Clinics in Surgery

Research Article
Published: 20 Feb, 2019

Oral Nutritional Supplements before Rectal Cancer Surgery-Hitting Two Birds with One Stone? Results of a Randomized Controlled Trial

Anderin K[1], Thorell A[2], Nygren J[2] and Gustafsson UO[3]*

[1]Center for Digestive Diseases, Karolinska University Hospital & Department of Clinical Sciences, Danderyd Hospital, Karolinska Institute, Stockholm, Sweden

[2]Department of Surgery, Ersta Hospital & Department of Clinical Sciences, Danderyd Hospital, Karolinska Institute, Stockholm, Sweden

[3]Department of Surgery & Department of Clinical Sciences, Danderyd Hospital, Karolinska Institute, Stockholm, Sweden

Abstract

Background: Preoperative weight loss and malnutrition is common among patients undergoing surgery for rectal cancer. We investigated the effect of Oral Nutritional Supplements (ONS) in combination with rectal enema compared to standard treatment with Mechanical Bowel Preparation (MBP), Polyethylene Glycol (PEG) before rectal cancer surgery on perioperative nutritional status, degree of bowel cleansing and postoperative morbidity.

Materials and Methods: Patients planned for rectal cancer surgery were randomized to either ONS treatment and rectal enema or no nutritional intervention and MBP before surgery. All patients were treated according to an Enhanced Recovery after Surgery (ERAS) protocol and prospectively registered in the international ERAS database.

Physiological and nutritional tests were performed at four occasions; after randomization (i.e. 4-6 weeks before surgery), one day before surgery, three days and four weeks after surgery, Degree of bowel cleansing was recorded during surgery. Postoperative morbidity and rate of recovery after surgery was registered in the ERAS database.

Results: A total of 29 patients were included: 13 in the ONS-group and 16 in the PEG-group. Basic characteristics, tumor stage and type of surgery performed did not differ. From randomization until surgery, patients in the ONS-group had a higher caloric intake; 34(24-65) kcal/kg/day in median (range) compared to 26(14-37) in the PEG-group (p 0.005) and gained 1.9% in body fat (p 0.041) whereas the PEG-group lost 1.6 mm in subcutaneous fat (p 0.019). From randomization until 4 weeks after surgery, the ONS-group lost less in weight, -1.6 kg *vs*. -4.6 kg in the PEG-group (p 0.028).

Right and mid colon were considered less clean in the ONS-group, as perceived by the surgeons, compared to the PEG-group (p 0.015 and 0.003, resp.), but there was no difference in the sigmoid and rectum. The postoperative complications, 23% in the ONS group compared to 38% in the PEG-group, was not significantly different (p 0.454).

Conclusion: ONS prior to rectal cancer surgery may improve patients' perioperative nutritional status and be a safe alternative to traditional bowel cleansing. However, further studies with a larger sample size are needed to verify this association.

Keywords: Rectal cancer; Rectal enema; Oral nutritional supplements; Polyethylene glycol

OPEN ACCESS

Correspondence:
Kajsa Anderin, Center for Digestive Diseases, Karolinska University Hospital, Solna, S-17176, Sweden, Tel: 46703749169; Fax: 460851770000; E-mail: kajsa.anderin@karolinska.se

Received Date: *17 Jan 2019*
Accepted Date: *18 Feb 2019*
Published Date: *20 Feb 2019*

Citation:
Anderin K, Thorell A, Nygren J, Gustafsson UO. Oral Nutritional Supplements before Rectal Cancer Surgery-Hitting Two Birds with One Stone? Results of a Randomized Controlled Trial. Clin Surg. 2019; 4: 2340.

Introduction

Weight loss and malnutrition prior to gastrointestinal surgery is common [1,2] and a well-known risk factor for postoperative morbidity and early mortality [3-8]. This may partly explain why rectal cancer surgery is associated with high risk of postoperative morbidity [9-11]. However, there are no clear recommendations on preoperative nutrition in rectal cancer patients including treatment with preoperative Oral Nutritional Supplements (ONS). Mechanical Bowel Preparation (MBP) may cause significant fluid and electrolyte shifts, where fluid imbalance is a known risk factor of worse postoperative outcome [12]. Moreover, the procedure is stressful for the patient,

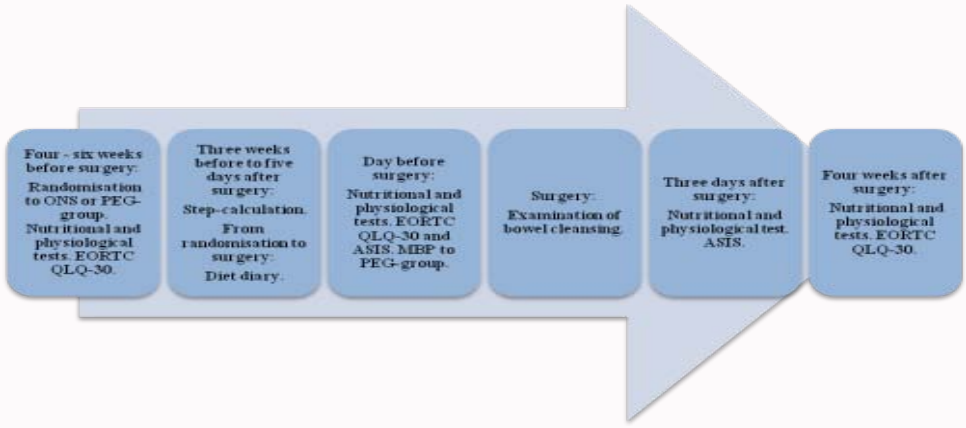

Figure 1: Flow-chart.

why compliance might be reduced with an unsatisfactory clean bowel as a consequence [13]. Due to no proven benefits MBP has been abandoned in colonic surgery [14,15].

However, rectal cancer patients undergoing low anterior resection are frequently diverted with a loop ileostomy, to reduce the risk of an astomotic leakage [16,17]. Thus, to avoid remaining stools in the diverted colon, MBP is routinely performed in this group of patients [18].

In a single center randomized controlled trial, ONS (residue free supplements) prior to colonoscopy, as compared to MBP with Polyethylene Glycol (PEG), resulted in inferior cleansing of the proximal colon [19], while similar cleansing was found in the sigmoid and rectum. Nevertheless, ONS was a procedure with high tolerability and compliance that allowed intubation of caecum in the majority of patients (78%). However, a total clean bowel prior to rectal cancer surgery might be less important compared to before colonoscopy, and a possible way to avoid the need for mechanical bowel preparation in patients undergoing low anterior resection with a diverting loop ileostomy.

The aim with this present study was to investigate if treatment with ONS instead of PEG before rectal cancer surgery was associated with improved perioperative nutritional status, sufficient bowel cleansing and equal rate of postoperative complications.

Materials and Methods

A single center randomized controlled trial was conducted at Ersta Hospital Stockholm, Sweden, between 11th of June 2008 and 5th of February 2013 (ClinicalTrials.gov number, NCT00687570).

Inclusion criteria were surgery for rectal cancer and informed consent. Patients with symptoms of acute intestinal obstruction, inability to understand and/or comply with the study protocol and/or metastatic disease were excluded.

4-6 weeks before surgery included patients were randomized, by the use of sealed envelopes with information on group allocation, to one of the two treatment arms; Oral Nutritional Supplements-group (ONS) or Polyethylene Glycol-group (PEG). The patients' treatment was not blinded to the surgeons and nurses involved.

ONS-group

From the day of randomization until one week before surgery, 50% of the recommended daily caloric intake (RDI) (30 kcal/kg and day) was provided as ONS (Fresurbin®, residue free, 300 kcal/200 ml) whereas the remaining 50% constituted of normal diet. During the last week before surgery, only ONS intake was allowed and therefore corresponded to the entire RDI. At the evening before and on the day of surgery patients were given two rectal enemas (Klyx®, 240 ml), while no further MBP was used.

PEG-group

Patients allocated to the PEG group received the standard treatment at our institution; no intervention in their normal diet and MBP with 4 L of PEG (Laxabon®) the day before surgery.

Prior to randomization nutritional and physiological tests were performed. Weight, Body Mass Index (BMI), Subjective Global Assessment (SGA) classification, circumference of the upper arm (non-dominant), % body fat (from bio impedance, Tanita® TBF-300, MA), subcutaneous fat (skin fold thickness of biceps, triceps, sub scapular and suprailiac subcutaneous fat, measured in mm with one decimal accuracy, with a Baseline skin fold caliper®, average of all four locations, three measures/location), spirometry and handgrip strength in the dominant and non-dominant hand (average of three measures) were measured. The same measurements were repeated one day before and three days and 4 weeks after surgery.

Degree of ambulation was determined with a step-calculator (3 weeks before until five days after surgery) and patients registered their daily intake of calories (from randomization until surgery). Weekly, a nurse phoned every patient and registered the caloric intake (two days/week; one day during the week and one during the weekend).

Quality of life was measured with EORTC QLQ-30 [20] (at randomization, day before and 4 weeks after surgery) and Abdominal Surgery Impact Scale (ASIS) [21] (day before and 4 days after surgery).

A flow-chart over the study protocol is shown in Figure 1.

The surgeons graded the degree of colonic and rectal cleansing during surgery as "empty", "half" or "full" and any spillage of intestinal content when dividing the bowel was recorded. All patients had postoperative ONS according to the ERAS-protocol [22]. Postoperative morbidity within 30 days after surgery was registered and classified according to Clavien-Dindo [23] and divided into surgical, infectious, cardio/pulmonary and neurological complications. All patients were treated according to a standardized ERAS-protocol [22]. Key components in this protocol were avoiding of preoperative fasting and perioperative fluid overload, preoperative

Table 1: Basic characteristics and preoperative investigations.

	ONS (n=13)	PEG (n=16)	P-value
Age: years ± SD	66.2 ± 9.2	62.4 ± 9.6	0.292$
Gender: Male/Female	08-May	10-Jun	0.958†
BMI ± SD	24.9 ± 4.2	26.6 ± 3.4	0.091$
SGA-A: n (%)	13(100)	16(100)	
ASA			1.000$
ASA1: n	1	1	
ASA2: n	12	14	
ASA3: n	0	1	
Smoker: n	0	0	
Comorbidity: n			1.000‡
Heartfailure	0	0	
Hypertension	6	7	
Pulmonarydysfunction	0	0	
Diabetes	0	0	
Cortisonetreatment	0	0	
Neoadjuvanttreatment: n (%)	10(77)	13(81)	1.000‡
Radio therapy: n	9	12	
Chemo/Radio therapy: n	1	1	
Stage: n			0.207‡
T-stage I	5	6	
T-stage II	5	2	
T-stage III	3	8	
T-stage IV	0	0	
Tumor level: cm, median (range)	10(3-18)	9(6-15)	0.707$
Procedure: n			0.553‡
LAR with loop ileostomy	7	12	
APR	2	2	
AR	4	2	
Stoma:n (%)	9(69)	14(88)	0.228‡

Mass Index, ASA: American Society of Anesthesiologists physical status; SGA: Subjective Global Assessment; LAR: Low Anterior Resection; APR: Abdomino Perineal Resection; AR: Anterior Resection; †: Pearson's x^2 test; ‡: Fisher's exact test; $: Wilcoxon rank sum test

carbohydrate treatment until 2 hrs before surgery, thoracic epidural analgesia, early oral diet and mobilization after surgery. All of these variables, together with several other ERAS-items, postoperative morbidity and recovery were prospectively registered in the international web-based ERAS database [24].

Exposure was randomization to ONS without preoperative MBP or preoperative MBP without any interventions in oral intake. Primary outcome was perioperative nutritional status and secondary outcomes were degree of bowel cleansing and postoperative morbidity. The regional ethics committee approved the study.

Statistical analyses

Values are presented as mean (± standard deviation) and median with range, when appropriate. For comparison of categorical variables, x^2-test or Fisher's exact test was used. When comparing continuous variables, t-test or Wilcoxon rank sum-test was used. For calculation of repeated measurements (i.e. physiological and nutritional data) one-way ANOVA analysis and paired t-test were conducted. P-value <0.05 was considered statistically significant. The study hypothesis was that 25% of the patients in the ONS-group would lose 2 kg, in 4 weeks before surgery, compared to 75% of the patients in the PEG-group. With a power of 80% and a one-sided 95% confidence interval, 18 patients were needed in each group for detecting such a difference in preoperative weight loss. Analysis was performed according to intention-to-treat. All statistical analysis was performed using STATA version 13.0 (StataCorp, College Station, Texas).

Results

During the study period, 279 patients were operated on for rectal cancer whereof 29 patients were included and randomized; 13 patients in the ONS-group and 16 in the PEG-group. There was no violation of the study protocol.

Basic characteristics and preoperative investigations are shown in Table 1.

All of the patients were classified as SGA-A (i.e. no malnutrition). Age, gender, American Society of Anesthesiologist (ASA)-

Table 2: Operative data, postoperative morbidity and recovery.

	ONS (n=13)	PEG (n=16)	P-value
Bleeding (perop.): ml, mean ± SD	280 ± 234	390 ± 303	0.294$
Anastomotic level: cm, median (range)	5(3-10)	4(3-10)	0.321$
Laparoscopic/open: n (%)	1(7.7)	3(18.8)	0.606‡
Complications: n (%)	3(23.0)	6(37.5)	0.454‡
Total complications	3(23.0	12(75.0)	0.009‡
Surgical complication	1(7.7)	5(31.3)	0.183‡
Anastomoticleakage	0	3(18.8)	0.232‡
Bleeding	0	1(6.2)	1.000‡
Woundinfection	1(7.7)	2(12.5)	1.000‡
Intra abdominal abscess	0	2(12.5)	0.488‡
Reoperation	0	3(18.8)	0.232‡
Infectiouscomplication	2(15.4)	4(25.0)	0.663‡
Urinarytractinfection	2(15.4)	4(25.0)	0.633‡
Cardiopulmonarycomplication	0	0	
Neurologicalcomplication	0	0	
Postoperative recovery: day after surgery, median (range)			
Flatus	2(1-10	2(1-9)	0.964$
Bowels	4(1-10)	2(1-9)	0.114$
EDA removal	4(2-12)	5(3-27)	0.799$
No drip	1(1-19)	4(1-28)	0.314$
Solid food	4(1-19)	4(1-28)	0.809$
KAD removal	5(2-22)	5(3-29)	0.615$
Fulfil all	7(3-17)	6(3-48)	0.941$
LOS: days, median (range)	8(4-29)	7(3-41)	0.522$
Readmissions	0	0	

Flatus: first flatus, Bowels: first stool, EDA: Epidural anaesthesia; No drip: No Intravenous Infusion; Solid food: intake of solid food, KAD: Urinary catheter, Fulfil all: fulfilled all of the recovery items measured; LOS: Length of Stay; ‡: Fisher's exact test; $: Wilcoxon rank sum test

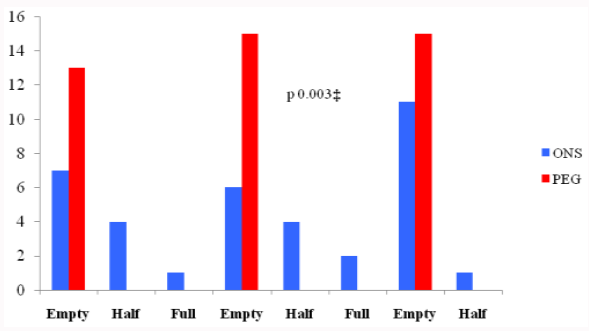

Figure 2: Cleansing of colon and rectum.
ONS: Oral Nutritional Supplements; PEG: Polyethylene Glycol; ‡Fisher's exact test. There were 4 missing data in colon ascendens, 2 missing data in colon transversum/descendens and colon sigmoideum/rectum.

classification and BMI did not differ between the groups. None of the patients were smokers, had a history of cardiopulmonary disease or diabetes. Ten patients (77%) in the ONS-group had neoadjuvant treatment compared to 13 patients (81%) in the PEG-group (NS). Tumor stage and level did not differ significantly. Operative data and cleansing of colon and rectum are shown in Table 2 and Figure 2.

One patient (7.7%) in the ONS-group underwent laparoscopic procedure and 3(18.8%) in the PEG-group (p 0.606). There was no significant difference in type of surgery or number of patients with a diverting stoma between the groups (7 patients in ONS-group and 12 patients in PEG-group, p 0.553, were diverted) (Table 1).

Seven patients in the ONS-group had an empty colon ascendens compared to 13 patients in the PEG-group (p 0.015). In colon transversum and descendens, 6 patients in the ONS-group were clean compared to 15 patients in the PEG-group (p 0.003). There were no significant differences in cleansing of the sigmoid and rectum (p 0.444), (Figure 2), orin spillage of fecal content when constructing the anastomosis (1 patient in ONS-group *vs.* 0 in PEG-group, p 0.481). Data on body weight are shown in Figure 3.

There was no difference in median (range) time from randomization to surgery, 5(1-11) *vs.* 3(2-11) weeks in ONS and PEG-group, respectively (p 0.142). During this period, the median daily caloric intake/kg was significantly higher in the ONS-group; 34 (24-65) kcal/kg/day compared to the PEG-group; 26 (14-37) kcal/kg/day, p 0.005. Twenty-three percent (3/13) in the ONS group did not reach their caloric RDI compared to 81% (13/16 patients) in the PEG-group, p 0.003.

In the ONS-group patients gained mean (SD) 0.5(± 2.7) mm subcutaneous fat (NS), from randomization to surgery, compared to the PEG-group who lost mean (SD)-1.6(± 2.4) mm during the same period. This reduction in subcutaneous fat, within the PEG-group,

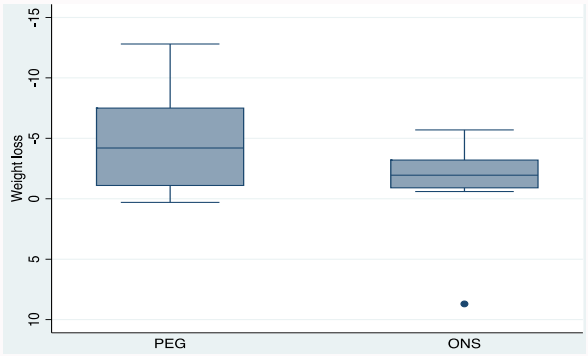

Figure 3: Weight loss from randomization to 4 weeks after surgery. PEG: Polyethylene Glycol; ONS: Oral Nutritional Supplements. *One-way ANOVA analysis. * P 0.028 ONS *vs* PEG. The underlying dot in the ONS-group represents an outlier.

was significant, p 0.019. In concordance, the ONS-group gained mean (SD) 1.9(± 2.5) % body fat from randomization to 3 days after surgery (p 0.041) whereas PEG-group lost mean (SD) -0.1(± 2.5) % (NS). Mean (SD), weight loss from randomization until 4 weeks after surgery was 1.6 (± 3.9) kg in the ONS-group compared to 4.6 (± 3.6) kg in the PEG-group (p 0.028 ONS *vs.* PEG) (Figure 3). From randomization until 4 weeks after surgery, the ONS-group lost less in muscle strength (-3/-2 pounds/cm^2, dominant and non-dominant hand, respectively) compared to the PEG-group (-9/-11 pounds/cm^2, dominant and non-dominant hand, respectively), p 0.001. Changes in HbA1c, BMI, and circumference of the upper arm, spirometry, physical activity (step-calculation during 3 weeks before surgery until 5 days after surgery) and Quality of life (measured with EORTC QLQ-30 and ASIS, before and after surgery) did not differ between the groups (data not shown).

Postoperative morbidity and recovery are shown in Table 2. Any postoperative complication occurred in 23 % of patients in the ONS-group and in 38% in the PEG-group (p 0.454). Adding all complications together, i.e. some patients had more than one complication; ONS-group 0.23 complication/patient compared to 0.75 in the PEG-group, p 0.009. All anastomotic leaks (3 patients) were found among patients in the PEG-group and all needed a reoperation. There were no significant differences between groups in rates of infectious, cardiopulmonary or neurological complications. For postoperative recovery (postoperative day when epidural catheter, urinary catheter, intravenous drip could be removed, patient ate solid food, had their first flatus and stools) no difference could be found between the groups. Among all patients there were no readmission and no mortality within 30 days after surgery.

Discussion

In this single center randomized controlled trial, well-fed patients, treated with ONS 4-6 weeks before surgery for rectal cancer, had a higher daily intake of calories, gained in nutritional status and lost less in weight compared to patients with regular nutritional intake and MBP (with PEG). The numerical lower rate of complications in patients receiving ONS was not statistically significant. In the ONS group, the bowel was less clean in the right and mid colon but was similar compared to patients in the PEG group in the sigmoid and rectum.

About 40% to 60% of patients planned for surgery due to gastrointestinal cancer are suffering from preoperative weight loss and malnutrition [1,2]. Most probably, malnutrition is one important factor contributing to the high rates of postoperative morbidity in rectal cancer surgery [9,10]. Perioperative treatment with Nutritional Supplements (NS) in severely malnourished patients has been shown to reduce postoperative morbidity, mortality and length of hospital stay [3-8]. Yet, previous studies differ in administration of NS; enter al or parenteral, duration and timing of treatment, amount calories given and in the definition of malnutrition.

Moreover, ONS after surgery has in some studies been shown to reduce postoperative morbidity and LOS [25] and is included in the ERAS-protocol [22]. However, guidelines and clinical routines for treatment with NS in colorectal cancer surgery are lacking and to our knowledge, few studies have been conducted regarding preoperative treatment with ONS in this cohort of patients.

MBP before colorectal surgery can cause significant fluid and electrolyte shifts, factors increasing the risk of postoperative morbidity [26,27]. A recently published Cochrane review showed no benefit from MBP in rectal cancer surgery [28]. Despite this, MBP is still considered standard of care before rectal cancer surgery in most centers since it is believed that faces left in the colon after deviation increases the risk of septic complications after anastomotic leakage [16,17]. Moreover, MBP with PEG (4 L of fluids) might be difficult to tolerate for older patients and lack of compliance results in about 25% insufficiently cleansed bowels during colonoscopy [29]. One recent study on treatment with residue free ONS alone and no MBP prior to colonoscopy indicated acceptable cleansing of the colon [19]. Expected nutritional benefits and the additional possibility to avoid MBP prior to rectal cancer surgery were the main rationale to conduct the current study.

One limitation of the present study is that only 29 of the required 36 patients were included. This was mainly due to hesitation of the surgeons to include patients with malnutrition and threatening stricture of the tumor. Therefore, only patients with nutritional status SGA-A and only minor co-morbidity were selected for inclusion. In our institution, in contrast to many others, full preoperative nutritional intake with ONS is mandatory in rectal cancer patients with a narrow rectal lumen. However, based on data from previous studies [3,4,6,8], if malnourished patients had been included the treatment effects from ONS might have been even more pronounced.

Two interventions were performed in each group, i.e. ONS and no MBP versus no ONS and MBP, making the true effect of each intervention difficult to compare and analyze. Yet, the study design could be seen as an ERAS-concept *vs.* standard treatment.

Despite these limitations, several important questions rise from the results in this study.

(1) Is preoperative treatment with ONS instead of MBP safe and can we thereby omit MBP before rectal cancer surgery?

There are no known side effects associated with treatment with ONS prior to surgery. Treatment with MBP however, causes fluid and electrolyte disturbances which may be a risk factor for anastomotic leakage [26]. Moreover, fluid imbalance has been shown to increase the risk of other postoperative morbidity and to prolong LOS [30-32]. Several studies, as in the present one, have found no benefit of MBP in rectal cancer surgery [15,28]. Although contradicting results in some studies [16,17], most data are suggesting that omitting MBP before rectal cancer surgery is preferable. Moreover, the use of

preoperative ONS instead, may reduce the risk of hard stools close to the anastomosis.

(2) Can patients treated with preoperative ONS gain in nutritional status?

The current study on well-fed patients showed a higher caloric intake in the ONS-group and a higher proportion of patients reaching their RDI, compared to the PEG-group. In concordance, the ONS-group lost less weight and muscle strength and gained in % body fat before surgery, whereas the PEG-group lost subcutaneous fat during the same period. Malnourished patients are likely to benefit even more from such treatment. Even if most previous studies have failed to demonstrate that nutritional treatment improves postoperative outcome in well-nourished patients, data from the present study indicate that avoiding catabolism in these patients might be beneficial [3,4,6].

(3) Can ONS prior to surgery reduce the risk of postoperative complications?

The lower total rate of complications/patient among patients treated with ONS in the current study should, because of the low sample size, be regarded more or less as an outcome of chance. However, there is a rationale for improved outcome with improved nutritional status. Despite adverse effects from malnutrition per se, extended fasting and malnutrition prior to surgery are both factors increasing the risk of insulin resistance and hyperglycemia [33,34], causing higher risk of postoperative morbidity and mortality [35]. In addition, patients with tumor related stricture might benefit from residue free ONS, with respect to symptoms and the risk of ileus from the stricture while waiting for neo adjuvant treatment and surgery.

In conclusion, ONS prior to rectal cancer surgery results in significantly better nutritional status, compared to those treated with PEG and may also be a safe alternative to traditional bowel cleansing. Whether ONS is “hitting two birds with one stone” with respect to improvement of perioperative nutritional status and avoiding negative effects associated with mechanical bowel preparation needs to be verified in larger studies.

Acknowledgement

The authors express their gratitude to Ann-Sofie Andersson, Anette Bratt, Monica Johansson and Nina Blommé for excellent nursing and technical assistance.

References

1. Baker JP, Detsky AS, Wesson DE, Wolman SL, Stewart S, Whitewell J, et al. Nutritional assessment: a comparison of clinical judgment and objective measurements. N Engl J Med. 1982;306(16):969-72.
2. Burden ST, Hill J, Shaffer JL, Todd C. Nutritional status of preoperative colorectal cancer patients. J Hum Nutr Diet. 2010;23(4):402-7.
3. Veterans Affairs Total Parenteral Nutrition Cooperative Study Group. Perioperative total parenteral nutrition in surgical patients. N Engl J Med. 1991;325(8):525-32.
4. Bozzetti F, Gavazzi C, Miceli R, Rossi N, Mariani L, Cozzaglio L, et al. Perioperative total parenteral nutrition in malnourished, gastrointestinal cancer patients: a randomized, clinical trial. JPEN J Parenter Enteral Nutr. 2000;24(1):7-14.
5. Braga M, Ljungqvist O, Soeters P, Fearon K, Weimann A, Bozzetti F; ESPEN. ESPEN Guidelines on Parenteral Nutrition: surgery. Clin Nutr. 2009;28(4):378-86.
6. Burden S, Todd C, Hill J, Lal S. Pre-operative nutrition support in patients undergoing gastrointestinal surgery. Cochrane Database Syst Rev. 2012;11:CD008879.
7. Schiesser M, Kirchhoff P, Muller MK, Schafer M, Clavien PA. The correlation of nutrition risk index, nutrition risk score, and bioimpedance analysis with postoperative complications in patients undergoing gastrointestinal surgery. Surgery. 2009;145(5):519-26.
8. Wu GH, Liu ZH, Wu ZH, Wu ZG. Perioperative artificial nutrition in malnourished gastrointestinal cancer patients. World J Gastroenterol. 2006;12(15):2441-4.
9. Anderin K, Gustafsson UO, Thorell A, Nygren J. The effect of diverting stoma on postoperative morbidity after low anterior resection for rectal cancer in patients treated within an ERAS program. Eur J Surg Oncol. 2015;41(6):724-30.
10. Knowledge support for those who work in cancer care.
11. Matthiessen P, Hallböök O, Rutegård J, Simert G, Sjödahl R. Defunctioning stoma reduces symptomatic anastomotic leakage after low anterior resection of the rectum for cancer: a randomized multicenter trial. Ann Surg. 2007;246(2):207-14.
12. ERAS Compliance Group. The Impact of Enhanced Recovery Protocol Compliance on Elective Colorectal Cancer Resection: Results From an International Registry. Ann Surg. 2015;261(6):1153-9.
13. Kastenberg D, Barish C, Burack H, Dalke DD, Duckor S, Putnam W, et al. Tolerability and patient acceptance of sodium phosphate tablets compared with 4-L PEG solution in colon cleansing: combined results of 2 identically designed, randomized, controlled, parallel group, multicenter phase 3 trials. J Clin Gastroenterol. 2007;41(1):54-61.
14. Jung B, Pahlman L, Nystrom PO, Nilsson E; Mechanical Bowel Preparation Study Group. Multicentre randomized clinical trial of mechanical bowel preparation in elective colonic resection. Br J Surg. 2007;94(6):689-95.
15. Contant CM, Hop WC, van't Sant HP, Oostvogel HJ, Smeets HJ, Stassen LP, et al. Mechanical bowel preparation for elective colorectal surgery: a multicentre randomised trial. Lancet. 2007;370(9605):2112-7.
16. Bretagnol F, Panis Y, Rullier E, Rouanet P, Berdah S, Dousset B, et al. Rectal cancer surgery with or without bowel preparation: The French GRECCAR III multicenter single-blinded randomized trial. Ann Surg. 2010;252(5):863-8.
17. Platell C, Barwood N, Makin G. Randomized clinical trial of bowel preparation with a single phosphate enema or polyethylene glycol before elective colorectal surgery. Br J Surg. 2006;93(4):427-33.
18. Nygren J, Thacker J, Carli F, Fearon KC, Norderval S, Lobo DN, et al. Guidelines for perioperative care in elective rectal/pelvic surgery: Enhanced Recovery After Surgery (ERAS(*)) Society recommendations. World J Surg. 2013;37(2):285-305.
19. Gustafsson UO, Segelman J, Ljunqqvist O, Thorell A, Nygren J. Can nutritional supplements and rectal enema be used as bowel cleansing for colonoscopy? Results of a randomized controlled pilot study. Scand J Gastroenterol. 2014;49(4):485-91.
20. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365-76.
21. Urbach DR, Harnish JL, McIlroy JH, Streiner DL. A measure of quality of life after abdominal surgery. Qual Life Res. 2006;15(6):1053-61.
22. Gustafsson UO, Scott MJ, Schwenk W, Demartines N, Roulin D, Francis N, et al. Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After Surgery (ERAS(*)) Society recommendations. World J Surg. 2013;37(2):259-84.
23. Dindo D, Hahnloser D, Clavien PA. Quality assessment in surgery: riding

a lame horse. Ann Surg. 2010;251(4):766-71.

24. Maessen J, Dejong CH, Hausel J, Nygren J, Lassen K, Andersen J, et al. A protocol is not enough to implement an enhanced recovery program for colorectal resection. Br J Surg. 2007;94(2):224-31.

25. Delmi M, Rapin CH, Bengoa JM, Delmas PD, Vasey H, Bonjour JP. Dietary supplementation in elderly patients with fractured neck of the femur. Lancet. 1990;335(8696):1013-6.

26. Kang CY, Halabi WJ, Chaudhry OO, Nguyen V, Pigazzi A, Carmichael JC, et al. Risk factors for anastomotic leakage after anterior resection for rectal cancer. JAMA Surg. 2013;148(1):65-71.

27. Holte K, Nielsen KG, Madsen JL, Kehlet H. Physiologic effects of bowel preparation. Dis Colon Rectum. 2004;47(8):1397-402.

28. Guenaga KF, Matos D, Wille-Jorgensen P. Mechanical bowel preparation for elective colorectal surgery. Cochrane Database Syst Rev. 2011;(9):CD001544.

29. Rostom A, Jolicoeur E, Dube C, Gregoire S, Patel D, Saloojee N, et al. A randomized prospective trial comparing different regimens of oral sodium phosphate and polyethylene glycol-based lavage solution in the preparation of patients for colonoscopy. Gastrointest Endosc. 2006;64(4):544-52.

30. Brandstrup B, Tonnesen H, Beier-Holgersen R, Hjortso E, Ording H, Lindorff-Larsen K, et al. Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. Ann Surg. 2003;238(5):641-8.

31. Varadhan KK, Lobo DN. A meta-analysis of randomised controlled trials of intravenous fluid therapy in major elective open abdominal surgery: getting the balance right. Proc Nutr Soc. 2010;69(4):488-98.

32. Gustafsson UO, Hausel J, Thorell A, Ljunggvist O, Soop M, Nygren J, et al. Adherence to the enhanced recovery after surgery protocol and outcomes after colorectal cancer surgery. Arch Surg. 2011;146(5):571-7.

33. Nygren J, Thorell A, Brismar K, Karpe F, Ljunggvist O. Short-term hypocaloric nutrition but not bed rest decrease insulin sensitivity and IGF-I bioavailability in healthy subjects: the importance of glucagon. Nutrition. 1997;13(11-12):945-51.

34. Svanfeldt M, Thorell A, Brismar K, Nygren J, Ljungqvist O. Effects of 3 days of "postoperative" low caloric feeding with or without bed rest on insulin sensitivity in healthy subjects. Clin Nutr. 2003;22(1):31-8.

35. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001;345(19):1359-67.