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Occult Obscure Gastrointestinal Bleeding (OGIB) in Colonic Diverticulitis using Polyglucosamine: A Registry Study Following a Standard Management Protocol

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ABSTRACT

Background: *Chitosan derivatives have coagulant and tissue repairing activity.*

Objective: *To test the activity of a polyglucosamine (PG) together with a Standard Management protocol (SM) on the occult and obscure bleeding (OGIB) and clinical symptoms in patients suffering from colonic diverticulitis (COD).*

Methods: *Registry study comparing the combination SM and PG (1000 mg x3) Vs the SM only. Sixty patients divided into two group of 30 cases. At baseline, after 1 and 3 months of treatment the following variables were measured: OGIB, Hb, red cells count (RC), body weight (BW), abdominal circumference (AC), body mass index (BMI), hs-CRP, and daily gastrointestinal discomfort (DGID).*

Results: *The combination SM+PG was more active ($p < 0.01$) than SM in reducing OGIB (respectively -79 % Vs 65 %, the AC (-4.0 Vs 1.7 cm), the DGID (-91 % Vs -73 %) and hs-CRP (- 63% Vs -37 %. The Hb and RC increased more with SM+PG than with SM (t test $p< 0.05$). SM+PG showed to reduce of 77% the DGID just after a week of treatment.*

Conclusion: *SM+PG was found more effective than SM in reducing OGIB and all the sign and symptoms of COD.*

Keywords

Gastrointestinal bleeding, Colonic diverticulitis, Polyglucosamine, Standard Management protocol, Daily discomfort.

Abbreviations

AC: abdominal circumference; BW: body weight; BMI: body mass index; COD: colonic diverticulitis; DICA: Diverticular Inflammation and Complication; DGID: daily gastrointestinal discomfort; FIA: Food Intake Assessment; gFOBT= guaiac fecal occult blood test; Hb: haemoglobin; hs-CRP: high sensititvity C reactive protein; IAPSS: Internation Agency for Pharma-Standard Supplements; MET-h: metabolic equivalent/hour; MW= molecular weight; NSAIDs: nonsteroidal anti-inflammatory drugs; OGIB: the occult/obscure gastrointestinal bleeding; PG: polyglucosamine; SM: Standard Management protocol; SVVSP: San Valentino Vascular Screening Project; VAS: visual analogue scale; WGO: World Gastroenterology Organization.

Introduction

During the monitoring phases of the San Valentino Vascular Screening Project (SVVSP) [1] the occult/obscure gastrointestinal bleeding (OGIB) vas one of the controlled variables together with colonscopy. OGIB refers to recurrent bleeding in which a source is not identified on upper endoscopy, colonoscopy, or small bowel radiography.

There are several causes of OGIB [2] and the most common are due to mass lesions (adenoma, carcinoma), inflammation (erosive esophagitis, ulcer), colonic diverticulitis (COD), vascular ectasia, and use of medications such as the nonsteroidal anti-inflammatory

drugs (NSAIDs) [3].

In particular COD in the acute and chronic phases can be a cause of OGIB. The disease still do not have clear pathogenesis [4,5] since is due to a complex interaction among diet, colonic microbiota, genetic factors, colonic motility that cause the diverticula formation. Studies on twins and siblings have shown that approximately 40%-53% of the disease liability is due to genetic factors and the remaining part is attributable to environmental factors [6-8].

The disease take time to develop and become a chronic condition characterized by acute phases and relapses [9] and diverticula are characterized by herniation of the colonic wall in the muscle layer at the site of penetration of the blood vessels [10]. The development of inflammation in diverticula and the relative tendency of bleeding is due to the obstruction of the fecal material in the form of fecoliths that produce an abrasion of the mucosa and bacterial infection.

OGIB as such is capable to generate and maintain the inflammatory environment and this last condition is the cause of gastrointestinal discomfort in the form of abdominal pain (constant or intermittent), bloating, and change in bowel habit with both constipation or diarrhea. The latter is more common in the acute phase, whereas constipation is more common in the chronic phase and may reach the absolute constipation [11-13].

At the end, the chronic bleeding may generate a silent anemia but also maintains the vicious cycle of inflammation/bleeding that should be the object of a specific therapy.

The need of new therapies for COD, aimed particularly to the OGIB and relief of gastrointestinal discomfort is a real challenge, and one candidate can be the chitosan which is a natural polycationic polymer, derived from the chitin deacetylation and under used since about 50 years [14,15] particularly as hypocholesterolemic agent or to reduce body weight.

It appears that the interaction of this polycationic polymer with the cell membrane of erythrocytes [16] allows clot formation in the absence of coagulation factors, because chitosan matrix tends to attract circulating plasma proteins and platelet adhesion allowing the thrombus formation [17]. Furthermore, it has been shown that chitosan as such is much more procoagulant than its fractionated oligosaccharides. Different MW chitosan from 200 to 700 kDa with at least 80-82% degree of acetylation was shown to bind erythrocytes in concentration dependent manner [18].

Chitosan is characterized also by an anti-inflammatory activity which is an indirect effect of the strong hydrogen-donating ability of this polymer [14,15] that limits the oxidative explosion which is a trigger for the production of inflammatory mediators.

An important aspect of chitosan is related to its safety. The repeated doses toxicity in experimental animals support the safety of chitosan for food use [19,20].

Long term treatment with a chitosan (polyglucosamine) to overweight and obese subjects was showing that the dosage of 1.6 g/day for one year was active in reducing significantly the body weight and the abdominal circumference without causing side effects [21]. Dosages of 3.2 g/day of the same product have been used for six months [22] and were very well tolerated. These data indicate that the product can be used in chronic diseases that need almost a continuous therapy.

The aim of the present research is to study the effect of an oral dosage of 3.0 g/day of chitosan in reducing the OBID in patients suffering COD.

Material and Methods

Study design

The experience was conducted in a single center as a Registry study within the Standard Managenent protocol (SM) of diverticulitis: the patients were free to choose the therapy that was proposed or just follow the SM only and be considered as a control group.

Sixty patients with history COD and OBID were interviewed and accepted to enter the Registry study. Following previous routine colonscopy the patients were considered positive to diverticulitis; they already participate to SVVSP and accepted to follow the Standard Management protocol for COD.

Admission criteria

Subjects aging between 55 to 65 years (males and females), with a diagnosis of COD. The DICA (Diverticular Inflammation and Complication) assessment [23] was used for admission criteria addressing only cases belonging to class DICA 2 or DICA 3, with recent (less than 1 month) OGIB positive to the Hemoccult Sensa Fecal Occult Blood Procedure, and not yet under any chronic therapy for the disease.

Exclusion criteria

Patients in class DICA > 3 or under therapy with mesalazine, antibiotics and probiotics. Patients suffering from cancer of any type (a part of benign polyposis), alcoholism, parkinsonism, Alzheimer's disease, severe depression, drug addictions were excluded. Patients under treatment for body weight (BW) reduction, or high dosage of Vitamin C (> 250 mg/day), or oral antiseptic containing iodine were also excluded to avoid interference with the . Therapy for chronic diseases (e.c. hypertension, diabetes, hormonal replacement therapy) were accepted provided that the therapy was stable at least since 3 months. Patients with more than one chronic disease other than COD were excluded. In case of relapses the patients were not excluded from the protocol; they were treated with the common therapies and considered as a negative outcome.

Standard Management protocol

This protocol has been established to treat COD. Patients were suggested to follow simple rules concerning the food intake with the substitution of those servings that are known to have negative/irritant impact on the GI. The increase of fiber intake and reduction

of lipids of any type (saturated, unsaturated) and alcoholic beverages were considered as a first line suggestions.

One of the main objectives of the SM was the discussion with the patient about the diet with the aim to avoid impositions that would be effective for few days or maximum for some week only. This method has been found very effective in previous studies [21] allowing a diet compliance in almost 95 % of the cases under treatment for overweight or mild obesity. Some of the most relevant details of the Standard Management for diverticulitis are reported in the following Table 1.

Variable	Measures	Details
Food intake	FIA (Food intake Assessment Questionnaire [21]	25 servings type; frequency during the week
Food limitation	No coffe and soda beverages; limiting any oil and butter, vinagre, fat meat, cacao	At least 50 % reduction of any oil; use of seasoned cheese (e.c.parmesan, pecorino, provolone); increase of eggs intake as omelette
Physical exercise	9 MET-h/week [21]	1 h of breasky walking/day : three 20 minutes periods
Hydration	2 L/day	No matter about the time of the fluid intake
Oral hygiene	-	Use of tooth paste and moisturing products twice/day

Table 1: Standard Management protocol for diverticulitis: variables, measures and some details.

Food Intake Assessment (FIA)

The FIA questionnaire consists of 25 different type of servings (Table 4) which are the most common in the geographical area (province of Pescara) were the study was conducted. The patients were belonging to the SVVSP where the diet monitoring is one of the most important aspects and they were already trained on how to fill up the daily food intake questionnaire for a week. In this specific study patients were instructed on how modify the servings to increase fibers, proteins and reduce fats. Particularly the added fats were addressed, such as butter, extra virgin olive oil, olive oil or any other type of oil (e.c. seed oil such as canola, sunflower). Omelette preparation was suggested to reduce fats intake, particularly those in the cheese and processed meat. With this method the volume of the serving was maintained or even increased and the fats were substantially reduced about one half; for the preparation was suggested the use of half a spoon of sunflower oil.

Alcohol consumption and soda beverages were addressed in order to minimize and possibly to stop their intake. Water intake of at least 2.0 L/day was also suggested.

Physical activity and oral hygiene

Physical activity increase was requested, summing up the MET-h of short periods (20 min) of brisk walking, that were easy to be followed. The suggestion was to reach the workplace by walking, or leave the car at 20 min walking distance from the workplace.

The oral hygiene was strongly recommended because in most of the cases caries and bad breath were detected, and sometimes inflammation of the oral cavity. These events may mirror microbiota modification in the mouth and in the gut. Despite there are no clear evidences they can be one of the causes of COD they may have an impact on the maintaining the COD.

Protocol outline

Patients were interviewed for entering the study that consisted into four periods.

The first period was the baseline control to determine all the variables under study; the second was after one week of treatment (either the SM or the SM+ PG) limited to the evaluation of gastrointestinal discomfort only; the third and the forth were respectively after 1 and 3 months of treatment where all the variables were measured.

Variables

The main variables were and OGIB determined with Hemoccult Sensa (gFOBT or guaiac smear test).
Three separate specimens of feces were requested for each control (baseline, 1 month, 3 month) to be collected in containers that was given by the center. Patients were recommended to avoid eating meat and hard spirits drinks the night before the collection.

Secondary variables were the Hb, red cells count, hs-CRP, abdominal circumference (AC), body weight (BW), body mass index (BMI), and the daily gastrointestinal discomfort (DGID).

Other variables such as lipids levels and vital parameters were not considered since the impact of PG on these variables is already well documented [21,22] and in Europe the hypocholesterolemic claim of 3g/day of chitosan is allowed.

Daily gastrointestinal discomfort (DGID)

This variable was aimed to measure all the gastrointestinal symptoms such as abdominal pain, abdominal swelling, diarrhea/constipation that may affect the patients. The DGID was measured using a visual analogue scale (VAS) of 10 cm (graduated from 0 = no discomfort to 10 = maximum discomfort). The VAS was presented by the investigator to the patient asking to indicate which was the average condition relative to the last week. To avoid possible bias, the evaluation after one and three months of therapy were done without showing to the patient the previous value.

Product under study

Polyglucosamine (PG) at the dosage of 1000 mg (two tablets of 500 mg) 3 times/day was given according to the following scheme; 1000 mg 30 min before lunch time; 1000 mg at 4 pm, and finally 1000 mg 30 min before the evening meal.

The control subjects were not treated with any product and followed the SM protocol only. Products were given in the amount of 3 boxes of 64 tablets that were sufficient for 1 month (30 days) At the end of each month the patients were given 3 more boxes. In total 9 boxes of product were given to each patient.

Compliance

The compliance was measured for the treatment of PG calculating the difference number of residual tablets at each monthly control. The compliance was measured also for SM controlling the FIA servings, addressing particularly the main components of the foods that had to be modified: fats and fibers. There was not measurement of the compliance for the physical activity and oral hygiene.

Blindness

The investigator that was visiting the patients was not aware about the treatment since the clinical record form was reporting only treatment A or B, and the biostatistician also was receiving electronic files were the treatments were reported also as A or B.

Statistical Analysis

Sample size

Since there was no data known on OGIB following SM, this study can be considered on heuristic base needing confirmation in a larger sample.

The sample size was calculated on the base of the OGIB frequency which was supposed to be present in 100 % of the cases. The hypothesis was that PG could eliminate this sign in > 50 % of the cases. Considering a 1-β = 90 and an α value of 0.05, the number of 20 cases/group will be sufficient to discriminate the different activity of the treatments.

Considering the possibility up to 50 % drop out at least 30 cases/group had to be enrolled. The large number of drop out was consistent with the OGIB that according to the experience of our center may not be constant over the time. The patients were allocated to the two group by computer randomization.

Randomization

A computerized random list was prepared considering 60 cases with two possibility of treatment and each patients was allocated a priori to one of the treatments. The patients were not obliged to enter one of the two arms, but none denied the indication given by the randomization.

The DICA 2 and DICA 3 were equally distributed within the two groups as follows:
the first 30 cases were belonging to the class DICA 2 and the cases from n 31 to 60 were belonging to the class DICA 3. According to this method, the first 30 cases were composed by 15 patients treated with SM+PG and 15 patients treated with SM only; from case 31 to 60, 15 patients were treated with SM+PG and 15 with SM only.

Data analysis

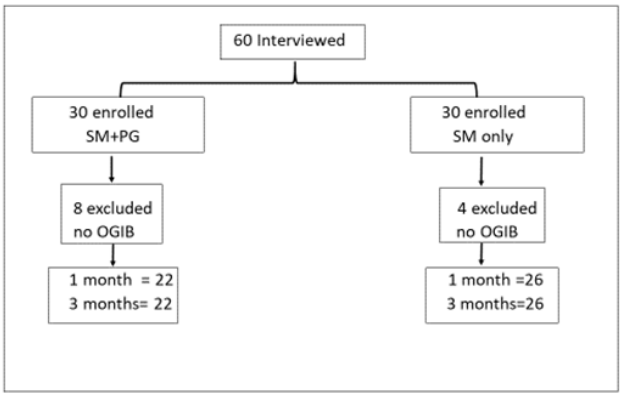
For the frequencies the chi square (with or without Yates correction) was applied, and in case of values < 5 the groups were compered using the Fisher test (exact chi square).

For parametric variables the average and the standard deviation were calculated; the values before and after the treatments were compared using the t test (independent data) or the Tukey test (interdependent data). The variance analysis was applied for the FIA data.

Results

The flow chart of the study is reported in Figure 1. At the baseline control 12 subject (8 in the SM+PG group and 4 in the SM group OBID was absent and they were excluded from the study. The trial was completed by 22 patients in the SM+PG group and 26 patients in the SM only.

Figure 1. Registry cross over flow chart



All the 48 patients concluded the experience, no relapses of the disease were occurring and there was no complain of side effects.

Variable	Measure	SM+PG	SM	p
Age	years	57.8 ± 4.29	55.8 ± 4.20	t test < 0.05
Sex	M F	14 8	17 9	X2 > 0.05
DICA 2-DICA 3[a]		11-11	12-14	X2 > 0.05
BW	Kg	69.0 ± 4.49	68.2 ± 4.31	t test > 0.05
Height	m	1.72 ± 0.042	1.70 ± 0.035	t test > 0.05
BMI	Kg/m^2	23.5 ± 1.62	23.6 ± 1.57	t test > 0.05
AC	cm	99.5 ± 5.94	99.0 ± 5.57	t test > 0.05
OGIB[a]	N/total	22/22	26/26	X2 > 0.05
Hb	g/dL	12.2 ± 0.66	12.4 ± 0.50	t test > 0.05
RC[b]	106	4.53 ± 0.352	4.88 ± 0.993	t test > 0.05
hs-CRP[c]	mg/L	5.4 ± 0.84	5.3 ± 0.83	t test > 0.05
DGID[d]	score	5.0 ± 1.09	4.9 ± 0.99	t test > 0.05
Hypertension	N/total	10/22	11/26	X2 > 0.05
Dyslipidemia	N/total	8/22	10/26	X2 > 0.05
Diabetes type II	N/total	4/22	5/26	X2 > 0.05
HRT[e]	N/total	2/8	3/9	X2 > 0.05

Table 2: General characteristics of the patients: Mean values ± SD or frequency.
[a]DICA = diverticula inflammation and complication assessment; [b]OGIB = Occult/obscure gastrointestinal bleeding; [c]RC = red cells count; [d]hs-CRP high sensititvity C reactive protein; [e]DGID = daily gastrointestinal discomfort; [f]HRT = hormonal replacement therapy.

The general characteristics of the two groups are reported in Table 2. No differences were found between the two groups in any of the

variable and the DICA2 /DICA 3 patients were equally distributed in the two groups. The results concerning all the food components at baseline and after 3 months of treatment are summarized in Table 3.

Variable	Measure	Baseline				Average at 3 months[a]				% variation Vs Baseline	
		SM+PG [22]	SD	SM[26]	SD	SM+PG [22]	SD	SM 26]	SD	SM+PG	SM
Total Kcal	Kcal	11165	540.4	11180	506.9	11119	533.4	11101	447.2	-0.4	-0.7
Proteins	g	459	35.0	468	39.2	528	38.2	521	41.6	+15.2§	+11.3§
Lipids	g	426	45.8	432	34.5	343	39.1	337	36.1	-19.5§	-21.8§
Carbohydrates	g	1234	108.8	1208	130.1	1350	110.4	1361	142.6	+9.3§	+12.6§
Fibre	g	95	16.6	96	15.8	149	16.3	126	15.9	+56.8§¥	+31.2§
Alcohol	g	118	94.8	106	77.8	77	89.2	71	72.6	-34.6§	-33.4§
% of total Kcal											
Carbohydrates	%	43.2	3.76	42.8	4.34	48.6	5.36	48.6	5.08		
Lipids	%	33.7	3.08	33.4	2.83	27.6	6.32	28.5	3.27		
Protein	%	16.1	1.03	16.6	1.69	19.0	1.66	18.6	1.18		
Alcohol	%	6.8	5.56	6.1	4.26	4.7	5.50	4.3	3.82		

Table 3: Main food components intake in the week before the treatment and during the treatment with SM+ PG and SM: Mean values, SD, [number of cases], and % variation Vs Baseline.
[a]Taken in one of the last two weeks of treatment. § Tukey test $p < 0.05$ Baseline Vs 3 months; ¥ Tukey test $p < 0.05$ SM+PG vs SM.

Servings	Baseline				During 3-month period				N of servings Vs Baseline	
	SM+PG [22]	SD	SM [26]	SD	SM+PG [22]	SD	SM [26]	SD	SM+PG	SM
sugar[a]	5.6	1.92	5.7	2.59	5.5	1.97	5.8	2.51	-0.1	+0.1
chocolate	1.2	1.05	1.3	1.54	0.5	0.80	1.2	1.59	-0.7§	-0.1
milk	4.4	1.94	4.8	2.06	4.5	2.01	4.8	2.01	-0.1	-0.0
biscuits	4.0	1.47	4.5	1.99	4.1	1.91	4.6	1.98	+0.1	+0.1
bread	5.5	1.37	6.0	2.12	6.0	2.17	6.1	2.02	+0.6§	+0.1
first dish[b]	5.5	1.63	5.4	1.72	5.6	1.59	6.0	2.18	+0.1	+0.6§
pizza	0.7	0.83	0.7	0.69	0.7	0.83	0.8	0.71	0.0	+0.1
vegetables[c]	4.6	1.59	4.9	1.31	8.8	1.82	8.2	1.44	+4.2§	+3.3§
fruit	8.9	3.22	8.2	3.45	12.3	1.88	12.3	2.57	+3.4§	+4.1§
dry fruit	0.5	0.80	0.5	0.76	0.4	0.73	0.5	0.76	-0.1	0.0
pulses	1.7	0.63	1.8	0.85	1.9	0.64	1.8	0.85	+0.1	0.0
meat	2.5	0.67	2.5	0.90	2.6	0.59	2.5	0.90	+0.1	0.0
processed meat[d]	2.6	1.43	2.3	1.19	2.6	1.43	2.3	1.13	0.0	0.0
fish	1.3	0.78	1.4	0.81	1.6	0.90	1.4	0.64	+0.3	0.0
cheese	3.8	1.41	3.8	1.47	3.7	1.45	3.8	1.48	-0.1	0.0
mozzarella	0.8	0.91	1.0	1.20	0.8	0.91	1.0	1.25	0.0	0-0
yogurt	2.5	3.11	2.5	3.18	3.2	2.89	3.2	3.17	+0.6§	+0.6§
wine	5.0	4.16	4.5	4.05	3.3	4.36	3.0	3.89	-1.7§	-1.5§
beer	0.9	1.70	0.8	1.36	0.8	1.38	0.8	1.21	-0.1	0.0
spirits	1.4	2.30	1.3	2.07	0.6	1.22	0.6	1.58	-0.7§	-0.6§
beverages	1.1	1.83	1.0	1.78	0.7	1.21	0.3	1.02	-0.4§	-0.6§
ice cream	1.0	1.00	1.0	1.23	1.0	0.98	1.0	1.13	0.0	0.0
eggs[e]	0.7	1.39	1.7¥	1.8	3.7	2.19	3.4	2.04	+3.0§	+1.7§
chips	0.2	0.43	0.3	0.60	0.3	0.57	0.3	0.68	+0.1	0.0
cake	1.4	1.33	1.0	1.08	1.3	1.32	0.9	1.02	-0.1	-0.1

Table 4: Number of servings at baseline and during 3 months of diet in subjects treated with SM+PG SM: mean values, SD, [number of cases], and mean differences Vs Baseline.
[a]: contains also candies; [b]: it refers to the complete dishes (containing also boiled vegetables/pulses, meat, oil/ butter, cheese added to the any pasta or rice, polenta, gnocchi, tortellini); [c]: contains also oil as seasoning; [d]: contains also hamburgers, cheese burgers, big burgers; [e]: contains also omelette and mayonnaise. §Tukey test $p< 0.05$, 3 months Vs Baseline; ¥ t test ($p< 0.05$), SM+PG Vs SM.

The main variable and ancillary variables modification are reported in Table 5. The OGIB was almost completely eliminated in the group SM+PG (21 cases over 22) just after one month of treatment, whereas for the group SM three months were necessary to obtain a significant effect (16 cases over 26). The difference of activity was statistically significant (chi square p< 0.05). The reduction of hs-CRP was very consistent for in the group SM+PG, and after 3month of treatment the average values were 63 % less that the baseline, whereas with the SM group the reduction was limited to the 36 % (PG +SM Vs SM p <0.05). Furthermore, the decrease of hs-CRP was much more rapid with SM+PG.

Variable	Measure	Treatment	Time		
			Baseline	1 month	3 months
OGIB	N/total	SM+PG	22/22	3/22 §¥	1/22§¥
		SM	26/26	12/26§	9/26 §
Hb	g/dL	SM+PG	12.2 ± 0.66	12.3 ± 0.64§	13.1 ± 0.32 §¥
		SM	12.4 ± 0.50	12.4 ± 0.52	12.7 ± 0.47
RC	106	SM+PG	4.53 ± 0.352	4.68 ± 0.303§	5.16 ± 0.325§¥
		SM	4.43 ± 0.342	4.42 ± 0.325	4.72 ± 0.279§
BW	Kg	SM+PG	68.6 ± 4.14	68.1 ± 4.00	67.6 ± 4.22§
		SM	68.2 ± 4.31	68.0 ± 4.01	67.9 ± 4.31§
AC	cm	SM+PG	99.5 ± 5.94	97.9 ± 5.42§¥	95.5 ± 5.40§¥
		SM	99.0 ± 5.57	98.6 ± 5.46	97.3 ± 5.26§
BMI	Kg/m^2	SM+PG	23.5 ± 1.62	23.3 ± 1.52	23.3 ± 1.61
		SM	23.6 ± 1.57	23.5 ± 1.48	23.5 ± 1.53
Hs-CRP	mg/L	SM+PG	5.4 ± 0.84	2.8 ± 0.47 §¥	2.0 ± 0.58 §¥
		SM	5.3 ± 0.83	3.6 ± 0.86 §	3.4 ± 0.35 §

Table 5: Variables modification during the time following SM+PG and SM treatment: Mean values ± SD or frequency.
§Tukey test p< 0.05 Vs baseline, 3 months Vs Baseline or chi square Vs baseline; ¥ t test or chi square (p< 0.05), SM+PG Vs SM.

The improvement of all the other variables was slower but statistically significant for both groups a part of the BMI. The BW was reduced minimally in both groups, whereas the AC was much more affected indicating a sort of dissociation between BW and AC probably due to the fat mass loss using PG.

The DIGD was measured after one week of treatment and after 3 months. The data are reported in Table 6. It was shown that the treatment SM+PG had an immediate impact on the gastrointestinal symptoms whereas for SM only a much longer period of time was necessary; the time needed to reduce significantly the daily discomfort with SM+ PG was 1 week in most of the patients, in the following period the reduction was continuous though less consistent.

DGID 1-10 score	Time				
	Treatment	Baseline	1 week	1 month	3 months
	SM+PG	5.0 ± 1.09	1.1 ± 0.94§¥	0.8 ± 0.75§¥	0.4 ± 0.51 §¥
	SM	4.9 ± 0.99	3.9 ± 0.74§	2.6 ± 0.85§	1.3 ± 0.74§

Table 6: Daily gastrointestinal discomfort (DGID) score modification at baseline, during the first week of treatment and after 3-month period: Mean value ± SD.
§Tukey test p< 0.05, 3 months Vs Baseline; ¥ t test (p< 0.05), SM+PG Vs SM.

Discussion

The limit of this experience is the lack of a placebo group and the short period of treatment. However, in the typical Registry studies, the investigator collecting the data was not aware of the treatment. The short period of treatment was purposely chosen in order to give PG more chance to define its effect. We supposed a longer period of treatment under SM regimen could have jeopardized the PG effect.

The first observation that can be drawn from the study is related to the SM per se, which showed some interesting activity since no relapses were found during the 3-month period and indicates that SM had some positive impact on the disease.

The improvement of the DGID was probably the most interesting finding because the reduction of about 37 % of the discomfort in the SM group can be considered a good achievement. A longer period of treatment, allowing the lifestyle (particularly physical activity) and healthy diet modification to become a new way of living, is expected to further improve the disease up to an affordable condition. However, these assumptions need more cases and a longer period of treatment.

The impact of the diet and its influence on the possible modification of the microbiota is an old and debated argument. Despite the fiber increase together with lipid decrease are considered the first line treatment of symptomatic uncomplicated diverticular disease (SUDD) by the World Gastroenterology Organization (WGO) [24], some criticism is still in place due to the poor methodology of most of the clinical trials conducted on the matter [25].

The low fiber intake -since its first analysis done in the 71 by Painter and Burkitt [26]- was considered a cause of COD but there are conflicting results. Their increase in the diet was showing positive [27] and negative [28] results. A large perspective study in UK women (the Million Women Study) [29] suggested that "the association with diverticular disease risk varied by the source of the fiber, the reduced risk being strongest for cereal and fruit fiber". This last sentence contains some indication that should be commented.

The ratio between water and fiber in cereals, pulses, fruit and vegetables in the way they are used (boiled or crude) is respectively about 9.9, 12.5, 32.4, 54.0 [30] which indicates that may be the water content makes the difference. At the end, the intimate interaction fiber/water can be determinant in transforming straining and constipation into normal stool transit, with normal intraluminal pressure within the bowel. It is supposed that the normal transit will avoid the formation of diverticula.

From our data it seems that the fiber increase, together with the decrease of lipids and alcohol, contribute to the clinical

improvement. In the SM+PG group the diet composition during the 3 months of treatment was very similar to the SM group, but the clinical outcome was much more favorable in every aspect and the capability of PG to keep the water (at least about 10 mL/ administration) inside the intestinal bulk can be important.

Comparing the two groups, the only difference in the food components was the fiber increase, consisting of the 57 % compared to the baseline intake reaching 22 g/day (from 14 g/day at the baseline value). These figures are not far from the recommended intake of fiber of 14 g/1000 Kcal/day [31]. Considering that the total calorie intake was not modified during the 3 months of treatment (see Table 3) the theoretical quantity of daily fiber intake for both groups was calculated to be about 22 g/day. This quantity was achieved with PG+SM whereas in the SM group it was not exceeding 18 g/day.

However, it is also true that PG is not a commonly used fiber, since it is a deacetylated chitin which is not present in foods. This last aspect make more interesting the compound since it has a consistent binding capacity, specific for negatively charged compounds and with pro-coagulant and anti-inflammatory activities. Furthermore, PG has a strong binding with water (1g binds about 10 mL); as a consequence 3 g/day (on the whole) allows to kip in the intestinal bulk 30 ml of more water, and this quantity may facilitate the intestinal transit.

All the PG activities are limited to the gut since the product is not absorbed, and binds also lipids bringing them to the colon. Due to labile binding with PG, fats can hydrolyzed by colonic bacteria and used as a fuel and avoid the phenomenon of steatorrhea. In experimental studies was shown also an increase the acetate content in feces [32].

This could mean one of the following possibilities: the acetate is overproduced (change in the microbiota) or alternatively, being a very polar and negatively charged compound, can be bound by PG and not made available for the general metabolism. Alternatively, since PG decreases the circulating levels of fats (e.g. cholesterol, triglycerides) [21,22] it seems also possible a modification of the microbiota, acting as a prebiotic for acetate producing bacteria. These activities, together with the binding of bile salts, and the antioxidant activity, may create in the gut a condition to reduce the inflammatory processes triggering the COD pathogenesis and maintenance.

Furthermore, other aspects of the treatment with PG should be focused. The main variable OGIB was significantly reduced within a month of treatment witnessing the pro coagulant action of PG. This activity was expected with some doubt about the dosage that should be given.

At the end, it seems that the quantity of 3 g/ day were sufficient, as it was for and the treatment schedule (1g for 3 times/day). The intermediate dosage between the main meals can be important because the PG is much less “diluted” by the food and can be more effective. On the other hand, the water retaining effect can be important in the progression of the intestinal bulk generated by food.

DGID was immediately improved and this was surprising; most probably is due to the antioxidant/antinflammatory activity of PG Which are determinant to limit the production of intestinal inflammatory cytokins preluding the spasm and pain, but may be due also to the reduction of bacteria producing gas. In experimental animals the antimicrobial activity of chitosan is well known [14,33] and the analysis of the microbiota could be a further step to investigate.

The reduction of BW (-1 kg in 3 months) and AC (- 4 cm in 3 months), are logical consequences of fats intake reduction and fat binding. BW modifications has been shown in other clinical studies [34,35] and in the present study it was not expected to be reduced consistently because none of the patient were overweight. However, the reduction of 1 kg in 3 months can be considered a good achievement and particularly interesting for fat loss in those patient that suffer from COD and concomitantly are overweight.

For what concerns the pro coagulant activity, the reduction of OGIB was found in 65 % of the cases (15 out 26) and in the same cases was concomitant to hs-CRP decrease and Hb and RC increase.

OGIB reduction was followed by the recovery of the Hb and RC. Despite the recovery of these variables was not dramatic, it was statistically and clinically significant, particularly taking into consideration the short period of time. It is known that the recovery from anemic condition is slow, particularly in the absence of iron administration.

With the combination SM + PG a 93 % reduction of the DGID was obtained which can be considered an extremely important achievement for the patients, because it allows a rapid return to an almost normal way of living.

Considering the entire picture, it seems that PG has amplified the effect of SM and the treatment can be hypothesized at least as an anticipation of the SM long term effect.

Conclusion

The combination of SM and PG reduced the OGIB and discomfort generated by diverticulitis; furthermore, an improvement of the anemic condition together with the reduction of inflammation was shown. These results have to be confirmed in long term studies with a larger set of patients.

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