Vaona et al. Top Ital. sci. j. 2025;2(1)
https://www.doi.org/10.62684/BYSU4717

Top Italian Scientists Journal

Open Access | Article | Clinical Sciences

ISSN 3033-5132

Prevention of Traveler's Diarrhea while Crossing the Amazon Rainforest by Bike with a Supplement Based on Lacticaseibacillus Rhamnosus LR04 (DSM 16605) + Streptococcus Thermophilus FP4 (DSM 18616) + Bifidobacterium Brevis BR03 (DSM 16604): a Phase Two, Randomized, Placebo-controlled, Double-blind, Cross-over Pilot Study

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Keywords: diarrhoea; probiotics; Amazon forest.

Published: 10 Jan 2025

Abstract

Traveler's diarrhea is a common gastrointestinal illness experienced by individuals traveling to countries with inadequate sanitation and hygiene standards. In this Phase Two, Randomized, Placebo-controlled, Double-blind, Cross-over Pilot Study, we aimed to explore whether a probiotic containing Lacticaseibacillus rhamnosus LR04 (DSM 16605) + Streptococcus thermophilus FP4 (DSM 18616) + Bifidobacterium breve BR03 (DSM 16604) could prevent traveler's diarrhea and improve quality of life over three months of follow-up in a cohort of athletes biking though the Amazon rainforest. In this pilot study including 3 cyclists randomly assigned to one of the two experimental groups (one probiotic, one placebo). The three participants were men aged 47, 63, 64 years. During the follow-up period, we observed one episode of diarrhea in the probiotic group and one in placebo (p=1.00). However, the number of days with diarrhea was only two in the active group and seven in the placebo group (p=0.33). No episodes of severe diarrhea were observed during the follow-up. At the end of the study, the active group showed a higher quality of life, but no statistically significant. In conclusion, our study suggests that the supplementation with Lacticaseibacillus rhamnosus LR04 (DSM 16605) + Streptococcus thermophilus FP4 (DSM 18616) + Bifidobacterium breve BR03 (DSM 16604) may help prevent traveler's diarrhea in extreme conditions such as to biking through the Amazon rainforest. However, future larger studies involving a more general population are needed to confirm our findings.

Introduction

Traveler's diarrhea is a common and often unpleasant gastrointestinal illness experienced by individuals traveling to countries with inadequate sanitation and hygiene standards.(1) Characterized by the sudden onset of diarrhea, abdominal cramps, nausea, and occasionally fever, traveler's diarrhea can significantly disrupt travel plans and negatively impact the overall travel experience.(1) Preventing traveler's diarrhea is a key priority for travelers, particularly those visiting regions where the risk of infection is high.

Preventive measures typically encompass a multifaceted approach that includes both behavioral and pharmacological interventions aimed at reducing the risk of exposure to enteric pathogens.(2) Behavioral interventions focus on adopting safe food and water

practices, practicing good hygiene, and avoiding high-risk foods and beverages.(2) Pharmacological interventions involve the use of antimicrobial agents, probiotics, or bismuth subsalicylate for prophylaxis or self-treatment of traveler's diarrhea symptoms. However, the widespread use of antimicrobial prophylaxis is controversial due to concerns about antibiotic resistance and adverse effects.

Among pharmacological interventions, biotics have garnered attention as potential preventive measure for traveler's diarrhea. However, not all biotics are identical, and the results of studies conducted with a particular agent cannot be generalized to suggest that any probiotic agent would be successful in the same clinical situation.(3) Probiotics such as Lactobacillus GG have been shown to reduce the incidence of diarrhea in travelers in randomized controlled trials.(3) In contrast, another Lactobacillus preparation, non-viable Lactobacillus acidophilus, showed no benefit over placebo in a randomized, double-blind, controlled trial of 174 travelers.(4) The reasons for these discrepancies are unclear but could be related to the viability of the bacteria or a peculiarity of the strain selected for testing.(4)

Given the variability in probiotic efficacy and the absence of a definitive prevention approach for traveler's diarrhea, there is a need for further investigation into specific probiotic strains and their benefits in unique travel environments, such as the Amazon rainforest. In this Phase Two, Randomized, Placebo-controlled, Double-blind, Cross-over Pilot Study, we aimed to explore whether a probiotic containing Lacticaseibacillus rhamnosus LR04 (DSM 16605) + Streptococcus thermophilus FP4 (DSM 18616) + Bifidobacterium breve BR03 (DSM 16604) could prevent traveler's diarrhea and improve quality of life over three months of follow-up in a cohort of athletes biking though the Amazon rainforest.

Materials and methods

Participants

This study was conducted in the Amazon rainforest across 3 countries (Brasil, Bolivia, and Chile) between July 10, 2023, and October 10, 2023, except for the randomization and allocation procedures which were performed at the University of Palermo, Italy. The study was registered in https://clinicaltrials.gov/ on 2023-11-04 (#NCT06125626).

Three healthy bikers, caable of biking thorugh the Amazonia rainforest, were contacted and enrolled on voluntary basis, whith no predefined exclusion criteria. This study is part of the iosonoamazzonia.org project.

No specific dietary information was given to the participants beforehand. They followed a diet consisting of available food along the road, which was rich in rice and chicken but also included vegetables and fruit juice.

The study was designed in accordance with the Helsinki Declaration and was approved by the local Ethical Committee (no. 153/2023). All participants were fully informed about the nature, purpose, procedures, and risks of the study and provided written informed consent. Our trial complied with the Consolidated Standards of Reporting Trials statement for randomized trials.(5) The study was registered on ClinicalTrials.gov (NCT06125626).

Randomization, intervention, and allocation

Volunteers were randomly assigned to one of the two experimental groups by using a computer-generated sequence of three nonunique, unsorted numbers with the range from 1 to 2, representing the groups. The main investigator (NV) kept the allocation sequence confidential and assigned the participants to one of the two groups.

Participants received 45 days of supplementation with a daily capsule of Lacticaseibacillus rhamnosus LR04 (DSM 16605) ($1x10^9$ AFU/dose) + Streptococcus thermophilus FP4 (DSM 18616) ($5x10^9$ AFU/dose) + Bifidobacterium breve BR03 (DSM 16604) ($5x10^9$ AFU/dose) (group A) or a daily capsule of placebo (group B). Before leaving Italy, the probiotics and the placebos were distributed to the participants according to their initial randomization.

After 45 days of intervention, the participants were allocated to the other group, being a cross-over randomized controlled trial.

Outcomes

The primary outcome of our study was the incidence of diarrhea during the 12 weeks of follow-up which was investigated daily. Diarrhea was defined using the Bristol stool scale with a value of 7 in a scale between 1 and 7, where higher values reflect more diarrheic stool consistency.(6)

Secondary outcomes included: i) quality of life, assessed using the 12-Item Short Form Health Survey (SF-12). The SF-12 produces a standardized score between 0 and 100%, compared to the Italian population (7). The results of the SF-12 are represented by one Physical Component Score (PCS) and one Mental Component Score (MCS). The PCS includes items assessing parameters of physical functioning and pain, while the MCS focuses on psychological and mental health questions. The SF-12 was assessed every 7 days; ii) incidence of severe diarrhea, defined as a diarrhea requiring hospitalization or intravenous hydration.

Statistical analysis

Being a pilot study focused on a unique condition (i.e., biking across the Amazon rainforest), we did not calculate a priori a sample size.

Data were reported by group as total frequencies with relative percentages for categorical variables and as median with range or means and standard deviations for continuous variables, after assessing the normal distribution. The incidence of diarrhea and severe diarrhea were compared using the chi-square test withFisher's correction, while SF-12 scores were analyzed using a generalized linear model (GLM) for repeated measures.

Significance was accepted if $P < 0.05$, and all tests were two-tailed. All analyses were performed by using SPSS 26.0 for Windows (SPPS Inc).

Results

The three participants were men aged 47, 63, 64 years. Two participants were initially allocated to the placebo group, and one to the active intervention group. After 45 days, the participants crossed over to the other group. Overall compliance was optimal: only one participant missed three days of supplementation, while another participant missed one capsule throughout the entire study.

Table 1 shows the main results of our study. During the follow-up period, we observed one episode of diarrhea in the probiotic group and one in placebo (p=1.00). However, the number of days with diarrhea was only two in the active group and seven in the placebo group (p=0.33). No episodes of severe diarrhea were observed during the follow-up.

Figures 1A and 1B show the changes in quality of life during the study period. At the end of the study, the active group showed overall higher mean values by 3.26 points in the SF12-PCS (95%CI: -2.47 to 8.99) (**Figure 1A**), although this difference was not statistically significant (p=0.19). Similarly, the active group reported better values at the SF12-MCS (mean difference =4.9 points), again not statistically significant (p=0.43) (**Figure 1B**).

Discussion

In this research, we conducted a Phase Two, randomized, placebo-controlled, double-blind, cross-over pilot study including three healthy bikers whose main aim was to traverse the Amazon rainforest. Likely due to the extremely small sample size, we found that the incidence of traveler's diarrhea was similar between the active and placebo groups. However, the number of episodes and the quality of life parameters overall suggest a positive role of the supplementation with Lacticaseibacillus rhamnosus LR04 (DSM 16605) + Streptococcus thermophilus FP4 (DSM 18616) + Bifidobacterium breve BR03 (DSM 16604) in preventing this important medical condition. It is important to note that our study was conducted in an unique situation, i.e., among bikers traversing the Amazon rainforest.

Before them, only two people, Louise Sutherland in 1978 and Michael Merz in 1994, are known to have successfully biked through the Amazon rainforest. This type of trip is not typically undertaken by tourists, and there is limited information available about the incidence of diarrhea in this area.

The findings of our study must be interpreted within its limitations. First, the small sample size reflects the extreme conditions of the project. Second, the diet of the participants was likely too healthy to significantly increase the risk of diarrhea; however, maintaining a healthy diet is one of the few preventive measures suggested to decrease the risk of traveler's diarrhea.(8) Finally, all information was self-reported. Although the Bristol Stool Scale and SF-12 are user-friendly tools, we cannot exclude the possibility of reporting biases.

In conclusion, our study suggests that the supplementation with Lacticaseibacillus rhamnosus LR04 (DSM 16605) + Streptococcus thermophilus FP4 (DSM 18616) + Bifidobacterium breve BR03 (DSM 16604) may help prevent traveler's diarrhea in extreme conditions such

as to biking through the Amazon rainforest. However, future larger studies involving a more general population are needed to confirm our findings.

Declarations

Acknowledgments

We thank Margherita Patrucco for her revision.

Conflict of Interest

The Authors declare that there is no conflict of interest.

Funding

The authors have no funding sources to report.

Author Contributions

Vaona: data collection; Veronese: data analysis; Amoruso, Pane: critical revision of the paper. All authors approved the final version of the manuscript submitted.

Figure 1A. Effect of probiotic compared to placebo on the incidence of diarrhea and severe diarrhea on physical aspects of quality of life (SF-12 PCS)

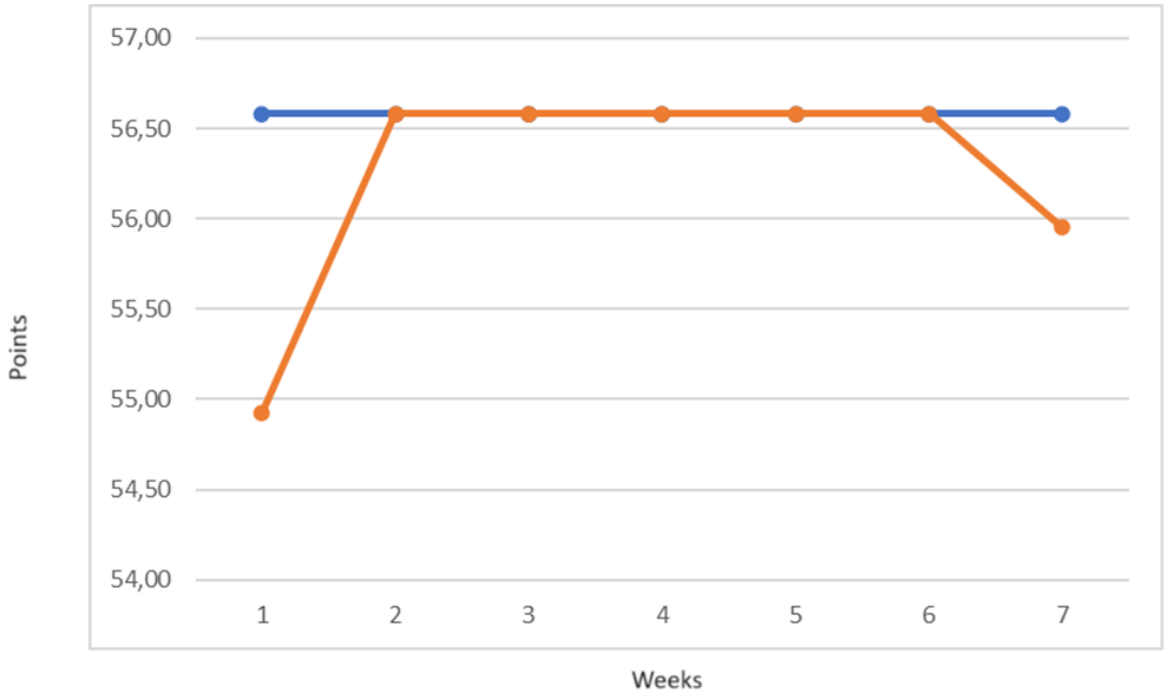

Figure 1B Effect of probiotic compared to placebo on the incidence of diarrhea and severe diarrhea on mental aspects of quality of life (SF-12 MCS)

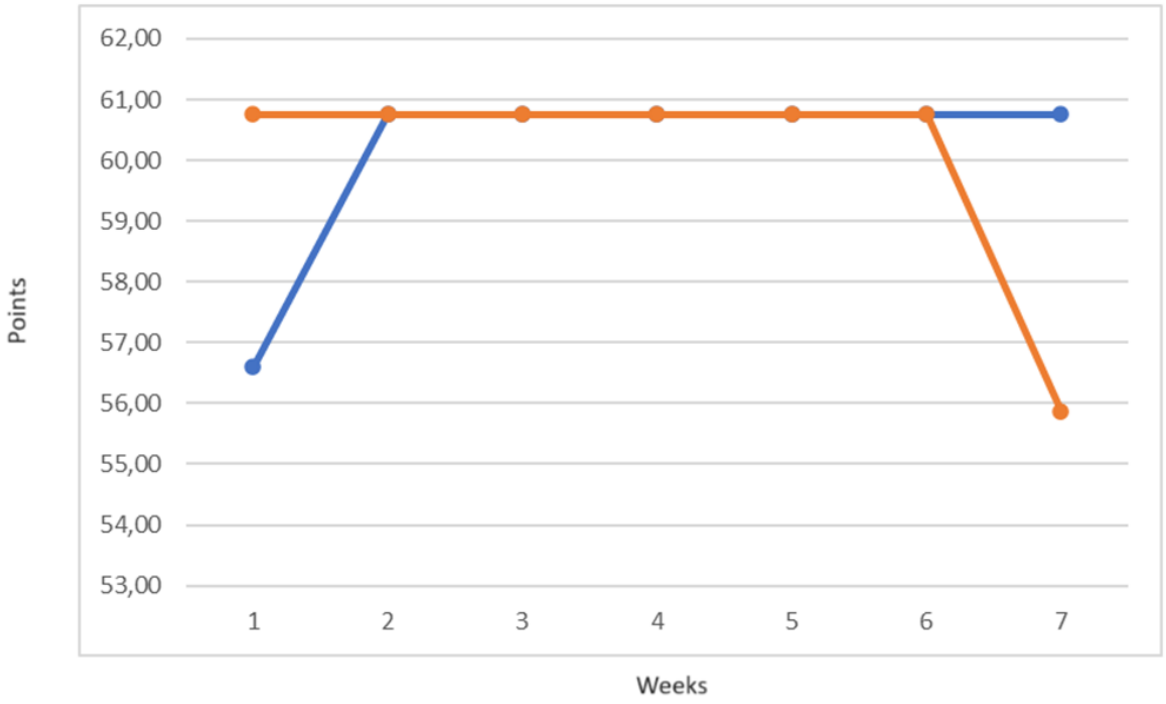

Table 1. Effect of probiotic compared to placebo on the incidence of diarrhea and severe diarrhea.

	Probiotic (n=3)	**Placebo (n=3)**	**p-value**
Incidence of diarrhea	1 (33%)	1 (33%)	1.00
Days with diarrhea	2	7	0.33
Severe diarrhea	0 (0)	0 (0)	1.00

Legend: Incidence is reported as the number of participants experiencing the outcome (percentage of total participants. Days with diarrhea is reported as the total number of days with diarrhea episodes observed in each group.

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