의학석사 학위논문

Insulin Therapy for Postreperfusion Hyperglycemia During Liver Transplantation

간이식 수술 중의 재관류 후 고혈당증에 대한 인슐린 치료

2018 년 2 월

서울대학교 대학원

의학과 마취통증의학 전공

김 보 림

A thesis of the Degree of Master of Medical Science

간이식 수술 중의 재관류 후 고혈당증에 대한 인슐린 치료

Insulin Therapy for Postreperfusion Hyperglycemia During Liver Transplantation

February 2018

Seoul National University College of Medicine

Department of Anesthesiology and Pain Medicine

Bo Rim Kim

ABSTRACT

Introduction: Glycemic control during liver transplantation can be challenging, especially after reperfusion of the liver graft. Numerous confounding factors make it difficult to predict glucose response to insulin during liver transplantation surgery.

Methods: 13-years of data were retrospectively analyzed to determine the relationship between the insulin dose and blood glucose levels in liver transplantation. Patients were divided into two groups according to insulin responsiveness. The probability and degree of responsiveness to insulin were calculated with probit regression analysis and multiple linear regression equation.

Results: Hyperglycemia was more common and severe in the postreperfusion period than in the prereperfusion period. Of 797 insulin administrations, 299 (37.5%) showed insulin resistance. DM patients were more resistant to insulin therapy showing greater 50% effective dose of insulin compared to non-DM patients during postreperfusion period. Reperfusion periods, history of DM, pretreatment glucose level, and sampling interval were determinants of insulin

dose-related changes in blood glucose. Assuming a glucose target of 180 mg/dL and a sampling interval of 20 minutes, a simple formula of glycemic control during postreperfusion period was derived as follows: glucose reduction (mg/dL) = 11.4 + 0.4 x insulin dose (IU) – 7.0 x history of DM (negative = 0, positive = 1).

Conclusion: Commonly administered doses of insulin seems mostly inadequate to treat postreperfusion hyperglycemia. The findings of this study will help establish guidelines to treat refractory hyperglycemia during liver transplantation.

Key Words: Diabetes Mellitus, Glycemic control, Hyperglycemia, Insulin, Insulin dose, Liver transplantation, Postreperfusion period

Abbreviations: DM = diabetes mellitus; ED50 = effective dose with 50% probability of responsiveness; ED95 = effective dose with 95% probability of responsiveness

Student number: 2015-23229

CONTENTS

LIST OF TABLES AND FIGURES

Tables

Figures

INTRODUCTION

Liver recipients show various degree of hyperglycemia during liver transplantation surgery. Hyperglycemia is frequent and severe, especially after graft reperfusion despite insulin therapy (1, 2). Glucose release from the graft liver, poor graft function, surgical and anesthetic stress, transfusion, organ preservative and immunosuppressants have been suggested as potential causes of postreperfusion hyperglycemia (3). Studies have shown that hyperglycemia during liver transplantation is associated with adverse postoperative outcomes such as increased 30-day infection and 1-year mortality, surgical site infection and acute kidney injury (4-6). These reports also suggest that glycemic control may contribute to the reduction of morbidity and mortality of liver recipients.

Perioperative glucose control is achieved through continuous infusion of insulin, whereas intermittent bolus of insulin using a sliding scale has been widely recommended for intraoperative glucose control due to its simplicity and safety (7, 8). However, since postreperfusion hyperglycemia is often refractory due to complex factors, empirical insulin dosing strategy based on clinical experience is frequently ineffective. Inadequate insulin administration may delay treatment and increase the number of unnecessary blood sampling. With no evidence-based consensus or treatment guidelines, determining the appropriate bolus dose of insulin to control intraoperative hyperglycemia during liver transplantation is very challenging.

The primary aim of this study is to retrospectively investigate the dose-response relationship between insulin doses and serum glucose levels in liver transplantations using 13-year record of Seoul National University Hospital. To evaluate the confounding factors that affect the inconsistent effects of insulin during liver transplantation surgery is another objective of the study.

MATERIALS AND METHODS

The institutional review board of Seoul National University Hospital approved the study protocol (H-1401-076-550). Informed consent was waived due to the retrospective design of this study.

Patient selection

Data from adult liver recipients (>18 years old) who underwent liver transplantation between October 2004 and February 2016 were analyzed. Patient data were retrieved from the electronic medical records system and the electronic anesthesia records. Patients who did not require insulin or received continuous infusion of insulin were excluded. Unmatched samples and samples at an inaccurate time were also excluded. Pretreatment or posttreatment blood glucose level data without a verifiable dose of insulin were excluded from the analysis.

Data collection

Patient characteristics including age, sex, weight, history of diabetes mellitus (DM), and preoperative insulin use were recorded. Amount of transfused red blood cells was recorded from electronic anesthesia chart.

Intraoperative blood glucose tests were performed with a point-of-care device (GEM Premier 3000, Instrumentation Laboratory, Bedford, MA, USA)

using the blood sampled from the radial artery. According to the anesthesia protocol of Seoul National University Hospital, blood glucose tests were routinely performed 4 times during the prereperfusion period (immediate after anesthesia induction; 60 minutes after induction; after hepatectomy; and 5 minutes before graft reperfusion) and 4 times during the postreperfusion period (5 minutes after graft reperfusion; 20 minutes after graft reperfusion, after hepatic artery anastomosis; and before surgery end). Additional blood glucose levels were tested when insulin was administered.

Intravenous human regular insulin (Humulin R, Lilly USA, LLC, Indianapolis, IN, USA) was used to treat intraoperative hyperglycemia. The dose of insulin and changes in glucose concentrations were recorded. All insulin boluses were administered immediately after measuring the pretreatment glucose level, however posttreatment glucose levels were checked at irregular intervals. Considering the onset and duration of intravenously administered insulin (9), only glucose levels that were measured between 15 and 60 minutes after insulin administration were considered for analysis, and the sampling interval was recorded.

Statistical analysis

The degree and prevalence of hyperglycemia were assessed with all blood samples measured at 8 sampling time points.

Delta glucose (Δglucose) was the primary outcome variable defined as the difference between pretreatment glucose concentration and posttreatment

glucose concentration. Patients were divided into either the insulin-responsive group (Δglucose >0 mg/dL) or the insulin-resistant group (Δglucose ≤0 mg/dL). The difference between the values of the two groups were expressed as the absolute standardized difference.

Insulin responsiveness was measured by the probability and degree of blood glucose changes to the insulin dose. Probit regression analyses were performed to calculate probability of responsiveness and corresponding insulin dose during postreperfusion period (10). Effective doses of insulin with 50% probability (ED50) and 95% probability (ED95) of responsiveness were evaluated with probit sigmoid dose-response curve.

A multiple linear regression model was built with stepwise selection method in the insulin responsive group to measure the degree of insulin responsiveness. Age, gender, weight, histories of DM and preoperative insulin use, administered insulin dose, pretreatment glucose level, sampling interval and either prereperfusion or postreperfusion period were independent risk factors, and the value of Δglucose was the dependent outcome. A multivariable equation was then reduced to have the insulin dose as the only independent variable by fixing other variables.

Probabilities of responsiveness were linked to Δglucose calculated from multiple linear regression equation via insulin doses calculated with probit curves for better comprehension of the combined results. A calculation table was provided as a practical guide of the insulin therapy.

SPSS software (version 21.0, IBM Corp., Armonk, NY, USA) and MedCalc (version 16.8.4, www.medcalc.org, Mariakerke, Belgium) were used for statistical analyses. A *P*-value <0.05 was considered significant.

RESULTS

A total of 11160 blood glucose levels were measured in 1421 liver recipients, of whom 126 pediatric patients were excluded (Fig. 1). After exclusion due to no insulin use, unmatched sample pairs and inaccurate sampling timing, a total of 797 insulin administrations in 539 patients were included in the final analysis.

Data from 1295 patients showed that hyperglycemia was more common after reperfusion of graft (Fig. 2). Blood glucose level continuously increased intraoperatively despite routine insulin treatment. There were no hypoglycemia events in any patient.

Of 797 insulin administrations, 299 (37.5%) showed insulin resistance (Table 1). A large difference was observed in the values of posttreatment glucose level, Δglucose, and Δglucose per unit insulin between the insulin-responsive and insulin-resistant groups. In the insulin-resistant group, insulin resistance was relatively frequent during the postreperfusion period compared to the prereperfusion period (41.4% [263/636] vs 22.4% [36/161]).

Probability of response curves show dose-response curves of insulin with 95% confidence interval during postreperfusion period in patients with DM (n = 117) and without DM (n = 519) (Fig. 3). The ED50 was greater but the ED95 was smaller in DM patients compared to patients without DM. The probit model equations for postreperfusion period are as follows;

DM (+): Probit(p) = 0.12 x insulin (unit) - 0.77 (P <0.001)

DM (-): Probit(p) = 0.05 x insulin (unit) - 0.13 (P <0.001)

After testing for multicollinearity, a multiple linear regression model determined reperfusion period, history of DM, pretreatment glucose level, sampling interval, and insulin dose as significant predictors of Δglucose after insulin administration (P <0.001, R = 0.52, adjusted R^2 = 0.27) (Table 2). The postreperfusion period and history of DM were negative predictors of Δglucose, and others were positive predictors. The predicted Δglucose can be calculated with the following multivariable equation.

Δglucose (mg/dL) = -10.5 – 20.1 x reperfusion period (prereperfusion = 0, postreperfusion = 1) – 7.0 x history of DM (negative = 0, positive = 1) + 0.2 x pretreatment glucose (mg/dL) + 0.3 x sampling interval (min) + 0.4 x insulin dose (IU)

The equation was reduced to assume the insulin therapy. If insulin is administered at glucose level of 180 mg/dL then the glucose level is checked 20 minutes later at the peak effect during the postreperfusion period, the expected Δglucose is calculated as follows;

Δglucose (mg/dL) = 11.4 + 0.4 x insulin dose (IU) – 7.0 x history of DM (negative = 0, positive = 1)

Probability of response and predicted Δglucose would depend on the

administered insulin dose (Table 3). For example, 5 units of insulin may decrease the blood glucose level by about 6 mg/dL with a probability of 44%, whereas 20 units of insulin can decrease the blood glucose level by 12 mg/dL with 96% probability in DM patients. The probability of response and the magnitude of the effect to the same dose of insulin are greater in patients without DM compared to those with DM.

Table 1. Comparison between insulin responsive and insulin resistant

	Insulin-responsive (n = 387)	Insulin-resistant (n = 243)	ASD
No of insulin use	498	299	
Prereperfusion period (%)	125 (15.7%)	36 (4.5%)	0.341
Postreperfusion period (%)	373 (46.8%)	263 (33.0%)	
Gender (M/F)	278/109	188/55	0.092
Age (years)	59 (54, 64)	59 (54, 65)	0.013
Weight (kg)	61 (54, 69)	60 (53, 68)	0.044
History of diabetes mellitus	72 (18.6%)	51 (21.0%)	<0.001
Preoperative insulin use	20 (5.2%)	13 (5.3%)	0.100
Erythrocytes transfusion (units)	7 (3, 14)	8 (4,14)	0.071
Glucose before treatment (mg/dL)	219 (205, 245)	213 (200, 228)	0.258
Glucose after treatment (mg/dL)	198 (179, 223)	228 (213, 250)	0.782
Insulin dose (IU)	6 (5, 10)	5 (4, 10)	0.357
Insulin dose/Wt (mIU/kg)	110 (70, 160)	90 (60, 140)	0.32
Sampling interval (min)	40 (28, 50)	36 (23, 50)	0.203
Δglucose (mg/dL)	20 (10, 36)	-13 (-27, -5)	1.847
Δglucose/unit insulin (mg/dL/IU)	2.7 (1.3, 5.2)	-2.3 (-5.1, -0.7)	1.381

groups

Data are number (%) or median (interquartile range).

Insulin responsive group included patients with Δglucose >0 mg/dL, and insulin resistant group included the remaining.

Total number of patients is 539, however some patients have duplicated entries in both groups.

Abbreviations: ASD = absolute standardized difference; Δglucose = change of blood glucose levels after insulin administration.

Table 2. Multiple linear regression to predict blood glucose change after insulin administration in the insulin responsive group

Variables	Coefficient	Standard error	$R_{partial}$	*P*-value
Postreperfusion period	-20.1	2.0	-0.4	<0.001
History of diabetes mellitus	-7.0	2.2	-0.1	0.002
Pretreatment glucose (mg/dL)	0.2	0.0	0.3	<0.001
Sampling interval (min)	0.3	0.1	0.2	<0.001
Insulin dose (IU)	0.4	0.2	0.1	0.049
Constant	-10.5			

Multiple correlation coefficient and adjusted coefficient of determination are 0.52 and 0.27, respectively (P <0.001).

Abbreviations: $R_{partial}$ = partial correlation coefficient.

Table 3. Insulin dose and expected blood glucose reduction during postreperfusion period

Insulin dose (units)	DM (+)		DM (-)	
	Probability of responsiveness	Expected Δglucose (mg/dL)	Probability of responsiveness	Expected Δglucose (mg/dL)
1	0.26	5	0.47	12
2	0.3	5	0.49	12
3	0.34	6	0.51	13
4	0.39	6	0.54	13
5	0.44	6	0.56	13
6	0.49	7	0.58	14
7	0.54	7	0.6	14
8	0.59	8	0.62	15
9	0.63	8	0.64	15
10	0.68	8	0.66	15
15	0.86	10	0.75	17
20	0.96	12	0.83	19
30	1.00	16	0.93	23
40	1.00	20	0.98	27

The table shows the combined results of probit and multiple linear regression analyses. Pretreatment glucose level of 180 mg/dL, sampling interval of 20 minutes and postreperfusion period was assumed for insulin therapy.

Abbreviations: DM = diabetes mellitus; Δglucose = reduction of blood glucose after insulin administration.

Figure 1. Flow diagram of study

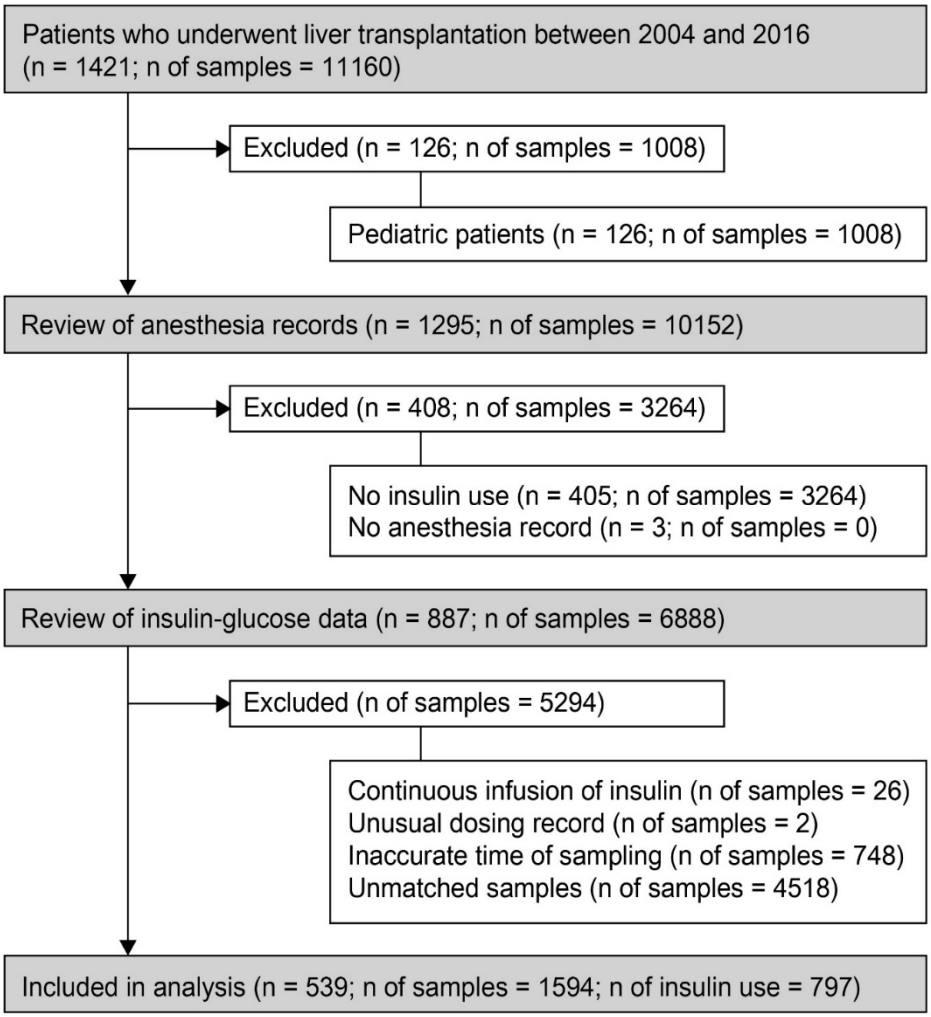
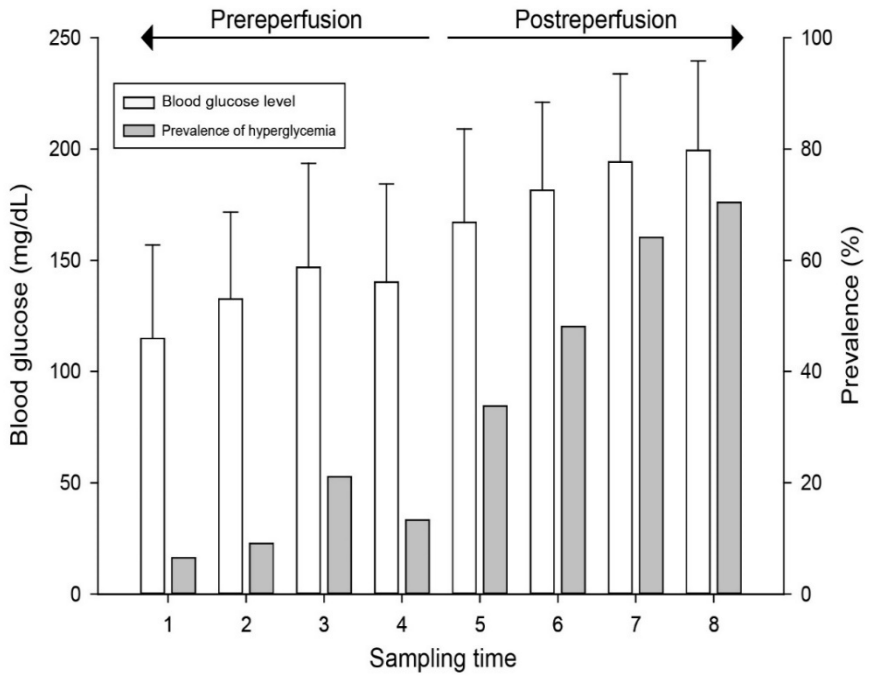


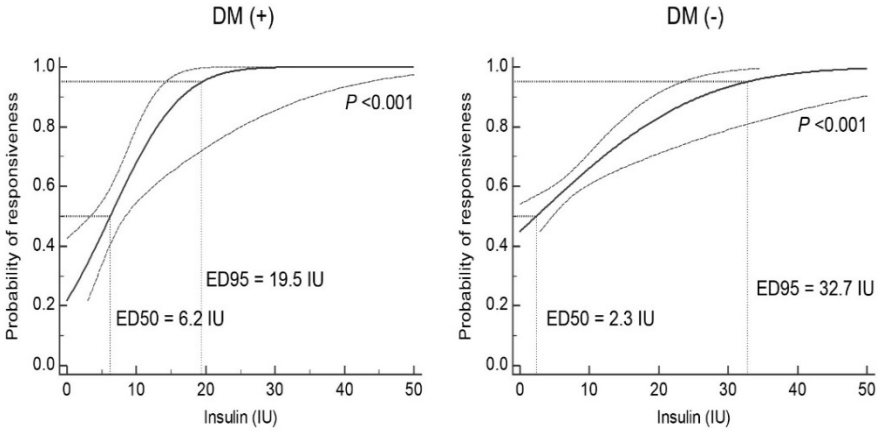
Figure 2. Degree and prevalence of hyperglycemia during liver transplantation (n = 1395 samples)



Routine blood tests were performed 8 times during surgery: for prereperfusion period, time 1 = immediate after anesthesia induction; time 2 = 60 minutes after induction; time 3 = after hepatectomy; and time 4 = 5 minutes before graft reperfusion. For postreperfusion period, time 5 = 5 minutes after graft reperfusion; time 6 = 20 minutes after graft reperfusion; time 7 = after hepatic artery anastomosis; and time 8 = before surgery end.

White vertical bars and whiskers show the mean and SD of blood glucose levels, respectively. Gray vertical bar shows the prevalence of hyperglycemia (blood glucose >180 mg/dL).

Figure 3. Insulin dose-response plots during postreperfusion periods in patients with and without DM



Probit curves with 95% confidence bands show dose-response relationships during the postreperfusion period in patients with DM (n = 117) and without DM (n = 519).

The horizontal dotted lines cross the curves and show ED50 and ED95 values of insulin dose.

In DM patients, the ED50 was greater and ED95 was smaller compared to patients without DM.

Abbreviations: DM = diabetes mellitus; ED50 = effective dose with 50% probability of responsiveness; ED95 = effective dose with 95% probability of responsiveness.

DISCUSSION

This retrospective cohort study identified that postreperfusion hyperglycemia was frequent and severe with reduced insulin responsiveness, especially in recipients with DM. A dose-response curve and multiple linear regression equation were derived to determine the probability and degree of blood glucose changes after insulin therapy. Finally, a simple formula and table were generated to estimate the insulin responsiveness assuming the clinical situation of hyperglycemia after reperfusion.

Diminished insulin responsiveness in liver transplantation patients, especially during the postreperfusion period has been reported. Flushing of glucose-containing organ preservative, glucose release from new graft, poor metabolic function of the graft, and exacerbation of innate insulin resistance were suggested as related factors (1, 11, 12). Recently, a multivariable analysis identified sex, emergency surgery, duration of surgery, and serum lactate level as predictors of refractory hyperglycemia after reperfusion in living donor liver transplantation (13). The use of 500-1000 mg of methylprednisolone adopted by most surgical protocols is considered as another major cause of persistent hyperglycemia after graft reperfusion (3). Dexamethasone 10 mg, the equivalent of methylprednisolone 50 mg, has been reported to increase the blood glucose level from 97 mg/dL to 149 mg/dL for 4 hour in neurosurgery patients (14). In addition, another important factor in

determining insulin responsiveness is the presence of DM. Approximately 30-60% of cirrhosis patients suffer from hepatogenous diabetes, which is characterized by hyperinsulinemia and insulin resistance in muscular, adipose, and hepatic cells (15). In cardiac patients, glycemic control with DM also required more aggressive therapy compared to non-DM counterpart (16). In the current study, figure 3 shows that ED50 of insulin is larger in DM patients compared to patients without DM during the postreperfusion period. Moreover, ED95 is smaller, but Δglucose is expected to be smaller for the same dose of insulin in DM patients compared to non-DM patients, according to the multiple linear regression equation.

The target intraoperative blood glucose for optimal postoperative outcomes is unclear with arguments for intensive (80-110 mg/dL) and conventional (<180-200 mg/dL) targets. In cardiac surgery patients, a meta-analysis reported less ICU mortality and lower hospital lengths of stay with intensive insulin therapy (17), whereas another report showed no difference in mortality between the two strategies (18). The optimal glucose target for liver transplantation is unknown and would be sensible to follow protocols for other surgical population (19). The Consensus Statement by the American Association of Clinical Endocrinologists and the American Diabetes Association suggests 180 mg/dL as a target level to start hyperglycemia control (20). The Society of Thoracic Surgeons guidelines also recommend to maintain blood glucose <180 mg/dL throughout the perioperative period (16).

A target glucose level of 180 mg/dL may be used in liver transplantation, however hypoglycemia should be avoided, too.

After insulin administration, it is mandatory to accurately measure the change of blood glucose. Insulin acts on the receptors of muscle and adipose cell membranes to enhance intracellular transport of blood glucose, however, signals generated during glucose utilization are immediately sent to the liver to suppress hepatic gluconeogenesis at the same time (21). As a result, insulin uniquely shows a delayed onset in vivo, which is explained by the indirect response model, unlike in vitro experiments (22). In a swine pharmacodynamic model, after bolus injection of 0.01, 0.02 and 0.04 IU/kg of insulin, blood glucose reached a nadir 16.1, 18.6 and 21.7 minutes after injection with maximum blood glucose decrease of 13.2, 19.8 and 28.3 mg/dL, respectively (9). In liver transplantation, the unsuppressed glucose release from the new graft is an acute and unique phenomenon during the postreperfusion period and may enhance the delayed insulin effect and refractory hyperglycemia. After an insulin bolus, premature blood sampling may prevent evaluation of the peak effect of insulin, but on the contrary, delayed sampling may interfere with subsequent dosing after failed or insufficient insulin therapy. The typical sampling interval may be 20 minutes after administrating 5-20 units of insulin.

Maintaining blood glucose levels during liver transplantation is challenging. Although continuous infusion of insulin is commonly used in the perioperative setting, it failed to prevent hyperglycemia after graft reperfusion despite stable hyperinsulinemia during liver transplantation surgery (11). Human and animal experiments suggested that bolus administration of insulin was better than continuous infusion of insulin for intraoperative glycemic control due to its simplicity, safety and effectiveness (7-9). In general, one unit of insulin rapidly and predictably reduce blood glucose of 25-30 mg/dL during surgery in adults (23). However, it was announced that to maintain blood glucose levels within a preoperatively sustained range was almost impossible by administering more than 20 units of insulin during liver transplantation (19). An experimental closed-loop system revealed that as much as 28.2 ± 14.9 units of insulin was required to achieve normoglycemia with 77.5% success rate (24). Tables 1 in this study shows that the postreperfusion period is especially associated with reduced rate and degree of response to insulin. Glucose reduction during the postreperfusion period was 0.7 mg/dL per unit of insulin, in contrast to the 3.7 mg/dL/unit during the prereperfusion period. The proportion of insulin resistant cases was 41.4% during the postreperfusion period compared to 22.4% during the prereperfusion period. But, increasing the insulin dose may not guarantee better glucose control as implied by the wide confidence interval of insulin at higher doses. Figure 3 shows that the confidence interval of ED95 insulin ranges between 14-43 units in DM patients. For insulin therapy of hyperglycemia, these probit and multiple linear regression models are

complex and limited because of the nonlinearity, undefined multiple confounding factors, and large confidence intervals of insulin in the models. However, if target glucose level and sampling interval are predefined to be 180 mg/dL and 20 minutes, respectively, the simple formula derived above and table 3 can help predict the Δglucose and adopt the sliding scale administration of insulin.

The current study has several limitations. First, the adequate dose of insulin for hyperglycemia control was not pursued by a more refined method such as direct-fitting pharmacodynamic approach based on reported two-compartment model (25). In spite of a relatively large sample, most of the insulin doses were too monotonous with interquartile range of 5-10 units to fit an Emax or sigmoidal Emax dose-response relationship. Accurate assessment of insulin sensitivity is known to be best measured by euglycemic clamp, minimal model approach, constant infusion of glucose with model assessment and homeostatic model assessment in vivo (26). Future trials should test the relationship between the insulin dose and the response during the postreperfusion period, especially in DM patients. Second, this study defined the responsiveness to insulin as whether or not to block further increase of blood glucose rather than lowering of blood glucose to normoglycemic level. However, normoglycemia was not the goal of intraoperative glycemic control (19). Rapid detection of blood glucose >180 mg/dL by frequent blood sampling and attenuation of hyperglycemia may be sufficient for surgical

patients, although the optimal target of intraoperative glucose level in liver recipients has never been defined. Finally, data from a single center has its own limitation since an established protocol often limits the variety of retrospective data. A multicenter study may be helpful to build a more robust model for insulin responsiveness.

In conclusion, this study revealed that postreperfusion hyperglycemia is frequent and severe during liver transplantation. Usual dose of insulin has been mostly inadequate to treat hyperglycemia, especially after reperfusion in DM patients. The simple formula and table of insulin responsiveness can be helpful to perform insulin therapy in a clinical setting. This result will help establish a practical and efficient guide for insulin dosing to treat postreperfusion hyperglycemia without adverse effects.

REFERENCES

1. Atchison SR, Rettke SR, Fromme GA, Janossy TA, Kunkel SE, Williamson KR, et al. Plasma glucose concentrations during liver transplantation. Mayo Clin Proc 1989; 64:241-245.
2. Mallett SV, Kang Y, Freeman JA, Aggarwal S, Gasior T, Fortunato FL. Prognostic significance of reperfusion hyperglycemia during liver transplantation. Anesth Analg 1989; 68:182-185.
3. Marvin MR, Morton V. Glycemic control and organ transplantation. J Diabetes Sci Technol 2009; 3:1365-1372.
4. Ammori JB, Sigakis M, Englesbe MJ, O'Reilly M, Pelletier SJ. Effect of intraoperative hyperglycemia during liver transplantation. J Surg Res 2007; 140:227-233.
5. Park C, Hsu C, Neelakanta G, Nourmand H, Braunfeld M, Wray C, et al. Severe intraoperative hyperglycemia is independently associated with surgical site infection after liver transplantation. Transplantation 2009; 87:1031-1036.
6. Yoo S, Lee HJ, Lee H, Ryu HG. Association Between Perioperative Hyperglycemia or Glucose Variability and Postoperative Acute Kidney Injury After Liver Transplantation: A Retrospective Observational Study. Anesth Analg. 2016 Oct 4. [Epub ahead of print]
7. Raucoules-Aime M, Ichai C, Roussel LJ, Romagnan MJ, Gastaud P, Dolisi C, et al. Comparison of two methods of i.v. insulin administration

in the diabetic patient during the perioperative period. Br J Anaesth 1994; 72:5-10.

8. Hemmerling TM, Schmid MC, Schmidt J, Kern S, Jacobi KE. Comparison of a continuous glucose-insulin-potassium infusion versus intermittent bolus application of insulin on perioperative glucose control and hormone status in insulin-treated type 2 diabetics. J Clin Anesth 2001; 13:293-300.
9. Skjaervold NK, Lyng O, Spigset O, Aadahl P. Pharmacology of intravenous insulin administration: implications for future closed-loop glycemic control by the intravenous/intravenous route. Diabetes Technol Ther 2012; 14:23-29.
10. Finney DJ. Assays based on quantal responses. In: Statistical Method in Biological Assay. London, UK: Charles Griffin & Company Ltd., 1978 pp. 468-490.
11. Shangraw RE, Hexem JG. Glucose and potassium metabolic responses to insulin during liver transplantation. Liver Transpl Surg 1996; 2:443-454.
12. Cheng KW, Chen CL, Cheng YF, Tseng CC, Wang CH, Chen YS, et al. Dextrose in the banked blood products does not seem to affect the blood glucose levels in patients undergoing liver transplantation. World J Gastroenterol 2005; 11:2789-2791.
13. Chung HS, Lee S, Kwon SJ, Park CS. Perioperative predictors for refractory hyperglycemia during the neohepatic phase of liver transplantation. Transplant Proc 2014; 46:3474-3480.

14. Pasternak JJ, McGregor DG, Lanier WL. Effect of single-dose dexamethasone on blood glucose concentration in patients undergoing craniotomy. J Neurosurg Anesthesiol 2004; 16:122-125.
15. García-Compean D, Jaquez-Quintana JO, Maldonado-Garza H. Hepatogenous diabetes. Current views of an ancient problem. Ann Hepatol 2009; 8:13-20.
16. Lazar HL, McDonnell M, Chipkin SR, Furnary AP, Engelman RM, Sadhu AR, et al. Society of Thoracic Surgeons Blood Glucose Guideline Task Force. The Society of Thoracic Surgeons practice guideline series: Blood glucose management during adult cardiac surgery. Ann Thorac Surg 2009; 87:663-669.
17. Haga KK, McClymont KL, Clarke S, Grounds RS, Ng KY, Glyde DW, et al. The effect of tight glycaemic control, during and after cardiac surgery, on patient mortality and morbidity: A systematic review and meta-analysis. J Cardiothorac Surg 2011; 6:3.
18. Hua J, Chen G, Li H, Fu S, Zhang LM, Scott M, et al. Intensive intraoperative insulin therapy versus conventional insulin therapy during cardiac surgery: a meta-analysis. J Cardiothorac Vasc Anesth 2012; 26:829-834.
19. Park CS. Predictive roles of intraoperative blood glucose for post-transplant outcomes in liver transplantation. World J Gastroenterol 2015; 21:6835-6841.
20. Moghissi ES, Korytkowski MT, DiNardo M, Einhorn D, Hellman R, Hirsch IB, et al. American Association of Clinical Endocrinologists and

American Diabetes Association consensus statement on inpatient glycemic control. Endocr Pract 2009; 15:353-369.

21. Bergman RN. New concepts in extracellular signaling for insulin action: the single gateway hypothesis. Recent Prog Horm Res 1997; 52:359-385; discussion 385-387.
22. Lin S, Chien YW. Pharmacokinetic-pharmacodynamic modelling of insulin: comparison of indirect pharmacodynamic response with effect-compartment link models. J Pharm Pharmacol 2002; 54:791-800.
23. Butterworth JF, Mackey DC, Wasnick JD. Anesthesia for Patients with Endocrine Disease. In: Clinical Anesthesiology 5th edition. Columbus, OH: McGraw-Hill Education, LLC, 2013 pp. 727-745.
24. Okada T, Kawahito S, Mita N, Matsuhisa M, Kitahata H, Shimada M, et al. Usefulness of continuous blood glucose monitoring and control for patients undergoing liver transplantation. J Med Invest 2013; 60:205-212.
25. Potocka E, Baughman RA, Derendorf H. Population pharmacokinetic model of human insulin following different routes of administration. J Clin Pharmacol 2011; 51:1015-1024.
26. Ferrannini E, Mari A. How to measure insulin sensitivity. J Hypertens 1998; 16:895-906.

국문 초록

서론: 간이식 수술 중의 혈당 조절, 특히 재관류 이후의 혈당 조절에 어려움을 겪는 경우가 많다. 간이식 수술 중 인슐린에 대한 혈당의 반응을 예측하기 위해서는 다양한 교란 변수를 고려해야 하기 때문이다.

방법: 본 연구에서는 간이식 수술 중의 인슐린 투여량과 혈당 수치의 상관 관계를 확인하기 위하여 지난 13 년 간의 의무기록을 후향적으로 분석하였다. 인슐린에 대한 반응성 유무에 따라 환자들을 두 군으로 분류한 후 프로비트 분석 방법과 다중 회귀식을 이용하여 인슐린에 반응할 가능성과 반응의 정도를 계산하였다.

결과: 총 797 회의 인슐린 투약 및 그에 따른 혈당 변화가 분석에 포함되었고, 이 중 299 회 (37.5%)에서 인슐린 저항성이 관찰되었다. 재관류 이전에 비해 재관류 이후에 고혈당이 발생하는 빈도가 높았고 그 정도도 심하였다. 재관류 후의 인슐린 투여량 및 혈당 변화를 분석했을 때, 당뇨가 동반된 환자군에서 당뇨가 동반되지 않은 환자군에 비해 인슐린 저항성이 더 크며 50% 유효량도 더 큰 것을

확인할 수 있었다. 재관류 전후, 당뇨 병력, 인슐린 투여 전 혈당, 채혈 간격 등의 변수가 인슐린 투여량에 따른 혈당 변화의 결정 인자로 작용하였다. 이 때 인슐린 투여 전 혈당을 180 mg/dL, 채혈 간격을 20 분으로 설정하면, 재관류 이후의 혈당 조절에 대한 다음과 같은 간단한 식이 도출된다. 혈당변화량 (mg/dL) = 11.4 + 0.4 x 인슐린 투여량 (IU) - 7.0 x 당뇨 병력 유무 (무= 0, 유= 1)

결론: 재관류 후 고혈당증 치료를 위해 투여하는 인슐린의 양은 대부분 불충분하며, 본 연구의 결과를 토대로 간이식 수술 중에 발생하는 인슐린 불응성 고혈당에 대한 치료의 지침을 확립하는 데 기여할 수 있겠다.

주요어: 당뇨, 혈당 조절, 고혈당, 인슐린, 인슐린 투여량, 간이식, 재관류

학번: 2015-23229