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Original Research

Racecadotril for the treatment of acute gastroenteritis in children received outpatient care in Qatar

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Abstract

Introduction: Acute gastroenteritis is a clinical syndrome often defined by increased stool frequency (eg, ≥3 loose or watery stools in 24 hours, also it is one of the most common causes of morbidity and mortality in children under 5 years in the developing world. Racecadotril is an antisecretory agent that can prevent fluid/electrolyte depletion from the bowel as a result of acute diarrhea without affecting intestinal motility. **Research question or hypothesis:** To investigate whether prescribing Racecadotril plus oral rehydrating solution in outpatient care helps to decrease the hospital revisit rate within 72 hours due to acute gastroenteritis in comparison with oral rehydrating solution alone. **Study design:** Retrospective cohort study. **Methods:** Pediatric patients aged 3 months to 14 years visited Al Wakra Pediatric emergency department due to acute gastroenteritis for outpatient care in the period between 1/1/2022 till 30/06/2022 were included. Case group was defined as patients who prescribed oral rehydrating solution plus Racecadotril upon their initial visit. Control group was defined as patients who prescribed only oral rehydrating solution upon their initial visit. **Results:** 2505 pediatric patients were included, 520 patients were enrolled in the control group, and 1985 patients were included in the case group. Most patients in both groups were 1 to 5 years old (67% in control group, and 59% in case group). The hospital revisit rate within 72 hours due to gastroenteritis was slightly less in case group 7.1% in comparison with 7.5% in control group (Relative risk 0.95, 95% CI 0.68 to 1.34). Most patients (88%) who revisited the hospital due to gastroenteritis within 72 hours showed no or mild signs of clinical dehydration in their initial visit (77% in control group, and 93% in case group) **Conclusion:** Racecadotril was found to have insignificant impact on hospital revisit rate in acute pediatric gastroenteritis managed at outpatient setting.

Keywords: racecadotril; gastroenteritis; electrolyte replacement solution; dehydration

INTRODUCTION

Acute gastroenteritis is a clinical syndrome often defined by increased stool frequency (eg, ≥3 loose or watery stools in 24 hours or several loose/watery bowel movements that exceeds the child's usual number of daily bowel movements by two or more), with or without vomiting or fever. It usually lasts less than one week and not longer than two weeks. Diarrhea that lasts >14 days is "persistent" or "chronic." Diarrhea that recurs after seven days is "recurrent. The illness usually resolves without treatment within days; however, symptoms are unpleasant and affect both the child, family and careers of parents. Severe diarrhea can quickly cause dehydration, which may be life threatening.[1]

Diarrhea is one of the most common causes of morbidity and mortality in children under 5 years in the developing world.[1]

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Oral rehydration is the first-line treatment for all the children with AGE, and an efficacy comparable with Intravenous fluid hydration has been reported also in children with severe dehydration,[2] and according to ESPEGAN, reduced osmolarity ORS (50/60 mmol/L Na) should be used as first-line therapy for the management of children with AGE (I, A) (strong recommendation, moderate-quality evidence).[3]

Racecadotril is a diesterified derivative of thiorphan which acts to increase the half-life of enterocyte methionine-enkephalin (a potent antisecretory agent). Racecadotril has been in use for the past 20 years in Europe and has been consistently useful in the management of diarrheal disease with an acceptable adverse effect profile.[4,5]

The aim of this study is to investigate whether prescribing Racecadotril plus oral rehydrating solution in pediatric gastroenteritis helps to decrease the hospital revisit rate within 72 hours due to gastroenteritis in comparison with oral rehydrating solution alone.

BACKGROUND

A recent meta-analysis assessed the efficacy of Racecadotril as an adjunct to ORS compared with ORS alone or with placebo. 9 RCTs involving 1348 children ages 1 month to 15 years with AGE were available for the analysis. The experimental treatment was compared with placebo, with no treatment (2 RCTs), and with kaolin–pectin (2 RCTs, the latter was not in line with the authors' objectives). There were 4 studies in the inpatient setting, and 5 studies in the outpatient setting. Compared with placebo, racecadotril significantly reduced the duration of

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diarrhea. The study found that some evidence that racecadotril is more effective than placebo or no intervention in reducing the duration of illness and stool output in children with acute diarrhoea. However, the overall quality of the evidence was limited due to sparse data, heterogeneity and risk of bias.[6]

Also, A systematic review of randomized controlled trials retrieved 58 trials from nine countries including six in comparison to placebo, 15 in comparison to various active treatments and 41 as add-on to various standard treatments, it was concluded that racecadotril is more efficacious than other treatments except for loperamide and has a tolerability like placebo and better than loperamide.[9]

A recent cost utility model found that the cost utility of racecadotril plus oral rehydration solution was favorable to oral rehydration solution (ORS) alone for the treatment of diarrhea in children under five years with acute watery diarrhea in four low-middle income countries.[7]

However, another metanalysis including seven RCTs, involving 1140 participants found that Racecadotril seems to be a safe drug but has little benefit in improving acute diarrhea in children under five years of age.[8]

Also, a randomized double-blinded placebo-controlled trial enrolled children between the age of 3 and 60 months who were admitted with severe acute gastroenteritis found that Racecadotril has no impact on the number of stools at 48 hours, the duration of hospital stay or the duration of diarrhoea.[10]

In a cohort study analyzed 568 845 admissions at 72 children's hospitals between July 1, 2009, and June 30, 2010, in the National Association of Children's Hospitals and Related Institutions, gastroenteritis was considered one of the 10 admission diagnoses with the highest readmission prevalence (readmission rate of 6.8%).[11]

Rational

In our setting, it was noticed that racecadotril was increasingly prescribed in outpatient setting for pediatric patients diagnosed with acute gastroenteritis even for cases showed mild or no signs of clinical dehydration trying to treat patients and decrease the disease progression that may reflects on hospital revisiting, so we tried to investigate such practice and its impact on hospital revisit rate in patient diagnosed with acute simple gastroenteritis.

OBJECTIVE

To compare the hospital revisit rate due to acute gastroenteritis within 72 hours among pediatric outpatients who were prescribed Racecadotril plus oral electrolyte replacement solution versus oral electrolyte replacement solution alone upon their initial visit to Al Wakra pediatric emergency center.

METHODOLOGY

Study design

This Study is a retrospective cohort study conducted at Al Wakra Hospital- HMC pediatric emergency department in the period between 1/1/2022 till 30/06/2022.

The study was approved by the hospital MRC, and data related to initial patients visit and hospital revisit within 72 hours was obtained through the hospital electronic medical records, then the initial and revisit diagnoses were validated by the research team to include only revisits due to gastroenteritis. The documented initial degree of dehydration and stool frequency for patients who revisited the hospital were also collected by research team.

Eligibility criteria

Children aged 3 months to 14 years visited Al Wakra Pediatric emergency department due to acute gastroenteritis and prescribed Racecadotril plus oral electrolyte replacement solution or ORS alone in outpatient setting in the period between 1/1/2022 till 30/06/2022.

Exclusions criteria

Children with a known diagnosis of liver or renal failure; children who had prescriptions of probiotics or any other antidiarrheal medication (loperamide), and children admitted with sever gastroenteritis required fluid resuscitation and inpatient admission.

Patients who were initially managed in inpatient setting.

Case group

Children visited AWH pediatric emergency department due to acute gastroenteritis and prescribed Racecadotril plus oral rehydrating solution in outpatient setting during the study period 1/1/2022 till 30/06/2022.

Control group

Children visited AWH pediatric emergency department due to acute gastroenteritis and prescribed only oral rehydrating solution in outpatient setting during the study period 1/1/2022 till 30/06/2022.

Outcome measures

The primary outcome measure will be the hospital revisit rate due to gastroenteritis within 72 hours from initial visit in pediatric patients with gastroenteritis and managed as outpatients in both the case group, and control group.

Statistical analysis

Relative risk of hospital revisit between the two groups will be calculated to assess the impact of Racecadotril on this outcome.

RESULTS

2505 pediatric patients were included, 520 patients were enrolled in the control group, and 1985 patients were included in the case group. Most patients in both groups were 1 to 5 years old (67% in control group, and 59% in case group) (Table 1).

Table 1. Demographics		
	Group 1 (n 520)	**Group 2 (n 1985)**
Age		
< 1 Year of age	28% (n 145)	11% (n 218)
1-5 Years of age	67% (n 348)	59% (n 1171)
>5 Years of age	5% (n 27)	30% (n 596)
Gender		
Male	46% (n 239)	59% (n 1171)
Female	54% (n 281)	41% (n 814)

Hospital revisit rate

520 patients were included in the control group in which 52 patients had revisited the hospital with 72 hours. After that research team cheeked the revisit diagnoses to include 39 patients from this group who revisited the hospital due to gastroenteritis, with hospital revisit rate of 7.5%.

Same process was done for the case group, 1985 patients were included in which 199 patients revisited the hospital through 72 hours from the initial visit, and 142 patients revisited the hospital due to gastroenteritis with hospital revisit rate of 7.1%.

So, pediatric hospital revisit rate within 72 hours due to gastroenteritis was slightly less in case group 7.1% in comparison to 7.5% in control group (Relative risk 0.95, 95% CI 0.68 to 1.34) (Table 2).

Table 2. Patient readmitted through due to gastroenteritis		
	Group 1 (n 520)	**Group 2 (n 1985)**
Patient readmitted due to gastroenteritis	7.5% (n 39)	7.1% (142)

The excluded hospital revisit diagnoses were mainly related to upper respiratory infections for example, otitis media, pharyngitis and flu like illness.

Statistical analysis

Relative risk	0.9538
95% CI	0.6783 to 1.3413
z statistic	0.272
Significance level	P = 0.7858
NNT (Benefit)	288.727
95% CI	46.435 (Harm) to ∞ to 35.134 (Benefit)

Also, the degree of dehydration and average number of stools were assessed for patients who revisited the hospital due to gastroenteritis within 72 hours. 88% of them showed mild or no signs of clinical dehydration in their initial visit with average of 4 episodes of loss stool per day (Table 3).

Table 3		
	Case Group hospital Revisited patients (n 39)	**Control Group hospital Revisited patients (n 142)**
Degree of dehydration in initial visit		
No signs of clinical dehydration	77 %	93 %
Mild dehydration	23 %	7 %
Average number of stools per day in initial visit	4 episodes per day	3.5 episodes per day

DISCUSSION

Gastroenteritis in general is a common childhood disease, and it is considered one of the major diagnoses with the highest readmission prevalence with a readmission rate of 6.8% (Berry JG, et al), that may increase the burden on patients, family and health care system as well. therefore, this study tried to investigate the impact of Racecadotril as antisecretory medication on pediatric outpatient hospital revisit rate due to acute gastroenteritis especially that it was noticed that Racecadotril was increasingly prescribed in our outpatient setting for pediatric acute gastroenteritis cases regardless to the severity or hydration status.

This study was carried out retrospectively on pediatric outpatients with acute gastroenteritis who visited the hospital pediatric emergency center during the study period and prescribed ORS alone or Racecadotril plus ORS, comparing hospital revisit rate among the two study groups. It was noticed that study patients who revisited the hospital in both groups showed mild or no signs of clinical dehydration in their initial hospital visits. That was expected as most patients especially less than 5 years of age who admitted with moderate to severe dehydration were candidate for inpatient management which is beyond our study scope.

The study found that there was insignificant difference between control group and case group regarding hospital revisit rate (7.5%, 7.1% respectively, Relative risk 0.95, 95% CI 0.68 to 1.34), concluding that Racecadotril plays insignificant role on hospital revisit rate in acute gastroenteritis pediatric outpatients with mild or no signs of clinical dehydration.

We didn't find previous trials assessed hospital revisit rate for pediatric patients prescribed racecadotril for acute pediatric gastroenteritis management to compare our result with, however, regarding the efficacy of Racecadotril in general, a metanalysis including seven RCTs, involving 1140 participants found that Racecadotril seems to be a safe drug but has little benefit in improving acute diarrhea in children under five years of age,[8] also another randomized double-blinded placebo-controlled trial enrolled children between the age of 3 and 60 months who were admitted with acute gastroenteritis found that Racecadotril has no impact on the number of stools at 48 hours, the duration of hospital stay or the duration of diarrhea.[10]

On other hand, another two-trial found that Racecadotriol was more effective than placebo or no intervention except for loperamide in reducing the duration of illness and stool output in children with acute diarrhea.[6,9]

As per CDC guide for managing acute gastroenteritis among

children, Racecadotril, an enkephalinase inhibitor does not slow intestinal transit or promote bacterial overgrowth, and it might be a useful adjunct in pediatric gastroenteritis, but more studies are needed to support that.

Racecadotril wasn't mentioned as an option in both of National Institute for Health and Care Excellence, and American Family Physicians Society guidelines for managing gastroenteritis in children.[12,13]

According to European Society for Pediatric Gastroenterology, Hepatology, and Nutrition's evidence-based guideline for the management of acute gastroenteritis in children in Europe, Racecadotril may be considered in the management of acute gastroenteritis (Strength of evidence and grade of recommendation II, B). However, well-designed prospective studies of efficacy and safety should be carried out in outpatient children.[14]

Limitations of study

Patients' data were collected retrospectively, and It was difficult to assess the impact of Racecdotril on number of stools/days, or duration of diarrhea in the study population as there was no follow-up for most patients after initial visit.

CONCLUSION

This study does not demonstrate a significant reduction in hospital revisiting rate in acute gastroenteritis pediatric patients managed at outpatient setting who prescribed Racecdotril plus ORS over those who prescribed ORS alone, especially for those with no or mild signs of clinical dehydration.

Further prospective studies are needed to combine this outcome with other outcomes like number of stools/day and diarrhea duration to provide a wider review for Racecdotril use at outpatient setting.

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