POSTOPERATIVE GLYCAEMIC CONTROL AND THE SURGICAL SITE INFECTION INCIDENCE AMONG LIVER TRANSPLANTATION RECIPIENTS: RANDOMIZED CLINICAL TRIAL

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ABSTRACT

Context: The hyperglycemia is an important independent risk factor for the Surgical Site Infection (SSI) development among liver transplantation recipients. **Objective:** To evaluate the effects of an intensive postoperative protocol of blood glucose management on the surgical site infection incidence among liver transplantation recipients. **Material and methods:** It is an open-label clinical trial that will be randomized into 2 groups of blood glucose (BG) control: patients will undergo BG control regular in the facility chosen to research development (BG targeted 130-180 mg/dL) and the second one will undergo intensive BG control (BG targeted 80 - 130 mg/dL) until patients are eating at least 50% of a full liquid diet or receiving bolus tube feedings. A computer program will be employed to generate the randomized schedule that will be put into sequentially numbered opaque sealed envelopes by an external expert to research. A finger prick device will be used to measure the blood glucose. A blinded adjudication committee to analyse the primary endpoint SSI will adopt the SSI criteria given by the Centers for Disease Control and Prevention. The research proposal will be registered on ClinicalTrials.gov database. Central tendency and dispersion measures, Pearson's χ^2 test, Fisher's Exact Test, Mann-Whitney, Wilcoxon-Mann-Whitney and survival analysis by Kaplan-Meier estimated and Log-rank test will be used for data analyses. **Expected outcomes:** The results of the study should contribute to establishing better clinical practices on glycemic control in the liver transplantation recipient's postoperative period aiming to reduce SSI incidence and its associated morbidity and mortality.

Descriptors: Glycemia. Surgical Wound Infection. Liver Transplantation. Perioperative Nursing.

1 INTRODUCTION

The Surgical Site Infections (SSI's) are the most frequent healthcare-associated infections and are an important infectious complication in the postoperative period among liver transplantation (LT) recipients [1-3]. SSI incidence among LT recipients, whose allografts were from deceased donors, varied from 9.6% to 35.5% according to a recent literature review[4]. In general surgical procedures, SSI increases the length of stay, morbidity and healthcare costs. Besides that, among LT recipients SSI can raise the risks of the allografts dysfunctions, acute rejections and as a consequence a reduction in the recipient's survival[5-7].

There are several risk factors for SSI among LT recipients. There is a relationship among supply sterilization quality, the characteristics of surgical procedure, the operation room environment as well as the allograft's and recipient's conditions and SSI occurrence[8-12]. In regard to LT recipients, results from previous research highlighted hyperglycemia as an important independent predictor of SSI. Furthermore, regarding this population, it is known from observational studies that LT recipients affected by hyperglycemia are exposed, approximately, to three times the risk of SSI comparatively to LT recipients not exposed[13-16].

The concern about maintaining normoglycaemia in acute care facilities is not recent; several studies have been done including on clinical and surgical patients from some medical specialities showing the morbidity and mortality reduction throughout the adoption of strict glycaemic control protocols [17-19].

However, among critical surgical patients the LT recipients are highlighted; since they are exposed to impairment in blood glucose metabolism in the perioperative period as a consequence of an intraoperative acute stress state, blood loss and transfusions, the reperfusion phase, use of glucocorticoids and catecholamines[20, 21].

Results from previous studies pointed the hyperglycaemia among LT recipient as a frequent complication, 94% of them presented it at least once in the transplantation's postoperative period[22, 23].

The high blood glucose levels can produce electrolyte and acid-base disturbances besides altered plasmatic distribution of sodium[24]. There are impairments to the white blood cells activities, such as reduction in the adherence, chemotaxis, phagocytosis and superoxide formation. Lymphocytes apoptosis combined with T-cell activities suppression besides attenuation of immunoglobulin's work as a consequence of glycosylation[25, 26].

In spite of evidence from laboratory studies that indicate remarkable impairments caused by hyperglycemia in immune model animals immunologic system, uncertainties remain to evaluate the glycaemic control as a strategy for SSI prevention. Analysing the guidelines to prevent SSI published by World Health Organization[27], Centers for Disease Control and Prevention (United States of America)[1], National Institute for Health and Care Excellence (United Kingdom)[28], Society for Healthcare Epidemiology of America (United States of America)[29] and Brazilian Health Regulatory Agency[30] conditional recommendation regard the adoption of strategies to strict glycaemic control in the postoperative phase, besides there is no consensus about how glycaemic level could work as a protective factor for SSI among patients who underwent general surgeries.

Moreover, there have been few investigations evaluating the hyperglycaemia effects or blood glucose control in the postoperative phase of LT recipients[15, 16, 23, 31]. Besides the few studies concerned on the topic among LT recipients[14-16, 20, 23, 31], the majority of them were observational studies, designed as retrospective cohorts, which could compromise the body's evidence quality[14, 15, 20, 23, 31]. Besides that, in the previous studies enrolled patients underwent liver-kidney transplantation[14-16,31], which can cause negative impact on the effects of glycemic control analyses and there is research where recipients presented lower means of Model for End-Stage Liver Disease (MELD) from 19.0 to 28.2[14-16, 20, 23, 31] that are lower MELD means than the observed in Brazilian transplantation centres. Finally, we observed the absence of clear criteria for SSI diagnosis in some studies[15, 16, 20, 23].

It is known that the preoperative screening in living donor LT of donors and recipients as baseline characteristics are different of LT whose allografts came from deceased donors; for

instance, liver-kidney recipients who undergo to distinct immunosuppression schemes. Furthermore, lower MELD scores represent LT recipients that could be exposed to diverse risk factors for SSI when compared to LT recipients who the MELD score is higher[32].

Thus, it sounds appropriate that research aiming to evaluate the effect of strict blood glucose control on SSI incidence among LT recipients should be made. In addition, nurse-initiated blood glucose control protocols, among critically ill patients, are frequently developed[23, 33, 34]. And, a recent literature review pointed to the lack of prospective studies that addressed the evaluation of the outcomes of strict glycaemic control among LT recipients on SSI incidence[21].

The study hypothesis is: the postoperative strict glycaemic control reduces the SSI incidence among LT recipients.

2   RESEARCH OBJECTIVE

To evaluate the effects of a postoperative strict blood glucose control protocol comparatively to an institutional protocol on the SSI incidence among LT recipients.

3   METHODS

The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) were used to write this methods chapter[35].

It is a randomized open-label clinical trial, in other words, the researchers will not try to blind the patients[36]. Among the research designs, the randomized clinical trial stands out on the observational designs as a result of the greater capacity to demonstrate causality. It particularly stems from a random allocation process that could remove the possibility of effects observed being explained by differences between the use of co-interventions or by other bias in the outcomes analyses[37, 38].

This study will be performed by two groups, the first one composed of LT recipients who undergo a standard blood glucose protocol, standardized in the facility selected to conduct this research. That protocol consists in a glucose control according to the result of finger prick test and

subcutaneous injection of regular insulin (BG targeted 130 - 180 mg/dL). The second group will be constituted of patients who undergo a strict blood glucose control (BG target 80 - 130 mg/dL) by a continuous intravenous insulin infusion.

3.1 STUDY SETTING

The study will be conducted in a tertiary referral hospital, service provider for Brazilian Public Health System situated in the countryside of São Paulo State. It is an academic and research hospital licensed by Brazilian Ministry of Health to perform LT since 2009; 40 LT are done each year[39].

3.2 ELIGIBILITY CRITERIA

Patients eligible for the trial must be 18 years of age or older, recipients of LT whose allograft came from deceased donors.

The patients that underwent any kind of surgery with or without prosthesis implant in the 30 days before the LT or are submitted to multiple organ transplantation will be excluded from the trial.

3.3 SAMPLE SIZE

Based on previous studies that showed the reduction of any infection incidence among LT recipients the sample size was calculated on the basis of the primary hypothesis[16, 40]. 58 patients are required to have an 80% chance of detecting, as significant at the 5% level, a decrease in the primary outcome measure from 40% in the control group to 10% in the experimental group. Thus, the sample calculation pointed will need 29 patients allocated in each group.

3.4 SEQUENCE GENERATION AND CONCEALMENT

Participants will be randomly assigned to either standard control or strict control with a 1:1 allocation as a per computer-generated randomisation schedule; the procedure will be performed by an independent statistician.

The randomization schedule will be put into sequentially numbered sealed opaque envelopes by an external expert to research.

3.5 RECRUITMENT

All the candidates for LT or representatives, during the ambulatory pre-transplant evaluation in the facility selected to conduct the study, will be contacted by the to check the inclusion and exclusion criteria, as well to explain the possible risks and the benefits of participating in research following the consent form will be signed.

3.6 ALLOCATION

After the patients' acceptance in participating in the research, in the ICU admission, any bedside blood glucose reading equal or superior to 130 mg/dL in the first 24 hours of the postoperative period will determine the LT recipient's allocation in the study. The sealed opaque envelope will be opened by an independent Registered Nurse to allocate the participant in the standard blood glucose control group or strict blood glucose control group.

3.7 INTERVENTIONS

To implement the protocols of glycaemic control, the researcher has established, in an earlier study, a previous relationship with the surgeons and intensive care doctors[13]. Consequently, there will be for each LT recipient a medical order of the randomised intervention.

3.7.1 STRICT GLYCEMIC CONTROL GROUP

The strict protocol adopted to conduct the study was proposed by Keegan e Cols.[23] (2010) to be used among adult LT recipients that consists of a continuous intravenous insulin infusion. The targeted blood glucose range is 80-130 mg/dL. The procedure must be stopped when the patient can ingest at least 50% of liquid diet or receive bolus tube feedings (Appendix A).

3.8 STANDARD GLYCEMIC CONTROL GROUP

The control group will be submitted to the standard (targeted BG: 130-180 mg/dL) institutional blood glucose control that is an escalating subcutaneous insulin dose for a given blood glucose reading, as follows:

Figure 1 - Subcutaneous insulin scheme. São Paulo, 2017.

Blood glucose reading	Subcutaneous human regular insulin dose
≤ 180 mg/dL	-
≥181 mg/dL and ≤250 mg/dL	5 IU*
≥251 mg/dL and ≤300 mg/dL	10 IU*
≥301 mg/dL	15 IU*

* UI: International Unity.
Source: Facility selected to conduct the study.

3.9 THE BLOOD GLUCOSE MEASURE

As an institution routine, either the standard group and the strict group will be submitted to a finger prick test each hour by nursing staff, trained by the researcher, under the supervision of a Registered Nurse employing a bedside glucose meter (FreeStyle Precision Pro® Abbott) calibrated following the manufacturer advice.

3.10 PRIMARY OUTCOME

Surgical site infection following the Centers for Disease Control and Prevention defining criteria:

SSI occurs within 30 or 90 days after the operation and involves skin or subcutaneous tissue of the incision, deep soft tissues or organ and spaces, which were opened or manipulated during an operation[1].

LT does not involve the presence of implants left in place thereby the period for detecting SSI is within 30 days after the operation, where day 1 = the procedure date[1].

3.11 SECONDARY OUTCOMES

The frequency of variables between both groups will be analysed as follows:

- Hyperglycaemia > 250 mg/dL[23];

- Hypoglycaemia < 60 mg/dL[23];

- Time for SSI development;

- Time of mechanical ventilation through ICU stay;

- ICU stay;

- Postoperative ward stay;

- Death within 90 days after LT.

3.12 EVALUATION OF PRIMARY OUTCOME

3.12.1 Through hospital stay

The researcher will evaluate the surgical wound on alternate days before the dressing changes and patient's bathing.

3.12.2 The period following the hospital discharge until the 30th postoperative day

The researcher will contact the liver transplant recipient on alternate days by telephone to detect any signs and symptoms of SSI. Also, the surgical wound will be evaluated every 7 days during the ambulatory doctor's assessment.

3.12.3 Evaluation of surgical wound during the hospital stay and after discharge

Facing a suspected SSI case, given the CDC criteria fulfilment, immediately the researcher will communicate with the healthcare team and proceed to register in the nursing records.

After that, the researcher will take a picture of the surgical site, using a digital camera designated for this activity. The clinical records and image will be sent to the adjudication committee for evaluation.

3.13 ADJUDICATION COMMITTEE

Will be formed by three health professional experts on SSI diagnosis and treatment. They will evaluate the classification in SSI or non-SSI only for the research purpose. As a result, these procedures will not affect the implementation or not of SSI treatment by the healthcare team.

In regard to the establishment of adjudicated SSI, the committee will follow the CDC SSI defining criteria and the simple majority will be respected.

3.14 SAFETY MONITORING

For unicentric open-labelled clinical trial, the Data Safety Monitoring Inboard is not necessary, following the National Institutes of Health from United States of America statement[41]. However, when 50% of the collected sample is reached the interim analyses will be done by an

independent statistician and a health professional expert, according to the criteria: strongly positive or negative results and futility proposed by Holubkov and cols.[42].

3.15 ETHICAL PROCEDURES

University of Sao Paulo School of Nursing Ethics Committee approved the research proposal (Approval number 2.444.780).

All the legal requirements from resolution Nº 466/2012 of Brazilian National Health Council will be followed[43].

The data from donors will be collected from the recipient medical records. In Brazilian Transplant System, the identities of donors are not available in the recipient records as a measure to maintain confidentiality[44].

3.16 STATISTICAL ANALYSES PLAN

A Microsoft Excel for Mac 2011® database will be constructed. The data will be typed into two different files to ensure accuracy by an automated check. Afterwards, the data will be transferred to the software Statistical Package for the Social Sciences® for Windows® version 22.0.

The results will be computed with a statistician support, following the research objectives and methods. The following tests will be employed:

- Central tendency and dispersion measures.

- The categorical variables will be analysed by the Pearson's χ^2 test or Fisher's exact test.

- The continuous variables will be analysed by the Student t-test or Mann-Whitney.

- Survival analysis by Kaplan-Meier estimate and Log-rank test.

- Visual inspection of residuals from QQ plot will be used to determine the normality.

- The significant level adopted will be $\alpha=0,05$.

4 SCHEDULE

Activity	Semester/Year
✓ Data collection	1º - 2º/2018 and 1º/2019
✓ Visitor student program	2º/2019
✓ Write chapters: results, discussion and conclusion	1º/2020
✓ Dissertation completion, deposit and defense	2º/2020

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