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ORIGINAL ARTICLE

Compliance with preoperative oral nutritional supplements in patients at nutritional risk—only a question of will?

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BACKGROUND/OBJECTIVES: Preoperative nutrition has been shown to reduce morbidity after major gastrointestinal (GI) surgery in selected patients at risk. In a randomized trial performed recently (NCT00512213), almost half of the patients, however, did not consume the recommended dose of nutritional intervention. The present study aimed to identify the risk factors for noncompliance.

SUBJECTS/METHODS: Demographic ($n = 5$) and nutritional ($n = 21$) parameters for this retrospective analysis were obtained from a prospectively maintained database. The outcome of interest was compliance with the allocated intervention (ingestion of $\geqslant 11/15$ preoperative oral nutritional supplement units). Uni- and multivariate analyses of potential risk factors for noncompliance were performed.

RESULTS: The final analysis included 141 patients with complete data sets for the purpose of the study. Fifty-nine patients (42%) were considered noncompliant. Univariate analysis identified low C-reactive protein levels ($P = 0.015$), decreased recent food intake ($P = 0.032$) and, as a trend, low hemoglobin ($P = 0.065$) and low pre-albumin ($P = 0.056$) levels as risk factors for decreased compliance. However, none of them was retained as an independent risk factor after multivariate analysis. Interestingly, 17 potential explanatory parameters, such as upper GI cancer, weight loss, reduced appetite or co-morbidities, did not show any significant correlation with reduced intake of nutritional supplements.

CONCLUSIONS: Reduced compliance with preoperative nutritional interventions remains a major issue because the expected benefit depends on the actual intake. Seemingly, obvious reasons could not be retained as valid explanations. Compliance seems thus to be primarily a question of will and information; the importance of nutritional supplementation needs to be emphasized by specific patients' education.

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INTRODUCTION

As up to 40% of surgical patients reveal preoperative impaired nutritional conditions, perioperative nutritional support has now been widely accepted as an adjunct of perioperative care.[1,2] There is an increasing body of evidence of its efficacy in reducing postoperative morbidity.[3] In particular, immune-enhancing formulae have proven to be effective in reducing postoperative complications, infections and length of hospital stay.[4–6]

Our group recently conducted a randomized controlled trial in surgical patients undergoing hepato-biliary, upper gastrointestinal (GI) and colorectal surgery in a tertiary referral center in Switzerland comparing immunonutrition (IN) with isocaloric-isonitrogenous nutrition (ICN) (NCT00512213).[7] Besides a trend towards a decrease in severe complications and a shortened ICU stay in the IN group, a superiority of IN in terms of overall and infectious complications as well as length of hospital stay was not observed. A possible reason was that patients' compliance with oral nutritional support was suboptimal, as 42% of patients had a limited intake of oral nutritional support below the recommended daily doses.[6] On the basis of this clinical finding, we hypothesized that the effect of perioperative nutrition could be probably improved by increasing individual patient's compliance. Hence, a thorough assessment would be mandatory to better understand the different reasons impacting on patients' compliance and to develop targeted interventions to improve intake of oral nutritional support.

The aim of the present study was to identify patient- and disease-related risk factors that could predict patients' compliance with preoperative nutritional supplementation.

METHODS

This analysis was conducted using a prospective database from a recent randomized trial (NCT00512213).[7] Briefly, all patients undergoing elective major GI surgery at Lausanne University Hospital (CHUV) underwent routine preoperative nutritional screening using the nutritional risk score (NRS).[8] Patients with a NRS $\geqslant 3$ were eligible for the randomized trial. Major GI surgery was defined as any esophageal, gastric, hepatic, pancreatic, intestinal and colorectal resection for benign and malignant disease or any other intra-abdominal open or laparoscopic procedures lasting >2 h. The present study focused on compliance with preoperative oral nutritional supplements (ONS). All patients were instructed by dedicated nurses who explained and insisted on the ONS preparation process. In order not to reduce appetite by ONS ingestion, patients were advised to take supplements right after the main meal. Further, patients were instructed to report effective oral intake of the allocated nutritional regimen day by day in a dedicated diary. This information was gathered by a study nurse in a prospective database. To objectively assess patient's compliance with the allocated nutritional supplementation, serum arginine and glutamine levels, both constituents of IN, were measured, both before and after

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nutritional intervention and cross-checked in 30 consecutive patients.[7] The study was approved by the institutional review board, and patients provided written consent.

A multitude of patient and disease characteristics ($n=5$) and nutritional parameters ($n=17$), as well as eating and lifestyle habits ($n=4$), were analyzed in order to identify risk factors for low compliance with ONS (Tables 1 and 2).

Outcomes/study end points

The primary end point was compliance with the allocated nutritional regimen. As the recommended dose consists of two-third of the maximum of 15 doses,[9] patients were divided into two groups: a compliant group, which consumed between 11 and 15 doses, and a noncompliant group, which consumed $\leqslant 10$ doses of ONS. Demographic information included age, gender, Charlson co-morbidity index,[10] the type of allocated nutritional support (either IN or ICN) and the underlying pathology, classified in upper GI, lower GI and retroperitoneal or hepatopancreatobiliary disease.

Nutritional parameters

The NRS score was calculated for each patient. Patients having an NRS = 3 only because of age $\geqslant 70$ were studied as a specific subgroup. Hospital nutritionists assessed the nutritional status of each patient who was considered to be well nourished (AM = absent malnutrition), moderately (MM) or severely malnourished (SM) according to weight loss and anthropometric measures. Body weight was assessed in the outpatient setting, weight loss was calculated and the time span was recorded. Preoperative BMI was calculated for each patient. Current appetite and food intake were assessed with a visual analog scale 1–10. Energy and protein intake were assessed by nutritionists with a 24 h dietary recall. According to ESPEN guidelines, energy and protein needs were calculated by nutritionists multiplying actual or usual body weight by 25–35 kcal/kg/day and 0.8–1.2 g protein/kg/day.[11] Respective energy and protein gaps were calculated by comparing effective energy and protein intake with energy and protein needs.[11,12] Further, caloric excess was calculated comparing energy charge (meals+ONS) with energy needs for the respective patient. Patients were asked about the presence of dysgeusia or nausea (distaste yes/no) and about abnormal GI transit (yes/no), regrouped as either diarrhea or constipation. Blood samples were obtained in an outpatient setting 10 days preoperatively to assess for pertinent nutrition-related serum biochemistry values: pre-albumin serum levels of <0.2 g/l (normal range 0.2–3.6 g/l), albumin levels of <35 g/l (normal range 35–55 g/l), hemoglobin levels of <133 g/l in men (normal range 133–172 g/l in men) or <117 g/l in women (normal range 117–156 g/l in women) and a CRP serum value of <10 mg/l (normal value <10 mg/l) Table 1 and 2.

Eating and lifestyle habits

All patients were asked about their cooking and eating routines. Information was gathered concerning self-prepared meals, eating in a social environment and consumption of home-made or precooked food, as well as different oral nutritional supplements. Further, overall physical activity level was assessed according to the lifestyle and stratified from inactive (score 1) to extremely active (score 5).[13]

All mentioned data points were prospectively entered in a confidential computer-based database by a clinical nurse.

Data synthesis and analysis

Descriptive statistics are reported as median (range) or mean (s.d.) for continuous variables and absolute or relative frequencies for categorical variables. Logistic regressions were used to test the effect of independent variables on the dichotomized outcome compliance (11–15 preoperative oral nutritional supplement units versus <11 units). First, dependent variables were tested individually in simple regressions. Variables with P-values $\leqslant 0.2$ were entered into a multiple logistic regression to provide adjusted estimations of the odds-ratios (OR). All tests were two-tailed. A P-value of <0.05 was considered statistically significant.

Data analysis was performed with Prism 5.2 (GraphPad Software, Inc., La Jolla, CA, USA) and Stata, version 11.0 (StataCorp LP, College Station, TX, USA).

RESULTS

There were 141 patients out of 152 patients with complete data sets available for final analysis. Four patients dropped out because of incomplete pertinent information. Mean and median values for compliance were 10.7/15 ingested supplements and 12/15 ingested supplements, respectively. There were 82 (58%) patients in the compliant and 59 (42%) patients in the noncompliant group. Of note, 85% of all patients suffered from malignant disease.[7] Figure 1 illustrates the distribution of compliance in detail. No significant difference in compliance was found between the two allocated nutritional regimens (IN versus ICN). Caloric excess was observed significantly more often in compliant patients ($P=0.005$).

Uni- and multivariate analysis of possible risk factors for decreased compliance

Patient-related univariate risk factors for decreased compliance were decreased current food intake in the context of the disease ($P=0.032$). Better compliance was observed in the specific subgroup of patients having an NRS = 3 obtained on the basis of the patients' age and severity of surgery, with no points given for nutritional impairment ($P=0.011$). In terms of biochemical markers, low CRP serum values ($P=0.015$) and as trends low pre-albumin serum levels ($P=0.056$) and low hemoglobin levels ($P=0.065$) were found to be associated with lower compliance to

Table 1. Univariate analysis for demographic parameters

Item	*Noncompliant patients* (n = 59)	*Compliant patients* (n = 82)	*OR*	95% *CI*	P
Age (y) (mean ± s.d.)	66 ± 15	68 ± 13	1.01[a]	0.99–1.03	0.438
Age > 70yrs	29	50	1.62	0.83–3.14	0.164
Gender (M: F)	30: 29	49: 33	1.44	0.73–2.82	0.294
Type of surgery					
Upper GI	7 (12%)	17 (21%)	1.62	0.58–4.49	0.355
Lower GI/retroperitoneal	28 (47%)	29 (35%)	0.69	0.33–1.44	0.322
Hepatopancreatobiliary	24 (41%)	36 (44%)	1.00[b]		
Nutritional support type					
IN: ICN	31: 28	39: 43	1.22[c]	0.62–2.39	0.560
Charlson index ⩾ 3	20	29	1.08	0.53–2.19	0.830

Abbreviations: IN, immunonutrition; ICN, isocaloric-isonitrogenous nutrition. Results from logistic regressions. An OR > 1 means an increased likelihood of being compliant. [a]OR for each increment of 1 year in age. [b]OR is calculated with hepatopancreatobiliary surgery as a reference. [c]OR is calculated with IN as reference.

Table 2. Univariate analysis for nutritional parameters

Nutritional parameter	*Noncompliant patients (n = 59)*	*Compliant patients (n = 82)*	*OR*	*95% CI*	P
Clinical scores					
NRS (median+range)	4 (3–6)	4 (3–6)	0.91	0.64–1.28	0.573
Subgroup NRS = 3 because of age > 70 years	11 (19%)	32 (39%)	2.79	1.27–6.16	**0.011**
Nutritional diagnosis					
AM	20 (34%)	37 (45%)	1.00		
MM	27 (46%)	35 (43%)	0.70[a]	0.33–1.47	0.346
SM	12 (20%)	10 (12%)	0.45[a]	0.17–1.22	0.118
Clinical and anamnestic measures					
Weight difference/initial weight (%) (mean ± s.d.)	− 8.2 ± 8.4	− 6.4 ± 7.7	1.03	0.99–1.07	0.185
Weight loss > 10%	21 (36%)	23 (28%)	0.71	0.34–1.45	0.341
Time span of weight loss (d) (median+range)	82.5 (30-180)	90 (30-180)	1.00	1.00–1.00	0.357
BMI (kg/m^2) (mean ± s.d.)	22.8 ± 4.3	23.9 ± 4.0	1.07	0.98–1.16	0.132
Appetite (mean ± s.d.)	6.2 ± 2.3	6.8 ± 2.3	1.10	0.95–1.27	0.200
Current food intake (median+range)	6 (5-9)	9 (6-9)	1.17	1.01–1.35	**0.032**
Energy gap (kcal) (mean ± s.d.)	286 ± 711	306 ± 546	1.00	1.00–1.00	0.850
Protein gap (g) (mean ± s.d.)	− 1.8 ± 27.6	− 3.2 ± 20.7	1.00	0.98–1.01	0.741
Caloric excess					
< 65%	6 (10%)	2 (2%)	0.37[b]	0.07–1.95	0.238
65–120%	34 (58%)	31 (38%)	1.00		
> 120%	19 (32%)	49 (60%)	2.83[b]	1.38–5.81	**0.005**
Distaste	13 (22%)	13 (16%)	0.67	0.28–1.57	0.352
Normal transit	43 (73%)	61 (69%)	1.08	0.51–2.31	0.841
Eating and lifestyle habits					
Eating alone	5 (8%)	7 (9%)	1.01	0.30–3.35	0.990
Self-prepared meal	56 (95%)	80 (98%)	2.14	0.35–13.25	0.412
Home-made nutritional support	5 (8%)	4 (5%)	0.55	0.14–2.16	0.394
Physical activity score 3+	17 (29%)	24 (29%)	1.02	0.49–2.14	0.953
Biochemical measures					
Albumin (< 35 g/l)	5 (8%)	8 (10%)	1.25	0.39–4.03	0.712
Prealbumin (< 0.2 g/l)	26 (44%)	22 (27%)	0.49	0.24–1.02	0.056
CRP (< 10 mg/l)	26 (44%)	18 (22%)	0.40	0.19–0.84	**0.015**
Hemoglobin (< 133 g/l for men; < 117 g/l for women)	34 (58%)	36 (44%)	0.52	0.26–1.04	0.065

Abbreviations: BMI, body mass index; NRS, nutritonal risk score; AM, absent malnutrition; MM, moderate malnutrition; SM, severe malnutrition; CRP, C-reactive protein. Results from logistic regressions. An OR > 1 means an increased likelihood of being compliant. [a]OR is calculated with AM as a reference. [b]OR is calculated with caloric excess 65–120% as a reference. Significant values are highlighted in bold.

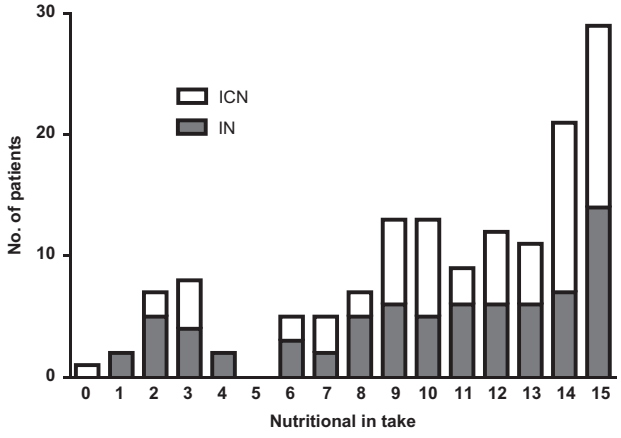

Figure 1. Compliance with preoperative ONS by allocated nutritional supplement.

allocated nutritional support. Table 1 shows demographic information and Table 2 nutritional parameters and eating and lifestyle habits and their respective influence on compliance.

After multivariate analysis, only the specific subgroup of patients with a NRS score of 3 because of an increased age of > 70 years was found to be independently associated with good compliance to the preoperative nutritional supplements (OR 3.42, CI 1.30–8.98). No other potential risk factor was retained after multivariate analysis (Table 3).

Seemingly, obvious risk factors were not retained in the analysis. Seventeen potential explanatory parameters, such as upper GI cancer, weight loss, reduced appetite or co-morbidities, did not show any significant correlation with reduced intake of nutritional supplements. Caloric excess was observed in compliant patients after multivariate analysis (OR 3.51, CI 1.53–8.05).

DISCUSSION

To explain the disappointingly low compliance with preoperative oral supplements in our patient cohort, we looked for seemingly obvious risk factors for reduced compliance. The present study evaluated about 30 potential explanations for reduced intake of preoperative nutritional supplements; interestingly, none of these was independently associated with low compliance. Most of the nutritional interventional studies were conducted in highly specialized centers with a particular interest in clinical nutrition. Therefore, compliance with allocated nutritional supplements was

Table 3. Multivariate analysis of compliance

Item	*OR*	*[95% CI]*	P
NRS ⩾3 because of age >70yrs	**3.19**	**1.14–8.87**	**0.027**
BMI (kg/m^2)	0.99[a]	0.88–1.10	0.792
Current food intake	1.13	0.96–1.34	0.137
CRP (<10mg/l)	0.65	0.26–1.65	0.365
Prealbumin (<0.2 g/l)	0.67	0.27–1.65	0.379
Hemoglobin (<133 g/l for men; <117 g/l for women)	0.72	0.31–1.69	0.453
Caloric excess	**3.51**	**1.53–8.05**	**0.005**

Abbreviations: NRS, Nutritional risk score; CRP, C-reactive protein. [a]OR for increments of 1 kg/m^2. Significant values are highlighted in bold.

expected to be high and not particularly assessed.[4] This contrasts with the findings of Hiesmayr *et al.*[14] who showed that >50% of their patients had an insufficient intake. In our patient cohort, only 58% of patients were able to consume at least 2/3 of the allocated nutritional regimen (IN or ICN), which corresponds to the minimal recommended dose.[7] As compliance did not differ between the two nutritional regimens, we assumed that other patient and disease-related risk factors must be responsible for decreased intake. In former attempts to identify factors related to non-tolerance of oral nutritional regimens, psychosocial factors such as anxiety and depression or chemotherapy-related taste changes or nausea, as well as different perceptions of fullness in severely ill patients have been described.[15] On the other hand, it has been shown that powder supplements that need to be reconstituted before consumption may have a negative impact and its use is not generally recommended.[15,16] Furthermore, it has been shown that nutritional supplementation is only effective when combined with early individualized nutritional counseling and education.[17]

Demographic and disease-related factors and risk scores

Demographic factors and co-morbidities as assessed by the Charlson co-morbidity score did not influence compliance, nor did objective parameters such as bowel habits or the presence of dysgeusia or nausea. Only the subgroup of patients with a NRS score of 3 only because of advanced age was more compliant. These particular patients do not necessarily suffer from malnutrition or metabolic imbalance, which might partly explain better tolerance of ONS. However, further conclusions seem bold. Elia *et al.*[18] showed that non-modifiable risk factors such as age were not suitable for predicting the outcome of nutritional support and, supposedly, tolerance of ONS either. Far more surprisingly, the diseased organ did not influence compliance, as one could imagine that patients suffering from upper GI pathology would be prone to difficulties in consuming nutritional products, because of the impaired transit or swallow mechanisms.[19–22]

Caloric excess was observed significantly more often in compliant patients, reflecting the important influence of ONS on caloric balance. Assessment of the degree of malnutrition by hospital's nutritionists did not correlate with compliance to nutritional regimens. Its validity as-risk or complication-predicting screening tool needs to be further analyzed.

Eating and lifestyle habits

As did other authors, we assumed that social factors or lifestyle habits such as increased physical activity might contribute to 'general well-being' and therefore have a role in adherence to protocol.[23] However, no such relation could be found in our study.

Biochemistry serum values

Several biochemical serum values are correlated with nutritional status and were thus accepted as screening tools. Hypoalbuminemia is considered as a marker to depict patients with severe nutritional risk who need preoperative enteral nutrition and reflects disease severity.[11,24,25] Prealbuminemia is an important marker of nutritional status.[26] Low serum levels of hemoglobin, albumin and pre-albumin reflect muscle wasting and increased catabolism in cancer patients and therefore point towards poor nutritional status.[27,28] More recently, hypoalbuminemia associated with elevated CRP values has been shown to be a predictor of poor outcome in septic patients.[29] However, confounding factors such as anemia in cancer patients or cancer-related elevated CRP values should be considered.

Several limitations of this study need to be addressed. Although almost 30 potential explanatory parameters for noncompliance were analyzed, other influencing factors such as social status or education were not available for the present analysis. The main outcome compliance is patient-reported and therefore rather subjective. However, in order to gain objectivity, serum arginine and glutamine levels were measured, both before and after nutritional intervention and cross-checked in 30 consecutive patients.[7] Many others of the analyzed potential risk factors, that is, dysgeusia or physical activity, depend likewise on the subjective assessment and patients' history, as they cannot be objectively measured either. Further, thresholds are patient-dependent and hardly comparable. We compared different pathologies and surgeries in an attempt to demonstrate that patients suffering from upper GI disease were prone to be less compliant to ONS. However, the sample size of patients might not have been sufficient for this subgroup analysis.

CONCLUSION

Reduced compliance with preoperative nutritional interventions remains a major issue because the expected benefit depends on the actual intake. Seemingly, obvious reasons for a decreased tolerance of oral supplements could not be retained as valid explanations. We hypothesize that compliance might thus be primarily a question of will, information and patient support. Besides attempts to improve taste and change composition or texture, future efforts should focus on specific patients' education.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

Study conception and design: M Hübner, F Grass, P Coti Bertrand and N Demartines. Acquisition of data: P Coti Bertrand, M Hübner, F. Grass and Y Cerantola. Analysis and interpretation of data: P. Ballabeni, M Hübner, F. Grass, P Coti Bertrand, M Schäfer and N Demartines. Drafting of manuscript: F Grass, M Hübner, M Schäfer, P Coti Bertrand, N Demartines and Y Cerantola. Critical revision of manuscript: all authors

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