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ORIGINAL PAPER

Influence of *E. coli* Strain Nissle 1917 (EcN) on Intestinal Gas Dynamics and Abdominal Sensation

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Abstract *E. coli* strain Nissle 1917 (EcN) is a probiotic clinically used with various indications. However, especially at the beginning of treatment, some patients report abdominal bloating. In a prospective, randomized, double-blind study in 30 healthy individuals we assessed the influences of EcN on intestinal gas dynamics and abdominal sensation. After one week without medication volunteers orally received 2.5–25 × 10^9 colony-forming units of EcN or placebo per day for 21 days. EcN was well tolerated and did not significantly affect abdominal symptoms, stool frequency or stool consistency. During gas challenge at different days no difference in the perception scores (range from 0 = no perception to 6 = pain) was observed between the two groups: the mean perception score was 1.2 (SD 0.2) in the EcN group and 1.4 (SD 0.2) in the placebo group. EcN had no relevant influence on intestinal gas dynamics.

Keywords Probiotics · *E. coli* strain Nissle 1917 · Abdominal bloating · Abdominal symptoms · Intestinal gas dynamics

Abbreviations

CFU	Colony-forming unit
EcN	*Escherichia coli* strain Nissle 1917
SF_6	Sulfurhexafluoride

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Introduction

The intestinal habitat of an individual human being contains 300–500 different bacterial species. In healthy individuals the composition of the microbiota is represented by both permanent and transient members that remain in constant equilibrium for long periods of time [1]. Probiotics have been defined as viable nonpathogenic microorganisms that, after being applied to humans or animals, confer health benefits on the host by improving the microbial balance of the indigenous microflora [2]. In humans, beneficial effects of various probiotics have been demonstrated for a variety of disorders such as acute infectious diarrhoea and inflammatory bowel disease [3–8].

One of the most intensively studied probiotics is *Escherichia coli* strain Nissle 1917 (EcN) of serotype O6:K5:H1, as a nonpathogenic representative of the human intestinal flora and the active ingredient of the probiotic drug Mutaflor®. The strain possesses none of the virulence properties typical for various intestinal and extraintestinal *E. coli* pathogens and shows competitive action against pathogenic microorganisms [9].

Positive effects of EcN on gastrointestinal function have been well documented for different indications such as acute and chronic diarrhoea, inflammatory bowel disease, chronic constipation, and irritable bowel syndrome. The most striking data for EcN exist with maintenance of remission of ulcerative colitis [10–11] and children's diarrhoea [12–13]. In a study the range of indications for EcN in clinical practice as well as safety and tolerance of EcN were investigated in 3,807 participants [14]. Stool frequency and consistency as well as abdominal bloating and pain improved in most patients. Nevertheless, one result of this trial was 2.8% of patients reporting side-effects, especially at the beginning of treatment, which

most frequently comprised abdominal bloating. However, it was not assessed how EcN affects the specific factors involved in the pathophysiology of abdominal bloating in healthy subjects under standardized and controlled conditions.

Materials and methods

Participants

We invited 30 healthy individuals without gastrointestinal complaints (17 women and 13 men, age 30–46 years) to participate in this study. Healthy subjects were recruited by public advertisement and completed a pre-entry questionnaire to establish the absence of gastrointestinal symptoms including difficulties in gas evacuation, feeling of excessive abdominal gas, or excessive gas evacuation. The protocol for the study was approved by the ethics committee II of the University of Heidelberg at Mannheim, Germany.

Study design

Using a double-blind design, participants were randomized to either verum (n = 15) or placebo (n = 15). From day 1–7 all participants were observed without receiving any medication. From day 8–28 they received two capsules of the study medication (verum or placebo) per day (Fig. 1). At study commencement, all participants underwent extensive examination including blood and pregnancy tests. After checking the inclusion and exclusion criteria all participants received diaries (see below). Control examinations on day 7 and day 11 included a check for compliance and completion of the diaries. A final examination at the end of the study (day 28) included an additional blood test, and assessment of adverse events and tolerance to the medication, which was marked on a scale ranging from 1 (*very good*) to 5 (*poor*) independently by the volunteer and by the physician.

As verum capsules of a bacterial preparation for oral use containing the nonpathogenic *Escherichia coli* strain Nissle 1917 (EcN) was chosen. Capsules were enteric coated in order to protect the microorganisms against gastric juice and contained 2.5–25 $\times$ 10^9 colony-forming units (CFU) of EcN (Mutaflor®, Ardeypharm, Herdecke, Germany). Placebo contained the same ingredients as verum but without EcN bacteria.

In a first group (group I) consisting of 20 participants (EcN: n = 10; placebo: n = 10) intestinal response to a jejunal gas challenge was measured at days 11 and 28 (after 4 and 21 days of treatment) in order to investigate differences between the treatment groups (Fig. 1). In a second group (group II) with 10 participants (EcN: n = 5; placebo: n = 5) gas challenge was measured on day 7 (before treatment), and on day 11 (after four days of treatment).

Diaries

During the entire observation period, all 30 participants completed a diary with questionnaires for each study day, regardless of the date of the gas transit test. We asked for stool frequency (total number of stools per day) and used a visualized scale to classify stool consistency (type 1: *hard and lumpy*; type 2: *sausage like but lumpy*; type 3: *sausage-like with superficial cracks*; type 4*: sausage like and soft*; type 5: *soft clots with sharp rims*; type 6: *fluffy clots with straggly rims* and type 7: *liquid, unformed*). Abdominal sensation, urge to defecate, bloating, flatulence, borborygmus, pain, nausea, and vomiting were separately scored on a 0–3 scale (0: *no or vague sensation*; 1: *bothersome but short duration*; 2: *frequently but not affecting daily activities*; 3: *severe and frequent sensation, affecting daily activity or other sensations*). Furthermore, daily nutritional habits and possible use of other probiotics or medication were assessed in order to control potentially confounding

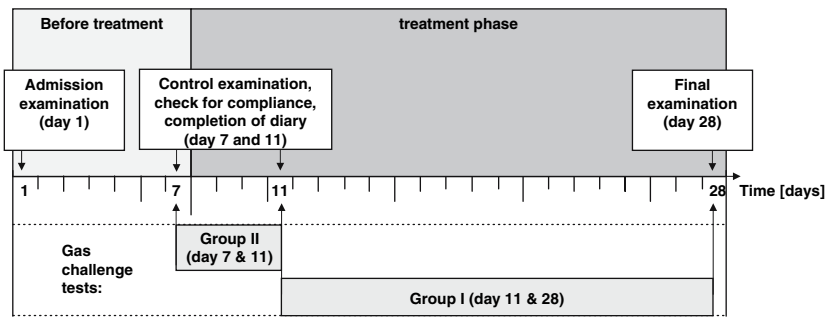

Fig. 1 Experimental design: all volunteers underwent an admission examination on day 1, control examinations, including check of compliance and diary (day 7 and 11), and a final examination on day 28. In group I (n = 20) gas-challenge testing was performed during the treatment phase on days 11 and 28. In group II (n = 10) gas-challenge testing was performed before treatment on day 7 and during the treatment phase on day 11

factors. The volunteers marked daily by ticking yes or no, whether they felt that their diet was well balanced, i.e., they ingested plenty of fruit and vegetables, whole wheat products, and milk products or nutrients rich in fat.

Gas transit test

Specific responses to an intestinal gas challenge can be measured under controlled conditions by aids of the intestinal gas transit test. During the two days preceding the gas transit test, participants were instructed to follow a diet excluding gas-producing foodstuffs. At the beginning of the tests, participants were intubated after an 8 h fast with a multilumen polyvinyl tube assembly (outer diameter 3.2 mm) that incorporated a gas infusion channel (inner diameter 1.2 mm) with several openings at the tip of the tube. The intestinal tube was orally introduced and fluoroscopically positioned with the gas infusion channel approximately 10 cm distal of the ligament of Treitz. After this, the rectal tube was introduced and the abdominal belt adjusted. All tests were conducted in a quiet, isolated room with the subjects placed supine in bed at an angle of 30°. Continuous gas infusion was started after a 30-min equilibration period for the remaining 120-min test period. Gas was infused continuously into the jejunum at 12 ml/min with a modified volumetric pump (Perfusor ED 2, B. Braun Melsungen AG, Melsungen, Germany), containing 88% nitrogen, 6.5% carbon dioxide, and 5.5% oxygen, bubbled into water for saturation. A nonabsorbable, stable gaseous marker, sulfurhexafluoride (SF_6), at a final concentration of 0.5% was added to the gas mixture and was continuously infused during the study to measure volumes of endogenous gas.

Intestinal gas evacuation was hermetically collected via a rectal tube (20F Folatex catheter, Mentor, Porges S.A.S., France) with a computerized electronic barostat (Tensostat-Barostat; Sicie, Barcelona, Spain) and a sample of gas, evacuated during each 15-min period, was stored in metallized bags (Iris-Wagner, Wagner-Analysen-Technik Vertriebs GmbH, Bremen, Germany) for later analysis of SF_6 concentration by infrared absorbance. A nonstretch 5-cm-wide band was adjusted around the abdomen over the umbilicus by means of four elastic bands after placing the subjects in bed. Girth measurements were taken at 15-min intervals while the subjects were breathing relaxed as the average of inspiratory and expiratory determinations over three consecutive respiratory excursions, as described and validated previously [15].

In each volunteer, conscious abdominal perception was measured at 15-min intervals. By using a graded questionnaire the intensity and type of sensation perceived was measured. It included individual graphic rating scales from 0 (no perception) to 6 (pain) for each of the following abdominal sensations: (a) *pressure/bloating*, (b) *cramp/colic*, (c) *stinging*, and (d) *other type*. A separate tick box (yes/no) was included to mark belching. Participants were asked to score any sensation (one or more perceived simultaneously) on the scales. In addition, an anatomical questionnaire was used to measure the location and extension of the perceived sensations. This second questionnaire incorporated a diagram of the abdomen divided into nine regions corresponding to the epigastrium, periumbilical area, hypogastrium, both hypochondria, flanks, and iliac fossae. Participants were instructed to mark the abdominal region(s) of the sensations.

Data analysis and statistics

Diaries

The homogeneity of the groups was tested by using the Mann–Whitney *U* test. Comparison of nonparametric data, including stool frequency and consistency, specific abdominal complaints and self assessment of nutritional habits and possible use of other probiotics or medication was performed by the Wilcoxon signed-rank test for intra- and intergroup analysis. Paired comparisons pre-treatment versus post-treatment and unpaired comparisons for intergroup comparisons were performed in each group of subjects for abdominal symptoms, bowel movements, and stool consistency.

Gas transit test and endogenous gas volumes

In each subject the volume of gas retained within the gut was calculated as the difference between the volume of gas infused and the volume of gas recovered. Based on SF_6 recovery (volume of gas collected × SF_6 concentration) the volume of exogenous gas recovered was calculated and subtracted from the total volume of gas in the evacuated probe [26]. Abdominal perception during the tests was measured and rated in intervals of 15 min. In order to calculate the frequency of a sensation (percentage distribution) each abdominal sensation in every subject was counted and scored. By using the anatomical questionnaire percentages of sensations in a single abdominal region as well as percentages in more than one region were calculated. Changes in abdominal perimeter during the tests were assessed. In each group mean values of parameters (gas retention, abdominal perception and girth changes) were measured in 15-min intervals.

Normally distributed parametric data were compared by using the Student *t*-test. Nonparametric data, including perception, were compared by using Wilcoxoń s signed-rank test. The frequency of symptoms was compared by using the chi-squared test. Correlations between paired data were examined by linear regression analysis.

Results

Abdominal complaints, stool frequency, and consistency

In the placebo group, the frequency of abdominal symptoms (pain, bloating, borborygmus, nausea and/or vomiting) before and at 7-days intervals during the treatment period were virtually unchanged ($P > 0.05$). Also, the frequency of defecation and stool consistency were not significantly changed during the 28 days of observation (Table 1).

In the verum group, abdominal symptoms before and at seven day intervals during treatment were not significant different. Especially in the first week of treatment with EcN, when changes were likely to occur, the frequency of abdominal symptoms was practically unchanged, including the following sensations: abdominal pain, bloating, flatulence, borborygmus, nausea, and/or vomiting (Table 1, $P > 0.05$). The frequency of defecation and stool consistency was not significantly changed by EcN during the observation period ($P > 0.05$).

Additionally, when abdominal symptoms did occur, their severity was comparable in both groups and also unchanged in the course of the observation ($P > 0.05$). There was mostly no or only a vague sensation (Table 2).

Intestinal gas transit test

General conditions

All subjects in both treatment groups tolerated the procedure and completed the 120-min gas infusion test. There were no signs of unobserved gas loss, including gas inflow or outflow problems.

Equilibration period

During the equilibration period 30 min prior to the intestinal gas infusion, endogenous gas evacuation was very small and similar (14 ± 4 ml/30 min; pooled data) on both study days.

Gas transit, abdominal perimeter, and perception

In all subjects gas infusion in the jejunum was effectively propelled without gas retention, and without showing difference between the groups (Figs. 2, 3).

Gas infusion was tolerated by all participants with minimal perception either before or during the treatment with verum or placebo (Figs. 4, 5). Perception scores were similar in both groups with a mean perception score of 1.2 ± 0.2 in the probiotic group (pooled data) and 1.4 ± 0.2 in the placebo group. No significant changes in abdominal perimeter during the jejunal gas infusion period were observed.

Volumes of endogenous gas

Volumes of expelled endogenous gas were small at the end of the 120-min gas infusion during the gas challenge, ranging between 28 and 49 ml in both groups without revealing significant differences between the groups. Also, no significant variations were detected during the first 60 min of jejunal gas infusion, again without significant differences between the groups ($P > 0.05$, Table 3).

Assessment of nutritional habits and use of other probiotics or concomitant medication

Nutritional habits were assessed in order to control potential influences on perception. The majority of volunteers rated their diet as well balanced during the whole study period. With regard to this potential confounding

Table 1 Influences of *E. coli* strain Nissle 1917 and placebo on frequency of abdominal symptoms (pain, bloating, flatulence, borborygmus, nausea, and/or vomiting in number of days per week volunteers perceived any abdominal complaint), frequency of defecations (in number of bowel movements per week) and stool consistency on a score from *hard and lumpy* (1) to *liquid, unformed* (7)

	Before treatment		Treatment phase					
	Days 1–7		Days 8–14		Days 15–21		Days 22–28	
	Verum	Placebo	Verum	Placebo	Verum	Placebo	Verum	Placebo
1. Abdominal pain	0.2 ± 0.1*	0.5 ± 0.3*	0.9 ± 0.3*	0.9 ± 0.5*	0.8 ± 0.3*	1.1 ± 0.6*	0.9 ± 0.4*	0.7 ± 0.4*
2. Bloating	1.3 ± 0.4*	1.7 ± 0.6*	2.0 ± 0.5*	1.8 ± 0.6*	2.5 ± 0.6*	1.9 ± 0.6*	2.2 ± 0.6*	1.8 ± 0.6*
3. Flatulence	1.7 ± 0.4*	2.2 ± 0.6*	2.6 ± 0.5*	2.3 ± 0.5*	2.3 ± 0.6*	2.4 ± 0.5*	2.2 ± 0.7*	2.1 ± 0.5*
4. Borborygmus	1.4 ± 0.4*	2.1 ± 0.7*	1.5 ± 0.3*	2.5 ± 0.7*	1.9 ± 0.6*	2.1 ± 0.6*	1.7 ± 0.5*	1.9 ± 0.6*
5. Nausea and/or vomiting	0.0 ± 0.0*	0.2 ± 0.2*	0.6 ± 0.2*	0.3 ± 0.2*	0.2 ± 0.1*	0.3 ± 0.3*	0.2 ± 0.1*	0.3 ± 0.3*
6. Stool frequency	9.9 ± 0.9*	9.8 ± 1.0*	10.2 ± 1.1*	10.1 ± 1.2*	9.8 ± 1.0*	10.4 ± 1.3*	8.6 ± 0.9*	8.9 ± 1.1*
7. Stool consistency	3.1 ± 0.1*	3.4 ± 0.1*	3.1 ± 0.1*	3.4 ± 0.1*	3.0 ± 0.1*	3.4 ± 0.1*	2.9 ± 0.1*	3.4 ± 0.7*

*$P > 0.05$

Table 2 Severity of abdominal symptoms (0: *no or vague sensation*; 1: *bothersome but short duration*; 2: *frequently but not affecting daily activities*; 3: *severe and frequent sensation, affecting daily activity or other sensations*) before and during treatment with EcN (verum) or placebo, expressed in percentage

	Severity	Before treatment		Treatment phase					
		Week 1		Week 2		Week 3		Week 4	
		Verum % (n = 15)	Placebo % (n = 15)	Verum % (n = 15)	Placebo % (n = 15)	Verum % (n = 15)	Placebo % (n = 15)	Verum % (n = 15)	Placebo % (n = 15)
Abdominal pain	0	97	90	87	88	90	84	89	90
	1	3	9	13	10	9	14	10	9
	2	0	1	0	2	1	2	1	1
	3	0	0	0	0	0	0	0	0
Bloating	0	83	76	72	74	66	79	66	73
	1	14	21	24	18	29	16	34	26
	2	3	3	3	8	5	5	0	1
	3	0	0	1	0	0	0	0	0
Flatulence	0	76	69	63	67	67	66	69	69
	1	21	29	30	28	31	31	26	27
	2	3	1	6	5	2	3	5	4
	3	0	1	1	0	0	0	0	0
Borborygmus	0	80	70	80	65	73	71	75	72
	1	18	29	15	30	23	22	25	25
	2	1	1	4	5	3	7	0	3
	3	1	0	1	0	1	0	0	0
Nausea and/or vomiting	0	100	97	92	97	98	95	98	97
	1	0	3	8	3	2	5	2	3
	2	0	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0	0

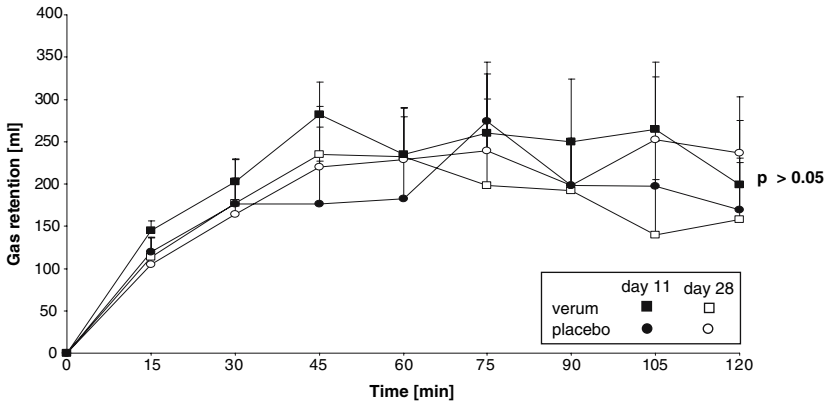

Fig. 2 Retained gas during gas-challenge tests in group I (n = 20) on days 11 and 28. Retained gas was calculated as volumes of infused gas (12 ml/min) minus volumes of gas evacuated in intervals of 15 min during continuous jejunal gas infusion

factor no statistically significant difference between the groups were found. No other probiotic or medication was used (data not shown).

Safety and tolerance

As assessed by the volunteers, the study medication was well tolerated; overall tolerance was rated as *very good* or *good* in the EcN group (100.0%) and in the placebo group (83.3%). According to the physician's assessment the corresponding values were both 100.0%. Laboratory tests showed no significant alterations. Adverse events and number of volunteers with remarks, which means volunteers with any adverse event, are given in Table 4, comprising nasopharyngitis, acute tonsillitis, pyrexia, headache, and initial insomnia.

Discussion

In this study we demonstrate for the first time under standardized and well-controlled conditions that high dosages of

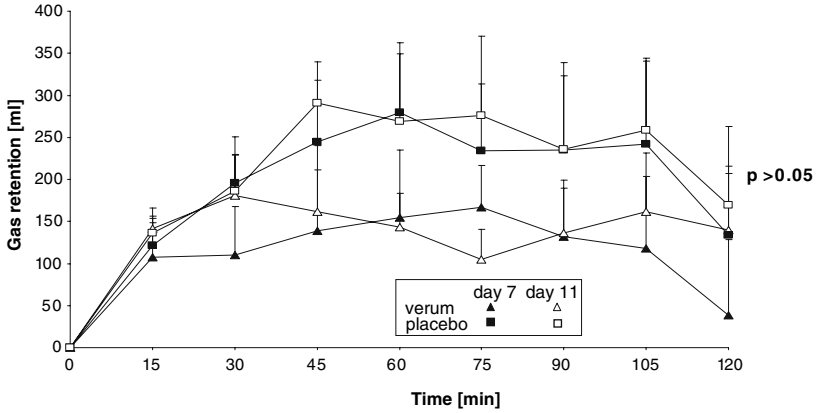

Fig. 3 Retained gas during gas-challenge tests in group II (n = 10) on days 7 and 11. Retained gas was calculated as volumes of infused gas (12 ml/min) minus volumes of gas evacuated in intervals of 15 min during continuous jejunal gas infusion

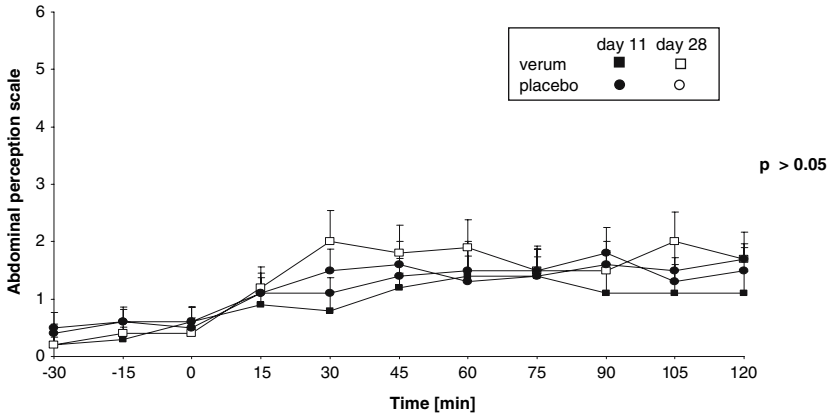

Fig. 4 Abdominal perception during gas challenge tests in group I (n = 20) on days 11 and 28. The questionnaire included four graphical rating scales graded from 0 (no perception) to 6 (pain)

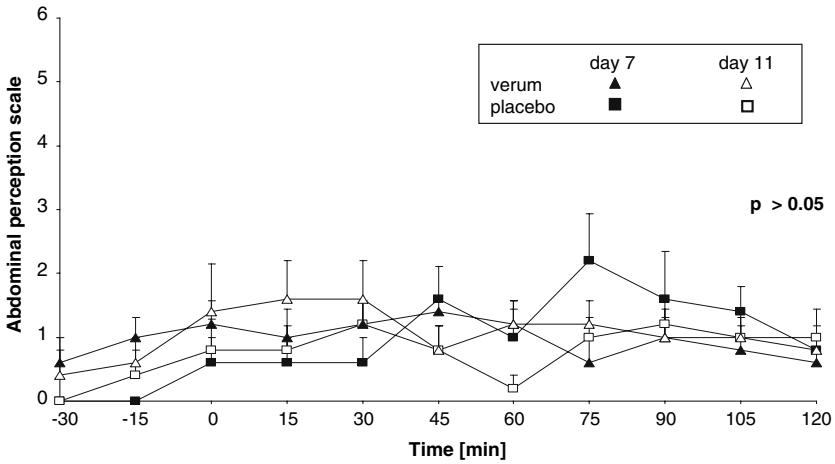

Fig. 5 Abdominal perception during gas challenge tests in group II (n = 10) on days 7 and 11. The questionnaire included four graphical rating scales graded from 0 (no perception) to 6 (pain)

Table 3 Volumes (ml) of expulsed endogenous gas during gas challenge tests on days 7, 11, and 28

	Day 7		Day 11		Day 28	
	Verum (n = 5)	Placebo (n = 5)	Verum (n = 15)	Placebo (n = 15)	Verum (n = 10)	Placebo (n = 10)
60 min	139 ± 40	93 ± 37	146 ± 30	125 ± 20	152 ± 41	133 ± 25
120 min	30 ± 10	28 ± 8	55 ± 14	45 ± 16	49 ± 9	46 ± 11

E. coli strain Nissle 1917 (EcN) do not affect intestinal gas dynamics or volumes of endogenous intestinal gas in healthy individuals. Organisms used as probiotics in humans include various species of bacteria and fungi. They especially improve symptoms such as bloating and flatulence in patients with functional abdominal disorders [16, 17].

One of the most intensively studied probiotic is EcN. We decided to investigate the effect of this *E. coli* strain on

Table 4 Adverse events and number of volunteers with remarks, meaning volunteers marking any adverse event

Adverse events	Safety analysis	Group I		Group II	
	Total $n = 30$	Verum $n = 10$	Placebo $n = 10$	Verum $n = 5$	Placebo $n = 5$
Nasopharyngitis	2	–	2	–	–
Acute tonsilitis	1	–	–	–	1
Pyrexia	1	–	–	–	1
Headache	1	–	1	–	–
Initial insomnia	1	1	–	–	–
Volunteers with remarks	5	1	2	–	1

intestinal gas dynamics because the rare side-effects reported are mostly cases of bloating and flatulence. These symptoms especially occur in patients with chronic constipation or at the beginning of treatment [18].

The cause of flatulence is well understood as it is linked to increased intestinal gas production [19]. The pathophysiology of bloating is more complicated; four main factors are involved: a subjective bloating sensation, objective abdominal distention, increased volume of intraabdominal contents, and low muscular activity of the abdominal wall [17, 20]. The mode of action of probiotics regarding bowel function is not fully understood. Changes within the intraluminal milieu are often discussed. Endogenous gas production is changed via modification of fermentation processes. In addition, via inactivation of bile acids, a decreasing effect on the secretion of colonic fluids and motility is described. This alteration of gastrointestinal motility may also contribute to symptoms improvement induced by probiotics.

We applied the intestinal gas challenge test before and during treatment with two capsules EcN (containing 2.5–25×10^9 CFU each) or placebo per day to focus on the different factors of abdominal bloating. We used a standardized, well-controlled, and comparable setting. In a randomized, double-blind, placebo-controlled fashion we evaluated the tolerance to EcN with special respect to the occurrence of symptoms such as abdominal bloating, flatulence, and abdominal pain as well as alterations of bowel habits. In a first group of healthy volunteers (group I), we applied the gas challenge test in order to compare abdominal symptoms, changes of girth and intestinal gas handling at different days of treatment with EcN or placebo. At this stage we observed no significant differences between the two groups. In a second set of subjects (group II) we applied the jejunal gas challenge before therapy and on day 4 of medication. In contrast to our initial hypothesis, intragroup analysis as well as comparison with the placebo group revealed no statistically significant differences. After summing up these observations we conclude that the given doses of EcN do not influence intestinal gas dynamics in healthy subjects.

Intestinal gas transit appears to be regulated by the normal balance of stimulatory and inhibitory reflexes, leading to healthy subjects tolerating a wide range of intraluminal gas loads without symptoms [15, 21–24]. Especially in constipated patients, symptoms such as abdominal pain and bloating seem to accompany increased bowel content, which might be responsible for many abdominal sensations. In addition, trapped colonic gas may worsen these complaints [25–27]. In contrast, rapid transit of liquids is sometimes misinterpreted as bloating in individual patients with diarrhoea [26, 27]. This is why it is important to document concomitant constipation and diarrhoea exactly when investigating sensations of abdominal pain and bloating. Both can significantly influence the study results as confounding factors.

Diet as one important factor contributing to increased colonic gas production [19, 28, 29] and being involved in abdominal symptoms was well controlled in our study. Nutritional habits were compared during the four weeks of the observation period and standardized two days prior to the gas infusion test. The standardized diet excluded gas-producing foodstuff. Another factor in the pathogenesis of abdominal bloating is the total volume of endogenous gas [19]. In patients with functional bloating, proof of a direct correlation between abdominal symptoms and an increase in intestinal gas volume is still being discussed. We expected EcN to cause side-effects explained by different endogenous gas volumes especially at the beginning of treatment. With the gas infusion test we performed endogenous gas washout with a marker gas (SF_6) at day 7 (before treatment), day 11 (after 4 days of treatment), and day 28 (after 21 days of treatment). Astonishingly, volumes of expelled endogenous gas were very similar in all volunteers groups.

The impact of our study is the provision of additional data on the effects of EcN on intestinal function and sensation in humans, which is necessary to understand the efficacy of this microorganism in maintaining of health.

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