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# Effect of a new *Lactobacillus plantarum* product, LRCC5310, on clinical symptoms and virus reduction in children with rotaviral enteritis

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**Abstract**

**Background:** Rotavirus is one of the most common causes of infantile enteritis. In common enterocolitis, probiotic organisms, including Lactobacilli, are effective in treating diarrhea. A new species, *Lactobacillus plantarum* (LRCC5310), which was shown to inhibit the adherence and proliferation of rotavirus in the small intestine through animal experiments, was investigated for the efficacy and safety of patients with rotaviral enteritis.

**Methods:** LRCC5310 (Group I) and control (Group II) groups consisting of children who were hospitalized for rotaviral enteritis were compared, and the medical records of patients (Group III) who were hospitalized for rotaviral enteritis during the same study period were retrospectively analyzed. Clinical symptoms were compared and stool samples were collected to compare changes in virus multiplication between Groups I and II.

**Results:** Groups I, II, and III comprised 15, 8, and 27 children, respectively. There were no differences in clinical information among the groups at admission. In Group I, a statistically significant improvement was noted in the number of patients with diarrhea, number of defecation events on Day 3, and total diarrhea period as opposed to Group II ($P = .033$, $P = .003$, and $P = .012$, respectively). The improvement of Vesikari score in Group I was greater than that in the other groups ($P = .076$, $P = .061$, and $P = .036$, respectively). Among rotavirus genotypes, 9 (22.5%) strains and 8 (20.0%) strains belonged to the G9P8 and G1P8 genotypes, respectively. The virus reduction effect, as confirmed via stool specimens, was also greater in Group I. No significant side effects were noted in infants.

**Conclusion:** LRCC5310 improved clinical symptoms, including diarrhea and Vesikari score, and inhibited viral proliferation in rotaviral gastroenteritis.

**Abbreviations:** AGE = acute gastroenteritis, LRCC5310 = *Lactobacillus plantarum*, PCR = polymerase chain reactions.

**Keywords:** children, enteritis, *lactobacillus*, rotavirus

## 1. Introduction

Acute gastroenteritis (AGE) can cause systemic symptoms, including fever, dehydration, and neurological symptoms, as well as gastrointestinal symptoms, including vomiting, diarrhea, and abdominal pain.[1,2] However, in patients from developing countries, immunodeficient patients, and younger patients, AGE is more likely to cause serious complications, such as severe dehydration or necrotizing enteritis, and it may even cause

*Editor: Oliver Schildgen.*

*This work was supported by the Lotte Foods Co. Ltd.*

*The data will not be shared because it will be used as material for other papers.*

*This study was conducted with approval from the Institutional Review Board (IRB) of Chung-Ang University Hospital (IRB number: 1710-009-303) and Soonchunhyang University Bucheon Hospital (IRB number: 2017-12-021) and the study was conducted in accordance with the tenets of the Declaration of Helsinki.*

*The authors have no conflicts of interest to disclose.*

*The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.*

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*How to cite this article: Shin DY, Yi DY, Jo S, Lee YM, Kim JH, Kim W, Park Mr, Yoon Sm, Kim Y, Yang S, Lim IS. Effect of a new Lactobacillus plantarum product, LRCC5310, on clinical symptoms and virus reduction in children with rotaviral enteritis. Medicine 2020;99:38(e22192).*

*Received: 20 April 2020 / Received in final form: 20 July 2020 / Accepted: 17 August 2020*

*http://dx.doi.org/10.1097/MD.0000000000022192*

death.[3–6] In developed countries, mortality caused by AGE is low, but it is a major reason for medical check-ups, hospitalizations, and emergency room visits, and it is an important cause of socioeconomic burden.[3] Globally, AGE is known to occur in approximately 111 million children aged <5 years, and several thousands of people die each year.[2,7]

Rotavirus is one of the most common causes of AGE in children. Its prevalence rate has declined sharply since the introduction of vaccination, but the incidence rate has recently increased again across countries worldwide, including South Korea. In particular, infections among the patients whose immune system has not yet been established, such as neonates and unvaccinated babies, are social problems.[8–10] Infections caused by new genotypes are increasing rather than those caused by genotypes commonly known in certain regions.[11,12] The prevalence of rotaviral enteritis is expected to increase again, and treatment and prevention plans for rotaviral enteritis are necessary because of the high risk of collective infection among newborns prior to vaccination. Long-term genotyping is also required.

In common enterocolitis such as rotaviral enteritis, supportive management (e.g., treatment of diarrhea to prevent malnutrition) is the principle in most cases, and it improves with adequate water and nutrient supply.[13] Probiotic microorganisms, including *Lactobacilli*, are effective in treating diarrhea for preventing dehydration. Animal experiments have demonstrated that a new *Lactobacillus plantarum* species (LRCC5310) inhibited the adherence and proliferation of rotavirus in the small intestine.[14] Thus, we investigated the efficacy and effectiveness of LRCC5310 in rotavirus and infants with rotaviral enteritis.

## 2. Methods

### 2.1. Patient selection and data extraction

From January 2018 to April 2019, among all the pediatric patients admitted for enteritis at Chung-Ang University Hospital and Soonchunhyang University Bucheon Hospital, those who were diagnosed with rotavirus by conducting the stool test on the day of admission were included. We prospectively collected and analyzed feces from the patients who agreed to participate in the study. The enrolled patients were randomly grouped. Group I received LRCC5310 but no other probiotics, whereas the control group (Group II) did not receive any probiotic agents. Neither group used any anti-diarrhea or anti-emetic drugs.

Additionally, the medical records of patients (Group III) who were hospitalized for rotaviral enteritis at Chung-Ang University Hospital during the same study period were analyzed retrospectively. The patients were not included in the prospective study on the day of admission owing to delayed fecal sampling or various other reasons but were subsequently diagnosed with rotavirus. The retrospectively investigated patients were treated with a probiotic formulation comprising *Saccharomyces* species, according to the AGE treatment policy of the hospital.

In all groups, patients with underlying problems that could affect the course of AGE, such as premature birth or chronic gastrointestinal disease, were excluded, and patients who failed to complete the study were excluded from data collection because of inconsistent treatment. Clinical information and clinical symptoms such as fever, vomiting, diarrhea, and abdominal pain were identified in all patients, and Vesikari score was calculated to confirm the severity of enteritis.[15] We also compared the results of laboratory markers tested at the time of hospitalization to confirm whether there was a difference in the degree of inflammation that could affect clinical outcomes in each group.

### 2.2. Collection and analysis of fecal samples

Initially, rotavirus was identified using a diarrhea polymerase chain reactions (PCR) Kit (Seeplex Diarrhea-V ACE Detection, Seegene, South Korea) and an Elisa Kit (RIDASCREEN, R-Biopharm AG, Germany). Stool samples that had been collected immediately after diagnosis of inpatients with enteritis were analyzed. In enrolled patients (group I and II), additional fecal samples were collected on Days 3 to 4 and 5 to 7 to analyze changes in virus titer. Stool samples of enrolled patients were vortexed with phosphate-buffered saline (1 mL) (PBS; pH 7.4) to prepare about 10% suspensions of stool samples. The sample suspensions were centrifuged at 12,000x g for 15 minutes, and supernatants was used as a fecal suspensions. Virus ribonucleic acid was extracted from the fecal suspensions using a QIAamp RNA Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions and was stored at −70 °C until it will be used in reverse transcription-PCR. To genotype strains, multiplex semi-nested PCR assays using sets of primers, for each genotypes, were performed.

### 2.3. Statistical analysis

Statistical analysis was performed using SPSS 18.0 statistical software (SPSS Inc., Chicago, IL). Pearson $\chi 2$ test and Mann–Whitney *U* test were applied to evaluate the differences between the groups. All continuous data were expressed as the median (Q50) and interquantile range (Q25 – Q75). The level of statistical significance was set at $P < .05$.

### 2.4. Ethics statement

This study was conducted with approval from the Institutional Review Board of Chung-Ang University Hospital (IRB number: 1710-009-303) and Soonchunhyang University Bucheon Hospital (IRB number: 2017-12-021) and the study was conducted in accordance with the tenets of the Declaration of Helsinki.

## 3. Results

### 3.1. Clinical features of patients with rotaviral enteritis

Between January 2018 and April 2019, 15 patients (Group I) who took LRCC5310 for the improvement of diarrhea caused by rotavirus enteritis were enrolled, and 8 patients were enrolled in Group II. In the same period, 37 patients were admitted for rotaviral enteritis at Chung-Ang University Hospital, and 10 patients who had premature or allergic colitis were excluded thus, the medical records of 27 patients (Group III were finally analyzed.

With regard to clinical information at admission, although age was slightly lower in Group II, Groups II, III, and II + III showed no significant difference in age, sex, or body measurements when compared with the clinical information pertaining to Group I (Table 1). The clinical symptoms and Vesikari score at the time of admission were also not significantly different from those treated with or without LRCC5310. Various laboratory inflammation

**Table 1**

**Clinical features on the day of admission in patients hospitalized for rotaviral enteritis.**

| Variable | Group I N = 15 | Group II N = 8 | *P* value | Group III N = 27 | *P* value | Group II + III N = 35 | *P* value |
|---|---|---|---|---|---|---|---|
| Age (mo) | 36 (19–59.00) | 14 (1–25.25) | .047* | 40 (20–69) | .763 | 29 (13–60) | .687 |
| Male: Female | 4: 11 | 4: 4 | .371 | 9: 18 | .739 | 13: 22 | .533 |
| Number of vomiting (times/d) | 1 (0–4) | 3 (0–9.25) | .506 | 1 (0–5) | .934 | 2 (0–5) | .756 |
| Number of defecation (times/d) | 3 (0–3) | 1 (0.25–4.25) | .776 | 1 (0–2) | .307 | 1 (0–2) | .351 |
| Patients with abdominal pain | 7 (46.7%) | 2 (25.0%) | .400 | 7 (25.9%) | .172 | 9 (25.7%) | .146 |
| Patients with fever | 8 (53.3%) | 4 (50.0%) | 1.000 | 15 (55.6%) | .890 | 19 (54.3%) | .951 |
| Maximum body temperatures (℃) | 38.0 (37.5–39.0) | 38.0 (37.1–38.475) | .265 | 38.1 (37.0–39.0) | .329 | 38.1 (37.0–38.9) | .247 |
| Vesikari score | 9 (7 –14) | 10.5 (3.5–12.5) | .428 | 9 (5–11) | .129 | 9 (5–11) | .134 |
| White blood cell (/mm$^3$) | 9,530 (6,555–14,120) | 10,370 (8,280–12,760) | .581 | 7,120 (5,110–9.080) | .061 | 8,180 (5,410–10,160) | .172 |
| Absolute neutrophil count | 7,041 (3,800–9,460) | 6,195 (4,137–11,458) | 1.000 | 4,507 (2,332–6,740) | .068 | 4,887.5 (2,748.5–7,775) | .134 |
| C-reactive protein (mg/L) | 12.8 (6.2–22.5) | 1.0 (0.6–16.6) | .106 | 15.8 (2.4–39.9) | .844 | 10.15 (2.2–27.675) | .728 |

Group I; patients received *Lactobacillus plantarum*, Group II; patients in the control group did not receive any probiotics, Group III; Non-clinical trial patients hospitalized and treated with rotaviral enteritis for the same period.

markers, such as white blood cells, absolute neutrophil count, and C-reactive protein, which may influence the prognosis of clinical symptoms, also did not differ across the groups.

### 3.2. Changes in clinical features on Day 3 compared with those noted on admission day

Comparative changes in the clinical features of each group on Day 3 with those on the day of admission are shown in Table 2. There were no differences in the length of hospital stay or the number of patients with persistent vomiting in Groups II, III, or II + III when compared with Group I. However, Group I showed a statistically significant improvement in the number of patients with persistent diarrhea until Day 3 of hospitalization, the number of defecation events per day on Day 3, and the total diarrhea period compared with Group II ($P = .033$, $P = .003$, and $P = .012$, respectively); furthermore, compared with patients who were treated with *Saccharomyces*-containing probiotic formulation and subsequently discharged (Group III), Group I also showed a slight improvement in the number of patients with loose stool until Day 3 of hospitalization (22.2%vs 6.7%), number of defecation events per day on Day 3, and diarrhea duration, but statistical significance was lacking. Vesikari scores on Day 3 of hospitalization were lower in Group I and Group III than in Group II. Although statistical significance with regard to the change in Vesikari score on Day 3 compared with the score noted on hospitalization day was slightly lacking, it was confirmed that Group I showed greater improvement than Group III, Group II, and Group II + III, with the difference being statistically significant for Group II + III ($P = .076$, $P = .061$, and $P = .036$, respectively). There were no significant side effects.

### 3.3. Rotavirus titer in enrolled patients

The genotypes of rotavirus were identified from fecal samples collected on hospitalization day, that is, Days 3 to 4 and Days 5 to 7 in Group I and Group II. Of the 69 samples from 23 patients (Group I: 15 patients and Group II: 8 patients), 40 samples were available for genotype identification. A total of 12 (30%), 9 (22.5%) and 8 (20.0%) strains were identified to belong to the G9P8, G8P8, and G1P8 genotypes. G3P8 (n = 5, 12.5%), G2P4 (n = 3, 7.5%), G4P6 (n = 2, 5%), and G9P4 (n = 1, 2.5%) types were subsequently identified for the rest of the isolated strains. In both groups, the titers of rotavirus following LRCC5310 treatment were compared (Fig. 1). The rotavirus titer was found to be significantly reduced in patients who received LRCC5310 (Group I) compared with those who did not take any probiotic formulations (Group II) ($P < .001$).

**Table 2**

**Clinical features on the day 3 in patients hospitalized for rotaviral enteritis.**

| Variable | Group I N = 15 | Group II N = 8 | *P* value | Group III N = 27 | *P* value | Group II + III N = 35 | *P* value |
|---|---|---|---|---|---|---|---|
| Duration of admission (d) | 4 (3 –6) | 4 (3–4.75) | .825 | 3 (2–4) | .127 | 3 (3–4) | .192 |
| Patients with vomiting | 1 (6.7%) | 0 (0%) | 1.000 | 0 (0%) | .357 | 0 (0.0%) | .300 |
| Vomiting duration (d) | 1 (0–1) | 1 (0.25–1) | .875 | 1 (0–1) | .556 | 1 (0–1) | .683 |
| Patients with diarrhea | 1 (6.7%) | 4 (50.0%) | **.033*** | 6 (22.2%) | .390 | 10 (28.6%) | .139 |
| Number of defecation (times) | 0 (0–0) | 2 (0–5) | **.023*** | 0 (0–0) | .175 | 0 (0–2) | .053 |
| Diarrhea duration (d) | 1 (0–2) | 2 (2–3) | **.013*** | 2 (1–2) | .125 | 2 (1–3) | **.039*** |
| Patients with abdominal pain | 0 (0.0%) | 0 (0%) | n/c | 2 (7.4%) | .530 | 2 (5.7%) | 1.000 |
| Abdominal pain duration (d) | 0 (0 –2) | 0 (0–0.75) | .392 | 0 (0–1) | .192 | 0 (0–1) | .158 |
| Patients with fever | 3 (20.0%) | 3 (37.5%) | .621 | 4 (14.8%) | .686 | 7 (20.0%) | 1.000 |
| Fever duration (d) | 2 (0–2) | 1.5 (0.25–2.75) | .776 | 1 (0–2) | .740 | 1 (0–2) | .877 |
| Vesikari score on the d 3 | 3 (2–5) | 5.5 (3.25–7) | .115 | 4 (2–5) | .811 | 4 (2–6) | .467 |
| Change of Vesikari score | 6 (4–9) | 3.5 (-0.5–5.75) | .076 | 4 (3–6) | .061 | 4 (3–6) | **.036*** |

Group I; patients received *Lactobacillus plantarum*, Group II; patients in the control group did not receive any probiotics, Group III; Non-clinical trial patients hospitalized and treated with rotaviral enteritis for the same period.

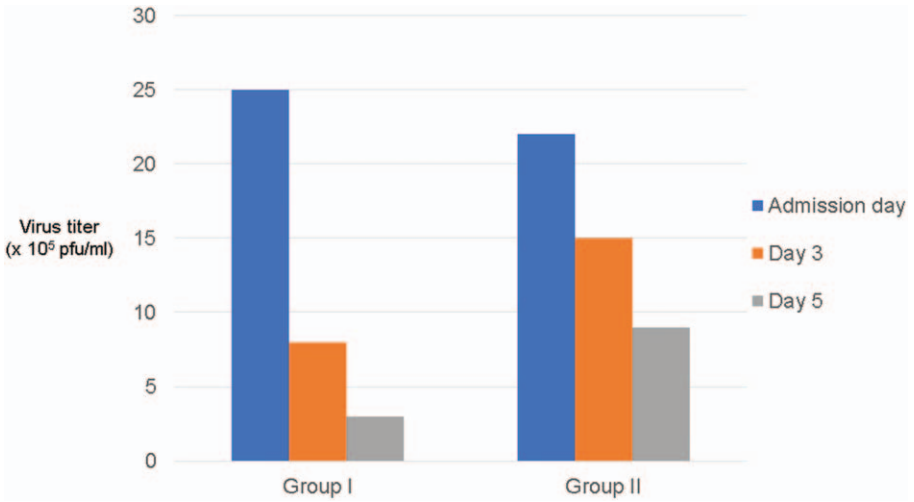


**Figure 1.** Change in virus titer according to *Lactobacillus plantarum* treatment (Group I: patients who received *L. plantarum* , Group II: patients in the control group who did not receive any probiotics, $P < .001$).

## 4. Discussion

In viral AGE, such as that caused by rotavirus, the goal of treatment is to prevent complications and control dehydration. Although dehydration is controlled by treatment such as fluid therapy or oral rehydration solution, treatment of other clinical symptoms varies depending on the symptoms, region, or age.[16] In viral AGE, duration of symptoms, such as vomiting, fever, and abdominal pain, is often short and often improves on its own over time, but diarrhea in infants can persist for a prolonged period. Particularly, in enteritis caused by rotavirus, diarrhea may last longer.[2,17] The use of antidiarrheal drugs is not desirable for the improvement of such diarrhea symptoms, and it is known that probiotic formulations containing zinc, *Lactobacillus* species, and *Saccharomyces* species are helpful.[3,18] Even in our study, symptoms such as vomiting, fever, and abdominal pain did not last long. Maybe this explains why symptoms did not last long in any of the groups and why there was no difference between the 3 groups in terms of duration or severity. However, in the case of diarrhea, it was found to be significantly more effective when LRCC5310 or a usual probiotic formulation containing *Saccharomyces* was taken compared with no intake of *Lactobacillus*. *Lactobacillus* intake helped to improve the number of patients who had diarrhea lasting up to 3 days after hospitalization, the number of daily defecation events on the third hospitalization day, and the overall diarrhea period. On comparing between the 2 *Lactobacillus* types, LRCC5310 was also more effective than *Saccharomyces*, although it slightly lacked statistical significance and the total number of patients. Similar results were found in the Vesikari score that had been surveyed to confirm the severity of AGE owing to the differences in diarrhea symptoms, as other checked items improved easily and there were no differences between groups. This observation can be attributed to the fact that the score related to diarrhea is reflected in the overall score. If we could investigate the effects of LRCC5310 in more patients, we can expect better results.

Comparison among various clinical symptoms on the day of hospitalization and laboratory inflammation markers was performed owing to the possibility that they could be given over or after if there was a difference in the severity of the enrolled patients in each group. However, there were no significant differences in this indicator that could affect the final outcome. However, the Vesikari score in Group I was somewhat high, and it is believed that this research is limited because only those subjects who have been identified to have rotavirus in their fecal sample via stool test performed on the same day were allowed to participate in the clinical trial additionally, there were more cases involving patients with obvious or severe clinical symptoms that could have been identified and included. However, symptoms of diarrhea and AGE were better in Group I compared with those in the other 2 groups.

The rotavirus consists of a segmented gene and can represent a variety of genes by a combination of G-P proteins. Generally, the genotypes of viruses that cause AGE in children are typically G1P [8], G2P[4], G3P[8], G4P[8], G9P[8], and G12P, but they vary according to region and time.[19,20] Recently, it seems that a new type of genotype has emerged via mutation or reassortment, possibly owing to resistance or immunization breakthroughs and globalization (i.e., genotypes that have spread in 1 region circulate and become prevalent in other regions).[21–23] This diversity can predict the future relapse of rotaviral enteritis, exacerbation of prognosis, or treatment difficult. Various genotypes have been identified in our patients, and the diversity of these genotypes was independent of vaccination or type of vaccine. Moreover, intake of LRCC5310 was found to be effective in the suppression of viral symptoms as well as in prognosis and treatment via virus titer reduction.

There were some limitations to our study. First, it was difficult to perform owing to the limitations associated with clinical trials for infants and children. The size of the control group was also small because participants often withdrew from research owing to anxiety pertaining to fluid-only therapy. Moreover, the investigation period was not long, and only few patients had been included. Because rotavirus has a prolonged period of prevalence, long-term studies performed over several years could have helped achieve more meaningful results. Additionally, if there were a large number of patients involved, the different effects of genotype and vaccination could have been identified. Finally, because our study only covered inpatients and those who had been confirmed to have rotavirus in their feces, patients with mild symptoms were not included. To reduce such limitations as much

as possible, medical records of patients who were not involved in forward-looking clinical studies were also identified and included for comparing clinical symptoms. These patients were not prospectively examined, and only their feces samples were collected separately from the prospectively registered patients all other clinical events remained the same. Therefore, there were no problems in comparing clinical symptom-related results. Rather, it would have been more objective to compare clinical symptoms with patients who have consumed LRCC5310 because they received existing treatments in accordance with general AGE without being affected by clinical research.

Despite the abovementioned limitations, we found that the new *Lactobacillus* species, LRCC5310, inhibits the growth of rotavirus, reduces virus titer, and improves AGE symptoms such as diarrhea and Vesikari score. We plan to investigate many more patients over a longer period and conduct further studies in infants with norovirus enteritis. We also expect to use LRCC5310 to prevent group infections in unimmunized neonatal units if we are able to confirm that it has the same effect as herd immunity by comparing the effects of administration to a mother or a caregiver in a group nursery as well as infants with rotaviral enteritis.

## Acknowledgments

We thank Editage language editing services for reviewing the manuscript and for editorial assistance and Jeong Lyn Song (researcher at Chung-Ang University Breast milk Research Institute) for helping with the writing of the manuscript.

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