RESEARCH

Evaluation of the efficacy and safety of two medical devices composed by Macrogol 4000 and Macrogol 4000 plus *psyllium* fiber in the treatment of constipation: A multicenter, non-comparative observational study

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ABSTRACT

Constipation is a pathological condition that interest around 15%-20% of the global population. Patients complain of difficulty in passing stools and defecation. Diagnosis of constipation is based on visual images, specific questionnaires and the knowledge of the patients' history. Current treatments are based on life style and dietary modification as first strategy, then patients can require the use of products that improves bowel movements using different mechanism of actions. Nowadays, osmotic laxatives represent the first strategy used in the treatment of constipation. Among them, Macrogol 4000 has been largely described to be effective and safe in the treatment of constipation in adults and children. Together with this, bulk-forming laxatives are employed as well. *Psyllium* fiber belongs to this class of laxatives and among fibers has been shown to be the most effective one. Starting from this evidence, we aimed to verify and confirm the efficacy and safety of two medical devices based on Macrogol 4000 alone (Macrostip®) or in combination with *psyllium* fiber (Macrostip® *Psyllium*). In this multicenter, non-comparative and observational study we collected clinical data that support the use of both products for the treatment of constipation in adults. Indeed, data analysis revealed that 15 days treatments are sufficient to improve constipation status in subjects treated with Macrostip® or Macrostip® *psyllium*. In addition, both treatments resulted to be safe, well tolerated and appreciated by participants supporting the use of these molecules in case of constipation.

Key Words: *Macrogol 4000; Evaluation; Medical devices; Multicenter; Psyllium fiber*

INTRODUCTION

The constipation is a pathological condition that affects around 15%-20% of the global population and carries a major health care burden [1,2]. Patients suffering of constipation complain of difficulty in passing stools and defecation. The definition of constipation can vary, with some sources describing it as a failure to evacuate the lower colon while others consider it a symptom that is challenging to define precisely [3,4]. Depending on the underlying causes, constipation can be classified as primary or secondary [1,5]. Primary constipation is due to neuromuscular dysfunction of the colon or anorectal sensory-motor function. Secondary constipation is often associated with organic disease (i.e. mass or malignancy), medication use (i.e. opioids,) or other underlying condition (i.e. metabolic or diabetic disorders). In adults the prevalence of constipation increases with age, and it is higher in elderly patients. This is due possibly to degeneration of epithelial, muscle and neural cells of the colon and pelvic floor [6,7]. Genetic factors, unbalanced diet, obesity and poor physical activity, microbiome changing/dysbiosis and behavioral factors are all factors associated with constipation prevalence both in adults and in children. Combination of visual images of stool and specific questionnaires vehiculated by physicians together with the knowledge of the patients' history help in the diagnosis of constipation. Stool frequency, stool shape and consistency are also key components of the diagnostic criteria, and the Bristol Scale FS is recommended for characterizing stool appearance [8-10]. Finally, comprehensive abdominal and thorough digital rectal examinations are also useful in evaluating chronic constipation. Initial therapies for constipation include lifestyle, dietary modification (i.e., increasing fluid and fiber intake) and physical activity. Increasing fiber intake, which should be done gradually to prevent abdominal distension, may improve constipation by stimulating the gut mucosa to secrete water and mucus and improve stool consistency by increasing its water-holding capacity. Prebiotics and probiotics (for example *Bifidobacterium* and *Lactobacillus* species) have been suggested as a potential treatment modality for constipation

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and have been reported to have a positive effect on colonic transit and defecation frequency. When constipation is not resolved, pharmacological approaches are used [2,7,9]. Laxatives, inexpensive, widely available and often Over-The- Counter (OTC) products, are good option for constipation refractory to lifestyle and dietary modifications. Using different mechanism of action, laxatives improve stool consistency, increase stool frequency and reduce defecation straining. Depending on their origin and activities, laxatives are classified in: bulk laxatives which increase the volume of the stool by drawing water (i.e. methylcellulose, bran, agar-agar and *Psyllium* seeds); irritating/stimulant laxatives that increase intestinal motility and secretion (Senna, Cascara, Frangula and Rhubarb); lubricating laxatives which facilitate the passage of stool by making it softer (i.e.glycerin) and osmotic laxatives which act by retaining water in the colon (PEG, lactulose, sorbitol, mannite, tamarind). Osmotic laxatives create an osmotic gradient that promotes water and electrolyte secretion into the intestinal lumen, softening stools, increasing fecal volume and improving peristalsis. Most studies have focused on PEG and demonstrated that PEG treatment shows greater resolution of constipation symptoms, improved stool consistency and frequency, shorter Gastro-Intestinal (GI) transit time, less straining, and less severe abdominal bloating and pain compared with placebo. Stimulant laxatives (i.e. bisacodyl and sodium picosulfate) are commonly pro-drug which, after assumption, are converted and activated in the intestinal mucosa. They irritate the intestinal cells causing the intestine to contract, thus stimulating defecation. Stimulant laxatives also promote water influx to the intestine, which in turn promotes bowel movement [11]. This class of drugs is usually recommended after patients have failed to respond to osmotic laxatives. The most common Adverse Events (AEs) with stimulant laxatives include diarrhoea, abdominal pain, nausea, vomiting and headache. Other classes of drugs are represented from serotonin or opioid receptor agonists and activators of chloride channel. These products are used in patients who fail traditional laxatives. Regarding PEG (Macrogol) formulations, they include macrogol 3350 and macrogol 4000, which have been shown to be safe, effective treatments for constipation, even in children and elderly patients. Macrogol 4000 alone has been observed to be more palatable than combined formulations (macrogol 3350 with electrolytes), which could help improve adherence to the long-term treatment required for chronic constipation. PEG with molecular weights <1500 are absorbed by the intestinal mucosa and are, thus, unsuitable as osmotic compounds. In contrast, those with higher molecular weights (i.e. 3350 or 4000) are not absorbed, thereby sequestering water in the bowel [12]. Since PEG/macrogol is an inert molecule which cannot be metabolized by the intestinal microflora, it should be delivered from the small intestine to the colon, where it evokes its osmotic activity. This causes the volume of the fecal mass to increase (due to a higher water content), which in turn triggers propulsive motor processes, such as peristalsis, via distension of the colonic wall. The increased hydration also softens the feces and eases defecation. In addition to osmotic laxatives, supplementation with fiber is also indicated as first-line management for chronic constipation in few international guidelines. Fiber encompasses all carbohydrates that are neither digested nor absorbed in the small intestine. This includes prebiotic fibers, which are substrates that might be utilized by host microorganisms, conferring a health benefit. Soluble, viscous fibers can influence stool bulking directly through water retention in the colon, resulting in softer stools. Insoluble, non-viscous fibers can cause mechanical stimulation of the gut mucosa that accelerates Gut Transit Time (GTT) [13,14]. Among soluble fibers, recently strong evidence has been published in support of the use of *psyllium* in the treatment of constipation. *Psyllium* is a powder ground from the seeds of Plantago ovate. *Psyllium* is rich in mucilage, which is a mixture of polysaccharides consisting of pentoses, hexoses, and uronic acids. In vivo studies demonstrated that *psyllium* could retain its water-holding capacity in the gut and can be employed as a laxative in clinics [15]. Moreover, a recent meta-analysis demonstrate that *psyllium* is the most effective investigated fiber at providing constipation relief, with improvements in stool frequency and severity of straining, which highlights *psyllium*'s potential to be used as a first-line strategy for the management of constipation [16,17]. Starting from these evidence, we aimed to verify and confirm efficacy and safety of two medical devices indicated for the treatment of constipation. The first product is composed only by Macrogol 4000 (Macrostip®), the second presents both Macrogol 4000 in combination with *psyllium* fiber (Macrostip® *Psyllium*).

MATERIAL AND METHODS

Tested medical devices

The tested products are two medical devices available in oral solution or sachets forms, produced by Pharma Line S.r.l. Milan, on the market since 2020. The products are based on Macrogol 4000 (10 g) (distributed in Italy as Macrostip and in many other countries; in Greece as Laxaney MACRO) and Macrogol 4000 (5 g) and *psyllium* fiber (3 g) (distributed in Italy as Macrostip *Psyllium* and in many other countries with different names). The composition of the products is shown in table 1.

TABLE 1
Composition of the products

	Macrogol 4000 per sachet	*Psyllium* fiber per sachet
Macrostip®	10 g	-
Macrostip® *Psyllium*	5 g	3 g

Patients and inclusion/exclusion criteria

Italian and Greek gastroenterologists, prescribers of the medical devices in their clinical practice, participated in the present clinical experiences and data collection. Participants had to be >18 years of age, have received a diagnosis of constipation from the investigator physician and follow a 15-days period of treatment with the tested product in the amount of 2 sachets per day. Patients with active infection, malignant pathologies of the digestive system, in hemodialysis, with history of gastric surgeries, pregnant or allergic to some components of the products have been excluded (Figure 1).

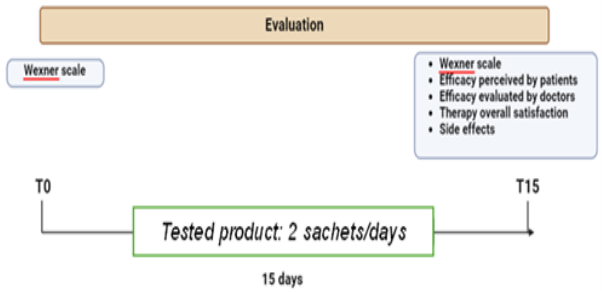


Figure 1) *Schematic representation of the study design*

Study design

A multicenter, non-comparative observational study for the confirmation of efficacy and safety and for the evaluation of patient satisfaction of the medical devices Macrostip® and Macrostip® *Psyllium* have been performed. Ideal patients are those who have not yet undertaken continuous therapies for the constipation treatment. The treatment consists of taking a sachet of the medical device dissolved in a glass of water 2 times a day, between meals, morning and evening. During the observation period, the intake of other drugs, dietary supplements or medical devices for the treatment of constipation was not allowed. The duration of treatment with Macrostip® or alternatively Macrostip® *Psyllium* is 15 consecutive days. The evaluation has been performed at the day of the enrollment (T0) and after 15 days of treatment (T15). Patients were asked at T0 and at T15 to fill a questionnaire for the evaluation of the constipation referred as Wexner scale [16-18]. This validated questionnaire is composed of 8 questions. The obtained score is used to classify patients in four stages for constipation gravity:

1. 1-5 mild
2. 6-10 moderate
3. 11-15 severe
4. 16-30 very serious

At the end of the observation period (T15) the investigator physicians and patients had to rate the efficacy of the therapy using a Likert scale (0-4: 0= no efficacy; 1=poor efficacy; 2=low efficacy; 3=good efficacy and 4= very good efficacy). In addition, the participants, through a Likert scale (0-4; 0=no satisfaction; 1=poor satisfaction; 2=low satisfaction; 3=good satisfaction and 4= very good satisfaction) rated their satisfaction with the therapy. And finally, at T15, adverse events were recorded.

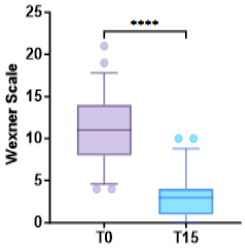
Statistical analysis

Given the limited number of subjects evaluated, the descriptive analysis of quantitative variables is reported as mean range and standard deviation (±SD), while qualitative variables are reported as percentages. Nonparametric, unpaired t-test was used for statistical analyses. Unpaired data assumes that the SD is the same in both comparisons. Statistical significance was set at 1% ($p<0.01$). All statistical analyses were performed using GraphPad Prism version 10.0.2.

RESULTS

Efficacy and safety of Macrostip® in the treatment of constipation

A total of 51 patients (37 involved by the Greek gastroenterologist and 14 involved by the Italian gastroenterologist) participated in the present clinical experience and assumed the product Macrostip®. On the day of Treatment Initiation (T0), subjects completed the "Wexner scale" questionnaire and a mean value of 10.57 (moderate constipation) has been obtained. After taking the product Macrostip® for 15 days in the amount of 2 sachets per day, the subjects repeated the questionnaire and an average score of 3.01 (mild constipation) has been obtained. This corresponds to a ~71% of reduction of the score between T0 and T15 (Figure 2). To assess the efficacy of the product after 15 days of treatment, a Likert scale (0-4) completed by both the physician and the participating subjects was used. The score obtained shows an average of 3 according to both the physicians' and to the subjects' evaluation (Figures 3A and 3B). The same mean value was obtained from the analysis of the scores obtained on the Likert scale (0-4) for patient satisfaction with the evaluated therapy (Figure 3C). Finally, no adverse events were recorded during the observation period.



	T0	T15	% decrease
Mean	10,57	3.01	- 71.52%

Figure 2) *Wexner scale score. Wexner scale has been used to assess the efficacy of Macrostip® in the treatment of constipation. ($p<0.0001$, ****). Box plot represents values distribution in the population at T0 and at T15 (left). Table represents the mean values with the percentage of decrease (right)*

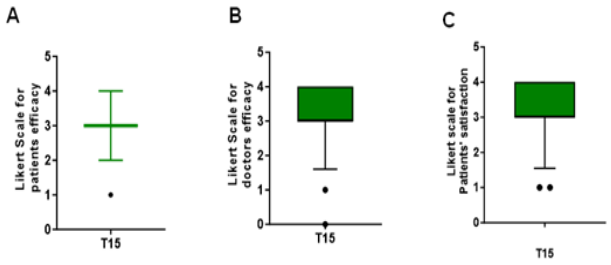
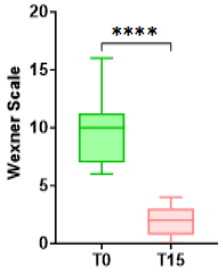


Figure 3) *Likert scale score for patient assessment of Macrostip® treatment efficacy (A), physician efficacy (B), and patients' satisfaction with therapy (C).*

Efficacy and safety of Macrostip® *Psyllium* in the treatment of constipation

A total of 14 patients (enrolled only in Italy) participated in the present clinical experience assuming Macrostip® *Psyllium*. On the day of treatment initiation T0, subjects completed the "Wexner scale" questionnaire and a mean value of 9.71 (moderate constipation) has been obtained. After taking the product Macrostip® *Psyllium* for 15 days in the amount of 2 sachets per day, the subjects repeated the questionnaire and an average score of 1.85 (mild constipation) has been obtained. This corresponds to a ~ 81% of reduction of the score between T0 and T15 (Figure 4). To assess the efficacy of the product after the 15 days of treatment, a Likert scale was used that was completed by both the physician and the participating subjects. The score obtained is an average of 3.07 for both the physician and the subjects' evaluations (Figures 5A and 5B). The same mean value was obtained from the analysis of scores obtained at the end of the treatment (T15) on the Likert scale for participants' satisfaction with the evaluated therapy (Figure 5C). Finally, no adverse events were recorded during the observation period.



	T0	T15	% decrease
Mean	9.71	1.85	- 80.94%

Figure 4) *Wexner scale score. Wexner scale has been used to assess the efficacy of* Macrostip® *Psyllium in the treatment of constipation. (p<0.0001, ****). Box plot represents values distribution in the population at T0 and at T15 (left). Table represents the mean values with the percentage of decrease (right).*

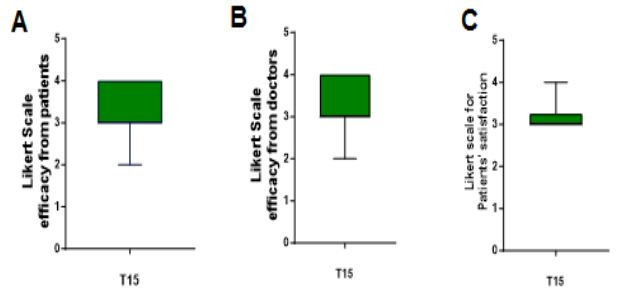


Figure 5) *Likert scales for patient assessment of Macrostip Psyllium treatment efficacy (A), physician efficacy (B), and patients' satisfaction with therapy (C).*

DISCUSSION

The present clinical investigation was conducted in parallel in two European Countries where the two tested medical devices Macrostip® and Macrostip® *Psyllium* are currently marketed: Greece and Italy. Specifically, the data related to Macrostip® were obtained from the experience and clinical evaluation performed in both countries. While the data related to Macrostip® *Psyllium* were obtained from the experience and clinical evaluation performed only in Italy. Macrostip® and Macrostip® *Psyllium* are two medical devices based on an osmotic laxative molecule referred to as Polyethylene Glycol (PEG) or Macrogol 4000. It is a synthetic polymer produced via polymerization of ethylene oxide molecules to make joining units of ethylene glycol by an ether linkage. PEGs are water-soluble polymers that can form hydrogen bonds in a ratio of 100 water molecules per one PEG molecule. Molecular weights of PEGs vary by time of the polymerization process and the molecular weight represents the weighted average of the individual PEG molecules. The most common preparations of PEGs, used to treat constipation, include PEG 3350 and PEG 4000 [19]. Both molecules belong to osmotic laxative class which works increasing water retention in the lumen of the colon by binding to water molecules, thus stimulating defecation. They are not absorbed and act solely in a mechanistic manner. PEGs have various applications in many fields, ranging from medical to industrial areas, however, the molecule have a long history of gastroenterology application: PEG 4000 has been also employed for colon cleansing in preparation for colonoscopy in adults and it is known that a relatively low dose of PEG 4000 improves stool frequency and consistency in patients with chronic constipation, as clearly shown in recent meta-analyses where it has been shown that the mean number of stools per week in 573 patients (included in 4 eligible studies) was significantly reduced in favor of Macrogol 4000 use compared to placebo or other treatment [12,20]. In addition, since constipation strongly affects quality of life, it has been demonstrated that macrogol, which is effective within 48 hours, improves quality of life even in the elderly [12]. The use of Macrogol represents one of the first line treatments for acute and chronic constipation in few countries [21]. Indeed, it has been shown to be effective and safe in different subgroup of patients: children, adults and pregnant women. In addition, PEG has been shown to be more effective than lactulose in increasing the stool frequency and improving the stool's consistency [22-27]. Moreover, in patients treated with PEG, there are also lower rates of rescue medication use and lower side effect incidence as flatulence. Furthermore, retrospective studies show that PEG remains effective for up two years of treatment. Finally, the use of PEG is supported by Level I evidence, Grade A recommendation as suggested in the "*World journal of Gastroenterology* "(2012) [28]. Together with laxatives, guidelines support the use of fiber for constipation. *Psyllium* has been largely employed in this context. Clinical studies demonstrate that *psyllium* led to an increase of 3 bowel movements/week, indicating that *psyllium* is as effective or even more effective than osmotic and stimulant laxatives, which increase stool frequencies by 2.5 bowel movements/week [29]. The effects of *psyllium* on stool frequency and consistency are documented and this is due to its high water-holding capacity, that is resistant to fermentation and forms a viscoelastic substance in the gastrointestinal tract, thus softening stools. Efficacy of *psyllium*, combined with other fiber source, has been tested also in children, supporting its usage in constipation in this class of patients as well. *Psyllium* supplementation has been also shown to support, in constipated patients, the well-being of beneficial intestinal microflora. In addition, in irritable bowel syndrome patients suffering of chronic constipation, *psyllium* has been shown to be effective and to reduce pain during defecation when compared to other fibers [30]. Finally, the use of *psyllium* is supported by Level II evidence and grade B recommendation. The critical analysis of the results obtained in our clinical evaluation, using both products Macrostip® and Macrostip® *Psyllium*, confirms the high efficacy of the two medical devices in reducing the signs and symptoms attributable to constipation. Interestingly, analysis of Wexner scale-derived data, demonstrated that the use of both products reduces the percentage of patients with serious or severe constipation after 15 days taking the product (Figure 6). In particular, at T0 observed subjects were mainly affected by very serious, severe or moderate constipation (Figures 6A and 6C)**;** after 15 days of treatment with Macrostip® or Macrostip® *Psyllium* the percentage of patients with serious or severe constipation was 0 and all the patients were presenting mild or moderate constipation (Figures 6B and 6D), supporting the efficacy of the two products. The positive and congruent evaluation by doctors and patients on the efficacy and on the therapy general satisfaction confirms that the products are appreciated and recognized as effective. In fact, some participants suffering from chronic constipation have confirmed that they want to continue treatment for a longer period. Finally, the absence of adverse event recording confirms and supports the safety of Macrostip® and Macrostip® *Psyllium* in the treatment of acute and chronic constipation.

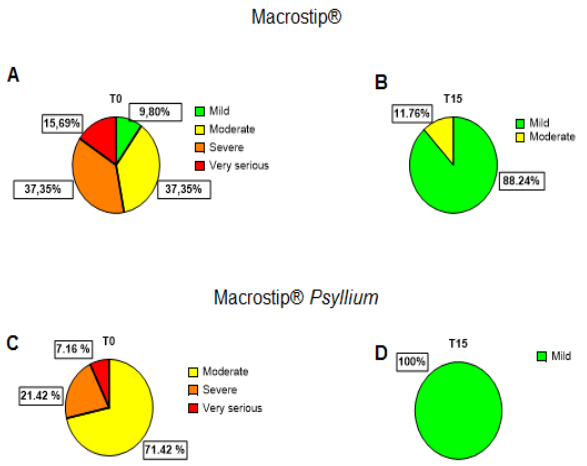


Figure 6) *Graphic representation of percentage of patients suffering of constipation with different levels referred to the Wexner scale score at T0 and T15. A-B) Subjects treated with Macrostip®. C-D) Subjects treated with Macrostip® psyllium*

CONCLUSION

In conclusion, data obtained in the present study support the use of the tested medical devices for the treatment constipation in adults. The products have been found to be effective in reducing signs and symptoms of constipation based on the score obtained using the validated questionnaire Wexner scale. According to this study, there is no major difference between the two medical devices in terms of efficacy and safety. However, from clinical practice, it results more adequate the use of PEG 4000 alone than PEG in combination with *Psyllium* in elderly patients. Indeed, in these patients, who have less physical activity and exercise ability due to various diseases (insomnia, Alzheimer disease, stroke, neuromuscular diseases) and who do not take the correct amount of water per day, *psyllium* might be contraindicated because as a balk-laxative needs combination with physical activity for better results. Therefore, the use of PEG 4000 could be a valuable strategy for constipation in elderly. Additionally, data emerged from the Likert scale suggest that patients and doctors positively evaluate the treatment, with an overall good satisfaction rated by the patients. The study also supports the safety of the tested products, since any side effect has been reported during the 15 days of active treatment. However, the data collection has some obvious limitations (low patients' number, no comparative analysis), but confirms the efficacy of the use of Macrogol 4000 alone or in combination with *psyllium* fiber and support the reliable employment of both products for constipation treatment.

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