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Racecadotril in Management of Infant Diarrhea

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Abstract: *Acute diarrhea is considered 2nd killer during infancy as commonly prescribed ant diarrheal agent ,constitute a composite of antimicrobial agent and anti protozoal drug, poses various drug induced untoward effects either due to super infection or drug adversity.*

Interaction between diarrheal disease and nutritional status are complex and synergistic and serious issues globally., as they affect thousands of millions of young children every year and causes >3 millions death of children < 5yrs in spite of intensive filed based diagnosis and treatment.

Thus a planned study with therapeutically established molecule Racecadotril (Acetorphan),an enkephalinase inhibitor antisecretory and anti diarrheal used as safe and effective therapeutics for dioarrhea in adult and children is evaluated in infants in dose of 1.5mg/kg at 8 hrly dosefor its therapeutic effect and safety profile [6] Infants taking Racecadotril as adjuvant orally ensures early change in consistency and frequency of lose motion without any drug adversity or disease's consequent squeal.

Keywords: *diarrhea, acetorphan, mortality, antisecretory.*

1. INTRODUCTION

Diarrhea ,a biggest infant killer worldwide specially in developing countries like India, Nepal, Bangladesh and Shrilanka , where a child suffers on an average 3-6 episodes of diarrhea in first year of life claiming death rate of 20-60/thousand children annually. Interaction between diarrheal disease and nutritional status are complex and synergistic and serious issues globally., as they affect thousands of millions of young children every year and causes >3 millions death of children < 5yrs in spite of intensive filed based diagnosis and treatment ,[1,2] usually 109 of every 1000 children dies before 5 yrs (Unicef report 2012) and 11% death is due to diarrhea, present deth rate of 38 per thousand in India to be achieved by 2015 ,though diarrheal death dropped in India Usually child loses water and electrolyte alike adult due to fairly large area of secreting intestinal mucosa [7].

The commonest cause of during infancy is virus (Rotavirus) or non specific though diarrheas significantly alter nutrition but simultaneously malnutrition also predisposes diarrhea due to declined immune response and aggravated secretory function of intestinal mucosa.

As during infancy the major cause of diarrhea is increased secretion due to increased cyclic AMP during dentition phase or due to organismal toxin[2]. Inspite of its non bacterial pathogenesis, the commonly prescribed preparation constituting even contra indicated antimicrobial agent (Quinolone) combination is quite in vogue and prescribed by qualified and specialized clinician, which not only causes therapy related untoward effect but also presents with manifestation of super infection eg-candidiasis, fungal diarrhea, urinary tract infectionand mucous colitis [4]. Though various anti diarrheal

are in vogue (even containing contraindicated molecules), which not only cause various therapeutic hazards like post diarrhea mucous colitis, urinary tract infection, fungal super infection and mortality due to post diarrhea dehydration and encephalopathy[7].

Hence considering the mortality and morbidity in infants due to altered secretory and absorptive mechanism of intestinal mucosa, a clinical study to evaluate an anti secretory prodrug RACECADOTRIL in declining the secretion of intestinal mucosa and promotion of fluid and electrolyte transport in changing the consistency and frequency of stool and safety profile in infant diarrhea is planned

2. MATERIALS AND METHODS

2.1. Design and Study

Comparative clinical study to evaluate RACECADOTRIL orally in limiting fluid and electrolyte loss in infant diarrhea.

2.2. Patients

1760 infants presenting with lose motion with various stage of dehydration without any other systemic disease or sequelae attending at pediatric out door of RA.Hospital & Research Centre during Jan 2008- March 2009 were selected by Centre for Diarrheal Disease Research (CDDR).

2.3. Method

After proper knowledge regarding the proposed study written consent of the parent was taken and selected infants were duly examined and patient's informants (parent or attendant) were interrogated thoroughly for frequency, consistency and odor of stool ,therapeutics taken and their effects and mode and type of feedings.

Patients were also assessed for their hydration and thermal state. Dehydration state was assessed as per following index of assessment.

Dehydration	Characteristic feature
Mild	Irritable, craving for water
Moderate	Irritable, weak pulse, restlessness, decreased urine volume , Depressed anterior fontanel, Face dry and pinched
Severe	Moribund, apathetic, peripheral circulatory Failure, marked reduction in urine volume, Eye ball markedly sunken, .lips parched, Face markedly dry and parched, buckle, Mucosa dry, loss of skin turgor, craving for Water (intense thirst)

Selected patients were investigated for serum electrolyte, stool routine and culture, urine routine and culture was duly done.

Selected patients were classified into two groups constituting equal number of infants of similar status to adjudge the comparative therapeutic status of RACECADOTRIL in infant diarrhea.

Group A	Anti diarrhea agent and Racecadotril
Group B	Anti diarrhea agent & ORS

Patients with severe dehydration irrespective of their therapeutic group were administered intravenous fluid in dose of 100ml/kg in schedule of –30ml/Kg in first 30 minutes while rest 30ml/Kg in next 1 hour and 40% in next 2 hours and index of hydration was adjudged by passage of urine.

In order to check or induce paralysis or neuritis in suspected cases of viral diarrhea as a precautionary measure intramuscular injections been duly avoided. Among the anti diarrheal recommended are Nitazoxnide dry syrup and Co -trimoxazole suspension in recommended therapeutic dose. Racecadotril powder was recommended in dose of 1.5mg/Kg every 8 hours with palatable water/Oral Rehydration Solution. Irrespective of the nutritional status and infant feeding type ,infant's mother were advised to feed their child on barley or rice water gruel for 72 hours to avoid a risk of lactose intolerance and milk or food induced intestinal cramps or agony.

Each mother or parent were given a follow up card to enter the following

- Frequency of lose motion every day

- Consistency of stool i.e.
- watery, semisolid or formed
- Fever
- Excessive crying
- Abdominal distension,
- Status of dehydration,
- Urine out put

After completion of 72 hrs of therapy, each patient were evaluated for consistency and frequency of stool, culture and sensitivity of stool and urine, blood for hematological status and renal statu Post therapy status of the patient was assessed as per following index i.e.

- any relapse,
- recurrence or persistence,
- urinary complaints,
- persistence of pyrexia,
- Mucous colitis.

Based on the therapeutic response and post therapy follow up, clinical response was graded as

Clinical grades	Characteristics
I	Completely formed stool within 48 hrs without any consequent sequel.
II	Decrease in frequency of stool and change in consistancy of stool in 48 hrs without any adversity.
III	Decline in frequency and consistency but no Formed stool with adversity
IV	No effect within 72 hrs

3. OBSERVATIONS

Among the selected infants, majorities (39%) were of age group 6-9 months and 17% were of age group 3-6 months. 32% infants had frequency of motion 4-6 every 24 hours while 19% shows >13 every 24 hours.(T-1)

Table1. *Distribution of patients as per their age, sex and frequency of motion*

Age group	Number of patients							
Frequency of motion/24hr	4-6		7-9		10-12		>13	
	M	F	M	F	M	F	M	F
1-3 months	50	46	56	40	32	20	42	30
3-6 months	60	48	46	35	30	22	32	25
6-9 months	120	89	110	78	94	68	76	45
9-12months	80	60	75	55	60	47	51	38
	310	243	287	208	216	157	201	138

Out of all 65% (1136) infants present with lose watery motion, 23% and 12% infants had greenish lose motion and lose motion with mucous and froth respectively, 85% had fever and 80% presented with scanty urine(T-2).

Table2. *Distribution of patients as per clinical presentation*

Particulars	Number of patients		
	Male	Female	Total
Lose watery motion	714	422	1136
Lose greenish motion	190	213	403
Lose motion with froth	110	111	221
Abdominal distension	880	530	1410
Prone lying	912	625	1537
Irritability	1006	703	1709
Scanty urine	718	698	1416
Depressed anterior fontanelle	886	526	1412
Fever	846	649	1495

As per hydration status all are dehydrated but 41% and 39% were with severe and moderate dehydration respectively (T- 3)

Table3. *Distribution of patients as per their dehydration status*

Dehydration state	Number of patients			
	Male	**Female**	**Total**	**%**
Mild	128	220	348	20
Moderate	450	244	694	39
Severe	436	282	718	41

Stool examination of the infants shows absence of respective pathogens in 33% male and 34% female though 12% of both male and female Show presence of Shigella and 16% of male and 15% female shows presence of Salmonella, (T- 4)

T**able4.** *Distribution of patients as per status of stool pathogen*

Isolated pathogen	Number of patients		
	Male	**Female**	**Total**
No organism	332	254	586
Salmonella	160	109	269
Shigella	124	088	212
Escheresia coli	198	121	319
Giardia	200	174	374

No infants with history of fever show significant bacteriuria or positive Microstix -N test for Urinary tract infection. Hematological status of majority infants was within normal limit or non reveal hemoglobin deficiency or any haemato pathology.

All infants taking Rcecadotril shows earliest change in consistency and frequency of stool with complete normalization within 72 hours while others had deterioration of hydration status (39%) and needed intravenous fluid administration with advocation of racecadotril.

Crave for water in infants on racecadotril ceased within 24 hours though some had within 12 hours while in others persisted for more than a week. 93% infants taking racecadotril had grade I clinicopathological cure while others had worsening of hydration state in majority (89%) and needed fluid transfusion and ad vocation of racecadotril.

4. DISCUSSION

In spite of enormous advancement in diarrheal management mortality and morbidity remain very common in infants due to acute diarrhea Present study reveals earliest decline in frequency and change in stool consistency, resulting in short duration of therapy and minimal loss of fluid and electrolytes, checks need of intravenous fluid and electrolyte supplementation.

Table5. *Outcome of the study*

Particulars	Number of patients			
	Group A		**Group B**	
	Male (588)	**Female (292)**	**Male (588)**	**Female (292)**
Hydration status:				
Improved	in all	in all	084	016
Declined	none	none	504	276
Untoward sequel:				
Abdominal distension	none	none	262	108
Vomiting	none	none	280	128
Irritability	none	none	314	192
Grade of clinical cure:				
I	546	272	046	012
II	042	020	488	072
III	-	-	054	208
Post therapy sequel:				
Mucous colitis	-	-	117	144
UTI	-	-	124	106
Persistent diarrhea	-	-	044	173

Not only this short duration of diseases check untoward effects as revealed by unaltered hematological , hepatic and renal function. Early change in consistency and decline in frequency of lose motion and loss of fluid and electrolytes in infants taking Racecadotril can be explained as- Racecadotril, a pro drug which gets hydrolyzed to THIORPHAN and inhibits intestinal encaphalin (a membrane bound metalo peptidase) and prolong the anti secretory effect of encaphalin resulting in reduced secretion of water and electrolyte in the intestinal lumen, ultimately declining the intestinal load and intestinal stretch receptor response , finally reduce stretch ,stimulation of the intestinal musculature leading to decline in tenesmus and defecation response.

Without increasing intestinal transit time and promoting bacterial colonization or fluid pooling in the distended bowel lumen or causing constipation

5. CONCLUSION

RACECADOTRIL, an anti secretory prodrug prolongs the anti secretory effect of encephalin decreases the intestinal over load ,promote water and electrolyte absorption and help change the consistency of stool ,checks water and electrolyte loss and cut short both the duration and cost of therapy.

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