Continuous Insulin Infusion: When, Where, and How?

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The association between inpatient hyperglycemia and adverse patient outcomes is well documented.[1–7] Thus, focus on inpatient glycemic control has increased in the past decade. However, optimal glycemic targets remain controversial, and significant barriers to optimal glycemic control persist.

Inpatient Glycemic Targets

After publication of the initial van den Berghe trial in surgical intensive care patients,[1] several professional organizations published guidelines supporting near-normal glycemic targets.[8,9] Subsequent trials documented an increased risk for hypoglycemia with tight glycemic control, suggesting that more modest glycemic targets may be optimal.[10–13] The Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study,[14] a large, randomized trial involving > 6,100 medical and surgical patients, documented higher 90-day mortality rates in patients managed with tight glycemic control than in those receiving conventional glucose management. Although hypoglycemia was more common among patients in the intensive treatment group, the association of hypoglycemia with an increased hazard ratio for death was similar in the two groups, suggesting that hypoglycemia contributed to the excess mortality in the intensively treated group.[15]

The increased risk for hypoglycemia and mortality with tight glycemic control does not justify ignoring glycemic control, but it does justify setting more moderate targets. The American Diabetes Association (ADA), the American Association of Clinical Endocrinologists (AACE), the Surviving Sepsis Campaign, and the Institute for Healthcare Improvement all updated their guidelines for glycemic control in 2009 in response to data from NICE-SUGAR.[16–18] All four sets of guidelines recommend initiating insulin therapy in patients with persistent hyperglycemia (blood glucose > 180 mg/dl). After insulin is initiated, the target blood glucose range should be 140–180 mg/dl for the majority of patients. However, a more stringent goal of 110–140 mg/dl may be appropriate for certain patients, provided it can be achieved without causing significant hypoglycemia. The Society of Critical Care Medicine recommends a slightly different target of 100–150 mg/dl, while still focusing on minimizing the risk for hypoglycemia.[19]

Rationale for Continuous Insulin Infusion

Insulin is the preferred treatment modality in the hospital setting because it is the most potent agent to lower blood glucose, is rapidly effective, is easily titrated, and has no absolute contraindications.[18,20] However, insulin is a high-alert medication that is consistently implicated in reports of preventable patient harm (from hypoglycemia) and thus requires accurate monitoring and standardized protocols to minimize risks while maximizing benefits.[21–24]

Intravenous (IV) infusion is the preferred route of insulin delivery in critical care, labor and delivery, and perioperative inpatient settings because the rapid onset and short duration of action associated with IV

Table 1. Potential Indications for IV Insulin Therapy[20]

- Diabetic ketoacidosis
- Hyperglycemic, hyperosmolar state
- Critical care illness (medical/surgical)
- Post-cardiac surgery
- Myocardial infarction or cardiogenic shock
- Prolonged NPO status in patients who are insulin deficient
- Labor and delivery
- Uncontrolled hyperglycemia during high-dose glucocorticoid therapy
- Perioperative period
- Post-organ transplantation
- Stroke
- Total parenteral nutrition therapy
- Dose-finding strategy before converting a patient to subcutaneous insulin

infusion allow for matching insulin requirements to rapidly changing glucose levels. Table 1 provides additional potential indications for IV insulin infusion.[20] Sliding-scale or correction algorithms with regular or rapid-acting insulin administered as needed for hyperglycemia without scheduled basal insulin or prandial insulin (for patients who are eating) are outdated treatment modalities that should be abandoned. Data are lacking to support the benefit of sliding-scale insulin or correction insulin algorithms without basal insulin, and these practices are associated with wide fluctuations in blood glucose, which have been linked to higher hospital mortality rates.[25]

Insulin infusion may be an alternative to a basal-bolus insulin regimen outside of the critical care setting for perioperative and other patients who are not eating (NPO status) and patients whose glycemia is poorly controlled with subcutaneous insulin. Insulin infusion can be safely administered outside of the critical care setting provided staff education, nurse-to-patient ratios, and blood glucose monitoring are adequate.[20,26] In addition, setting more moderate glycemic targets for patients outside of the critical care setting may minimize nursing time for blood glucose monitoring and titration of the insulin infusion. For patients starting parenteral or enteral nutrition, the use of IV insulin infusion with appropriate monitoring may allow for more rapid titration and determination of patients' insulin requirements than one could expect from either a subcutaneous insulin regimen or from the practice of including insulin in the parenteral nutrition solution. The use of IV insulin infusion in patients who are eating or are receiving intermittent enteral/parenteral nutrition requires proactive increases in infusion rate with the start of nutritional intake and decreases when nutritional intake is stopped, and thus, in most situations, conversion to subcutaneous insulin is appropriate because it is less labor intensive.

Barriers to Implementing a Continuous Insulin Infusion Protocol

Potential barriers to implementing an insulin infusion protocol include fear of hypoglycemia, confusion regarding appropriate glycemic targets, insufficient nurse-to-patient ratios, insufficient availability or convenience of glucose-monitoring devices, lack of administrative support, various system and procedural issues, and resistance to change. Before implementing an IV insulin infusion protocol, it is imperative to evaluate the current glycemic-related practices within the institution and address the following crucial questions: What is the current level of glycemic control? Who is checking patients' blood glucose and how often? How interested is the staff in optimizing glycemic control, and do they have the support they need to achieve this goal?

Key steps to overcoming these barriers include building support with multidisciplinary champions, involving key staff members in the process, educating staff and administrators about the benefits of optimizing glycemic control, and internally marketing the clinical success of the protocol. Descriptions of several models of implementation have been published, including endocrinologist consultation models, glycemic control teams, and system-wide models.[27–32] It is important to adapt whichever model is selected to meet the needs of the specific institution.

Selecting an Insulin Infusion Protocol

Numerous insulin infusion protocols have been published. However, head-to-head comparisons are rare, and efficacy and safety are difficult to determine because of differing patient populations, glycemic targets, metrics for evaluation, and definitions of hypoglycemia used in the various protocols.[26,33–37] Selecting a validated protocol allows for more rapid implementation but does not eliminate the need for ongoing safety and effectiveness monitoring and continuous quality improvement.

Some paper protocols are table-based, whereas others require mathematical calculations. The level of clinical judgment and physician oversight also varies among the available protocols. Computerized protocols allow for more complex mathematical calculations and can provide alerts or alarms to remind staff members to check patients' blood glucose level and adjust infusion rates.

Several studies comparing computerized and paper-based protocols have found improved protocol adherence, improved glycemic control, and less hypoglycemia with computerized protocols.[38–49] It is worth noting that evaluations of computerized glucose control programs have used glycemic targets that are tighter than currently recommended, and although the percentages of blood glucose readings within the target range were higher than with paper protocols, they still were not optimal in most studies. It is not clear how computerized glucose control programs compare to paper-based protocols when currently recommended targets are used.

Several computerized decision-support systems for insulin infusion management are commercially available; however, licensing fees and

Table 2. Components of a Safe and Effective Insulin Infusion Protocol

- Includes appropriate glycemic targets
- Identifies threshold for implementation
- Is nurse-managed and easy to implement
- Provides clear, specific directions for blood glucose monitoring and titration
- Includes titration based on both current blood glucose level and rate of change*
- Is safe: carries a low risk for hypoglycemia and includes an embedded protocol for treatment of hypoglycemia should it occur
- Is effective: gets patients to target quickly and maintains blood glucose within the target range with minimal titration
- Includes a plan for transition to subcutaneous insulin

**Rate of change is calculated based on the slope of the blood glucose trend line and is frequently incorporated into column-based protocols by movement to a more aggressive algorithm if blood glucose is not declining by ~ 40–75 mg/dl or to a less aggressive algorithm if blood glucose is declining too rapidly.*

compatibility with institutional computer systems may limit their use. An institution's culture, finances, computer/technical support, and patient populations will dictate the best type of protocol for that specific setting. Table 2 lists characteristics to consider when selecting an insulin infusion protocol.

Successful implementation of an insulin infusion protocol requires multidisciplinary interaction and ongoing staff education to ensure optimal patient outcomes. An ideal protocol achieves the desired target blood glucose quickly (within 3–12 hours in published protocols) and maintains blood glucose in the target range.[40] The protocol should have a clear algorithm for dose titration, which includes not only a patient's current blood glucose, but also the rate of change in the patient's blood glucose. The rate of change is calculated based on the slope of the blood glucose trend line. It is frequently incorporated into table-based protocols by movement to a more aggressive algorithm/column if blood glucose is above the target range and not declining rapidly enough or movement to a less aggressive algorithm if blood glucose is declining too rapidly or approaching the target range. Finally and most importantly, the protocol should minimize hypoglycemia and provide specific instructions for prompt treatment of hypoglycemia should it occur. The reported incidence of hypoglycemia with insulin infusion is highly variable (< 1 to > 20%) and dependent on multiple factors.[40,46] Minimizing the risk of hypoglycemia with any insulin infusion protocol requires ongoing evaluation of hypoglycemia episodes and the contributing factors such that the protocol can be revised to address and minimize the risk.

Hypoglycemia Prevention and Treatment

Recent data have brought renewed appreciation of the risk for hypoglycemia.[10,13–15,50] Historically, hypoglycemia has been variably defined as a blood glucose level of anywhere from < 40 to < 70 mg/dl. The ADA currently defines hypoglycemia as a blood glucose level < 70 mg/dl. The most effective strategies to prevent hypoglycemia include frequent blood glucose monitoring and proactive adjustment of the infusion rate if the blood glucose level decreases too rapidly. In addition, more frequent blood glucose monitoring (every 15–20 minutes) should be implemented until blood glucose is consistently > 100 mg/dl. Some hypoglycemia protocols temporarily stop the insulin infusion for hypoglycemia and restart it at a lower rate once hypoglycemia has resolved. However, failure to restart the infusion can result in profound hyperglycemia and ultimately diabetic ketoacidosis (DKA) in patients with type 1 diabetes. Thus, some hypoglycemia protocols do not stop the infusion, but significantly reduce the rate.

The ADA and AACE recommend hourly blood glucose monitoring for patients receiving IV insulin therapy except for patients with stable blood glucose within the target range, for whom monitoring can be performed every 2 hours. Some protocols have used a monitoring schedule of every 4 hours. However, the incidence of hypoglycemia exceeds 10% with many of these protocols.[11–13] In practice, monitoring blood glucose every 1–2 hours can be difficult, especially outside of the critical care setting. Additional strategies that may improve safety include targeting higher blood glucose levels, titrating the insulin infusion rate less aggressively, and providing staff education and policies regarding when a patient must be transferred and additional nursing resources must be allocated.

An embedded hypoglycemia treatment protocol is imperative for the safety of insulin infusion therapy. A hypoglycemia protocol allows bedside nurses to immediately implement treatment without additional orders. Key components of a hypoglycemia protocol include specific instructions regarding temporarily turning off or reducing the infusion rate, treating with dextrose or other glucose sources, and monitoring more frequently, as well as when the insulin infusion, if temporarily stopped, should be restarted and at what rate.

Point-of-Care Glucose Monitoring

Although point-of-care (POC) blood glucose monitoring is the most practical option for bedside blood testing, there are limitations to its accuracy, and thus a strong quality control program is necessary. Some situations may render capillary blood glucose monitoring inaccurate, including shock, hypoxia, dehydration, extremes in hematocrit, elevated bilirubin and triglycerides,

and the use of some medications (e.g., mannitol, icodextrin/maltose, and acetaminophen). The degree of interference and thus inaccuracy of the blood glucose measurement varies depending on the concentration of the interfering substance and the POC methodology (e.g., glucose oxidase vs. glucose dehydrogenase).[51] Thus, it is important to carefully assess the specific device limitations and patient populations to optimize quality control policies and procedures. There is concern that the safety and effectiveness of POC blood glucose monitoring systems are not sufficiently evaluated in hospitalized acutely ill patient populations before marketing. The U.S. Food and Drug Administration has issued draft recommendations requiring additional testing of POC blood glucose monitoring devices for use in the hospital setting before approval.[52]

Arterial or venous whole blood sampling is recommended instead of finger-stick capillary testing for patients in shock, receiving vasopressor therapy, or with severe peripheral edema.[19] In these situations, samples from an arterial or venous site should be used. Bedside POC blood gas analyzers are frequently use in the operative and critical care settings and can be used to monitor blood glucose, as well as electrolytes and blood gases. However, they require a larger volume of blood, are substantially more expensive, and utilize the same methodology (glucose oxidase) as many of the available POC blood glucose meters. Any time a POC blood glucose value does not match the clinical situation, it should be verified with a repeat test or laboratory blood glucose determination.

Continuous glucose sensors are available for ambulatory patients and have demonstrated benefits in select patients over intermittent POC testing. However, data are mixed regarding the performance of these U.S. Food and Drug Administration–approved ambulatory devices in the critical care setting.[53–55] Preclinical testing of an intravascular continuous glucose monitoring sensor has been promising.[56] Perhaps in the future, the use of continuous glucose sensors in combination with a computerized decision-support system for insulin therapy will improve the safety of insulin infusion therapy for critically ill patients, allowing for the achievement of tighter glycemic goals without hypoglycemia.

Staff Education

The safety of any insulin infusion protocol is tied to the ability of staff members to understand and follow the protocol; thus, ongoing education and competence assessment are crucial. The best educational approach is a varied one that allows for differing learning styles and differing work schedules and that can be repeated at frequent intervals. Each institution will have unique educational needs; thus, the education plan will differ from site to site. However, education is a key component of successful insulin infusion protocols in all settings.

Metrics for Evaluating Insulin Infusion Protocols

Ongoing evaluation of efficacy and safety is also crucially important to the successful implementation of an insulin infusion protocol. Such evaluation facilitates continuous improvement and staff education and builds momentum to support expansion of the protocol into additional patient populations or additional settings within the institution. Evaluation metrics can be as simple as tracking *1*) mean or median blood glucose with standard deviations or interquartile ranges by unit or patient population and *2*) incidence of hypoglycemia. It is also important to evaluate glucose variability because increased variability is also associated with poor patient outcomes.[57] Depending on the institution's specific goals and barriers, metrics can include more advanced evaluation, including financial analysis. Several institutions have published their metrics and financial impact assessments.[58–60] Similar to staff education, evaluation metrics will differ from one institution to another but remain a crucial tool for safe and effective insulin infusion programs in all institutions.

Transition from IV to Subcutaneous Insulin

To avoid loss of glycemic control and optimize patient outcomes, it is important that patients are appropriately transitioned from IV to subcutaneous insulin. This is especially important for patients with type 1 diabetes, because they can develop DKA if scheduled basal insulin and prandial insulin (for patients who are eating) are not initiated before stopping the insulin infusion. A transition protocol provides guidance regarding which patients are likely to require transition to subcutaneous insulin and when and how to make the transition. Patients with type 1 diabetes and most patients with type 2 diabetes who were treated with insulin before hospitalization will require such a transition. In addition, patients receiving > 2 units/hour of insulin on the infusion protocol will likely require subcutaneous insulin unless there is a significant change in their clinical situation, such as discontinuation of parenteral/enteral nutrition, tapering of steroids, or gastric bypass surgery.[61]

The appropriate timing for the transition from IV to subcutaneous insulin depends on institutional policies regarding where and when insulin infusion can be used. Ideally, the transition occurs when patients begin an oral diet and their blood glucose levels are stable within the target range. IV insulin has a very short duration of action (minutes), and the onset of basal subcutaneous insulin is 1–2 hours. Thus, IV insulin should be continued for 1–2 hours after the first administration of subcutaneous basal insulin.

Once a patient has been identified as needing to transition to subcutaneous insulin, the patient's 24-hour insulin requirement can be calculated by extrapolating from the average IV dose required over the previous 6–8 hours in a stable patient. Most authorities recommend using 60–80% of the total daily insulin requirement calculated from the insulin infusion rate to minimize the risk of hypoglycemia. An additional factor to consider is the caloric intake of the patient while on the

insulin infusion protocol. If intake is minimal, the calculated daily insulin dose reflects primarily the patient's basal insulin requirement. If the caloric intake is more substantial (e.g., parenteral or enteral nutrition), the calculated insulin requirement reflects both basal and nutritional insulin requirements. Patients who will be eating will require both basal and prandial insulin, with correction doses as needed. For patients who will be on NPO status or eating very little, basal insulin with correction doses can be used. Several authors have published protocols for the transition from IV to subcutaneous insulin.[62–67]

Conclusion

Although the past decade has seen great controversy regarding optimal glycemic targets for inpatients, it is clear that extremes of blood glucose lead to poor outcomes, and continuous IV protocols are the preferred treatment modality for glycemic control in the critical care setting. In addition, insulin infusion can be an effective treatment modality in other acute care settings with appropriate glycemic targets, monitoring, and education. The safety of insulin infusion protocols hinges on appropriate blood glucose monitoring and titration. Using a computerized infusion protocol and a continuous blood glucose sensor may allow for tighter glycemic control without increasing hypoglycemia and mortality rates.

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