ELSEVIER

Nutrition 24 (2008) 1217–1219

NUTRITION

www.elsevier.com/locate/nut

International ward rounds

Hepatic protection by perioperative metabolic support?

Mazen Hassanain, M.D.[a], Thomas Schricker, M.D., Ph.D.[b], Peter Metrakos, M.D.[a], George Carvalho, M.D.[b], Dionisios Vrochides, M.D.[a], and Ralph Lattermann, M.D., Ph.D.[b,*]

[a] *Department of Surgery, McGill University, Royal Victoria Hospital, Montreal, Quebec, Canada*
[b] *Department of Anaesthesia, McGill University, Royal Victoria Hospital, Montreal, Quebec, Canada*

Manuscript received July 23, 2007; accepted May 17, 2008.

Abstract

Objective: We report the case of a 63-y-old woman undergoing left hepatectomy for hilar cholangiocarcinoma who was at high risk of postoperative liver failure due to an atrophic right liver lobe. She participated in a randomized clinical trial investigating the effect of perioperative glucose infusion on hepatic function after major liver resection.

Methods: Intravenous glucose was initiated the night before the operation at 2 $mg \cdot kg^{-1} \cdot min^{-1}$. During and after the operation, glucose was administered with a continuous insulin infusion until the first postoperative day. Postoperative liver function was assessed by the score proposed by Schindl, evaluating total serum bilirubin and plasma lactate concentrations, prothrombin time, and the grade of encephalopathy.

Results: The patient's liver dysfunction was classified as "mild" on postoperative day 1 and as "none" on postoperative day 2. Postoperative liver function scores were better than those observed in a control group of patients who underwent hepatic resection of similar magnitude without glucose/insulin therapy.

Conclusion: Perioperative glucose/insulin administration was associated with a surprisingly small deterioration of liver function after left lobe liver resection in the presence of an atrophic right lobe. A randomized clinical trial will have to determine whether glucose/insulin therapy can improve hepatic function after major liver resections.

Keywords: Liver surgery; Liver failure; Glucose; Insulin

Introduction

Advances in anesthetic and surgical care have expanded the indications for major hepatectomy, i.e., the removal of three or more liver segments. Although this operation carries a relatively low mortality rate, it is still associated with significant morbidity [1,2]. Depending on the extent of the resection and the definition of liver dysfunction, the incidence of postoperative liver failure ranges between 20% and 70% [2–4].

Low hepatic glycogen content, a consequence of preoperative fasting and surgical trauma, has been shown to limit the liver's capacity to regenerate in response to injury [5,6]. Conversely, maintaining hepatic glycogen stores by providing intravenous glucose perioperatively has been shown to improve surgical outcomes [5,7,8].

Case report

We describe a patient who underwent left hepatectomy for hilar cholangiocarcinoma and participated in a randomized clinical trial designed to study the effect of glucose infusion on hepatic function after major liver resection. Her clinical course was complicated by the unexpected finding of an atrophic right liver lobe during surgery, leaving the patient with minimal vital liver tissue and a high risk of postoperative liver failure.

DB is a 63-y-old, jaundiced Caucasian woman with a body mass index of 26 kg/m^2. She presented with severe jaundice and her blood tests showed a total bilirubin level of 386 μmol/L, an alanine transaminase (ALT) level of 50 U/L, an aspartate transaminase (AST) level of 55 U/L, an

* Corresponding author. Tel.: +514-934-1934, ext. 35802; fax: +514-843-1723.

E-mail address: ralph.lattermann@muhc.mcgill.ca (R. Lattermann).

0899-9007/08/$ – see front matter
doi:10.1016/j.nut.2008.05.019

international normalized ratio (INR) of 1.17, and an albumin level of 27 g/L. Renal function parameters and blood cell count were normal. A triphasic computed tomographic scan demonstrated evidence of intrahepatic duct dilatation with a cutoff sign at the proximal common bile duct (CBD). The magnetic resonance cholangiopancreatogram confirmed the presence of a proximal CBD mass with extension into the left duct system. An endoscopic retrograde cholangiopancreatogram revealed similar findings and a covered plastic stent was inserted. Four weeks later, the patient's total bilirubin level decreased to 46 μmol/L and she was scheduled for resection of the left hepatic and caudate lobe. The patient consented to participate in a study on the effect of perioperative intravenous glucose administration on liver function after liver resection and was randomized to the treatment group. As per study protocol, on the day before surgery, she received three meals providing a total of 35 kcal/kg (60% carbohydrate, 20% protein, and 20% fat). At 2000 h, a continuous infusion of 10% glucose was initiated at a rate of 2 $mg \cdot kg^{-1} \cdot min^{-1}$. On arrival in the operating room, an epidural catheter was inserted at the thoracic level T6/7 and a bilateral segmental sensory block was produced with 0.5% bupivacaine. After induction of general anesthesia, the 10% glucose solution was replaced by 20% glucose with 30 mmol/L of potassium phosphate, and intravenous insulin commenced at 2 $mU \cdot kg^{-1} \cdot min^{-1}$ to avoid hyperglycemia. Blood glucose was measured every 5–10 min and the glucose infusion rate was adjusted to maintain normoglycemia, i.e., a blood glucose level between 4 and 6 mmol/L.

The laparotomy did not reveal any evidence of distant metastasis. Portohepatic dissection was performed and the portal triad was identified. In accordance with the preoperative imaging results, a small solid mass was palpated at the proximal CBD extending into the left duct system.

The decision was made to proceed with the planned procedure, i.e., resection of the left hepatic and caudate lobe. The left liver lobe was mobilized, and the left vascular inflow was taken down together with the adjacent lymphatic tissue. Thereafter, the CBD was resected just above the duodenum and portal lymph node dissection was carried out. This facilitated better examination of the proximal bile duct, which revealed cancer extension into the secondary radicals of the right system. There was no bile return from the right side and mucus discharge was noticed. The right liver lobe also appeared atrophic. It had to be concluded that the cancer was unresectable. The patient unfortunately had lost her functioning left liver lobe during prior dissection and the caudate lobe was the only vital segment. In light of the small amount of remaining viable liver tissue, the surgical team considered urgent listing for liver transplantation, but decided to use the damage control principles. To minimize further trauma to the vital liver tissue, the bile ducts (anterior right and posterior right) were externally drained, the abdomen was packed open, and the patient was transferred intubated to the intensive care unit. The duration of surgery was 3 h 55 min. The estimated blood loss was 500 mL and a total of 4500 mL of crystalloid fluid was administered. The patient's relatives were informed of the high likelihood of liver failure and the potential urgent need of a liver transplant.

Epidural analgesia was maintained by the continuous infusion of 0.1% bupivacaine with 3 μg/mL of fentanyl at a rate of 8–12 mL/h. On arrival in the intensive care unit, the insulin infusion rate was reduced to 1 $mU \cdot kg^{-1} \cdot min^{-1}$ and the glucose infusion adjusted accordingly to maintain normoglycemia, i.e., a blood glucose level between 4 and 6 mmol/L. In the first 2 h after the operation, there was no bile production. ALT peaked to 472 U/L, AST to 519 U/L, INR to 1.17, lactate to 1.4 mmol/L, total bilirubin to 47 μmol/L, alkaline phosphatase to 233 U/L, and white blood cell count to 13×10^9/L. In the following 8 h, 100 mL of bile was produced. After 12 h, the patient was extubated with no signs of encephalopathy. The ALT and AST levels were approximately 400 U/L, INR was 1.59, lactate was 1.5 mmol/L, total bilirubin was 44.5 μmol/L, alkaline phosphatase was 218 U/L, and the white blood cell count was 11.4×10^9/L.

By the end of postoperative day 1, the glucose and insulin infusions were stopped, and oral food intake was commenced and well tolerated. The total amount of glucose administered was 108 g before and 170 g during and after the operation.

On postoperative day 3, 400 mL of bile was produced every 8 h and there was no evidence of encephalopathy. ALT and AST levels were approximately 200 U/L, INR was 1.13, lactate was normal, total bilirubin was 27 μmol/L, and the white blood cell count was 12×10^9/L. The patient returned to the operating room for reconstruction of her bile duct system. The abdomen was closed and a drain was left at the anastomosis site.

By postoperative day 7, the patient had normal liver enzyme levels, a normal coagulation profile, and a total bilirubin level of 24 μmol/L. The drain was removed on day 10 and the patient was discharged on day 15.

Discussion

The patient's postoperative liver function scores were better than those observed in a control group of patients who underwent hepatic resection of similar magnitude without receiving glucose/insulin therapy (Table 1). This surprisingly uncomplicated recovery despite the minimal amount of remaining viable liver tissue lends further support to the hypothesis that the preoperative restoration of hepatic glycogen stores may prevent or attenuate hepatic dysfunction after extensive liver resection. Results from animal studies have indicated that the preservation of hepatic glycogen increases the liver's tolerance to oxidative and ischemic stresses [5,6,9–11]. In perfused rat livers, hepatocyte integrity after continuous perfusion and warm ischemia was notably impaired in glycogen-

Table 1
Liver dysfunction score as proposed by Schindl et al. [3] in patient DB versus control patients*

	Segments removed	6 h after surgery	POD 1	POD 2	POD 7
Patient DB	4	1	1	0	0
Control ($n = 5$)	4.1	2.4 ± 1.3	1.8 ± 1.9	1.6 ± 0.5	2.0 ± 2.8

Control, no metabolic therapy; POD, postoperative day

* Values are means ± SDs. Severity of hepatic dysfunction as assessed by the score proposed by Schindl et al.: 0, none; 1–2, mild; 3–4, moderate; >4, severe.

depleted animals compared with animals with preserved hepatic glycogen [5]. Fasting was also associated with increased lipid peroxidation in response to liver reperfusion, which may contribute to the induction of organ failure [10]. Furthermore, maintenance of hepatic glycogen content reduced the oxidative damage in normal and fatty rat livers exposed to ischemia–reperfusion injury [11]. In fact, the extent of oxidative damage in mitochondria positively correlated with prolonged food deprivation. A beneficial effect of preserving hepatic glycogen has also been demonstrated in allogenic liver transplantation in humans as reflected in improved graft function [12,13].

The continuous infusion of insulin may have also contributed to the patient's remarkable clinical course. Insulin, especially when administered at higher doses, exerts nonmetabolic effects including anti-inflammatory, antioxidative, and cardioprotective effects, with particular benefits for patients exposed to major surgical trauma [14].

It is of further interest to note that this patient received epidural anesthesia during surgery followed by postoperative epidural analgesia using local anesthetic. Neuraxial blockade has long been recognized to suppress the counterregulatory endocrine responses to abdominal surgery, thereby reducing glycogenolysis and gluconeogenesis and facilitating the formation of hepatic glycogen [15].

Conclusion

In conclusion, perioperative glucose/insulin administration was associated with an unexpectedly small deterioration of liver function after left lobe liver resection in the presence of an atrophic right lobe. A large randomized clinical trial is necessary to determine whether glucose/insulin therapy can improve hepatic function after major liver resections.

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