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Research Article

EVALUATION OF RACECADOTRIL IN TREATMENT OF ACUTE DIARRHEA IN CHILDREN

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ABSTRACT

Objective: The aim was to assess efficacy of racecadotril as an adjuvant therapy in children 2-6 years in age with acute diarrhea.

Materials and Methods: A randomized control study on two major groups, Group I 60 patients hospitalized, treatment group received oral rehydration solution (ORS) plus oral racecadotril (1.5 mg/kg 3 times/day) and control group had only ORS (30 patients each), Group II 90 outpatients, allotted into three 30 patients each (15 as control and 15 as treatment group each), Group II a, control used nitazoxanide (100 mg/5 ml oral suspension 3 times/day), treatment group used nitazoxanide and racecadotril, Group II B, control had metronidazole (40 mg/ml syrup 3times/day), treatment had racecadotril and metronidazole, Group II C, control used ORS only, treatment used racecadotril and ORS, outcome measures was stool output (in g); total stool output, duration of diarrhea and number and consistency of stools in Group I and number and consistency of stools, duration of diarrhea and number of children followed-up after treatment in Group II.

Results: In Group I racecadotril with ORS reduced 48 hrs stool output significantly (91.55 g/kg ± 4.86) as compared to ORS group (183.4 ± 9.91) ($P<0.001$), duration of diarrhea in days reduced significantly (4.56 ± 0.38 vs. 5.93 ± 0.30), in Group II racecadotril with nitazoxanide, metronidazole and ORS improved duration of diarrhea (2.9 ± 0.3, 3.9 ± 0.3, 4.9 ± 0.2) respectively ($P<0.001$) number of solid stools increased from initial visit to the 7 days visit in whole group.

Conclusion: Racecadotril is effective as an adjuvant therapy for treatment acute diarrhea in children.

Keywords: Children, Acute diarrhea, Racecadotril, Adjuvant therapy.

INTRODUCTION

Diarrheal disease is a leading cause of illness and death in children worldwide, many of the deaths are caused by dehydration resulting from loss of water and electrolytes due to intestinal malabsorption or increased secretion. Replacement of these losses by oral rehydration solution (ORS) is the mainstay of therapy for children with acute diarrhea [1]. Acute diarrhea continues to cause high morbidity and mortality worldwide. Although oral rehydration therapy has reduced mortality associated with acute diarrhea, the diarrheal attack remains unchanged, and stool volume often increases during the rehydration process [2]. Over the past few years, new drugs have been developed for the treatment of diarrhea, including inhibitors of enkephalinases [3]. Enkephalins are endogenous opioid peptides that function as intestinal neurotransmitters. Among their functions is the inhibition of intestinal secretions [4]. Racecadotril is an enkephalinase inhibitor that decreases intestinal hypersecretion, but not motility in animals and humans [5]. It has proved effective and safe in children and adults with acute diarrhea when taken orally [6]. It exerts its antidiarrheal effects by preventing the breakdown of endogenous enkephalins in the gastrointestinal tract [7]. This causes a reduction in intracellular cyclic adenosine monophosphate levels and a decrease in the secretion of water and electrolytes [8]. These effects occur without altering the motility or duration of intestinal transit and without promoting bacterial overgrowth. Furthermore, it does not affect the basal absorption of water or electrolytes [3,9]. Hence, the aim of the current study was to assess the effects of racecadotril as an adjuvant therapy to either ORS or to nitazoxanide and metronidazole in children with acute diarrhea.

MATERIALS AND METHODS

This was a prospective, observational study to evaluate the effect of racecadotril as an adjuvant therapy to either ORS or to nitazoxanide and metronidazole in children with acute diarrhea. Research Ethical Committee letter was taken to perform human study; the study protocol, patient information sheet and formed consent were approved by Research Ethical Committee of Faculty of Medicine, in Beni Suef University, Beni Suef, Egypt. The guardian of each child signed the informed consent form in the presence of a witness prior to inclusion in the study.

Study site

The study was conducted at in-patient and out-patient departments of Beni Suef University Hospital, Beni Suef, Egypt.

Study design and duration

The controlled and observational study was carried out in clinical settings for a period of 6 months (from March 2013 to September 2013) to study evaluate the effect of racecadotril as an adjuvant therapy to either ORS in hospitalized patients or to nitazoxanide and metronidazole in out-patients in treatment of acute diarrhea in children.

Source of data

Baseline demographic and clinical characteristics were recorded, which included age, weight, history of fever, vomiting, or other symptoms, prior use of any medication, duration of diarrhea, number of motions, frequency, character of stools and degree of dehydration in addition to laboratory reports.

Selection of patients

Inclusion criteria

Age between 2 and 6 years, gender: Both (male/female), acute diarrhea of different etiology, onset of diarrhea <3 days, children with mild to moderate dehydration in hospitalized group and mild dehydration in an out-patient group.

Exclusion criteria

Children with severe dehydration, severe malnutrition, chronic diarrhea, who received antibiotics or antidiarrheal drugs 48 hrs before study, previous use of antibiotic for more than 48 hrs, vomiting and inability to drink and children with fructose intolerance or glucose malabsorption syndrome or succharase-isomaltase deficiency.

Distribution of patients

The patients were distributed into two major groups as follows:

Group I (hospitalized, n=60) – 30 patients had racecadotril and ORS in the treatment group, and 30 patients had ORS only in the control group; Group II (Outpatient, n=90); Group II A - 15 patients had racecadotril and nitazoxanide in the treatment group, and 15 patients had nitazoxanide only in the control group. Group II B - 15 patients had racecadotril and metronidazole in the treatment group, and 15 patients had metronidazole only in the control group; Group II C - 15 patients had racecadotril and ORS in the treatment group, and 15 patients had ORS only in the control group.

Data collection and data analysis

All the information needed was recorded in a predestined case report form, follow-up was done after 24 hrs, 48 hrs and 7 days, for outpatients group in cases of failure to follow-up, a telephonic check was carried out daily. Any episode of complication, adverse effects was recorded in all groups.

Outcome measures

In Group I stool weight and intake of ORS, measured every 8 hrs. The primary efficacy criterion was stool output in the first 48 hrs, because of the high risk the of dehydration during this period, total stool output and number of motions and duration of diarrhea in days also recorded.

In Group II primary efficacy criterion is duration of diarrhea in days followed by consistency of stool after initiation of treatment, cure rate after 7 days and number of children who followed up after treatment.

Statistical analysis

All results were expressed as mean ± standard deviation, data were collected coded and analyzed using SPSS software (version 17.0), descriptive analysis were performed and methods like student *t*-test and one-way ANOVA were used to calculate the significance with *P<0.05, **P<0.01.

RESULTS

In Group I, base-line patients' characteristics of the 30 child in the racecadotril (1.5 mg/kg) and ORS group and the 30 child in the ORS group were similar, rotavirus was assessed in both of groups, salmonella species and *Escherichia coli* was 40% in racecadotril group and 43.3% in ORS group as shown in the Table 1.

Duration and total stool output

Racecadotril showed a highly significant reduction in 48 hrs stool output 91.55 ± 4.86 g/kg in patients received racecadotril with ORS (treatment group) and 183.40 ± 9.91 g/kg those who received ORS only (control group). Reduction in total stool output before recovery to be 160.13 ± 20.81 g/kg in the treatment group and 348.58 ± 21.94 g/kg in the control group. Duration of diarrhea: Racecadotril reduced duration of diarrhea (in days) significantly in treatment group compared to control group (**P=0.001). Number of bowel movements: Reduction of a number of bowel movements after 48 hrs compared with who received ORS only (control group) with (**P=0.001) as shown in the Table 2.

There was a high significance in outcome measures between positive rotavirus in treatment group and control group (**P=0.001) as shown in the Table 3.

Stool consistency

A decline in the percentage of loose stools and an increase in solid stools noted after inclusion to be 76.7% in treatment group and 56.7% in the control group at the end of therapy (after 7 days).

Table 1: Base-line patient's characteristics in Group I (mean±SD)

Patient characteristic	Treatment group	Control group
Number of patients	N=30	N=30
Age (year)	3.4±1.28	3.6±1.35
Gender (%)		
Male	63.30	56.70
Female	36.70	43.30
Weight (kg)	18.3±2.29	19.1±2.32
Duration of diarrhea before inclusion (day)	1.80±0.35	1.9±0.34
Severity of diarrhea (%)		
Mild	6.70	13.30
Moderate	33.30	30.00
Severe	60.00	56.70
Number of bowel movement	7.56±0.68	7.5±0.68
Stool consistency (%)		
Liquid	90.00	10.00
Soft	86.70	13.30
Positive rotavirus (%)	60.00	56.70
Negative rotavirus (%)	40.00	43.30
Respiratory frequency	32.10±1.44	32.0±1.36
Systolic blood pressure	101.70±2.67	101.5±2.35
Diastolic blood pressure	62.80±2.05	62.00±1.67
Cardiac frequency	133.10±1.49	132.60±1.99

SD: Standard deviation

Table 2: Treatment outcomes in Group I (mean±SD)

Evaluation criteria	Treatment group	Control group
24 hr stool output/body wt. (g/kg)	92.90 ± 4.42	186.75 ± 9.61
48 stool output/body wt. (g/kg)	91.55 ± 4.86**	183.40 ± 9.91
Total stool output /body wt. (g/kg)	160.13 ± 20.81**	348.58 ± 21.94
48 hr stool wt. per hour (g/kg/hr)	19.08 ± 2.16**	32.35 ± 2.22
Duration of diarrhea (days)	4.56 ± 0.38**	5.93 ± 0.30
Number of bowel movements After 48 hrs	4.20 ± 0.63**	5.10 ± 0.69

SD: Standard deviation, **Highly Significant at P= 0.001

Table 3: Positive rotavirus patients characteristics in Group I (mean±SD)

Evaluation criteria	Positive rotavirus	
	Treatment group	Control group
Number of patients	N=18	N=17
Duration of diarrhea (days)	4.59±0.33**	5.89±0.21
24 hrs stool output/body weight (g/kg)	96.35±0.75**	194.86±2.32
48 hrs stool output/body weight (g/kg)	95.41±0.49**	191.72±2.63
Total stool output/body weight (g/kg)	176.81±1.26**	367.43±0.52
48 hrs stool weight/hr (g/kg/hr)	20.65±1.08**	34.16±0.76

SD: Standard deviation, **P=0.001

Adverse effects
There were no adverse effects found during the study in this group.

In Group II, base-line patients' characteristics of the 90 child, the whole group patients were similar as shown in the Table 4.

Number of bowel movements
Racecadotril in showed a reduction in a number of bowel movements in all treatments compared within control groups in Group II A (P=0.023*), Group II B (P=0.005**) and Group II C (P=0.008**) within 48 hrs. Duration of diarrhea: Duration of diarrhea (in days) a highly significant reduction shown by racecadotril in all treatments groups (**P < 0.01) compared with that of control groups as shown in the Table 5.

Recovery rates within 7 days
Recovery within 7 days or less was obtained as 86.7% with treatment Group (II A) and 80.0% for control Group (II A), 80.0% for treatment Group (II B) and 73.3% for control Group (II B) finally 73.7% for treatment Group (II C) and 60.0% for control Group (II C).

Adverse effects
There were no adverse effects found in these groups either by us or parents.

DISCUSSION

Acute diarrhea is one of the most common diseases in children [10]. The therapy mainly recommended by the most important guidelines is the oral rehydration with glucose-electrolyte solutions, but this approach, although effective, is poorly accepted by parents because it doesn't decrease the duration of disease [11]. Racecadotril is a potential antidiarrheal drug [12]. The results of the first part of this study that conducted on hospitalized children provide evidence that racecadotril is an effective treatment for acute diarrhea. In Group I When treatment group (racecadotril and ORS) compared with control group ORS, the treatment group had a significant reduction (P<0.001) in 48 hrs stool output, total stool output before recovery, duration of diarrhea and stool consistency [13]. Hence that use of racecadotril as adjuvant therapy to ORS reduces severity of diarrhea and that results in a reduction of hospitalization duration. Racecadotril when used with diarrhea with different etiology (bacterial and viral), it was effective in both positive and negative rotavirus.

The results of the second part of this study conducted on out-patient children, racecadotril in treatment groups when used with nitazoxanide, metronidazole and ORS had a significant reduction in number of bowel movements after 48 hrs, duration of diarrhea (in days) and recovery rates within 7 days when compared to results of control groups when nitazoxanide, metronidazole or ORS used alone and this may decrease propability to hospitalization especially when used with metronidazole or nitazoxanide in children with acute gastroenteritis. The risk of dehydration and the rate of conversion to parentral therapy also decreased in children with acute diarrhea. Either in hospitalized or outpatients group. There were no side-effects or adverse reactions reported. Hence, racecadotril could be a simple, acceptable and tolerable adjuvant therapy in acute diarrhea treatment in children in hospitalized and/or out-patients children. The results obtained in the present study are preliminary in nature and require further confirmatory studies with larger sample size and it will be useful to assess laboratory tests.

Table 4: Base-line patient's characteristics in Group II

Patients characterestics	Group II A		Group II B		Group II C	
	Treatment	Control	Treatment	Control	Treatment	Control
Number of patients	N=15	N=15	N=15	N=15	N=15	N=15
Age (year)	3.70±0.90	3.70±1.00	4.70±1.4	5.00±1.2	3.50±1.20	3.50±1.10
Gender (%)						
Male	33.34	80.00	90.00	53.34	80.00	10.00
Female	66.66	20.00	10.00	64.66	20.00	90.00
Weight (kg)	17.60±1.40	18.40±1.40	19.70±3.20	20.60±3.10	18.20±1.40	17.20±1.70
Duration of diarrhea (initial)	1.80±0.40	1.70±0.30	1.60±0.40	1.70±0.40	1.90±0.040	1.90±0.30
Severity of diarrhea (%)						
Mild	13.33	6.67	6.67	6.67	13.33	13.34
Moderate	20.00	20.00	26.67	33.33	33.34	40.00
Severe	66.67	73.33	66.66	60.00	53.33	46.66
Number of bowel movement	7.00±0.90	7.00±0.70	7.00±0.70	8.00±0.60	7.40±0.51	7.50±0.52
Stool consistency (%)						
Liquid	93.33	80.00	86.66	93.33	93.00	93.33
Soft	6.67	20.00	13.43	6.67	7.00	6.67
Positive rotavirus (%)	80.00	90.00	73.34	33.34	60.00	66.67
Negative rotavirus (%)	20.00	10.00	26.66	66.66	40.00	33.33
Respiratory frequency	30.03±1.90	29.00±0.90	30.30±1.60	29.30±0.80	30.20±1.50	28.40±0.90
Systolic blood pressure	102.10±1.20	103.70±1.0	102.60±1.20	102.60±1.40	103.00±1.40	103.00±1.60
Diastolic blood pressure	61.80±1.90	62.70±2.00	61.70±1.90	102.60±1.40	62.50±1.60	63.50±1.90
Cardiac frequency	133.60±1.80	132.40±1.50	133.00±1.30	132.90±1.50	132.00±1.90	133.30±1.30

Table 5: Treatment outcomes in Group I (Mean±SD)

Evaluation criteria	Group II A		Group II B		Group II C	
	Treatment	Control	Treatment	Control	Treatment	Control
Number of patients	N=15	N=15	N=15	N=15	N=15	N=15
Number of bowel movements						
Initial	7.00±0.90	7.00±0.70	7.00±0.70	8.00±0.60	7.40±0.51	7.50±0.52
After 24 hrs	4.00±0.70**	5.00±0.50	5.00±0.60	5.20±0.60	5.00±0.50	6.00±0.50
After 48 hrs	3.4±0.51*	3.90±0.63	3.00±0.60**	4.00±0.60	4.00±0.60**	5.00±0.60
Duration of diarrhea (days)	2.90±0.30**	3.70±0.40	3.90±0.30**	4.50±0.30	4.90±0.20**	5.50±0.30

SD: Standard deviation, **P<0.01

CONCLUSION

Racecadotril therapy is effective in the treatment of acute diarrhea in children; it was effective in reducing the volume and frequency of stool output and in reducing the duration of diarrhea. However, more data in out-patients are needed and safety of racecadotril, needs to be defined.

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