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Original article

Post-surgical intestinal dysbiosis: use of an innovative mixture (*Lactobacillus plantarum* LP01, *Lactobacillus lactis subspecies cremoris* LLC02, *Lactobacillus delbrueckii* LDD01)

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Summary. Abdominal surgery represents a high risk for hospital-acquired infections and complication that may compromise the surgery outcome. Patients with recent abdominal surgery have an intestinal dysbiosis. There is evidence that probiotics may counterbalance the impaired microbiota. Therefore, the current survey evaluated the efficacy and safety of Abincol®, an oral nutraceutical containing a probiotic mixture with *Lactobacillus plantarum* LP01 (1 billion of living cells), *Lactobacillus lactis subspecies cremoris* LLC02 (800 millions of living cells), and *Lactobacillus delbrueckii* LDD01 (200 millions of living cells), in 612 outpatients (344 males and 268 females, mean age 58 years) undergoing digestive surgery. Patients took 1 stick/daily for 8 weeks. Abincol® significantly diminished the presence and the severity of intestinal symptoms and improved stool form. In conclusion, the current survey suggests that Abincol® may be considered an effective and safe therapeutic option in the management of patients undergoing digestivesurgery. (www.actabiomedica.it)

Key words: digestive surgery, dysbiosis, microbiota, probiotic, survey

Introduction

It is well known that complications after abdominal surgery, mainly concerning in cancer patients, are often a result of bacterial infections, leading to a significant increase in morbidity and mortality, as well as the duration of hospitalization and the subsequent economic costs (1). The gut pathophysiology exerts a crucial role in this context. Indeed, impaired gut barrier function may lead to an imbalanced intestinal physi-

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ology. In addition, bacteria and their toxins may enter the blood stream and provoke systemic inflammatory response, which may lead to multiple organ failure or even death. It has been reported that some patients after open-abdomen surgery have experienced translocation of live bacteria to the mesenteric lymph nodes or to the serosa of the bowel wall (2, 3).

In recent years, there has been growing interest in the human gut microbial ecosystem, which ultimately appears to be involved in both disease onset and progression, as well as in the development of complications. The complex gut ecosystem coexists in a fragile balance (symbiosis), that can easily be disturbed (dysbiosis). Actually, dysbiosis has been linked with severe diseases, not only infections, but also autoimmune and autoinflammatory disorders, (4, 5).

In addition, the use of probiotics to prevent and cure the surgery complications has become popular in hospital setting as recently pointed out (6). The rational for probiotics use in abdominal surgery derives from the evidence that probiotics significantly affect gut dysbiosis resulting from both intestinal preparation and abdominal operation. Actually, peri-operatory use of probiotics reduces the mucosal damage consequent to surgery and medications.

Abdominal surgery is also associated with bowel preparation and antibiotic prophylaxis: both have additional detrimental effects on the ecology of commensal bacteria, ranging from self-treated "functional" diarrhoea to life-threatening pseudomembranous colitis (7, 8). Moreover, food restriction, even in the setting of complete intravenous nutrition, leads to a scarcity of macronutrients for the bacteria within the gut, and thus to a relative loss of *Firmicutes* and to an expansion of *Proteobacteria* and *Bacteroidetes*. All these factors contribute to the severity of intestinal dysbiosis associated to abdominal surgery.

Probiotics are live microbial food supplements, such as nutraceuticals, that may beneficially improve the host by acting on the intestinal microbial balance (9).

Probiotics are able to maintain gut barrier function by restoring intestinal permeability and ameliorating the intestinal anti-inflammatory response and the release of cytokines, and can also maintain the homeostasis of the normal gut microbiota. Therefore, probiotics have been extensively studied as an adjuvant perioperative treatment modality to reduce infectious complications in surgical patients (10). There is therefore evidence that modulation of the intestinal microbiota with probiotics seems to be an effective method to reduce infectious complications in surgical patients. In this regard, probiotics may have an additional indication concerning the endurance of surgical anastomosis as they modulate the oxidative metabolism and peptide metabolism (11). Consistently, Van Praagh and colleagues demonstrated an association between *Lachnospiracea* and anastomosis failure (12). In addition, a recent review reported a microbiota change including the increase of pathogens and reduction of protective bacteria after abdominal surgery (13).

Abincol® is an oral nutraceutical containing a probiotic mixture with *Lactobacillus plantarum* LP01 (1 billion of living cells), *Lactobacillus lactis subspecies cremoris* LLC02 (800 millions of living cells), and *Lactobacillus delbrueckii* LDD01 (200 millions of living cells) and it has been recently placed on the market.

On the basis of this background, an Italian survey explored the pragmatic approach of a group of gastroenterologists in the management of patients undergoing abdominal surgery in clinical practice. Therefore, the aim of the current survey was to evaluate the efficacy and safety of Abincol® in outpatients after digestive surgery.

Materials and Methods

The current survey was conducted in 83 Italian Gastroenterology centers, distributed in the whole Italy, so assuring a wide and complete national coverage, during the fall-winter 2018-2019. Gastroenterologists were asked to recruit all consecutive outpatients visited because of recent digestive surgery.

Patients were consecutively recruited during the specialist visit. The inclusion criteria were: to have recent abdominal surgery, both genders, and adulthood. Exclusion criteria were to have comorbidities and concomitant medications able to interfere the evaluation of outcomes.

Digestive surgery included appendicectomy, polypectomy, hemorrhoidectomy, gastrectomy, adherence lysis, ileum resection, sigma resection, hemicolectomy, and rectal resection.

All patients signed an informed consent. All the procedures were conducted in a real-world setting.

The treatment course lasted 8 weeks. The oral nutraceutical Abincol® (Aurora Biofarma, Milan, Italy) was taken following the specific indications, such as one stick/daily. Patients were visited at baseline (T0), after 4 weeks (T1), and after 8 weeks (T2).

Clinical examination was performed in all patients at T0, T1, and T2. The following parameters were investigated: abdominal pain, abdominal bloating, flatulence, borborygmi, eructation, malaise, weakness, headache. These symptoms were assessed as present/absent and were scored using a four-point scale (0=absent, 1=mild, 2=moderate, 3=severe), but for abdominal pain the scale was 5-point (4=very severe). A physical examination of stool was performed using the Bristol stool form scale (16).

Safety was measured by reporting the occurrence of adverse events.

All clinical data were inserted in an internet-platform that guaranteed the patients' anonymity and the findings' recording accuracy.

The paired T-test was used. Statistical significance was set at $p < 0.05$. Data are expressed as medians and 1th and 3rd quartiles. The analysis was performed using STATA, College Station, Texas, USA.

Results

Globally, 612 outpatients (344 males and 268 females, mean age 58 years) were visited and completed the treatment course.

The frequency of symptoms (abdominal pain, abdominal bloating, flatulence, borborygmi, eructation, malaise, weakness, and headache) at baseline (T0), and at T1 and T2 is reported in Table 1 and 2. In particular, abdominal pain and abdominal bloating were the most common symptoms at baseline. The frequency of both significantly diminished after the treatment course.

Consistently, the severity of the most relevant symptoms did significantly diminish after the treatment (Figure 1). In particular, abdominal pain and bloating significantly diminished at T1 and T2 ($p<0.001$ respectively for both symptoms).

In addition, stool form significantly improved as a normal form (type 3 and 4) was detectable in 25.8% at baseline, in 46.4% at T1, and in 47% at T2 ($p<0.001$ as linear trend).

The treatment was well tolerated by all patients and no clinically relevant adverse event was reported.

Table 1. Frequency of patients for each symptom at baseline (T0). M=males; F=females, Mean age in years

N=612	T0			
	n	%	M/F	Mean age
Abdominal pain	503	82.2%	282/221	58
Abdominal bloating	464	75.8%	253/211	58
Flatulence	421	68.8%	241/180	58
Borborygmi	352	57.5%	199/153	57
Eructation	325	53.1%	176/149	57
Malaise	206	33.7%	116/90	60
Weakness	140	22.9%	84/56	61
Headache	43	7.0%	26/17	57

Table 2. Comparison of proportion of patients with symptoms at baseline (T0), and at T1 and T2

Symptoms	T0	T1				T2			
	n	n	%	Diff %	p	n	%	Diff %	p
Abdominal pain	503	319	63.4%	-36.6%	<0.001	191	38.0%	-62.0%	<0.001
Abdominal bloating	464	318	68.5%	-31.5%	<0.001	185	39.9%	-60.1%	<0.001
Flatulence	421	258	61.3%	-38.7%	<0.001	166	39.4%	-60.6%	<0.001
Borborygmi	352	183	52.0%	-48.0%	<0.001	105	29.8%	-70.2%	<0.001
Eructazioni	325	190	58.5%	-41.5%	<0.001	132	40.6%	-59.4%	<0.001
Malaise	206	58	28.2%	-71.8%	<0.001	14	6.8%	-93.2%	<0.001
Weakness	140	39	27.9%	-72.1%	<0.001	10	7.1%	-92.9%	<0.001
Headache	43	7	16.3%	-83.7%	<0.001	2	4.7%	-95.3%	<0.001

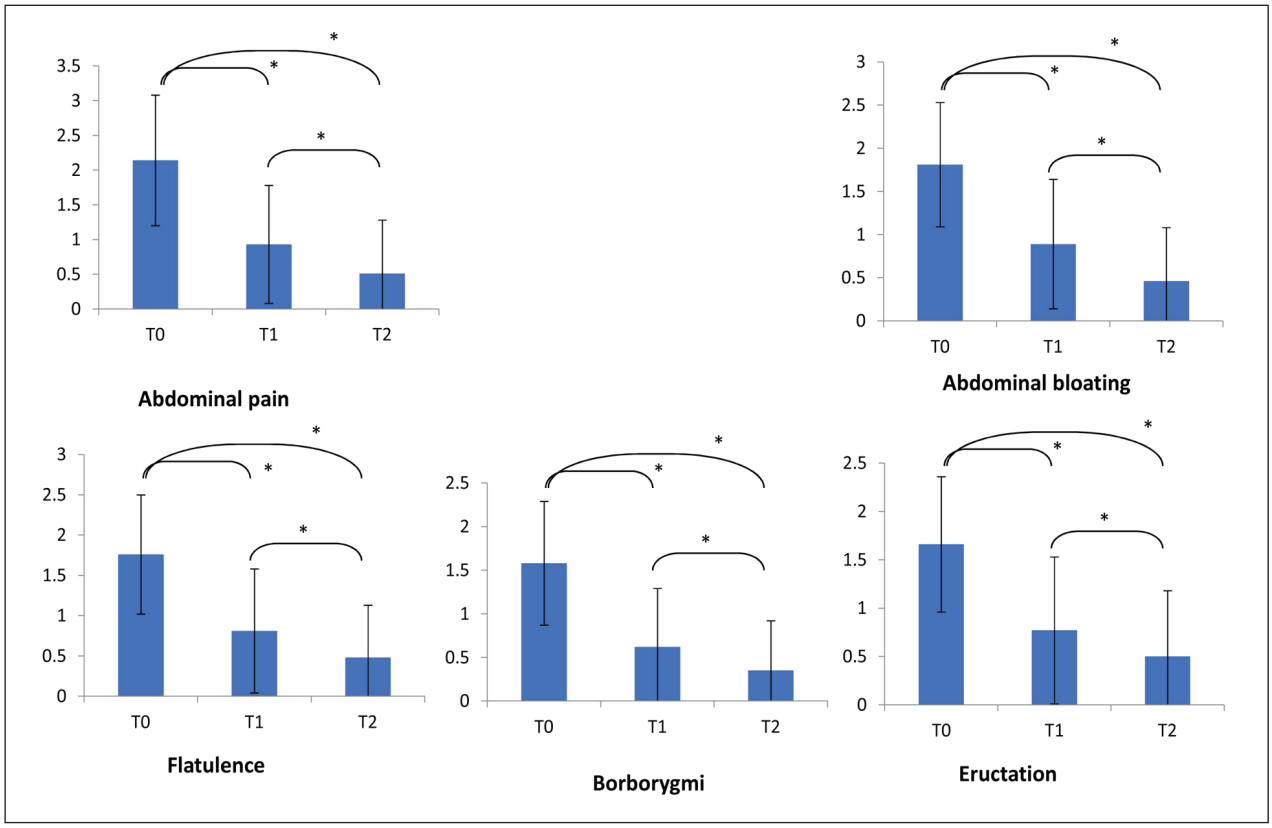

Figure 1. Symptoms severity at baseline (T0), at T1 and T2. Symptoms' score scale was 0-3 for all symptoms but abdominal pain (0-4). Comparisons were made by paired Wilcoxon test. *= p<0.001

Discussion

There is evidence that any surgery represents a high risk for hospital-acquired infections (HAIs): in fact, surgical site infections (SSIs) are the most frequent HAI in the surgical population, in particular, abdominal surgery has the highest ratio (2-20%) as recently reported (14, 15). In this regard, a promising novel infection-prevention strategy may be the administration of probiotics, which are live microbial preparations that may confer a positive benefit to the host when taken in sufficient amounts. A recent systematic review and meta-analysis of RCTs suggests that probiotics/synbiotics in adult patients undergoing elective abdominal surgery reduce the risk of SSIs compared to placebo or standard of care (14). However, the currently available evidence was found to be of low to very low quality, mainly due to risk of bias and imprecision; thus, a large, methodologically sound RCT is needed to corroborate the safety and efficacy of their use in surgical patients.

The rational for probiotic use in preventing infections depends on the characteristics of microbiota (16). However, it has to be underlined that the efficacy of probiotic products is both strain-specific and disease-specific. Important factors involved in choosing the appropriate probiotic include matching the strain(s) with the targeted disease or condition, type of formulation, dose used and the source, including manufacturing quality control and shelf-life (17). Therefore, choosing an appropriate probiotic is multifactored, based on the mode and type of disease indication and the specific efficacy of probiotic strain(s), as well as product quality, formulation, and conservation. For example, it has been very recently demonstrated that two probiotic mixtures obtained by combining

taxonomically similar species produced with different manufacturing methods exert divergent effects in mouse models of colitis (18).

Anyway, we know that gut microbiota is associated with the pathogenesis of many diseases and the emerging new therapeutic targets in gut microbiota represent an intriguing challenge (19, 20).

The current survey demonstrated that Abincol® was able to significantly and progressively reduce the most common digestive complaints occurring in patients after abdominal surgery. In particular, Abincol® did diminish impressively abdominal pain and bloating that are bothersome symptoms and affects the quality of life. The improvement of stool form in many patients could be considered the indirect proof of the mechanism of action of Abincol® as it modified the intestinal microbiota inducing a physiological digestive function.

In addition, Abincol® was safe and well tolerated.

All these issues suggest that this probiotic mixture may be useful in the management of patients undergoing abdominal surgery.

Of course, the present survey cannot be considered a formal investigative study. Consequently, further studies should be conducted by a rigorous methodology, such as designed according to randomized-controlled criteria. Another relevant issue is the need of investigating the microbiota before and after probiotics supplementation.

On the other hand, the strength of this survey is the huge number of enrolled patients and the real-world setting. The outcomes could therefore mirror the facts observable in clinical practice. In particular, the sample consisted of patients undergoing elective surgery.

Finally, it has to be noted that the probiotics effects are strain-dependent and outcomes cannot be generalized for all probiotic species.

In conclusion, the current survey suggests that Abincol® may be considered an effective and safe therapeutic option in the management of patients undergoing digestive surgery.

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