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# A Comparative Study of Racedrotril and Single Dose Octreotide in Acute Diarrhoea

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**Abstract**

To assess the efficacy of single dose of octreotide and compare it with another antisecretory agent racecadotril in the management of acute infective diarrhoea. A Randomised control study was carried out on the acute diarrhoeal disease patients who were admitted to the Department of General Medicne at R.L. Jalappa Hospital and Research Center, Tamaka, Kolar. 90 patients (≥ 18 years of age) with moderate to severe acute diarrheal illness of less than 5 days duration were randomly allotted into 3 treatment categories of 30 patients each with the help of random number table method after taking written informed consent from them. The control group received only fluids and antibiotics, the racecadotril group received fluid, antibiotics and oral racecadotril at dose of 1.5 mg/kg three times a day. The octreotide group received octreotide (100 microgram stat at the time of hospitalization) along with fluid and antibiotics. Fluid was given according to the severity of dehydration. Intravenous ciprofloxacin and metronidazole were given to all the patients. A detailed history and clinical examination was done in all patients. Routine blood investigations and stool examination was carried out. All the patients in the three groups were matched for age and sex. 81.1% of patients (73/90) were males and majority of them belonged to 25-44 age group. 74.4% of them (67/90) belonged to Lower Class as per Modified B G Prasads Classification. 47 out 90 were from Rural Area. This study results have shown that provide that Octreotide is an effective treatment for acute infective diarrhoea in adults who were admitted and were of unknown etiology. As compared with the control and Racecadotril groups, the Octreotide group had clinically consistent and significant results with respect to the Duration of diarrhoea, Stool Volume and Fluid requirement for the management.

**Keywords:** Study, Diarrhoea, Fluid, Bacteria, Dehydration.

## Introduction

Infections with bacteria, viruses, and parasites are the most important cause of acute diarrhea; while bacteria are the leading cause of acute diarrhea in the developing countries, viruses are its most frequent cause in industrialized countries.[1] Transmission occurs in most cases *via* contaminated water or foodborne.[2] Acute infectious diarrhea continues to cause high morbidity and mortality worldwide. Although oral rehydration therapy has reduced the mortality associated with acute diarrhea, the diarrheal attack remains unchanged and stool volume often increases during rehydration process.[3]

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As dehydration is the most frequent cause of death in acute diarrhea, oral rehydration therapy is the most important component of treatment. Its increasing use has been associated with a major reduction in deaths due to acute diarrhea.[1] While infectious acute diarrhea tends to be self-limiting in otherwise healthy people, it is not only unpleasant but also has social impact such as lost working days.[4] Moreover, even in adults in industrialized countries, diarrhea may lead to death due to visceral failure secondary to dehydration, particularly in the elderly.[5]In recent years, the standard of therapy of acute diarrhea involves antibiotics, fluid and anti-diarrheal agents. There are a variety of anti-diarrheal agents already available in the market– e.g. racecadotril, loperamide, diphenoxylate etc. However all these agents have many drawbacks.

A number of potential targets for antisecretory agents have emerged which include loci within the enterocyte (chloride channel, calcium calmodulin) and recently enteric nerves and endogenous mediators (5-HT, substance P, VIP).[6]

Racecadotril, an enkephalinase inhibitor, potentiates the action of enkephalins which are endogenous opiods, antisecretory activity occurs mainly through delta receptor activation.2However its antisecretory activity is weak.[6-9]

Octreotide is a somatostatin analogue which has documented antisecretory activity in neuroendocrine tumors of GIT like VIPoma, gastrinoma and carcinoid syndrome.[10,11] There are reports that somatostatin and its analogues can inhibit intestinal secretions in VIPoma patients in absence of reduction of plasma VIP indicating that antisecretory activity may be operating through a direct effect either on enterocyte nervous system or enterocyte itself.[11]

In view of the antisecretory role of octreotide in neuroendocrine tumors and cholera,[12] and much data available about the role of octreotide in acute gastroenteritis. So, this was planned to establish the role and to fill up the lacunae regarding octreotide in acute gastroenteritis.

## Objectives

To assess the efficacy of single dose of octreotide and compare it with another antisecretory agent racecadotril in the management of acute infective diarrhoea.

## Materials and Methods

A Randomised control study was carried out on the acute diarrhoeal disease patients who were admitted to the Department of General Medicne at R.L. Jalappa Hospital and Research Center, Tamaka, Kolar. 90 patients (≥ 18 years of age) with moderate to severe acute diarrheal illness of less than 5 days duration were randomly allotted into 3 treatment categories of 30 patients each with the help of random number table method after taking written informed consent from them.

The control group received only fluids and antibiotics, the racecadotril group received fluid, antibiotics and oral racecadotril at dose of 1.5 mg/kg three times a day. The octreotide group received octreotide (100 microgram stat at the time of hospitalization) along with fluid and antibiotics. Fluid was given according to the severity of dehydration. Intravenous ciprofloxacin and metronidazole were given to all the patients. A detailed history and clinical examination was done in all patients. Routine blood investigations and stool examination was carried out.

**Study Variables**

1. Frequency of stools- Number of stools passed by the patients in 24 hours was counted by attendant and duty doctor.
2. Quantity of stool per day- Patients' attendants were asked to bring calibrated jar and instructed to collect stool in jar. Quantity of each stool was noted by the duty doctor.
3. Fluid requirement per day- fluid requirement in litres was calculated by adding total amount of IV fluid plus oral intake of liquids.

Statistical analysis – Data were entered in excel sheet and analyzed with help of IBM SPSS 22 Version. Quantitative data were summarized in form of mean ± S.D and average value of different treatment groups were compared using ANOVA test (analysis of variance) and post hoc test. Qualitative data were summarized in form of proportions and analyzed using chi square test. For all statistical analysis, level of confidence was kept 95%.

Institutional Ethical Clearance was taken before the study was started. All the information was kept confidential and was used only for research Purpose. Written informed consent was taken from all the participants who took part in the study.

## Results

All the patients in the three groups were matched for age and sex. 81.1% of patients (73/90) were males and majority of them belonged to 25-44 age group. 74.4% of them (67/90) belonged to Lower Class as per Modified B G Prasads Classification. 47 out 90 were from Rural Area.

Table 1 shows mean (±SE) frequency of stools in all groups at the time of admission. On day 2 the average frequency of stools passed in the octreotide group was 2.05±1.71.It was almost the same in the control and racecadotril group at 6.54±2.41 and6.21±2.57 respectively ($p<0.001$). Diarrhea stoppedin 53.3% of patients (16/30) in octreotide group by day 3 and allthe patients by day 4. Nearly 43.3% of patients (13/30) in controlgroup and 50% (15/30) in racecadotril group continued to have diarrhea by day 4.

**Table 1: Day-wise average frequency of stools in different treatment groups**

| Day | Control Group | Racecadotril Group | Octreotide Group | ANOVA | Post hoc test (Tukeys test) p value | | |
|---|---|---|---|---|---|---|---|
| | | | | | Control vs Racecadotril | Control vs Octreotide | Racecadotril vs Octreotide |
| Admission | 11.47±2.91 (n=30) | 12.67±3.12 (n=30) | 13.83±7.21 (n=30) | >0.05 | >0.05 | >0.05 | >0.05 |
| 2ND | 6.54±2.41 (n=28) | 6.21±2.57 (n=30) | 2.05±1.71 (n=30) | <0.001 | >0.05 | <0.001 | <0.001 |
| 3RD | 3.59±1.41 (n=26) | 3.13±1.69 (n=24) | 1.63±0.67 (n=14) | | | | |
| 4TH | 1.97±1.09 (n=13) | 2.05±1.31 (n=15) | _ | | | | |
| 5TH | 1.71±0.39 (n=6) | 1.78±0.29 (n=3) | _ | | | | |

The mean (±SE) quantity of stools passed (in ml) was same at the time of admission in all three groups (Table 2). On day 2 it was 382.1±178.17 ml in octreotide group, as compared to 717.0±292.84 ml in control group and 597.47±267.14 in racecadotril group. Thus there was a 57% and 39% reduction in stool quantity in octreotide group compared from control and racecadotril group respectively.

**Table 2: Day-wise average quantity of stools passed (in ml) in different treatment groups**

| Day | Control Group | Racecadotril Group | Octreotide Group | ANOVA | Post hoc test (Tukeys test) p value | | |
|---|---|---|---|---|---|---|---|
| | | | | | Control vs Racecadotril | Control vs Octreotide | Racecadotril vs Octreotide |
| Admission | 1208±421.00 (n=30) | 1128.00±389.05 (n=30) | 1270±967.31 (n=30) | >0.05 | >0.05 | >0.05 | >0.05 |
| 2ND | 717.0±292.84 (n=28) | 597.47±267.14 (n=30) | 382.1±178.17 (n=30) | <0.001 | >0.05 | <0.001 | <0.001 |
| 3RD | 381.64±174.8 (n=26) | 324.37±171.38 (n=24) | 178.67±55.64 (n=14) | | | | |
| 4TH | 247.4±88.49 (n=13) | 212.2±102.14 (n=15) | _ | | | | |
| 5TH | 189.52±26.29 (n=6) | 133.00±29.26 (n=3) | _ | | | | |

On day 1 the average fluid (in litres) required in octreotide group was 5.03±1.71 litres, as compared to 5.23±0.81 litres in control and 5.14±0.50 in racecadotril group respectively (Table 3). The respective values on day 2 were 3.47±0.39 litres for octreotide group; while it was 4.23±0.49litres for control group and 4.11±0.63 litres for racecadotril group respectively. Thusmean (±SE) quantity of fluid required was least in octreotide group (p<0.001).

**Table 3 : Mean±SD average quantity of fluid required (intravenous and oral, in litres) in all 3 groups**

| Day | Control Group | Racecadotril Group | Octreotide Group | ANOVA | Post hoc test (Tukeys test) p value | | |
|---|---|---|---|---|---|---|---|
| | | | | | Control vs Racecadotril | Control vs Octreotide | Racecadotril vs Octreotide |
| Admission | 5.23±0.81 (n=30) | 5.14±0.50 (n=30) | 5.03±1.71 (n=30) | >0.05 | >0.05 | >0.05 | >0.05 |
| 2ND | 4.23±0.49 (n=28) | 4.11±0.63 (n=30) | 3.47±0.39 (n=30) | <0.001 | >0.05 | <0.001 | <0.001 |
| 3RD | 3.32±0.74 (n=26) | 3.55±0.55 (n=24) | 3.18±0.21 (n=14) | | | | |
| 4TH | 3.16±0.63 (n=13) | 3.14±0.41 (n=15) | _ | | | | |
| 5TH | 3.03±0.09 (n=6) | 3.07±1.64 (n=3) | _ | | | | |

**Discussion**

Diarrhea occurs as a result of increased intestinal secretion or decreased intestinal absorption or a combination of both. It is now well established that enteric nervous system is involved in the promotion of intestinal secretory process. A potent inhibitor of enkephalinase, racecadotril offers a novel and promising approach to the control of secretory diarrhea.[7]

Eduardo et al. showed that treatment with racecadotril and oral rehydration therapy was more effective than oral rehydration alone in the treatment of acute watery diarrhea in children which were consistent with the present study findings.[9]

Loperamide and diphenoxylate are orally active antidiarrheal agent act by intestinal μ opiate receptors, leading to increased intestinal transit time. Side effects include constipation and bacterial overgrowth and hence can be harmful hence their use is controversial.

Octreotide has also been evaluated in a randomized studyin patients with cholera by Moid I Khan et al. Patients were treated conventionally with fluid and antibiotics, but in addition were randomized to receive octreotide or placebo. There was a reduction in stool volume, frequency and duration of diarrhea with octreotide.[12] Similar results were observed by this study as well.

The results of the present study show that octreotide is effective in treatment of acute watery diarrhea. As compared to the control and racecadotril group, the octreotide group had clinically consistent and significant (p<0.001) reduction in the frequency and volume of stools passed. The fluid requirement was also least in the octreotide group. Similar findings were observed in a RCT done by Mehta S et al at a tertiary care hospital.[13]

**Conclusion**

This study results have shown that provide that Octreotide is an effective treatment for acute infective diarrhoea in adults who were admitted and were of unknown etiology. As compared with the control and Racecadotril groups, the Octreotide group had clinically consistent and significant results with respect to the Duration of diarrhoea, Stool Volume and Fluid requirement for the management.

Hence, octreotide as an antisecretory agent is very effective in management of acute infective diarrhoea in adults. Moreover, that study unfortunately has not

reported on adverse events observed with the two treatments. Additional studies will be required to define the benefit/ risk ratios of octreotide and racecadotril in patients with severe diarrhoea requiring hospitalization.

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