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Lactobacillus reuteri DSM 17938 and quality of life associated with functional constipation

Lactobacillus reuteri DSM 17938 in kakovost življenja, povezana s funkcionalnim zaprtjem

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Abstract

Background: Functional constipation (FC) defines the form of constipation without an organic aetiology and influences the quality of life of the child in many aspects. In the present study, we aimed to compare the effects of *Lactobacillus reuteri* (*L. reuteri*) DSM 17938 and lactulose treatments on the health-related quality of life (HR-QoL) of constipated children and their families.

Methods: Children with FC were divided into two groups to receive either *L. Reuteri* DSM 17938 (n = 25) or lactulose (n = 24), for four weeks. All patients and their parents completed the KINDL® HR-QoL questionnaire before and at the end of the treatment period.

Results: The final total and disease perception scores and the subscale analyses of the probiotic and lactulose groups were comparable. The final mean total scores of parent questionnaires increased in both groups (68% to 71.3% in the probiotic group, 66.1% to 70.9% in the lactulose group), and the increase in the lactulose group was found statistically significant.

Conclusion: In our study, *L. reuteri* DSM 17938 has showed to have comparable effects on the HR-QoL in children with FC, when compared to lactulose. Lactulose was more efficient regarding satisfaction of families and the family perception of HR-QoL.

Izvleček

Izhodišče: Funkcionalno zaprtje (FC) je oblika zaprtja brez organskega vzroka in v mnogih pogle-dih vpliva na kakovost otrokovega življenja. V tej študiji smo želeli primerjati učinke zdravljenja z *Lactobacillus reuteri* (*L. reuteri*) DSM 17938 in laktulozo na zdravstveno kakovost življenja (HR--QoL) otrok s funkcionalnim zaprtjem in njihovih družin.

Metode: Otroci s funkcionalnim zatjem (FC) so bili razdeljeni v dve skupini, ki sta štiri tedne pre-jemali bodisi *L.reuteri* DSM 17938 (n = 25) ali laktulozo (n = 24). Vsi bolniki in njihovi starši so iz-polnili vprašalnik KINDL® HR-QoL pred začetkom in po koncu zdravljenja.

Rezultati: Končni rezultati skupne ocene in zaznave bolezni ter analize podkategorij za skupi-ni probiotikov in laktuloze so bili primerljivi. Končni povprečni skupni rezultati vprašalnikov za starše so se v obeh skupinah zvišali (z 68 % na 71,3 % v skupini s probiotiki in s 66,1 % na 70,9 % v skupini z laktulozo), povečanje v skupini z laktulozo pa je bilo statistično pomembno.

Zaključek: Naša raziskava je pokazala, da ima *L. reuteri* DSM 17938 pri otrocih s FC v primerjavi z laktulozo primerljiv učinek na HR-QoL. Laktuloza je bila ocenjena kot bolj učinkovita glede za-do-voljstva družin in družinskega dojemanju HR-QoL.

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1 Introduction

Functional constipation (FC) defines the form of constipation without an underlying organic aetiology, which comprises 90% of overall constipation cases in children. The symptoms associated with FC, such as flatulence, abdominal pain and soiling are uncomfortable, may lead to emotional, behavioural and social problems and may affect the quality of life of the child in many aspects, especially if they are chronic (1-3).

The treatment phases for constipation comprise child and family education, improvement of nutrition, toilet training and the regulation of bowel movements with the help of laxatives. Undesired effects of laxatives such as abdominal pain, bloating, flatulence, diarrhoea, nausea and the fact that only half of the patients benefit from the treatment have led to research into new treatment options (3).

Lactulose, an unabsorbable carbohydrate, is a widely used osmotic laxative in childhood constipation. It is metabolised by the intestinal flora and increases water accumulation in the colon with the help of its osmotic effects, which also imparts lactulose the feature to act as a prebiotic. Prebiotics are compounds that support the reproduction and growth of beneficial microorganisms found in the intestine; they cannot be digested but are fermented by microorganisms. The fermentation of lactulose by colonic microflora causes flatulence and abdominal pain, and a decrease in its effectiveness is seen as a result of changes in the microflora with long term usage. Despite its side effects, lactulose is widely preferred by pediatricians due to its safety in paediatric population (1-3).

Recently, probiotics have been widely used in gastrointestinal disorders (4-10). The colonic florae of constipated children display increased *clostridia, Enterobacteriacea* and *Bifidobacterium* species compared to *Bacteriodes* and *Escherichia coli*, which is termed dysbiosis. It is suggested that dysbiosis treatment may lead to regression in symptoms of constipation (5). Also, it is known that the colonic microflora increases peristalsis, thus lowering the colonic transit time and reducing the intestinal pH by production of lactic and acetic acid. Although the beneficial effects of probiotics on the gastrointestinal system (GIS) are well known, studies on the use of probiotics in childhood constipation are still insufficient (6).

Lactobacillus reuteri DSM 17938 (*L. Reuteri* DSM 17938) is a microorganism belonging to the *Lactobacillus* family, and is one of the most commonly studied probiotics among the species in the treatment of childhood GIS disorders. Many studies have shown that *L. Reuteri* DSM 17938, normally found in the human intestinal flora, may be effective in the treatment of infantile constipation and may support immune response (7-9).

In the present study, we aimed to compare the effects of *L. reuteri* DSM 17938 and lactulose treatments on the health-related quality of life (HR-QoL) of constipated children and their families.

2 Patients and methods

The prospective randomised trial was carried out at Baskent University Hospital, Paediatric Gastroenterology Department between March 2011 to February 2012. Patients were eligible to participate if they met two out of six Rome III H3a criteria for FC (2) and had been suffering from FC for the last 2 months. Fifty-three patients with FC, aged between 4–16 years, were included in the treatment group. Children who were treated for constipation less than a month before the beginning of study, used an antibiotic or any medication known to influence GIS motility treatment in the previous month, those with diagnoses of any gastrointestinal, endocrinological, metabolic or neurological disease, and those who had taken any prebiotic or probiotic products prior to the treatment, were excluded.

Children were randomly divided into two groups: 31 patients received 1×10^8 cfu (colony forming units) of *L. Reuteri* DSM 17938 (5 drops/day), and 30 patients received 1 ml/kg/d of lactulose, for four weeks. Patients in whom abdominal or rectal faecal impaction were detected received enemas for disimpaction. All patients were advised about proper nutrition. Daily bowel habits were recorded in a standardised bowel diary. Patients were weekly interviewed and information about compliance and response to therapy, need for rescue therapy including enemas were collected and lactulose doses were adjusted according to side effects. The results of the clinical findings of the patients have previously been published in Turkish in a national journal in Turkey (10).

All patients and their parents (mother or father) completed the Turkish version of the KINDL® HR-QoL questionnaire (KINDL®: 4–6 years of age; KINDL®: 7–13 years; KINDL®: teenagers 14–17 years) before the initiation of the treatment and at the end of the 4-week treatment period. Also, age-matched healthy controls without any known chronic illnesses were asked to complete the same questionnaire once only. All children and their parents gave written informed consent to participate in the study.

The KINDL® questionnaire is analysed by adding the item responses marked on each subscale, with certain items being reversed beforehand. Only subscales in which less than 30% of the items are missing can be analysed, whereby mean value replacement is used to deal with such missing values. A computerised analysis program exists for the KINDL® questionnaire, which carries out both item reversal and the summarisation of the subscales and their addition (11).

QoL was measured by using the Turkish validated version of KINDL® questionnaire. KINDL® was developed in Germany in 1994 and has been used worldwide ever since for extensive and broad assessment of QoL in healthy children and adolescents aged 4–17 years and those with chronic conditions. The self-report for age 4–7 years encompasses 12 items with three categorical answers. The other forms consist of 24 items equally distributed into the following six subscales: physical well-being (PWB), emotional well-being (EWB), self-esteem (SWB), well-being related to family (FAWB), well-being related to friends/ peers (FRWB), school-related wellbeing (SCWB), and additionally, a disease perception subscale for chronic conditions. Each item addresses experiences over the previous week and is rated on a 5-point scale (1 Never, 2 Seldom, 3 Sometimes, 4 Often, 5 Always). Mean scores are calculated for each of the six subscales and for the total scale and linearly transformed to a 0–100 scale. Higher scores indicate better QoL. Details of the questions can be found on the KINDL® Web site (www.KINDL.org).

The primary endpoint was the disease perception - HRQoL dimension that measures the disease impact of the constipation symptoms on HRQoL at week 4. The secondary endpoints of HRQoL were the seven other dimensions (physical well-be-

ing, emotional well-being, self-esteem, well-being related to family, well-being related to friends/peers, school-related wellbeing) investigated by the KINDL® questionnaire.

Data were analysed in SPSS (Statistical Package For Social Sciences) for Windows 17.0 (SPSS Inc, Chicago, IL) programme. Chi-square and McNemar tests were used for hypothesis analyses, t-test was used for the analysis of difference between groups.

All study participants provided informed consent to participate in this study.

This study has been approved by the Ethics Committee of Baskent University Hospital in 2011 (Report number: KA 10/153).

3 Results

Eight patients were lost to follow-up during the treatment (5 in the probiotic group and 3 in the lactulose group). One patient in the probiotic group refused to continue the treatment due to bad taste. Three patients in the lactulose group discontinued medication due to such side effects as abdominal pain, flatulence, and diarrhoea. The study was completed with 25 patients in the probiotic group, 24 patients in the lactulose group and 50 healthy children forming the control group, which were divided into different age groups. The 4–6 age group consisted of 25 healthy controls, 15 probiotic, 11 lactulose; the 7–13 age group consisted of 15 controls, 7 probiotic, 8 lactulose; and the 14–17 age group included 8 controls, 3 probiotic, 5 lactulose subjects.

No statistically significant differences were detected in terms of age, sex, duration of constipation, dietary habits, and baseline scores at the beginning of the intervention.

The details of the clinical findings of this study have been published in Turkish. In short, while both *L. reuteri* DSM 17938 and lactulose were effective in diminishing constipation related symptoms including defecation frequency, stool consistency, abdominal pain, painful defecation and stool withholding behaviour, *L. reuteri* DSM 17938 was found to be more effective for alleviating abdominal pain and flatulence symptoms than lactulose (10).

At the end of the 4-week treatment period, the total HR-QoL scores of the patients increased from 63.1% to 74.9% in the probiotic group and from 64.3% to 72.6% in the lactulose group. Disease perception scores, where higher scores indicate improvement in the perception of the disease, increased from 54.3% to 77.9% in the probiotic group and from 61.3% to 73.0% in the lactulose group, which were both statistically significant. There were no differences between the final total and disease perception scores of the probiotic and lactulose groups ($p > 0.05$).

When the patients' results were analysed according to ages, in the 4–6 age group, the total and disease perception scores at four weeks increased significantly in both treatment groups, while there were no statistically significant difference between both groups regarding the final scores ($p > 0.05$) (Table 1). In the 7–13 age group, the total and disease perception scores increased in both groups, while significant effect was observed in the disease perception scores of the probiotic group ($p = 0.005$) and total scores of the lactulose group ($p = 0.005$). No statistical significance was found between the groups ($p > 0.05$). Although the total and disease perception scores increased in both treatment groups of 14–17 age group, the increase in the total scores ($p = 0.036$) and disease perception scores ($p = 0.029$) was found significant in the lactulose group ($n = 5$) only.

When the patients' subscale scores were analysed according to age groups, in the 7–13 age group, no differences were shown for any of the subscales, including physical well-being (PWB), emotional well-being (EWB), self esteem (social well-being-SWB), family related well-being (FAWB), friends related well-being (FRWB) and school related well-being

Table 1: Comparison of Patients' Quality-of-Life (QoL) Scores of *L. Reuteri* DSM 17938 and Lactulose Groups.

	Baseline Score		Final Score		
Subscales according to age groups	***L. reuteri***	**Lactulose**	***L. reuteri***	**Lactulose**	**p**
4–6	(n = 15)	(n = 11)	(n = 15)	(n = 11)	
DP	56.0	55.3	78.8**	75.7**	>0.05
Total	66.9	65.9	74.9**	78.7**	>0.05
7–13	(n = 7)	(n = 8)	(n = 7)	(n = 8)	
PWB	71.4	67.1	89.2	73.4	>0.05
EWB	68.7	65.6	82.1	74.2**	>0.05
SWB	68.7	59.3	76.7	58.5	>0.05
FAWB	70.5	69.5	66.9	74.2	>0.05
FRWB	80.3	71.1	88.3	87.5	<0.05
SCWB	20.5	26.5	16.0	25.0	>0.05
DP	61.3	69.7	81.5**	75.0	>0.05
Total	63.3	58.3	69.9	64.7**	>0.05
14–17	(n = 3)	(n = 5)	(n = 3)	(n = 5)	
PWB	62.5	63.7	75.0	72.5	>0.05
EWB	70.8	67.5	77.0	80.0**	>0.05
SWB	29.1	71.2	52.1**	66.2	>0.05
FAWB	72.9	62.5	79.1	73.7**	>0.05
FRWB	62.5	86.2	87.5	96.2	>0.05
SCRW	58.3	61.2	68.7	58.7	>0.05
DP	45.8	59.1	73.6	68.3**	>0.05
Total	59.3	68.7	73.2	74.5**	>0.05
DP Scores of all age groups	54.3%	61.3%	77.9%**	73.0%**	>0.05
Total*	63.1%	64.3%	74.9%**	72.6%**	>0.05

DP: Disease perception, PWB: Physical well-being, EWB: Emotional well-being, SWB: Self-esteem associated well-being, FAWB: Family associated well-being, FRWB: well-being related to friends/peers, SCRW: School-related well-being.

**Statistically significant changes of HR-QoL scores within a treatment group compared to baseline HR-QoL scores.

(SCWB), either at the beginning or at the end of the 4-week period between the probiotic and lactulose groups ($p > 0.05$). In the lactulose group, scores of subscales for emotional well-being ($p = 0.045$) improved significantly and there was a marginal improvement in well-being related to friends/peers ($p = 0.056$). In the 14–17 age group, no differences were detected between the groups in subscale scores of the questionnaires performed before and after the treatment period ($p > 0.05$). While SWB increased significantly ($p = 0.032$) in the probiotic group, EWB ($p = 0.034$) and FAWB ($p = 0.01$) improved significantly in patients that were treated with lactulose (Table 1). In the 4–6 age group, subgroup analysis could not be performed due to inadequate number of patients.

When the scores of the parent questionnaires were evaluated, it was seen that the baseline total and disease perception scores between probiotic and lactulose groups were comparable. At the end of the 4-week treatment period, mean total scores increased in both treatment groups (68% to 71.3% in the probiotic group, 66.1% to 70.9% in the lactulose group), and the increase in the lactulose group was found statistically significant ($p = 0.033$). The final total scores of probiotic and lactulose groups were comparable ($p > 0.05$) (Table 2).

When subscales were evaluated according to age groups, it was seen that in the 4–6 age group, the final total and disease perception scores and all subscale scores were comparable ($p > 0.05$). In the lactulose group, parent perception of physical well-being ($p = 0.34$) and emotional well-being ($p = 0.31$) were significantly increased. In the probiotic group, although increases in scores were detected in all subscales, none of them were significant (Table 2).

In the 7–13 age group of parent perception, while the final scores of both treatment groups were comparable, the increase in the disease perception scores within the probiotic and lactulose groups were found statistically significant ($p < 0.05$) (Table 2).

In the 14–17 age groups, increase in all scores including total and disease perception and all subscales were demonstrated in both groups. The initial and final scores of all groups were comparable ($p > 0.05$). While none of the subscales showed significant improvement in the lactulose groups, the increase in the probiotic groups showed significance for family related QoL (Table 2).

4 Discussion

Our trial aimed to compare the effects of *L. Reuteri* (DSM 17938) and lactulose in the HR-QoL of children between ages 4–17 years with FC by using the KINDL® QoL questionnaires for children and adolescents and to evaluate the effects of treatment for chronic constipation in terms of HR-QoL, also in relation to healthy children.

HR-QoL refers to the impact of illnesses or adverse circumstances on well-being and life satisfaction in relation to the individual's perception of their predicament and is considered by regulatory authorities as an important endpoint in the evaluation of therapeutics (12).

It is known that unpleasant symptoms related to chronic constipation such as abdominal discomfort, abdominal pain, flatulence and soiling affect QoL negatively and lead to emotional, behavioural and social problems of children and their families (12). We hypothesized to improve QoL with the use of either *L. Reuteri* (DSM 17938) or lactulose, since the unfavourable effects of constipation diminish with appropriate treatment. The primary findings of our study showed the HR-QoL to be significantly poor in children with FC, but both treatments improved it to the level of healthy children.

A scarce number of studies exist in literature about the use of *L. Reuteri* DSM 17938 in FC, and some of them showed it to be effective when compared with place-

Table 2: Comparison of Quality of-Life (QoL) Scales of *L. reuteri* and Lactulose groups of parents.

Subscales according to age groups	Baseline Score		Final Score		
	L. reuteri	Lactulose	*L. reuteri*	Lactulose	p
4–6	(n = 15)	(n = 11)	(n = 15)	(n = 11)	
PWB	70.0	65.9	70.0	80.6**	p > 0.05
EWB	76.6	65.3	76.6	74.4**	p > 0.05
SWB	70.5	61.9	70.5	72.1	p > 0.05
FAWB	59.4	64.2	59.4	62.5	p > 0.05
FRWB	77.5	67.0	77.5	69.8	p > 0.05
SCWB	78.1	61.4	78.1	62.5	p > 0.05
DP	65.8	57.9	65.8	69.1	p > 0.05
Total	69.5	63.1	69.5	68.8	p > 0.05
7–13	(n = 7)	(n = 8)	(n = 7)	(n = 8)	
PWB	56.2	61.8	70.5	64.5	p > 0.05
EWB	70.5	63.1	75.8	74.3	p > 0.05
SWB	72.3	68.7	82.1	76.3	p > 0.05
FWB	71.4	59.0	68.7	68.7	p > 0.05
FRWB	76.7	73.6	73.6	80.5	p > 0.05
SCWB	66.9	72.9	73.2	81.2	p > 0.05
DP	61.9	61.9	79.7**	82.8**	p > 0.05
Total	69.0	66.5	74.7	74.3	p > 0.05
14–17	(n = 3)	(n = 5)	(n = 3)	(n = 5)	
PWB	52.0	60.4	60.4	54.1	p > 0.05
EWB	68.7	77.0	72.9	79.1	p > 0.05
SWB	56.2	75.0	62.5	64.5	p > 0.05
FAWB	68.7	79.1	70.8	64.5	p > 0.05
FRWB	79.1	85.4	89.5**	87.5	p > 0.05
SCWB	68.7	70.8	62.5	79.1	p > 0.05
DP	52.7	65.2	59.7	84.7	p > 0.05
Total	65.6	69.42	69.7	69.64	p > 0.05
Mean DP scores of all age groups	**60.1%**	**61.6%**	**68.4%**	**78.8%**	**p > 0.05**
Total*	**68%**	**66.34%**	**71.3%**	**70.9%****	**P < 0.05**

DP: Disease perception, PWB: Physical well-being, EWB: Emotional well-being, SWB: Self-esteem associated well-being, FAWB: Family associated well-being, FRWB: well-being related to friends/peers, SCRW: School-related well-being.
**Statistically significant changes of HR-QoL scores within a treatment group compared to baseline HR-QoL scores.

bo (13).

In our study, in accordance with the clinical findings, an improvement in the disease perception scores (primary endpoint) was seen in both *L. Reuteri* DSM 17938 and lactulose group by means of total scores. Both treatments resulted in a significant improvement in at least one of the HR-QoL subscales of different age groups. And the changes of HR-QoL of both treatment groups were almost comparable (significant difference only in FR-WB of the 7–13 age group). As a result, we consider the effect of probiotics and lactulose on the HR-QoL of children in our study group to be similar.

Scientific studies on QoL questionnaires emphasize the importance of the opinions of people who are in close relationship with children (especially those that are not old enough to express themselves objectively) (14). To evaluate the HR-QoL in chronic conditions, it is important to take into account the opinions of patients as well as their parentssince the evaluation will be multidirectional (12-15). Knowing the family perception of their children's QoL may help to determine the anxieties of parents and may lead to co-operation between the physician and parents when guiding the treatment of the child (16,17).

In our study, the scores at baseline of parental QoL questionnaires showed statistically significant lower perception of HR-QoL than by parents of the control group. At week 4, in contrast to their children, a significant improvement in parental perception of HR-QoL was detected only in the lactulose group. Also, when analysed according to different age groups and subscales of HR-QoL, a significant improvement in a few aspects of HR-QoL was detected, being more apparent in the lactulose group (Table 2). The clinical results of the study that was published previously by Olgac et al. (10) showed the clinical effects of lactulose to be more rapid, although its side effects were noticeable when compared to *L. reuteri* DSM 17938. The parents of children treated with lactulose may be more satisfied with rapid effects of medications, and the difference between parental perceptions of HR-QoL between treatment groups may reflect the more rapid effect of lactulose on the GIS, while more time is needed for probiotics to show their effects (18).

Studies on HR-QoL in children with various chronic health conditions emphasize the discrepancies within specific domains between parent and child reports. Parent and child reports overlap for observable functioning and tend to diverge for emotional and social functioning. To better interpret the child's well-being, child reports should be considered together with parent reports. These findings emphasize the importance of considering parent reports in conjunction with child self-reports to better depict the child's overall functioning (19-21).

Our study has several limitations. First of all, parental perceptions of child functioning and the children's perceptions of QoL could be influenced by many factors including parental psychopathology, life stressors, socio-economic status or medical history. Secondly, the KINDL® QoL measures are generic instruments that lack specificity for constipation. Although disease-specific HR-QoL questionnaires have been developed for children with constipation (15), we were unable to use disease-specific measures, because no such validated instruments exist in Turkish. However, the measures used in this study are categories of child and family functioning and measure the aspects of child and family well-being. Also, the sample size was inadequate for evaluating some of the purposes of the present study, so a larger sample size would be necessary for future quantitative studies.

During our trial, no side effects due to probiotics were seen. The high tolerance rates of probiotics by patients in our study support previous research that advocates the safety of probiotics in children (23-26).

In conclusion, when the lack of re-

sponse to traditional treatment methods of FC and the relapse rates are considered, the search for new treatment strategies is inevitable. Our study has shown that the effect of *L. reuteri* DSM 17938 on the HR-QoL in children with FC was comparable to that of traditional treatment agent lactulose. In addition, lactulose was more efficient as regards the satisfaction of families and the family perception of HR-QoL of these children. Further double-blind, placebo controlled studies are needed to confirm our findings.

5 Acknowledgement

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6 Compliance with ethical standards

The Ethics Committee of The Başkent University has approved the study protocol. This study is in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

7 What's known

The symptoms associated with functional constipation, such as flatulence, abdominal pain and soiling are uncomfortable, may lead to emotional, behavioural and social problems and may influence the quality of life of the child in many aspects, especially if they are chronic.

8 What's new

- HR-QoL associated with functional constiption is compromised including physical well-being, emotional well-being, self-esteem, well-being related to family, friends, and school related quality of life.
- Probiotiotics have favourable effects on HR-QoL associated with functional constipation; also, these effects are comparable to the effects of lactulose.

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