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A randomized double-blind placebo-controlled trial of *Lactobacillus* GG for abdominal pain disorders in children

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SUMMARY

Background
Functional abdominal pain disorders (FAPD) are common in school-aged children; however, there is no reliable treatment.

Aim
To determine the efficacy of *Lactobacillus rhamnosus* GG (LGG) for treating FAPD in children.

Methods
A total of 104 children who fulfilled the Rome II criteria for functional dyspepsia (FD), or irritable bowel syndrome (IBS), or functional abdominal pain (FAP) were enrolled in a double-blind, randomized controlled trial in which they received LGG ($n = 52$), or placebo ($n = 52$) for 4 weeks.

Results
For the overall study population, those in the LGG group were more likely to have treatment success (no pain) than those in the placebo group (25% vs. 9.6%, relative benefit (RB) 2.6, 95% confidence interval (CI): 1.05–6.6, number needed to treat (NNT) 7, 95% CI: 4–123). For children with IBS ($n = 37$), those in the LGG group were more likely to have treatment success than those in the placebo group (33% vs. 5%, RB 6.3, 95% CI: 1.2–38, NNT 4, 95% CI: 2–36) and reduced frequency of pain ($P = 0.02$), but not pain severity ($P = 0.10$). For the FD group ($n = 20$) and FAP group ($n = 47$), no differences were found.

Conclusion
The LGG appears to moderately increase treatment success, particularly among children with IBS.

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BACKGROUND

Functional abdominal pain disorders (FAPD) are common, especially in school-aged children. Estimates of the incidence and prevalence vary depending on the diagnostic criteria and setting, but about 10–20%[1, 2] of the school-aged population may be affected. According to the Rome II criteria,[3] FAPD may be classified as functional dyspepsia (FD), irritable bowel syndrome (IBS), functional abdominal pain (FAP), abdominal migraine and aerophagia. Most recently, the Rome III criteria[4] were published, in which the category of FAP was split into two separate disorders, childhood FAP and childhood functional abdominal syndrome. No specific medical treatment is usually required for most children with functional abdominal disorders, and very few of the currently available treatment options have been subjected to controlled trials carried out to modern standards.[5] However, there is an interest on the part of patients, caregivers and practitioners as to simple and effective measures to relieve symptoms.

Probiotics are live micro-organisms administered in adequate amounts, which confer a beneficial health effect on the host.[6] In adults, several studies have shown that some probiotic strains are clinically more effective than placebo in the treatment of some categories of FAP, particularly of IBS.[7–16] However, only limited paediatric data are available.[17]

The goal of our study was to find out whether *Lactobacillus rhamnosus* GG (LGG), a probiotic strain with well-documented properties,[18] is effective in treating FAPD in children. Both overall data and data categorized into specific diagnoses are reported, as the division between specific diagnoses, particularly between FD, IBS and FAP, is not always clear-cut in all children.

METHODS

Participants

Patients were recruited from children referred to the Department of Pediatric Gastroenterology and Nutrition, The Medical University of Warsaw. Each potentially eligible patient was evaluated by a full review of their clinical history and performance of a physical examination. Potentially eligible subjects received a diary to record symptoms and the frequency of daily pain, drug use and any symptoms they considered important for 4 weeks before study inclusion. Patients were considered for study inclusion, if they were 6–16 years of age and had an abdominal pain disorder (i.e. FD or IBS or FAP) according to the Rome II diagnostic criteria[3] valid at the time of the design of the study. To establish the diagnosis, the patients completed questionnaires covering baseline assessment, exclusion criteria and the Rome II diagnostic criteria.

The diagnostic criteria for FD were a pain history of at least 12 weeks, which need not be consecutive, within the preceding 12 months consisting of (i) persistent or recurrent pain or discomfort centred in the upper abdomen (above the umbilicus); (ii) no evidence (including at upper endoscopy) that organic disease is likely to explain the symptoms and (iii) no evidence that dyspepsia is exclusively relieved by defaecation or associated with the onset of a change in stool frequency or stool form.

The diagnostic criteria for IBS were a pain history of at least 12 weeks, which need not be consecutive, in the preceding 12 months consisting of (1) Abdominal discomfort or pain that has two of three features: (i) relieved with defaecation and/or (ii) onset associated with a change in stool frequency and/or (iii) onset associated with a change in the form (appearance) of the stool and (2) There are no structural or metabolic abnormalities to explain the symptoms.

The diagnostic criteria for FAP were symptoms of at least 12 weeks consisting of (i) continuous or nearly continuous abdominal pain in a school-aged child or adolescent; (ii) no or only occasional relation of pain with physiological events (e.g. eating, menses, or defaecation); (iii) some loss of daily functioning; (iv) the pain is not feigned (e.g. malingering) and (v) the patient has insufficient criteria for other functional gastrointestinal disorders that would explain the abdominal pain.

Exclusion criteria included organic disease (as established by medical history, complete blood count, urinalysis, stool examination for occult blood, ova and parasites, blood chemistries, abdominal ultrasound, breath hydrogen testing and endoscopy, if needed), other chronic disease and growth failure.

We randomized patients to receive LGG (3×10^9 colony forming units, CFU) or matching placebo, twice daily, orally, for 4 weeks. Both the LGG and the placebo were manufactured and supplied by Dicofarm SpA (Rome, Italy) as powder in identical capsules and were kept refrigerated until use. The manufacturer had no role in the conception, design or conduct of the study or in the analysis or interpretation of the data.

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Randomization, assignment and masking

Randomization was carried out according to a computer-generated list using a permutated block design. Stratification was by initial diagnosis. The investigators and the patients were blinded to the assignment.

Documentation and follow-up

We recorded eligibility criteria and history on the day of randomization. All patients received a diary to record symptoms and the frequency of daily pain, drug use and any symptoms they considered important. To assess the severity of the pain, the Faces Pain Scale, which is a scale for measurement of pain intensity by self-report,[19] was used. This scale was derived through a phased piece of research from children's drawings of pain. The scale consists of seven faces that show pain effect ranging from a relaxed face on the left (no pain) to a face showing intense pain on the right (most pain possible). For the purposes of this study, facial responses were transformed into a score that ranged from 0 (a relaxed face) to 6 (intense pain). The children were evaluated clinically at study entry and at 4 weeks after enrolment. The study physician assessed the patient's diary during the follow-up visit, evaluating pain scale (face) scores, the prevalence of other symptoms of FAPD, use of medications and school absenteeism rates. Treatment responses were evaluated by measuring changes in these outcome measures over the course of the study. To ensure adherence, one of the investigators (AG) regularly contacted the participants.

Outcome measures

The primary outcome measure was treatment success defined as no pain (a relaxed face, score of 0, on the Faces Pain Scale) at the end of the intervention. The secondary outcome measures were improvements defined as a change in (i) the Faces Pain Scale by at least two faces scores; (ii) self-reported severity of pain during the preceding week measured on the Faces Pain Scale; (iii) self-reported frequency of pain during the preceding week; (iv) use of medication for abdominal pain and (v) school absenteeism because of abdominal pain.

Ethical considerations

Parents were fully informed about the aims of the study, and informed consent was obtained from at least one parent. The study protocol was reviewed and approved by the ethical review committee of the Medical University of Warsaw.

Sample size

For the primary outcome measure, we calculated the sample size on the assumption that the use of LGG would result in a 30% increase in treatment success. We estimated that, with a power of 80% and at a significance level of 0.05, we needed 39 children per group to show a 30% difference between the groups. For continuous outcomes (difference in pain severity scores), we set the total sample size at 34 to achieve a power of 80% for detecting differences between the groups in the severity score of 2 (S.D. 2).

Statistical analysis

The Chi-squared test or Fisher's exact test was used, as appropriate, to compare percentages, and Wilcoxon's test was used for comparison of the mean values of patients' age, weight, pain frequency and pain severity. Data were analysed with SAS 9.1 software (SAS Institute, Cary, NC, USA). The mean difference (MD), relative risk (RR) or relative benefit (RB), 95% confidence interval (CI) and number needed to treat (NNT) were calculated using the computer software StatsDirect (StatsDirect Ltd, Cheshire, UK) [2,5,6 (15 May 2006); Iain E. Buchan]. The difference between study groups was considered significant when the *P*-value was <0.05 or when the 95% CI for RR/RB did not exceed 1.0 or for MD did not exceed 0 (equivalent to $P < 0.05$). All statistical tests were two tailed and performed at the 5% level of significance. All analyses were performed on the intention-to-treat basis, in which all of the participants in a trial are analysed according to the intervention to which they were assigned, whether or not they received it.

RESULTS

A total of 112 children were eligible for inclusion from October 2003 until May 2006. Eight children were excluded because of their refusal to participate in the trial. Of the 104 children enrolled in the study, 52 received LGG and 52 received placebo. There were no withdrawals or dropouts. Table 1 summarizes the subjects' baseline demographic and clinical characteristics for the overall group. The two

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Characteristic	LGG	Placebo	*P*-value
n	52	52	
Age	11.9 ± 3	11.2 ± 2.7	0.23*
Body weight (kg)	43 ± 16	41 ± 13	0.64*
Sex (M/F)	29/23	19/33	0.08†
Self-reported frequency of pain	3.3 ± 1.3	3.7 ± 1	0.15*
Self-reported severity of pain	3.9 ± 1.3	4.2 ± 1.3	0.23*
Use of drug treatment for abdominal pain	16 (31%)	15 (29%)	1.00†
School absenteeism because of abdominal pain	7 (14%)	11 (21%)	0.44†
Initial diagnosis			
Functional dyspepsia	10 (19%)	10 (19%)	>0.99‡
Irritable bowel syndrome	18 (35%)	19 (37%)	0.78‡
Functional abdominal pain	24 (46%)	23 (44%)	0.85‡

Values are presented as the mean ± S.D. or number (%).
* Wilcoxon's test.
† Chi-squared test.
‡ Fisher's exact test.

Table 1. Baseline characteristics

groups were comparable in regard to age, sex and baseline features of abdominal pain. Figure 1 is a flow diagram showing the subjects' progression through the study.

Overall study population

Overall, 18 of the 104 (17%) participants reported treatment success. Those in the LGG group were more likely to have treatment success than those in the control group (25% vs. 9.6%, RB 2.6, 95% CI: 1.05–6.6, NNT 7, 95% CI: 4–123). We found no significant difference between the groups for any other outcome measure (Table 2).

Functional dyspepsia

Overall, 3 of the 20 (15%) patients with FD reported treatment success, however, there was no statistically significant difference between the LGG and control groups. No difference between groups was found for any other outcome measure (Table 3).

Irritable bowel syndrome

Overall, 7 of the 37 (19%) participants with IBS reported treatment success. Those in the LGG group were more likely to have treatment success than those in the control group (33% vs. 5%, RB 6.3, 95% CI: 1.2–

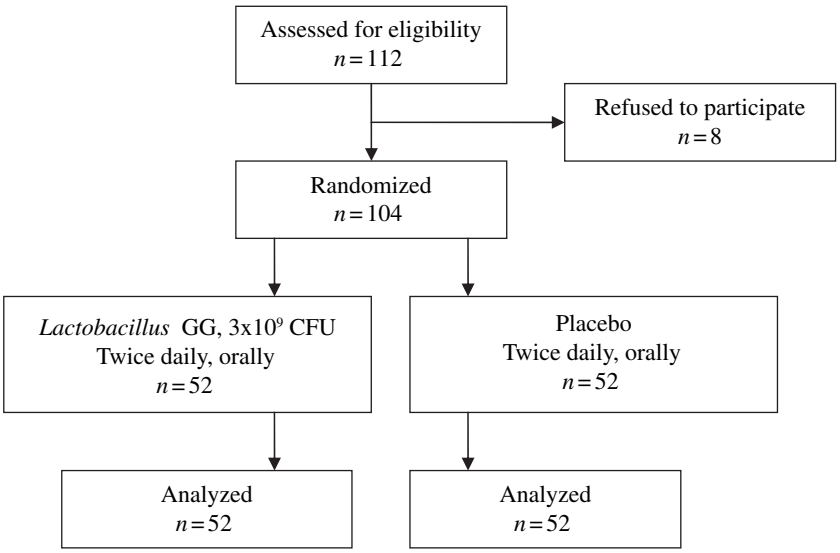

Figure 1. Flow diagram of the progress through the study.

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Table 2. Overall study population – outcome measures at baseline and at 4 weeks

Outcome	LGG ($n = 52$)	Placebo ($n = 52$)	Statistical method	Effect size (95% CI)	*P*-value
Treatment success	13 (25%)	5 (9.6%)	RB	2.6 (1.05–6.6)	0.08*
Improvement of symptoms	25 (48%)	23 (44%)	RB	1.1 (0.7–1.7)	0.76*
Self-reported severity of pain at baseline	3.9 ± 1.3	4.2 ± 1.3	MD	−0.3 (−1.4–0.8)	0.23†
Self-reported severity of pain at 4 weeks	2.5 ± 1.9	2.9 ± 1.5	MD	−0.4 (−1.9–1.1)	0.4†
Self-reported frequency of pain at baseline	3.3 ± 1.3	3.7 ± 1	MD	−0.4 (−1.4–0.6)	0.15†
Self-reported frequency of pain at 4 weeks	2.2 ± 1.7	2.6 ± 1.4	MD	−0.4 (−1.8–1.0)	0.32†
Use of medication at baseline	16 (31%)	15 (29%)	RR	1.1 (0.6–1.9)	1.00*
Use of medication at 4 weeks	9 (17%)	11 (21%)	RR	0.8 (0.4–1.8)	0.77*
School absenteeism at baseline	7 (14%)	11 (21%)	RR	0.6 (0.3–1.5)	0.44*
School absenteeism at 4 weeks	5 (10%)	0 (0%)	RR	5 (0.8–32)	0.07*

RB, relative benefit; RR, relative risk; MD, mean difference; CI, confidence interval.
Values are presented as the mean ± S.D. or number (%).
* Chi-squared test.
† Wilcoxon's test.

Table 3. Functional dyspepsia – outcome measures at baseline and at 4 weeks

Outcome	LGG ($n = 10$)	Placebo ($n = 10$)	Statistical method	Effect size (95% CI)	*P*-value
Treatment success	1 (10%)	2 (20%)	RB	0.5 (0.07–3.3)	1.00*
Improvement of symptoms	4 (40%)	4 (40%)	RB	1.0 (0.3–2.9)	1.00*
Self-reported frequency of pain at baseline	3.3 ± 1.2	3.1 ± 1.2	MD	0.2 (−0.9–1.3)	0.70†
Self-reported frequency of pain at week 4	2.7 ± 1.3	2.0 ± 1.6	MD	0.7 (−0.6–2.0)	0.26†
Self-reported severity of pain at baseline	4.2 ± 1.4	3.7 ± 1.3	MD	0.5 (−0.7–1.7)	0.58†
Self-reported severity of pain at week 4	2.9 ± 1.5	1.9 ± 1.3	MD	1 (−0.2–2.2)	0.14†
Use of medication at baseline	4 (40%)	4 (40%)	RR	1.0 (0.3–2.9)	1.00*
Use of medication at week 4	3 (30%)	2 (20%)	RR	1.5 (0.4–6.5)	1.00*
School absenteeism at baseline	2 (20%)	3 (30%)	RR	0.7 (0.2–2.8)	1.00*
School absenteeism at week 4	3 (30%)	0 (0%)	RR	Infinity (infinity to 0.9)	0.21*

RB, relative benefit; RR, relative risk; MD, mean difference; CI, confidence interval.
Values are presented as the mean ± S.D. or number (%).
* Fisher's exact test.
† Wilcoxon's test.

38, NNT 4, 95% CI: 2–36). The self-reported frequency of pain at 4 weeks was reduced in the LGG group, compared with the placebo group ($P = 0.02$); however, there was no difference between the groups in the severity of the pain ($P = 0.10$). We found no significant difference between the groups for any other outcome measure (Table 4).

Functional abdominal pain

Overall, 8 of the 47 (17%) patients with FAP reported treatment success. However, neither for this outcome nor for any other outcome, was there a significant difference between the LGG and control groups (Table 5).

Adverse effects

The LGG was well tolerated, and no adverse effects were reported.

DISCUSSION

In the overall study population, treatment with LGG, compared with placebo increased the chance of treat-

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Table 4. Irritable bowel syndrome – outcome measures at baseline and at 4 weeks

Outcome	LGG ($n = 18$)	Placebo ($n = 19$)	Statistical method	Effect size (95% CI)	*P*-value
Treatment success	6 (33.3%)	1 (5.3%)	RB	6.3 (1.2–38)	0.04*
Improvement of symptoms	10 55.5%)	6 (31.6%)	RB	1.8 (0.8–3.9)	0.19*
Self-reported frequency of pain at baseline	3.3 ± 1.4	3.7 ± 1.0	MD	−0.4 (−1.5–0.7)	0.41†
Self-reported frequency of pain at week 4	1.8 ± 1.7	3.1 ± 1.1	MD	−1.3 (−2.6–0.1)	0.02†
Self-reported severity of pain at baseline	3.7 ± 1.0	4.2 ± 1.0	MD	−0.5 (−1.4–0.4)	0.34†
Self-reported severity of pain at week 4	2.2 ± 2.1	3.2 ± 1.5	MD	−1 (−2.6–0.6)	0.10†
Use of medication at baseline	6 (33.3%)	4 (21.1%)	RR	1.6 (0.6–4.6)	0.48*
Use of medication at week 4	4 (22.2%)	3 (15.8%)	RR	1.4 (0.4–5.1)	0.69*
School absenteeism at baseline	4 (22.2%)	2 (10.5%)	RR	2.1 (0.5–9.1)	0.41*
School absenteeism at week 4	1 (5.5%)	0 (0%)	RR	Infinity (infinity to 0.3)	0.49*

RB, relative benefit; RR, relative risk; MD, mean difference; CI, confidence interval.
Values are presented as the mean ± S.D. or number (%).
* Fisher's exact test.
† Wilcoxon's test.

Table 5. Functional abdominal pain – outcomes measures at baseline and at 4 weeks

Outcome	LGG ($n = 24$)	Placebo ($n = 23$)	Statistical method	Effect size (95% CI)	*P*-value
Treatment success	6 (25%)	2 (9.1%)	RB	2.9 (0.7–11.7)	0.25*
Improvement of symptoms	11 (45.8%)	13 (59.1%)	RB	0.8 (0.5–1.4)	0.39*
Self-reported frequency of pain at baseline	3.4 ± 1.4	4.0 ± 0.7	MD	−0.6 (−1.6–0.4)	0.12†
Self-reported frequency of pain at 4 weeks	2.3 ± 1.8	2.4 ± 1.4	MD	−0.1 (−1.5–1.3)	0.93†
Self-reported severity of pain at baseline	4.0 ± 1.4	4.6 ± 1.4	MD	−0.6 (−1.8–0.6)	0.15†
Self-reported severity of pain at 4 weeks	2.6 ± 2.0	3.0 ± 1.5	MD	−0.4 (−1.9–1.1)	0.57†
Use of medication at baseline	6 (25%)	7 (30%)	RR	0.8 (0.3–2.0)	0.75*
Use of medication at week 4	2 (8.3%)	6 (27.3%)	RR	0.3 (0.1–1.2)	0.13*
School absenteeism at baseline	1 (4.2%)	6 (26.1%)	RR	0.2 (0.03–0.9)	0.05*
School absenteeism at week 4	1 (4.2%)	0 (0%)	RR	Infinity (infinity to 0.3)	1.00*

RB, relative benefit; RR, relative risk; MD, mean difference; CI, confidence interval.
Values are presented as the mean ± S.D. or number (%).
* Fisher's exact test.
† Wilcoxon's test.

ment success (defined as no pain); however, the wide CI around the result suggests that this evidence should be interpreted with caution. This difference did not impact the frequency and severity of the pain, as well as the use of medication for abdominal pain and school absenteeism. For the subgroup of patients with IBS, more children in the group taking LGG experienced treatment success. The number of patients who need to be treated to benefit from LGG treatment was four. Again, this result should be interpreted with caution, given the wide CIs. More participants in the IBS LGG group reported reduced frequency of pain, although there was no significant difference between the two groups in pain severity. We did not find any benefit of LGG treatment for a subgroup of patients with FD or FAP.

Several factors may explain the lack of an obvious effect of LGG. Some of them are related to the probiotic itself (e.g. wrong selection of the probiotic strain, too short a duration of treatment, inadequate dose). Others are related to the nature of the functional disorders, which were summarized in a recent paper.[20] In brief, these include a natural variation in symptoms,

regression towards the mean and unidentified or unintended cointerventions. Regression to the mean is the likelihood that patients consult when symptoms are particularly severe and improve with time owing to the natural variation in symptom severity and irrespective of trial participation.[21]

Dose and duration of treatment

We chose a daily intake of 3×10^9 CFU, which exceeds the minimum dose of 10^9 CFU/day suggested in the literature for therapeutic purposes.[22] The chosen duration of treatment (4 weeks) is in line with the current recommendations.[20] It is noteworthy, however, that the optimal dose and treatment duration of LGG therapy have not been clearly established.

Comparison with previous reports

Only one previous trial assessed the effect of LGG in paediatric patients with IBS.[17] In that study, 50 children fulfilling the Rome II criteria for IBS were given LGG 10^{10} CFU, twice daily, or placebo for 6 weeks. The primary outcome was the change in the abdominal pain severity score from baseline to the end of the treatment period. Secondary outcome measures included the number of responders vs. nonresponders in each group and changes in the remaining symptoms. The probiotic treatment was not superior to placebo (40% response rate in the placebo group vs. 44% in the LGG group, $P = 0.8$). There was no difference in other gastrointestinal symptoms, except for a lower incidence of perceived abdominal distention ($P = 0.02$ favouring LGG). The two studies are not directly comparable, primarily because of the differences in defining the outcomes measures.

Strengths and limitations

We used adequate methods for the generation of the allocation sequence and allocation concealment. We made efforts to maintain blinding of throughout selection, treatment, monitoring, data management and data analyses.

The potential limitations of this trial are that although the overall number of patients is adequate, the study may be underpowered for specific diagnosis; thus, the conclusions for patients with FD or IBS or FAP have to be interpreted with caution.

We used a placebo control group, which is considered an essential requirement for interventional studies of functional gastrointestinal disorders.[20] However, one cannot exclude the placebo effect that, at least, in adults ranges from 10% to 70% for FD[23] and 0% to 84% for IBS.[24] The placebo effect may be responsible for the lack of an obvious effect of the LGG treatment.

The trial was conducted in an academic centre oriented towards the diagnosis and treatment of children with functional gastrointestinal disorders. Thus, we cannot exclude the possibility that only more severely affected patients were included. The pattern of response to treatment may differ from that in the primary or secondary care setting.

As recommended,[20] we used diaries to measure outcomes and minimize recall bias. The validity of paper diary records is sometimes questioned.[25] Well-known problems with paper diaries include poor adherence and retrospective or just before a visit recording.[25] Limited resources did not allow us to use more reliable electronic diaries. To ensure adherence, one of the investigators contacted the participants by telephone.

For assessment of the severity of pain, we used the validated Face Pain Scale for self-assessment. The use of self-assessed outcome measures is recommended;[20] however, it is noteworthy that currently no measures for the functional gastrointestinal disorders are sufficiently validated to be recommended unequivocally as the primary outcome measure.[20]

CONCLUSIONS

Effective measures for treating FAPD are much needed. If confirmed in future trials, the administration of a probiotic strain with proved efficacy could constitute an easy and acceptable method. Our results suggest that LGG, as dosed in this study, may moderately increase treatment success, particularly among children with IBS, but does not affect pain severity. Further, larger trials are needed to confirm our findings.

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