Effects of Intensive Blood Glucose Control on Surgical Site Infection for Liver Transplant Recipients: A Randomized Controlled Trial

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ABSTRACT

Background. The evidence supporting intensive blood glucose control to prevent surgical site infections (SSIs) among liver transplant recipients is insufficient. We aimed to assess the effects of postoperative intensive blood glucose control (IBGC) against standard blood glucose control (SBGC) on the incidence of SSIs among adult liver transplant recipients.

Methods. We performed a randomized controlled trial (ClinicalTrials.gov identifier NCT03474666). The IBGC target was 80 to 130 mg/dL, and the SBGC target was below 180 mg/dL. Analyses were made on an intention-to-treat basis.

Results. Of the 41 recipients enrolled onto the trial, 20 were randomly allocated to the IBGC group and 21 to the SBGC group. There were no significant differences in SSIs among recipients allocated to either group (relative risk [RR], 0.78; 95% confidence interval [CI], 0.21-2.88; $P = .69$). Mean (SD) blood glucose levels were significantly lower in the IBGC group in the 24-hour period after surgery (145.0 [20.7] mg/dL and 230.2 [51.6] mg/dL; $P = .001$). While there were fewer episodes of hypoglycemia in the IBGC group, this was not statistically significant. There were no episodes of severe hypoglycemia in either group. Hyperglycemia and severe hyperglycemia were significantly more frequent in the SBGC group (RR, 0.70; 95% CI, 0.52-0.93; $P = .001$ and RR, 0.07; 95% CI, 0.01-0.48; $P = .001$, respectively). Length of hospital stay was significantly shorter for recipients in the IBGC group (13.1 [5.5] days vs 19.3 [12.1] days; $P = .04$).

Conclusions. Although this small trial did not find intensive control reduced SSI, it was associated with lower blood glucose levels, fewer episodes of hyperglycemia and severe hyperglycemia, and shorter length of hospital stay.

Surgical site infections (SSIs) are one of the most frequently occurring health care-associated infections and are an important infectious complication after liver transplant [1,2]. Deceased donor liver transplant recipients are among the highest patient groups for developing an SSI, with an incidence of 9.6% to 35.5% [3]. The consequences of developing an SSI for this group of patients are severe, with liver transplant recipients being twice as likely to experience graft loss or death, spending up to 24 additional days in hospital, having higher readmission rates, and costing up to an additional $130,000 US dollars [2,4-6].

Hyperglycemia is one of the risk factors for SSI and is common among liver transplant recipients, with an incidence of up to 94% in the first few hours after liver transplant [7,8]. Liver

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Clinical Trial Registration No.: NCT03474666.

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transplant recipients with hyperglycemia are 3 times more likely to develop an SSI than recipients without hyperglycemia [7−10].

Hyperglycemia can be prevented through blood glucose control, although the level of control has not been determined. Studies comparing intensive blood glucose protocols (glucose levels lower than 140 mg/dL) with standard protocols (glucose levels higher than 180 mg/dL) have found a reduction in SSIs [11,12]. However, these studies involve patients having cardiac surgery or trauma surgery and the findings may not be applicable to liver transplant recipients. Liver transplant recipients present different challenges from most other surgical patient groups because they commence immunosuppression therapy at the start of the intraoperative period and have longer than standard operation duration times (up to around 8 hours) [8].

A recent literature review highlighted the lack of prospective studies evaluating the outcome of intensive blood glucose control among liver transplant recipients on SSI incidence and called for more high-quality trials on this topic [13]. This article describes a clinical randomized trial designed to test the hypothesis that postoperative intensive blood glucose control reduces the incidence of SSI among liver transplant recipients.

MATERIALS AND METHODS

Design and Setting

This randomized controlled trial compares 2 blood glucose control protocols beginning at the postoperative admission to the intensive care unit (ICU). The primary outcome, SSI, was assessed at 30 days. Secondary outcomes were blood glucose levels, length of stay, and death. The study was conducted in a Brazilian teaching referral hospital. Participant enrollment took place between March 2018 and October 2019, with data collection continuing until January 2020. Ethical approval was obtained by the relevant Institutional Review Board. Participants were allowed to withdraw at any time, and anonymity, privacy, confidentiality, and data protection were maintained throughout the study. The study is registered at ClinicalTrials.gov (NCT03474666). Consolidated Standards of Reporting Trials reporting guidelines were followed.

Population

Since 2009, 342 liver transplants were performed at the selected center. The recipients' mean (SD) age was 55.5 (10.1) years, and 253 (73.9%) were male. The mean (SD) body index (calculated as weight in kilograms divided by height in meters squared) was 27.4 (4.66), with cirrhosis due to chronic hepatitis C as the primary cause leading to liver transplant (111 recipients; 32.4%), and the mean (SD) of Model of End-Stage Liver Disease score was 17.8 (7.0). The 1-year survival rate is around 87% on the entire cohort.

Participants

All liver transplant candidates attending preoperative patient assessment during the study recruitment dates who met the inclusion and exclusion criteria were invited to take part in the study, and informed consents were given. Inclusion criteria were 18 years of age or older and receiving a liver transplant from a deceased donor. Exclusion criteria were any previous surgery in the 30 days before the liver transplant.

Sample Size

The sample size was calculated based on a good-quality study of 777 liver transplant recipients, where the SSI rate was found to be 38% [2]. Fifty-eight recipients were needed to have an 80% chance of detecting, as significant at the 5% level, a decrease in SSI from 40% in the standard control group to 10% in the intensive control group. Thus, the sample would need 29 recipients allocated to each group.

Randomization and Allocation

A computer-generated random numbers table was used to allocate recipients to one of the 2 groups in a 1:1 ratio. Group allocations were placed inside sequentially numbered, sealed, opaque envelopes by an independent researcher. An independent critical care nurse opened the allocation envelope when the patient was admitted to the ICU, after the recipient had been enrolled onto the study.

Blinding

Patients were unaware of their group allocation status. ICU nursing staff who provided routine care and delivered insulin as per study protocol were aware of the recipients' allocation status. The panel that assessed SSI outcomes was blinded, and the researcher who collated secondary outcome data was aware of allocation status.

Interventions

Recipients were randomized to either intensive blood glucose control or standard blood glucose control protocols.

Intensive Blood Glucose Control Group

The intensive blood glucose control (IBGC) protocol was used in a previous study [7]. Continuous intravenous human regular insulin infusion with a targeted blood glucose level set between 80 and 130 mg/dL was initiated after surgery on admission to the ICU. The protocol was discontinued after 24 hours or earlier if recipients resumed at least 50% of their intake orally or through tube feeding. When the trial intervention discontinued, recipients received the standard glucose control protocol routinely implemented in the hospital for liver transplant recipients.

Standard Blood Glucose Control Group

The standard blood glucose control (SBGC) protocol was the standard protocol routinely used within the participating hospital. A sliding scale of subcutaneous human regular insulin for a given blood glucose reading, with a targeted blood glucose level set at < 180 mg/dL, was initiated on admission to the ICU and continued until the recipients' discharge from hospital. This range is recommended by the Centers for Diseases Control and Prevention (CDC) [1].

Blood Glucose Measurement

Blood glucose levels were read hourly for the first 48 hours. If patients were considered stable after 48 hours, readings were reduced to 4 times a day continuing until discharge from hospital. Blood samples were taken at the recipients' bedside using a capillary blood sample with a calibrated finger prick device (Abbot FreeStyle Precision Pro, Witney, Oxon, United Kingdom). If the recipient was receiving a high dose of vasopressors, which affects peripheral perfusion, a blood sample from an arterial line

was used instead. In the ICU, nurses adjusted the insulin doses, depending on the blood glucose level reading following the allocated protocol.

Outcome Measurements

Primary Outcome - SSI. The primary outcome was the incidence of superficial, deep, or organ/space SSIs diagnosed according to the CDC criteria [14].

All wounds were followed up for 30 days. While recipients were in the hospital, wound sites were photographed every second day. If recipients were discharged before 30 days, photographs were taken at the weekly outpatient clinic, and a validated post discharge SSI surveillance questionnaire was completed with recipients over the telephone [15].

A wound culture swab was taken from all recipients who displayed signs or symptoms of SSI and a computed tomography scan was carried out for all recipients who presented with pus in their abdominal drain. At the end of the study, all wound data (photographs, laboratory results, surveillance questionnaires, computed tomography scans) were assessed by a blinded adjudication panel comprising transplant clinicians or experts in SSI diagnosis.

Secondary Outcomes – Blood Glucose Levels, Length of Stay, and Death. Blood glucose levels were recorded hourly for the first 24-hour period after surgery while recipients received either the intensive or the standard glucose protocol and also during the follow-up period (hours 25-48) when both groups of recipients were receiving the hospital's standard glucose control. The following definitions were used: hypoglycemia - blood glucose level < 70 mg/dL [16], severe hypoglycemia - blood glucose level < 40 mg/dL [9], hyperglycemia -blood glucose level > 180 mg/dL and < 250 mg/dL [16], and severe hyperglycemia - blood glucose level ≥ 250 mg/dL [7].

Data relating to length of ICU stay, length of postoperative hospital stay, and incidences of death by any cause within 90 days after transplant were collated from recipients' electronic medical records [17].

Statistical Analysis

Analysis was based on intention-to-treat information. Categorical variables were analyzed by Pearson χ^2 test or Fisher exact test, as appropriate. Normality was tested using the Kolmogorov-Smirnov test. Continuous variables were analyzed by the Student t test for normally distributed data and the Mann-Whitney test for all other data. Variables that failed randomization and had significant differences among the groups were included in a Cox regression model based on residual analysis of the Schoenfeld test. All results are reported as relative risk (RR) at 95% confidence interval (CI). Statistical significance was set at $P = .05$. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 20.0 (IBM, Armonk, NY, United States) and Stata for Windows, version 12.0 (StataCorp, College Station, Tex, United States).

RESULTS

All 81 liver transplant candidates who attended the preassessment clinic during the recruitment phase of the study consented to participate. Two candidates underwent surgery in the 30 days prior to the liver transplant and were excluded from the study. Thirty-eight liver transplant candidates who consented to take part were not offered a transplant during the study period and were therefore unable to be enrolled onto the study. Forty-one liver transplant recipients were enrolled onto the study; 20 recipients were randomized to the IBGC group and 21 to the SBGC group. All 41 recipients had initial blood glucose higher than 180 mg/dL. One recipient from each group died within 24 hours of surgery before the completion of blood glucose protocols. There were no other losses to follow-up. Data from all randomized recipients, including the incomplete data from the 2 recipients who died within the first 24 hours, were included in the analysis (Fig 1). Data are reported for all outcomes specified at the outset of the study.

Baseline Characteristics

Liver transplant recipients randomized to the 2 groups were similar for all baseline demographic, medical history, and surgical characteristics. Although, while mean preanesthesia blood glucose levels were similar for IBGC and SBGC groups (126.2 vs 106.95 mg/dL; $P = .27$), the mean blood glucose level on admission to ICU was significantly higher among recipients allocated to the IBGC group than the SBGC group (222.8 vs 176.6 mg/dL; $P = .004$) (Table 1). Donors' characteristics by recipients' allocation group were also well matched. Although blood cultures from 2 donors in the SBGC group tested positive for oxacillin-resistant *Staphylococcus epidermidis*, and there were significantly more donors with a history of tobacco use in the SBGC group than the IBGC group (95.2% vs 60.0%; $P = .01$)

Outcomes

Surgical Site Infection. SSI outcome data are shown Table 2. The incidence of SSI among the entire cohort of liver transplant recipients was 19.5% (8/41 recipients). There were no significant differences in SSIs among recipients allocated to the IBGC group compared with the SBGC group (RR, 0.78; 95% CI, 0.21-2.88; $P = .69$). There was no significant difference by classification of SSI (superficial, deep, or organ space) between the 2 groups ($P = .35$). The main microorganisms identified from all culture swabs were *Staphylococcus aureus* (3; 37.5%); *Klebsiella pneumoniae* (2; 25.0%), *Escherichia coli* (2; 25.0%), and *Enterobacter cloacae* (1; 12.5%).

Blood Glucose Levels. In the initial 24-hour period after surgery, the mean blood glucose level for recipients allocated to the IBGC group was significantly lower than that observed among the SBGC group (145.0 vs 230.2 mg/dL; $P = .001$). In the follow-up period, 25 to 48 hours after the transplant, no significant differences were observed between the mean (SD) blood glucose levels for the IBGC and SBGC groups, 165 (38.6) mg/dL and 170.6 (30.0) mg/dL, respectively ($P = .66$).

There were fewer recipients in the IBGC group who presented with at least 1 episode of hypoglycemia in the initial 24 hours after liver transplant compared with those allocated to the SBGC group, with 2 (10.0%) and 3 (14.3%), respectively (RR, 0.70; 95% CI, 0.13-3.76); $P > .99$); this is not significant. Similarly, during the following 25- to 48-hour period, none of the recipients from the IBGC group and 1 recipient (4.8%) from SBGC group presented with hypoglycemia; this is not significant (RR, 7.33; 95% CI, 0.60-88.94; $P > .99$). None of the recipients assigned to either the IBGC or the SBGC group

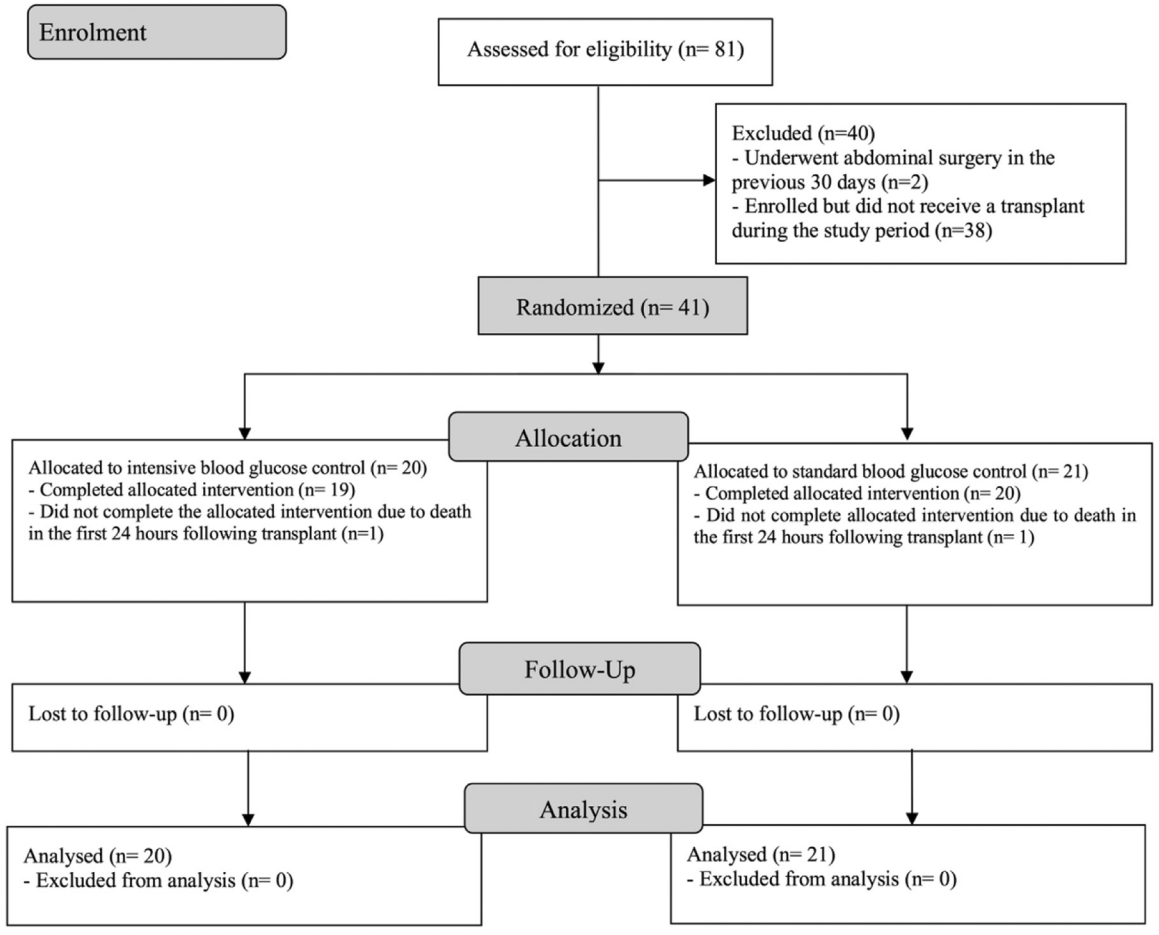

Fig 1. Trial enrollment and randomization flowchart

presented with severe hypoglycemia during the 48 hours after liver transplant.

During the initial 24 hour postoperative period, there were significantly more recipients in the SBGC group with at least 1 episode of hyperglycemia than in the IBGC group, with 21 (100.0%) and 14 (70.0%), respectively (RR, 0.70; 95% CI, 0.52-0.93; P = .001). Even after the intensive control protocol ended at 24 hours, there continued to be more recipients allocated to the SBGC group having hyperglycemia (18; 85.7%) than those in the IBGC group (9; 47.4%) (RR, 0.52; 95% CI, 0.31-0.87; P = .01). Similarly, during the initial 24-hour period, the number of recipients having at least 1 episode of severe hyperglycemia was significantly greater among recipients allocated to the SBGC group than the IBGC group, with 15 (71.4%) and 1 (5.0), respectively (RR, 0.07; 95% CI, 0.01-0.48; P = .001) (Table 2).

Length of Stay. Recipients in the IBGC group showed a tendency toward spending less time in the ICU than recipients in the SBGC group (8.7 vs 14.3 days, respectively; P = .07). The mean length of postoperative hospital stay was also significantly shorter, by around 6 days, for recipients having intensive control than those having standard control (13.1 vs 19.3 days, respectively; P = .04). Of the recipients who developed an SSI, the mean of postoperative length of stay for those having intensive control was 15.0 days compared with those having standard control 30.8 days; this was not significant (P = .15) (Table 2).

Deaths. Seven of the 41 recipients died (17.15%) by any cause within 90 days. Primary cause of death was septic shock (4/7; 57.1%), hemorrhagic shock (1/7; 14.3%), primary allograft dysfunction (1/7; 14.3%), and ischemic stroke (1/7; 14.3%) (Table 2). Four recipients in the IBGC group died (20.0%) compared with 3 recipients in the SC group (14.3%) (RR, 1.40; 95% CI, 0.35-5.48; P = .69); this is not significant.

There did not appear to be a relationship between SSI and deaths. Of the 8 recipients who developed an SSI, 3 died (37.5%), and of the 33 recipients who did not develop an SSI, 4 died (12.1%). This is not statistically significant (RR, 3.09; 95% CI, 0.85-11.15; P = .08). However, there did appear to be a significant relationship between deep incisional or organ space SSIs and deaths. Of the 5 recipients with a deep incisional or organ/space SSI, 3 died (60.0%), and of the 33 recipients who

Table 1. Recipient and Donor Baseline Characteristics

Variable	All Recipients N = 41	IBGC n = 20	SBGC n = 21	*P* Value
Recipient characteristics				
Age, mean (SD), y	55.7 (8.9)	54.9 (9.7)	56.6 (8.4)	.55*
Female sex, No. (%)	10 (24.4)	5 (25.0)	5 (23.8)	> .99†
Race, No. (%)				
White	31 (75.6)	16 (80.0)	15 (71.4)	.74‡
Black	3 (7.3)	1 (5.0)	2 (9.5)	
Multiracial	7 (17.1)	3 (15.0)	4 (19.0)	
BMI, mean (SD)	25.1 (4.6)	26.0 (4.0)	24.3 (5.0)	.23*
MELD score before transplant, mean (SD)	17.4 (6.5)	16.9 (5.3)	17.9 (7.5)	.62*
Pre-existing conditions, No. (%)				
Diabetes mellitus	14 (34.1)	6 (30.0)	8 (38.1)	.58‡
Hypertension	9 (21.9)	4 (20.0)	5 (23.8)	> .99‡
Dyslipidemias	1 (2.4)	1 (5.0)	0 (0.0)	.48‡
Previous abdominal surgery	12 (29.3)	7 (35.0)	5 (23.8)	.43‡
Pretransplant complications, No. (%)				
Ascites	27 (65.9)	15 (75.0)	12 (57.1)	.22‡
Encephalopathies	29 (70.7)	14 (70.0)	15 (71.4)	.92‡
Upper gastrointestinal hemorrhage	11 (26.8)	6 (30.0)	5 (23.8)	.65‡
Hepatorenal syndrome	2 (4.9)	1 (5.0)	1 (4.8)	> .99‡
Paracentesis	15 (36.6)	9 (45.0)	6 (28.6)	.27‡
CMV, No. (%)				
Positive CMV IgM	1 (2.4)	1 (5.0)	0 (0.0)	.48‡
Positive CMV IgG	36 (87.8)	17 (85.0)	19 (90.5)	.66‡
Positive hepatitis C virus, No. (%)	10 (24.4)	5 (25.0)	5 (23.8)	> .99‡
Donor characteristics by the recipient allocation group				
Age, mean (SD), y	43.9 (15.7)	44.0 (17.3)	43.8 (14.6)	.96*
Female sex, No. (%)	15 (36.6)	9 (45.0)	6 (28.6)	.27†
Race, No. (%)				
White	25 (61.0)	14 (70.0)	11 (52.4)	.27‡
Multiracial	10 (24.4)	5 (25.0)	5 (23.8)	
Black	6 (14.6)	1 (5.0)	5 (23.8)	
History of tobacco use, No. (%)	32 (78.0)	12 (60.0)	20 (95.2)	.01†
BMI, mean (SD)	25.2 (4.1)	25.5 (4.7)	24.9 (3.7)	.66*
Allograft weight, mean (SD), g	1446.1 (320.2)	1485.0 (384.2)	1407.2 (244.4)	.45*
ICU stay, median (IQR), d	4.0 (3.0-7.0)	5.5 (3.2-9.5)	4.0 (2.5-5.0)	.01§
Causa mortis, No. (%)				
Cardiovascular diseases	8 (19.5)	2 (10.0)	6 (28.6)	.27‡
Cerebrovascular diseases	24 (58.5)	12 (60.0)	12 (57.1)	
External causes	9 (21.9)	6 (30.0)	3 (14.3)	
Antibiotic use, No. (%)	27 (65.8)	13 (65.0)	14 (66.7)	.91†
Positive blood culture, No. (%)	2 (4.9)	0 (0.0)	2 (9.5)	.48‡
Positive CMV IgM, No. (%)	2 (4.9)	1 (5.0)	1 (4.8)	> .99‡
Positive CMV IgG, No. (%)	37 (90.2)	19 (95.0)	18 (85.7)	.60‡

BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CMV, cytomegalovirus; IBGC, intensive blood glucose control; ICU, intensive care unit; MELD, Model for End-Stage Liver Disease; SBGC, standard blood glucose control.

* Student *t* test.

† Pearson χ^2 test.

‡ Fisher exact test.

§ Mann-Whitney test.

did not develop an SSI, 4 (12.2%) died (RR, 4.95; 95% CI, 1.54-15.86; *P* = .01).

DISCUSSION

Blood Glucose Control and SSI

While this trial found fewer SSIs in the IBGC group, this was not statistically significant. This is a similar finding to 2 other randomized controlled trials (RCTs), 1 with 164 recipients [10] and 1 with 100 recipients [18] comparing blood glucose controls among liver transplant recipients. Neither of these 2 trials found a difference in SSI rates. Because the sample sizes in the 2 trials plus the present trial are comparatively small, it is possible that a larger study or meta-analysis may produce a different result. A systematic review published in 2017 including 2836 patients having a range of surgical procedures (except transplant

Table 2. Postsurgical Outcomes

Variable	All Recipients N = 41	IBGC n = 20	SBGC n = 21	*P* Value
Recipients with SSI, No. (%)	8 (19.5)	3 (15.0)	5 (23.8)	.69*
SSI by topography, No. (%)				
Incisional superficial	3 (37.5)	0 (0.0)	3 (60.0)	.35*
Deep incisional	3 (37.5)	2 (66.7)	1 (20.0)	
Organ/cavity	2 (25.0)	1 (33.3)	1 (20.0)	
Blood glucose 0-24 h after liver transplant, mean (SD), mg/dL	188.7 (58.2)	145.0 (20.7)	230.2 (51.5)	.001†
Blood glucose 25-48 h after liver transplant, mean (SD), mg/dL	168.0 (38.6)	165.2 (47.1)	170.6 (30.0)	.66†
Recipients having hypoglycemia 0-24 h after liver transplant, No. (%)	5 (12.2)	2 (10.0)	3 (14.3)	> .99*
Recipients having hypoglycemia 25-48 h after liver transplant, No. (%)	1 (2.5)	-	1 (4.8)	> .99*
Recipients having severe hypoglycemia 0-24 h after liver transplant, No. (%)	-	-	-	-
Recipients having severe hypoglycemia 25-48 h after liver transplant, No. (%)	-	-	-	-
Recipients having hyperglycemia 0-24 h after liver transplant, No. (%)	35 (85.4)	14 (70.0)	21 (100.0)	.001*
Recipients having hyperglycemia 25-48 h after transplant, No. (%)	27 (67.5)	9 (47.4)	18 (85.7)	.001*
Recipients having severe hyperglycemia 0-24h following liver transplant, n (%)	16 (39.0)	1 (5.0)	15 (71.4)	.001*
Recipients having severe hyperglycemia 25-48 h after liver transplant, No. (%)	11 (27.5)	3 (15.8)	8 (38.1)	.11*
Time on mechanical ventilation, mean (SD) h	17.8 (12.9)	19.6 (14.7)	16.2 (11.3)	.88†
Length of ICU stay, mean (SD), d	11.6 (10.0)	8.7 (5.4)	14.3 (12.5)	.07†
Length of postoperative hospital stay, mean (SD), d	16.3 (9.9)	13.1 (5.5)	19.3 (12.1)	.04†
Length of postoperative hospital stay for recipients with an SSI, mean (SD), d	24.8 (17.1)	15.0 (1.0)	30.8 (19.9)	.15†
Death to 90 d after transplant, No. (%)	7 (17.1)	4 (20.0)	3 (14.3)	.69*

IBGC, intensive blood glucose control; ICU, intensive care unit; SBGC, standard blood glucose control; SSI, surgical site infection.
* Fisher exact test.
† Student *t* test.

surgery) showed a 57% reduction in risk of SSI among patients having intensive glycemic control compared with those having standard control [19].

National guidelines remain cautious over recommendations. The updated Surgical Care Improvement Project recommends a blood glucose level < 180 mg/dL but only for patients post cardiac surgery [20]. The World Health Organization [21] supports perioperative blood glucose control but decided not to state an optimal blood glucose level because of lack of evidence, and the CDC [1] recommends perioperative glycemic control using target levels < 200 mg/dL.

Blood Glucose Levels, Length of Stay, and Death

Mean blood glucose levels in this study were significantly lower while recipients were receiving the intensive protocol. Wallia et al [10] also found significantly lower blood glucose levels among recipients allocated to the intensive blood glucose control compared with the standard control in the postoperative period. However, the levels in this study were not sufficiently low to increase the risk of hypoglycemia. While there were slightly fewer recipients in the intensive control group who presented with hypoglycemia during 0 to 24 hours and 25 to 48 hours, this was not significant, and no recipients in either group presented with severe hypoglycemia. Conversely, the Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation Study found an increased risk of hypoglycemia during hospitalization associated with an intensive blood glucose protocol in a study that included 3054 clinical and surgical patients [22].

This trial found recipients having intensive blood glucose control were at significantly lower risk of developing hyperglycemia or severe hyperglycemia during the first 24 hours while the protocols were in place. This continued in relation to hyperglycemia during the subsequent follow-up period (25-48 hours). Hyperglycemia and severe hyperglycemia are associated with higher rates of allograft rejection [23], prolonged mechanical ventilation [23], and death [24].

Recipients having the intensive blood glucose control tended to spend less time in the ICU and postoperatively spent an average of 6 days fewer in hospital. This is not supported by either of the 2 trials [10,18] that compared blood glucose controls in liver transplant recipients. These trials found no difference in duration of postoperative stay. To date, it would appear that no other studies have identified blood glucose levels as a predictor of postoperative length of stay [25−27]. This warrants further investigation because of the potential cost savings.

Death did not appear to be significantly associated with blood glucose control protocols in this trial or in an earlier systematic review comprising 17,582 surgical patients [28], although an association was found between death at 90 days and allocation to an intensive blood glucose protocol in the Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation Study [22]. However, death was associated with recipients having deep or organ/space infections [29,30]. This finding is consistent with 2 studies including 370 and 331 liver transplant recipients that estimated that patients who developed deep or organ/space SSIs were at higher risk of death at 30 and 90 days after transplant [29,30].

Strengths and limitations

This study appears to be the first RCT assessing the effects of blood glucose control on SSI as a primary outcome after liver

transplant. It benefits from using an internationally accepted definition for SSI, and SSIs were assessed by a blinded panel. Although it was not possible to extend the duration of the study in an attempt to reach full a priori sample size recruitment, the findings are valuable because they can contribute to a meta-analysis.

Implications for Research and Practice

This RCT finds the benefit of intensive glycemic control in reducing SSIs is uncertain. However, intensive blood glucose control is shown to be associated with shorter lengths of postoperative stay, reduced risk of hyperglycemia, no increased risk of hypoglycemia, and no episodes of severe hypoglycemia. Taking this into consideration, we cautiously suggest the use of intensive blood glucose control to reduce the length of stay and other complications arising from hyperglycemia but not as a measure to prevent SSIs among liver transplant recipients.

Because we found a tendency toward reduction in SSI in the IBGC group with this trial, which did not reach full recruitment, we suggest further larger RCTs comparing the effects of intensive blood glucose control against standard control after liver transplant with SSI as the primary outcome. These trials should follow Consolidated Standards of Reporting Trials and use a validated definition for SSI such as that given by the CDC [14].

This study was carried out in a single hospital in a middle-income country among deceased donor liver transplant recipients. It would be interesting to see if the results were supported by a multicentered trial in a developed country.

CONCLUSIONS

There were no significant differences in SSIs among recipients allocated to the IBGC group compared with the SBGC group. However, the study under-recruited, and a larger sample may have achieved significance. Recipients having intensive blood glucose protocol presented with significantly lower levels of blood glucose and fewer episodes of hyperglycemia but no episodes of severe hypoglycemia, and the risk of hypoglycemia was not increased. The length of postoperative hospital stay was significantly shorter among recipients allocated to intensive blood glucose control.

DATA AVAILABILITY

Data will be made available on request.

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