HSR&D

Management of Inpatient Hyperglycemia: A Systematic Review

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EXECUTIVE SUMMARY

BACKGROUND

Hyperglycemia is a common finding in hospitalized patients and has been associated with worsened outcomes in a variety of inpatient subpopulations. The use of insulin to control blood glucose has been advocated as a way to improve health outcomes in hospitalized patients with hyperglycemia, but the evidence for the efficacy of this approach and the thresholds for initiating insulin management are unclear.

The key questions were:

1. Does strict blood glucose control compared to less strict blood glucose control improve final health outcomes in the following patients?
- patients in the medical intensive care unit
- patients in the surgical intensive care unit
- acute myocardial infarction patients
- acute stroke patients
- post coronary artery bypass graft patients
- general surgical ward patients
- general medicine ward patients

2. What are the harms of strict blood glucose control in the above subpopulations?

3. What are the most effective and safest means of normalizing blood glucose in the above subpopulations?

METHODS

We conducted searches in Medline and the Cochrane database of systematic reviews of literature published from 1950 through May 2008, and obtained additional articles from systematic reviews, reference lists of pertinent studies, reviews, editorials, and by consulting experts. We also searched for information about unpublished studies on clinicaltrials.gov and included these studies if the authors provided enough detail to enable quality rating. Reviewers trained in the critical analysis of literature assessed for relevance the abstracts of citations identified from literatures searches. Full-text articles of potentially relevant abstracts were retrieved for further review. We assessed the overall quality of evidence for outcomes by considering the consistency, coherence, and applicability of a body of evidence, as well as the internal validity of individual studies, using a method developed by the Grade Working Group.(1) We performed a meta-analysis of trials conducted in critical care settings to estimate the effects of achieving normoglycemia using intensive insulin therapy on short-term mortality and risk of hypoglycemia.

RESULTS

We reviewed 2313 titles and abstracts from the electronic search, an additional 44 from reference mining and recently published studies, and also 9 unpublished studies. We retrieved 356 full-text articles for further review. We included 26 RCTs and 3 systematic reviews in synthesizing evidence for key question 1. For key question 2, we evaluated the results of 23 RCTs, 2 systematic reviews, and 10 studies that were either observational studies or trials without health outcomes. To address key question 3, we included 3 systematic reviews and 2 RCTs, as well as the 10 observational studies and trials without health outcomes.

KEY QUESTION #1. Does strict glycemic control compared to less strict glycemic control improve final health outcomes in the following patients?

Very little intervention data is available to help clearly define a glucose threshold that should prompt glucose lowering efforts in various inpatient subpopulations. The benefits of achieving normoglycemia with aggressive insulin use are inconsistent and may be limited to subgroups of critically ill patients receiving aggressive nutrition and in whom reliable glucose monitoring methods are used. Use of insulin to achieve normoglycemia is associated with a considerable risk of hypoglycemia. Higher glucose targets can likely be relatively safely achieved in inpatients, though the impact of this practice on health outcomes is uncertain.

Patients in Medical and Surgical Intensive Care Units

We found eight unblinded randomized, controlled trials examining the efficacy of tight glycemic control using intensive insulin regimens in critically ill patients, including two in the medical ICU (MICU) setting, two in the surgical ICU (SICU) setting, and four in mixed MICU/SICU settings. Single-center evidence had initially shown a mortality and morbidity benefit from IIT in subgroups of patients requiring prolonged ICU stays, but the applicability of these data to other ICUs may be limited and subsequent trials have not confirmed this benefit. Our meta-analysis found the use of intensive insulin therapy to achieve normoglycemia had a neutral effect on short-term mortality, but increased the risk of hypoglycemia more than five-fold. (GRADE: Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.)

Acute Myocardial Infarction Patients

We found good evidence that insulin used as part of a fixed-dose glucose-insulin-potassium infusion does not consistently improve final health outcomes in acute myocardial infarction patients, and may increase short-term mortality. (GRADE: High = Further research is unlikely to change our confidence on the estimate of effect.)

Six trials have examined tight glycemic control using adjustable dose insulin-based regimens.   As a body of evidence, these studies fail to demonstrate consistent evidence

of the benefits of adjustable dose insulin-based regimens in acute myocardial infarction patients, but variation in trial design, achievement of recruitment goals, glucose level achieved, and concomitant therapy for myocardial infarction limit the strength of this conclusion. (GRADE: Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and may change the estimate.)

Acute Stroke Patients

The largest trial to date in stroke patients reported largely negative results, but was hampered by low participation rates and incomplete data reporting. A second much smaller fair-quality trial in patients with subarachnoid hemorrhage failed to find a long-term clinical benefit from tight glycemic control, but did find a reduced infection rate in the short-term. Thus there is very little good-quality evidence investigating tight glycemic control in patients who have suffered a cerebrovascular accident. (GRADE: Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and may change the estimate.)

Post Coronary Artery Bypass Graft Patients and General Surgical Ward Patients

We found five trials which varied widely in design, blood glucose levels attained, and in the inclusion of patients with diabetes, limiting the comparability of results across studies. Several studies were underpowered to evaluate the outcomes of interest in this review. Neither insulin infusion nor GIK infusion given perioperatively provided a clear benefit among cardiac surgery patients in any of the studies. One good-quality meta-analysis reviewed a diverse group of GIK and insulin infusion studies in peri- and postoperative settings and found largely negative results when the largest trial (reviewed under the ICU section above) was excluded.

Overall, there is no clear evidence showing a benefit of tight glycemic control strategies in the perioperative setting, but the trial evidence is methodologically limited. (GRADE: low = Further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.)

General Medicine Ward Patients

There were no studies evaluating a tight glycemic control strategy to less tight glycemic control in general medical ward patients. Thus, the overall level of evidence in this subpopulation is very low (GRADE: Very Low = Any estimate of effect is very uncertain.)

KEY QUESTION #2. What are the harms of strict blood glucose control in the above subpopulations?

There is a considerable risk of hypoglycemia in medical ICU patients treated with intensive insulin protocols designed to normalize blood glucose. This risk was lower in

surgical ICU patients receiving similar therapy, and in myocardial infarction, stroke, and perioperative patients in whom the target glucose level was generally not aimed at strict normoglycemia. Data from numerous mainly single-center observational studies and trials not examining health outcomes suggest the incidence of hypoglycemia may be considerably lower when less strict glucose targets are used. There was very little evidence that hypoglycemia from tight glycemic control protocols resulted in short-term adverse health outcomes, but the long-term effects of inpatient hypoglycemia have not been well studied.

KEY QUESTION #3. What are the most effective and safest means of normalizing blood glucose in the above subpopulations?

A number of insulin infusion protocols (IIPs) have been evaluated, but comparative effectiveness data are lacking. The protocols differed in terms of patient characteristics, target glucose ranges, the time required to achieve the target glucose, the incidence and definition of hypoglycemia, the rationale or algorithm used for adjusting the insulin rates, the methods used to assess effectiveness and the methods of glucose monitoring. Given this variety of factors, reviewers have suggested each institution should individualize its approach to protocol implementation based on its patient population as well as its institutional and provider resources. Based on comparisons across studies, some reviewers speculate better protocols incorporate bolus insulin doses, account for the direction and rate of glucose change, and make allowances for "off-protocol" adjustments, although this conclusion is not based on direct comparisons of protocols.

Basal bolus subcutaneous insulin regimens may be more effective in lowering blood glucose than sliding scale regimens, though there is very limited evidence comparing methods of blood glucose control in ward patients.