Randomized Comparison of Metabolic Control Achieved by Intraperitoneal Insulin Infusion With Implantable Pumps Versus Intensive Subcutaneous Insulin Therapy in Type I Diabetic Patients

JEAN-LOUIS SELAM, MD
DENIS RACCAH, MD
NATHALIE JEAN-DIDIER, MD
JIM L. LOZANO, BS
KEN WAXMAN, MD
M. ARTHUR CHARLES, MD, PHD

OBJECTIVE— To compare intraperitoneal implantable insulin infusion (IP) to subcutaneous (SC) intensive insulin therapy.

RESEARCH DESIGN AND METHODS— Twenty-one insulin-dependent (type I) diabetic patients aged 24–61 yr underwent a 3-mo treatment optimization using multiple SC daily injections or external pumps. Patients were then randomized (time 0 mo) to IP infusion using Infusaid-programmable pumps or continuation on SC intensive insulin for 6 mo.

RESULTS— No differences were noted between study and control group data. However, longitudinal within-group comparisons from baseline showed that glycosylated hemoglobin improved to near-normal in both groups: IP, 9.0 ± 0.5 vs. 7.8 ± 0.6% ($P < 0.05$) and SC, 8.4 ± 0.5 vs. 7.5 ± 0.3% ($P < 0.05$) at 0 and 4 mo, respectively (normal <6.9%). The percentage of blood glucose tests >11 mM at 0 and 6 mo was 28 ± 5 vs. 16 ± 4% in the IP group ($P < 0.05$) and 22 ± 5 vs. 24 ± 7% in the SC group (NS). At 0 and 6 mo, the standard deviation of blood glucose values, an index of glycemic fluctuations, was 4.3 ± 0.4 vs. 3.2 ± 0.5 mM in the IP group ($P < 0.05$) and 3.7 ± 0.3 vs. 4.0 ± 0.4 mM in the SC group (NS). Weight, insulin dosages, circulating lipid levels, and the frequency of severe hypoglycemic reactions and biochemical hypoglycemias were similar and did not change in the two groups.

CONCLUSIONS— IP-implantable pumps compared with SC intensive insulin therapy have similar effects on most metabolic variables and are equally effective at achieving near-normal glycemic levels. Only longitudinal data suggest that IP treatment may be more effective at limiting glycemic fluctuations.

FROM THE DIABETES RESEARCH PROGRAM, DEPARTMENTS OF MEDICINE AND SURGERY, COLLEGE OF MEDICINE, UNIVERSITY OF CALIFORNIA AT IRVINE, IRVINE, CALIFORNIA.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO JEAN-LOUIS SELAM, MD, DEPARTMENT OF DIABETOLOGY, HOTEL-DIEU 1, PLACE PARVIS NOTRE-DAME, 75181, PARIS CEDEX 04, FRANCE.

RECEIVED FOR PUBLICATION 20 FEBRUARY 1991 AND ACCEPTED IN REVISED FORM 26 JULY 1991.

Most of the alternatives to conventional subcutaneous (SC) insulin therapy for improving diabetes control have shown serious limitations (e.g., increased risk of hypoglycemia with intensive SC insulin therapy), including use of continuous SC insulin infusion (CSII) with external pumps (1), major technical problems with pancreas islet transplantation (2), bioartificial pancreas (3), glucose sensors (4), and surgical limitations with organ pancreas transplantation (5). Conversely, after years of slow development (6), implantable pumps for intravenous (IV) or intraperitoneal (IP) insulin delivery have shown promise in several recent clinical trials (7–11). According to the 1989 International Registry update, 280 pumps have been implanted in diabetic patients, and this number may double within 1–2 yr (11). The implantable insulin delivery technique appears safe and feasible, because *1*) the number of deaths do not exceed those of a similar diabetic population (11), 2) ketoacidotic episodes are rare and do not exceed the number seen with conventional insulin (11,12), 3) severe hypoglycemic events do not seem to be more frequent than with conventional insulin (8) and may be less than observed with intensive SC insulin (11), and 4) more recent insulin preparations and pump units have shown safe and prolonged function (8,10), although pump catheters have a shorter life span, averaging 2.5 yr (8,9,11). We cannot exclude, however, that these favorable comparisons with conventional insulin may be due in part to the higher degree

of motivation, education, and selection of pump patients.

The clinical issue of comparative efficacy with the best existing treatment methods (i.e., intensive SC insulin with multiple injections or with CSII) has not been assessed, because all trials have been pilot safety-feasibility studies with uncontrolled longitudinal designs (7,8,10). In this study, we evaluated the degree of diabetes control achieved by IP-implantable pump insulin delivery versus intensive SC insulin in 21 insulin-dependent (type I) diabetic patients who were randomly assigned to treatment and followed for 6 mo.

RESEARCH DESIGN AND METHODS

— Twenty-one diabetic patients (11 men, 10 women, aged 38 ± 3 yr) signed an informed consent approved by the University of California at Irvine Institutional Review Board. The criteria for selection included the presence of type I diabetes for at least 1 yr, as documented by basal and stimulated C-peptide levels after 1 mg of i.v. glucagon <0.2 and 0.5 pmol/ml, respectively; ability to recognize hypoglycemia and no more than two severe hypoglycemic episodes in the past 2 yr; and absence of proliferative retinopathy, clinical nephropathy, and other major medical or emotional disorders.

During a 3-mo baseline period, intensive SC insulin therapy was used with CSII (10 patients) or ≥3 daily injections (11 patients). All patients used human insulin with a dual basal (daytime and nighttime) bolus insulin administration pattern. Patients were then randomized to IP-implantable insulin delivery (study group) or continued on SC intensive insulin (control group) for 6 mo. Control patients were assured of receiving an implantable pump at the end of the study. Patients from both groups were followed by the same health-care team at monthly intervals. Patients adjusted their insulin dosages daily with the use of Skyler's algorithms (13) and a minimum of four self-monitoring of blood glucose tests daily (Glucometer MR, Miles, Elkart, IN). Treatment goals for both groups included near-normal fasting and preprandial blood glucose levels, and the absence of severe hypoglycemic reactions, as defined by the Diabetes Control and Complications Trial (1). Physical activity and diet were kept constant throughout the study, as monitored by monthly physical activity questionnaires, 3-day diet diaries, and visit by a dietician every 3 mo.

The delivery system (model 1000, Infusaid, Norwood, MA), the surfactant-stabilized insulin used in the pump (Hoechst 21PH, 100 U/ml, Hoechst, Frankfurt, Germany), and the procedures for implantation and the maintenance of the pump are described by Wood et al. (14). Briefly, the pump is disk-shaped, weighs 300 g, and is telemetry controlled. The rate limits are preprogrammed by the physician. The patient may then adjust the basal profile (usually 2–3 rates/day) and the bolus dose (preprogrammed as a 1-h bolus resulting in 50% of the dose in 15 min, followed by 50% in 45 min). The pumps were SC implanted in the lower-left quadrant of the abdomen, and the catheters were indwelled into the peritoneal cavity. The pump reservoirs were emptied and refilled with new insulin every month.

The occurrence of severe hypoglycemic events was recorded at each visit. Self-monitored blood glucose data were transferred from the glucose meters into a computer during the monthly visits (Glucofacts programme, Miles; 15) for calculation of the monthly blood glucose averages of the requested four daily tests, the percentage of tests <3.4 and >11 mM, and the standard deviation of blood glucose values that was used as an index of glycemic fluctuations (16). Glycosylated hemoglobin was measured monthly with affinity chromatography (17). The normal range was 4.9–6.9%. Fasting serum total cholesterol and triglycerides were measured every 3 mo, according to the Lipids Research Clinics' methodology (18). Circulating lipoproteins, apoproteins, and enzymes of the reverse cholesterol transport were also measured and are presented in CONCLUSIONS.

Results are expressed as means ± SE. Within-group data (i.e., longitudinal comparisons between preimplant and postimplant data) were analyzed with one-way analysis of variance for repeated measures. Then, paired comparisons were assessed using Student's *t* tests, with the level of significance corrected by the Bonferoni method (19). Study versus control group data were analyzed with unpaired *t* tests. Significant differences were reassessed with nonparametric tests (Wilcoxon's rank-sum test).

RESULTS

— We observed no significant differences between study and control groups for any of the variables measured. Therefore, the results are presented according to the within-group longitudinal changes seen during the study.

Glycosylated hemoglobin and mean blood glucose levels improved significantly in the pump and in the SC group (Fig. 1). Values decreased during the 3-mo baseline period, then further decreased and stabilized after the first 3 mo of the study. Minimum glycosylated hemoglobin levels were 7.8 ± 0.4 and 7.5 ± 0.4% at 4 mo in the pump and control group, respectively (NS). When compared with time 0, glycosylated hemoglobin and blood glucose values at time 4 mo were significantly different ($P < 0.05$) in both groups.

The frequency of blood glucose tests <3.4 mM, the daily insulin dosages, and the circulating levels of total cholesterol and triglycerides were similar in the two groups and did not change significantly during the study. There were no severe hypoglycemic events during the study in either group.

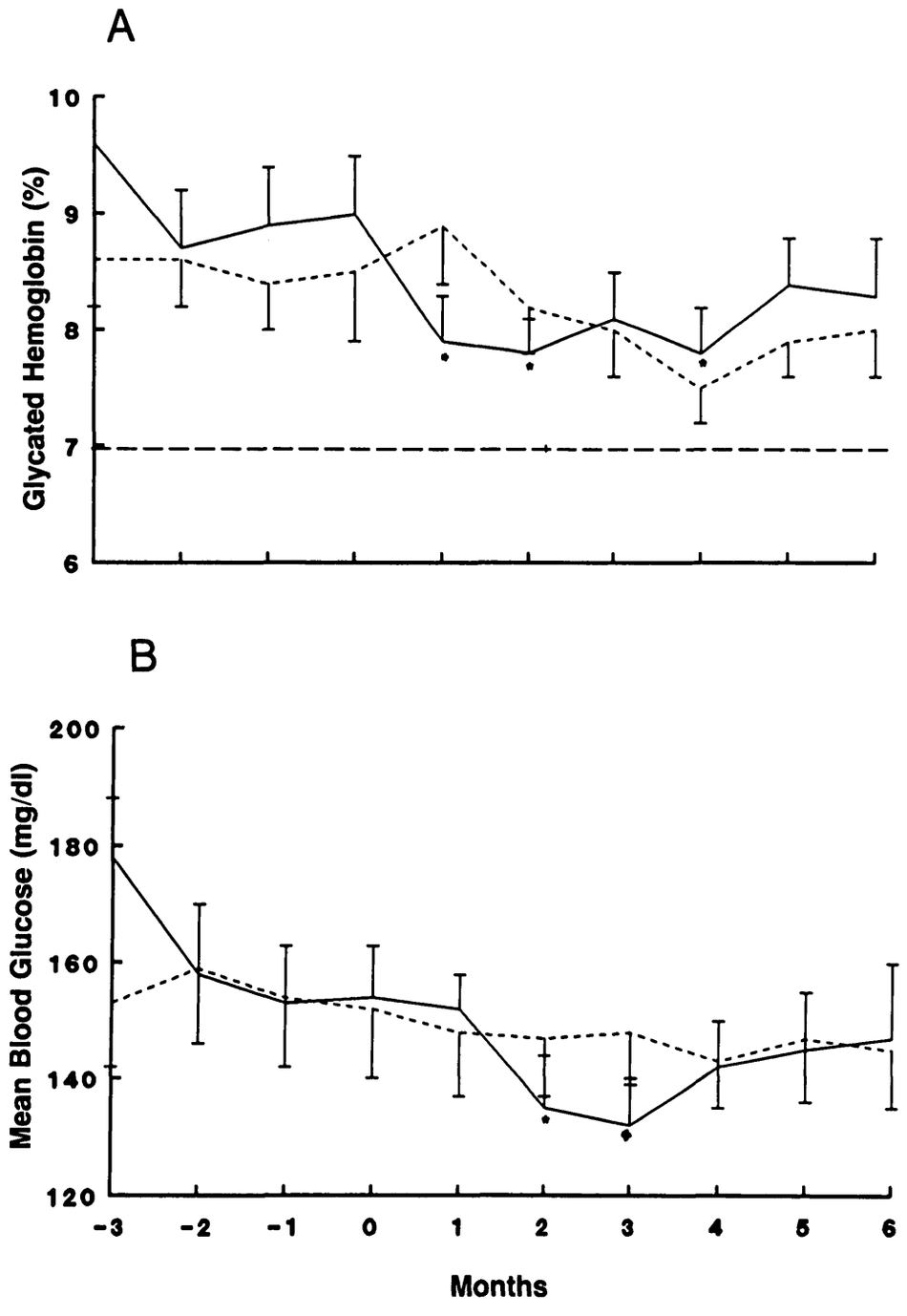

Figure 1—*Glycosylated hemoglobin (A) and mean blood glucose levels (B) in pump-treated patients (solid line) and subcutaneous insulin-treated control patients (dashed line). Horizontal dashed line, upper normal value (6.9%) of glycosylated hemoglobin; bars, mean ± 1SE. Asterisks mark significant changes from time 0 in a given group ($P < 0.05$). All other longitudinal and all between-group comparisons were not significant.*

The total daily calorie intake and the patients' weight did not change throughout the study.

The frequency of blood glucose tests >11 mM and the standard deviation of individual blood glucose values decreased, respectively, from 28 ± 3% and 4.3 ± 0.4 mM at time 0 to 16 ± 4% and 3.2 ± 0.5 mM at 6 mo in the study group ($P < 0.05$). Values in the control group were lower than those of the study group at baseline, although not significantly, and remained unchanged during the study (Fig. 2).

CONCLUSIONS — This study confirms previous reports from uncontrolled pilot trials (7,8) and controlled but short-term (<6 wk) studies (20–22). These studies suggested that insulin delivery through central routes (e.g., IP or IV using programmable infusion devices) is capable of satisfactorily controlling blood glucose levels in type I diabetic patients and possibly much better than SC intensive insulin therapy (e.g., multiple injections or CSII). Our study further extends these previous studies with *1*) a prospectively randomized design, 2) a longer period of evaluation (6 mo), and 3) an identification of specific parameters of diabetes control that have changed due to IP-implantable insulin delivery versus SC intensive insulin. However, the study could not be blinded, and control patients were promised a pump after the study. We, therefore, cannot exclude that these two conditions may have influenced patients' and/or doctors' preferences for one of the two treatments, and thus the results.

Mean blood glucose and glycosylated hemoglobin levels improved significantly and durably with IP pump delivery. However, a similar improvement was also seen in the control patients, and this improvement was already present during the baseline period in both groups, suggesting the possible contribution of a study effect

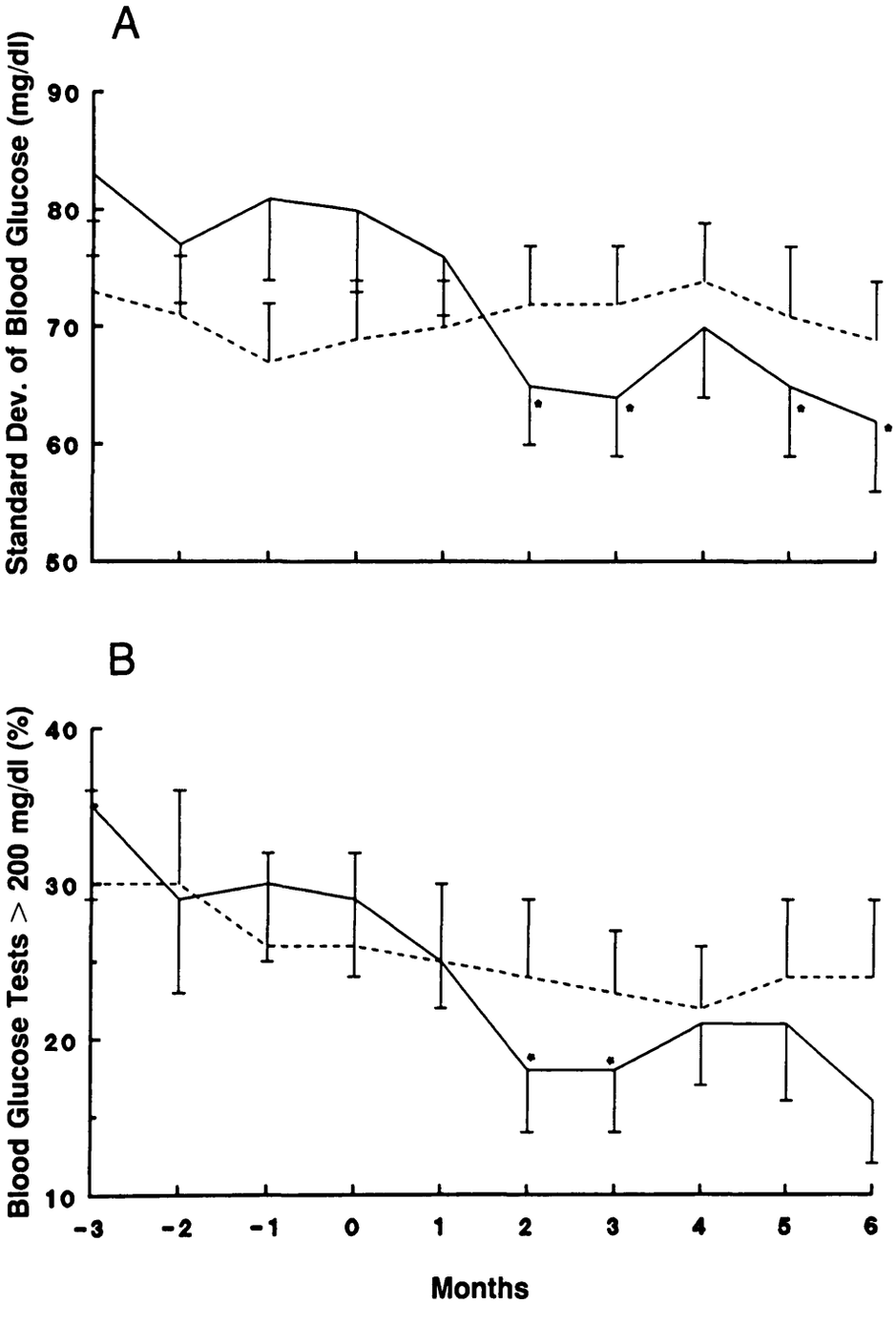

Figure 2—*Frequency of standard deviation of blood glucose values (A) and blood glucose tests >11 mM (B). Bars, mean ± 1SE. Asterisks mark significant changes from time 0 in a given group ($P < 0.05$). All other longitudinal and all between-group comparisons were not significant. All longitudinal comparisons, other than those marked with an asterisk, and all between-group comparisons were not significant.*

in the mechanisms of glycemic improvement. It should also be noted that both treatments (IP and SC) were unable to normalize completely the glycemic levels. These data indicate that, in the context of a study and intensive management, IP-implantable insulin and SC intensive treatment methods are as effective at near-normalizing blood glucose levels for periods up to 6 mo. One might speculate that we cannot exclude a type 2 error and/or that the results may be different (i.e., more striking with 1 of 2 therapies emerging as more effective) if the patients were chosen on the basis of poor metabolic control.

The average glucose improvement was not associated with an increased frequency of severe hypoglycemic reactions nor biochemical hypoglycemias in either group, whereas a significant reduction of hyperglycemic excursions from the baseline was observed only in the IP pump group. The absence of an increased risk of hypoglycemia with intensive diabetes control is not in agreement with Diabetes Control and Complications Trial data (1), but confirms the results of earlier smaller-scale pilot studies (12,23,24). Although possibly biased by their small scale and short duration, these studies suggested that intensive insulin therapy is not more dangerous than conventional insulin therapy in highly selected and closely monitored patients. Our data on standard deviations of blood glucose values, a simple and accurate index of glycemic instability, supports this idea: longitudinal within-group but not between-group data suggest a reduction of glycemic fluctuations in the IP pump patients. Keeping in mind the limitations of a post hoc within-group comparison, such an effect has never been reported with SC insulin treatment methods which, when intensified, only tend to move down the average glycemia without affecting the amplitude of glycemic fluctuations.

Daily insulin usage was also similar with IP and SC insulin, con-

firming our previous findings (8). One would have expected lower insulin requirements with IP administration because of the more physiological portohepatic entry. Animal data, however, have shown that intraportal (25,26) and IP (27) insulin delivery have the same effects as direct IV insulin delivery on glucose metabolism (e.g., hepatic release and peripheral uptake), provided peripheral circulating insulin levels are matched. Peripheral, rather than portal, insulin seems to control hepatic glucose metabolism through hepatic artery insulin levels (27) or through the supply of peripheral substrates to the liver (25).

Serum total cholesterol and triglycerides levels were similar and unchanged with IP and SC insulin. These data contrast with studies reporting that triglycerides increase (21) or total cholesterol increases (28) with IP insulin administration compared with SC insulin. However, our new data confirm our earlier study (29). The strict and consistent exercise and diet program imposed on our patients—and evidenced by their unchanged weight throughout the study—may account for our different results. On the other hand, we and others have reported cholesterol subfraction modifications with IP insulin (21,28,29). Similar analyses, but expanding to reverse cholesterol transport pathways evaluation, have been performed during this study (unpublished observations).

We conclude that continuous IP insulin delivery with implantable programmable pumps and SC intensive insulin therapy with multiple injections or CSII have a similar impact on the major metabolic parameters of diabetes control (e.g., mean blood glucose and glycosylated hemoglobin levels, hypoglycemic events, insulin dosages, and circulating lipids levels). Although not having the value of a between-group comparison, within-group (IP) longitudinal analysis of data suggests that IP insulin delivery may be more effective at limiting glycemic fluctuations. If confirmed by further controlled studies, this advantage (combined with the lack of daily injections) may make this new method of insulin therapy more acceptable and, thus, applicable in the long term for the routine type I diabetic patients, although longer-term studies are required.

Acknowledgments— This study was supported in part by a grant from the Food and Drug Administration (Orphan Products, Grant FDR-000197) and by a grant from the Juvenile Diabetes Foundation (Grant 188206).

The authors are indebted to E. Chan (Diabetes Program, University of California at Irvine) for measuring free insulin, and to V. Bucci, T. Wingrove, and M. Cafferty (Infusaid Corporation) for providing the pumps and insulin.

This article was presented in part at the 26th annual meeting of EASD, Copenhagen, 10–14 September 1990, and at the 50th annual meeting of the American Diabetes Association, Atlanta, Georgia, 16–19 June 1990.

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