Evaluating the efficacy of current treatments for reducing postoperative ileus: a randomized clinical trial in a single center

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***Aim*. Postoperative ileus has been considered an inevitable consequence of abdominal surgery. The aim of the study was to investigate the efficacy of same treatments in resolving postoperative ileus in various surgical approaches.**

***Methods*. A total of 360 patients underwent abdominal surgery, and was divided into four groups: videolaparoscopic cholecystectomy, laparotomic colo-rectal surgery, laparotomic Hartmann procedure, laparotomic gastric surgery. In each group, patients received different postoperative treatments: chewing gum, olive oil, both, and water. Each group was compared with a control group.**

***Results*. In patients who underwent videolaparoscopic cholecystectomy, median postoperative first passage of flatus and stool in the water group was 10 and 34 hours, respectively (P=0.006, P=0.021) and significantly earlier than in the control group (median postoperative 24 and 72 hours). Postoperative stay for the water group was lower (median day 1, 3rd interquartile 2.5) compared with control (median day 3; 3rd interquartile 7.0, P=0.01). In patients who underwent gastric surgery, median postoperative first passage of stool in the olive oil and chewing gum group was 48 hours, significantly earlier than in the control (median postoperative hour 120, P=0.04). Median time to first passage of flatus and stool was also earlier in the other groups compared with the control group, though this difference was not significant.**

***Conclusion*. Chewing gum, olive oil or both do not induce a relevant reduction of ileus after surgery. Water may be a safe and inexpensive option in reducing ileus. (United States National Institutes of Health, www.clinicaltrial.gov, number NCT01869231).**

KEY WORDS: Ileus - Chewing gum - Olive oil - Abdomen, surgery.

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Healthy bowel function depends on a combination of many factors, including the enteric and central nervous systems, hormonal influences, neurotransmitters, and local factors, including inflammatory pathways. Postoperative ileus (POI) has been defined as "transient cessation of coordinated bowel motility after surgical intervention, which prevents effective transit of intestinal contents and/or tolerance of intake". It has long been considered an inevitable consequence of abdominal surgery, and results in increased hospital stay, morbidity, and treatment costs.[1]

It is also a major contributing factor to postoperative pain and discomfort associat-

ed with abdominal distension, nausea, vomiting, and cramping.[2] Recent experimental studies have shown that the pathogenesis of the endogenous component of POI can be divided into two distinct phases: the first phase, or neural phase, results from activation of mechanoreceptors and nociceptors by stimuli, such as incision of the skin and, more importantly, by direct manipulation of the intestine.[3] The second, more protracted, inflammatory phase is caused by formation of an inflammatory infiltrate in the muscular layers of the intestine.[4, 5] Animal studies have also illustrated how the degree of surgical manipulation is directly related to the degree of POI.[6, 7] Treatment of POI has traditionally been supportive, with nasogastric decompression, intravenous fluids, and watchful waiting. Some new treatments are based on the physiologic theory of "sham feeding" for reducing POI, for example cephalic-vagal stimulation from chewing alone gives rise to propulsive and hormonal gastrointestinal activity similar to that seen with normal eating.[8] Several studies have tested the sham-feeding hypothesis using only chewing gum during the early postoperative period. It has the advantage of being inexpensive, well tolerated, and widely available,[9] though in the literature there are conflicting results on effectiveness.[10]

The aim of this study was to evaluate the effectiveness of different treatments - chewing gum, olive oil, chewing gum and olive oil, and water in accelerating resolution of POI, and reducing duration of hospitalization in patients who had undergone abdominal surgery. The rationale of the use of olive oil is based on its possible anti-inflammatory effect through a reduction in ROS (reactive oxygen species) production. Water was used as a placebo.

Materials and methods

Patients who underwent abdominal surgery at the General and Emergency Surgery Unit of the Paolo Giaccone University Hospital, in Palermo, between April 2010 and December 2012 were considered for the study. Patients were eligible for inclusion if they were scheduled to undergo any of the following procedures: videolaparoscopic cholecystectomy (VLC), laparotomic colorectal surgery (left or right colectomy, upper or mid rectum surgery), sigmoid-colon resection with colostomy (Hartmann procedure), laparotomic gastric surgery (gastric resection [Roux-en-Y] or total gastrectomy [Roux-en-Y]). Patients were excluded from the study if they had postoperative complications, metastatic disease, a history of inflammatory bowel disease, postoperative fever, gastrointestinal fistula, mint or olive allergy, and/or earlier abdominal radiation. We enrolled prospectively a total of 480 patients undergoing abdominal surgery, 120 of them for various reasons (not meeting inclusion criteria, declined to participate, other reasons) were excluded from the study (Figure 1), so only 360 patients were screened for participation in this study after signing an informed consent. Institutional Ethics Committee (Comitato Bioetico A.O.U.P.) approval was also obtained. Patients were classified according to type of surgery undergone: VLC, colo-rectal surgery (left and right colectomy, upper or mid rectum surgery), or gastric surgery (gastric resection, total gastrectomy), and Hartmann procedure, the last three ones carried out with laparotomic access. The anastomoses after both gastric and colorectal surgery were always performed with staplers: after gastric resection and total gastrectomy, a Roux-en-y reconstruction was done with a gastro-enteric anastomosis and an entero-enteric with a 25-E.E.A. stapler; the gastric shear after gastric resection was sutured with a 75-G.I.A. Stapler. After right colectomy an entero-colic termino-lateral anastomosis was performed with a 25-E.E.A Stapler. After left colectomy or anterior rectal resection a colo-rectal anastomosis was performed with a 29-31 E.E.A. Stapler. No ileostomy was made after rectal resection. The drains were positioned near the anastomoses and, after colonic surgery, as well in Douglas. All patients were randomly assigned to type of surgery and after assigned to one of five postoperative therapy groups

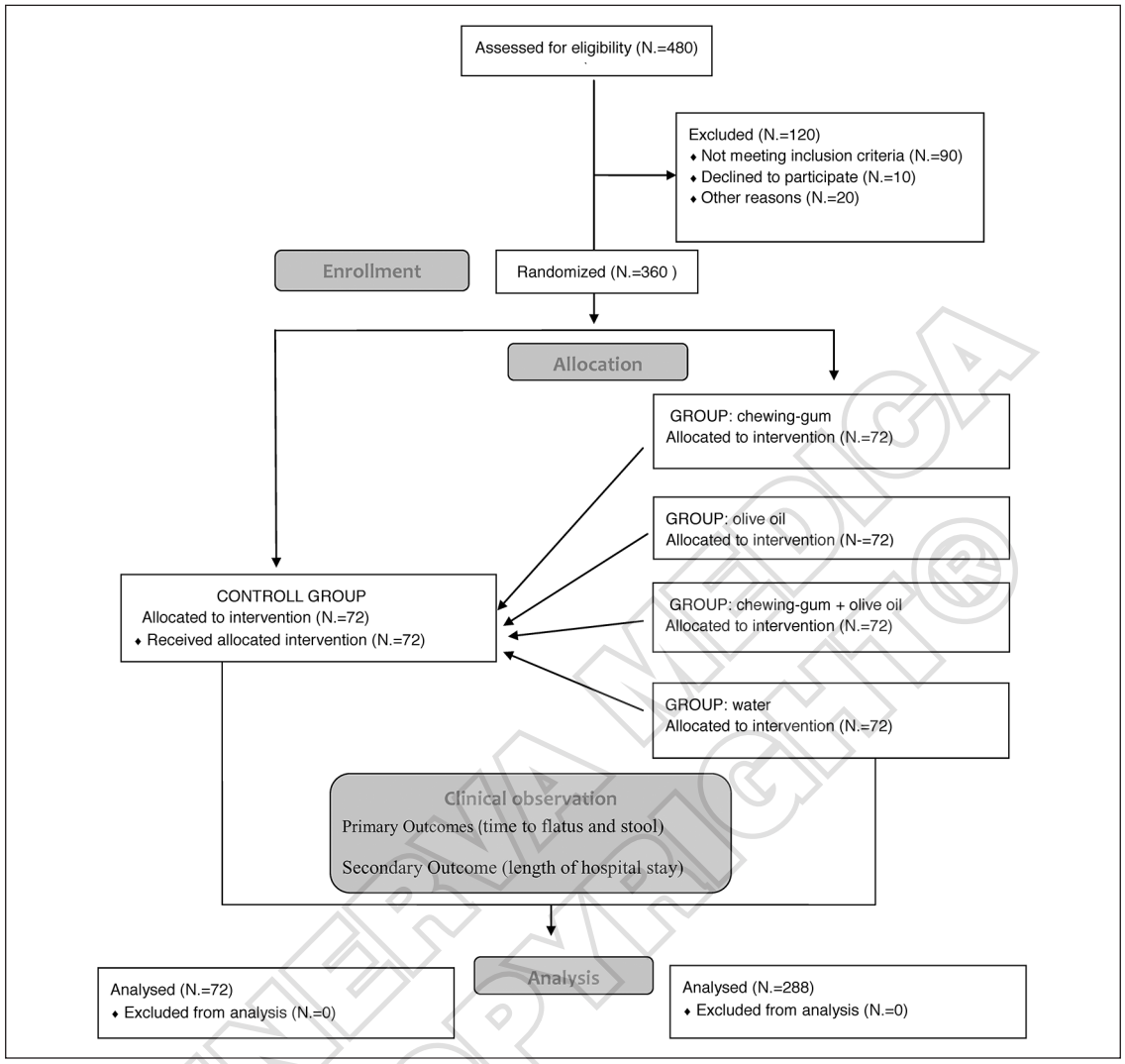

Figure 1.—CONSORT 2010 flow diagram.

with a draw. The groups were homogeneous in number of patients, age, gender, and type and duration of surgery (Table I). All patients underwent standard therapy, with IV saline solution, antibiotic therapy and parenteral nutrition if necessary. The treatments were given on the day of the operation after 6 hours. In the control group, 72 patients (22 males, 55 females, mean age 61.49±20.49 years, range 14-91) underwent only standard therapy. In the chewing gum group, 72 patients (30 males, 42 females, mean age 56.67±18 years, range 15-88) chewed gum for half an hour three times a day (8:00 a.m., 4:00 p.m., 8:00 p.m.). Patients received a sugar-free peppermint-flavored gum, the ingredients of which included sorbitol, gum base, mannitol, glycerol, maltitol, aspartame, acesulfame K, softeners, and natural and artificial flavors. In the olive oil group, 72 patients (30 males, 42 females, mean age 62.93±21.33 years, range 15-88) were treated with an olive-oil based multivitamin supplement (a 10-mL supplement was given twice a day, at 8:00 a.m. and 8:00 p.m.). In the olive oil/chewing gum group

TABLE I.—*Patients' demographic characteristics, type of surgery, and preoperative drug.*

Characteristics	No treatment	Water	Chewing gum	Olive oil	Chewing gum + olive oil
Mean age	61.4 (±20.5)	58.4(±21)	56.6 (±18)	62.9 (±20.4)	55.3 (±17)
M/F	22/50	24/48	30/42	30/42	36/36
Length of operation	140.6 (±15)	144 (±13.5)	145.3 (±36.4)	138.3 (±23)	137.7 (±32.3)
Colo-rectal surgery					
Length of operation (min)	65.5 (±4.3)	63.2 (±5.6)	67.8 (±6.8)	62.8 (±5.5)	66.7 (±7.5)
Videolaparoscopic cholecystectomy					
Length of operation (min)	85.5 (±20)	82.4(±18.5)	88.5(±19.5)	83.5 (±16.6)	85.8 (±19.8)
Hartmann procedure					
Length of operation (min)	110 (±47.8)	108 (±45.7)	115.8 (48.6)	109.5 (±47.7)	113.3 (±45.5)
Gastric surgery					
Type of operation					
Colo-rectal surgery	25	25	25	25	25
– Left colectomy	10	9	8	13	12
– Right colectomy	10	12	10	8	6
– Upper and mid rectum	5	4	7	4	7
Videolaparoscopic cholecystectomy	23	23	23	23	23
Hartmann Procedure	7	7	7	7	7
Gastric surgery	17	17	17	17	17
– Total Gastrectomy	7	6	6	7	7
– Gastric resection	10	11	11	10	10
Drug before surgery	31	33	44	42	50
None	0	5	2	2	1
Prokinetic	34	32	22	27	21
Constipating	7	2	4	1	0
Both					

72 patients (36 males, 36 females, mean age 55.33±17 years, range 19-85) were treated with both olive-oil-based multivitamin supplement and chewing gum, as described above. In the water group (24 males, 48 females, mean age 58.44±20.92 years, range 15-89), 72 patients were treated with 10 cc. of water per os, twice a day (8:00 a.m. and 8:00 p.m.). For each type of surgery, patients received the same postoperative care regimen, including NSAID pain control if necessary, removal of nasogastric tube, and early ambulation (1st postoperative day). Patients who underwent videolaparoscopic cholecystectomy generally received food on postoperative day 1 (light diet). We did not carry out fast track program in this patients because it could be a bias in this specific study. The patients who underwent colo-rectal surgery on postoperative day 3 (liquids). Patients who underwent gastric surgery received food on postoperative day 4 (liquids) or Hartmann procedure patients received food on postoperative day 1 (light diet). The experimental treatments were administered by a nurse, and receipt was recorded on a specific form. In order to ensure blinding of the study's investigators and surgical team, patients were instructed during enrollment not to inform the surgeon, nurse or research team of the group to which they were randomized and they were instructed to record exact time of flatus and bowel movement. No clinical rounds were made by the investigating team during the administration of the treatment. The primary outcomes (time to flatus and time to stool) and secondary outcome (length of hospital stay) were recorded by a doctor who did not know which treatment the patient received. Patients were discharged by the surgical team once they were passing flatus and/or stool in the absence of complications.

Statistical analysis

Continuous variables are summarized as median and 3rd interquartile. The non-para-

TABLE II.—*Median and 3rd interquartile time to passage of flatus and stool, and postoperative length of stay.*

Type of surgery and treatment	Median time to P value flatus (hours)	Median time to P value feces (hours)	Median length of hospital stay P value (days)
Videolaparoscopic cholecystectomy			
Control	24; (72) 0.006	72; (120) 0.021	3; (8) 0.01
Olive oil	12; (21.5)	36; (58,5)	2; (4,5)
Chewing gum	12; (28)	44; (71)	3; (6,5)
Water	10; (18) *	34; (54.5) *	1; (2.5) *
Chewing gum + olive oil	24; (24)	70; (78)	2; (2)
Colo-rectal surgery			
Control	48; (72) n.s.	96; (144) n.s.	7; (9) n.s.
Olive oil	31; (64)	105; (121)	7; (9)
Chewing gum	33; (43)	60; (132)	7; (9)
Water	34 (57)	83; (126)	7; (9)
Chewing gum + olive oil	24; (36)	72; (72)	7; (8)
Hartmann procedure			
Control	36; (48) n.s.	96; (114) n.s.	10; (10.5) n.s.
Olive oil	22; (40)	46; (71.5)	8; (11.5)
Chewing gum	7; (26)	60; (89,5)	9; (10)
Water	32; (51.5)	80; (101.5)	9; (17.5)
Chewing gum + olive oil	24; (54)	48; (84)	7; (7)
Gastric surgery			
Control	24; (72) n.s.	120; (192) 0.04	6; (9) n.s.
Olive oil	32; (54)	89; (106)	5; (7)
Chewing gum	24; (36)	84; (80.75)	6; (8)
Water	30; (48)	64; (85)	5; (8)
Chewing gum + olive oil	24; (32)	48; (72) *	6; (7)

n.s.: No statistically significance P>0.05. * Median and 3rd Interquartile statistically significance (P<0.05).

metric Friedman test was used for continuous variables in multiple comparisons. A P value <0.05 was considered statistically significant. All statistical analyses were done with XLSTAT version 7.5. The sample size of patients undergoing surgery was established at 360. This dimension was calculated assuming that the distribution of the times of flatus and stool was similar to normal population with a confidence interval of 95%, to an accuracy equal to 0.05 and that comes from a population symmetric between the different treatments. This sample size provides a power of the test equal to 80%. Subsequently, the patients were divided randomly according to the type of intervention. Statistical power was set *a priori* at least 80%, with reductions of 50% and 60%, depending on the type of surgery, compared with a median time of the control group. A Relative Risk Test (RR) were used to evaluate the influence of the variable "taking drug" to the times of the flatus and stool. A RR>1 were considered significant for independence.

Results

There were no differences in demographic and surgical characteristics among the groups (Table I). All of the patients tolerated treatment from the first postoperative morning. No postoperative or treatment-related complications were observed. The first passage of flatus was considered resolution of POI, and the first passage of stool as complete recovery of gastrointestinal function. The times of the first flatus and defecation, and length of the postoperative hospital stay, are shown in Table II. In patients who underwent VLC, the first passages of flatus and stool, in the water group, were seen at median postoperative 10 and 34 hours respectively (P=0.006, P=0.021), which were significantly earlier than in the control group (median postoperative 24 and 72 hours, Figures 2-3). Their median postoperative stay was also less (median 1 day) compared with the control group (median 3 days, P=0.01) (Figure 4). Median time

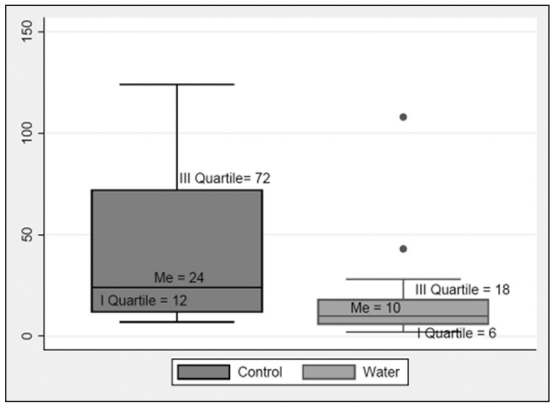

Figure 2.—Videolaparoscopic cholecystectomy: time to flatus, control *vs.* water.

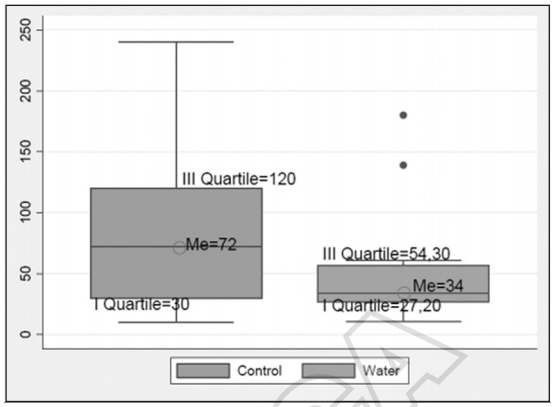

Figure 3.—Videolaparoscopic cholecystectomy: time to stool, control *vs.* water.

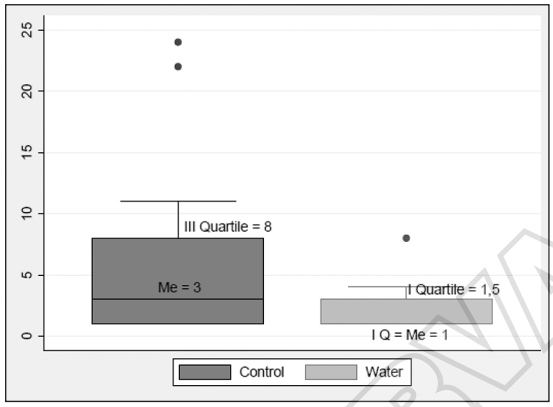

Figure 4.—Videolaparoscopic cholecystectomy: postoperative hospital stay (days): control *vs.* water.

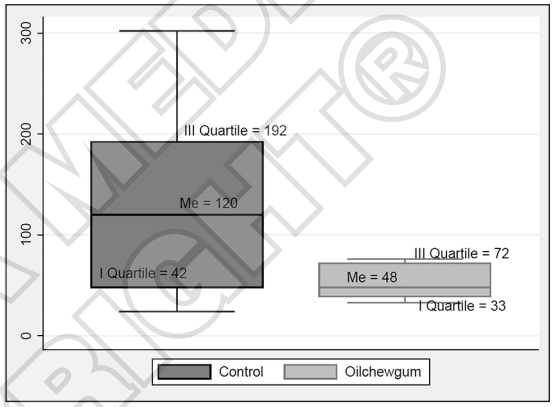

Figure 5.—Gastric surgery: time to stool: control *vs.* olive oil/chewing gum.

to first passage of flatus was also earlier in the other groups compared with the control group, though this difference was not significant (Table II). No significant differences among the groups were observed regarding the passage of stool. In patients who underwent gastric surgery, the median first passage of stool in the olive oil and chewing gum group was seen at postoperative hour 48, which was significantly earlier than in the control group (median postoperative hour 120, P=0.04) (Figure 5), though there was no statistical significance in terms of postoperative stay between them. Median time to first passage of stool was earlier in the other groups compared with the control group, though not statistically significant (Table II). In patients who underwent the Hartmann procedure, colo-rectal surgery or gastric surgery, no significant differences with respect to time to first passage of flatus were observed among the different treatments. No differences were observed among the treatments with respect to time of first passage of stool in patients who underwent colo-rectal surgery or the Hartmann procedure.

The RR test showed that the drugs potentially interfering with flatus and stool timing did not influence them. The relationship between patients taking medication and those not taking into groups with statistically significant values (time of flatus and stool in VLC group and time of stool in gastric surgery group), were respectively RR>1.22, >1.13 and >2.12; then, there was

no correlation between taking drugs or not taking and the times of flatus and stool. In addition, we also examined whether there was relationship between the different medications (prokinetics, constipating and/or both) and times of flatus and stool in the same groups: also in this case, the relative risk test was respectively RR>1.2, >1.07 and >2.05. Therefore we can conclude that the intake of drugs (regardless of the type of drug) or less does not represent a bias in our study.

Discussion

POI is a common condition in patients who have undergone abdominal surgery, and is characterized by absence of bowel movement and cessation of gas and stool transit. It is considered a natural physiologic response of the bowel to abdominal surgery.[11] POI is also one of the major causes of prolonged hospital stay in surgery wards, and of increased health care costs.[11] A number of studies in the literature have attempted to investigate the causes of POI.[1, 2] Bowel manipulation, duration of surgery, and surgical stress seems to be among the most important factors determining the extent of POI.[12] The role of inflammatory response in the etiology of POI has also been reported. Bowel manipulation may trigger an inflammatory cascade that leads to inflammation in the intestinal muscle layer, and an influx of leucocytes,[4] activating inhibitory neural pathways and possibly triggering inflammation in distant untouched areas, leading to a generalized impairment of gastrointestinal motility.[14] Gao *et al*. found that bowel inflammation is characterized by efferent vagal modulation via acetylcoline receptors on intestinal macrophages in rat models.[13] Following this study, a number of treatments aimed at decreasing the duration of POI were reported. Chewing gum, one of the most common postoperative treatments, may act through a "sham feeding" pathway in which activation of the cephalic phase of digestion leads to upregulation of such gastrointestinal hormones as gastrin, neurotensine, pancreatic polipeptyde, and to intestinal motility. Chewing gum also stimulates the salivary glands, stomach, and pancreatic secretion through neuronal and hormones pathways.[15] Our study attempted to evaluate the effects of different types of treatment, such as olive oil, and water, compared with chewing gum and standard therapy (control group). The rationale of the use of olive oil is based on its well known laxative effect [16] and its possible anti-inflammatory effect through a reduction in ROS (reactive oxygen species) production.[17] There are no studies in the literature on the effect of these treatments, and most of the available studies focus their attention only on colorectal surgery. In our study we evaluated these treatments in surgery, such as videolaparoscopic cholecystectomy (VLC), colo-rectal surgery (left and right colectomy, upper and mid rectum surgery), sigmoid-colon resection with colostomy (Hartmann procedure), gastric surgery (gastric resection and total gastrectomy). In a recent study, Matros *et al*. found that chewing gum does not ameliorate POI in patients who have undergone colonic surgery, a finding that is in agreement with our results.[10] Our data suggest a positive effect of water in patients who have undergone VLC, but this was not found in patients in the chewing gum group, the olive oil group, and the combined chewing gum and olive oil group, compared with control. This effect is perhaps due to early activation of hormone-related gastric biliopancreatic secretion. In fact, water is expelled from the stomach sooner than oil, and this may determine an earlier mobilization of the gut, as a possible mechanical effect. We found no positive effect of the different treatments (water, oil, chewing gum) compared with control groups in patients who underwent bowel resection, a finding that is in contrast with studies that found a positive effect of chewing gum on duration of POI.[9] This is probably due to the resection of intestinal wall nerves that may delay nerve conduction between the stumps. Furthermore, it could depend on the kind of surgical access: we performed only open-abdomen colorec-

tal surgery, and this could have negatively influenced to the POI duration. Moreover, perianastomotic scar tissue and/or edema may delay nerve conduction of the Meissner's submucosal and Auerbach's myenteric plexuses. A reduction in stool transit compared with the control group was found in patients who underwent other types of surgery and were treated with both olive oil and chewing gum. The sham-feeding effect of chewing gum could be enhanced by the laxative effect of the oil in these patients. We have also assessed in the groups in which treatments were effective, the effect of the assumption or otherwise of any medications (prokinetics, constipating and/or both) on the timing of flatus and stool to see if these could be bias. In our study we found no influence in times of flatus and stool in patients who did not take drugs than in those taking drugs regardless of the type of drug taken. A possible explanation could be that the constipating action or prokinetic drugs taken at therapeutic doses, is poorly influential in people who have a postoperative ileus. Probably, the opening of the peritoneum and the visceral manipulation have a determinant role on its severity. In this context, the postoperative ileus could mask or reduce the effect of the drugs interfering with bowel motility. Further studies should be made to understand other possible pathophysiological mechanisms (including any action of drugs) at the base of postoperative-ileus in view of the fact that the studies conducted to date on the possible efficacy of some treatments, such as chewing gum, suffer for lack of data.

In conclusion, our preliminary results suggest that chewing gum, olive oil, and a combined therapy of chewing gum and olive oil do not induce a relevant reduction in the duration of POI after abdominal surgery, particularly in those in whom a complete interruption of the bowel wall is performed during surgery. Water may well be a safe and inexpensive option for reducing duration of POI in the early postoperative period for patients who have undergone VLC. Further prospective studies are needed to confirm the efficacy of the various treatments for reduction in duration of POI that we tested in our study.

Riassunto

Valutazione dell'efficacia degli attuali trattamenti per ridurre l'ileo postoperatorio: studio clinico randomizzato condotto in un unico centro

Obiettivo. L'ileo postoperatorio è considerato una inevitabile conseguenza della chirurgia addominale. Lo scopo di questo studio è valutare l'efficacia di alcuni trattamenti nel risolvere l'ileo postoperatorio in diversi approcci chirurgici.

Metodi. Sono stati sottoposti a chirurgia addominale e suddivisi in quattro gruppi 360 pazienti: videolaparocolecistectomia, chirurgia colo-rettale e gastrica laparotomica, intervento di Hartmann. In ciascun gruppo, i pazienti hanno ricevuto differenti trattamenti postoperatori: chewing gum, olio d'oliva, entrambi e acqua. Ciascun gruppo è stato confrontato con un gruppo di controllo.

Risultati. Nei pazienti sottoposti a videolaparocolecistectomia, la mediana del primo passaggio postoperatorio di gas e feci nel gruppo acqua era rispettivamente 10 e 34 ore (P=0,006, P=0,021), significativamente più breve rispetto al gruppo di controllo (mediana postoperatoria 24 e 72 ore). La degenza postoperatoria nel gruppo acqua era più breve (mediana 1 giorno, terzo interquartile 2,5) rispetto al gruppo di controllo (mediana 3 giorni; terzo interquartile 7.0, P=0,01). Nei pazienti sottoposti a chirurgia gastrica, la mediana del primo passaggio postoperatorio di feci nel gruppo chewing gum e olio d'oliva era 48 ore, significativamente più breve rispetto al gruppo di controllo (mediana postoperatoria 120 ore, P=0,04). Il tempo mediano del primo passaggio postoperatorio di gas e feci era anche più breve negli altri gruppi rispetto al gruppo di controllo, sebbene questa differenza non era significativa.

Conclusioni. Chewing gum, olio d'oliva e l'uso di entrambi non inducono una rilevante riduzione dell'ileo dopo chirurgia. L'acqua può essere una valida e poco costosa opzione nella riduzione dell'ileo.

PAROLE CHIAVE: Ileo postoperatorio - Chewing gum - Olio d'oliva - Chirurgia addominale.

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