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Abstract

Hyperglycemia is associated with poor outcomes in hospitalized medical and surgical patients. Although some early evidence showed benefits of intensive insulin therapy (IIT), recent evidence does not show a consistent benefit and even shows harm associated with the use of IIT. The overuse of some therapeutic interventions and the resulting harms to a patient are an important component of unnecessary health care costs. The goal of this article is to address the management of hyperglycemia and evaluate the benefits and harms associated with the use of IIT to achieve tight glycemic control in hospitalized patients with or without diabetes mellitus. This article is based on the evidence review and the guideline developed by the American College of Physicians on this topic. Best Practice Advice 1: Clinicians should target a blood glucose level of 7.8 to 11.1 mmol/L (140 to 200 mg/dL) if insulin therapy is used in SICU/MICU patients. Best Practice Advice 2: Clinicians should avoid targets less than 7.8 mmol/L (<140mg/dL) because harms are likely to increase with lower blood glucose targets.

Keywords

high-value care, inpatient glycemic control, intensive insulin therapy, blood glucose level

Hyperglycemia is associated with poor outcomes in hospitalized medical and surgical patients.^{1–6} Although some early evidence showed benefits of intensive insulin therapy (IIT), recent evidence does not show a consistent benefit and even shows harm associated with the use of IIT.^{7–11} In addition, IIT consumes more resources and is a more expensive approach to managing hyperglycemia than standard therapy.¹² Thus, it is important to evaluate the health benefits of IIT in order to justify its harms and costs.¹³ The American College of Physicians (ACP) developed this Best Practice Advice paper to discuss evidence on the management of hyperglycemia with the use of IIT in hospitalized patients. The goal of ACP's High-Value Care initiative is to promote the use of diagnostic tests and therapeutic interventions that provide high value while discouraging the use of low-value tests and interventions that are not beneficial or may be harmful. This article is based on the evidence review and ACP guideline on inpatient glycemic control.^{14,15} The target audience for this article is all clinicians, and the target patient population is all adults with hyperglycemia in a hospital setting. In this study, *IIT* is defined as the use of intravenous insulin to achieve a targeted blood glucose level with frequent

blood glucose testing and adjustment of insulin doses.^{14,15} In intensive care unit (ICU) settings, the usual target of IIT is normoglycemia (blood glucose level = 4.4–6.1 mmol/L [80–110 mg/dL]), whereas targets in non-ICU settings have been more variable (ranging from normoglycemia to <11.1 mmol/L [<200 mg/dL]).

Benefits of IIT

The potential benefit of a well-controlled glucose level is a reduction in morbidity and mortality and improved health outcomes in hospitalized patients. However, evidence comparing IIT with normoglycemia or targeted strict blood glucose control in patients with or without diabetes mellitus has not shown decreased mortality

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among patients in the medical intensive care unit (MICU) or surgical intensive care unit (SICU), in patients with myocardial infarction, stroke, or acute brain injury, or in the perioperative setting.¹⁴ Data on the effects of IIT targeted to normoglycemia on reduction in length of ICU stay are mixed. In addition, studies evaluating the incidence of infection with the use of IIT showed that there is some evidence of a marginally significant reduction in the risk of sepsis and a nonsignificant reduction in the incidence of infection.¹⁴

Harms of IIT

The major harm of IIT is an increased risk of hypoglycemia; all of the studies showed the excess risk, especially in critically ill patients.¹⁶⁻¹⁹ Although the evidence is not clear regarding the consequences of hypoglycemia in hospitalized patients, some studies have shown that increased mortality is associated with IIT and hypoglycemia²⁰ or extended length of stay among patients experiencing 1 or more episodes of hypoglycemia.²¹⁻²⁴ Additional concerns about the impact of hypoglycemia include an increased risk for dementia,²⁵ transient ischemia, and catecholamine surges.²⁶⁻²⁸ Although the target blood glucose levels in the trials evaluated in the evidence review ranged widely, avoiding targets less than 7.8 mmol/L (<140 mg/dL) should be a priority because harms are likely to increase at lower blood glucose targets.

Impact of IIT on Costs

Currently, there are no cost-effectiveness studies that have incorporated results from the recent trials to evaluate the impact of IIT in light of the new evidence.

There is some evidence evaluating the impact of IIT on resource utilization, and a multicenter ICU study showed that intensive glucose monitoring and dosing adjustments could cost up to 2 hours of nursing personnel time for a given patient per 24-hour period (\$182 488 nurses' salaries and \$58 500 for supplies per year).²⁹

Current Practice

In the United States, many hospitals and health care systems developed protocols intended to implement IIT routinely in critically ill patients^{30,31} based on evidence from one trial that showed mortality benefit.¹⁰ However, there is no evidence supporting that the benefits of IIT outweigh its harms. Even in light of the new evidence, many systems continue to recommend moderate blood glucose control because of the association of high blood glucose with infection, poor wound healing, dehydration, and other complications. Clinicians caring for these

patients must keep the harms of hypoglycemia in mind when managing hyperglycemia and should avoid aggressive glucose management.

ACP Best Practice Advice

Best Practice Advice 1: Clinicians should target a blood glucose level of 7.8 to 11.1 mmol/L (140-200 mg/dL) if insulin therapy is used in SICU/MICU patients.

Best Practice Advice 2: Clinicians should avoid targets less than 7.8 mmol/L (<140 mg/dL) because harms are likely to increase with lower blood glucose targets.

Our review of the evidence shows that IIT with a goal of achieving normoglycemia or near-normoglycemia in patients with or without diabetes does not provide any beneficial effects and may lead to harm. The results from various studies indicate that using IIT to achieve strict glucose control compared to standard therapy with less strict control did not reduce mortality or length of hospital stay but did substantially increase the risk for severe hypoglycemia. In addition, aside from the costs associated with the implementation of IIT in a hospital, there are also downstream costs that are incurred with the management of consequent harms. Hence, IIT should not be used to strictly control blood glucose or to normalize blood glucose in SICU and MICU patients with or without diabetes mellitus. However, it is important to keep in mind that poorly controlled hyperglycemia is associated with increased morbidity, mortality, and worsened health outcomes in patients in the ICU. Although the evidence is not sufficient to give a precise range for blood glucose levels, target values of 7.8 to 11.1 mmol/L (140-200 mg/dL) is a reasonable option for patients in the ICU because insulin therapy targeted at blood glucose levels of 7.8 to 11.1 mmol/L (140-200 mg/dL) is associated with similar mortality outcomes as IIT targeted at blood glucose levels of 4.4 to 6.1 mmol/L (80-110 mg/dL) and is associated with a lower risk for hypoglycemia.

Table 1 summarizes ACP's Best Practice Advice for managing inpatient hyperglycemia with evidence-based guidance for providing high-value care that is safe, effective, and cost-conscious.

Members of the Clinical Guidelines Committee

Individuals who served on the Clinical Guidelines Committee from initiation of the project until its approval: Paul Shekelle, MD, PhD, Chair; Roger Chou, MD; Paul Dallas, MD; Thomas D. Denberg, MD, PhD; Nick Fitterman, MD; Mary Ann Forciea, MD; Robert

Table 1. The American College of Physicians Best Practice Advice: Inpatient Glycemic Control.

The American College of Physicians Best Practice Advice: Inpatient Glycemic Control	
Disease/condition	Inpatient hyperglycemia
Target audience	Internists, family physicians, physicians caring for hospitalized patients, other clinicians
Target patient population	Hospitalized adults with hyperglycemia
Interventions	Intensive insulin therapy (IIT)
Outcomes	Short-term mortality (28-day, hospital, intensive care unit)
Evidence on the use of IIT to treat inpatient hyperglycemia	<ul style="list-style-type: none"> There is no difference in mortality for insulin therapy targeted at blood glucose levels of 7.8 to 11.1 mmol/L (140-200 mg/dL) compared to IIT targeted at blood glucose levels of 4.4 to 6.1 mmol/L (80-110 mg/dL). The use of IIT is associated with an excess risk of hypoglycemia (relative risk = 6.00; confidence interval = 4.06-8.87)
Best practice advice	<p>Best Practice Advice 1: Clinicians should target a blood glucose level of 7.8 to 11.1 mmol/L (140-200 mg/dL) if insulin therapy is used in SICU/MICU patients.</p> <p>Best Practice Advice 2: Clinicians should avoid targets less than 7.8 mmol/L (<140 mg/dL) because harms are likely to increase with lower blood glucose targets.</p>

Abbreviations: SICU, surgical intensive care unit; MICU, medical intensive care unit.

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Authors' Note

The authors of this article are responsible for its contents, including any clinical or treatment recommendations.

Conflicts of Interest

The authors declared no conflicts of interest with respect to the research, authorship, and/or publication of this article. Any financial and nonfinancial conflicts of interest of the group members were declared, discussed, and resolved. A record of conflicts of interest is kept for each Clinical Guidelines Committee meeting and conference call and can be viewed at www.acponline.org/clinical_information/guidelines/guidelines/conflicts_cgc.htm.

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