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Perioperative Management of Diabetes Mellitus

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Hourly plasma glucose concentrations in 191 diabetic patients undergoing 200 operations were measured. The glucose infusion rate was controlled. Insulin-taking diabetics given no insulin or a fraction of their usual dose preoperatively developed rising plasma glucose concentrations beginning with the start of operation. The mean rate was 22 $mg \cdot dl^{-1} \cdot h^{-1}$ (no insulin) and 17 $mg \cdot dl^{-1} \cdot h^{-1}$ (one-half to one-fourth the usual dose of insulin). Eight per cent of the patients achieved plasma glucose concentrations greater than 400 mg/dl. Patients given regular insulin during the operation had no hourly rise in plasma glucose. However, hypoglycemia occurred in 5.5 per cent of these patients.

The authors suggest that arbitrary management regimens should be abandoned. Plasma glucose levels should be measured frequently and insulin and/or sugar should be given to each patient as needed. (Key words: Complications: diabetes mellitus. Hormone: insulin. Metabolism: diabetes; glucose; insulin; hyperglycemia; hypoglycemia.)

MANY REGIMENS for the management of the diabetic patient undergoing surgery have been described.[1–9] There is, however, a paucity of information concerning the effectiveness of these regimens in a clinical setting. A prospective study was designed to compare three commonly used regimens. We measured plasma glucose hourly in 191 diabetic patients during 200 operations. Our findings and recommendations for the management of diabetic patients are presented.

Material and Methods

Studies were done on adult diabetic patients who were being treated with insulin or oral hypoglycemic drugs. Patients in diabetic ketoacidosis during the preoperative period were not considered candidates for study. We placed no restrictions on the administration of nonglucose containing solutions, anesthetic drugs, or the methods of anesthesia. No operation excluded the diabetic patient from the study except cardiac surgery utilizing cardiopulmonary bypass.

Glucose was administered to prevent the exhaustion of glycogen stores and to prevent ketosis. Five per cent glucose was infused intraoperatively at a fixed rate of 125 ml (6.25g) per hour. Plasma glucose and qualitative acetoacetate determinations were made hourly beginning just prior to the induction of anesthesia and terminating on discharge from the recovery room (referred to as intraoperative). Further determinations were made at approximately 10 P.M. and the following day at 7 A.M. (referred to as postoperative). A Beckman® glucose analyzer (glucose oxidase technique) was used to measure plasma glucose concentration. The presence of plasma ketone bodies was determined using the Ames Acetest® tablet.

Diabetic patients who received insulin preoperatively were managed by one of three methods usually selected by their hospital admission number. Group I, control (31 studies): no insulin or glucose was given the morning of operation; Group II, partial dose (58 studies): most patients were given one-third of their usual dose of insulin at 7 A.M. However, one-half of the usual dose was given to 11 patients and one-fourth of the usual dose was given to 2 patients, as ordered by the primary treating physician. An infusion of 5 per cent glucose (at a rate of 6.25 g/h) was begun at the time of the insulin administration and continued throughout the intraoperative period. Group III, titration (33 studies): no insulin or glucose was given on the morning of operation. If the plasma glucose concentration rose above 200 mg/dl, 10 units of regular insulin was injected intravenously. Insulin was not administered more often than once every 2 h.

If plasma glucose concentration rose above 400 mg/dl, the management was considered a failure and 20 units of regular insulin was injected intravenously. Any patient whose plasma glucose concentration fell below 60 mg/dl was also deemed a management failure and treated with additional intravenous glucose. If failure occurred, measurements of plasma glucose were no longer used in calculating intraoperative hourly mean values.

Approximately one-half of the patients from each of the three groups were given one-third of their usual dose of intermediate-acting insulin upon discharge from the recovery room. Postoperative fluid and insulin management was left to the primary treating physician.

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TABLE 1. Diabetics Controlled on Insulin Compared Perioperatively*

Group	Mean Age (yr)	Usual Insulin Units	Preoperative Plasma Glucose (mg/dl)	4 Hour Plasma Glucose (mg/dl)	Evening Plasma Glucose (mg/dl)	Following A.M. Plasma Glucose (mg/dl)
Control (No preoperative insulin)	52	42 ± 12	190 ± 77 (n = 31)	281 ± 80 (n = 17)	299 ± 93 (n = 22)	285 ± 97 (n = 28)
Partial dose (¼ to ½ usual dose of insulin in A.M.)	52	36 ± 15	181 ± 81 (n = 58)	258 ± 73 (n = 25)	249 ± 94 (n = 46)	265 ± 108 (n = 48)
Titration (Regular insulin given during operation)	55	34 ± 15	167 ± 70 (n = 33)	160 ± 61 (n = 22)	265 ± 78 (n = 25)	264 ± 102 (n = 26)

* Values are means ± SD; n = number of studies.

Diabetic patients treated with oral hypoglycemic drugs were managed by one of two techniques. Group IV, control (47 studies), was managed similarly to Group I, and Group V, titration (31 studies), was managed similarly to Group III. The choice of treatment was keyed to hospital admission number. Results from these patients were analyzed separately.

There was some deviation in the assignment of patients into a study group. Primary treating physicians wishing to specify insulin orders did so. This resulted in a disproportionate number of patients receiving a partial dose of insulin preoperatively.

Data were analyzed as to mean preoperative glucose values and mean hourly changes in plasma glucose values during operation. A slope for the hour-to-hour changes in plasma glucose was calculated for each patient and a multiple stepwise regression analysis was done in Groups I (control) and II (partial dose) to determine factors which might influence the slope. The following variables were analyzed: time of operation, choice of anesthetic drug, age of patient, preoperative insulin dose, duration of operation, and severity of operation. Only four anesthetic drugs and techniques were used in sufficient numbers to be incorporated into the analysis. These were: 1) nitrous–narcotic, 2) nitrous–halothane, 3) nitrous–enflurane, and 4) spinal anesthesia. Operations were judged as minor (superficial), moderately severe (extremity amputation, tubal ligation, vitrectomy), or major (bowel resection, major vessel operations, sympathectomy).

Mean plasma glucose values at 10 P.M. and the following day (7 A.M.) were compared among the three

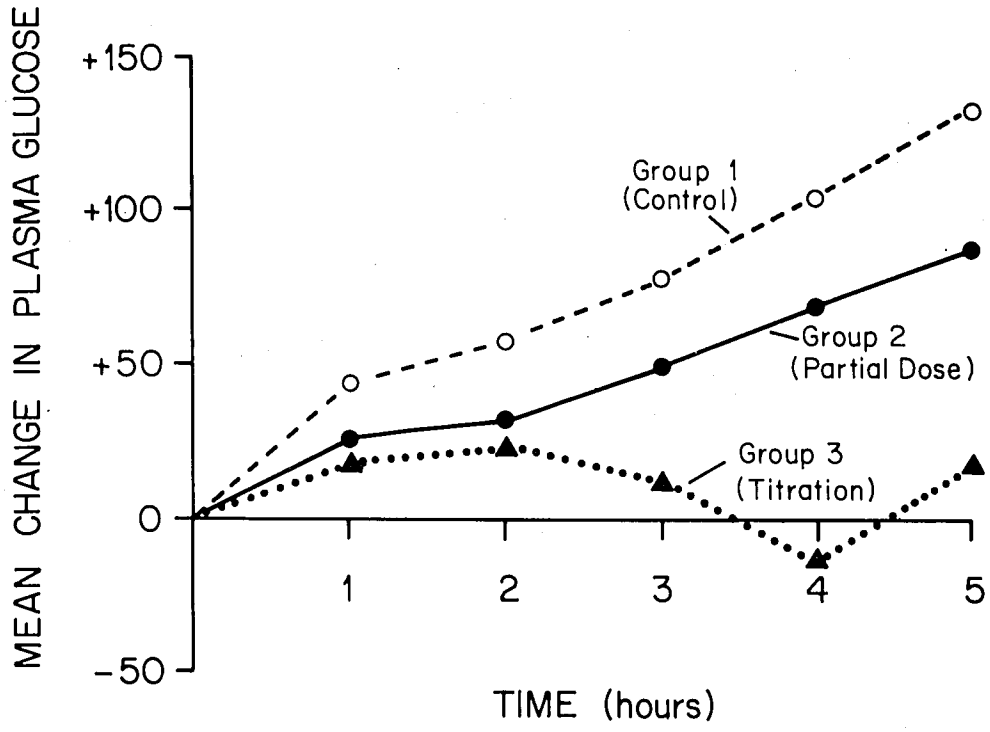

FIG. 1. Diabetics controlled on insulin. Change in mean plasma glucose concentration with time.

TABLE 2. Effect of Giving One-third the Usual Dose of Intermediate-acting Insulin on Discharge from the Recovery Room

	One-third the Usual Dose Insulin Postoperative	No Insulin Postoperative
Number of Patients		
Group I (control)	12	10
Group II (partial dose)	23	23
Group III (titration)	10	15
Total	45	48
Mean time of discharge from recovery room, (h)	2:40 P.M.	3:00 P.M.
Mean plasma glucose (mg/dl)		
On discharge from recovery room	240	234
10 P.M.	264	267

treatment groups. Records of patients whose plasma glucose rose to greater than 400 mg/dl or fell to 60 mg/dl were examined.

The protocol was reviewed and approved by the anesthesia department research committee and the UCLA Human Subject Protection Committee. We obtained no written patient's consent for management.

Results

A total of 122 studies were done on insulin-taking diabetic patients. The average age, insulin dose, and preoperative plasma glucose concentrations are shown in table 1. These values do not significantly differ between the groups. A separate analysis of age, preoperative insulin dose, preoperative blood glucose, severity and duration of operation among patients in Groups II not placed in a treatment group according to hospital number, revealed these values to be similar to the others.

Patients in Group I (control) and Group II (partial dose), developed rising plasma glucose concentrations following the onset of anesthesia and operation. The mean rise in glucose in Group I patients was 22 $mg \cdot dl^{-1} \cdot h^{-1}$. For Group II patients, the average rise was 17 $mg \cdot dl^{-1} \cdot h^{-1}$. This difference is not statistically significant. The rise continued throughout the duration of the hour-to-hour observation period. Patients in Group III (titration) had no significant change in hourly mean plasma glucose concentration (fig. 1).

To determine whether the rise in plasma glucose was associated with the onset of operation and anesthesia, the following analyses were undertaken: 1) Mean preoperative control plasma glucose concentrations were compared between patients undergoing operations prior to 9 A.M. and patients having operations at 1 P.M. or later. Patients in Groups I and III were pooled (no insulin given before operation). Prior to 9 A.M. the mean ± SD of the plasma glucose concentration was 156 ± 67 mg/dl (n = 26). After 1 P.M. the mean ± SD plasma glucose concentration was 192 ± 72 mg/dl (n = 19). This difference is not significant. 2) Plasma glucose concentrations of patients in Group I were compared at a specific time of day, 1 P.M. Those patients undergoing operations at 1 P.M. had a mean ± SD of 297 ± 85 mg/dl (n = 10). Patients whose operations had not begun had a mean ± SD value of 186 ± 86 mg/dl (n = 10). These values are significantly different ($P = 0.01$).

Thus, we conclude that the rise in the glucose concentration of the fasting patient can be attributed primarily to the anesthesia and operation and/or the infusion of glucose and not to the passage of time.

The results of the multiple stepwise regression analysis revealed that time of operation, choice of anesthetic drug, age of patient, preoperative insulin dose, or magnitude of operation did not significantly affect the rate of intraoperative rise of the plasma glucose levels.

At 10 P.M. on the day of the operation and 7 A.M. the following day, the mean plasma glucose concentration was elevated in all groups (table 1). The effect of administering intermediate-acting insulin at time of discharge from the recovery room is shown in table 2. Note that the following are similar for patients who did or did not receive insulin: 1) the mean time at which patients were discharged from the recovery room; 2) the mean plasma glucose concentration at the time of discharge from recovery room; and 3) the

TABLE 3. Diabetics Controlled on Oral Hypoglycemic Agents Compared Perioperatively*

Group	Mean Age (yr)	Preoperative Plasma Glucose (mg/dl)	4 Hour Plasma Glucose (mg/dl)	Evening Plasma Glucose (mg/dl)	Following A.M. Plasma Glucose (mg/dl)
Control	66	165 ± 61 (n = 47)	237 ± 70 (n = 33)	249 ± 83 (n = 32)	212 ± 77 (n = 40)
Titration	62	163 ± 65 (n = 31)	186 ± 51 (n = 16)	211 ± 67 (n = 22)	181 ± 69 (n = 27)

* Values are means ± SD; n = number of studies.

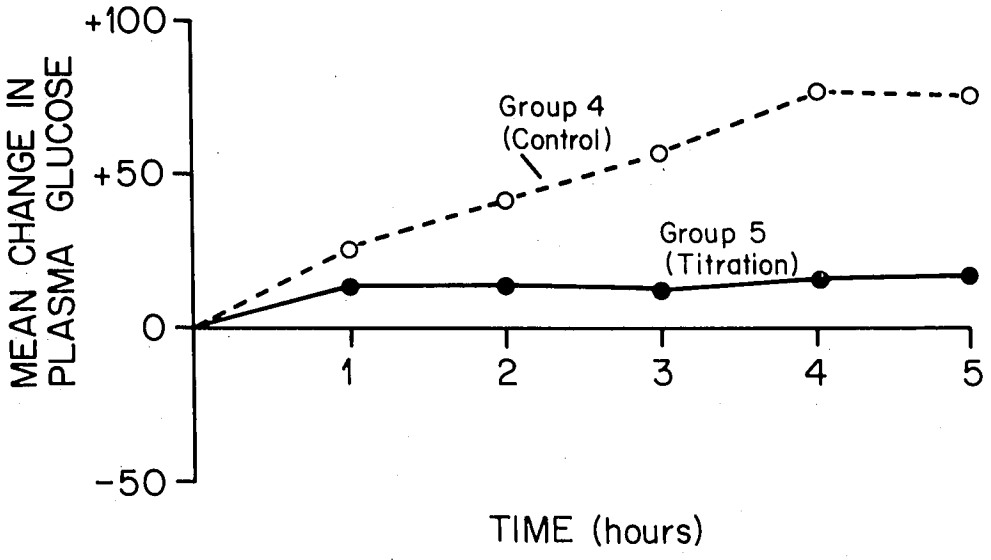

FIG. 2. Diabetics controlled on oral hypoglycemic agents. Change in mean plasma glucose concentration with time.

mean plasma glucose concentration at 10 P.M. Thus, the treatment was found to be without discernible benefit at a time when intermediate-acting insulin would be expected to have a peak effect.

DIABETIC PATIENTS TREATED WITH ORAL HYPOGLYCEMIC AGENTS

Seventy-eight studies were completed on diabetic patients taking oral hypoglycemic agents (table 3). No significant difference was noted in patient's age or mean preoperative plasma glucose concentration between control (Group IV) and titration (Group V) groups. Control patients had rising mean plasma glucose concentration throughout the study while titration patients did not (fig. 2). The mean rise in plasma glucose in the control group was 15 $mg \cdot dl^{-1} \cdot h^{-1}$. Similar to our finding with the insulin-taking diabetic patients, we found no difference between the mean plasma glucose concentrations of the two groups at 10 P.M. or at 7 A.M. the following day.

TREATMENT FAILURES

Among 200 studies we found 14 intraoperative protocol failures (tables 4 and 5). All failures were

TABLE 4. Intraoperative Hyperglycemic Protocol Failures

Group	Age (yr)	Usual Medication	Operation Starting Time	Time of Failure	Anesthesia	Operation	Comment
Diabetics controlled on insulin							
Control	58	NPH 45 U	8:15 A.M.	1:00 P.M.	Nitrous–enflurane	Femoral endarterectomy	
	69	NPH 45 U	8:15 A.M.	3:30 P.M.	Nitrous–enflurane	Choledocho-jenunostomy	
	68	NPH 60 U	8:20 A.M.	3:15 P.M.	Nitrous–narcotic	Femoral popliteal bypass	
	66	NPH 50 U	8:50 A.M.	11:15 A.M.	Spinal	T.U.R.P.	
Partial Dose	45	NPH 40 U	8:00 A.M.	3:00 P.M.	Nitrous–narcotic	Pylolithotomy	17 U NPH 7:00 A.M.
	45	NPH 40 U	8:00 A.M.	5:00 P.M.	Nitrous–narcotic	Ileal bladder	13 U NPH 7:00 A.M.
	65	Lente® 60 U	8:30 A.M.	10:00 A.M.	Nitrous–halothane	Lymbar laminectomy	30 U Lente® 8:00 A.M.
Diabetics controlled on oral hypoglycemic agents							
Control	71	Tolbutamide 500 mg, qid	11:35 A.M.	2:30 P.M.	Nitrous–narcotic	Bowel resection	
	69	Tolazamide 250 mg, tid	11:45 A.M.	5:45 P.M.	Nitrous–narcotic	Vaginal hysterectomy	

TABLE 5. Intraoperative Hypoglycemic Protocol Failures

Group	Age (yr)	Usual Medication (units)	Operation Starting Time	Time of Failure	Blood Glucose Concentration (mg/dl)	Anesthesia	Operation	Comment
Diabetics controlled on insulin								
Partial dose insulin	52	NPH 35	1:50 P.M.	1:15 P.M.	56	—	BK amputation	11U NPH 7:00 A.M.
	59	Reg 10 Ultralente® 15 Semilente® 4	12 Noon	12:30 P.M.	52	Nitrous-halothane	Shoulder repair	10U NPH 8:00 A.M.
	63	NPH 50	3:00 P.M.	2:45 P.M.	60	—	BK amputation	20U NPH 7:00 A.M.
Titration	34	NPH 40	4:30 P.M.	6:30 P.M.	25	Nitrous-narcotic	Carotid endarterectomy	10U reg. insulin 3:30 P.M.
	72	NPH 26	8:00 A.M.	12:10 P.M.	32	Nitrous-narcotic	Laryngectomy	10U reg. insulin 9:30 A.M.

due to either hyper- or hypoglycemia. No patient developed ketosis. No patient treated for hyperglycemic failure became hypoglycemic.

Twenty-two patients were classified as postoperative treatment failures; 21 of these patients had a plasma glucose concentration greater than 400 mg/dl. A multiplicity of treatments and infrequency of monitoring blood glucose made it impossible to analyze the cause of failure in each case.

Five additional failures were not related to the planned protocol. Two of these patients were poorly controlled diabetics with plasma glucose levels greater than 400 mg/dl prior to anesthesia. One patient came to the operating room hypoglycemic as a result of regular insulin given by the primary treating physician and not as part of the study. Intraoperative overdose with intravenous glucose accounted for hyperglycemia greater than 400 mg/dl in two patients.

Discussion

The use of empirical regimens for the management of the diabetic patient undergoing an operation has been widely recommended. Strong personal biases have been noted, but little substantive information has been published. We have compared three commonly used regimens in a group of diabetic patients undergoing a variety of surgical procedures. We have found that all were imperfect.

Regimens specifying that no insulin be given will be associated with patients who have plasma glucose concentrations greater than 400 mg/dl. We have found the mean rise in glucose concentration during an operation to be 22 $mg \cdot dl^{-1} \cdot h^{-1}$. This rate of rise might be higher if patients who exceeded 400 mg/dl were neither given insulin nor excluded from further study. The achievement of high glucose values was related primarily to the plasma glucose concentration prior to the onset of anesthesia and to the duration of operation and recovery room stay.

Protocols specifying that a partial dose of intermediate duration insulin be given on the morning of operation do not afford protection from intraoperative hyperglycemia. Since the latency period of NPH insulin is 2–4 h and its peak action is 8–12 h, we did not expect to see any protection against rising blood glucose in patients undergoing a morning operation. However, we also noted that the morning insulin afforded no protection to patients undergoing an afternoon operation. The use of the morning partial dose of insulin, on the other hand, was associated with several instances of hypoglycemia. The infusion of glucose beginning at the time of administration of the insulin did not prevent the hypoglycemia. It should be emphasized that although the glucose concentration had not reached a dangerously low level, the measurement of the glucose concentration was related temporally to the onset of the operation. Had the operation been delayed, it is quite possible that the glucose level would have been lower. Fletcher *et al.*[10] have cited another instance of hypoglycemia in a patient treated with a partial dose of insulin preoperatively. Our results also support Fletcher's contention that neither the preoperative dose of insulin nor the time of day of the operation influence the intraoperative change in glucose concentration.

We also encountered failures in Group III patients. In spite of using small and judicious doses of insulin, two patients became hypoglycemic. The hypoglycemia is noteworthy not only because it followed only 10 units of regular insulin, but also because the time to

lowest measured plasma glucose concentration was not one but nearly three hours after the insulin injection (table 5).

Taitelman, Reece, and Bessman have proposed another way to manage the diabetic patient during an operation.[9] They recommend that insulin be continuously infused during the operative period. According to their data, rigid adherence to their protocol was no more successful than adherence to others. Four of six patients given two units of regular insulin per hour developed plasma glucose concentrations which required either slowing the infusion rate or adding additional amounts of glucose.

The use of a regimen for the management of the diabetic patient undergoing an operation has been a matter of expediency. The primary treating physician or consulting endocrinologist does not often accompany the patient to the operating room. At best, he has knowledge of the patient's endocrine status before the anesthesia begins and at the termination of the operation. In the past, regimens had to be designed to fit the "average" patient during the intervening critical period. Although the protocols may, in fact, be useful for the average patient, the high incidence of failure attests to the obvious, all patients are not average.

Medicine, as it is practiced today, no longer requires that treatment be designed for the average patient. The anesthesiologist has become the intensivist in the operating room. The anesthesiologist can ascertain the plasma glucose concentration, alter the rate of glucose infusion, and inject insulin when necessary. Given these controls, we recommend that all protocols be abandoned.

Recommendation

The plasma glucose concentration should be measured early on the morning of the operation. If the operation is scheduled for midmorning or later, a repeat determination should be obtained prior to inducing anesthesia. Intraoperative monitoring of glucose should be no less frequent than every 2 h. If regular insulin is given to the patient, frequent determinations are mandatory for at least 3 h.

The rate of glucose administration must be limited. It is our practice to give 50 g of glucose every 8 h. For convenience, we "piggyback" the glucose infusion to a second solution of Ringer's lactate or normal saline. By so doing, the rate of electrolyte administration and glucose load can be varied independently.

One can set limits as to what one believes is a reasonable plasma glucose level. If one chooses limits between 100 and 250 mg/dl, this can be achieved by giving an increased infusion of glucose when the level is less than 100 mg/dl, or giving 10 or fewer units of regular insulin intravenously when the glucose concentration approaches 250 mg/dl.

We were impressed at finding a large number of patients who had postoperative plasma glucose values greater than 400 mg/dl. Glucose infusion rates were not carefully monitored and plasma glucose values were not determined for many hours. The failure to observe a beneficial effect of insulin given on discharge from the recovery room, we believe, is not evidence of lack of value of insulin. Rather, it is an indication of the overall poor patient management. If this situation is to be avoided, better patient supervision will be necessary. We recommend creation of an endocrine intensive care unit to which the patients can be admitted until they are able to resume their normal oral intake. While this may seem an unnecessary extravagance, not too many years ago the thought of a respiratory or cardiac intensive care unit was also deemed extravagant.

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