Original Article

Efficacy of Lactobacillus Reuteri in Acute Watery Diarrhea

Muhammad Aqeel Khan[1], Muhammad Bilal Khattak[2], Arshia Munir[3] and Irum Naz[3]

ABSTRACT

Objective: To evaluate the efficacy of lactobacillus reuteri in acute watery diarrhea
Study Design: Randomized Clinical Trial study.
Place and Duration of Study: This study was conducted at the Department Pediatrics, KGMC / HMC Peshawar from 24th April to 23th October 2015
Materials and Methods: This RCT included 96 patients from age 6 to 55 months admitted as a case of acute watery diarrhea were enrolled in the study. After consent taken from attendants, the patients were randomly assigned to one of the study groups; either L. reuteri (5drops or 100 million cfu per day of L. reuterior) or the other group with placebo and the therapy was given for 5 days in each case. The outcome was measured in severity (frequency) and duration of the diseased.
Results: Out of 96 patients, half were subjected to L. reuteri. L.reuteri was given in a dose of 5 drops daily and patients were observed for effectiveness. The effectiveness was observed in 58 patients 24 (50%) from the placebo group and 34 (70%) from the L.reuteri group. This showed that L. reuteri was more effective than placebo in children with acute watery diarrhea with a P value of <0.05.
Conclusion: The study showed that lactobacillus reuteri group not only decreased the severity of the acute watery diarrhea but it also decreased the duration of the disease as compared to the placebo group.
Key Words: Acute watery diarrhoea, probiotics, frequency of stools

Citation of article: Khan MA, Khattak MB, Munir A, Naz I. Efficacy of Lactobacillus Reuteri in Acute Watery Diarrhea. Med Forum 2017;28(11):7-11.

INTRODUCTION

The diarrheal is mainly classified under four headings i.e. acute watery diarrhea, acute dysentery (acute bloody diarrhea), persistent and diarrhea with malnutrition[1]. Acute watery diarrhea is occurs suddenly and ranges from hours to days and defined as a increase in the water component of stools or big watery stool and /or an increase in the frequency of stool than the usual one i.e. more than 3 in 24 hours, with or without other symptoms like fever and vomiting[1,2,3] . In most of the cases acute watery diarrhea lasts for or less than a week and never equal to or more than 14 days. With more than 1.4 of the 9 million child deaths occurred due to diarrhea and almost half of this mortality burden was shared by five countries of the world including Pakistan. The incidence of acute watery diarrhea is quite common before three years of age ranges from 0.5 to 1.9 episodes per child per year[4-7].

[1.] Department of Pediatrics / Medicine[2], KGMC / HMC Peshawar.
[3.] Department of Pediatrics, KMC / HMC Peshawar.

Correspondence: Dr. Muhammad Aqeel Khan, Assistant Professor Department of Pediatrics KGMC / HMC Peshawar.
Contact No: 0333 9343865
Email: drarshia@yahoo.com

Received: May 10, 2017; Accepted: July 03, 2017

Oral rehydration therapies (ORT) is playing vital role in managing acute watery diarrhea with no or some dehydration[8]. Though the composition of oral rehydration solution heals the dehydration status or helps dehydration not to happen, it neither shortens the duration of the illness nor reduces the stool loss[9,10]. Probiotics including Lactic acid bacteria are non pathogenic bacteria which is important constituent of the normal flora. The probiotics have multiple beneficial effects on human beings and produce multiple beneficial effects for human beings like helping in lactose intolerance, all types of diarrhea. It also helps in healing the peptic ulcer disease, stimulates the immune system and helps in decreasing or healing allergies including atopy and lower allergic airway disorder[11]. The World Health Organization defines the probiotics as living organisms which in certain amount produce health benefit effects on the body of the host [12]. Studies have strongly favored that probiotics are extremely beneficial effects on acute watery diarrhea. The probiotics not only decreases the frequency of the diarrheal diseases but also decreases the duration of the diarrheal diseases. Probiotics along with the oral rehydration therapy it has got a vital effect on the severity and duration of the diarrheal diseases[13].

The rationale of this study was to determine the efficacy of lactobacillus reuteri in patients presenting with acute watery which is easy to introduce to all age groups and study on this very probiotics has not been done in our setup.

MATERIALS AND METHODS

This randomized controlled trial was conducted at the department of Paediatrics, KGMC / HMC, Peshawar. Non-probability consecutive sampling was used for sample selection. Using WHO calculator sample size in each group was 48 using P1 = 74% and P2 = 45% power of test is 90 % and level of confidence is 5 %. Both genders with age range between 6months to 5 years of age and duration of illness less than 7 days were included in the study. Clinical signs of some dehydration (skin pinch goes back slowly <2sec, sunken eyes and eager to drink) which was confirmed clinically. All patients who had some dehydration but could not tolerate probiotic orally. All patients with chronic diarrhea, blood in stool, using antibiotics/probiotics, in coma, shock and persistent vomiting were excluded from the study.

All patients who presented with acute diarrheal illness were admitted to pediatrics ward. The biodata, anthropometry and status of the dehydration were documented at the time of admission. All children were randomly assigned whether they will receive Lactobacilli reuteri (dose 5drops or 100million cfu per day irrespective of weight) or placebo. The therapy was started at the time of admission according to random group allocation. Detailed history and clinical examination were performed for all patients. All patients were managed using standard management protocol for diarrhea including ORT (oral rehydration therapy). Relevant laboratory investigations were performed such as stool R/E, Serum electrolytes, Full blood count.

The data was analyzed on SPSS version 20. Descriptive statistics were used to calculate Mean ± SD for numerical variables like age and duration of illness. Frequencies and percentages were calculated for categorical variables like gender, and proportion of patient having shown clinical efficacy in both the groups. Efficacy was stratified among age, gender and duration of illness to control effect modifiers. Chi-square test was used to determine the difference in the proportion of two groups keeping p–value of≤ 0.05 as significant.

RESULTS

A total of 96 cases of children presenting with acute watery diarrhea were included in the study and followed up for efficacy of treatment. Amongst 96 patients 58 (60.4%) were males and 38(39.6%) were females. The maximum number of patients (more than 60%) was in the age groups 6 to 18 months and only a small percentage in age groups more than 55months. The minimum age of our sample was 6months and the maximum age was 60months with a mean age of 20.3 months.

Effectiveness of treatment was observed in different genders .Among 58 male patients 31 patients (53%) improved with treatment, while in 38 female patients treatment was effective in 27 patients (71%) with P. Value of 0.093 as given in Table 1.

Table No.1: Effectiveness of treatment among both genders n=96

Effectiveness	Gender of the patient			P. value
	Male	Female	Total	
Effective	31	27	58	
Non effective	27	11	38	
Total	58	38	96	0.093

These patients were divided equally in placebo and h lactobacillus reuteri group. They were further subdivided into different age groups with maximum number of patients in age group 6-18months. 30 patients from the placebo and 31 from the L.reuteri group belonged to this age group given in table 02.

Table No.2: Age wise distribution into both treatment groups n=96

Age in Months	Lact. Reutri not given	Lact Reutri given	Total
6-18 months	30	31	61
19-30	08	07	15
31-42	05	02	07
43-54	05	05	10
>55	00	03	03
Total	48	48	96

While stratifying children with acute diarrhea with regards to gender groups, we found that among 58 male patients 26 (45%) were given L.reuteri and among 38 female patients 22 (58%) were subjected to L.reuteri group as shown in table 3.

Table No.3: Effectiveness of treatment among both genders n = 96

Treatment group of patient	**Gender of the patient**		
	Male	**Female**	**Total**
L. Reuteri not given	32	16	48
L. Reuteri given	26	22	48

Table No.4: Cross tabulation of effectiveness among both treatment groups

Efficacy of treatment	Treatment group of patients		Total	P.value
	L. Reuteri Not given	L. Reuteri Given		
Effective	20	31	51	
Non Effective	28	17	45	0.04
Total	48	48	96	

On the basis of operational definition efficacy was observed in 58 patients 24 (50%) from the placebo group and 34 (70%) from the L.reuteri group. This showed that L.reuteri was more effective than placebo

in children with acute watery diarrhea with a p value of <0.05 given in table 4 and 5.

Table No.5: Effectiveness of treatment among different age groups

Age group	Efficacy of treatment			P.value
	effective	Non effective	Total	
6-18	36	25	61	
19-30	8	7	15	
31-42	4	3	7	0.015
43-54	7	3	10	
>55	3	0	3	
	58	38	96	

Duration of illness was observed in both groups. Among 48 patients who were given L.Reuteri, 30 patients (62.5%) had duration of illness less than 36 hours. In the placebo group only 19 patients (39.5%) got improved in 36hours with p value of 0.041 as shown in table 6.

Table No.6: Duration of illness in both groups of patients

Groups of patients	Duration of illness		
	0-36 hours	37-72hours	Total
L.Reuteri not given	19	29	48
L.Reuteri given	30	18	48
Total	49	47	96

p Value : 0.041

DISCUSSION

Acute watery diarrhea is one of the important causes of mortality throughout the world. The mortality due to diarrheal diseases in the early days i.e. 70s was as high as 5 million childhood deaths globally each year. The invention of oral rehydration solution played an unbelievable role in reduction of deaths from dehydration secondary to acute watery diarrhea especially under five years of age [15]. Acute diarrheal diseases are the second to pneumonia in causing under five mortality globally [15,16].

The research and original work done till date about the role of various probiotics; have confirmed its efficacy in acute watery diarrhea. Not only nonpathogenic bacteria but also yeast has been found useful in this regard. Lactobacilli and bifidobacteria make major part of infants and early childhood human flora. A Cochrane review including 56 trials confirms the role of probiotics in decreasing the severity and duration of the diarrhoeas[17]. The efficacy about various probiotics has been proved through original work including lactobacilli [L.rhamnosus GG, L.reuteri(ATCC 55730), L. acidophilus, LB, Bifidobacteria, Saccharomyces boulardii, and Streptococcus thermophilus [18-21].

These findings are quite similar to the results of my study which showed that 70% of patients in L. reuteri group responded to treatment. The current study showed that children receiving L. reuteri DSM 17938; on days 2 and 3 were statistically significantly more likely to be diarrhea free and passed significantly fewer stools compared with those receiving placebo. Internationally study conducted found almost the same results; where they found that on second day of treatment only 26% of patients receiving L.reuteri had watery diarrhea compared with 81% of those receiving placebo ($p=0.0005$)[22]. The slightly difference of effectiveness compared to the above study may be related to the dose of L. reuteri given to these patients. Another reason for the difference may be due to the timing of administration of L. reuteri, since most of our patients usually present late in the illness. The efficacy of this probiotics is much effective when started earlier at the onset of the disease.

We found Lactobacilli reurteri DSM 17938 extremely effective and safe in the treatment of acute watery diarrhea and can be used in acute watery diarrhea irrespective of age and status of the diarrhea. Almost same results have been documented by other international studies where they found the efficacy and safety of this strain[23]. So the strain can easily be recommended by various physicians and no doubt the children included in this study i.e. six to 55 months is the most crucial age and some dehydration as was in our study case is carrying the same value. Therefore, we can argue with ease that the L.reuteri can easily be recommended in all crucial age and less severe type of diarrhea with confidence. L. reuteri is no doubt an outstanding probiotics and has been in use of food additives regularly to enhance safety of the human gut, as probiotic has been extensively studied and is widely used as food additives [24].

Two randomized controlled trials were documented in a systemic review[25]. One study included 74 cases with age range 6 to 36 months, with treatment duration of seven days and having L. reuteri group and a placebo group. There was significant reduction in the frequency and duration of acute diarrhea as compared to the placebo grou (3.3 ± 2.1 vs. 2.1 ± 1.7 days, respectively; $P < 0.03$)[26]. The second RCT was having a total number of 127 patients with age range of 3 to 60 months where patients were randomly assigned to L.retuteri or no intervention group. The group with L.reuteri had marked improvement in severity in frequency of acute diarrhea (mean difference (MD) −33.1 h, 95 % confidence interval (CI) −42.6 to −23.6) and duration of the disease period (4.3 ± 1.3 vs. 5.5 ± 1.8 days, respectively; $P < 0.001$) as compared to the control group [27].

The two RCTs of this systemic review showed that L. reuteri DSM 17938 is far better in efficacy as compared to placebo or no intrervention. Our study results closely

resemble this systemic review justifying the effect of L.reuteri resulting in reducing the duration of diarrhea and improving consistency of stool.

In another prospective, randomized and placebo-controlled study where they focus on the efficacy of of L. reuteri ATCC 55730 in children hospitalized with acute diarrhea, 50 cases, aged 6–36 months, were randomized to receive L. reuteri two times a day a dose of 10^8 CFU for the whole time period admission in the hospital or for 5 days, or a matching placebo. Rehydration therapy was the same in either group. They found that mean duration of the diarrhea was 2.3 days in L.reuteri group as compared to the placebo which was 2.9 days. On the very second day of the therapy the watery diarrhea persisted in 64% of the L. reuteri group while 84% in the placebo group, mean frequency of diarrhea (1.9 in the Lactobacillus reuteri vs. 3.4 in the placebo group. The result of this study was similar to our study which also showed a significant reduction in severity of diarrheal illness in L. reuteri treated group [28].

CONCLUSION

The study showed that lactobacillus reuteri is beneficial in the treatment of the children with acute watery diarrhea. It has dual effect i.e. it not only reduces the duration of diarrhea but also improves the consistency of stool in hospitalized patients.

Recommendations: More study and data is needed to confirm the efficacy of the Lactobacilli reuteri role in the treatment of the acute watery diarrhea in both admitted and outdoor patients. Moreover, on large scale studies are also recommended to evaluate the mechanisms of action of L. reuteri DSM 17938.

Author's Contribution:

Concept & Design of Study:	Muhammad Aqeel Khan
Drafting:	Muhammad Bilal Khattak
Data Analysis:	Arshia Munir, Irum Naz
Revisiting Critically:	Muhammad Aqeel Khan, Muhammad Bilal Khattak
Final Approval of version:	Muhammad Aqeel Khan

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Boschi-Pinto C, Velebit L, Shibuya K. Estimating child mortality due to diarrhea in Organ developing countries. Bull World Health 2008; 86(9): 710-17.
2. Soriano-Gabarro M, Mrukowicz J, Vesikari T, Vestraeten T. Burden of rotavirus disease in European Union countries. Pediatr Infect Dis J 2006;25(1):7-11.
3. Kosek M, Bern C, Guerrant RL. The global burden of diarrheal disease, as estimated from studies published between 1992 and 2000. Bull World Health Organ 2003; 81(3):197-204.
4. Ogbo PU, Aina BA, Aderemi-Williams RI. Management of acute diarrhea in children by community pharmacist in Lagos, Nigeria. Pharmacy Practice 2014;12 (1): 1-6.
5. Thapar N, Sanderson IR. Diarrhea in children: an interface between developing and developed countries. Lancet 2004; 363: 641-53.
6. Guarino A, Albano F, Ashkenazi S. Infectious Diseases evidence-based guidelines for the management of acute gastroenteritis in children in Europe. J Pediatr Gastroenterol Nutr 2008;46(5): 619–21.
7. Hussein A, Ibrahim MIM. Management of diarrhea cases by community pharmacists in 3 cities of Pakistan. East Mediterr Health J 2012; 18(6):635-40.
8. Saengcharoen W, Lerkiatbundit S. Practice and attitude regarding the management of childhood diarrhea among pharmacies in Thailand. Int J Pharm Pract 2010; 18(6): 3213-31.
9. Koletzko S, Osterrieder S. Acute infectious diarrhea in children. Dtsh Arztebl Int 2009;106 (33): 539-48.
10. Salazar-Lindo E, Miranda-Langschwager P, Campos-Sanchez M, Chea-Woo E, Sack RB. Lactobacillus casei strain GG in the treatment of infants with acute watery diarrhoea: a randomized, double-blind, placebo controlled clinical trial. BMC Pediatr 2004; 4: 18-25.
11. Masood MI, Qadir MI, Shirazi JH, Khan IU. Beneficial effects of lactic acid bacteria on human beings. Crit Rev Microbiol. 2011; 37(1): 91-8.
12. Francavilla R, Lionetti E, Castellaneta S, Ciruzzi F, Indrio F, Masciale A, et al. Randomised clinical trial: Lactobacillus reuteri DSM 17938 vs. placebo in children with acute diarrhoea--a double-blind study. Aliment Pharmacol Ther 2012;36 (4):363-9.
13. Ng SC, Hart AL, Kamm MA, Stagg AJ, Knight SC. Mechanisms of action of probiotics: recent advances. Inflamm Bowel Dis 2009;15:300–10.
14. National Institute for Health and Clinical Excellence. Diarrhoea and vomiting: diagnosis, assessment and management in children younger than 5 years. Clinical Guideline.[cited on March 5 ,2012]
15. Elliott EJ. Acute Gastroenteritis in Children. BMJ 2007;334:35–40.
16. Forsberg BC, Petzold MG. Diarrhoea case management in low-and middle-income countries –an unfinished agenda. Bulletin of the WHO Jan 2007;85(1).

17. Allen SJ, Martinez EG, Gregorio GV, Dans LF. Probiotics for treating acute infectious diarrhoea. Cochrane Database Syst Rev 2010;11: CD003048.
18. Jonkers D, Stockbrügger R. Review article: probiotics in gastrointestinal and liver diseases. Aliment Pharmacol Ther 2007;26:133–48.
19. Szajewska H , Skorka A , Dylag M . Meta-analysis: Saccharomyces boulardii for treating acute diarrhoea in children. Aliment Pharmacol Ther 2007;25: 257–64.
20. Szajewska H, Skórka A, Ruszczyński M, Gierus zczak-Białek D. Meta-analysis: Lactobacillus GG for treating acute diarrhea in children. Aliment Pharmacol Ther 2007; 25: 871–81.
21. Szymański H, Pejcz J, Jawień M, Chmielarczyk A, Strus M, Heczko PB. Treatment of acute infectious diarrhoea in infants and children with a mixture of three Lactobacillus rhamnosus strains–a randomized, double-blind, placebo-controlled trial. Aliment Pharmacol Ther 2006; 23: 247–53.
22. Shornikova AV, Casas IA, Isolauri E, Mykkänen H, Vesikari T. Lactobacillus reuteri as a therapeutic agent in acute diarrhea in young children. J Pediatr Gastroenterol Nutr 1997;24: 399–404.
23. Savino F, Cordisco, Tarasco V, Palumeri E, Calabrese R, Oggero R, et al. Lactobacillus reuteri DSM 17938 in infantile colic: a randomized, double-blind, placebo-controlled trial. Pediatr 2010;126:526–33.
24. Indrio F, Riezzo G, Raimondi F, Bisceglia M, Filannino A, Cavallo L, et al. Lactobacillus reuteri accelerates gastric emptying and improves regurgitation in infants. Eur J Clin Invest 2011; 41:417–22.
25. Szajewska H, Urbańska M, Chmielewska A, Weizman Z, Shamir R. Meta-analysis: Lactobacillus reuteristrain DSM 17938 (and the original strain ATCC 55730) for treating acute gastroenteritis in children. Benefic Microbes 2014;24: 1–9.
26. Dinleyici EC, PROBAGE Study Group. Vandenplas Y. Lactobacillus reuteri DSM 17938 effectively reduces the duration of acute diarrhoea in hospitalised children. Acta Paediatr 2014
27. Francavilla R, Lionetti E, Castellaneta S, Ciruzzi F, Indrio F, Masciale A, et al. Randomised clinical trial: Lactobacillus reuteri DSM 17938 vs. placebo in children with acute diarrhoea--a double-blind study. Aliment Pharmacol Ther 2012;36(4):363-9.
28. Eom TH, Oh EY, Kim YH, Lee HS, Yang PS, Kim DU, et al. The therapeutic effect of Lactobacillus reuteri in acute diarrhea in infants and toddlers. Korean J Ped 2005;48: 986-89.