

Preoperative nutritional support for patients undergoing elective colorectal cancer surgery – does it really work?

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Aims. This study aimed to evaluate the effect of preoperative administration of oral nutritional supplements (ONS) on the self-sufficiency, physical status, and nutritional status of patients undergoing elective colorectal resections.

Methods. This prospective randomized clinical trial was conducted in a single institution. Patients scheduled to undergo colorectal cancer surgery were randomized to either ONS twice per day for 7 days before surgery or no ONS.

Results. We enrolled 120 patients in the study. The two study groups had comparable hospital stay times and comparable numbers of postoperative complications. Laboratory parameter (albumin and prealbumin) values declined in the postoperative period, but differences between study groups were not significant. The groups had comparable arm circumference measurements, muscle mass and fat proportions, and water weights. Patient self-sufficiency in the postoperative period was comparable between groups ($P=0.313$). Lower limb force declined after surgery, but differences between the groups were not significant ($P=0.579$).

Conclusion. Preoperative administration of ONS to patients undergoing elective colorectal surgery did not reduce postoperative morbidity or enhance recovery. Moreover, patient self-sufficiency, physical status, and nutritional status were not influenced by preoperative ONS. Patients should be properly selected for malnourishment before providing nutritional support to manage costs efficiently.

Trial Registration: ClinicalTrials.gov (NCT03930888).

Key words: nutritional supplements, malnutrition, colorectal cancer, self-sufficiency, postoperative morbidity

Received: December 8, 2021; Revised: January 28, 2022; Accepted: February 14, 2022; Available online: March 1, 2022

<https://doi.org/10.5507/bp.2022.009>

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INTRODUCTION

Colorectal cancer is the most common cancer of the gastrointestinal tract and the second most frequently diagnosed malignancy in adults¹. The presence of malignancy can induce weight loss and malnutrition. It is estimated that two of every three patients with colorectal cancer lost weight preoperatively, and one of every five patients lost more than 10% of their body weight².

Malnutrition is associated with impaired wound healing after surgery, compromised defense against infections, and reduced muscle strength³. A reduction in muscle strength results in ineffective rehabilitation, impaired coughing, poor mobility, and increased risk of bronchopneumonia. It is generally accepted that patients with cancer who are malnourished should receive nutritional support prior to surgery to minimize the negative effects of malnutrition. Nutritional support is thought to modify the physiological responses to major surgery, reduce postoperative complications, shorten the hospital stay, and accelerate recovery^{3,4}.

Preoperative administration of oral nutritional supplements (ONS) to patients at nutritional risk is recom-

mended by The European Society for Clinical Nutrition and Metabolism (ESPEN) and the Enhanced Recovery After Surgery (ERAS) societies^{4,5}. However, the outcomes of a recent systematic review on this topic have contradicted these recommendations. Recent review, published by E. Bruns, incorporated the results of 6 prospective clinical studies that had been realized between 2004 and 2016 (ref.⁶). They concluded that the overall complication rate was not significantly reduced in patients who had received preoperative ONS (ref.⁷⁻¹²). However, all those studies were focused on the correlation between preoperative ONS and postoperative morbidity. To the best of our knowledge, no study has investigated the impact of ONS on the physical status, nutritional status, or self-sufficiency of patients undergoing elective colorectal surgery.

The present study aimed to evaluate the effects of preoperative nutritional supplementation on the postoperative physical status, nutritional status, and self-sufficiency of patients that underwent an elective colorectal resection.

METHODS

Design and Setting

This prospective, randomized clinical trial was designed to assess self-sufficiency, loss of muscle mass/strength, and the possibility of returning to normal activities, when preoperative ONS was provided to patients scheduled to undergo elective surgery for colorectal cancer. The trial was conducted at the University Hospital Ostrava, Czech Republic. All patients with colorectal cancer scheduled to undergo an elective colorectal resection within the study period (1 January 2019 to 30 June 2020) were assessed for study eligibility. The study was approved by the Ethics Committee of the University Hospital Ostrava (ref. Number 447a/2018). It was performed in accordance with the ethical standards of the Declaration of Helsinki (1964) and its subsequent amendments. Written informed consent was obtained from all included patients, and anonymity was ensured. The trial was registered at <http://www.clinicaltrials.gov> (trial identifier NCT 03930888).

The primary outcomes were changes in muscle strength, muscle mass, and self-sufficiency in patients that underwent elective colorectal surgery, with or without preoperative ONS. The secondary outcome was the change in nutritional status of study patients. In addition, we compared postoperative surgical complications in patients with/without nutritional support.

The inclusion criteria were age ≥ 18 years and an indication for an elective resection of colorectal carcinoma. Exclusion criteria were: a generalized disease, intestinal co-morbidity (Morbus Crohn etc.), duplicate malignancy, and incomplete data for the follow-up. Within the study period, all included patients were randomized to one of the trial arms (ONS group and no-ONS group), with the envelope randomization method (all envelopes were prepared in advance, at a ratio of 1:1).

Patients in the ONS group received oral nutritional supplements (125 mL), twice per day, for 7 days before surgery. Patients with diabetes received oral nutritional supplements for diabetics (200 mL), twice per day. These supplements provided patients with additional energy intakes of 2525 kJ or 2520 kJ (supplement for diabetics) per day; the additional protein intakes were 24 g or 30 g per day (supplement for diabetics).

Nutritional status was assessed with a Nutritional risk screening (NRS 2002) instrument and blood levels of prealbumin (transthyretin) and albumin (g/L) (ref.¹³). Nutritional status was assessed on the day before surgery and on the 5th or 6th day after surgery. The NRS 2002 is a specialized scoring system and prognostic nutritional index, which was designed to assess malnutrition and its severity. The NRS 2002 was recommended by the ESPEN for routine use in clinical practice⁴.

We assessed postoperative surgical complications according to the Clavien-Dindo classification system¹⁴. We measured muscle strength, muscle mass, and patient self-sufficiency on the day before surgery and on the 5th or 6th day after surgery. Muscle strength was measured dynamo-

metrically (expressed in kg) by rehabilitation workers. We measured body weight and analyzed the proportions of muscle, fat, and water in the body with a TANITA MC-780 MA body analyzer (expressed in % of whole-body weight).

We assessed self-sufficiency with the Barthel Index for Activities of Daily Living. The Barthel Index comprised ten variables for describing activities of daily living and mobility. The amount of time and physical assistance required to perform each activity were rated on a scale of 0–100. Higher numbers were associated with a greater likelihood of living at home with a degree of independence following hospital discharge.

Data collection

All data were collected prospectively. All presurgical demographic and clinical data on study patients, including age, sex, body mass index (BMI, kg/m²), tumor localization, pTNM classification, carcinoembryonic antigen (CEA) value, and NRS 2002 value, were entered into the study database before surgery. One day before surgery, and on the 5th or 6th day after surgery, the following data (measurements) were recorded: body mass (kg); blood levels of albumin level (g/L), prealbumin (g/L), creatinine (mmol/L), and C-reactive protein (CRP, mg/L); body weight; the percentages of muscle, water, and fat in the body (%); arm circumference (cm); muscular strength of the upper and lower limbs (kg); and the Barthel index score. The time spent in the intensive care unit (ICU, days), the hospital stay (days), and the 30-day postoperative complications were recorded during follow-up.

Statistical analysis

We performed standard descriptive statistics, and continuous data are expressed as the mean, standard deviation (SD) or the median (range). Categorical data are expressed as the frequency. Comparisons were performed with the t-test, ANOVA, Fisher, or Kruskal-Wallis test, according to the nature of the data, and the chi-square test. *P*-values ≤ 0.05 were considered significant. All analyses were performed with the mathematical-statistical programs available from the R-project (The R Foundation for Statistical Computing).

RESULTS

Within the study period (1 January 2019 to 30 June 2020), 251 patients met the inclusion criteria and were assessed for study eligibility. Of these, 66 (26%) patients were excluded, based on the exclusion criteria, and 62 patients (24.7%) declined to participate in the study (CONSORT diagram, Fig. 1). In total, 120 patients with complete data were enrolled in the study.

The patient demographics and clinical characteristics are presented in Table 1. The mean age of the patients was 65.3 ± 11.5 years (SD); there were 41 (34.2%) women and 79 (65.8%) men. The mean BMI on the day of admission was 26.6 ± 5.41 kg/m². Tumors were localized in the

Table 1. Demographics and preoperative status of patients that underwent surgery for colorectal cancer.

Parameter	All n=(120)	Intervention (n=60)	Control (n=60)	<i>P</i>
Sex, n (%)				
Female,	41 (34.2%)	17 (28.3%)	24 (40.0%)	0.248
Male	79 (65.8%)	43 (71.7%)	36 (60.0%)	
Age (years) Mean \pm SD	65.3 \pm 11.5	67.5 \pm 10.0	63.1 \pm 12.5	0.034
Admission BMI (kg/m ²), Mean \pm SD	26.6 \pm 5.41	27.2 \pm 4.79	26.0 \pm 5.83	0.382
Stage, n (%)				
I	44 (36.7%)	21 (35.0%)	23 (38.3%)	0.745
II	42 (35.0%)	23 (38.3%)	19 (31.7%)	
III	34 (28.3%)	16 (26.7%)	18 (30.0%)	
CEA value (μ g/L), Mean \pm SD	10.00 \pm 29.1	14.2 \pm 39.6	5.79 \pm 9.83	0.115
Localization of tumor, n (%)				
Right colon	43 (35.8%)	24 (40.0%)	19 (31.7%)	0.171
Left colon	29 (24.2%)	17 (28.3%)	12 (20.0%)	
Rectum	48 (40.0%)	19 (31.7%)	29 (48.3%)	
Surgical technique, n (%)				
Laparoscopy	91 (75.8%)	50 (83.3%)	41 (68.3%)	0.088
Laparotomy	29 (24.2%)	10 (16.7%)	19 (31.7%)	

Table 2. Pre- and post-operative nutritional parameters in patients that underwent surgery for colorectal cancer.

Parameter	All (n=120)	Intervention (n=60)	Control (n=60)	<i>P</i>
BMI (kg/m ²), Mean \pm SD				
Admission	26.6 \pm 5.41	27.2 \pm 4.79	26.0 \pm 5.83	0.382
Follow up	25.2 \pm 7.12	25.9 \pm 7.62	24.6 \pm 6.60	0.342
Albumin (g/L), Mean \pm SD				
Admission	39.5 \pm 4.14	39.9 \pm 4.35	39.1 \pm 3.93	0.332
Follow up	34.4 \pm 4.87	35.2 \pm 4.96	33.7 \pm 4.70	0.098
Prealbumin (g/L), Mean \pm SD				
Admission	0.22 \pm 0.06	0.22 \pm 0.06	0.21 \pm 0.05	0.682
Follow up	0.15 \pm 0.04	0.15 \pm 0.04	0.14 \pm 0.05	0.460
Admission NRS 2002, Mean \pm SD	2.25 \pm 1.42	2.33 \pm 1.40	2.17 \pm 1.45	0.532
Admission NRS 2002 over 3, n (%)	35 (29.2)	18 (30%)	17 (28.3%)	
Weight loss n (%)				
Pre-operation	43 (35.6)	19 (31.7)	24 (40)	0.445
More than 10% of body weight	26 (21.7)	13 (21.7)	13 (21.7)	1

rectum in 40.0% of patients. Stage I colorectal carcinoma was diagnosed in 35.8% of study patients. Laparoscopic resections were performed in 75.8% of patients.

Data on the nutritional status of study patients are shown in Table 2. According to the principles of the NRS 2002, all study patients were nutritionally at risk (i.e., all patients were seriously ill, due to colorectal cancer). The mean NRS score was 2.25 ± 1.42 in the entire study group before surgery. We identified 35 (29.2%) patients that were malnourished (NRS score ≥ 3 points). The two study subgroups had comparable NRS scores ($P=0.532$). We found that 43 (35.8%) patients had lost weight prior to surgery, and 26 (21.7%) patients had lost more than 10% of their body weight.

The perioperative outcomes (i.e., hospital stay, ICU stay, and postoperative complications) are presented in Table 3. The mean hospital and ICU stays were comparable between study groups ($P=0.855$ and $P=0.073$, respec-

tively). The 30-day postoperative surgical morbidity was 34%. Minor complications (Clavien-Dindo grades I-II) were noted in 32 (26.6%) study patients. Serious postoperative complications (Clavien-Dindo grades III-V) were observed in 9 (7.5%) patients. The prevalence of postoperative complications was comparable between study groups ($P=0.73$). The 30-day postoperative mortality was 0.8% (one patient with multiple organ failure died, due to anastomosis dehiscence after a right hemicolectomy).

Changes in patient nutritional parameters are reported in Table 2. The mean BMI dropped from 26.6 ± 5.41 to 25.2 ± 7.12 kg/m² on the fifth postoperative day. The decline in BMI was similar in both groups ($P=0.342$). The monitored laboratory parameters (albumin and prealbumin) also declined in the postoperative period. The mean albumin level dropped from 39.5 ± 4.14 g/L to 34.4 ± 4.87 g/L, and the mean prealbumin levels dropped from 0.22 ± 0.06 g/L to 0.15 ± 0.04 g/L. Although the declines

of these parameters were more noticeable in the no-ONS group than in the ONS group, the differences between groups were not significant ($P=0.098$ and $P=0.460$, respectively).

Parameters related to body composition, muscle strength, and self-sufficiency are presented in Table 4. The analysis of body composition before surgery revealed that the mean proportion of muscle mass was $69.9\% \pm 8.5$, the mean proportion of water was $51.2\% \pm 6.3$, and the mean proportion of fat was $28.3\% \pm 10.5$. The proportions of muscle mass and water weight were not significantly different between groups. Patients in the no-ONS group had a lower mean fat percentage than patients in the ONS group, but the difference was not statistically significant ($P=0.108$ before surgery, $P=0.095$ after surgery). The

groups had comparable preoperative and postoperative arm circumference measurements ($P=0.157$ and $P=0.118$, respectively).

Self-sufficiency (assessed with the Barthel index) was comparable between groups, before and after surgery ($P=0.862$ and $P=0.313$, respectively). Dynamometric measurements showed that muscular strength in the upper limbs did not change after the surgery (preoperative values were nearly equal to postoperative values). There was a slight reduction in the force of the lower limbs after surgery (mean preoperative strength 15.6 ± 4.53 kg, and mean postoperative strength 14.6 ± 4.61 kg), but no significant difference was observed between groups (preoperative $P=0.496$ and postoperative $P=0.579$).

DISCUSSION

To the best of our knowledge, all previous clinical studies were focused on the correlation between ONS and postoperative morbidity. In contrast, the primary focus of the present study was to investigate the effect of ONS on physical status, nutritional status, and postoperative self-sufficiency. Thus, the innovative concept of our study provided data on different aspects of perioperative nutritional support.

Our patients had demographic and clinical characteristics comparable to those reported in recent nutritional clinical studies that were subsequently cited in various meta-analyses^{6-10,15-17}. According to the NRS 2002 score, all of our study patients were at nutritional risk; however, malnutrition was diagnosed in only 29.2% of patients. Colorectal cancer had induced weight loss in 35.6% of patients. The prevalences of nutritional risk and malnourishment in our study were consistent with those reported previously^{2,18-20}.

Previous studies have unequivocally shown that malnutrition was associated with many negative postsurgical consequences, such as impaired wound healing, decreased muscle strength, compromised defense against infections, prolonged recovery after surgery etc.^{3,21-23}. Without doubt, malnourished patients should receive ONS prior to surgery. However, these patients represent a minor proportion of patients that undergo elective colorectal cancer surgery.

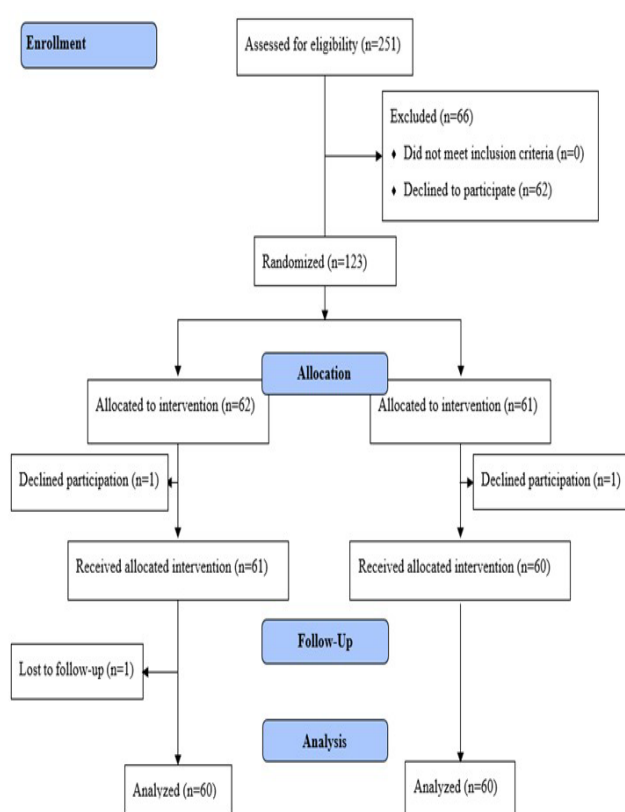


Fig. 1. CONSORT diagram.

Table 3. Perioperative outcomes of patients that underwent surgery for colorectal cancer.

Parameter	All (n=120)	Intervention (n=60)	Control (n=60)	P
Complications, n(%)				
Clavien-Dindo I	23 (19.2%)	14 (23.3%)	9 (15.0%)	0.520
Clavien-Dindo II	9 (7.50%)	3 (5.00%)	6 (10.0%)	
Clavien-Dindo III	7 (5.83%)	4 (6.67%)	3 (5.00%)	
Clavien-Dindo IV	1 (0.83%)	0 (0.00%)	1 (1.67%)	
Clavien-Dindo V	1 (0.83%)	1 (1.67%)	0 (0.00%)	
All	41 (34.2%)	22 (36.7%)	19 (31.7%)	0.73
ICU stay (days), Mean \pm SD	3.94 \pm 3.13	3.42 \pm 2.46	4.45 \pm 3.61	0.073
Hospital stay (days), Mean \pm SD	11.0 \pm 8.45	10.9 \pm 8.95	11.2 \pm 8.00	0.855

Table 4. Pre- and post-operative body composition, muscle strength, and self-sufficiency in patients that underwent surgery for colorectal cancer.

Parameter	All (n=120)	Intervention (n=60)	Control (n=60)	<i>P</i>
Muscle weight (%), Mean \pm SD				
Admission	69.6 \pm 8.5	67.3 \pm 8.2	71.9 \pm 8.2	0.607
Follow up	70.1 \pm 8.2	67.7 \pm 7.4	72.3 \pm 8.3	0.645
Water weight (%), Mean \pm SD				
Admission	51.2 \pm 6.3	52.6 \pm 6.1	49.7 \pm 6.2	0.724
Follow up	51.2 \pm 6.1	52.6 \pm 6.2	49.7 \pm 5.7	0.877
Fat weight (%), Mean \pm SD				
Admission	28.3 \pm 10.5	29.3 \pm 9.7	27.3 \pm 10.9	0.108
Follow up	26.8 \pm 8.8	27.6 \pm 7.7	26.0 \pm 9.5	0.095
Arm circumference (cm), Mean \pm SD				
Admission	29.7 \pm 3.95	30.2 \pm 4.45	29.2 \pm 3.34	0.157
Follow up	29.1 \pm 3.66	29.7 \pm 3.89	28.6 \pm 3.38	0.118
Muscular strength of the upper limbs (kg), Mean \pm SD				
Admission	10.5 \pm 3.73	10.3 \pm 3.05	10.8 \pm 4.32	0.486
Follow up	10.5 \pm 3.84	10.3 \pm 3.10	10.7 \pm 4.48	0.560
Muscular strength of the lower limbs (kg), Mean \pm SD				
Admission	15.6 \pm 4.53	15.8 \pm 4.33	15.3 \pm 4.73	0.496
Follow up	14.6 \pm 4.61	14.3 \pm 4.55	14.8 \pm 4.70	0.579
Barthel index (points), Mean \pm SD				
Admission	96.8 \pm 5.22	96.8 \pm 4.77	96.9 \pm 5.68	0.862
Follow up	88.0 \pm 12.9	89.2 \pm 9.51	86.8 \pm 15.6	0.313

In contrast, for the majority of patients with colorectal cancer, there is no evidence that patients at nutritional risk, but not malnourished, might profit from ONS. Nevertheless, current ESPEN guidelines recommend (strong consensus, GPP grade of recommendation) peri-operative nutritional therapy to all patients at nutritional risk (recommendation No. 7) (ref.⁴). However, the published data that support this ESPEN recommendation are unconvincing.

Clinical studies published on this topic have shown contradictory outcomes. Some authors report a positive effect of preoperative ONS on the postoperative complications rate, but other studies reported no effect⁷⁻¹². Several authors have found no significant effect of ONS on the postoperative course, when ONS was given to all patients undergoing colorectal cancer surgery^{6,10,15,16}. A recent meta-analysis published by E. Bruns failed to show a significant reduction in the overall complications rate in patients that received ONS. The same lack of effect was found for the hospital and ICU stays⁶. Our study also showed no significant difference between groups regarding the postoperative morbidity, hospital stay, or ICU stay (Table 3). In fact, we found a slightly higher number of postoperative complications in patients that received ONS than in those without ONS (36.7% vs. 31.7%, $P=0.73$).

We evaluated nutritional status with a standardized questionnaire (NRS 2002), laboratory parameters, and anthropometric measurements. Our outcomes (BMI, albumin level, prealbumin level, and the NRS 2002 score) showed that all patients with stages I–III colorectal cancer were at nutritional risk, but only 1/3 were malnourished. Indeed, the nutritional parameter values measured in pa-

tients that received ONS were not significantly different than those measured in the control group. The fact that a majority of patients with colorectal cancer were not malnourished might explain why most available studies have failed to show a significant benefit of ONS for patients undergoing colorectal surgery^{6-10,15,16}.

In our study, we analyzed body composition to determine whether ONS administration increased the proportion of muscle mass in patients. However, our data did not confirm this hypothesis; we recorded slight decreases in muscle mass in both study groups after surgery. Thus, according to our data, preoperative ONS had no influence on body composition or the proportion of muscle mass.

The present study focused on whether ONS administration could improve patient self-sufficiency in the postoperative period (assessed with the Barthel index). Normally, self-sufficiency declines postoperatively, as a consequence of surgical trauma and perioperative stress. As shown in Table 4, the fall in the Barthel index was more distinct among patients without ONS than among patients with ONS, but the difference was not significant. No previous study has examined the effect of ONS on patient self-sufficiency; therefore, we could not compare our findings with other data. However, two studies by Gillis and Smedley investigated the association between ONS and patient quality of life at one month after surgery. Both of those studies failed to show a higher quality of life in patients that received ONS (ref.^{11,16}).

Muscular strength is an important clinical parameter that influences patient self-sufficiency and recovery after the surgery. Measurements of muscular strength provide an objective functional assessment of nutritional status;

a decline in muscular strength is considered a sign of malnutrition and a predictor of postoperative morbidity²⁴. In our study, upper limb strength did not change during the postoperative period. We did observe a decline in lower limb strength after surgery, probably due to limited postoperative mobility and prolonged bed rest. However, our muscular strength measurements were not significantly different between study groups. Moreover, the dynamometric measurements did not show a positive effect of ONS on muscular strength during the postoperative period.

The strengths of this study were the study design (a prospective controlled randomized clinical trial), the innovative study concept of investigating different aspects of perioperative ONS administration, and the complex assessment of nutritional status in study patients (i.e., standardized questionnaire NRS 2002, laboratory parameters, and anthropometric measurements). Nevertheless, this study has several limitations. The study sample size was not calculated by a statistician prior to the study; the heterogeneity in operative techniques could have influenced postoperative recovery; and the limited sample size could have introduced a selection bias.

CONCLUSION

In conclusion, to the best of our knowledge, this clinical trial was unique in its aim to investigate the effects of pre-operative ONS on the physical and nutritional statuses of patients that underwent an elective colorectal resection. We found that preoperative ONS for patients undergoing elective colorectal surgery did not reduce postoperative morbidity or enhance recovery. Specifically, patient self-sufficiency, physical status, and nutritional status were not influenced by preoperative nutritional support. Although ONS administration did not harm the patient, patients should be properly selected for malnutrition before providing nutritional support to improve the cost effectiveness of this intervention.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the University Hospital Ostrava (ref. Number 447a/2018). It was performed in accordance with the ethical standards of the Declaration of Helsinki (1964) and its subsequent amendments. Written informed consent was obtained from all included patients, and anonymity was ensured. The trial was registered at <http://www.clinicaltrials.gov> (trial identifier NCT 03930888).

Acknowledgement: Supported by Ministry of Health, Czech Republic – conceptual development of research organization (FNOs/2018).

Author contributions: MT: data curation, investigation, project administration, original draft; VK: investigation, methodology, project administration, visualization; LM: formal analysis, methodology, review and editing; SD: conceptualization, validation, review and editing; PI:

conceptualization, formal analysis, funding acquisition, methodology, resources, validation, review and editing.

Conflict of interest statement: The authors state that there are no conflicts of interest regarding the publication of this article.

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