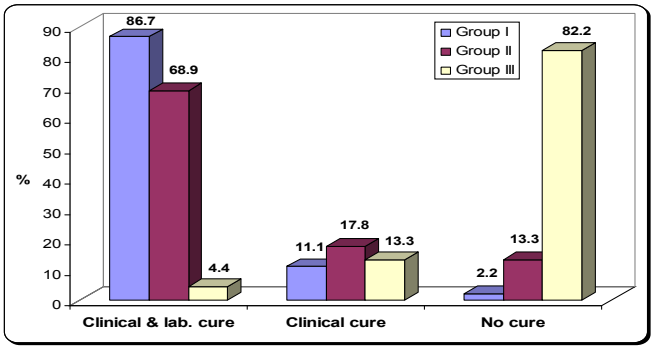

Figure 3: Efficacy of Nitazoxanide and Paromomycin treatment in groups.

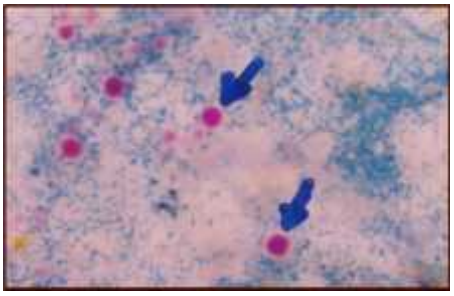

Fig. 4: Ziehl-Nelseen stained *Cryptosporidium* oocysts in stool smear before treatment.

Table 4: Efficacy of Nitazoxanide and Paromomycin treatment in groups

Efficacy of treatment	G I (n= 45)		GII (n= 45)		GIII (n= 45)	
	No.	%	No.	%	No.	%
Clinical & lab. cure	39	86.7	31	68.9	2	4.4
Clinical cure	5	11.1	8	17.8	6	13.3
No cure	1	2.2	6	13.3	37	82.2
P-value	0.000*					

Discussion

Cryptosporidiosis causes diarrheal disease with 10 *Cryptosporidium* species infecting nearly all mammals worldwide (Fayer *et al*, 2000). *C. parvum*, the most important species, was an endemic zoonotic coccidian highly prevalent in many of the developing countries, and responsible for up to 20% of the childhood diarrhea (Mosier and Oberst, 2000). The common mode of transmission included waterborne, animal contact, food-borne, or man to man contact with oocysts. *Cryptosporidium* infection continues to be a significant health problem in both developed and developing countries (Harp, 2003), where it is recognized as an important cause of persistent diarrhea in both immunocompromised and immunocompetent people (DuPont *et al*, 1995; Kjos *et al*, 2005). Persistent diarrhea is a leading cause of death in children younger than five years of age in developing countries, where it accounts for 30 to 50% of childhood mortality (Ochoa *et al*, 2004). In Egypt cryptosporidiosis is one of the serious zoonotic parasites (Azab *et al*, 1985). Many authors dealt with incidence of human cryptosporidiosis in Egypt (Rezk and Soliman, 2001; Antonios *et al*, 2001; Abdel-Messih *et al*, 2005; El Shazly *et al*, 2007; Massoud *et al*, 2008; Youssef *et al*, 2008). Cryptosporidiosis was also reported as zoonosis (El-Sherbini and Mohammad, 2007) and nosocomial in a pediatric hospital (El-Sibaei *et al*, 2003). The availability of an effective treatment might alleviate requirement for hospitalization due to acute illness and might limit potential long-term disease consequences.

The present study showed that in G1 out of 45 children with cryptosporidiosis received Nitazoxanide drug for 3 consequent days, 39 showed complete clinical and laboratory cure which represent 86.6 %, 5 showed clinical improvement and one showed no cure. This result agreed with Rossignol *et al.* (2001) who reported that 36 (80%) cryptosporidiosis patients treated with Nitazoxanide showed improvement of the diarrhea and reduction in oocysts shedding. Open-label Egyptian study on 49 adults and children, reported 67% rate of eradication of parasites 7-10 days after initiation with Nitazoxanide 3-day course (Abdel-Maboud *et al*, 2000). Clinical and parasitological lower rates were reported by Amadi *et al.* (2002) in 14/25 (56%) of HIV seronegative children with cryptosporidiosis receiving Nitazoxanide. In G2 of 45 malnourished children with cryptosporidiosis received Paromomycin for 2 weeks, 31 showed complete clinical and laboratory cure (68.6%), 8 cases showed clinical improvement and 6 cases were not cured. The results agreed with Scaglia *et al.* (1994) who successfully treated

AIDS patients with chronic cryptosporidiosis by Paromomycin 2000mg/day for 4 weeks followed by 1000 mg/day for another 4 weeks. Ross *et al*. (2000) reported that a meta-analysis of data from 11 previously reported studies of 300 patients who received Paromomycin treatment from 1990 to 1996, the overall response rate was 67% (21/30). Also, lower cure rates were 47.1% (Ross *et al,* 2000) and 45% (Ahmed *et al,* 2008) reported with Nitazoxanide and Paromomycin in cryptosporidiosis malnourished children. In the present study, Nitazoxanide was effective than Paromomycin, in G1 (11/15) with complete clinical and laboratory cure without oocysts shedding 3 days post treat ment. However, 3 showed some clinical and laboratory cure with few oocysts shedding after 3 days treatment and one was not clinically or laboratory cured after 3 days treatment who suffered severe marasmic-kwashiorkor condition. In G2 (7/14 showed complete clinical and laboratory cure without oocysts shedding after14 days treatment (3 showed some clinical and laboratory cure with few oocysts shedding in stools 14 days post treatment and 4 showed no clinical or laboratory cure (with no change in oocysts shedding in stools 14 days post treatment). Thus, Nitazoxanide proved to be highly effective agent against cryptosporidiosis than Paromomycin. This agreed with the US Food and Drug Administration report approving Nitazoxanide parasiticial action (David and Bobak, 2006) and with Ross *et al*. (2000) who reported that Paromomycin was not more effective than placebo for treatment of symptomatic cryptosporidial enteritis. In the present study, patients' sex had no marked effect on the course or disease prognosis after using Nitazoxanide and Paromomycin in G1 & G2 respectively. On the other hand, the patients' age had an important role in the course and prognosis of cryptosporidiosis in in G1, 14/19 (73.6%) patients less than 4 years who were clinically and laboratory cured, whereas 25/26 (96.1%) patient aged 4-10 years were clinical and laboratory cure. In G2 11/18 (61.1%) patients less than 4 years showed complete clinical and laboratory cure, whereas 20/27 (84.6 %) aged 4-10 years showed complete clinical and laboratory cure. This fact can be explained by gradual development and solidification of the immunity with age. These results agreed with Jonathan *et al*. (2012) who reported that cryptosporidiosis affects all age groups, butthe number of cryptosporidiosis cases and rates were highest among children aged 1-4 years, followed by those aged 5-9 years and adults aged 25-29 years. Similar findings were reported in USA, Canadian provincial, Australian State, and National Finnish and United Kingdom surveillance data (Waldron *et al*, 2011). This explained the efficacy of immunity on the development, course, prognosis and response to treatment.

Conclusion

Nitazoxanide represents a significant step forward in the treatment of gastrointestinal infection not only due to its high effect against Cryptosporidiosis but also for its broad range of activity against nearly all major types of gastrointestinal parasites, also the short term

of treatment (3 days) in comparison to Paromomycin (14 days) play important role in completion of the course of treatment by patients, as cryptosporidiosis is commonest among poor families with low education level.

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