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NUTRITION CLINIQUE et MÉTABOLISME

Nutrition clinique et métabolisme 32 (2018) 178–183

Original article

Preoperative immunonutrition for esophageal cancer

Immunonutrition préopératoire pour le cancer de l'œsophage

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Received 4 March 2018; received in revised form 4 June 2018; accepted 7 June 2018
Available online 13 July 2018

Abstract

Introduction. – Preoperative malnutrition is a demonstrated risk factor for adverse outcomes after esophagectomy. Optimizing patients' nutritional and immunological status may have beneficial impact.
Objective. – The aim of the present study was to evaluate the impact of preoperative oral immunonutrition (IN) on postoperative outcomes after oncological esophagectomy.
Methods. – Retrospective single-centre study of consecutive patients operated for esophageal cancer between 2011-2015. IN was introduced in our institution in 2013 and was given 7 days preoperatively. IN patients were compared to a control group in terms of postoperative complications, mortality and length of stay.
Results. – Thirty-eight IN patients were compared to 38 control patients, with comparable baseline characteristics. Seven (19%) and 11 (31%) patients were malnourished preoperatively in IN and control groups respectively (*P = 0.209*). Overall complication rate was 74% in the IN group and 68% in the control group (*P = 0.801*). Major complications occurred in 13 patients (34%) in the IN versus 8 patients (21%) in the control group (*P = 0.192*) and there was no significant difference in terms of mortality (respectively 11 vs. 3%, *P = 0.358*). Median length of stay was significantly higher in the IN group (24 days, IQR 14-53) than in controls (16 days, IQR 12-23, *P = 0.034*).
Conclusion. – A positive impact of IN on postoperative outcomes after oncological esophagectomy could not be measured.

Keywords: Esophageal cancer surgery; Immunonutrition; Outcomes

Résumé

Introduction. – La dénutrition préopératoire est un facteur de risque de résultats indésirables après œsophagectomie. L'optimisation de l'état nutritionnel et immunologique des patients pourrait donc avoir un impact bénéfique sur les résultats postopératoires.
But. – Le but de l'étude était d'évaluer l'impact de l'immunonutrition (IN) orale préopératoire sur les complications postopératoires après œsophagectomie oncologique.
Méthodes. – Étude rétrospective monocentrique de patients opérés consécutivement d'un cancer de l'œsophage entre 2011 et 2015. L'IN a été introduite dans notre institution en 2013 et est administrée 7 jours avant l'intervention. Les patients du groupe IN ont été comparés à un groupe témoin en termes de complications postopératoires, de mortalité et de durée de séjour.
Résultats. – Trente-huit patients IN ont été comparés à 38 patients contrôles. Les données démographiques étaient comparables. Le taux global de complications était de 74 % dans le groupe IN et de 68 % dans le groupe témoin ($p = 0{,}801$). Des complications majeures sont survenues chez 13 patients (34 %) du groupe IN versus 8 patients (21 %) dans le groupe témoin ($p = 0{,}192$) et il n'y avait pas de différence significative en termes de mortalité (respectivement 11 vs 3 %, $p = 0{,}358$). La durée médiane de séjour était significativement plus élevée dans le groupe IN (24 jours) que chez les contrôles (16 jours, $p = 0{,}034$).

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https://doi.org/10.1016/j.nupar.2018.06.003

Conclusion. – Un impact positif de l'IN sur les résultats postopératoires après œsophagectomie oncologique n'a pas pu être mesuré.

Mots clés : Cancer de l'œsophage ; Immunonutrition ; Chirurgie ; Complications

1. Abbreviations

IN	immunonutrition
ESPEN	European Society for Parenteral and Enteral Nutrition
BMI	body mass index
NRS	nutritional risk score
CCI	Comprehensive Complication Index
LOS	length of stay

2. Introduction

Patients who require elective surgery for esophageal cancer often present with preoperative malnutrition in up to 30% of cases (weight loss > 10% at diagnosis) [1]. Malnutrition is one of the most important modifiable risk factors for negative clinical outcomes and decreased quality of life [2,3]. In recent years, emphasis has been given to the impact of improving nutritional status on perioperative and even long-term outcomes of surgical oncologic patients [4,5]. It has been suggested that optimization of nutritional status may decrease overall and infectious complications after major gastrointestinal surgery [5,6]. New formulas have emerged, with agents that modulate the immune system (glutamine, arginine, omega-3 fatty acids and ribonucleic acid) with beneficial effects on the acute stress response [7,8]. Thus, immunonutrition (IN) is increasingly used preoperatively before major surgery as it has been suggested to provide a decrease in postoperative complication rates and hospital stay [9,10]. The current European Society for Parenteral and Enteral Nutrition (ESPEN) guidelines recommend oral/enteral IN in upper gastrointestinal cancer patients undergoing surgical resection [11]. However, the evidence is weak and controversial, and robust data for the use of IN in patients with esophageal cancer are currently lacking.

The aim of the present study was to evaluate the effect of preoperative oral IN on postoperative morbidity and mortality after oncological esophagectomy.

3. Methods

3.1. Study design and participants

Following a meta-analysis on major abdominal surgery conducted in our department, IN (Oral Impact®) has been systematically introduced in May 2013 [9]. Three sachets (74 g) per day were given for 7 days preoperatively. In the current retrospective single-center study we analysed all consecutive patients operated for esophageal cancer with curative intent between 2011-2015, and separated them in two groups. Patients who received IN were compared to a control group, operated before the date of IN introduction. There were no excluded patients. Data were collected prospectively in a computerized coded database for all patients.

Nutritional assessment was performed before surgery by a specialized clinical nutrition team in an outpatient setting. According to this evaluation, patients received some form of preoperative nutritional supplementation by intravenous feeding (StructoKabiven®) or enteral feeding via nasogastric or nasojejunal tube (Isosource® Standard), to which IN was added systematically since May 2013. Preoperative nutritional support and its duration was individually assessed for each patient. In addition, some patients received neoadjuvant treatment and preoperative nutritional support in other hospitals before they were referred. Severe malnutrition was defined as a preoperative weight loss of more than 10% of normal body weight in less than 6 months or a body mass index (BMI) of less than 18.5 kg/m^2, while mild malnutrition was defined as a nutritional risk score (NRS) greater than or equal to 3 according to the Kondrup risk score [12].

The standard operative technique was the transthoracic Lewis procedure, with two-field lymphadenectomy (abdominal and lower mediastinal) for tumors of the oeso-gastric junction (Siewert I and II) and of the lower third. The McKeown procedure was performed for middle third tumors. Tumors of the proximal third were treated by definitive radiochemotherapy, reserving surgical resection for highly selected cases.

Preoperative patient demographics included age, gender, BMI, alcohol abuse, active smoking, malnutrition, ASA score, nutritional supplementation, tumor stage and localisation, and neoadjuvant treatment. Perioperative details included surgical procedure, use of laparoscopy, operative time, blood loss, resection margin (R0/R1/R2) and lymph nodes resected. Complications were graded according to the Clavien classification during 30 postoperative days [13]. Major complications were defined as grade IIIb to IVb, whereas mortality is represented as grade V. Only the highest grade was retained in patients presenting more than one complication. The Comprehensive Complication Index (CCI) was calculated in addition taking into account all postoperative complications and giving thus an estimation of overall morbidity in an individual patient [14]. For complications specific to esophageal surgery, such as anastomotic leakage and conduit necrosis, a recent international consensus was used [15]. Length of stay (LOS) was calculated from day of surgery to discharge at home or to a rehabilitation center.

3.2. Statistical analyses

Quantitative variables were presented as mean (standard deviation) or median (interquartile range) and compared with Student's t test or Mann-Whitney U test if distribution was not normal. Qualitative variables were presented as frequencies (%) and compared with chi-square or Fisher's exact test as appropriate. A P-value ≤ 0.05 was considered statistically significant and all tests were two-sided. Analysis was performed using SPSS 22.0 software (SPSS Inc., Chicago, IL).

4. Results

Thirty-eight patients who received preoperative IN were compared to 38 control patients who did not. There was no significant difference between the comparative groups in terms of demographic or surgical details characteristics (Tables 1 and 2), allowing for direct comparison with no matching needed between the groups.

Postoperative outcomes are detailed in Table 3. The rate of minor complications was higher in the control group, while the rate of major complication was higher in the IN group, however, without significant differences. Note a trend towards higher median CCI in controls (42.3 *vs*. 34.7 in the IN group, $P = 0.125$). There were 4 postoperative deaths (11%) in the IN group *vs.* 1 death (3%) in the control group ($P = 0.358$).

The only significant difference between the two groups was a longer median hospital stay in the IN group (24 *vs*. 16 days in control group, $P = 0.034$).

Table 1
Preoperative patient demographics.

	Immunonutrition, $n = 38$	Controls, $n = 38$	*P-value*
Mean age (SD)	61.7 (7.8)	62.4 (9.0)	0.603
Mean BMI in kg/m^2 (SD)	25.8 (4.7)	24.5 (3.7)	0.220
Male gender, *n* (%)	30 (79)	29 (76)	0.500
Alcohol abuse, *n* (%)	12 (32)	15 (40)	0.632
Active smoking, *n* (%)	13 (34)	14 (37)	1.000
Malnutrition, *n* (%)[a]	7 (19)	11 (31)	0.209
Mean preoperative albumin in g/L (SD)	37 (6.0)	36 (5.8)	0.962
Enteral nutrition, *n* (%)	6 (16)	10 (26)	0.399
Parenteral nutrition, *n* (%)	2 (5)	5 (13)	0.430
Enteral and parenteral nutrition, *n* (%)	2 (5)	3 (8)	1.000
Mean duration of nutritional support, days (SD)[b]	116 (78)	112 (83)	0.877
Tumor localisation: Upper/Middle/Lower third	8/8/22	6/14/18	0.313
Tumor stage, *n* (%)[c]			0.520
Stage 0	1 (3)	0 (–)	
Stage I (A and B)	10 (26)	7 (18)	
Stage II (A and B)	13 (34)	14 (37)	
Stage III (A, B and C)	13 (34)	13 (34)	
Stage IV	1 (3)	4 (11)	
Neoajduvant treatment, *n* (%)[d]	28 (74)	30 (83)	0.394
ASA score, *n* (%)			0.173
I–II	26 (68)	21 (58)	
III–IV	12 (32)	17 (42)	

ASA: American Society of Anesthesiologists; SD: standard deviation.
[a] Severe malnutrition with BMI ≤ 18.5 kg/m^2 or $> 10\%$ weight loss in less than 6 months, or mild malnutrition with nutritional risk score (NRS) ≥ 3.
[b] Missing data for respectively 13 (immunonutrition) and 10 (control) patients.
[c] UICC (Union for International Cancer Control) stage.
[d] Radio- and/or chemo-therapy.

Table 2
Surgical procedures and perioperative details.

	Immunonutrition$n = 38$	Controls, $n = 38$	*P*-value
Surgical procedure, *n* (%)			0.838
Lewis	29 (76)	31 (81)	
Mc Keown	8 (22)	6 (16)	
Transhiatal	1 (3)	1 (3)	
Laparoscopy, *n* (%)	29 (76)	22 (58)	0.142
Operative time, minutes (SD)	309 (68.9)	329 (65.9)	0.278
Estimated blood loss, mL (SD)	242 (158)	243 (183)	0.747
Resection: R0/R1/R2	35/3/0	32/6/0	0.480
Lymph nodes resected, mean (SD)	21 (7.6)	23 (10.0)	0.216

SD: standard deviation.

Table 3
Postoperative complications and clinical outcomes.

	Immunonutrition, $n = 38$	Controls, $n = 38$	P-value
Median LOS (IQR)	24 (14–53)	16 (12–23)	0.034
Median ICU stay (IQR)	4.5 (2–13)	5 (3–10)	0.758
Discharge: home/rehabilitation center	23/15	22/16	1.000
Reintervention, *n* (%)	9 (24)	6 (16)	0.565
In-hospital complications, *n* (%)[a]			
Overall	28 (74)	26 (68)	0.801
Minor (I–IIIa)	11 (29)	17 (45)	0.234
Major (IIIb–IVb)	13 (34)	8 (21)	0.192
Death (V)	4 (11)	1 (3)	0.358
Median CCI (IQR)	34.7 (0–47.4)	42.3 (0–75.6)	0.125
Anastomotic leak, *n* (%)[b]			
Type I	4 (11)	0 (–)	0.058
Type II	1 (3)	1 (3)	0.753
Type III	5 (13)	3 (8)	0.356
Conduit necrosis, *n* (%)[b]			
Type I	1 (3)	1 (3)	0.753
Type II	0 (–)	0 (–)	
Type III	3 (8)	0 (–)	0.120
Deep SSI, *n* (%)	12 (32)	9 (24)	0.609
Superficial SSI, *n* (%)	3 (8)	2 (5)	1.000
Pneumonia, *n* (%)	18 (47)	13 (34)	0.351
Pleural effusion, *n* (%)[c]	12 (32)	9 (24)	0.609
ARDS, *n* (%)	1 (3)	2 (5)	1.000
Arrythmias, *n* (%)	10 (26)	7 (18)	0.583
Delirium, *n* (%)	7 (18)	6 (16)	1.000

LOS: length of stay; IQR: interquartile range; ICU: intensive care unit; CCI: comprehensive complication index; SSI: surgical site infection; ARDS: adult respiratory distress syndrome.

[a] According to Clavien classification [13].

[b] According to ECCG consensus [15].

[c] Pleural effusion requiring drainage.

5. Discussion

In the present study, no benefit was observed in favour of preoperative IN administration in postoperative outcomes after oncological esophagectomy.

Deep and superficial surgical site infections were similar in both groups, in contrast to what was recently described in a meta-analysis which suggests a decrease in postoperative infectious complications for patients receiving IN [10]. Specifically for esophageal cancer surgery, a review was unable to determine whether IN positively influences key clinical outcomes such as hospital length of stay, postoperative mortality and morbidity [16]. However, a small retrospective study, including 55 esophageal cancer patients, reported fewer postoperative infections for IN compared to a control group (19 *vs.* 35%, $P = 0.007$). In that study, the length of hospital stay was 34 days for IN versus 48 days in the control group ($P = 0.008$). In addition, two meta-analyses focusing on gastrointestinal surgery also showed a significant decrease in the duration of hospital stay with the use of IN (respectively -1.88 and -2.12 days) [9,10]. These findings are not confirmed by our study, where a longer length of stay was observed for the IN group (24 vs 16 days, $P = 0.034$) despite comparable rates of complications between the two groups.

A very important aspect to consider, is the value of IN in relation of the patients' nutritional status. First of all, how can we reliably identify a malnourished patient? Many definitions have been proposed concerning malnutrition and the criteria vary between anamnestic, biometric and biological data. Initially, the ESPEN group recommended the Nutritional Risk Score (NRS-2002) as a screening tool [12]. Studies have proven its reliability to identify patients at risk who benefit from perioperative nutritional support [17,18]. Schiesser et al. clearly showed that nutritional risk defined by the NRS score correlates with the incidence as well as the severity of postoperative complications, with patients with NRS ≥ 3 considered to be at risk [18]. However, a study published by our group showed that early nutritional support based upon NRS only might result excessive supplementation, with potentially deleterious clinical consequences post-operatively [19]. More recently, the new ESPEN guidelines have defined surgical patients at severe nutritional risk by the presence of at least one of the following criteria: weight loss > 10–15% within 6 months, BMI < 18.5 kg/m^2, subjective Global Assessment (SGA) Grade C or NRS > 5, and preoperative serum albumin < 30 g/L in the absence of hepatic or renal dysfunction [20]. Other national guidelines focused more on cancer-associated weight loss and cachexia [21–23]. Of note, the prevalence of malnourished patients undergoing esophageal resection in our study was about 25% according to the definition originally described in 2002 (Kondrup risk score), which is lower than other recent reports, from 30 to 80% [2,12,24,25].

Nutritional support addressing the specific needs of the surgical oncological patient is required to improve outcomes and

reduce the consequences of cancer-associated nutritional decline [3]. In this context, some authors suggest that IN might reduce length and cost of hospital stay, regardless of the patient's nutritional status [26,27]. A previous randomized controlled trial from our center, including patients at nutritional risk in major abdominal surgery, showed no difference in terms of clinical outcomes between preoperative IN and isocaloric iso-nitrogeneous oral feed [28]. However, two other recent randomized studies suggested that IN significantly reduced postoperative infections and length of stay in patients undergoing surgery for cancer in general [29], and major upper gastrointestinal surgery in specific [30]. The benefit seems to be most important in patients with an NRS score of ≥ 5, reducing complication rates by 50% [31].

The timing of supplementation is also subject to controversy. Although in our center IN is administered only during the 7 days preceding the operation, other studies have compared preoperative and perioperative IN with no difference found [7,27]. One randomized controlled trial compared perioperative with postoperative IN administration in oncological surgery, and reported reduced systemic perioperative inflammation and postoperative complications after perioperative administration of IN [32]. Finally, a recent meta-analysis showed that IN significantly reduced overall complications when used before surgery, both before and after operation or after surgery [9].

The main limitation of our study is its retrospective character and a small number of patients. Inference from traditional historical controls may be subject to unknown confounders, although the two groups were well balanced and comparable in terms of baseline characteristics. During the study period, surgeons, surgical technique and perioperative care evolved and thus potentially introduced confounding, which was not adjusted in the stage of analysis. Length of stay was significantly longer in the IN group but a cause-effect relationship cannot be formally affirmed with our study as no other difference in postoperative outcomes was observed. Furthermore, other types of perioperative nutritional support were not considered, including enteral tube feeding or oral hypercaloric/carbohydrate drinks. The nutritional support and its preoperative duration was individually adapted to each patient, without a specific decisional algorithm. In addition, some patients have received neoadjuvant treatment and preoperative nutritional support in other hospitals before they were addressed to our referral center. Another limitation is the fact that the tolerance and compliance with IN have not been evaluated; as it was observed in previous studies, about half of the patients did not consume the recommended dose, with limited compliance mostly due to lack of will and information [28,33].

6. Conclusion

The use of IN before oncological esophagectomy may not show any positive impact on postoperative outcomes in the present series and its routine use cannot be supported yet in every patient.

Ethical standards

The study was approved by Research Ethics Committee, protocol number 2016-00097, and conducted in accordance with the Declaration of Helsinki. Informed consent or substitute for it was obtained from all patients.

Contribution of authors

All the authors have significantly contributed to this article. All authors read and approved the final manuscript.

Financial support

The authors received no financial support of any kind in relation to this study.

Disclosure of interest

The authors declare that they have no competing interest.

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