Universidade Federal do Rio Grande do Sul

Programa de Pós-Graduação em Ciências Médicas: Endocrinologia

Tempo de jejum perioperatório e permanência hospitalar de pacientes oncológicos submetidos à cirurgia eletiva: Estudo prospectivo

Caroline Fachini

Dissertação de Mestrado

Porto Alegre, março de 2020.

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“O maior inimigo do conhecimento não é a ignorância, é a ilusão do conhecimento.”

Stephen Hawking

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Lista Geral de Abreviaturas:

Fundamentação Teórica

ACERTO – Acelerando a recuperação total pós-operatória

ASG PPP – Avaliação subjetiva global pelo próprio paciente

ERAS - Enhaced recovery after surgery

IBNO – Inquérito brasileiro de nutrição oncológica

NE – Nutrição Enteral

NP – Nutrição Parenteral

NPO – *Nil per os* (Nada por via oral)

OMS – Organização mundial de saúde

UTI – Unidade de Terapia Intensiva

Artigo Original

ACERTO – Acelerando a recuperação total pós-operatória

APACHE score II - Acute Physiology and Chronic Health II

BMI – Body mass index

ERAS - Enhaced recovery after surgery

HIPEC – Hyperthermic introperative intraperitoneal chemotherapy

ICU – Intensive care unit

LOS – Lenght of stay

MNA - Mini Nutritional Assessment

NPO – *Nil per os* (Nothing by oral route)

NUTRIC - Nutrition Risk in Critically Ill

SAPS 3 – Simplified Acute Physiology Score 3

SGA PP – Subjective Global Assessment by own patient

SOFA – Sequential Organ Failure Assessment

PN – Parenteral nutrition

PO - Postoperative

GI – Gastrointestinal

Lista Geral de Tabelas

Lista Geral de Figuras

Supplemental

Sumário

Capítulo I – Fundamentação Teórica

As neoplasias constituem a segunda causa de mortalidade na população brasileira, totalizando 17% dos óbitos. No Brasil, a estimativa do Instituto Nacional do Câncer no ano de 2018, apontava a ocorrência de aproximadamente 600 mil novos casos de câncer. [1] A Organização Mundial de Saúde (OMS) estima para 2030, 27 milhões de novos casos de câncer e 75 milhões de pessoas vivendo com a doença [2].

Atualmente o tripé para o tratamento oncológico é a cirurgia ao lado da quimioterapia e da radioterapia. O câncer em sua fase inicial pode ser controlado, ou mesmo curado, através do tratamento cirúrgico com ou sem adjuvância. No entanto, o estado nutricional dos pacientes oncológicos, a presença de desnutrição, pode afetar diretamente os desfechos clínicos e cirúrgicos destes pacientes [3][4][5].

A incidência de desnutrição em pacientes oncológicos é muito maior do que em qualquer outra especialidade clínica [6], variando entre 20 e 70 % na literatura mundial, sendo que as diferentes taxas são atribuídas a idade, localização da neoplasia e estágio da doença. No Inquérito Brasileiro de Nutrição Oncológica (IBNO) [7], foram avaliados 4822 pacientes oncológicos, internados em 45 instituições brasileiras, utilizando como ferramenta de triagem a Avaliação Subjetiva Global produzida pelo próprio paciente (ASG-PPP[8]). A prevalência de desnutrição ou risco nutricional foi de 45,1% na população geral e de 55,6% nos idosos, mostrando a maior vulnerabilidade desses pacientes [7].

A desnutrição está mais associada a alguns tipos de neoplasias como as do trato digestório superior, tumores de cabeça e pescoço e neoplasias de pulmão. Na literatura já existem evidências associando desnutrição com maior quantidade de efeitos adversos pela quimioterapia e pior resposta à mesma, maior tempo de internação hospitalar, maiores complicações cirúrgicas, incluindo as complicações infecciosas e fístulas, e também maior mortalidade [9][10][11].

A desnutrição em pacientes oncológicos pode resultar de efeitos locais do tumor, resposta imune ao câncer e dos tratamentos quimioterápicos e cirúrgicos. Além disso, pacientes com câncer possuem diminuição da ingestão alimentar devido a efeitos sistêmicos, locais e psicológicos da doença e de efeitos adversos do tratamento. Esses pacientes contam com alterações no metabolismo dos nutrientes e aumento no gasto energético de repouso que também contribuem para a desnutrição. Muitos fatores derivados do próprio tumor, especialmente citocinas inflamatórias e hormônios, estão implicados na patogênese da desnutrição e caquexia nesses pacientes [9][12][10].

Quando falamos de pacientes críticos, muito tem se estudado sobre a influência do estado nutricional e das modalidades de dietas nos desfechos desses pacientes [13]. Desnutrição foi associada com aumento da permanência hospitalar e em unidade de terapia intensiva (UTI) de pacientes cirúrgicos críticos [14][15] e com aumento de mortalidade em pacientes críticos [16]. Em UTI, receber quantidades de dieta inferior à meta calórica calculada é associado com mais infecções e maior tempo de internação (hospital e UTI)[17][18]. Outro fator de muito estudo nessa população de doentes críticos é justamente qual a via preferencial para nutrição. Resultado de uma revisão sistemática mostra que o uso de nutrição enteral (NE) comparado com nutrição parenteral (NP) diminui as taxas de complicações infecciosas e tempo de permanência na UTI [19], porém sem diferença quando o desfecho é mortalidade.

Juntamente com a desnutrição, o tempo de jejum perioperatório está associado com piores desfechos cirúrgicos. O jejum usual para procedimentos cirúrgicos, que consiste em *Nil per ois* (NPO), nada por via oral, por oito horas no pré-operatório e alimentação somente com o retorno do funcionamento intestinal, acarreta alterações metabólicas que influenciam na recuperação dos pacientes podendo piorar a resposta catabólica ao trauma cirúrgico. Essas alterações são resultado de adaptações fisiológicas para garantir a homeostase durante esse período e irão suscitar a resposta metabólica ao jejum [20].

No jejum, mesmo com a diminuição do gasto energético basal, persiste a necessidade energética dos tecidos para a manutenção de funções vitais. Para isso acontecer ocorre a degradação de substâncias que funcionam como depósito de energia, como o glicogênio e o triacilglicerol, em vários locais do organismo[20][21]. Metabolicamente, períodos longos de jejum resultam em redução no nível sérico de insulina, aumento do glucagon e resistência insulínica. A gliconeogênese é um fenômeno que acontece concomitante com as mudanças hormonais, aumentando a produção endógena de glicose. Altos níveis de depleção de glicogênio contribuem para o estresse metabólico no pós-operatório, que estimula a produção de citocinas (interleucinas, proteína C reativa) desencadeada pelo dano tecidual e exacerbando a resistência insulínica [22][3].

A resistência à insulina não afeta apenas as células insulino-dependentes, mas também células imunológicas, endoteliais, renais e neurais. Como essas células aumentam a absorção de glicose, porém não conseguem armazená-la, se inicia a produção de radicais livres de oxigênio, que pode contribuir para o aparecimento de complicações. Esse fenômeno geralmente é transitório e dura até três semanas após a realização de cirurgias abdominais eletivas não complicadas, mas pode ser maior conforme aumenta o porte da cirurgia [23][24].

Na tentativa de minimizar o estresse cirúrgico e a resposta metabólica ao trauma, foram desenvolvidos protocolos multimodais para acelerar a recuperação de pós-operatório. Esses protocolos consistem em mais de dez itens que permeiam pré , trans e pós-operatório, envolvendo várias etapas e profissionais. Entre protocolos mais conhecidos estão o ERAS (Enhanced Recovery After Surgery), internacionalmente, e o ACERTO (Acelerando a Recuperação Total Pós-operatória), no Brasil [25][26]. Ambos incluem entre seus componentes a redução dos tempos de jejum através da abreviação do jejum pré-operatório e início precoce de alimentação no pós-operatório, visando diminuir o tempo total de jejum dos pacientes [27][28].

A manutenção do jejum para sólidos de 6 a 8 horas e a abreviação do jejum para líquidos, enriquecidos com maltodextrina, para 2 horas antes da cirurgia, estaria relacionado à diminuição da resistência insulina no pós-operatório bem como a benefícios para a manutenção de massa e força musculares [29][30], manutenção da função imunológica, redução de ansiedade e fome, além da diminuição do tempo de internação hospitalar [31][28].

Na literatura, a análise do impacto dos protocolos multimodais é feita com a implementação de todo o pacote de medidas, sendo que existem poucos estudos avaliando unicamente a associação da abreviação do jejum pré-operatório e redução de desfechos duros, especialmente em pacientes oncológicos e submetidos a cirurgias de grande porte [32]. Alguns estudos avaliam isoladamente apenas a segurança da abreviação de jejum quanto aos riscos de aspiração [33], com resultados extremamente positivos. Embora os protocolos multimodais preconizem abreviações de tempo de jejum perioperatório, muitas vezes estudos de vida real demonstram que há grande dificuldade em sua implementação, devido à baixa aderência dos profissionais de saúde [34].

Face ao alto risco nutricional e a alta prevalência de desnutrição em pacientes oncológicos e aos potenciais danos que o jejum pode provocar a essa população, especialmente se submetida à cirurgia de grande porte (aumento de resistência insulínica, perda de massa muscular) é imperativo avaliar as práticas de jejum e prescrição nutricional nesses pacientes. Além disso, o impacto dessas práticas sobre o tempo de internação hospitalar, tempo de internação em UTI e custos não é bem estabelecido. Sendo assim, o objetivo desse nosso estudo é avaliar as consequências do jejum perioperatório nos seguintes desfechos: tempo de internação hospitalar e em CTI, mortalidade em 28 dias e complicações infecciosas em pacientes oncológicos submetidos a cirurgias eletivas de grande porte internados em UTI.

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Capítulo II – Artigo Original

O jejum pós-operatório está associado a maior permanência na UTI em pacientes oncológicos submetidos à cirurgia eletiva.

Resumo

Introdução: Pacientes com câncer tem maior risco nutricional e de complicações durante o período pós-operatório. O jejum contribui para o dano catabólico cirúrgico. Objetivo deste estudo foi avaliar os efeitos do tempo de jejum perioperatório em desfechos cirúrgicos em pacientes oncológicos submetidos a cirurgias eletivas.

Métodos: Estudo de coorte prospectivo. Pacientes foram divididos em duas categorias de acordo com o tempo de jejum pós-operatório: menor ou maior que 24 horas. Tempo de hospitalização, tempo de internação na UTI, mortalidade em 28 dias e taxas de infecção foram avaliadas.

Resultados: No total, 109 pacientes foram incluídos no estudo (57% homens, 60±15 anos, IMC 26 ±5 kg/m^2, SAPS3 43 ±12). A cirurgia mais frequente foi a hepatectomia (13.8%), e a neoplasia mais comum de cólon e reto (18.3%). A permanência na UTI (5.5 [4 - 8.25] vs. 3 [2 - 5], p = 0.000) foi maior no grupo de pacientes com tempo de jejum pós-operatório >24 horas. Em análise multivariada corrigida para escores de gravidade e estado nutricional, jejum >24 horas permaneceu como fator de risco para internação prolongada em UTI. Não houve diferença de mortalidade na análise em 28 dias (10.8% (7) vs. 4.8% (2), p = 0.478) e no tempo total de hospitalização (25.5 [17 - 57] vs 24 [13 - 41], p = 0.244) entre os dois grupos de jejum. Uma tendência a maior taxa de infecção foi observada no grupo de pacientes que ficaram em jejum >24 horas [34.8% (23) vs. 16.3% (7), p = 0.057].

Conclusão: Inicio da dieta após as primeiras 24 horas de pós-operatório é um fator de risco para maior tempo de permanência na UTI em pacientes com câncer e submetidos a cirurgias de grande porte.

Palavras- Chave:

Jejum perioperatório, cirurgia oncológica, tempo de permanência na UTI

Original Communication

Postoperative fasting is associated with longer ICU stay in oncologic patients undergoing to elective surgery.

Caroline Fachini[1]; Claudio Z. Alan M.Sc.[2]; Luciana V. Viana Ph.D.[3]

Abstract

Background: Cancer patients present greater nutritional risk and complications during the postoperative period. Fasting contributes to surgical catabolic damage. We analyzed the consequence of perioperative fasting time on the surgical outcomes of cancer patients undergoing elective surgeries. *Methods:* Prospective cohort study. Patients were divided into two categories according to postoperative fasting time: less than or greater than 24 hours. Hospitalization time, mortality within 28 days, time of ICU stay and infection rate were evaluated. *Results:* In total, 109 patients were included in the study (57% man, 60 ± 15 years, BMI 26 ± 5 kg/m^2, SAPS3 43 ± 12). Hepatectomy was the most frequent surgery (13.8%), and colon and rectum the most common neoplasia (18.3%). The ICU stay (5.5 [4 - 8.25] vs. 3 [2 - 5], p <0.001) was longer in the group of patients with postoperative fasting > 24 hours. Fasting longer than 24 hours persisted as a risk factor for longer LOS in ICU after adjusted for severity scores and nutritional risk. There was no difference in mortality analysis within 28 days (10.8% (7) vs. 4.8% (2),

[1] Critical Care Unit, Hospital Casa de Misericórdia, Rua Prof. Annes Dias 295, Porto Alegre, RS, Brazil.
[2] Critical Care Unit, Hospital Mãe de Deus, Rua José de Alencar, 286, Porto Alegre, RS ,Brazil.
[3] Endocrin Division and Medical Nutrition Division, Hospital das Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil.

p = 0.478) and total hospitalization time (25.5 [17 - 57] vs 24 [13 - 41], p = 0.244) between fasting groups. A tendency to have more infections was observed in patients who fasted for more than 24 hours (34.8% (23) vs. 16.3% (7), p = 0.057). *Conclusions:* Onset of diet after the first 24 hours postoperative is a risk factor to longer ICU stay in cancer patients who underwent major surgeries.

Keywords

“Fasting”; “Surgical Oncology”; “Length of Stay”.

Clinical Relevancy Statement

Traditionally, perioperative fasting consists of *Nil per ol* (NPO) from midnight of the day before surgery until recovery of intestinal function in the postoperative period.[1] This outdated practice persists despite new evidence that excessive fasting results in negative outcomes and delayed recovery after surgery.[2] Our data suggest that fasting for more than 24 hours in the postoperative period is a risk factor for longer ICU stay in oncologic patients submitted to elective surgery without add complications. This is relevant for all health professionals that work with oncology patients.

Introduction

Traditionally, perioperative fasting consists of *Nil per ol* (NPO) from midnight of the day before surgery until recovery of intestinal function in the postoperative period.[2] This outdated practice persists despite new evidence that excessive fasting results in negative outcomes and delayed recovery after surgery.[2]

Nutritional status is a strong predictor independent of poor postoperative outcomes.[3] Malnourished surgical patients have higher mortality rate, morbidity, hospitalization time, readmission and hospital costs.[4-6] Therefore, perioperative nutritional therapy has been shown to be useful to improve surgical outcomes in these patients.[5,7] There are many evidence-based protocols for rapid postoperative recovery,[3,8-10] that endorses reduction of perioperative fasting but the implementation and adherence to them is still limited.[9] The main populations of interest in these study groups are patients undergoing gastrointestinal (GI) and oncological surgeries, since this population has the greatest risk of malnutrition.

However, most rapid recovery guidelines for the postoperative period do not assess the impact of an isolated measure, but rather the whole bundle to improve surgical outcomes and discharge time.

We hypothesize that perioperative fasting time may be an independent marker of outcomes in the postoperative period of oncological surgeries. Thus, we evaluated the impact of perioperative fasting time on hospitalization time, mortality, and length of intensive care unit (ICU) stay and the occurrence of infectious complications in adult patients submitted to oncologic elective surgery hospitalized in ICU.

Methods

This is a prospective cohort study conducted with adult cancer patients undergoing elective surgery, hospitalized for at least 48 hours in the intensive care unit of *Hospital Santa Rita*, between April 2018 and September 2019. The *Hospital Santa Rita* integrates the *Complexo Hospitalar Santa Casa de Misericórdia de Porto Alegre* located in Porto Alegre, Rio Grande do Sul. It is a reference hospital in cancer treatments, receiving patients from all over southern Brazil. The hospital has an ICU with 10 beds where clinical and surgical patients are hospitalized, most of them after major oncological surgeries and clinical patients with solid or hematological neoplasia with serious clinical diseases.

The following patients were excluded: patients under 18 years of age, undergoing emergency surgery, with length of stay in the ICU of less than 48 hours, life expectancy of less than 24 hours or imminent risk of death, pregnant women and patients with exclusive palliative care.

On the first day of ICU hospitalization, data on age, gender, weight, comorbidities and severity scores: APACHE score II (Acute Physiology and Chronic Health II),[11] SAPS3 score (Simplified Acute Physiology Score 3),[12] SOFA score (Sequential Organ Failure Assessment),[13] NUTRIC score (Nutrition Risk in Critically Ill)[14] and Charlson score[15] were collected from the patients included. Weight was measured with a portable scale in the ward or bed scale in the first day of ICU, height was measured with measuring tape or estimated with Chumlea predictive formula[16], both were used to estimate BMI [i.e., weight (kg)/height^2 (m^2)]. The calf circumference was measure in the ICU bed when patient arrived, preferably in the left calf, with a measuring tape. Criteria related to the severity of the patient in the ICU were evaluated, such as the use of vasopressors, mechanical ventilation and the need for renal replacement therapy. All data were collected from the electronic medical records in the Tasy System and data from the Sistema Epimed Monitor®[17], which is a web-based system used in several ICU to store patient data and evaluate care quality.

The patients were classified in nourished or malnourished by criteria of at least one nutritional assessment scale: PG-SGA (Patient–Generated Subjective Global Assessment) or MNA (Mini Nutritional Assessment).[18,19] In case of disagreement between scales, the PG-SGA was used for tiebreaker because it is the most validated scale in the literature for the oncology population.[20] The NUTRIC tool was used to assess the nutritional risk of ICU patients; the cutoff point used was greater than or equal to 5 and without the evaluation of Interleukin-6 since it is not available in our service.[14]

Was a observational study so all aspects related to surgical technique followed the usual routine of the service and the surgeon, such as the use of drains or probes, manual or staple suture, open or minimally invasive surgery or colon preparation. Postoperative care in the ICU was individualized according to test results, type of anesthesia and surgical complications.

Preoperative and postoperative fasting times and data on the duration of surgery were obtained from the anesthetic sheet and surgical report in the medical records. From this data, the fasting times were calculated. Patients were categorized into two groups according to postoperative fasting time: postoperative fasting <24 hours, including 24 hours, or postoperative fasting >24 hours. The time of the beginning of the diet in the postoperative period were obtained through medical prescription. After the onset of the diet, the patients were followed for three days, or until the moment of discharge from the ICU, if it occurred before. The route of administration and type of diet, amount of calories per kilo of the patient and the 3-day caloric target was analyzed, total caloric intake was considered adequate if it was between 20 to 25 kcal/kg in the third day.[21] Diet tolerance was verified with clinical signs and symptoms such as nausea, vomit and bloating. The acceptance of oral diet was assessed with intake control performed by the nutritionist, and acceptance of enteral and parenteral nutrition was assessed based on infusion records. Glycemic control was performed according to the routine of the service and hyperglycemia was defined as HGT > 180 mg/dl.[22] The variable norepinephrine use (categorical) was considered as yes when the dose of norepinephrine was bigger than 0.1 mcg/kg/min. Infection rate (at any site) was also evaluated.

To mortality outcome patients was follow-up for 28 days after surgery. Patients who stay hospitalized after that date, data were extracted from the medical record. Patients who were discharged from the hospital before 28 postoperative days were approached by telephone call using a phone number provided during hospital admission.

Statistical Analysis

Considering a previous study showing prolonged hospital LOS, defined as hospital LOS higher than the median in the period, was present in 47,4% of patients with more than 24 h of perioperative fasting vs 20,6 % of patients with less than 24 h of perioperative fasting[23] ,we estimate a sample size of 108 patients . During the study period, median hospital LOS in our patients was 22 days. The collected data were entered in the Excel program and later exported to the SPSS v.20.0 program for statistical analysis. Categorical variables were described by frequencies and percentages. The symmetry of the variables was verified with the Kolmogorov-Smirnov test. The quantitative variables with symmetric distribution were described by mean and standard deviation and those with asymmetric distribution by median and interquartile interval.

Categorical variables were associated by the Chi-square test. The quantitative variables with symmetric distribution were compared by Student's t test for independent samples. The variables with asymmetric distribution were compared by the Mann-Whitney test. A Linear Regression Analysis was used to evaluate the relationship between factors associated with the outcome length of ICU stay. The significance level established for the comparisons was 5%. The linear regression model was used for multivariate analysis. Nonparametric data were logged to meet the model's premise. The dependent variables were chosen based on their significance in the univariate analysis or their biological relevance.

Ethics

This study was conducted in accordance to the Declaration of Helsinki and was approved by the Ethics Committee of the Irmandade Santa Casa de Misericórdia de Porto Alegre (CAAE: 81019617.3.0000.5335). An informed consent form was obtained from all patients or relatives of the patients who participated in the study.

Results

Population overview:

Of the 559 patients admitted to the ICU of *Hospital Santa Rita* during the study period, 109 patients admitted for elective oncological surgeries were included, as shown in Figure 1. Most patients were men (57%), aged 60 ± 15 years, BMI 26 ± 5 kg/m^2. The mean SAPS3 score was 43 ± 12, as shown in Table 1. Hepatectomy was the most frequent surgery, with 13.8%, and colon and rectum neoplasia was the most frequent neoplasia, accounting for 18.3% of the operated patients. The prevalence of malnutrition was 38.3%. Length of stay in hospital was 25[15.5 - 47.5] days, with 4[3 - 7] days of stay in ICU, mortality in 28 days was 8.4%, infection rate was 27.5% and surgical reintervention was 10.1%.

Nutritional Characteristics:

Patients with postoperative fasting longer than 24 hours presented nutricional risk estimated by NUTRIC bigger than those with fasting time shorter than 24 hours (15.2% (10) vs. 2.3% (1) with p = 0.047), but NUTRIC was not associated with worse outcomes. There was no statistical difference on malnutrition prevalence between the two fasting groups (37.5% (21) vs. 39.5% (15), p = 1.00).

The preferred postoperative route of nutrition was the oral route (66.1%), followed by enteral nutrition (13.8%) and parenteral route (8.3%). Of the 10 patients who received parenteral nutrition (PN) early in the postoperative (PO) (before the 5th day), 5 of them underwent cytoreductive surgeries with hyperthermic intraperitoneal chemotherapy (HIPEC – Hyperthermic introperative intraperitoneal chemotherapy) and 3 of surgeries cytoreductives. Only 46.8% (51) of the patients reached the caloric target until the third day of ICU stay, and there was no difference between the two groups (31% (31) vs. 46% (20), p = 1.00). We found a diet acceptance data of 86%, considered as moderate to high acceptance on the first day, followed by 84% and 82.4% on the second and third day, respectively. The most frequent symptom after the beginning of the diet was abdominal bloating, which reached 11.9% on the first day, while the other signs of intolerance such as vomit or diarrhea were 6.4% and 0.9%, respectively.

Fasting time:

Perioperative fasting time was 42 (34.5 - 60.5) hours, preoperative was 8[7.7-10.3] hours and postoperative fasting time was 30 (20.7 - 46) hours. There were no correlation between preoperative fasting time and perioperative fasting time. A strong correlation (r = 0.988, p= 0,000) was identified only between perioperative fasting time and postoperative fasting time. Therefore the division of groups was done by postoperative fasting time.

The length of ICU stay was bigger in the group that fasted for more than 24 hours in the postoperative period (5.5 [4 - 8.25] vs. 3[2 - 5], p <0,001), without difference for mortality analysis within 28 days (10.8% (7) vs. 4% (8.25), p = 0.478) or length of hospital stay (25.5 [17 - 57] vs. 24 [13 - 41], p = 0.244). The proportion of patients with prolonged hospital LOS was not different comparing patients that fasted more than 24h with <24h group (65.2% vs 60.5%, p = 0.686). A trend suggesting higher infection rate was observed in patients who fasted for more than 24 hours (34.8% (23), vs 16.3% (7), p = 0.057).(Table 3. Suplemental)

On the multivariate analysis (Table 2), postoperative fasting longer than 24 hours persisted as a risk factor for longer ICU stay (in this logarithmic form) after correction for severity and nutritional risk score (Model 1). A second model was elaborated (Model 2), with inclusion of the variable mechanical ventilation and the statistical power of postoperative fasting longer than 24 hours was maintained. In a sensitivity analyses, exclusion of patients who received parenteral nutrition did not alter the results (data not shown).

Higher capillary glucose levels in patients fasting <24 hours were seen in first day of postoperative. There was no difference between groups relative to hyperglycemia or administration of insulin in none of the others days of analysis. Remembering that the use of insulin was made when hyperglycemia was diagnosed by means capillary glucose level higher than 180 mg/dl. (Table 4. Supplemental)

Discussion

This study was designed to evaluate the impact of surgical fasting and length of hospital and ICU stay, mortality and infectious complications. In this prospective study, conducted exclusively with cancer patients, we showed that postoperative fasting time greater than 24 hours is a risk factor to longer ICU stay, even adjusting for severity of the patients according to SAPS3, SOFA and NUTRIC. To our knowledge, it is the first study in oncologic patients submitted to elective surgery that demonstrated longer fasting periods in postoperative is a risk factor for longer length of stay (LOS) in ICU. We also showed a tendency in higher infectious rate in the category of patients with more than 24 hours postoperative fasting.

The safety of reducing pre- and postoperative fasting time is already defined by international and national postoperative guidelines.[3,9,24-28] Analysis of surgical outcomes in this protocols are thought a bundle that includes surgical preparation, the procedure itself and recovery in the postoperative period. Evidence suggests that no isolated measure has the effect as most measures combined.[29]An ancient meta-analyses evaluated early versus late feeding in patients submitted to gastrointestinal surgery and similar to our study there were no reduction of mortality or in LOS in hospital but ICU stay was not analyzed.[30] Also, in another study conducted in the south of Brazil, prolonged fasting was an independent risk factor both for infection and for prolonged hospital stay,[31] however this study was conducted general surgery patients (ward and ICU).

There are no robust data in the literature evaluating only the impact of fasting time on postoperative outcomes specifically for cancer patients, which also differentiates our study from the others. Cancer patients differ from the general surgical population because they have a higher incidence of malnutrition, both due to the neoplasia itself and due to the treatments,[28] resulting in higher incidence of postoperative complications. The prevalence of malnutrition in cancer patients ranges from 20% to more than 70% worldwide, and GI, head and neck, liver and lung cancers have the highest rates of malnutrition.[32,33] In our study we had a prevalence of 38.3% of malnourished patients. In cancer treatment, surgical complications and prolonged hospital stay may delay the onset of postoperative chemotherapy, which in turn can reduce long-term survival,[34] in addition to greatly increasing treatment-related costs.[35]

Although the objective of implementing evidence-based approaches is the improvement in patient care, reduced ICU stay results in reduced hospital costs. Estimates in the literature on the costs of a daily ICU stay differ considerably, according to the complexity of the Health Institution, location and type of hospitalized patients, ranging from U$ 1,000.00/day to U$ 5,000.00/day. Surgical hospitalizations use to be cheaper than clinical hospitalizations.[36] In our study we had a median reduction of ICU stay of 2 days. Sogayar et al. found a cost of U$ 934 (IQR 735 - 1170; 95% CI 897, 963) per day of ICU stay of septic patients, in a large multicenter study conducted in the Brazilian population,[37] but we have no studies with surgical population in Brazil.

According to the studies reviewed, although the patient's tolerance to restarting the diet is not universal, it is usually high, above 70%.[38,39] We had an acceptance greater than 80% to the diet in the postoperative period, and abdominal bloating was the most important complication on the first day, which is in accordance with international literature. Thus, while it seems to be safety to start diet early in the PO[34,40], only 46.8% of our patients reached the calculated caloric target in three days after the diet onset.[21,40]. Althought data remains controversial regarding the caloric target for critically ill patients,[42-44] the time in which the target should be reached and the impact on ICU outcomes, length of ICU stay and mortality, for example. We could not find differences in the outcomes, mortality, length of ICU and hospital stay and infection rate between patients who reached or not the caloric target stipulated in 3 days, however, our sample size was not calculated for this outcome. (Data not shown)

Hyperglycemia could interfere in ICU outcomes, mainly related to infection rates[41] , but we find a higher glucose blood level only in the first day, and in the group who fasten less than 24 hours, who also was the group who has less infection rate. However, there were no difference in hyperglycemia or use of insulin in our analysis. A more specific analysis could have been done through glycemic variation, which was not performed in this study.

Our study had some limitations. The first limitation is its observational nature. Nutritional data should be carefully evaluated in the ICU population, since many factors can influence the outcomes. Patients who fasted for more than 24 hours were also the most severe cases (greater need for mechanical ventilation, noradrenaline use, higher SAPS3 and SOFA scores), which could have delayed the onset of diet due to the contradictory data in the literature about the onset of diet in patients with hemodynamic instability.[24-26] Nonetheless, our results were maintained in the multivariate analysis which included severity scores as cofactors, even when a second model was done including mechanical ventilation as cofactor.

We limited our study to a single center, specialized and with a high number of cancer patients to standardize the procedures among the teams responsible for the care (surgeons, anesthetist, intensivists, nurses, nutritionists and physical therapists) and hospital resources, the beginning of diet was not consider a discharge criteria in this ICU. However, extrapolation of our data and results to other centers and countries require additional analysis. We could not perform subgroup analysis and evaluate if a type of surgery benefited more from some type of fasting due to the number of our sample.

Conclusion

Onset of diet after the 24 hours postoperatively is a risk factor for longer ICU stay in cancer patients undergoing large surgeries. More studies are needed to verify that the data found in our study can be extrapolated to other centers and countries.

Statement of Authorship

C.Fachini, L. Viana contributed equally to the conception and design of the research; acquisition, analysis and interpretation of data. C.Fachini, L. Viana and C.Alan draft the manuscript. All authors read and critically revised the manuscript and gave final approval.

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Figure 1 . Participant Flow

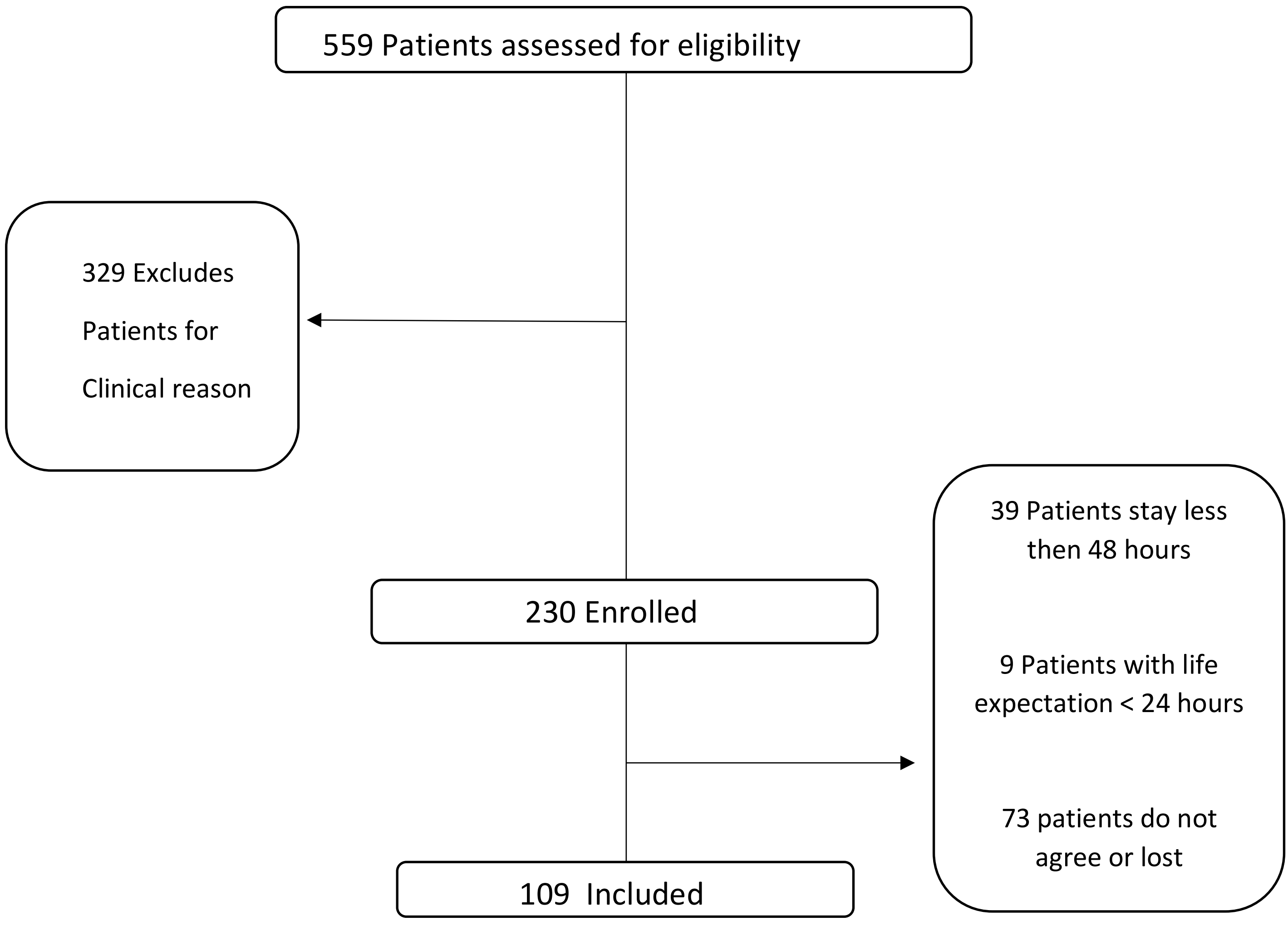

Table 1. ***Patients characteristics according to postoperative fasting time.***

Patients characteristics	Overall n = 109	Fasting < 24 hours n = 43	Fasting > 24 hours n = 66	*P*
Age (years)	60.03 ± 15.2	58.81 ± 13.97	60.82 ± 16.09	0.478
Men (%)	57 (52.3)	25(58.1)	32 (48.5)	0.429
Weight (kg)	73 [62 - 82.5]	73 [62 - 79]	73 [62 - 86]	0.91
BMI (kg/m²)	26.91 ± 5.7	26.76 ± 4.83	27.00 ± 6.2	0.831
SAPS3	43.6 ± 12.09	39.4 ± 9.42	46.48 ± 12.8	0.01
SOFA	3 [1 - 6]	2 [1 - 4]	4 [1 - 7]	0.02
NUTRIC	2 [2 - 4]	2 [1 - 3]	3 [2 - 4]	0.07
Malnutrition (%)	36 (38.3)	15(39.51)	21(37.5)	1.000
CC (cm)	35.6 ± 4.12	35.87 ± 3.4	35.55 ± 4.5	0.680
Charlson	3 [2 - 6]	2 [2 - 6]	3 [2 - 6]	0.22
Ischemic heart disease (%)	11 (10.6)	5 (11.6)	6 (9.1)	0.75
Cardiac failure (%)	6 (5.5)	0 (0.0)	6 (9.1)	0.79
Diabetes (%)	21 (19.3)	8 (18.6)	13(19.7)	1.00
Hypertension (%)	38 (34.9)	16 (37.2)	22 (33.3)	0.834
COPD (%)	9 (8.3)	2 (4.7)	7 (10.6)	0.478
Smoking (%)	26 (23.9)	11 (25.6)	15 (22.7)	0.911
Alcoholism (%)	8 (7.3)	3 (7.0)	5 (7.6)	1.00
Liver disease (%)	2 (1.8)	2 (4.7)	0 (0.0)	0.153
HIV (%)	2 (1.8)	1(2.3)	1 (1.5)	1.00
Other comorbidities (%)	39 (35.8)	16 (37.2)	23 (34.8)	0.963
Pre-Fasting (hours)	8 [7.7 - 10.5]	8 [8 - 13]	8 [7.5 - 9.62]	0.856

Pos-Fasting (hours)	30 [20.7 - 46]	19.5 [15.5 - 22]	45 [31 - 63.12]	0.000
Total Fasting (hours)	42 [34.5 - 60.5]	34 [32 - 36]	58 [46 - 81]	0.000
Primary tumor (%)	71 (65.1)	28 (65.1)	43 (65.2)	1.00
Metastases (%)	57 (52.3)	21 (48.8)	36 (54.5)	0.69
Chemotherapy (%)	45 (41.3)	17 (39.5)	28 (42.4)	0.92
Radiotherapy (%)	21 (19.3)	5 (11.6)	16 (24.2)	0.166
Reintervention (%)	11(10.1)	2 (4.7)	9 (13.6)	0.195
RRT (%)	6 (5.5)	1 (2.3)	5 (7.6)	0.4
Mechanical ventilation (%)	43 (39.4)	1(23.3)	33 (50)	0.010
Noradrenaline (%)	28 (25.7)	9 (20.9)	19 (28.8)	0.000
Another vasopressor	11 (10.1)	0 (0.0)	11 (16.7)	0.003

BMI, body mass index; CC, calf circumference; COPD, chronic obstructive pulmonary disease; HIV, acquired immunodeficiency syndrome; RRT, Renal replacement therapy.

Table 2. Multivariated linear regression model-depended variable length of ICU* stay (log).

	B	T	CI	P
First Model				
Fasting > 24 hours	0.208	2.28	0.039 - 0.565	0.025
SAPS3*	0.341	3.282	0.008 - 0.032	0.001
SOFA *	0.139	1.180	-0.024 - 0.093	0.241
NUTRIC*	-0.091	-0.797	-0.147 - 0.063	0.427
Second Model				
Fasting > 24 hours	0.274	2.092	0.014-0,534	0.039
SAPS3*	0.015	2.288	0.002- 0.028	0.024
SOFA *	0.02	0.683	-0.039 - 0.079	0.496
NUTRIC*	-0.032	-0.609	-0.136 – (- 0.072)	0.544
MV ICU	-0.318	-0,218	-0.612 – (-0.024)	0.034

ICU, intensive care unit; SAPS3, Simplified Acute Physiology Score 3; SOFA, Sequential Organ Failure Assessment; NUTRIC, Nutrition Risk in Critically Ill; MV , Mechanical ventilation.

Supplemental

Table 3 .Outcomes.

	Over all n=109	Fasting < 24 h n=43	Fasting > 24 h n=66	*P*
Primary outcome				
LOS* Hospital (days)	25[15.5-47.5]	24[13-41]	25.5 [17-57]	0.244
Secondary Outcome				
LOS* ICU* (days)	4[3-7]	3[2-5]	5.5[4-8.25]	0.000
Mortality 28 days (%)	8.4(9)	4.8(2)	10.8(7)	0.478
Infection (%)	27.5(30)	16.3(7)	34.8(23)	0.057

LOS – Lenght of stay; ICU – Intensive care unit

Table 4. Glucose blood level and use of insulin.

	Fasting < 24 h n=43	Fasting > 24 h n=66	*P*
HGL 1° day	167[140-204]	140 [128 -180]	0.006
LGL 1° day	120 [105-139]	114 [98-129]	0.114
Administration of Insulin 1° day (%)	32.6 (14)	19.7 (13)	0.099
HGL 2° day	150 [120-181]	142[122-166]	0.455
LGL 2° day	110 [96-137]	110 [87-127]	0.445
Administration of Insulin 2° day (%)	20.9 (9)	14.3 (9)	0.269
HGL 3° day	137 [114 -150]	145 [123- 170]	0.373
LGL 3° day	103 [96 -121]	112 [89-131]	0.427
Administration of Insulin 3° day (%)	14.3 (6)	15.1 (10)	0.585

HGL – High Blood Glucose level; LGL – Low Blood Glucose level

Considerações finais e perspectivas:

Os resultados desse estudo sugerem que o tempo de jejum pós-operatório é um fator de risco para maior tempo de internação na UTI em pacientes oncológicos submetidos a cirurgia eletiva, mesmo após ajuste para gravidade e risco nutricional. Nosso estudo também mostrou uma tendência a maiores taxas de infecção nos pacientes que permaneceram em jejum por mais de 24 horas no período pós-operatório.

Sabe-se que os custos de internações hospitalares em UTI são exorbitantes. Qualquer esforço para reduzir tempo de internação é uma estratégia válida e deve ser perseguida. Abreviar o jejum, especialmente no pós-operatório, seria uma alternativa de baixo custo e associada a baixo risco de complicação e boa tolerância nesses pacientes. Em nosso trabalho, mostramos que esta medida isolada (diferentemente do pacote usado em protocolos multimodais) mostrou uma redução mediana de 2 dias de internação.

A natureza observacional deste estudo é um ponto fraco do mesmo, uma vez que dados nutricionais devem ser avaliados com cautela em pacientes de UTI, tendo em vista que muitos fatores podem influenciar os desfechos. Apesar disso, houve o cuidado de avaliar os pacientes em um único centro, especializado em pacientes oncológicos e com profissionais dedicados aos cuidados quase que exclusivos dessa população. Apesar disso, a extrapolação dos nossos dados requer mais estudos.

Através dos resultados dessa dissertação, defendemos o início de dieta precoce em pacientes oncológicos submetidos a cirurgias eletivas, como já preconizado por várias sociedades. Nosso estudo está de acordo com as mais recentes diretrizes e é mais uma evidência de que nutrição precoce nesse grupo de pacientes é capaz de reduzir desfechos. Mais estudos, especialmente avaliando a melhor via e velocidade de progressão da dieta nesses pacientes, devem ser realizados.