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Влияние раннего перорального питания на нутритивный статус пациентов после субтотальной эзофагэктомии с одномоментной пластикой пищевода желудочной трубкой: рандомизированное одноцентровое исследование

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АННОТАЦИЯ

Обоснование. Давно доказана польза раннего начала перорального питания в послеоперационном периоде, однако в хирургии пищевода всё ещё отдают предпочтение другим способам нутритивной поддержки после эзофагэктомии с одномоментной пластикой желудочной трубкой.

Цель исследования — сравнить эффективность, безопасность и нутритивный статус пациентов после субтотальной эзофагэктомии и одномоментной пластики пищевода желудочной трубкой при начале перорального и полного парентерального питания в раннем послеоперационном периоде.

Материалы и методы. Проведено проспективное рандомизированное одноцентровое исследование. Всем пациентам (n=60) выполнили эзофагэктомию с одномоментной пластикой желудочной трубкой. До операции и в 1; 3; 6-й послеоперационные дни осуществляли оценку результатов лечения, частоты и характера осложнений, а также антропометрических и лабораторных показателей нутритивного статуса.

Результаты. В исследование включили пациентов без высокого риска развития нутритивной недостаточности. Больных разделили на две группы: пациенты основной группы (n=30) получали раннее (с первого послеоперационного дня) пероральное питание; пациенты контрольной (n=30) — классическую схему нутритивной поддержки (полное парентеральное питание в течение 4 послеоперационных дней). В основной группе отмечены достоверно более раннее отхождение газов (2 дня против 4 в группе контроля, p=0,000042) и появление стула (3 дня против 5 в группе контроля, p=0,000004) после операции, а также тенденция к снижению длительности послеоперационной госпитализации (8 дней против 9 в группе контроля, p=0,13). Раннее пероральное питание не влияло на частоту (46,6 против 53,3% в группе контроля, p=0,66) и характер послеоперационных осложнений. При анализе показателей нутритивного статуса отмечено влияние начала раннего перорального питания на концентрацию преальбумина в сыворотке крови, уровень которой достоверно снижался на 3-й послеоперационный день (0,17 против 0,2 в группе контроля, p=0,03) в связи с невозможностью восполнения суточной нормы калорий в первые дни после операции. На 6-й послеоперационный день концентрация преальбумина была сопоставимой в обеих группах. Других достоверных отличий между группами не было.

Заключение. Раннее пероральное питание после эзофагэктомии с одномоментной пластикой желудочной трубкой безопасно, т.к. не увеличивает частоту несостоятельности анастомоза и других осложнений. При оценке нутритивного статуса отмечено снижение уровня преальбумина на 3-й послеоперационный день при начале раннего перорального питания.

Ключевые слова: эзофагэктомия; пластика пищевода; нутритивная поддержка; раннее пероральное питание; ускоренная реабилитация.

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The effect of early oral feeding after subtotal esophagectomy with immediate esophageal reconstruction on patients' nutritional status: randomized single-center study

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ABSTRACT

BACKGROUND: The efficiency of early oral feeding in the postoperative period is well known. Though doctors still prefer other types of nutritional support after esophagectomy with immediate gastric tube reconstruction in the esophagus surgery.

AIMS: To compare the efficacy, safety and nutritional status of patients after esophagectomy with gastric tube reconstruction while beginning of oral and full parenteral nutrition in the early postoperative period.

MATERIALS AND METHODS: We've conducted prospective single-center randomized study. Subtotal esophagectomy with immediate gastric tube reconstruction was performed to 60 patients. In the postoperative period we evaluated the results of treatment, the frequency and severity of complications, anthropometric and laboratory indicators of the nutritional status before the operation on the first, third and sixth postoperative days.

RESULTS: Patients without high risk of malnutrition were randomly divided in 2 groups: main group (n=30) starting early oral feeding on the first postoperative day and control group (n=30) that remained nil by mouth and got parenteral feeding within 4 postoperative days. The patients of early oral feeding group had statistically significant earlier gas discharge (2 vs 4 postoperative days, p=0.000042) and stool appearance (3 vs 5 postoperative days, p=0.000004). There was a tendency towards a decrease in the duration of postoperative hospitalization in early oral feeding group (8 vs 9 postoperative days, p=0.13). Early oral feeding did not affect on frequency (46.6% vs 53.3%, p=0.66) and character of postoperative complications. After evaluation of the parameters of nutritional status we found statistically significant decrease of prealbumin level on the third postoperative day in early oral feeding group (0.17 vs 0.2, p=0.03) of due to inability to compensate daily calorie needs in the first days after the operation. On the sixth postoperative day prealbumin became the same in both groups. There were no other significant differences between the groups.

CONCLUSIONS: Early oral feeding after esophagectomy with immediate gastric tube reconstruction is safe. Early oral feeding doesn't increase the frequency of anastomotic insufficiency and other complications. The decrease of prealbumin on the third postoperative day was noted in early oral feeding group while evaluating nutritional status.

Keywords: esophagectomy; esophagoplasty; nutrition support; early oral feeding; enhanced recovery after surgery.

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ECO•VECTOR

BACKGROUND

Dysphagia is the main symptom of oesophageal diseases. Of patients with complaints of swallowing difficulties at the initial visit to a doctor, 25% have nutritional deficiency [1]. Dysphagia induces solid food intake restriction up to the complete impossibility of oral intake of nutrients. A radical method of treating oesophageal disorders includes subtotal esophagectomy with immediate gastric tube reconstruction. This technically complex surgery with a high risk of complications is performed in patients with stage IV cardiac achalasia, extended cicatricial stricture and oesophageal cancer. The Society for Enhanced Recovery After Surgery (ERAS) and the European Society for Clinical Nutrition and Metabolism (ESPEN) [2] recommended the need for preoperative assessment of nutritional status, nutritional deficiency corrections before surgery and the early onset of enteral nutrition in the postoperative period. Literature indicates a decreased incidence of postoperative complications in the course of correction and further maintenance of the nutritional status within the normal range [2].

Methods for preoperative nutritional deficiency treatment are described in detail both in the global [3] and Russian literature [1]. Special attitude is paid to enteral nutrient administrations [4], and parenteral nutrition (PN) is auxiliary even in patients with complete dysphagia [5]. In the postoperative period, this category of patients is at risk of developing or aggravating nutritional deficiency; however, the methods of nutritional support provision after surgery remain a matter of debate.

Oesophageal surgery is traditionally prescribed with complete PN in the postoperative period to prevent anastomotic leakage [6]; however, nowadays enteral nutrition is recognised as safe and economically more profitable compared to PN [7]. Enteral nutrition maintains the viability of enterocytes, improves gastrointestinal motility and maintains the intestinal barrier, which reduces the incidence of postoperative complications [8] and the number of hospital postoperative days (POD) [9]. Several ways are available to conduct postoperative enteral nutrition, namely oral, tube (through a nasojejunal tube or jejunostomy), and in most cases after esophagectomy, tube nutrition is recommended [3]. However, when using a nasojejunal tube, 13%–38% of patients experience its displacement or obstruction, as well as intestinal content microaspiration [10]. Soft tissue inflammation at the jejunostomy tube insertion area, parastomal fluid leakage, tube transposition and malabsorption are registered in 44.4% of cases in patients after jejunostomy imposition [11]. Additionally, the jejunostomy tube causes acute intestinal obstruction in 7% of patients due to complete intestinal obstruction [12].

The problem of early oral nutrition (EON) in patients after esophagectomy remains controversial. Currently, the literature provides isolated works on EON studies that showed positive results [13–17]; however, none of the works has assessed the nutritional status of patients with EON.

Four groups of methods are used to assess the patient's nutritional status, namely somatometric (anthropometric), laboratory, functional and clinical [18].

Anthropometric methods assess the nutritional status including body weight, height, body mass index (kg/m^2), shoulder circumference at the middle third level and actual body weight deviation from the recommended and initial value before the disease. Additional indicators for nutritional deficiency diagnostics include the skin-fat fold thickness above the triceps, the shoulder muscle circumference, total fat content and body lean mass, which assesses the somatic protein pool.

Laboratory methods for assessing nutritional status clarify the degree of nutritional deficiency and assess the body's protein supply and assess the visceral pool of protein, which is closely related to the state of protein-synthetic function of the liver, haematopoietic organs and immunity. Therefore, the absolute count of lymphocytes is determined, as well as the concentration of total protein, albumin, transferrin, prealbumin, retinol-binding protein, cholesterol and triglycerides in the blood [19].

Albumin is a protein that is synthesised in the liver, with a half-life of 20 days. With insufficient protein intake in the body, a pronounced albumin synthesis rate decreases with a simultaneously increased decay, as well as redistribution from the interstitial space into the blood plasma. Thus, the change of the albumin level over time is insufficiently reliable for a quick assessment of nutritional therapy adequacy [20]. However, hypoalbuminemia indicates prolonged protein starvation and is an unfavourable prognostic sign of the disease course [21].

Transferrin is a serum β-globulin with a half-life of 8 days, is synthesised in the liver and transports iron in the blood. The extravascular transferrin pool is negligible and the half-life is shorter than that of albumin. Its decreased concentration in the blood serum reveals earlier changes in the protein status; however, with iron deficiency anaemia, a compensatory increase in the blood concentration of transferrin occurs even under protein deficiency conditions [22].

Prealbumin (transthyretin) is synthesised in the liver and participates in the transport of thyroxine and retinol, with a half-life of 2 days. It circulates in the blood in strong complexes with retinol-binding protein. Prealbumin prevents the release of retinol-binding protein from the bloodstream and is responsible for the transfer of retinol into tissues [23].

Cholesterol and triglyceride determination in the blood serum assesses the intensity of lipolysis in the body [24]. The presence of hypertriglyceridemia and hypercholesterolemia indicates active lipolysis under energy deficiency conditions. With a severe nutritional deficiency, hypocholesterolemia may occur.

An absolute count of lymphocytes is a rather simple and informative indicator that assesses the severity of the nutritional deficiency, as the state of the immune system can be characterised by its count. Immunosuppression correlates with the degree of protein and visceral protein pool deficiencies.

Functional assessment methods include metabolic monitoring with the determination of the patient's current energy expenditures.

The screening protocols were developed for the clinical assessment of the degree of nutritional deficiency, namely Nutrition Risk Screening 2002 (NRS-2002), Malnutrition Universal Screening Tool, European Society for Medical Oncology 2008 and others. The NRS-2002 scale is currently generally accepted for assessing nutritional status and is recommended for the Federation of Anaesthesiologists and Reanimatologists, ESPEN and the American Society for Parenteral and Enteral Nutrition.

Safety evaluation of the most physiological method of postoperative nutrient delivery and its effect on the nutritional status of patients is an urgent subject, which is under-analysed.

The study aimed to compare the efficacy, safety and nutritional status of patients after subtotal esophagectomy and immediate oesophageal reconstruction using a gastric tube at the beginning of oral and total PN in the early postoperative period.

MATERIALS AND METHODS

Study design

A prospective, experimental, randomised, controlled and single-centre study was performed. Patients were distributed into two groups, namely the main group (n=30) where the EON protocol was used, and the control group (n=30) with complete PN within 4 POD.

Inclusion criteria

The study included patients with malignant oesophageal tumours, oesophageal cicatricial strictures and stage IV cardiac achalasia, with a history of transthoracic or transhiatal esophagectomy with immediate posterior mediastinal reconstruction using an isoperistaltic gastric tube. Patients were operated on by the same surgeon with standardised anaesthetic management.

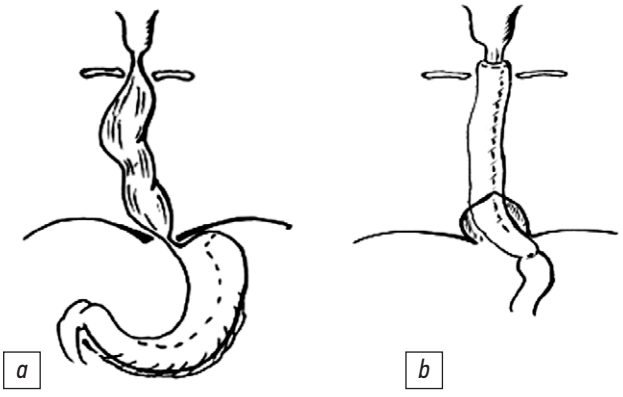

Fig. 1. Surgery scheme: esophagectomy with immediate isoperistaltic gastric tube reconstruction: *a* — before surgery, *b* — after surgery.

Study conditions

The study was performed at the A.V. Vishnevsky National Medical Research Center for Surgery of the Ministry of Health of Russia. Controlled follow-up of each patient was performed on the eve of the surgery, on PODs 1, 3 and 6.

Study duration

The study was performed from January 2016 to March 2021. Patients were monitored throughout the entire perioperative period, from the hospital admission, on the eve of the surgery, and until hospital discharge.

Description of the medical intervention

Before a hospitalisation, patients were examined by a multidisciplinary team of doctors, and individual preoperative plans were drawn up.

Food intake was stopped 6 h before the surgery, and the patient drank 200 ml of a high-carbohydrate drink 2 h before anaesthesia induction, excluding patients with a high risk of aspiration (cardiac achalasia and high oesophageal stricture). Premedication and mechanical bowel preparations were not prescribed. Purpose-oriented infusion therapy, protective lung ventilation and warming of the patient were intraoperatively performed. Thromboembolic complications, postoperative nausea and vomiting and multimodal analgesia preventions were performed during the entire perioperative period.

Figure 1 presents the surgical scheme. After the cervical esophagogastric anastomosis formation, the operating surgeon decided the possibility of EON for patients based on satisfactory viability of the oesophageal stump and the graft and the absence of technical errors in the anastomosis formation. With a positive decision, the patients were randomised into groups using an online random number generator. At the end of the surgery, the trachea was immediately extubated.

Figure 2 presents the protocol of postoperative nutritional support for patients in the main and control groups. Patients of the EON group on POD 1 were allowed to drink water, and sipping with balanced cocktails at the rate of 10 kcal/kg was permitted on POD 2. On POD 3, the energy value of the sipping was increased to 20 kcal/kg, and patients switched to mashed food intake on POD 4. PN with official mixtures of 30 kcal/kg was prescribed to patients in the control group from POD 1 to POD 4. Patients began to drink water on POD 5, started sipping at 10 kcal/kg on POD 6, and the intake was prescribed with mashed food on POD 7. Perioperative transfusion of albumin and fresh frozen plasma was not performed.

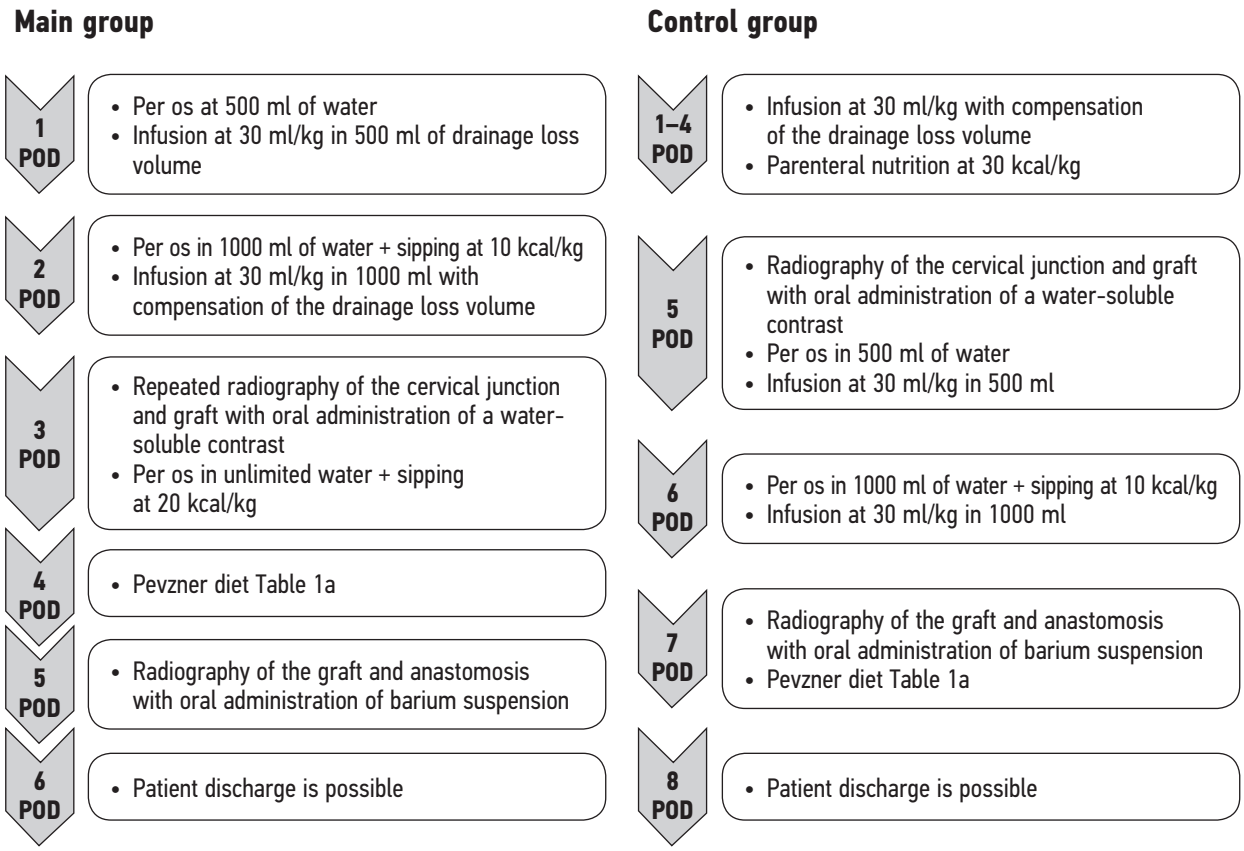

Fig. 2. The protocol of postoperative nutritional support for patients of the main and control groups.
Note. POD: postoperative day.

In the EON group, Nutridrink and Nutricomp Drink Plus were used for nutritional support with a ratio of proteins, fats and carbohydrates of 5.9 g/100 ml, 5.8 g/100 ml and 18.4 g/100 ml and 6 g/100 ml, 5 g/100 ml and 20 g/100 ml, respectively. Patients in the control group received drugs Oliclinomel N7-1000E, Nutriflex 48/150 lipid and Nutriflex 70/180 lipid with a ratio of proteins, fats and carbohydrates of 4 g/100 ml, 4 g/100 ml and 16 g/100 ml; 3.8 g/100 ml, 4 g/100 ml and 12 g/100 ml; and 5.6 g/100 ml, 4 g/100 ml and 14.4 g/100 ml, respectively, for nutritional support.

On average, the ratio of nutrients in mixtures was 5.95 g/100 ml (5.9–6) of proteins, 5.4 g/100 ml (5–5.8) of fats 19.2 g/100 ml (18.4–20) of carbohydrates for the EON group, whereas 4.5 g/100 ml (3.8–5.6), 4 g/100 ml and 14.1 g/100 ml, respectively, in the control group [12–16]. Thus, the groups did not significantly differ in the composition of nutrients used for nutritional support of drugs and can be comparable.

Study outcomes

The main study outcomes. Safety intervention parameters, namely duration of hospitalisation, the term of gas discharge and the recovery of bowel movements, the assessment of the nature of complications and their severity according to the Clavien–Dindo classification of surgical complications [25], and the Esophagectomy Complications Consensus Group (ECCG) [26], were used in the study.

Additional study outcomes. The study evaluated anthropometric (body weight, kg; thickness of the skin-fat fold above the triceps, mm) and laboratory (albumin, g/l; prealbumin, g/l; transferrin, g/l; blood serum iron, μmol/l; cholesterol, mmol/l; triglycerides, mmol/l; C-reactive protein, mg/l; and lymphocytes, 10^9/l) indicators of the nutritional status of patients.

The functional activity assessment of patients was performed before the surgery, on PODs 3 and 6 using a 6-min walk test (the patient's task was to walk the maximum distance in 6 min at his own pace).

Subgroup analysis

Inclusion criteria include the consent of the operating surgeon to EON, based on a visual assessment of the viability of the graft and oesophageal stump and the absence of technical errors in the anastomosis formation; low risk of nutritional deficiency in the postoperative period.

The following are the exclusion criteria of the study:

- the severity of the patient's condition and postoperative complications that prevent X-ray control of the cervical anastomosis on POD 1;
- aspiration detected on POD 1 during X-ray control of esophagogastric anastomosis;
- impossibility of the patient to fulfil all the doctor's recommendations due to the initial cognitive impairment;

- presence of nutritional deficiency (<3 points on the NRS-2002 scale). Based on the type of nutritional support in the postoperative period, patients were divided into two groups:

1) Group 1 (main (*n*=30) with EON starting from POD 1;
2) Group 2 (control (*n*=30) with PN starting from POD 1 and oral nutrition started on POD 5.

Patients were intraoperatively randomised into groups using a random number generator after cervical esophagogastric anastomosis formation.

Outcome registration methods

The researcher filled in individual registration cards, and entered the preoperative study parameters and the patient's scores on the NRS-2002 scale in them, as well as the postoperative results of tests, radiography, and the 6-min walk test on PODs 1, 3 and 6. These cards recorded the duration of hospitalisation and postoperative complications.

Ethical considerations

The study was approved by the local ethical committee of the A.V. Vishnevsky National Medical Research Center for Surgery of the Ministry of Health of Russia (protocol No. 001-2019 dated January 25, 2019).

Statistical analysis

Principles for calculating the sample size. The sample size was not pre-calculated.

Statistical data analysis methods. Statistical data analysis was performed using Statistica software (data analysis software system), version 6 StatSoft, Inc. 2001, and Microsoft Office Excel 2010. The Shapiro–Wilk test was used to determine the normal distribution. The obtained data with abnormal distribution were presented as a median and 25th and 75th percentile (Me [25; 75]) for statistical analysis. The Mann–Whitney test and Pearson's chi-square test were used to analysing nonparametric data. The Student's *t*-test was used to analyse the parametric data. The indicators at which the criterion value corresponded to *p*-values of <0.05 were considered statistically significant.

RESULTS

Subjects (participants) of the study

The study included 60 patients who are distributed into 2 groups (30 patients in the main group of EON and 30 patients in the control group). Postoperative management of patients in both groups was performed according to the traditional protocol of accelerated rehabilitation, adopted in the hospital. The group characteristics are presented in Table 1.

No statistically significant differences were found between the groups. The group gender compositions did not differ and 43% of women in the main and 40% in the control group corresponded to the epidemiology of oesophageal diseases. The physical examination revealed that most patients had grades II–III on the American Society of Anesthesiologists scale. Most of the surgeries were performed for cardiac achalasia in the EON group, and the main cause of intervention was oesophageal malignant neoplasm in the PN group; however, no significant difference was revealed between the groups (*p*=0.43).

Weight deficit was established in 13% of patients in both groups. Additionally, 37% of the study group and 43.3% of the control group were overweight. A moderate risk of nutritional deficiency was noted in 23.3% of patients in the EON group, whereas in 16.7% of the control group. Patients with a high risk of nutritional deficiency were excluded from the study. Most patients underwent a transhiatal esophagectomy. The transthoracic approach was chosen for oncological reasons or in surgical complications during the oesophageal mobilisation.

Main research findings

The efficiency of EON was assessed by the resumption of gas discharge, the emergence of bowel movements and the duration of hospitalisation (Table 2).

Enteral nutrition in the EON group provided a significantly earlier recovery of intestinal motility in the form of gas discharge (2 [2; 3] versus 4 [3; 6] in the control group, *p*=0.000042) and the emergence of bowel movements (3 [2; 4] versus 5 [4; 7] in the control group, *p*=0.000004).

Postoperative complications occurred in 14 (46.7%) patients of the EON group, whereas 16 (53.3%) in the PN group. One postoperative complication was determined in 13 (33.3%) patients in the EON group and 15 (50%) in the control group. Each group had one (3.3%) patient with a combination of two types of complications. The severity of postoperative complications was assessed according to the Clavien–Dindo classification (Table 3).

All developed complications were attributed to complications of grades II and IIIa. Thus, medical treatment or minimal surgical intervention (puncture treatment of hydrothorax and pneumothorax) was required as a solution. These complications had minimal impact on the course of the postoperative period. No statistically significant difference was found between the incidence of postoperative complications in the main and control groups.

Postoperative complications were classified according to the international complication system of the 2015 ECCG consensus group (Table 4).

Pulmonary complications after surgery were the most common and were registered in 12 (40%) patients of the EON group, including hydrothorax in 10 (33.3%) patients and pneumothorax in 2 (6.7%) patients. Pulmonary complications in the form of hydrothorax were noted in 13 (43.3%) patients in the PN group. All pulmonary complications required puncture treatment in the postoperative period.

Cardiac complications in the form of a hypertensive crisis were recorded in 1 (3.3%) patient in the EON group. Postoperative atrial fibrillation, which requires

Table 1. Characteristics of patients in the main and control groups

Parameter assessed		EON group *n* (%)	PN group *n* (%)	*p*
Number of patients, *n*		30	30	
Gender	Male	17 (57)	18 (60)	0.82
	Female	13 (43)	12 (40)	
Age, years		49 [45; 59]	55 [49; 65]	0.1
ASA grade, class	I	4 (13.3)	3 (10)	0.72
	II	17 (56.7)	17 (56.7)	
	III	9 (30)	10 (33.3)	
Indication for surgery	Benign stricture	9 (30)	8 (26.7)	0.43
	Achalasia	12 (40)	9 (30)	
	Malignant tumour	9 (30)	13 (43.3)	
BMI, kg/m^2	<18.5	4 (13.3)	4 (13.4)	0.53
	18.5–25	15 (50)	13 (43.3)	
	>25	11 (36.7)	13 (43.3)	
NRS-2002, score	0	12 (40)	10 (33.3)	0.94
	1	11 (36.7)	15 (50)	
	2	7 (23.3)	5 (16.7)	
Surgical approach	Transthoracic EE	11 (36.7)	12 (40)	0.82
	Transhiatal EE	19 (63.3)	18 (60)	

Note. EON: early oral nutrition; PN: parenteral nutrition; BMI: body mass index; EE: esophagectomy; ASA (American Society of Anesthesiologists): the scale of the American Society of Anesthesiologists; NRS-2002: Nutrition Risk Screening 2002.

pharmacological cardioversion with subsequent sinus rhythm restoration within 12 h, was detected in 2 (6.67%) patients in the control group.

The main group recorded 2 (6.7%) complications in the gastrointestinal tract organs, namely anastomotic leakage (1, 3.3%) and postoperative intestinal paresis (1, 3.3%). The cervical anastomosis leakage occurred on POD 6 in presence of a hypertensive crisis, accompanied by profuse repeated vomiting. Oesophageal X-ray examination with a water-soluble contrast (PODs 1 and 3) and with barium (POD 5) revealed a consistent anastomosis in the patient. With complete PN, the salivary fistula closed and the patient was discharged on POD 27. Postoperative intestinal paresis accompanied by dynamic intestinal obstruction developed in 1 (3.3%) patient. On the eve of the surgery, the patient underwent mechanical preparation of the large intestine with macrogol (Fortrans) due to the high probability of its use for oesophageal plastic surgery. On POD 3, the patient complained of bloating and abdominal pain, without audible bowel sounds. A plain abdominal X-ray revealed gas levels in the colon. In the conservative treatment, bowel sounds appeared at POD 4, and gases started to discharge. Bowel movements emerged on POD 6.

The control group had gastrointestinal tract organ complications in 1 (3.3%) patient. The esophagogastric anastomosis leakage with a delimited flow was recorded during the repeated oesophageal X-ray with oral administration of a water-soluble contrast on POD 5. Over time, the amount of the flow did not increase, and the contents of the cavity were independently evacuated within 5 min. The patient was discharged from the hospital on POD 15.

Neurological complications were registered in 1 (3.3%) patient of the control group in the form of a transient ischaemic attack. The patient developed right hemiparesis on POD 5. Neurological symptoms independently regressed within 20 min. In the main group, neurological complications were not recorded.

Assessment of the frequency, nature and severity of postoperative complications did not reveal significant differences between the EON and PN groups. The type of nutritional support in the postoperative period did not affect the number and nature of postoperative complications.

Additional research findings

Nutritional status was assessed before surgery, on PODs 1, 3 and 6. Bodyweight changes in both groups

Table 2. Patient treatment results

Parameter assessed	EON group Me [25; 75]	PN group Me [25; 75]	*p*
Number of patients, *n*	30	30	
Gas discharge	2 [2; 3]	4 [3; 6]	0.000042
Emergence of bowel movements	3 [2; 4]	5 [4; 7]	0.000004
Number of PODs	8 [7; 9]	9 [8; 9]	0.13

Note. EON: early oral nutrition; PN: parenteral nutrition; POD: postoperative day.

Table 3. Evaluation of the frequency and severity of postoperative complications according to the Clavien–Dindo classification

Parameter assessed		EON group *n* (%)	PN group *n* (%)	*p*
Number of patients, *n*		30	30	
Total number of patients with complications		14 (46.7)	16 (53.3)	0.66
Postoperative complications	Grade I	-	-	
	Grade II	3 (10)	4 (13.4)	0.69
	Grade IIIa	12 (40)	13 (43.3)	0.8
	Grade IIIb	-	-	
	Grade IV	-	-	
	Grade V	-	-	

Note. EON: early oral nutrition; PN: parenteral nutrition.

Table 4. Evaluation of the nature of postoperative complications by ECCG scale

Parameter assessed	EON group *n* (%)	PN group *n* (%)	*p*
Number of patients, *n*	30	30	
Total number of patients with complications	14 (46.7)	16 (53.3)	0.66
Pulmonary complications:	12 (40)	13 (43.3)	0.8
• hydrothorax (puncture)	10 (33)	13 (43.3)	0.51
• pneumothorax	2 (6.7)	-	0.66
• atelectasis	-	-	
• pneumonia	-	-	
Cardiac complications	1 (3.3)	2 (6.67)	0.57
GIT complications	2 (6.7)	1 (3.3)	0.57
Urological complications	-	-	
Thromboembolic complications	-	-	
Neurological complications	-	1 (3.3)	0.82
Infectious complications	-	-	
Other	-	-	

Note. EON: early oral nutrition; PN: parenteral nutrition; GIT: gastrointestinal tract.

synchronously occurred and did not significantly differ. On POD 1, increased body weight was noted due to a positive water balance attained during the surgery. On PODs 3 and 6, the body weight decreased gradually due to fluid redistribution in the internal environment of the body and excess extracellular fluid removal.

Moreover, the thickness measurement of the skin-fat fold above the triceps did not reveal a significant difference between the groups. On POD 1, the thickness of the skin-fat fold above the triceps increased due to the developing tissue oedema associated with intraoperative positive water balance. On PODs 3 and 6, it synchronously decreased with bodyweight as excess fluid was removed from the body.

Laboratory indicators of nutritional status, which are used to assess protein metabolism, are presented in Table 5.

The albumin concentration before surgery in the EON and PN groups was within the reference values. On POD 1, a decrease in this indicator below normal values was registered in both groups due to intraoperative blood loss. On PODs 3 and 6, the albumin level tended to increase both in the EON and PN group, without a significant difference between the albumin concentrations in both groups.

Serum transferrin level synchronously changed with the albumin level and was within the normal range before the surgery in both groups. A decreased transferrin level was noted due to the intraoperative blood loss on POD 1. By PODs 3 and 6, a gradual increase in this protein in the blood serum was registered but without statistically significant differences either before the surgery or in PODs 1, 3 and 6.

The level of free iron in the blood serum synchronously changed with the transferrin level. Before the surgery, it was within the normal range and decreased by almost 2 times due to intraoperative blood loss on POD 1. The iron level insignificantly changed on POD 3 and tended to increase on POD 6; however, these values corresponded to the iron deficiency state. No significant difference was found between the serum iron levels in both groups.

The blood serum prealbumin level before surgery and on POD 1 in patients of both groups did not significantly differ,

Table 5. Laboratory methods for evaluating nutritional status: protein metabolism

Parameter assessed		EON group Me [25; 75]	PN group Me [25; 75]	*p*
Number of patients, *n*		30	30	
Albumin, g/l	Before surgery	42 [40; 44]	40.5 [39; 43]	0.21
	POD 1	31 [29; 33]	30 [29; 33]	0.33
	POD 3	33.5 [32; 35]	32.5 [31; 34]	0.12
	POD 6	35 [34; 37]	34.5 [33; 37]	0.42
Transferrin, g/l	Before surgery	2.75 [2.01; 3.01]	2.31 [2.04; 2.7]	0.35
	POD 1	1.9 [1.65; 2.15]	1.74 [1.43; 2.13]	0.36
	POD 3	1.86 [1.65; 2.19]	1.76 [1.55; 2.01]	0.31
	POD 6	2.07 [1.81; 2.35]	1.89 [1.7; 2.18]	0.16
Blood serum iron, μmol/l	Before surgery	12.4 [8.9; 16.1]	12.25 [9.2; 18.1]	0.51
	POD 1	5.8 [3.1; 8.2]	4.9 [2.7; 6.8]	0.42
	POD 3	5.9 [4.1; 8.5]	5.65 [4.5; 8.0]	0.79
	POD 6	7 [5.7; 9.3]	6.55 [5.2; 9.1]	0.54
Prealbumin, g/l	Before surgery	0.29 [0.22; 0.39]	0.3 [0.21; 0.41]	0.87
	POD 1	0.18 [0.14; 0.23]	0.2 [0.17; 0.34]	0.09
	POD 3	0.17 [0.13; 0.21]	0.2 [0.16; 0.34]	0.03
	POD 6	0.25 [0.19; 0.34]	0.23 [0.18; 0.3]	0.7
CRP, mg/l	Before surgery	4.5 [2.5; 7.3]	4.55 [3; 7]	0.51
	POD 1	94.5 [78; 108]	103 [76; 134]	0.54
	POD 3	52 [38; 80.1]	71.5 [40; 86]	0.43
	POD 6	30 [23; 35]	32.5 [24; 45]	0.47

Note. EON: early oral nutrition; PN: parenteral nutrition; CRP: C-reactive protein.

as, before the surgery, it was within the normal range, and it decreased on POD 1. However, it was significantly lower in the EON group than in the traditional PN group on POD 3. The difference between the groups levelled off on POD 6.

The blood plasma level of C-reactive protein was measured to assess the overall level of the systemic inflammatory response and was within the reference values before the surgery. On POD 1, its twenty-fold increase was noted and tended to decrease towards its gradual on PODs 3 and 6; however, without normal indicator restoration. No significant differences were found between the groups in the C-reactive protein levels.

Laboratory assessment results of the nutritional status, which assess lipid metabolism and immunity level, are presented in Table 6.

The serum cholesterol level before surgery in both groups was within the reference values. On POD 1, its decrease was noted, and a gradual increase in the level of cholesterol was registered in PODs 3 and 6; however, no significant difference was found between the groups before the surgery, on PODs 1, 3 and 6.

The triglyceride concentration in blood plasma before surgery in the main group was within normal values. A decreased level of triglycerides in both groups was noted on POD 1, the concentration increased and became higher than the initial one on POD 3, and a further increased indicator on POD 6. No significant difference was determined between the groups.

The absolute lymphocyte count as an indicator of the immune status of patients in both groups did not have a statistical difference since it was at the lower limit of the norm before the surgery, reduced even greater on POD 1, and no significant changes over time in the absolute count of lymphocytes in the EON group on PODs 3 and 6. The count of lymphocytes increased in the control group on POD 3 and became equal to those in the EON group. Additionally, changes over time were not noted on POD 6.

A 6-min walk test was performed to assess the efficiency of early rehabilitation and activation of patients after surgery (Table 7).

Table 6. Laboratory methods for evaluating nutritional status: lipid metabolism, immunity

Parameter assessed		EON group Me [25; 75]	PN group Me [25; 75]	*p*
Number of patients, *n*		30	30	
Cholesterol, mmol/L	Before surgery	4.65 [4.32; 5.32]	4.89 [4.37; 5.56]	0.3
	POD 1	3.14 [2.93; 3.67]	3.35 [2.76; 4.06]	0.62
	POD 3	3.48 [3.32; 3.92]	3.79 [3.06; 4.31]	0.64
	POD 6	4.26 [4.04; 4.65]	4.12 [3.54; 4.87]	0.43
Triglycerides, mmol/L	Before surgery	1.16 [1.11; 1.48]	1.17 [0;98; 1.34]	0.53
	POD 1	1.02 [0.88; 1.14]	0.98 [0.78; 1.09]	0.23
	POD 3	1.33 [1.17; 1.41]	1.34 [1.17; 1.83]	0.63
	POD 6	1.45 [1.26; 1.78]	1.54 [1.28; 1.85]	0.56
Lymphocytes, 10^9/L	Before surgery	1.84 [1.45; 2.09]	1.77 [1.12; 2.24]	0.58
	POD 1	1.46 [0.96; 2.1]	1.31 [0.88; 2.09]	0.87
	POD 3	1.41 [1.07; 1.85]	1.5 [1.06; 2.09]	0.75
	POD 6	1.45 [1.06; 1.84]	1.45 [1.22; 2.01]	0.73

Note. EON: early oral nutrition; PN: parenteral nutrition.

Table 7. Results of the 6-minute walk test

Parameter assessed		EON group Me [25; 75]	PN group Me [25; 75]	*p*
Number of patients, *n*		30	30	
6-minute walk test, m	Before surgery	550 [480; 610]	505 [460; 580]	0.16
	POD 3	345 [280; 390]	300 [250; 350]	0.17
	POD 6	450 [410; 480]	380 [330; 410]	0.0002

Initially, the indicators of the functional activity of both groups did not significantly differ. The results of the 6-min walk test in patients of both groups on POD 3 were worse than the initial ones; however, the difference between the groups remained insignificant and patients who received the EON significantly tolerated physical activity better on POD 6.

Adverse events

No adverse events were registered. The incidence of postoperative complications in both groups did not significantly differ.

DISCUSSION

Summary of the main research finding

EON after subtotal esophagectomy with immediate isoperistaltic gastric tube reconstruction is safe because it does not increase the incidence of anastomotic leakage and other complications. An early start of oral nutrition contributes to a significantly earlier gas discharge, the emergence of bowel movements and the restoration of physical activity in patients.

Discussion of the main research results

The introduction of EON in minimally invasive surgery has demonstrated its safety, without increasing the number of postoperative complications [13–17], which was also confirmed by our research.

According to various sources, complications after esophagectomy are detected in 20.5%–63.5% of cases [27]. The most common are pulmonary complications, particularly, pneumonia, which is registered in 22.6%–30.7% of cases [27, 28]. Our results revealed the overall percentage of complications in the EON group and the control group as 46.7% and 53.3%, respectively. Pulmonary complications were noted in 40% of patients in the EON group and 43.3% in the PN group; however, their treatment required only a single pleural cavity puncture. Postoperative pneumonia did not occur in our study.

The second most frequent complication after esophagectomy is the esophagogastric anastomosis leakage, which is registered in 19.7% of cases [29]. Anastomotic leakage was detected in 3.1% of patients in our study.

Cardiac complications are noted in 13.5% of patients after esophagectomy [29] and are the third most common, wherein 3.3% of cases in the EON group and 6.67% in the control group but without statistical insignificance (p=0.57).

Postoperative mortality after esophagectomy with simultaneous plastic surgery ranges from 0% to 5.4% when performing surgery due to benign oesophageal diseases [30], and up to 7.8% in patients with cancer [31, 32]. Our study did not register lethal cases.

Anthropometric indicator assessment of nutritional status did not reveal significant differences between both groups. Laboratory parameter assessment of protein metabolism registered synchronous changes in the levels of albumin, transferrin and prealbumin. Before the surgery, they were within the reference values, and a sharp decrease in the blood plasma protein level was noted on POD 1. Their number gradually increased on PODs 3 and 6 but did not reach the initial values. Prealbumin has the shortest half-life; therefore, its concentration best reveals the efficiency of nutritional support. Its level significantly decreased on POD 3 in the EON group due to the impossibility of replenishing the daily calorie intake in the first days after the surgery. The albumin level was comparable in both groups on POD 6. No other significant differences were established between the groups. Evaluation of laboratory parameters of fat metabolism and the absolute count of lymphocytes also did not show significant differences in both groups.

Research limitations

When planning and conducting the study, the sample size was not calculated to achieve the required statistical power of the results. Therefore, the sample of participants obtained during the study cannot be considered sufficiently representative and does not extrapolate the results obtained and their interpretation to the general population of similar patients beyond the study.

CONCLUSION

EON in patients with a history of esophagectomy is safe and effective. The inclusion of EON in the concept of perioperative maintenance of esophagectomy, along with other principles of accelerated rehabilitation does not increase the incidence of postoperative complications; however, it improves the quality of recovery, enhances patient's comfort and avoids specific complications associated with complete PN and enteral nutrition through a nasojejunal tube or jejunostomy. However, its use in routine work is advisable as a component of the perioperative maintenance protocol in specialised hospitals.

ADDITIONAL INFORMATION

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Authors' contribution. N.B. Kovalerova performed anaesthetic support and supervision of patients, reviewed the literature, collected and analysed the literary sources, and prepared and wrote the text of the article; D.V. Ruchkin performed the surgical treatment of patients and wrote and edited the text of the article; G.P. Plotnikov wrote and edited the text of the article. All authors made a substantial contribution to the conception of the work, research and preparation of the article, and read and approved the final version before its publication.

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