

Basal Versus Sliding-Scale Regular Insulin in Hospitalized Patients With Hyperglycemia During Enteral Nutrition Therapy

A large number of hospitalized patients are in a catabolic state, with resultant increased caloric and protein needs. In such patients, inadequate oral intake can lead to undernutrition in 8 to 12 days (1). A collaborative study involving nutrition screening of 3,047 patients at admission to 33 hospitals reported that more than 50% of hospitalized patients were malnourished (2). Malnutrition is seen in several patient groups with diabetes, especially in the elderly (3) and those with complications such as renal failure or neurological dysfunctions (4). Nutrition guidelines state that any patient unable to consume adequate nutrients orally (60% nutrition needs) for at least 5 days in the critically ill or 7 to 14 days in the general population should be a candidate for specialized nutrition support (5,6). Delayed feeding, resulting in malnutrition, may increase the risk of hospital complications (relative risk 1.60), higher mortality (12.4 vs. 4.7% in the well-nourished patients [relative risk 2.63]), and longer hospital stay (16.7 ± 24 vs. 10.1 ± 12 days in the nourished patients) and may increase hospital costs by 308% (7). A recent meta-analysis reported that providing early versus delayed nutrition support results in lower infectious complications and length of hospital stay (8). Nutritional support via enteral or parenteral nutrition in malnourished patients may prevent such complications. Although both forms of nutrition support have been shown to be successful in preventing the effects of starvation and malnutrition, oral or enteral nutrition is preferable to parenteral nutrition in clinical practice (9,10). Advantages of enteral feeding over parenteral nutrition include lower costs, avoidance of central catheter-related complications, its more physiological route, and its trophic effect on gastrointestinal cells (11).

Standard enteral formulas reflect the reference values for macro- and micronutrients for a healthy population. Most

standard formulas contain whole protein, lipid in the form of long-chain triglycerides, and fiber. Most diabetes-specific enteral formulas comply with this rule in two different ways: standard formulas provide low amounts of lipids (30% of total calories) combined with a high supply of complex carbohydrates (55–60% of total calories), most of these being starch, possibly containing fructose; newer diabetic formulas have replaced part of carbohydrates with monounsaturated fatty acids (up to 35% of total calories) and may include dietary fiber (5). A number of outpatient and inpatient studies in subjects with type 2 diabetes have reported better glycemic control (lower mean, fasting, and/or postprandial glucose levels), a trend toward decreased A1C levels, and lower insulin requirements with low-carbohydrate high-monounsaturated fatty acid (LCHM) formulas compared with standard high-carbohydrate formulas (12,13). Based on these results, it is generally accepted that newer diabetic enteral formulas (LCHM) are preferable to standard high-carbohydrate formulas in hospitalized patients with type 1 and type 2 diabetes (4,5).

Hyperglycemia is a common complication of enteral nutrition therapy reported in up to one-third of adult patients in the hospital (14) and in up to one-half of elderly patients in long-term services (15). Increasing evidence indicates that the development of hyperglycemia during acute medical or surgical illness is not a physiological or benign condition but is a marker of poor clinical outcome and mortality (16,17). Insulin, given either intravenously as a continuous infusion or subcutaneously, is the most effective agent for immediate control of hyperglycemia in the hospital. In the critical care setting, continuous insulin infusion has been shown to be effective in achieving glycemic control (17,18). In general medicine and surgery services, however, few

studies have focused on the optimal management of hyperglycemia during enteral nutrition therapy. Several clinical reviews and small uncontrolled studies recommend a variety of subcutaneous regimens including the administration of regular insulin (every 4–6 h), NPH insulin (every 8–12 h), or once- or twice-daily insulin glargine (17,19).

In this issue of *Diabetes Care*, Korytkowski et al. (20) report the first randomized study comparing subcutaneous insulin regimens in non-critically ill adult patients with type 2 diabetes receiving enteral nutrition therapy. Fifty patients with or without a history of diabetes and with two or more blood glucose levels >130 mg/dl (7.2 mmol/l) were randomized to receive sliding-scale regular insulin (SSRI) ($n = 25$) or glargine insulin once daily ($n = 25$). NPH insulin was added in the SSRI group for persistent hyperglycemia (more than two blood glucose levels >180 mg/dl). In such patients, NPH insulin was given every 12 h at a starting dose equal to 50% of prior-day total regular insulin dose. Subjects in the glargine group who were insulin naïve were started at an evening dose of 10 units/day, while those already receiving basal insulin were changed or continued at the same number of units per day. In addition, supplemental SSRI was administered every 4–6 h for any blood glucose level >130 mg/dl (7.1 mmol/l) in both groups. To prevent hypoglycemia, dextrose-containing intravenous fluids were initiated within 30 min of any unanticipated discontinuation of enteral nutrition if the dose of basal insulin had been given in the prior 12-h time period. The glycemic target goal in both groups was to achieve glucose levels between 100 and 180 mg/dl (5.6 and 10 mmol/l).

Mean daily blood glucose as well as mean daily peak and nadir blood glucose values were similar in the SSRI and glargine groups. In the SSRI group, 13 of 25 patients (52%) remained on regular

insulin alone with blood glucose within the target range and 12 patients (48%) required the addition of NPH insulin twice daily because of persistent hyperglycemia during the hospital stay. Patients who failed SSRI treatment and required the addition of NPH insulin had a higher mean baseline blood glucose level (203 vs. 150 mg/dl) and were more likely to have a previous history of diabetes (67 vs. 46%). Total daily insulin dose (~27 units/day) and the number of insulin units per body weight (0.33 units/kg) were similar between treatment groups.

There were no group differences in the overall frequency of hypoglycemia (1.3 ± 4.1 vs. $1.1 \pm 1.8\%$; $P = 0.35$) or in the percentage of patient days with hypoglycemia (4.8 vs. 2.7%; $P = 0.34$). Four patients in the glargine group and seven patients in the SSRI group had a blood glucose level <70 mg/dl. Six of the seven episodes of hypoglycemia in the SSRI group occurred in patients receiving NPH insulin.

Despite the small number of patients, this study provides a valuable guide for insulin administration in patients, with and without a history of diabetes, who develop hyperglycemia during enteral nutrition therapy. More prospective randomized studies are clearly needed in order to determine the optimal management of hyperglycemia in hospitalized patients receiving nutrition support. Such studies should include larger numbers of medical and surgical patients in intensive care unit and non-intensive care unit settings. In addition, clinical trials are needed to determine the efficacy and safety of glycemic control in diabetic subjects receiving intravenous parenteral nutrition. The rate of hyperglycemia in patients receiving parenteral nutrition is higher compared with enteral nutrition due to the higher glucose load, which may lead to an increased number of complications and hospital mortality (21,22). Prospective randomized trials in patients with critical illness have shown that aggressive glycemic control can reduce short- and long-term mortality, multiorgan failure, and systemic infections (23,24); however, it is not clear if intensified insulin therapy in patients with parenteral nutrition-induced hyperglycemia will result in improved clinical outcomes and mortality reduction.

In summary, the study by Korytkowski et al. provides important clinical information. First, this study indicates that similar levels of glycemic control

were achieved in the SSRI and glargine groups. Treatment with SSRI alone was effective in maintaining glycemic control in about two-thirds of nondiabetic patients with mild hyperglycemia; however, two-thirds of patients with a history of diabetes in the SSRI group required the addition of NPH insulin twice daily because of persistent hyperglycemia. Second, in patients with known diabetes, early treatment with basal insulin glargine or with NPH insulin is effective and safe and should be preferred over SSRI alone in the management of hyperglycemia during enteral nutrition therapy. These results are in agreement with those reported in recent randomized control studies in hospitalized patients with type 2 diabetes (25–27). Finally, the results of this study indicate that implementing standardized nutritional support orders together with basal insulin order sets are key interventions that might reduce complications associated with severe hyperglycemia and hyperglycemia in hospitalized patients.

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