Insulin Therapy in the Diabetic Surgical Patient: Metabolic and Hormone Response to Low Dose Insulin Infusion

NEIL J. GOLDBERG, TERENCE D. WINGERT, SEYMOUR R. LEVIN, SAMUEL E. WILSON, AND JOHN F. VILJOEN

We examined carbohydrate metabolism and endocrine responses during elective abdominal surgery in nondiabetic and in insulin-treated diabetic patients. The diabetic patients were divided into two groups: those receiving preoperative subcutaneous (s.c.) insulin and those receiving continuous, low dose intravenous (i.v.) insulin infusions. Glucose, glucagon, cortisol, growth hormone, and insulin levels were measured preoperatively, intraoperatively, and for up to 6 h postoperatively. In the nondiabetic subjects glucose levels rapidly rose at initiation of surgery and continued to increase slowly, reaching a peak of 269 ± 26 (SEM) mg/dl at 60 min into the recovery period. Insulin levels also slowly increased throughout surgery, peaking at 103 ± 32.6 (SEM) uU/ml at 60 min into the recovery period, which was followed by a prompt decline in glucose levels. Glucagon levels remained relatively stable during surgery, but increased steadily during the recovery period to 300 ± 59 (SEM) pg/ml at the end of the observation period. Both cortisol and growth hormone rose during surgery, with growth hormone reaching a peak at 45 min [31.1 ± 13.8 (SEM) ng/ml], while cortisol continued to increase, plateauing during the recovery period at about 30 μg/dl. In the diabetic patients there were no differences in preoperative glucose, glucagon, cortisol, and growth hormone levels between the two treatment groups, and only the glucose level was different from the nondiabetic group. During surgery, there were trends toward lower plasma glucose levels in the early intraoperative phase in the diabetic patients receiving the continuous, low dose i.v. insulin infusion compared with those who received conventional preoperative s.c. insulin. There was no difference in the timing or magnitude of the rise of the measured hormones between the two groups. We conclude that a continuous, low dose i.v. insulin infusion at the dose used (1 U/h) is as effective in the treatment of the diabetic surgical patient as conventional preoperative s.c. insulin administration. Endocrine and metabolic responses to surgery are not different in the two forms of insulin administration. DIABETES CARE 4: 279–284, MARCH–APRIL 1981.

The essential goal of the treatment of the insulin-dependent diabetic surgical patient is preventing hypoglycemia, ketoacidosis, and/or severe fluid loss. This is accomplished by giving glucose to prevent hypoglycemia and insulin to prevent ketoacidosis and fluid loss. Insulin-dependent diabetic patients need insulin during surgery.

A common practice in treating diabetic surgical patients is to give some insulin subcutaneously (s.c.) preoperatively (usually ⅓ to ⅔ the usual daily dose) and supplement this postoperatively with regular insulin.[1,2] Continuous, low dose intravenous (i.v.) insulin infusion has also been used in patients undergoing orthopedic procedures under general anesthesia.[3] Taitelman et al. concluded that preoperative neutral protamine Hagedorn (NPH) insulin at two-thirds of the maintenance dose and a continuous, low dose i.v. infusion of regular insulin at 1 U/h gave equivalent control in their patients. At 2 U/h, hypoglycemia became a problem, even though lower euglycemic levels were achieved.

Surgical stress produces hyperglycemia, and insulin antagonistic hormones increase during surgery.[4–7] The hyperglycemic state has been reproduced by infusing combinations of counterregulatory hormones in animals.[8] Diabetic control during surgery might be ameliorated if one type of insulin administration reduced insulin antagonistic hormones. The theoretical goal is that with improved control, susceptibility

to infection will be minimized and gluconeogenesis, which diverts protein necessary for tissue regeneration, will be limited.[9–11] Since continuous, low dose i.v. insulin infusion has been successfully used in the treatment of ketoacidosis,[12,13] we compared preoperative s.c. and continuous, low dose i.v. insulin infusion in stable insulin-treated diabetic patients undergoing elective abdominal surgery and measured glucose and insulin antagonistic hormones throughout the perioperative period.

MATERIALS AND METHODS

Clinical methods. Eighteen male patients (12 diabetic and 6 nondiabetic) admitted for elective abdominal surgery were studied. Their ages ranged from 39 to 72 (mean 54 ± 2) yr. The study protocol was approved by the hospital Human Research Committee. All subjects gave informed consent. Selection of the diabetic subjects was based only on whether they were lean and were an insulin-dependent patient with a need for elective abdominal surgery. Six diabetic patients were assigned to the conventional preoperative s.c. insulin group and six to the continuous, low dose i.v. insulin infusion group. Conventional insulin was defined as one-half of the usual daily maintenance type and dosage of insulin, administered on call to the operating room. This dose was given regardless of whether the patient was taking a combination of intermediate- and short-acting insulin, whether the insulin was given in more than one injection per day, or the magnitude of the total daily dose. Continuous, low dose i.v. infusion was defined as 1 U/h of regular insulin during surgery and 0.5 U/h during the recovery period. The control group consisted of six nondiabetic subjects who had no history of diabetes mellitus and had normal fasting glucose levels. They were monitored in the same way as the diabetic patients but received no insulin. None of the subjects had edema, renal failure, or received drugs known to affect glucose or insulin levels.

The operations were all abdominal procedures and were carried out as the first case on the day of the study. All patients took nothing orally from the evening before. The study did not alter the usual surgical or anesthetic procedure. Routine premedication was given intramuscularly "on call" to the operating room, usually 1 h before anesthesia. All patients had an infusion of 5% dextrose throughout the surgery and in the postoperative period. However, the type and administration rate were at the discretion of the anesthesiologist, independent of the study, and invariably was 5% dextrose in Ringer's lactate. General anesthesia was similar in all cases. The types of surgical procedures are listed in Table 1.

Insulin was administered via plastic syringes and tubing. No additive such as albumin was mixed in the solution.[14] A portion of the solution was run through the intravenous set to saturate the tubing and filter surfaces with adsorbed insulin.[15]

Samples were obtained in the preoperative period, after the start of the operation (which was taken as the time of incision), and during the recovery period for glucose, glucagon, growth hormone, and cortisol levels. In addition, insulin levels were obtained in the nondiabetic subjects. Glucagon samples were collected on ice.

TABLE 1
Types of operations

Group	Operation	No. of cases
Nondiabetic	Cholecystectomy	4
	(with incidental appendectomy)	(2)
	Left hemicolectomy	1
	Vagotomy and pyloroplasty with fundoplication	1
Diabetic		
Low dose insulin infusion	Cholecystectomy	3
	Aortofemoral bypass with bilateral sympathectomies	1
	Cholecystojejunostomy	1
	Colostomy	1
Subcutaneous insulin	Cholecystectomy	1
	Aortofemoral bypass	2
	Esophageal resection	1
	Pancreatic pseudocyst (external drainage)	1
	Colonic reanastomosis	1

Laboratory methods. Venous blood was collected in chilled EDTA tubes for glucagon and as whole blood for growth hormone, cortisol, and insulin. Blood for glucose was collected in sodium fluoride tubes. All samples were centrifuged and frozen at −20°C and analyzed in groups. Glucose values were determined by the glucose-oxidase method[16] using a Beckman Glucose Analyzer. Immunoreactive insulin was measured according to the description of Lundquist et al.[17] Immunoreactive glucagon was measured using a 30K antibody as described by Faloona and Unger.[18] Nonspecific binding controls were included for each patient's plasma. Growth hormone was measured by radioimmunoassay using the method of Schalch and Parker.[19] Cortisol determinations were done by the Mattingly fluorimetic method.[20]

Statistical analysis was performed using a nonpaired *t* test. The data are presented as the mean ± SEM.

RESULTS

The clinical characteristics of the patients are listed in Table 2. The mean age of the three groups did not differ. Preoperative maintenance insulin requirements in the two groups of diabetic patients were similar.

The surgical data are listed in Table 3. The length of surgery was shorter for the nondiabetic versus the diabetic patients (140 ± 20 versus 187 ± 13 min) but this was not significant. There was no difference in operating time between the two diabetic groups. Fluid replacement was greater in the diabetic patients (2183 ± 237 versus 3241 ± 378 ml), but this was not statistically different between the nondiabetic and diabetic groups nor was there a significant difference be-

TABLE 2
Clinical data of patients studied

Group	Subject	Age (yr)	Wt. (lbs)	Ht. (in)	Usual insulin RX	Diagnosis
Nondiabetic	1	55	188	74	None	Cholelithiasis
	2	72	180	74	None	Ca colon with mets.
	3	52	197	73	None	Cholelithiasis
	4	53	159	64	None	Cholelithiasis
	5	44	165	68	None	Cholelithiasis
	6	47	167	66	None	Esophageal stricture
		54 ± 4	176 ± 6	70 ± 2		
Diabetic						
Continuous, low dose intravenous insulin infusion	7	62	121	66	NPH 20 U q.a.m. NPH 5 U q.p.m.	Peripheral vascular dis.
	8	43	150	71	NPH 24 U, Reg 10 U q.a.m.	Cholelithiasis
	9	49	153	67	NPH 40 U, Reg 5 U q.a.m.	Cholelithiasis*
	10	53	142	—	NPH 50 U, Reg 10 U q.a.m.	Ca rectum with mets.
	11	56	154	—	NPH 8 U q.a.m.	Cholelithiasis
	12	59	138	69	NPH 35 U q.a.m.	Cholelithiasis
		54 ± 3	143 ± 5	68 ± 1	34 ± 7 U q.day	
Preoperative subcutaneous insulin	13	46	138	65	NPH 28 U q.a.m.	Cholelithiasis
	14	52	135	73	NPH 25 U, Reg 5 U q.a.m.	Pancreatic pseudocyst
	15	60	153	70	NPH 25 U q.a.m.	Peripheral vascular dis.
	16	63	145	69	NPH 20 U q.a.m.	Peripheral vascular dis.
	17	64	130	66	NPH 16 U q.a.m.	Carcinoma esophagus
	18	39	138	—	NPH 40 U, Reg 10 U q.a.m.	Colostomy for divert. perf.
		54 ± 4	140 ± 3	69 ± 1	28 ± 4 U q.day	

* Preoperative diagnosis was in error. Postoperative diagnosis was cholangiocarcinoma.

tween the diabetic groups. The diabetic preoperative s.c. insulin group received 19 additional grams of i.v. glucose than the continuous, low dose i.v. insulin infusion group, but this was not significant either.

The glucose and hormonal data are illustrated in Figures 1 and 2. The shaded area represents the mean ± 1 SEM for the nondiabetic controls.

Preoperative period. The high preincision glucose in the nondiabetic patients (138 ± 16 mg/dl) represents i.v. glucose and perhaps the stress of anticipating surgery. The preoperative glucose levels of the diabetic patients were obtained before any i.v. dextrose administration or the initiation of insulin therapy. They are not different between the diabetic patients who subsequently received continuous, low dose i.v. insulin infusion (195 ± 28 mg/dl) versus those who received preoperative s.c. insulin (200 ± 16 mg/dl). The preoperative glucagon, cortisol, and growth hormone levels are not statistically different among the three patient groups.

Intraoperative period. Glucose levels rose steadily throughout surgery, reaching 259 ± 20 mg/dl in the nondiabetic patients at the end of the procedure. The glucose levels in the two diabetic groups followed a similar pattern, but started at a higher level than the nondiabetic patients and rose to 345 ± 31 mg/dl and 390 ± 80 mg/dl in the continuous, low dose i.v. insulin infusion and the preoperative s.c. insulin groups, respectively. The glucose values in the two diabetic groups are not statistically different. No diabetic patient became hypoglycemic. One patient in the preoperative s.c. insulin group (no. 17) was given two additional 10-U doses of regular insulin intravenously during surgery when the glucose level was greater than 500 mg/dl.

Glucagon levels were similar in all three groups and showed little change during surgery. Cortisol levels rose by 30 min after the start of surgery in the nondiabetic and in the diabetic subjects who received the continuous, low dose i.v. insulin infusion and by 45 min in the diabetic subjects who received preoperative s.c. insulin. These levels continued to rise throughout surgery. Growth hormone initially increased in an identical pattern to cortisol, but reached its peak by 60 min and declined through the remaining intraoperative period. Other than the late rise in the diabetic group who received preoperative s.c. insulin, there was no difference among the three groups.

Postoperative. During the postoperative period, the peak glucose of the nondiabetic patients was 269 ± 26 mg/dl and occurred 1 h into the recovery period. This was not statistically different from the peak intraoperative level of 259 ± 20 mg/dl at the end of surgery. The insulin concentrations that were minimally elevated during surgery in the nondiabetic subjects rose in the early recovery period, reflecting a marked increase in endogenous insulin secretion. Consequently, a reduction in glucose concentration ensued despite a marked increase in glucagon at that time. Comparing the glucose levels in the diabetic groups, those who re-

TABLE 3
Surgical data on patients studied

Group	Subject	Operation	Length of surgery (min)	Fluids (ml) 5%D or 5%DRL	Fluids (ml) Other*	Insulin	POD discharged
Nondiabetic	1	Cholecystectomy	120	1800	300	None	8
	2	Left hemicolectomy	120	2000	1000	None	23 (Died)
	3	Cholecystectomy	150	1100	None	None	42
	4	Cholecystectomy	120	1500	500	None	6
	5	Cholecystectomy	90	2000	500	None	5
	6	V & P with fundoplication	240	2000	400	None	13
			140 ± 20	1733 ± 137	450 ± 122		16 ± 5
Diabetic							
Continuous, low dose intravenous insulin infusion	7	Aortofemoral bypass	180	750	2800	1 U Reg/h	6
	8	Cholecystectomy	270	2250	1275	1 U Reg/h	14
	9	Cholecystojejunostomy	180	700	600	1 U Reg/h	9
	10	Colostomy	180	1950	1450	1 U Reg/h	11
	11	Cholecystectomy	120	1000	650	1 U Reg/h	14
	12	Cholecystectomy	180	1000	850	1 U Reg/h	33
			185 ± 18	1275 ± 245	1170 ± 351	1 U Reg/h	14 ± 4
Preoperative subcutaneous insulin	13	Cholecystectomy	120	2000	400	NPH 14 U	6
	14	Panc. pseudocyst evac.	150	1000	2250	NPH 13 U	9
	15	Aortofemoral bypass	240	1300	2550	NPH 12 U	16
	16	Aortofemoral bypass	210	1650	2075	NPH 10 U	8
	17	Esophageal resection	240	2100	4350	NPH 8 U†	73 (Died)
	18	Colonic reanastomosis	180	1900	2050	NPH 20 U Reg 5 U	17
			190 ± 18	1658 ± 161	2279 ± 471	14 ± 2 U	22 ± 10

* Indicates normal saline, Ringer's lactate, and blood products.
† Required 20 U Reg insulin additional when glucose >500 mg/dl.

ceived a continuous, low dose i.v. insulin infusion showed a lowering trend while the glucose of those who received preoperative s.c. insulin increased, but the difference was not significant.

The glucagon values of all three groups tended to increase in the recovery period. There was no statistical difference between any of the groups. This was also true for growth hormone levels, which continued to decline in all three groups during the recovery period. The cortisol levels were higher in both diabetic groups compared with the nondiabetic subjects. This reached statistical significance in the diabetic subjects who received the continuous, low dose i.v. insulin infusion at 240 min (33 ± 2.6 versus 22.4 ± 2.9 μg/dl, $P < 0.05$) and 300 min (38.0 ± 2.1 versus 20.3 ± 3.7 μg/dl, $P < 0.02$). There was no statistical difference between the diabetic groups.

DISCUSSION

Continuous, low dose i.v. infusion of insulin has been shown to be effective therapy for diabetic ketoacidosis,[12,13] orthopedic surgery,[3] and labor and delivery.[21] In assessing its use in the diabetic general surgical patient, we maintained the usual perioperative surgical conditions, including the use of i.v. glucose. Intraoperative hyperglycemia may, in part, be attributed to this. In addition we have not excluded the possibility that hepatic disease in those patients undergoing biliary surgery may have affected glucose handling, but the liver function abnormalities were mild and the glucose patterns were similar for patients who had biliary versus nonbiliary surgery. The glucose levels in our patients were higher than those reported in previous studies[5,6] where i.v. glucose was not given.

We chose to give the preoperative s.c. insulin as one-half the usual maintenance dose regardless of the type of insulin used or the timing of administration, and the continuous, low dose i.v. insulin infusion as 1 U/h regardless of the preoperative dosage as a practical method that could be done routinely with different surgeons, anesthesiologists, and nurses.

There was a trend for an increase in glucose in the early intraoperative period in those diabetic patients receiving the preoperative s.c. insulin therapy compared with those on a continuous, i.v. insulin infusion of 1 U/h. One patient in the preoperative s.c. insulin group required additional insulin. These observations could not be accounted for by alterations in the other measured hormones. These findings are similar to those of Taitelman et al.[3] despite some differences in study design. Their patients underwent orthopedic surgery, the

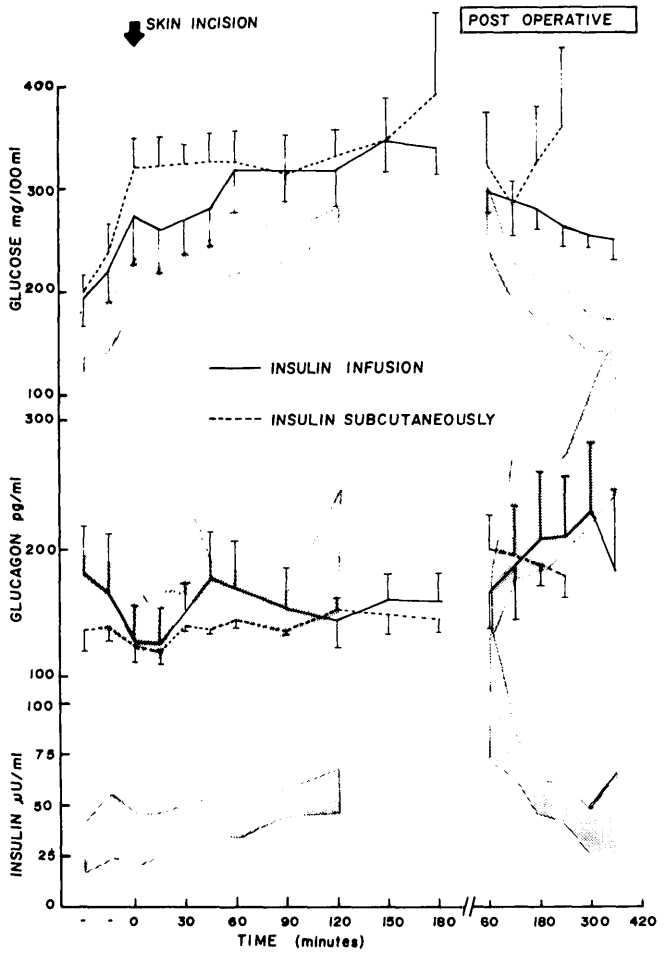

FIG. 1. Effect of elective abdominal surgery on perioperative glucose, glucagon, and insulin in nondiabetic subjects (shaded area), diabetic subjects who received a continuous, low dose intravenous insulin infusion (solid line), and diabetic subjects who received preoperative subcutaneous insulin (broken line). The preincision samples, indicated by (—) on the abscissa, were taken at variable times. Data shown as mean ± SEM.

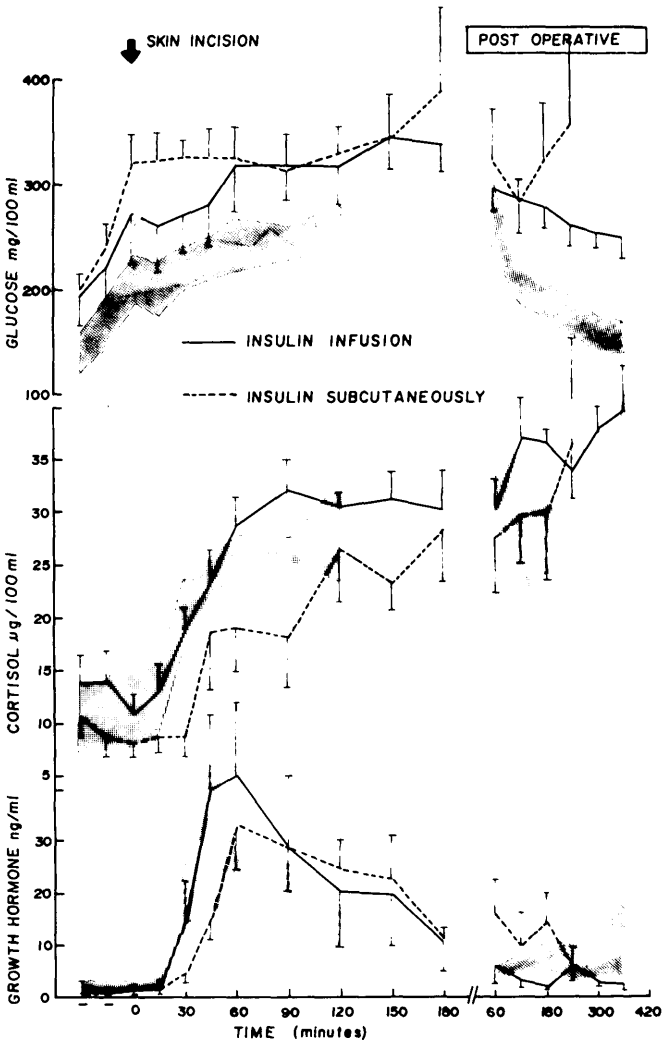

FIG. 2. Effect of elective abdominal surgery on perioperative glucose, cortisol, and growth hormone in nondiabetic subjects (shaded area), diabetic subjects who received a continuous, low dose intravenous insulin infusion (solid line), and diabetic subjects who received preoperative subcutaneous insulin (broken line). The preincision samples, indicated by (—) on the abscissa, were taken at variable times. Data shown as mean ± SEM.

mean anesthesia time was only 40 min, and preoperative s.c. insulin therapy was two-thirds of the usual maintenance dose.

Hypoglycemia was not seen with either method of insulin administration.

We have demonstrated that a continuous, low dose i.v. insulin infusion at 1 U/h is an effective form of management of stable diabetic surgical patients. Furthermore, there is no statistical difference in glucose levels or counterregulatory hormones to insulin compared with diabetic surgical patients who received preoperative s.c. insulin administration at one-half of the usual maintenance dose. There is minimal danger of hypoglycemia with either treatment method.

We conclude that perioperative maintenance of glucose in the nondiabetic state is the result of insulin secretory response to hyperglycemia. The upsurge of insulin in the postoperative period confirms the findings of Schwartz et al.[22] and is probably the result of the loss of inhibition induced by increased intraoperative catecholamines. In diabetic patients who have inadequate endogenous insulin, insulin administration allows adequate control of serum glucose while avoiding hypoglycemia. The findings support the efficacy of continuous, low dose i.v. insulin infusion in the treatment of the diabetic surgical patient. We were unable to demonstrate, however, any statistical differences between continuous, low dose i.v. insulin infusion and conventional preoperative s.c. insulin therapy, with regard to hormonal and metabolic responses. In a setting where perioperative serum glucose levels can be obtained, the i.v. route offers the theoretical advantage of more precise minute-to-minute control over the metabolic state.

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From the Medical, Surgical and Anesthesiology Services, Diabetes Research Laboratory, Wadsworth Veterans Administration Medical Center, UCLA School of Medicine, Los Angeles, California.

Address reprint requests to Seymour R. Levin, Chief, Special Diagnostic & Treatment Unit, 691/111K, Wadsworth VA Medical Center, Bldg. 500, Room 3077N, Los Angeles, California 90073.

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