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ORIGINAL SCIENTIFIC REPORT

Pre-surgical Administration of Microbial Cell Preparation in Colorectal Cancer Patients: A Randomized Controlled Trial

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Abstract

Introduction Disruption of normal gut function is a common side effect post abdominal surgery. It may result in reduced tolerance to oral nutrition and progress to postoperative ileus. Microbial cell preparation is beneficial as a pre-surgical nutritional supplement to aid in bowel recovery and promote the return of normal gut function following abdominal surgery. The aim of this study was to evaluate the efficacy of pre-surgical administration of microbial cell preparation in promoting the return of normal gut function.

Method The study is a randomized, double-blind, placebo-controlled trial. In total, 40 patients were recruited. Patients were randomized to receive either microbial cell preparation ($n = 20$) or placebo ($n = 20$) for 7 days prior to elective surgery. The primary end point was the time to return of normal gut function, while the secondary end point was the duration of hospital stay.

Results The treatment group demonstrated significantly faster return of normal gut function with a median of 108.5 h (80–250 h) which was 48 h earlier than the placebo group at a median of 156.5 h (94–220 h), $p = 0.022$. The duration of hospital stay in the treatment group was also shorter at a median of 6.5 days (4–30 days), in comparison to the placebo group at 13 days (5–25 days), $p = 0.012$.

Conclusion Pre-surgical administration of microbial cell preparation promotes the return of normal gut function in patients after colorectal cancer surgery, thus associated with faster recovery and shorter duration of hospital stay.

Registered in Australian New Zealand Clinical Trials Registry: ACTRN12615000545561.

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Introduction

Disruption of normal gut function is a common consequence post abdominal surgery; the inability to restore gut function can in extreme cases lead to the onset of ileus. Studies have shown that the longest duration of ileus usually occurs after open colonic surgery [1, 2]. Ileus is defined as hypomotility of the gastrointestinal tract in the absence of any mechanical bowel obstruction. It has been noted that postoperative ileus, due to the inhibition of colonic motility, can be resolved within 2–3 days whereas paralytic ileus which is usually due to the inhibition of

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small bowel motility can persist for more than 3 days [3]. Ileus is clinically characterized by bowel distension, reduced or absent bowel sound, flatus, and bowel movement. Symptoms of ileus include nausea, vomiting, and stomach cramps. Ileus also contributes to increased postoperative pain, delayed oral intake, poor wound healing, delayed postoperative mobilization, increased risk of pulmonary complications, prolonged hospitalization and decreased quality of life [4]. Overall, the disruption of normal gut function increases medical costs as a result of prolonged hospital stay. An analysis of 161,000 major bowel resections performed between 1999 and 2000, as listed in the Health Care Financing Administration database, reported that the duration of hospital stay increased by 5 days in cases with a coded postoperative ileus [5]. In the United States, ileus develops in approximately 50 % of patients who undergo major abdominal surgery [5].

Microbial cell preparation therapy was first introduced in 1965 and is believed to be able to improve the clinical outcome of patients undergoing abdominal surgery [6]. Lately, microbial cell preparation has been extensively studied as a pre-surgical nutritional support to aid in bowel recovery following surgical procedures. Microbial cell preparations of health promoting strains such as *Lactobacillus* and *Bifidobacterium* are usually nonpathogenic [7]. Previous studies revealed that using oral preparation of specific *Lactobacillus* strains in pre- and postoperative periods may help to maintain gastrointestinal motility and prevent disruption of normal gut function leading to the onset of ileus after surgery [8]. Nevertheless, pre-surgical administration of microbial cell preparation has not been widely implemented, and further studies are still crucial to determine the exact efficacy and significance of their use.

The return of normal gut function is defined as at least 80 % tolerance of an individual's daily caloric requirement [9]. Tolerance of less than this value may be associated with poor clinical outcome, and very low tolerance may indicate significant disruption of normal gut function leading to the onset of ileus. Besides, tolerance of at least 80 % of nutritional requirement for a consecutive period of at least 48 h is currently considered as the best way to represent improvement in the health status and potential for recuperation in terms of gut function [9].

This study evaluated the efficacy of the pre-surgical administration of microbial cell preparation in promoting the return of normal gut function in patients after colorectal cancer resection. The outcome of this study can be used as evidence to support the pre-surgical use of microbial cell preparation as part of an enhanced recovery program for patients with colorectal cancer undergoing surgery to improve the overall clinical outcome and reduce medical costs.

Materials and methods

The study protocol was reviewed and approved by the Institutional Review Board of University of Malaya Medical Centre's Ethical Committee (reference number:895.19).

This study was a randomized, double-blind, placebo-controlled trial. Patients aged 18 years and above, diagnosed with colorectal cancer, and scheduled for surgery were recruited. The exclusion criteria for this study were acute intestinal obstruction, immunodeficiency, evidence of preexisting infection, emergency surgery, inability to tolerate regular oral ingestion of probiotics within 1 week prior to recruitment.

Non-continuous data were assessed using Chi square test and Fisher's exact test, and results with a p value of <0.05 were considered statistically significant [10]. Stat Trek's Random Number Generator, which uses a statistical algorithm to produce random numbers, was used to randomize subjects into the treatment and placebo groups, respectively. Blinding to treatment and placebo samples was handled by an independent body, and unblinding was done only upon completion of data analysis.

The treatment sample used in this study was HEXBIO®. It is an orange-flavored granular powder, containing 30 billion colony-forming units of highly compatible, acid- and bile-resistant strains of *Lactobacillus acidophilus* (BCMC™12130), *Lactobacillus casei* (BCMC™12313), *Lactobacillus lactis* (BCMC™12451), *Bifidobacterium bifidum* (BCMC™02290), *Bifidobacterium longum* (BCMC™02120), and *Bifidobacterium infantis* (BCMC™02129). The placebo sample possessed similar appearance and taste, but it did not contain any live cultures. Both preparations were prepared in 3 g aluminum foil sachets with the label A for placebo and B for microbial cell preparation. These were administered orally twice daily—one sachet in the morning and one sachet in the evening for a consecutive 7 days prior to surgery [11].

The caloric requirement for patients were calculated according to the Harris–Benedict equation [12], and patients in both groups were allowed to continue with their respective normal diets with no particular restrictions. Administration of placebo and microbial cell preparation was done by a dietitian. The dietitian was responsible to assess the quality of gut function over time to determine the exact point in time when the patient is able to tolerate at least 80 % of their respective caloric requirement for a period of 48 h without any adverse effects such as, nausea, diarrhea and constipation.

Medians and ranges of nonnormally distributed continuous variables were calculated for the microbial cell preparation and placebo groups. The difference between the two groups were tested using the Mann–Whitney U test and Fisher's exact test. They were analyzed on an intention

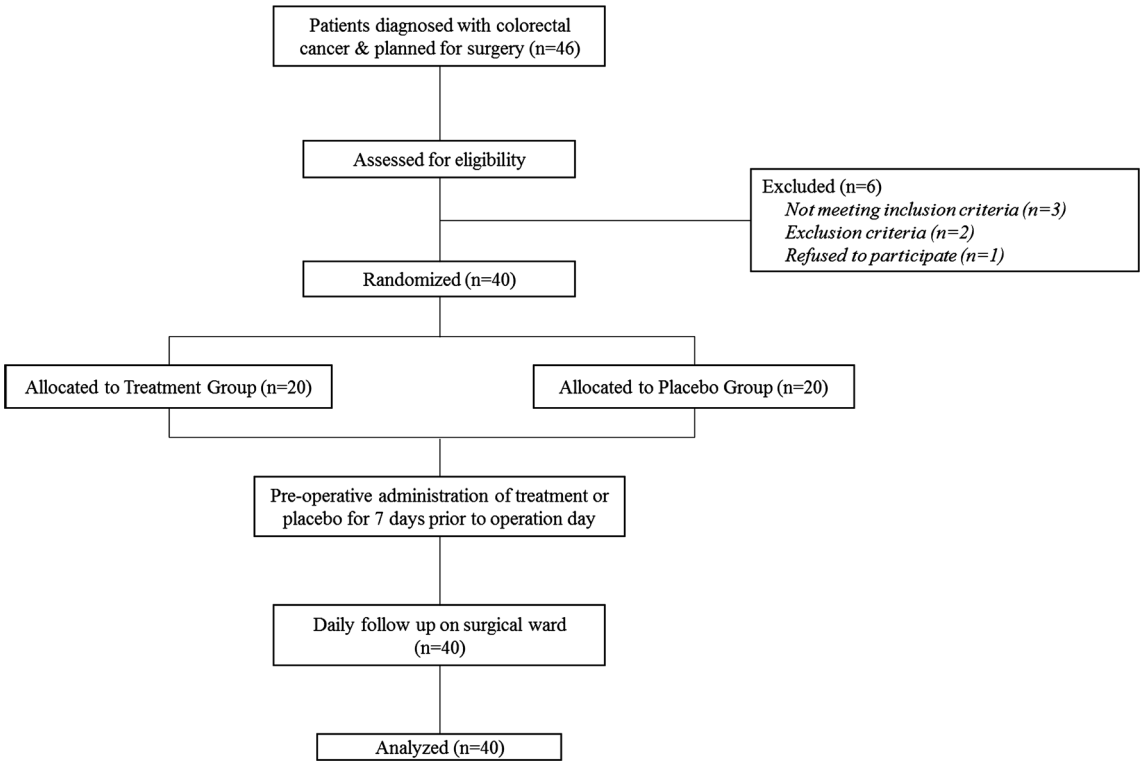


Fig. 1 Consort diagram of patient recruitment and analysis

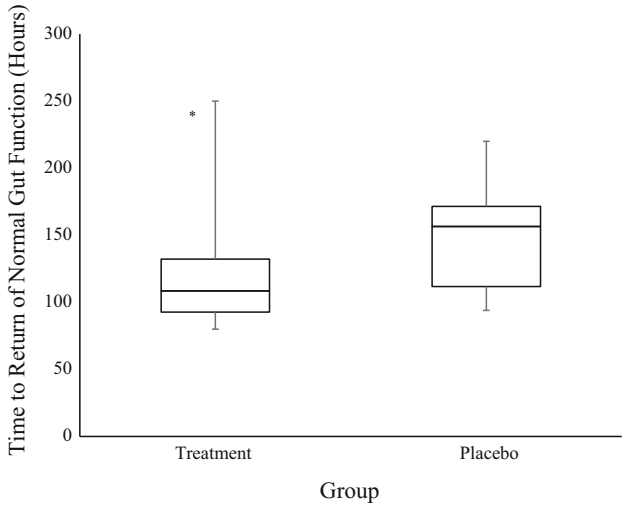
to treat basis. Statistical data were analyzed using SPSS for Windows version 21.

Normal gut function was defined as the tolerance of food intake to achieve 80 % of nutritional requirement (kcal/-day) within 48 h [9]. The primary end point of this study was the time to return of normal gut function, and the secondary end point was the duration of hospital stay. The recoveries over time between the treatment and placebo groups were analyzed using the Kaplan–Meier method and compared by the log-rank test. The consort diagram of patient recruitment and analysis is shown in Fig. 1.

Results

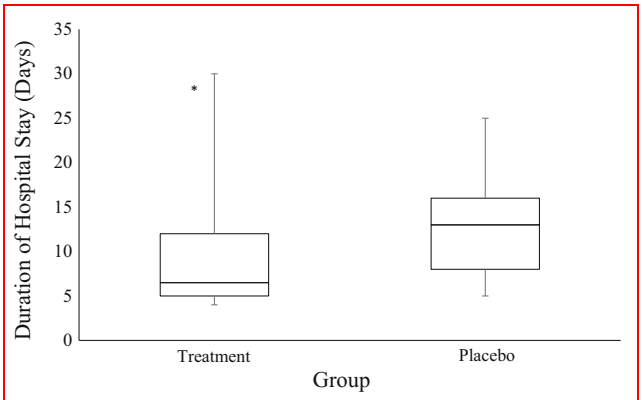
Forty patients were recruited with consent, and they were randomized equally into two groups. There were no statistically significant differences between the microbial cell preparation and placebo group in terms of age, gender distribution, and staging of disease. Although the duration of surgery was shorter in the treatment group compared with the placebo group (median 265 vs. 297.5 min), the difference was not statistically significant ($p = 0.165$). There was also no statistically significant difference in wound infection, pneumonia, anastomotic leak, abdominal collection, and line infection. The treatment group demonstrated significantly earlier return of normal gut function compared to the placebo group: 108.5 h (80–250 h) versus 156.5 h (94–220 h), respectively, $p = 0.022$ (Mann–Whitney test) as shown in Fig. 2. In this study, the duration of hospital stay was shorter for the treatment group in comparison to the placebo group, 6.5 versus 13 days as shown in Fig. 3. The difference between the two groups was statistically significant, $p = 0.012$ (Mann–Whitney test). The results are tabulated in Table 1. The exact types of surgery for both treatment and placebo groups are stated in Table 2. Differences between the two groups were not statistically significant for all surgery types using the Fisher's exact test. The recovery over time was shorter for the treatment group in comparison to the placebo group (Fig. 4); however, the difference was not significantly different based on the Kaplan–Meier method ($p = 0.23$).

Eight and four patients developed post-surgical complications in the placebo and treatment groups, respectively. The treatment halved the risk of post-surgical complications but the difference was not statistically significant ($p = 0.30$, Fisher's exact test), possibly due to the



Value	Group	
	Treatment	Placebo
Maximum	250	220
3rd Quartile	132.25	171.5
Median	108.5	156.5
1st Quartile	92.75	111.75
Minimum	80	94

Fig. 2 Time to return of normal gut function. Time to return of gut function of treatment and placebo groups. *$p < 0.05$ significantly different from the placebo group using Mann–Whitney test



Value	Group	
	Treatment	Placebo
Maximum	30	25
3rd Quartile	12	16
Median	6.5	13
1st Quartile	5	8
Minimum	4	5

Fig. 3 Duration of hospital stay. Duration of hospital stay of treatment and placebo groups. *$p < 0.05$ significantly different 259 from the placebo group using Mann–Whitney test

small sample size of this study. Patients with post-surgical complications in both treatment and placebo groups were graded as shown in Table 3 [13].

Table 1 Baseline characteristic and other outcomes in treatment and placebo groups

Parameter	Treatment ($n = 20$)	Placebo ($n = 20$)	p value*
Age (years), mean ± SD	64.3 ± 14.5	68.4 ± 11.9	0.779
Sex			0.519
Male (n)	11	13	–
Female (n)	9	7	–
Pathology stage			0.407
I (n)	7	4	–
II (n)	7	11	–
III (n)	6	5	–
IV (n)	0	0	–
Duration of surgery (min), median (range)	265 (115–520)	297.5 (150–570)	0.165
Duration of hospital stay (days), median (range)	6.5 (4–30)	13 (5–25)	**0.012**
Return of gut function (h), median (range)	108.5 (80–250)	156.5 (94–220)	**0.021**
Stoma (n)	3	2	0.633
Epidural analgesia (n)	19	20	0.311
ICU admission (n)	0	0	–
Wound infection (n)	1	2	0.548
Pneumonia (n)	1	1	1.000
Anastomotic leak (n)	1	2	0.548
Abdominal collection (n)	0	2	0.147
Line infection (n)	1	1	1.000
Urinary tract infection (n)	0	0	–
Deep vein thrombosis (n)	0	0	–
Morphine usage—subcutaneous (n)	5	4	0.705
Renal failure (n)	1	0	–
Liver failure (n)	0	0	–
Respiratory failure (n)	0	1	–
Hematological failure (n)	0	0	–
Mortality (n)	0	2	–

* Significant p values in bold

Overall the study concluded that the time to return of normal gut function and duration of hospital stay were shorter in the treatment group compared to the placebo group.

Discussion

The results from this study support the hypothesis that the pre-surgical use of microbial cell preparation helps to promote earlier return of normal gut function. Since the gut is the single, largest immunological, and cytokine production organ in the body, earlier return of normal gut function appears to be beneficial to post-surgical patients.

Table 2 Types of surgery in treatment and placebo groups

Type of surgery	Treatment ($n = 20$)	Placebo ($n = 20$)	p value
Anterior resection (n)	6	8	0.594
Extended right hemicolectomy (n)	2	0	–
Hartmann's procedure (n)	0	1	–
Left hemicolectomy (n)	1	1	1.000
Low anterior resection (n)	4	4	1.000
Panproctocolectomy (n)	1	0	–
Resection with ileoanal pouch (n)	0	1	–
Right hemicolectomy (n)	3	1	0.341
Sigmoid colectomy (n)	0	1	–
Ultralow anterior resection (n)	3	2	0.657
Total colectomy (n)	0	1	–

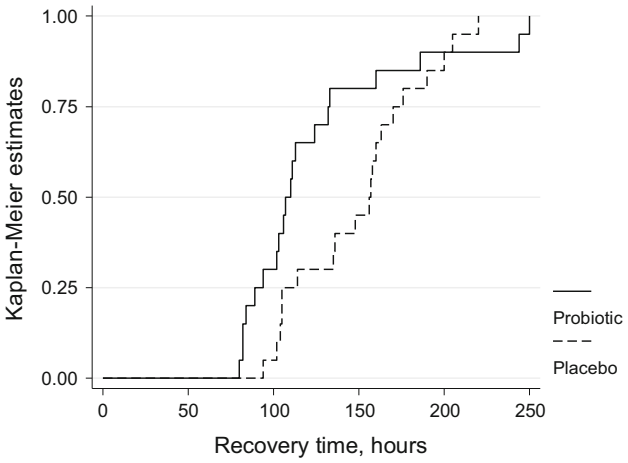


Fig. 4 Recovery over time between groups. Recovery time of microbial cell preparation and placebo groups constructed based on Kaplan–Meier method and compared by the log-rank test. The Kaplan–Meier method is a survival analysis tool. However, the difference was not statistically significant ($p = 0.23$)

The pre-surgical administration of microbial cell preparation resulted in significantly earlier return of normal gut function (Fig. 2) and shorter hospitalization (Fig. 3) in patients with colorectal cancer after surgery. Paralytic ileus is not uncommon among patients undergoing elective colorectal surgery as a result of inadequate gut function. Thereby, it is vital to promote earlier return of normal gut function, as failure to meet sufficient nutritional requirement has been associated with increased mortality and morbidity [14]. Previous studies reported the role of multimodal optimization packages in promoting early return of normal gut function, leading to enhanced recovery and improved outcome [15]. Microbial cell preparation promotes post-surgical health by stabilizing the intestinal barrier, stimulating epithelial growth, revitalizing mucus secretion and motility, and enhancing overall immunity [16].

Among the risk factors encountered post surgery are the post-surgical infections which are commonly caused by nosocomial infections [17]. In fact, post-surgical infections are one of the most common nosocomial infections in surgical patients, causing significantly higher medical costs and resulting in higher morbidity and mortality rates in post-surgical patients [18]. As microbial cell preparation promotes faster recovery resulting in shorter duration of

Table 3 Grading of surgical complications in treatment and placebo groups [13]

Group	Type of complication	Grade	All complications (n)	Major complications >2 (n)	Minor complications <2 (n)
Treatment	Anastomotic leak	4	4	3	1
	Line infection	1			
	Wound infection	3			
	Pneumonia	3			
Placebo	Anastomotic leak	2	8	5	3
	Anastomotic leak	5			
	Wound infection	3			
	Wound infection	3			
	Abdominal collection	5			
	Pneumonia	2			
	abdominal collection	4			
	Line infection	2			
p value			0.30	0.70	0.60

hospital stay, it helps reduce post-surgical infections caused by nosocomial infections [19]. Bacteria of enteric origin can also be causal agents of surgical site infections, mainly due to dysfunction of the gut barrier, and dysbiosis of the gut microflora [16]. The trauma caused by surgery predisposes the patient to a compromised gut barrier function thus promoting bacterial translocation from the gut into the systemic circulation, leading to increased incidences of post-surgical morbidities in these patients [14]. Despite prophylactic use of antibiotics prior to gastrointestinal surgery, a reported 10–30 % of patients still developed post-surgical infections [16]. Thus, this clearly indicates the importance of gut barrier function to prevent bacterial translocation in post-surgical patients. Due to the shorter hospital stay and decreased infection-related complications the patient's quality of life would be improved, and this may also decrease the risk of emergence of antimicrobial resistance as a result of shorter period of antibiotic administration.

A study [10] reported a significant reduction in the post-surgical rates of diarrhea, cramps, and distention with a faster return to normal bowel function in the treatment group ($p < 0.05$). In this study, the duration of hospital stay was significantly lower among patients who received microbial cell preparation pre-surgically (Fig. 3). Previous studies have reported that the use of microbial cell preparation after surgery markedly improved intestinal microbial populations and significantly decreased the incidence of complications [18–20]. Those studies mainly demonstrated the beneficial effects of microbial cell preparation in patients undergoing colectomy [18–20]. There was a significant improvement in gut function and decrease of infection-related complication among patients receiving pre-surgical oral microbial cell preparation [21].

Table 4 Studies using microbial cell preparation in surgical patients

Procedure	Strains	Treatment duration (days)	Results	Administration	Reference
Major abdominal surgery	*Lactobacillus plantarum* 299	4	Reduction of postoperative infections in treatment group	Postoperative	Rayes et al. [23]
Liver transplantation	*Pediococcus pentosaceus*, *Leuconostoc mesenteroides* 77:1, *Lactobacillus paracasei* ssp. *paracasei* F19, *Lactobacillus plantarum* 2362	15	Reduction of postoperative infections in treatment group	1 day preoperatively, 14 days postoperatively	Rayes et al. [26]
Liver, and extrahepatic bile duct resection	*Lactobacillus casei* strain Shirota, *Bifidobacterium breve* strain Yakult	28	Reduction of postoperative infections in treatment group	2 weeks preoperatively, 2 weeks postoperatively	Sugawara et al. [18]
Liver, and extrahepatic bile duct resection	*Bifidobacterium breve*, *Lactobacillus casei*	14	Reduction of postoperative infections in treatment group	Postoperative	Kanazawa et al. [20]
Pancreatoduodenectomy	*Bifidobacterium bifidum*, *Bifidobacterium infantis*, *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus salivarius*, *Lactococcus lactis* (ECOLOGIC 641)	14	No influence on bacterial translocation, intestinal permeability and expression of inflammatory mediators	7 days preoperatively, 7 days postoperatively	Diepenhorst et al. [29]
Colorectal resection	*Bifidobacterium longum*, *Lactobacillus johnsonii*	6	Immune cells are higher in treatment group, reduction of pathogens in stools of treatment group	3 days preoperatively, 3 days postoperatively	Gianotti et al. [30]
Colorectal carcinoma resection	*Lactobacillus plantarum* (CGMCC No. 1258), *Lactobacillus acidophilus* 11, *Bifidobacterium longum* BL-88	16	Reduction of postoperative septicemia and serum zonulin in treatment group	6 days preoperatively, 10 days postoperatively	Liu et al. [31]
Colorectal liver metastases resection	*Lactobacillus plantarum (CGMCC No. 1258), Lactobacillus acidophilus 11, Bifidobacterium longum BL-88*	16	Reduction in postoperative septicaemia in treatment group, maintenance of liver barrier in treatment group	6 days preoperatively, 10 days postoperatively	Liu et al. [32]

Overall, post-surgical infections can be brought on by longer hospital stay and in the same time, the development of post-surgical infections can also lengthen hospital stay; having said so, the key issue that this study aimed to address was enhanced recovery to avoid both issues.

The ideal number of colony-forming units for each bacterial strain to be delivered remains unknown. This is due to the lack of dose–response studies. Furthermore, most doses of microbial cell preparation in human trials are based on those used in animal studies despite differences in intestinal surface area. Microbial cell preparation may produce their effects with viable as well as nonviable bacteria, suggesting that their effects may be exerted by extracellular metabolites, or structural and cellular components. Furthermore, several experiments have indicated that the secretion of various cytokines are mediated by large cellular wall components of microbial cell preparation [22].

The microbial cell preparation used in this study contained six strains of bacteria (*L. acidophilus*, *L. casei*, *L. lactis*, *B. bifidum*, *B. longum* and *B. infantis*). The pre-surgical use of microbial cell preparation has shortened the time required for return of normal gut function and the duration of hospital stay. Previous two studies involving patients undergoing elective surgery who were administered microbial cell preparation containing one type of bacteria failed to provide statistically significant results [23, 24]. Recent randomized controlled trials using microbial cell preparation containing more than one bacterial strain had showed statistically significant outcome [19, 20, 25–27]. These findings suggest that the efficacy of microbial cell preparation containing more than one bacterial strain may be higher in comparison to those containing only one bacterial strain. However, most randomized trials have focused more on the effect of microbial cell preparation in reducing post-surgical infections than on the return of gut function as their endpoints as shown in Table 4.

The benefits of pre-surgical administration of microbial cell preparation have been studied in animal models. Results have shown that the immune responses were higher in animals on microbial cell preparation prior to surgery [28]. Thereby, future human clinical trials should focus extensively on immune parameters for a better understanding of the role of pre-surgical optimization using microbial cell preparation to promote early recovery in post-surgical patients.

The recovery of bowel function of the patient over time in accordance to the amount of calories taken were not recorded in this study; however, this would be useful to determine the true recovery of bowel function. Hence, this is a limitation of this study. Further studies are needed in order to emphasize the role of microbial cell preparation in the return of normal gut function. Future studies should also consider other endpoints such as first flatus, first bowel movement, colonic transit time, and first oral intake.

Conclusion

Pre-surgical use of microbial cell preparation promotes faster return of normal gut function and shorter duration of hospital stay when used in elective surgery in colorectal cancer patients. Administration of microbial cell preparation as nutritional supplementation prior to surgery can be implemented as a part of a fast recovery program in elective colorectal cancer surgery.

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