Randomized controlled trial of the effect of hyperinsulinemic normoglycemia during liver resection on postoperative hepatic function and surgical site infection

Keisuke Omiya^, Bon-Wook Koo, Hiroaki Sato, Tamaki Sato, Stanislas Kandelman, Abdulwahaab Nooh, Thomas Schricker

Department of Anesthesia, McGill University Health Centre Glen Site, Royal Victoria Hospital, Montreal, Canada

Contributions: (I) Conception and design: K Omiya, T Schricker; (II) Administrative support: H Sato, T Sato, T Schricker; (III) Provision of study materials or patients: K Omiya, H Sato, T Sato, T Schricker; (IV) Collection and assembly of data: K Omiya, BW Koo, H Sato, T Sato, S Kandelman, A Nooh; (V) Data analysis and interpretation: K Omiya, H Sato, T Sato, T Schricker; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Keisuke Omiya. Department of Anaesthesia, McGill University Health Centre Glen Site, Royal Victoria Hospital, 1001 Blvd, Decarie, Montreal, QC H4A3J1, Canada. Email: kohmiya@yamanashi.ac.jp.

Background: While avoidance of preoperative fasting followed by hyperinsulinemic-normoglycemic clamp (HNC) reduced postoperative hepatic dysfunction and surgical site infection (SSI), the effect of HNC restricted to the intraoperative period is unknown. This study examined whether HNC restricted to the intraoperative period has similar effects in patients undergoing elective liver resections.

Methods: This study is a post hoc exploratory analysis of a randomized-controlled trial in patients undergoing hepatobiliary surgery and receiving the HNC as a potential preventative intervention to reduce infectious morbidity postoperatively. Patients (>18 years old) undergoing elective transabdominal resection of liver malignancy were enrolled. We implemented the random allocation by labelling cards. Consenting patients were randomly assigned to receive the HNC during surgery or standard metabolic care. The HNC was initiated by insulin (2 mU/kg/min) followed by 20% dextrose infusion titrated to keep blood glucose between 4.0 and 6.0 mmol/L until the end of surgery. In the control group, glycemia >10.0 mmol/L prompted insulin treatment according to a standardized sliding scale. The primary outcome was hepatic function on postoperative day (POD) one, assessed by Schindl score. Secondary outcome was the incidence of SSIs within 30 days after surgery. The Schindl score was analyzed by Mann-Whitney U test and the incidence of SSIs was analyzed by Fisher's exact test. Two-sided P values <0.05 were considered statistically significant.

Results: From October 2018 to May 2022, 32 patients in the control group and 34 patients in the HNC group were analyzed. Patient characteristics were similar in the two groups. There was no significant difference in the mean Schindl score on POD1 between the HNC group and the control group (0.8±0.9 *vs.* 1.2±1.6, P=0.61). However, the incidence of SSIs in the HNC group was significantly lower than in the control group (6% *vs.* 31%, P=0.01).

Conclusions: The HNC restricted to the intraoperative period did not improve postoperative hepatic function but reduced SSIs. Preoperative carbohydrate loading may contribute to the preservation of hepatic function.

Trial Registration: ClinicalTrials.gov NCT01528189.

Keywords: Hyperinsulinemic-normoglycemic clamp (HNC); Schindl score; surgical site infection (SSI); liver resection

^ ORCID: 0000-0003-3882-5772.

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Introduction

Postoperative hepatic dysfunction is associated with morbidity in patients undergoing liver resection surgery (1,2). Previous studies had shown that the avoidance of preoperative fasting followed by strict maintenance of normoglycemia during surgery using the hyperinsulinemic-normoglycemic clamp (HNC) technique improved liver function and, led to a (non-significant) decreased incidence of infectious complications after hepatic cancer surgery (3,4). HNC can provide glucose nutritional support while avoiding glucotoxicity and it may increase liver glycogen and improve liver function (4,5). Furthermore, blood glucose levels are maintained between 4.0 and 6.0 mmol/L. The strict maintenance of a normal blood glucose levels may lead to decrease infectious complications (6). However, the effect of HNC restricted to the intraoperative period is unknown. This study examined whether HNC restricted to the intraoperative period has similar effects in patients undergoing elective liver resections and receiving standardized anesthesia care. We present the following article in accordance with the CONSORT reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3721/rc).

Highlight box

Key findings

- The hyperinsulinemic-normoglycemic clamp (HNC) restricted to the intraoperative period did not improve postoperative hepatic function but reduced surgical site infection (SSI).

What is known and what is new?

- Avoidance of preoperative fasting followed by HNC reduced postoperative hepatic dysfunction and SSI.
- This study tested whether HNC restricted to the intraoperative period has similar effects in patients undergoing elective liver resections. HNC restricted to the intraoperative period did not improve postoperative hepatic function but reduced SSI.

What is the implication, and what should change now?

- Preoperative carbohydrate loading may contribute to the preservation of hepatic function.

Methods

This study is a *post hoc* exploratory analysis of a randomized-controlled trial in patients undergoing hepatobiliary surgery and receiving the HNC (ClinicalTrials.gov NCT01528189). This study was performed in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the institutional ethics review board of McGill University Health Centre (No. 2019-4623) on 26 September 2018 and conducted between October 2018 and May 2022 at the Royal Victoria Hospital (McGill University Health Centre, Montreal, Quebec, Canada). Informed consent was taken from all the patients.

Study participants and eligibility criteria

Following approval from the McGill University Health Centre ethics review board, written informed consent was taken from patients scheduled for elective transabdominal resection of liver cancer. Patients <18 years, suffering from chronic liver disease (Child-Pugh grade B or C), and renal failure on dialysis were not eligible. Patients who did not receive epidural anesthesia and analgesia and those who were accidently given steroids intraoperatively were excluded from analysis.

Randomization

Patients were randomly assigned to receive standard metabolic care or HNC. We implemented the random allocation by labelling cards. Before surgery, a researcher took out a card from an envelope. Only the researcher who randomized the patient and the attending anesthesiologist were aware of the patient's group assignment. The surgical and postoperative care team as well as the patient were blinded to group allocation.

Blood glucose management

The HNC was initiated by insulin (2 mU/kg/min) followed by 20% dextrose infusion titrated to keep blood glucose between 4.0 and 6.0 mmol/L. Glucose levels were calibrated at

5–30 min intervals (StatStrip® Glucose Hospital Meter System, Nova Biomedical, Waltham, MA, USA) in blood samples taken from an intra-arterial catheter. The insulin infusion was stopped at the end of surgery, while 20% dextrose was kept in the post anesthesia care unit for at least one hour.

In the control group, blood glucose levels were measured at 30–60 min intervals. Glycaemia >10.0 mmol/L was treated with 2U of intravenous insulin followed by 1 U/h insulin infusion. Further adjustments were made according to a standardized sliding scale (Table S1, supporting information).

Anesthetic care

All patients received combined general and epidural anesthesia according to departmental guidelines. Epidural catheters were inserted at a thoracic level between Th7 and Th10. Epidural anesthesia was established and maintained by intermittent epidural boluses of bupivacaine. Postoperative epidural analgesia was provided by continuous epidural infusion of bupivacaine (0.1%) and fentanyl (2 μg/mL). General anesthesia was induced with intravenous fentanyl (1.5 μg/kg) and propofol (2–4 mg/kg). Intravenous rocuronium was used to provide complete surgical muscle relaxation throughout the procedure. Norepinephrine was infused to keep mean blood pressure above 65 mmHg. Normal saline was administered at 4–6 mL/kg/h. Albumin 5% was used to replace the first 500 mL blood loss. Ongoing needs for fluid replacement were met by blood transfusion aiming at a hematocrit >25%.

Perioperative clinical care

All patients were encouraged to ingest a preoperative carbohydrate drink (400 mL apple juice, equivalent to 40 g carbohydrates) two hours before surgery.

After the operation, glycaemia >10.0 mmol/L in all patients was treated with subcutaneous insulin according to a standardized sliding scale (Table S2, supporting information). Patients were allowed to take clear liquids accompanied by intravenous hydration with saline and dextrose (5%). The central venous catheter and nasogastric tube were removed after patients resumed a regular diet, typically within the first 12 and 24 postoperative hours. Early mobilization was encouraged.

Outcomes

The primary outcome was the patient's liver function as assessed by Schindl score (7) taking into account the total serum bilirubin, prothrombin time, serum lactate and presence or absence of encephalopathy, on postoperative day (POD) 1. The total scores of 0, 1–2, 3–4, or higher than 4 were used to classify hepatic dysfunction as none, mild, moderate, or severe, respectively (7).

Secondary outcome was the incidence of surgical site infections (SSIs) within 30 days of surgery. SSIs were defined according to the National Nosocomial Infections Surveillance system of the Centers for Disease Control and Prevention (8). By these criteria, SSIs are distinguished as being either incisional (superficial or deep) or organ/space. Criteria for a superficial incisional SSI included an infection occurring at the incision site within 30 days of surgery that involved only the skin and subcutaneous tissue and at least one of the following: bacteria isolated from the superficial incision; pus discharge from the incision; localized pain, tenderness, redness, swelling, or heat; and wound dehiscence. Criteria for a deep incisional SSI included an infection of the fascia or muscle related to the surgical procedure occurring within 30 days of surgery and at least one of the following: spontaneous dehiscence; pus drainage from the deep incision; or consider opening of the incision when the patient had the previously described signs and symptoms of infection. Criteria for an organ/space SSI included intraabdominal abscess within 30 days of surgery (an intraperitoneal collection of pus diagnosed by ultrasonography, computed tomography, or laparotomy).

Statistical analysis

Per protocol analysis was taken. Continuous data were analyzed by the unpaired *t* test or Mann-Whitney U test and proportions were analyzed by Fisher's exact test. The data were analyzed for normality using the Kolmogorov-Smirnov test. Two-sided P values <0.05 were considered statistically significant. All statistical analyses were performed using GraphPad Prism version 8 for Windows (GraphPad Software, San Diego, CA, USA).

Sample size calculation was based on the results of our previous study (3) showing a 35% lower Schindl score in the treatment group. In order to achieve a power level of 80%, with an alpha error of 5%, at least 26 patients were required in each group.

Results

A total of 88 patients were randomized. After eliminating

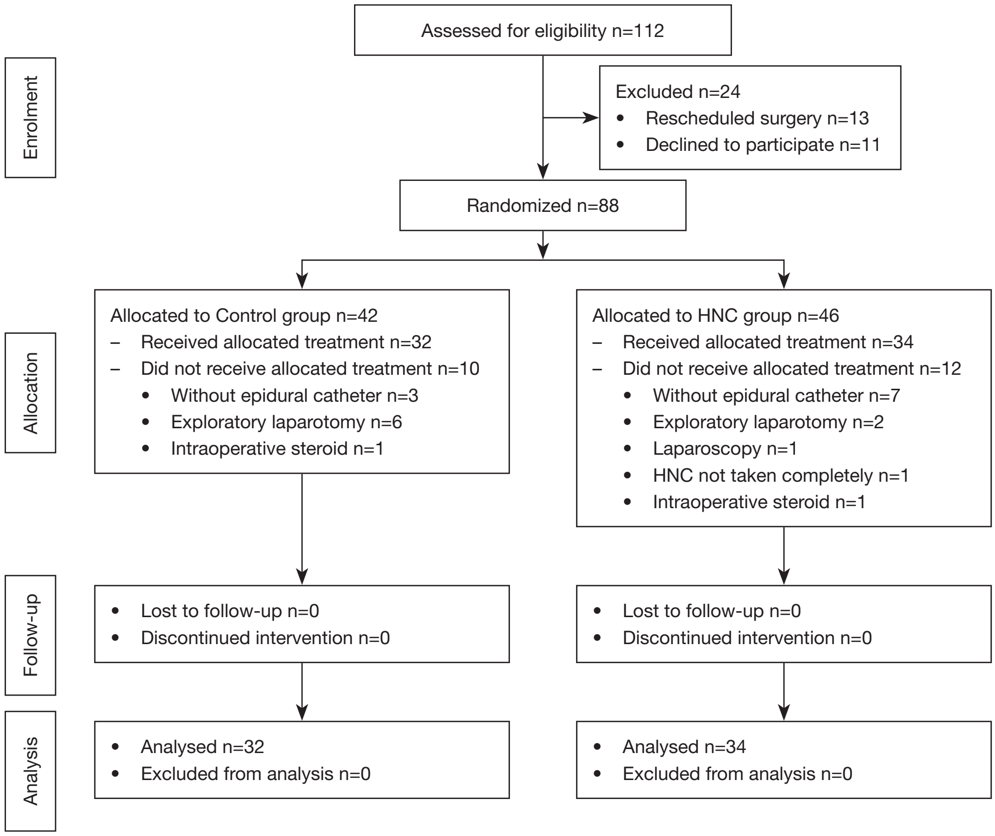

Figure 1 CONSORT diagram for the trial. HNC, hyperinsulinemic-normoglycemic clamp.

22 patients because of protocol violation (*Figure 1*), 32 patients were analyzed in the control group and 34 patients in the HNC group.

Patient characteristics as shown in *Table 1* were similar in the two groups. All patients with diabetes mellitus (DM) were type 2 DM.

Mean Schindl score was comparable on POD1 (HNC group: 0.8±0.9, control group: 1.2±1.6, P=0.61, *Table 2*). The incidence of SSIs in the HNC group (6%: one patient: organ/space SSIs and one patient: deep incisional SSI) was significantly lower than in the control group (31%: four patients: superficial incisional SSI, one patient: deep incisional SSI, four patients: organ/space SSIs and one patient: superficial incisional SSI and organ/space SSI, P=0.01, *Table 2*).

No severe hypoglycemia was observed in either study group (*Figure 2*).

Discussion

The results of the present study demonstrate that hyperinsulinemic normoglycemia using the HNC restricted to the intraoperative period does not improve hepatic function after liver resection but may reduce the incidence of SSIs.

The glycogen content of the liver has been identified as a key regulator of hepatic function (4,9). Hence fasting induced depletion of glycogen stores gains clinical relevance in patients undergoing liver surgery (4,10). Previous studies have shown that continuous preoperative intravenous glucose administration followed by the HNC technique during liver resection maintained hepatic glycogen and improved hepatic function (3,4). Perioperative metabolic therapy was associated with a significantly lower Schindl score (2.3±1.1) when compared to fasted patients (3.5±1.9) (3). Furthermore, a lower infectious morbidity was observed in the HNC group.

In the present study, while intraoperative HNC did not improve hepatic function, the average Schindl score of the control group was 1.2±1.6 indicating only mild liver dysfunction. Contrary to the previous trial, routine clinical care in the present protocol followed a clinical pathway including the prescription of a carbohydrate drink two

Table 1 Patient characteristics

Items	Control (n=32)	HNC (n=34)	P value
Age (y)	60.5±16.9	61.9±11.4	0.88
Female	15 [47]	14 [41]	0.80
BMI (kg/m^2)	26.4±5.6	27.7±5.3	0.34
Hypertension	9 [28]	15 [44]	0.21
Dyslipidemia	9 [28]	12 [35]	0.60
DM	4 [13]	10 [29]	0.13
HbA1c (%)	5.9±0.8	6.1±1.0	0.37
Fasting time before surgery (h)	14.8±2.9	13.7±2.6	0.10
Blood glucose levels before surgery (mmol/L)	5.7±0.9	6.2±1.3	0.06
No. of segments resected	2.0±1.1	2.1±1.0	0.57
Pringle maneuver	5 [16]	2 [6]	0.25
Duration of Pringle maneuver (min)	22.0±11.2	22.0±7.1	>0.99
Duration of surgery (min)	219.3±151.2	185.9±70.5	0.77
Estimated blood loss (mL)	685.3±379.9	695.6±539.0	0.93
Crystalloids (mL)	1,967.2±951.4	1,897.1±837.6	0.75
Artificial colloids (mL)	34.4±123.4	73.5±217.9	0.79
5% albumin (mL)	304.7±282.1	358.8±256.0	0.42
RBC (unit)	1.0±1.8	1.1±2.6	0.36
FFP (unit)	0.1±0.7	0.6±2.0	0.48
The infusion rate of norepinephrine (μg/kg/min)	0.04±0.04	0.05±0.03	0.40

Data are expressed as mean ± standard deviation or n [%]. The infusion rate of norepinephrine was the average during surgery. HNC, hyperinsulinemic-normoglycemic clamp; BMI, body mass index; DM, diabetes mellitus; HbA1c, glycated hemoglobin A1c; RBC, red blood cells; FFP, fresh frozen plasma.

Table 2 Clinical outcomes

Items	Control (n=32)	HNC (n=34)	P value
Schindl score on POD1	1.2±1.6	0.8±0.9	0.61
Hospital stay (d)	13.5±22.3	5.6±1.9	0.08
SSI within 30 days after surgery	10 [31]	2 [6]	0.01
Superficial incisional SSI	5 [16]	0 [0]	0.02
Deep incisional SSI	1 [3]	1 [3]	>0.99
Organ/space SSI	5 [16]	1 [3]	0.10

Data are expressed as mean ± standard deviation or n [%]. In the control group, one patient had superficial incisional SSI and organ/space SSI concurrently. HNC, hyperinsulinemic-normoglycemic clamp; POD, postoperative day; SSI, surgical site infection.

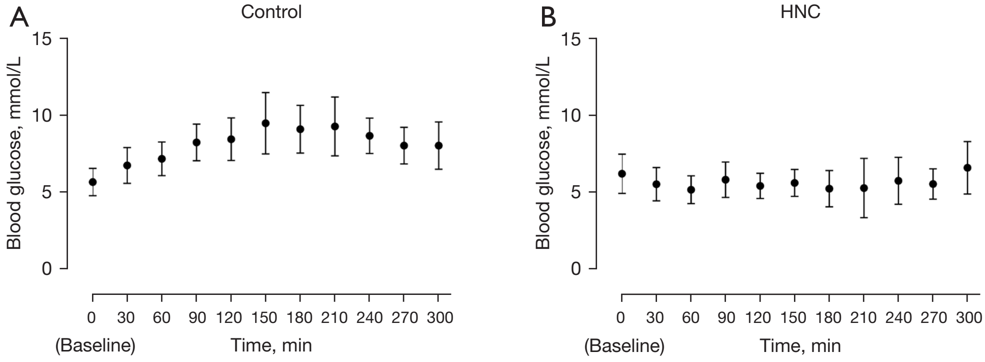

Figure 2 Time course of intraoperative blood glucose levels. Data are expressed as mean blood glucose levels ± standard deviation. (A) Control group. (B) HNC group. HNC, hyperinsulinemic-normoglycemic clamp.

hours before surgery. Although hepatic glycogen content could not be measured, one may speculate that preoperative carbohydrate loading attenuated or prevented glycogen depletion and subsequent liver dysfunction also in the control group. While the median number of resected liver segments in this study (two segments) were fewer than in the previous studies (four segments) (3,4), the Schindl score of the control group in the present study was almost one-third of previous studies. Therefore, one may speculate that the oral ingestion of a carbohydrate drink two hours before surgery contributed to the preservation of hepatic function.

In this study, patients receiving HNC developed less SSIs than patients receiving standard metabolic care. The following two mechanisms may have contributed: the effect of insulin itself and maintenance of normoglycemia.

While several intraoperative factors such as hypothermia, administration of volatile anesthetics, propofol and opioids impair the cellular immune response as required for proper wound healing (11), insulin has been shown to enhance neutrophil phagocytotic capacity (12,13) and decrease the incidence in infectious morbidity after cardiac surgery (6).

Secondly, a previous study demonstrates that strict maintenance of a normal blood glucose using HNC techniques similar to the one used in present protocol led to a nearly 50% reduction in blood stream and sternal wound infections in cardiac surgical and critically patient (6).

We acknowledge some limitations of the present study. Because of the small number of major hepatic resections (>three segments) in our cohort the hepatoprotective effects of HNC in these patients remain to be investigated. As we did not measure the liver glycogen content, we can only speculate that preoperative oral ingestion of carbohydrates mitigated glycogen depletion during surgery.

Conclusions

In non-fasted patients undergoing liver resection and receiving standardized anesthesia care, HNC during surgery has no significant influence on liver function. The intraoperative use of HNC, however, may have benefits for wound healing and the prevention of SSI.

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Footnote

Reporting Checklist: The authors have completed the CONSORT reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-3721/rc

Trial Protocol: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-3721/tp

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-3721/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3721/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The present study was performed in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional ethics review board of McGill University Health Centre (No. 2019-4623) and informed consent was taken from all the patients.

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Supplementary

Table S1 Intravenous insulin infusion sliding scale while in operating room

Blood glucose (mmol/L)	Action
<4.0	Stop insulin infusion. Give 10 mL infusion of dextrose (20%) and recheck level in 10 min
4.0–7.9	Maintain current infusion rate
8.0–10.0	Increase insulin infusion by 1 U/h
>10.0	Increase insulin infusion by 2 U/h

Table S2 Subcutaneous insulin sliding scale after surgery

Blood glucose (mmol/L)	Insulin dose (units)	Additional instructions
<4.0	0	Contact on-call doctor
4.0–9.9	0	
10.0–11.9	2	
12.0–13.9	4	
14.0–15.9	6	
16.0–17.9	8	
18.0–20.0	10	
>20.0	12	Contact on-call doctor

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