

## Original Article

# Probiotics as prevention of radiation-induced diarrhoea

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## Abstract

**Aim:** To assess the efficacy of a probiotic preparation on the prevention of radiation-induced diarrhoea in cancer patients.

**Methods:** Group of 42 radio-oncology patients who had undergone adjuvant post-operative radiation therapy (RT) after abdominal and pelvic cancer were randomised to receive either the probiotic preparation "5" Strain Dophilus (twice per day; L-Group), or the preparation Hylak Tropfen Forte (40 drops, three times per day; H-Group). Supplementation started on the first day and lasted until the end of RT. Efficacy endpoints were the incidence and the severity of the radiation-induced diarrhoea. All patients received a paper form in which they recorded monitored parameters on a daily basis during RT.

**Results:** The mean daily number of bowel movements during the whole period was 4.16 in the L-Group and 2.52 in the H-Group; 62.5% of patients in L-Group and 81% in H-Group had a mean daily number of bowel movements of  $\leq 4$ /day. Abdominal pain was recorded in 25% of the patients in L-Group and 22% of the patients in H-Group. Blood in the bowel movement was found in one patient from H-Group (9 days). Of patients in L-Group, 27% required diphenoxylate treatment during pelvic radiotherapy, compared with 55% in H-Group. Of patients from L-Group, 9% required antibiotics administration, compared with 25% in H-Group.

**Conclusion:** We concluded that the prophylactic probiotic therapy produced a highly favourable benefit/risk ratio. Supplementation with the probiotic preparation is an easy and safe approach to protect cancer patients from the risk of radiation-induced diarrhoea and carry out improvement in their quality of life.

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## Keywords

Diarrhoea; Hylak; probiotics; radiotherapy

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## INTRODUCTION

Since the 1980s, the incidence of acute radiation enteritis appears to have increased, most likely because more than 50% of patients with cancer receive radiotherapy as a component of

their treatment.<sup>1</sup> Radical radiation therapy (RT) to pelvic cancers carries a risk of complications to normal tissues around the tumour. Acute complications affecting the gastrointestinal tract occur in ~80% of patients, but they are usually mild and only rarely affect planned treatment.<sup>2,3</sup> Symptoms tend to start during the second week of treatment (when histological change is probably at its maximum) and

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peak by the fourth to fifth week (when histological changes are stable or improving). The retrospective study by Gami et al.<sup>5</sup> suggests that the quality of life is affected in approximately every second patient after radiotherapy by diarrhoea or constipation, in every tenth patient by pain and in every twentieth patient by rectal bleeding.

Post-radiation enteritis and colitis accompanied mainly by diarrhoea is the most serious complication of gastrointestinal symptoms in cancer patients and results from morphological and functional modifications of the intestinal epithelium after radiation. As diarrhoea often worsens the quality of life of irradiated patients, the general goal of anti-diarrhoeal therapy is to reduce fluid loss in the stool by inhibiting intestinal secretion, promoting absorption, and decreasing intestinal motility.<sup>4</sup> The most commonly used agents for non-specific symptomatic treatment of radiotherapy-induced diarrhoea include opiate agonists such as loperamide and diphenoxylate.

In the last few years, the preventive use of probiotics appears to be one of the most promising strategies to lower undesirable acute gastrointestinal symptoms.<sup>6–8</sup> Both experimental and clinical studies have shown that probiotic preparations can effectively modulate intestinal inflammation through altering the composition and the metabolic and functional properties of gut indigenous flora.<sup>9,10</sup> Probiotics represent preparations containing viable and defined microorganisms in certain numbers which upon ingestion bring health benefits, e.g. probiotics increase concentrations of beneficial bacteria such as lactobacillus and bifidobacteria, and reduce the levels of pathogenic microorganisms.<sup>11</sup>

VSL#3 was effective in reducing chemotherapy (CHT)-induced diarrhoea in rats.<sup>12</sup> Osterlund et al.<sup>13</sup> conducted a randomised, controlled trial to examine the effect of lactobacillus and fiber supplementation in 5-fluorouracil (5-FU) CHT patients. The authors found that patients who received lactobacillus had less grade 3 or 4 diarrhoea, reported less abdominal discomfort, needed less hospital care and had fewer CHT dose reductions due to bowel

toxicity compared with the control group. The benefits of probiotic therapy with VSL#3 have also been recorded in 490 patients during adjuvant radiotherapy after surgery for abdominal and pelvic cancer in a double-blind, placebo-controlled trial.<sup>14</sup> The mean daily number of bowel movements for patients with radiation-induced diarrhoea was  $12.3 \pm 4$  and  $4.6 \pm 2$  among placebo and VSL#3 recipients, respectively. Similarly, a randomised study<sup>15</sup> has demonstrated a decrease in the mean number of bowel movements ( $p < 0.05$ ) and a decrease in the incidence of diarrhoea ( $p < 0.01$ ) in patients ingesting *Lactobacillus acidophilus*. Another multi-centre, randomised, placebo-controlled nutrition trial reported that yogurt containing *Lactobacillus casei* DN-114 001 significantly improved the consistency of stool, without reducing the incidence of radiation-induced diarrhoea.<sup>16</sup> Conclusions from meta-analyses and systematic reviews should be interpreted with caution, because in these studies different types of probiotics are used to examine the effects on state of disease.<sup>17</sup> Literature searches identified three randomised, controlled for prevention and one for the treatment of radiation-induced diarrhoea. These studies did not provide definitive conclusions that probiotic supplementation may be effective.<sup>18</sup>

Oncologists in our hospital have been using Hylak preparation for the revitalisation of the ecosystem of the gut during and after radiotherapy. Their experience with the use of probiotics has been limited until now.

The aim of our study has been to evaluate and compare the clinical effects of preventive administration of the preparation “5” Strain Dophilus and Hylak in patients during radiotherapy with a closer focus on the amount and severity of the diarrhoea.

## METHODS

The study design was that of a randomised parallel-group non-placebo-controlled trial in which 42 oncology patients underwent adjuvant post-operative RT in the abdominal and

pelvic region. Patients who received RT with CHT were included, too. All study subjects did not suffer from gastrointestinal disorders. The patients were randomly selected when they were admitted to hospital from June 2005 till March 2006. They were subdivided into two groups: the first group was administered "5" Strain Dophilus (L-Group) and the second group was administered Hylak (H-Group). The treatment arms were not balanced with gender and primary tumour site.

With regard to acute gastrointestinal symptoms influencing the quality of life of the patients during RT, we monitored the daily number of bowel movements, their consistency (solid, semi-solid, liquid), the presence of bleeding, abdominal pain, and the use of anti-diarrhoeal medication (diphenoxylate) or antibiotics. All patients received a paper form in which they recorded monitored parameters on a daily basis during RT. The patients were instructed to report on every complaint or symptom.

Exclusion criteria were: previous radiation treatments, current antibiotics therapy, the use of antibiotics during the previous 2 weeks, established gastrointestinal disease (chronic diarrhoea, Crohn's disease, ulcerative colitis). Any patient whose medical condition required antibiotic therapy during RT was excluded from the group.

Each patient was advised about the treatment, and a note indicating that informed consent to participate had been given was inserted in his/her medical record.

The design of this study was approved on April 28, 2005 by the Ethics Committee at the Central Military Hospital Ruzomberok. Participants signed a written informed consent form, according to the Helsinki Declaration.

Study participants in L-Group were administered the probiotic preparation "5" Strain Dophilus with an enteric coating and containing five probiotic cultures (55% *Lactobacillus rhamnosus*, 20% *Bifidobacterium adolescentis*, 5% *L. acidophilus*, 5% *Bifidobacterium longum*, 15% *Enterococcus faecium*) with a count of 6 billion

active bacteria/capsule at a daily dosage of  $2 \times 1$  capsule.

Patients in H-Group were administered the Hylak Tropfen Forte preparation, i.e., cell-free fermentation products of *Lactobacillus helveticus* and gut symbionts (100 ml containing: 24.95 g *Escherichia coli* metabolita, 12.5 g *Streptococci faecalis* metabolita, 12.5 g *Lactobacilli acidophili* metabolita, 49.9 g *Lactobacilli helveticus* metabolita) in doses of 40 drops, three times per day.

Radiation was delivered by a Cobalt-60 unit by using the four-field box technique. The doses were divided into 2 Gy per day over 5–7 weeks to give the total cumulative dose of 50 Gy (2 Gy/day). High-risk patients (e.g. patients with prostate cancer), received dosage 65–67 Gy (2 Gy/day).

Data were analyzed statistically. The significance of differences between the groups was evaluated by the Student's *t*-test (Microsoft Excel, version 2002).

## RESULTS

The median age of the 22 patients from L-Group was 62 years (range, 34–82 years); 10 patients were diagnosed with colorectal cancer, 4 with rectosigmoid junction cancer, 3 with uterine cancer, 3 with urinary bladder cancer, 1 with cervical cancer and 1 with sigmoid colon cancer. The gender ratio (male/female) was 12/10. Ten patients had normal body weight [body mass index (BMI) < 25], 10 were overweight (BMI < 30), and 2 suffered severe obesity (BMI > 30).

The median age of the 20 patients from H-Group was 67 years (range, 43–83 years); 3 patients were diagnosed with colorectal cancer, 6 with rectosigmoid junction cancer, 1 with uterine cancer, 1 with anus and anal canal tumour, 8 with prostate tumour and 1 with urinary bladder cancer. The gender ratio (male/female) was 16/4. Seven patients had normal body weight (BMI < 25), 10 were overweight (BMI < 30), and 3 suffered severe obesity (BMI > 30).

At the same time, 55% of the patients in L-Group and 50% in H-Group received CHT, viz., 500 mg 5-FU i.v. lx/week together with RT.

The mean daily number of bowel movements for patients in L-Group was 4.16 (1.2–9.7) and 2.52 (0.7–5.3) in H-Group. A 62.5% of patients in L-Group and 81% of patients in H-Group had the mean daily number of bowel movements  $\leq 4$  bowel movements/day.

The mean weekly numbers of bowel movements in L-Group were significantly higher from second week onward ( $p < 0.01$ ). The number of bowel movements did not rise until the third week in H-Group ( $p < 0.01$ ) (Figure 1).

Marked differences could be observed when comparing the mean numbers of bowel movements in patients receiving only radiotherapy and patients undergoing a combination of radiotherapy and CHT (Figure 2).

The mean weekly numbers in L-Group with RT varied from 1.3 to 2.8, compared with 4.1–5.3 in the same group but with RT+CHT. The mean weekly numbers in H-Group with RT varied from 1 to 1.5, compared with 2–5.1 in the same group but with RT+CHT. These differences between patients with only RT or with RT+CHT can be seen in Figures 3–5, which also demonstrate that the increase in the number of bowel movements occurred in the second week of receiving pelvic radiation.

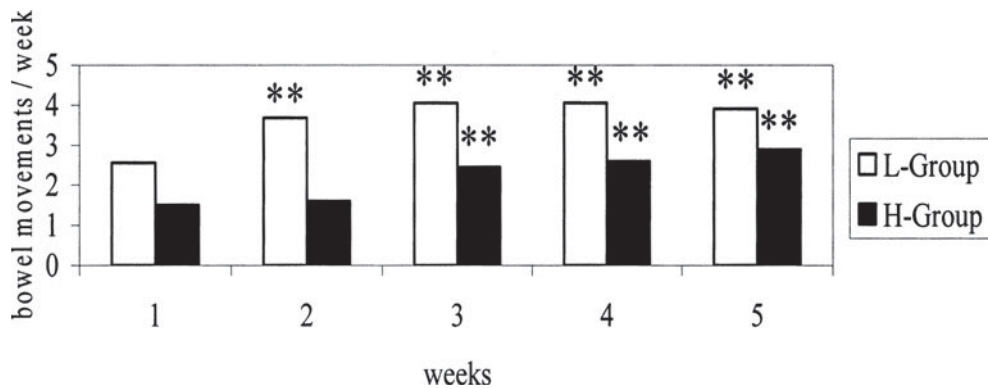


Figure 1. Comparison of mean weekly numbers of bowel movements during RT (\* $p < 0.05$ , \*\* $p < 0.01$ ).

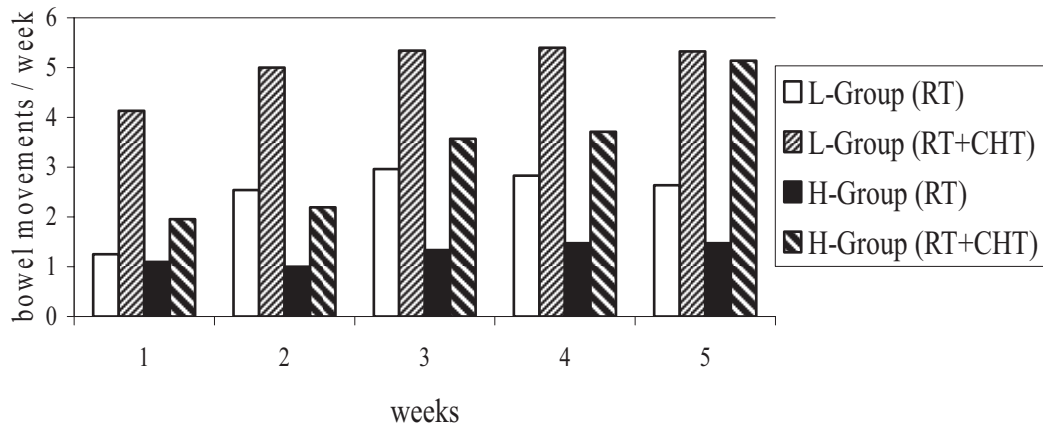


Figure 2. Comparison of mean weekly numbers of bowel movements during only RT or during RT+CHT.

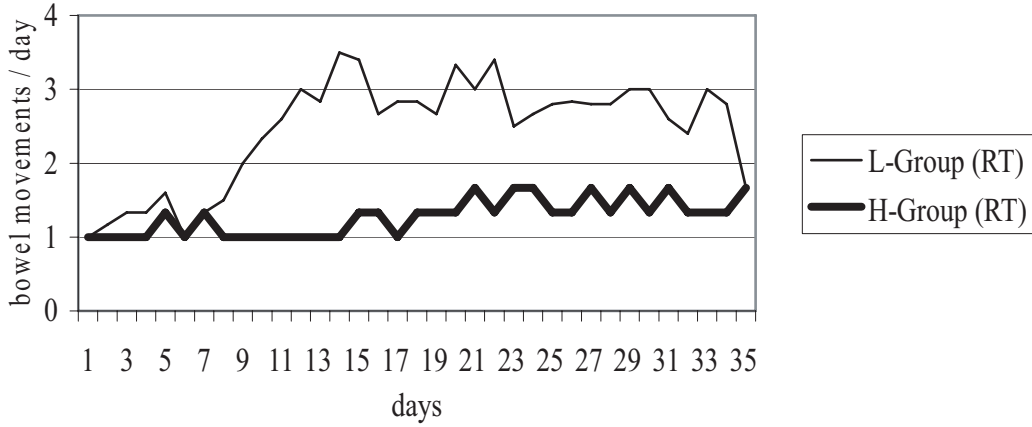


Figure 3. Comparison of mean numbers of bowel movements per day during only RT.

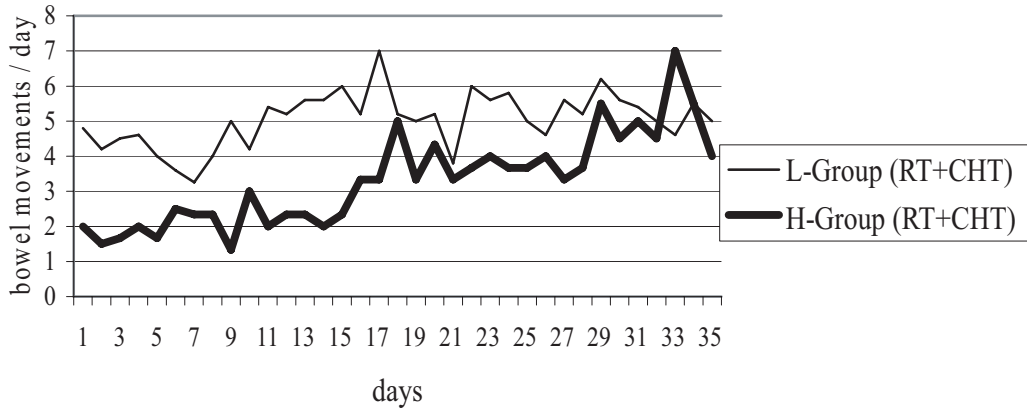


Figure 4. Comparison of mean numbers of bowel movements per day during RT+CHT.

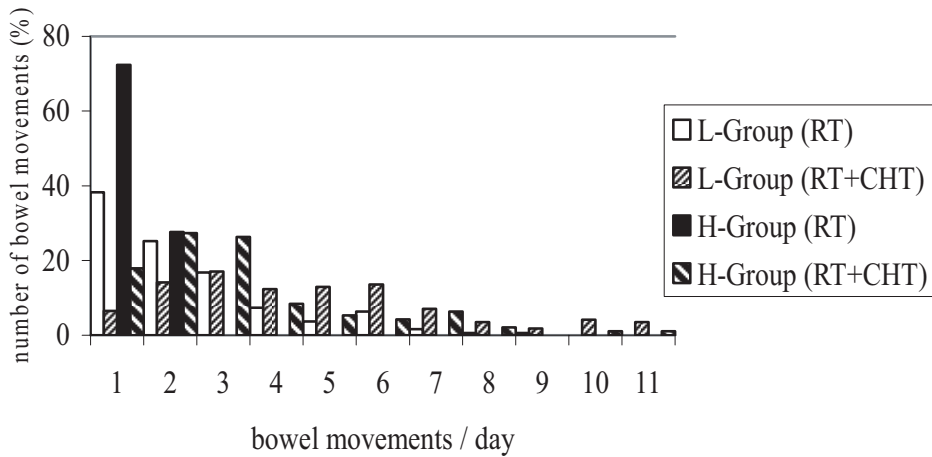


Figure 5. Frequency distribution of mean daily bowel movement throughout treatment period.

During RT, 27% of patients in L-Group required diphenoxylate treatment compared with 55% in H-Group, and 9% needed administration of antibiotics compared with 25% in H-Group. As we could not estimate the way in which these treatments influenced the composition of intestinal bacterial flora, these patients were excluded from our comparisons. In terms of the stool consistency, the L-Group produced 39% solid, 57% semi-solid and 4% liquid stools, whereas the H-Group produced 43%, 35% and 22%, respectively (Table 1).

Abdominal pain was reported by 25% of L-Group patients and by 22% of H-Group patients. All these patients were being treated with pelvic radiotherapy with CHT, except for one patient of L-Group. CHT thus seemed to result in increased toxicity.

Blood in the bowel movement was reported by one patient of H-Group (9 days).

None of the patients discontinued treatment for gastrointestinal toxicity. Based on the paper forms of patients, compliance regarding consumption of the preparations was 95%.

## DISCUSSION

Our results demonstrate that the probiotics used improve the quality of life of radiated patients by positively influencing the incidence of diarrhoea. The mean daily number of bowel movements in both L-Group and H-Group (4.16 vs. 2.52) is comparable to the Figure 5.1  $\pm$  3, which Delia et al.,<sup>19</sup> mention in their study with VSL#3. The higher values in L-Group could be related to probiotic administration, which causes an increase of bacterial mass volume by the higher creation of short-chain fatty acids, lower pH, and increased

osmolarity.<sup>20</sup> When analyzing average daily numbers of bowel movements within the groups in more detail, we observed that higher average daily number of bowel movements occurred in patients who had received both pelvic radiotherapy with CHT (5-FU), but the number did not reach the values presented by Delia et al.,<sup>19</sup> in the placebo group ( $14.7 \pm 6$ ). A comparison of the consistency of the stools showed fewer liquid stools in L-Group than in H-Group (4% vs. 22%).

Administration of anti-diarrhoeal agents (diphenoxylate) was required by 27% of patients from L-Group and 55% of patients from H-Group. The result in L-Group was more favourable than the results of the study by Kollmorgen et al.,<sup>21</sup> who recorded a 58% use of Imodium or Lomotil in the group with chemoradiotherapy, compared with 5% in a group without radiotherapy.

Analogous to study by Gami et al.,<sup>5</sup> we concluded that abdominal pain and rectal bleeding are a significantly less-frequent complication of pelvic irradiation than diarrhoea.

Malnutrition *per se* is an independent adverse prognostic factor in many cancers. It may occur due to physiological, metabolic, psychological or iatrogenic processes, which exist as a result of malignancy.<sup>22</sup> Immediately before the start of pelvic radiotherapy treatment, the incidence of malnutrition varied by 11–33% and about 83% of patients lost weight during treatment.<sup>23</sup> Despite the patients in our groups not having been on an identical diet, we observed no significant changes in the body weights of the patients when we compared their average BMI values before and after radiotherapy.

A number of radiotherapy techniques are used to treat cancers within the pelvis. These may influence the dose that is delivered to the tumour and surrounding structures. Acute radiation injury reflects direct damage to the epithelium resulting in direct injury to the cell nucleus with cell death. Radiation enteritis is a summary of inflammatory and degenerative processes affecting all parts of gastrointestinal tract that develop following a radiation dose of 8 Gy

**Table 1.** Comparison of the stool consistency during RT

	Bowel movements/day	Stool consistency (%)		
		Solid	Semi-solid	Liquid
L-Group	3.5	39	57	4
H-Group	2.2	43	35	22

and higher approximately after 5–8 days after exposure<sup>24</sup> Acute symptoms include diarrhoea, abdominal pain, tenesmus or nausea that usually start during the second or the third week of a radical radiotherapy course and resolve within 2 weeks after radiotherapy completion. Micro-metastasis or subclinical disease within the pelvic tissues should respond to 50 Gy; however, gross or bulky disease requires higher doses.<sup>25</sup> The fact that radiation-caused damage of the gastrointestinal tract area limits the effectiveness of abdominal radiotherapy treatment is well known from clinical and experimental studies. Our results support the notion of Delia et al. that bacteria therapy by means of a probiotic preparation can protect patients from the risk of radiation-caused diarrhoea, a side-effect that can lead to the interruption of RT or the lowering of the radiation dose.<sup>14</sup> Thus, the administration of probiotics during RT could ultimately allow patients to receive a greater cumulative radiation tumour dose, thereby increasing the effectiveness of radiotherapy on tumours.

Although a higher average number of bowel movements was seen in L-Group compared to H-Group, the probiotic preparation seemed to be more favourable than the Hylak preparation with respect to other monitored parameters. In spite of our observations that both preparations improve the quality of life of radiated patients in terms of the occurrence and severity of diarrhoea, these effects should be verified on more extensive groups of patients.

In our study, the supplemented preparations were well accepted and did not reveal any adverse effects.

## CONCLUSION

This study has demonstrated the benefits of probiotic therapy with “5” Strain Dophilus for the prevention and/or reduction of both the incidence and severity of radiation-induced diarrhoea associated with adjuvant radiation treatment after surgery for abdominal cancer.

Results from our study also indicate that probiotics can be of value in the prevention of radi-

ation-induced diarrhoea. Further studies are needed for confirmation of this suggestion.

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