



ORIGINAL ARTICLE

Efficacy and safety of non-specific anti-diarrheal agents in the management of acute diarrhea in children.

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ABSTRACT... Objective: To compare the efficacy and safety of racecadotril, smectite and placebo among children having acute diarrhea. **Study Design:** Randomized Controlled trial. **Setting:** Department of Pediatrics, Allama Iqbal Memorial Teaching Hospital, Sialkot. **Period:** January 2021 to June 2021. **Material & Methods:** A total of 120 children (40 in each group) of both gender, aged above 6 months to 5 years with acute diarrhea were enrolled. All children were prescribed oral rehydration therapy (ORT). As co-adjuvant treatment, children in Group-A (n=40) were prescribed smectite, racecadotril in Group-B (n=40) while placebo was given in Group-C (n=40). Among all children, treatment duration was 7 days and all children were asked to follow up on 3rd, 5th and 7th day for the evaluation of stool frequency, stool consistency and dehydration status. **Results:** In a total of 120 children, 62 (51.7%) were male. Overall, mean age was noted to be 17.9+9.4 months. Stool frequency significantly reduced in Group-A and Group-B in comparison to Group-C at day-3 (p<0.001), day-5 (p<0.001) and day-7 (p=0.018). During the follow ups, need for IV rehydration was 1 (2.5%) in Group-A, 1 (2.5%) in Group-B and 6 (15.0%) in Group-C (p=0.035). Significant improvement was observed in stool grading of children in Group-A and Group-B when compared to Group-C at day-3 (p<0.001), day-5 (p<0.001) and day-7 (p=0.043). No side effects were recorded in any of the patients. **Conclusion:** Along with oral rehydration therapy, non-specific anti-diarrheal agents like smectite and racecadotril were found to have good efficacy and safety in the management of acute diarrhea in children.

Key words: Acute Diarrhea, Racecadotril, Smectite.

INTRODUCTION

Although last few decades have seen major improvement treating acute diarrhea among children but it still represents an important cause of morbidity and mortality in the pediatric age groups.¹ Acute diarrhea is described as diarrhea occurring within a minimum period of 24 hours and lasting < 14 days.² Acute diarrhea causes anxiety as well as socio-economic burden to the parents taking care of the affected children. In children, diarrhea causes 16% of all death in Pakistan.³ Globally, diarrhea is the cause of 15% deaths in children aged less than 6 years which is estimated to be 8.8 million deaths annually.⁴

Lots of variation exists regarding treatment approaches towards acute diarrhea among children while data from developed countries

have shown that only 28% of the emergency physicians were efficiently applying existing clinical practice guidelines for the treatment of pediatric gastroenteritis.⁵ Almost all of the global guidelines and recommendations regarding treatment of acute diarrhea among children endorse use of low-osmolarity oral rehydration solutions (ORS) as a fundamental choice of treatment while other co-adjuvant treatment options like racecadotril, smectite, probiotics and zinc are some of the most popularly adopted treatment agents for acute diarrhea among children.^{6,7}

Lots of data is available from around the world regarding effectiveness of various non-specific anti-diarrheal agents among children but lack of evidence is observed in Pakistan regarding

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efficacy and safety of various non-specific anti-diarrheal agents. So, the present study was planned to compare the efficacy and safety of racecadotril, smectite and placebo among children having acute diarrhea.

MATERIAL & METHODS

This randomized controlled trial was conducted at The Department of Pediatrics, Allama Iqbal Memorial Teaching Hospital, Sialkot, from January 2021 to June 2021. Approval from institutional Ethical Committee was acquired (Ref.No.07/PAEDS/KMSMC, dated: 03/06/2021). Informed written consent was sought from the parents/guardians of all study participants.

A total of 120 children (40 in each group) of both gender, aged above 6 months to 5 years with acute diarrhea were enrolled. Acute diarrhea was labeled as > 3 stools/day for duration not more than 3 days. All children having any kinds of antimicrobial, antidiarrheal or antimotility agents in the past 7 days were excluded. Children with clinical diagnosis of dysentery or those having chronic liver or kidney disease were also not enrolled. Children with bloody diarrhea or severe diarrhea (cholera) were also excluded. Children presenting with severe malnutrition as body weight below 60% of expected for that age were also not included.

All children were prescribed oral rehydration therapy (ORT). As co-adjuvant treatment, children in Group-A (n=40) were prescribed smectite, racecadotril in Group-B (n=40) while placebo was given in Group-C (n=40). Racecadotril was prescribed as 1.5 mg per kg per dose thrice a day. Smectite was prescribed as 6 to 12 g/day divided in 3 equal doses. Among all children, treatment duration was 7 days and all children were asked to follow up on 3rd, 5th and 7th day for the evaluation of stool frequency, stool consistency and dehydration status. Stool consistency was evaluated by asking the parents/guardians about the state of the last stool and graded in 5 types as per "Modified Bristol Stool from Scale for Children (mBSFS-C)".⁸ All parents were given a questionnaire with instructions to be filled the diarrheal episodes. In case patients missed the

follow up, a telephone call was made to know the status of the child.

All study information was noted a specific proforma designed for this study. SPSS version 26.0 was used for data analysis. Qualitative variables like gender, stool grading and need for IV rehydration were represented as frequency as well as percentage. Quantitative variables like age, weight, duration of diarrhea and stool frequency were shown as mean and standard deviation (SD). Qualitative variables were compared using chi-square test in between groups while "Analysis of Variance (ANOVA)" was used to compare quantitative variables. P value < 0.05 was considered significant.

RESULTS

In a total of 120 children, 62 (51.7%) were male. Overall, mean age was noted to be 17.9+9.4 months. Mean duration of diarrhea was found to be 2.1+0.9 days. Table-I is showing comparison of baseline characteristics in between study groups and no statistical significance observed (p>0.05).

Table-II is showing comparison of stool frequency at baseline and during the course of follow ups. There was no significant difference in stool frequency at baseline in between study groups (p=0.858) but stool frequency significantly reduced in Group-A and Group-B in comparison to Group-C at day-3 (p<0.001), day-5 (p<0.001) and day-7 (p=0.018).

During the follow ups, need for IV rehydration was 1 (2.5%) in Group-A, 1 (2.5%) in Group-B and 6 (15.0%) in Group-C and difference in between groups was noted to be statistically significant (p=0.035) as children in using smectite and racecadotril required significantly less IV rehydration in comparison to placebo. Table-III is showing stool grading at baseline and during the course of follow ups. No significant difference was observed in stool grades of children in between different study groups at baseline (p=0.677) but significant improvement was observed in stool grading of children in Group-A and Group-B when compared to Group-C at day-3 (p<0.001), day-5

($p < 0.001$) and day-7 ($p = 0.043$). No side effects were recorded in any of the patients.

| Characteristics | | Group-A (n=40) | Group-B (n=40) | Group-C (n=40) | P-Value |
|-------------------------|--------|----------------|----------------|----------------|---------|
| Gender | Male | 20 (50.0%) | 22 (55.0%) | 20 (50.0%) | 0.935 |
| | Female | 20 | 18 (45.0%) | 20 (50.0%) | |
| Age in months (Mean+SD) | | 21.8+15.1 | 16.6+8.1 | 16.1+11.1 | 0.247 |
| Weight in kg (Mean+SD) | | 13.2+11.4 | 14.4+10.8 | 13.8+12.1 | 0.947 |
| Duration of Diarrhea | | 1.95+0.9 | 2.20+0.8 | 2.08+0.9 | 0.662 |

Table-I. Comparison of baseline characteristics of children. (n=120)

| Stool Frequency | Group-A (n=40) | Group-B (n=40) | Group-C (n=40) | P-Value |
|------------------|----------------|----------------|----------------|---------|
| Day-1 (Baseline) | 8.0+1.8 | 8.0+2.2 | 8.3+1.9 | 0.858 |
| Day-3 | 3.9+1.1 | 4.1+1.3 | 6.1+1.8 | <0.001 |
| Day-5 | 2.1+0.8 | 2.6+0.7 | 4.0+1.1 | <0.001 |
| Day-7 | 1.6+0.6 | 1.6+0.7 | 2.2+0.9 | 0.018 |

Table-II. Comparison of stool frequency at baseline, Day-3, Day-5 and Day-7 in between study groups. (n=120)

| Stool Grading | Group-A (n=40) | Group-B (n=40) | Group-C (n=40) | P-Value | |
|------------------|----------------|----------------|----------------|------------|--------|
| Day-1 (Baseline) | 3 | 6 (15.0%) | 2 (5.0%) | 2 (5.0%) | 0.677 |
| | 4 | 16 (40.0%) | 22 (55.0%) | 18 (45.0%) | |
| | 5 | 18 (45.0%) | 16 (40.0%) | 20 (50.0%) | |
| Day-3 | 2 | 12 (30.0%) | 20 (50.0%) | 0 | <0.001 |
| | 3 | 26 (65.0%) | 20 (50.0%) | 20 (50.0%) | |
| | 4 | 2 (5.0%) | 0 | 10 (25.0%) | |
| Day-5 | 5 | 0 | 0 | 10 (25.0%) | <0.001 |
| | 1 | 22 (55.0%) | 8 (20.0%) | 2 (5.0%) | |
| | 2 | 16 (40.0%) | 28 (70.0%) | 10 (25.0%) | |
| | 3 | 2 (5.0%) | 4 (10.0%) | 24 (60.0%) | |
| Day-7 | 4 | 0 | 0 | 4 (10.0%) | 0.043 |
| | 1 | 36 (90.0%) | 30 (75.0%) | 20 (65.0%) | |
| | 2 | 4 (10.0%) | 10 (25.0%) | 16 (30.0%) | |
| | 3 | 0 | 0 | 4 (10.0%) | |

Table-III. Stool grading among children of different study groups. (n=120)

DISCUSSION

Although, majority of the children with acute gastroenteritis have mild to self-limited disease conditions but still it is one of the most frequent reasons for hospitalization in the pediatric age groups.⁹ Oral rehydration solutions are the cornerstones of acute gastroenteritis treatment but it is estimated that less than 20% of pediatric cases suffering with acute gastroenteritis receive optimal therapeutic treatments which goes on to contribute to increased rates of hospital stays, complications and economic burden.¹⁰ It is also recorded that ORT might prevent occurrence of

major complications in acute diarrhea but it does not reduce disease course in most cases as it has not beneficial effects on frequency of bowel motions.¹¹

The present study showed a significant improvement in stool consistency as well as reduction in stool frequency among children who were using therapeutic co-adjuvants like smectite or racecadotril. A meta-analysis done by Gutierrez-Castrellon P et al analyzing 50 RCTs evaluating different anti-diarrheal treatment regimens and placebo revealed significant efficacy of various

therapeutic options for acute diarrhea in children except Lactobacillus GG at doses less than 10^{10} CFU and zinc among children aged less than 6 months. In terms of co-adjuvant therapeutic options, the authors noted that racecadotril was the most superior option followed by smectite.¹² A review endorsed smectite as an adjunct to ORT and when required, can be used along with antimicrobial agents as well.¹³

In the present study, we noted that need for IV rehydration was similar (2.5%) in each group using smectite or racecadotril but it was seen to be 15% in the placebo group ($p=0.035$). A study done by Shanmugham SB et al from India found only 1.7% of children in racecadotril group to require IV oral rehydration in comparison to 7.4% in placebo groups which is close to what we noted in the present study.¹⁴ Manfredi M and colleagues revealed a much higher proportion of children in racecadotril group (27%) who required IV rehydration and 43% in placebo group.¹⁵ Large proportion of children requiring IV rehydration in Manfredi M et al findings could be because of the reasons that they might have included children progressively worsening acute diarrhea.

Our study had some limitations as well. Relying on parents/guardians observations might have its own repercussions regarding evaluation of the stool related information in this study. Although, we recorded stool frequency among children in the present study but stool weight could have given us further insight about the stool output in the studied children. We did not evaluate the impact of comorbidities when the children were recruited. We were unable to compare cost of treatments in the different groups.

CONCLUSION

Along with ORT oral rehydration therapy, non-specific anti-diarrheal agents like smectite and racecadotril were found to have good efficacy and safety in the management of acute diarrhea in children.







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AUTHORSHIP AND CONTRIBUTION DECLARATION

| No. | Author(s) Full Name | Contribution to the paper | Author(s) Signature |
|-----|---------------------|----------------------------------------------|---------------------------------------------------------------------------------------|
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| 2 | Saman Zahid | Methodology, Discussion. |  |
| 3 | Samina Batool | Study Concept, Data Analysis, Proof Reading. |  |
| 4 | Akasha Islam | Data Collection, Literature Review. |  |
| 5 | Saman Jamal | Data Collection, Literature Review. |  |
| 6 | Taiba Aslam | Data Collection, Literature Reivew. |  |