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Auswirkung von Lactobacillus casei Shirota auf die Transitzeit bei Patienten mit chronischer Obstipation

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Effect of *Lactobacillus casei* Shirota on colonic transit time in patients with chronic constipation

Introduction

Chronic constipation is one of the leading health problems in western countries. Its prevalence is variable with 5–30%, causing 2.5 million physician visits, 92,000 hospitalizations and resulting in laxative sales of several hundred million dollars a year in the U.S. alone [1]. A recent review reported constipation rates of 5–35% in the general population in Europe [2].

Chronic constipation can be classified into three subgroups: 1. normal-transit constipation, 2. defecatory disorders and 3. slow-transit constipation (STC) [1]. Idiopathic STC is based on a motility disorder of the colon which leads to severely delayed transit (colonic transit time >72 h) and a reduced stool frequency (twice a week or less) [3, 4]. This clinical syndrome mainly affects women.

During the past 10 years several clinical studies have already been conducted to evaluate the effect of probiotics on functional bowel disorders, such as the irritable bowel syndrome (IBS) and constipation. The composition of the intestinal flora might be directly or indirectly linked to various disorders. Lower amounts of *Lactobacillus* spp. were present in the samples of diarrhea predominant IBS patients, whereas constipation predominant IBS patients showed increased amounts of *Veillonella* spp. [5]. Adminstration of a probiotic preparation containing *Escherichia coli* Nissle 1917 has shown an improvement of IBS-related constipation [6, 7] and a probiotic beverage containing *Lactobacillus casei* Shirota (LcS) resulted in a significant improvement in self-reported severity of constipation, stool frequency and stool consistency [8]. Therefore, the administration of LcS may enhance transit time in the colon.

The impact of LcS on the colonic transit time in STC patients (colonic transit time >72 h) was investigated in a double-blind, placebo-controlled, randomized clinical trial.

Methods

Subjects

Included in the study were 24 female patients with an average age of 50 years and with STC characterized by a transit time >72 h. For confirmation of diagnosis a measurement of colonic transit time (Hinton test) during the last 6 months was used.

Patients who had regularly consumed probiotic products or had taken laxatives, anticholinergics or antibiotics during the past 4 weeks were excluded. In addition, patients who regularly consumed more than 40 g of alcohol per day or were smokers and patients with organic causes or milk protein allergy were not included in this study. Patients were asked to maintain their usual behavioral and nutritional patterns during the course of the study.

The study protocol was approved by the Ethics Committee of the University Clinic Mannheim and all subjects signed a written informed consent prior to participation in the study.

Experimental design

The 24 female STC patients were randomly assigned to the verum (fermented milk drink containing 6.5×10^9 cfu of LcS) (n=12) or placebo (milk drink without LcS) (n=12) group. The whole study period had a duration of 10 weeks. A run-in period of 2 weeks without intervention patients was used for the initial investigation. During the 4-week intervention period verum or placebo was taken daily with the breakfast meal. At the end of the 4-week follow-up period a final examination of the patients took place.

During the whole study period patients were asked to fill out diaries and questionnaires. The Bristol Stool Form Scale was completed daily to obtain information about stool frequency and consistency [9]. Presence of constipation-related symptoms was recorded by a weekly questionnaire [10] during the entire study period of 10 weeks. In this questionnaire, frequency of bowel movements, painful evacuation, incomplete evacuation, ab-

Tab. 1 Transit times before and after intervention with LcS

	Before intervention (h)				After intervention (h)			
	Total	Right colon	Left colon	Sigmoid/ rectum	Total	Right colon	Left colon	Sigmoid/ rectum
Verum	95.6	22.7	44.6	28.3	76.5	22.5	37.3	16.7
Placebo	95.8	26.8	47.5	21.5	87.1	26.2	43.9	17.0

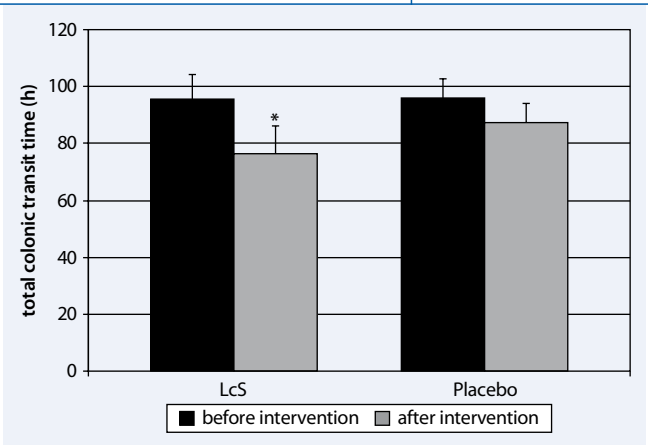

Fig. 1 ▲ Total colonic transit times of STC patients before and after a 4 week intervention with a fermented milk drink containing LcS or placebo (p=0.05, LcS before vs. after intervention)

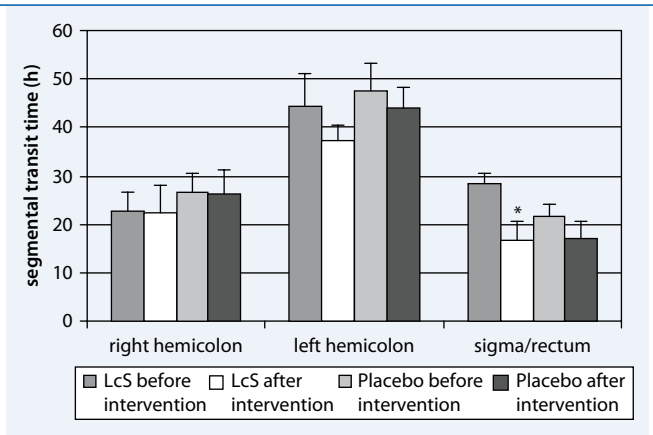

Fig. 2 ▲ Segmental colonic transit times of STC patients before and after a 4 week intervention with a fermented milk drink containing LcS or placebo (p=0.007, sigmoid transit time, LcS before vs. after intervention).

dominal pain, length of time per attempt, assistance for defecation and unsuccessful attempts for evacuation per 24 h were determined and a scoring range of 0–4 was derived (with the exception of "assistance of defecation", which is 0–2). The global score was obtained by adding individual scores. A score of zero indicates normal bowel habits and a maximum score of 26 indicates severe constipation.

The general gastrointestinal symptoms were compared by a weekly questionnaire [11]. This gastrointestinal symptom rating scale (GSRS) consists of 15 items including abdominal pain, heartburn, acid regurgitation, sucking sensations in the epigastrium, nausea and vomiting, borborygmus, abdominal distension, eructation, increased flatus, decreased passage of stools, increased passage of stools, loose stools, hard stools, urgent need for defecation and feeling of incomplete evacuation. A scoring range of 0–3 was derived where zero (0) indicates absence and 3 an extreme degree of the symptom.

The colonic transit time was measured by the modified Hinton test within 6 months before the start of intervention and directly after the intervention with LcS or placebo.

Modified Hinton test

The patients ingested two gelatin capsules containing together 20 radiopaque pellets in total on 6 consecutive days and at the same time of the day. On day 7 a single abdominal X-ray in standing position was obtained. On this X-ray picture the following lines were drawn from the spine of the fifth lumbar vertebra (L5): one cranial line in the middle of the spine and one tangential line along the inner rim of the wing of the ileum to the right and to the left, down to the hip joints. In this manner the right and the left hemicolon and the rectosigmoid were defined as separate regions for evaluation. Only the number of remaining markers in the respective segment of the large intestine, as well as the total number of markers in the complete colon was determined.

The transit time was calculated by the following equation [12]: Colonic transit time (h)=sum of retained markers x 1.2 (corresponding to the time interval between the marker intake).

The normal values (in hours) for segmental transit times are as follows [10]: right hemicolon 11±1, left hemicolon 11±1 and rectosigmoid 12±1.

Statistical analysis

Medians with minimum and maximum values were assessed for each test or questionnaire and compared at different time points to baseline per treatment group using the Friedman test or Wilcoxon-test. The Friedman test is a non-parametric test for comparing more than two dependent samples without assuming normal distribution. Differences between verum and placebo were analysed by the Mann-Whitney U-test. This non-parametric test assesses whether two independent samples of observations have equally large values.

Results

There were no differences in the baseline characteristics (age and body mass index) between the verum and placebo groups. They were also similar in characteristics such as gender, smoking habits, consumption of tea, coffee and keeping a special diet. Patients were not allowed to consume other probiotic products during the intervention but two patients took laxatives during the intervention period and were omitted from the statistical analysis. The primary endpoint was a change of the colonic transit time before and after the consumption of a probiotic drink versus placebo. The secondary endpoints were the impact of this probiotic drink on stool frequency and consistency and general gastrointestinal symptoms compared with placebo.

Measurement of colonic transit time (modified Hinton test)

The Hinton test was performed within a maximum of 6 months before the intervention period and 1 day after the intervention period (first day week 5). Patients receiving verum showed a significant decrease in the total colonic transit time after LcS intake (p=0.05, **Fig. 1**). The mean value of colonic transit time was accelerated from 95.6 h before to 76.5 h after the treatment (**Tab. 1**). This difference was mainly due to the improvement of the sigmoid transit time from 28.3 h to 16.7 h (p=0.007, **Tab. 1**, **Fig. 2**).

In the placebo group, the total colonic transit time as well as the segmental colonic transit times were not significantly affected during the intervention period (p=0.282).

Stool frequency and consistency

Medians of stool frequency and consistency with minimum and maximum values were assessed and compared to baseline on weeks 0, 2, 4 and 8 for verum and placebo separately by the Friedman test. Some improvement on stool frequency without statistical significance could be observed in STC patients receiving verum when analyzing the whole course of the study from week 0 to week 8 (Friedman test: p=0.07) but not in patients receiving placebo. However, the direct comparison of the number of defecations at week 0 (3 defecations) and week 4 (4 defecations) was not statistically significant (Wilcoxon test: p=0.16). The Mann-Whitney U-test showed no differences between groups.

Constipation-related and gastrointestinal symptoms

Regarding the constipation-related symptom score, medians with minimum and maximum values were assessed. The Friedman test was used to see whether the score differed during the study compared to week 0. Differences between verum and placebo were analyzed by the Mann-Whitney U-test. The global score of STC patients improved during the study in both groups (verum: p=0.042, placebo: p=0.008).

The course of gastrointestinal symptoms was analyzed according to the medians with minimum and maximum values. Groups started at different baselines: verum patients complained about more gastrointestinal symptoms at week –1 in comparison to the placebo group. As in all other statistical analyses about the questionnaires before, only week 0 but not week –1 was taken into consideration. Gastrointestinal symptoms in STC patients who received verum improved during the study in a combined analysis of weeks 0, 2, 4 and 8 (p=0.045, Friedman test). The placebo group did not change significantly. However, a direct comparison of weeks 0 and

Abstract · Zusammenfassung

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Effect of *Lactobacillus casei* Shirota on colonic transit time in patients with chronic constipation

Abstract

Background. Slow-transit constipation (STC) is caused by a motility disorder of the colon which leads to delayed transit (>72 h). The probiotic strain *Lactobacillus casei* Shirota (LcS) has been shown to improve constipation-related symptoms, such as stool frequency and consistency. A randomized double-blind placebo-controlled trial was performed to determine the effect of LcS on the colonic transit time in patients with STC.
Patients and methods. Colonic transit time of all consecutive outpatients with chronic constipation was determined by the Hinton test using radiopaque markers. Patients with a transit time longer than 72 h were included in the study. A total of 24 patients received either a dairy drink containing 6.5×10^9 colony forming units (cfu) of LcS or a placebo daily for 4 weeks. General gastrointestinal symptoms were evaluated weekly by a questionnaire and the measurement of colonic transit time was repeated after the intervention.
Results. The intake of LcS resulted in a significant acceleration of the total colonic transit time from 95.6 h to 76.5 h (p=0.05). This effect was most pronounced in the sigmoid and rectum transit time (p<0.007). In the placebo group no statistically significant change in the total colonic transit time was observed (before: 95.8 h, after: 87.1 h, p=0.282)
Conclusion. The daily intake of a probiotic drink containing LcS significantly reduced the colonic transit time in patients with STC.

Keywords

Probiotics · Constipation · Transit time · Shirota · Clinical trial

Auswirkung von *Lactobacillus casei* Shirota auf die Transitzeit bei Patienten mit chronischer Obstipation

Zusammenfassung

Hintergrund. Slow-transit constipation (STC) basiert auf einer Kolonmotilitätsstörung, welche zu einer verzögerten Transitzeit führt (>72 h). Es wurde bereits gezeigt, dass der probiotische Bakterienstamm *Lactobacillus casei* Shirota (LcS) Verstopfungssymptome wie Stuhlfrequenz und – konsistenz verbessern kann. Der Effekt von LcS auf die Transitzeit bei STC-Patienten wurde nun randomisiert doppelblind und Placebo-kontrolliert untersucht.
Patienten und Methoden. Bei ambulanten Patienten mit chronischer Verstopfung wurde konsekutiv die Kolontransitzeit durch den Hinton-Test mit röntgenfähigen Markern gemessen. Patienten mit einer Transitzeit über 72 Stunden wurden in die Studie eingeschlossen. Insgesamt 24 Patienten erhielten täglich ein Getränk mit LcS (6,5-mal 10^9 KBE) oder ein Placebo über einen Zeitraum von 4 Wochen. Danach wurde die Messung der Transitzeit wiederholt. Allgemeine gastrointestinale Symptome wurden durch einen wöchentlichen Fragebogen erfasst.
Ergebnisse. LcS führte zu einer signifikanten Beschleunigung der Kolontransitzeit von 95,6 auf 76,5 Stunden (p=0,05). Dieser Effekt war bei der sigmoiden und rektalen Transitzeit am ausgeprägtesten (p<0,007). Die Veränderung der Transitzeit von 95,8 auf 87,1 Stunden (p=0,282) in der Placebogruppe erreichte keine statistische Signifikanz.
Schlußfolgerung. Die tägliche Gabe eines probiotischen Getränks mit LcS reduzierte signifikant die Kolontransitzeit bei STC-Patienten.

Schlüsselwörter

Probiotika · Obstipation · Transitzeit · Shirota · Klinische Studie

2 as well as weeks 0 and 4 did not display significant differences.

Discussion

This double-blind, randomized, controlled study demonstrates that 65 ml (6.5×10^9 cfu) per day of a fermented milk drink with LcS improves the delayed colonic transit times in patients with STC. This effect is mainly due to an acceleration of the transit in the sigmoid and rectum. The number of stools per week and the stool consistency, however, did not differ significantly between verum and placebo groups. Maybe a trend towards an increase in stool frequency could be observed. Recording constipation-related and gastrointestinal symptoms displayed no significant changes during the intervention period in either group. The number of patients included in this study was too low to expect clear data on symptoms.

An improvement of constipation, stool frequency and consistency by a probiotic drink containing LcS was already proven in 70 individuals with chronic constipation over a period of 4 weeks in a double-blind, placebo-controlled, randomized study [8]. From the second week of the study onwards the consumption of a probiotic led to significant improvements in the severity of the constipation and stool frequency and consistency. At the end of the study 89% of patients receiving the active sample reported a reduction of constipation symptoms. Several reasons can be assumed for the increased gut motility: (a) the consumption of LcS results in increased bacterial cell mass, hence increases stool weight [13] and thereby the intestinal wall is dilated and peristalsis is stimulated, thus shortening transit time [14]. (b) The consumption of LcS may lead to the formation of organic acids (acetate, butyrate, propionate, lactate etc.) during fermentation in the colon [15]. It has been demonstrated in *in vitro* and animal studies that these short chain fatty acids (SCFA) produced by bacterial fermentation of carbohydrates are capable of stimulating motility in the ileum and colon [16, 17, 18]. Research on a pig model showed an increase in the motility of the sigmoid colon after 2 weeks of feeding with LcS [19]. The pig model is considered as one of the best models for these types of studies due to the similarities with humans in diet, defecation habits, contractile activity and structure to the human digestive system [20]. Interestingly, this increase in motility did not promote defecation frequency [19], which is in line with our findings.

Other studies have also proven the significant effect of probiotics in gut motility in humans. It was shown that bowel transit rate in healthy volunteers is a determinant of stool SCFA concentration including butyrate and distal colonic pH [21]. Lactobacilli are known to ferment carbohydrates with production of SCFA suggesting that an intake of LcS might stimulate distal colonic transit. A significant effect of *Bifidobacterium animalis* DN-173010 on the total transit time was demonstrated in a study with healthy individuals. As in our study the main effect was displayed in the rectosigmoid transit time by the modified Hinton test [22, 23]. In patients with normal transit time a clear correlation of the dosis intake and the effect was shown [24].

In conclusion, our study showed that especially patients with a delayed transit time profit from probiotic intervention. Surprisingly the stool frequency and consistency in this study was not significantly affected. Moreover, the placebo response rates of the patients need to be considered when interpreting the results of this study. Choosing a different study design, such as a cross-over study or an examination of a larger number of patients could show more significance about the efficacy of LcS on the colon transit time.

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Conflict of interest. The corresponding author states the following: This study was sponsored by Yakult Honsha Co. Ltd, Japan. Dr. Schaumburg is employed by Yakult Deutschland GmbH. Prof. Dr. H. Krammer, Dr. von Seggern. Dr. F. Neumer state that there are no conflicts of interest.

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