BACKGROUND

Inpatient hyperglycemia particularly in the Intensive Care settings is associated with increased mortality and morbidity but optimal management of these patients is controversial. Despite conflicting data from studies of Intensive Insulin Therapy, the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE) consensus panels have issued gynecologic targets for critically ill patients with hyperglycemia based on their review of published literature including Randomized Controlled Trials (RCTs), meta-analyses and Systematic reviews. Many meta-analyses however have used the Jadad Scale for assessing quality of included RCTs in which points are awarded for randomization, double blinding, and reporting of withdrawals or dropouts. However this scale is often inadequate in assessing bias because a low quality study with no commitment of allocation, a large number of dropouts, multiple differences in care delivered to study groups and other biases could be considered a study of the highest quality using this scale and be included in the meta-analysis. A valid evidence supporting specific targets lacking, implementation of guidelines may not result in improved care. Our concern about heterogeneity in recently published meta-analyzes which may have included trials with high risk of bias, prompted us to conduct an updated qualitative systematic review of the literature on the effect of intensive insulin therapy on mortality and hyperglycemia in adult ICUs. Hospital ICU coulds to determine if results would be altered by the exclusion of trials at high risk of bias.

OBJECTIVE

The following key questions were investigated for a population of adult, hospitalized ICU patients:

1. Is there evidence of sufficient robustness in any critically ill population to justify a specific glycemic control range that is likely to reduce mortality?

2. Is there evidence sufficient to conclude that reported hyperglycemia occurring with intensive insulin therapy results in clinically meaningful adverse outcomes in any critically ill population?

METHODS

We utilized the extensive search from three recently published meta-analyses and conducted an updated search using MEDLINE (1980-2009), the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews. We assessed the rate of trials using a detailed checklist to document the overall quality of the evidence for mortality and hyperglycemia in intensive care populations.

Findings:

We included a total of 17 clinical trials totaling 12,345 patients. All included trials were rated as being at medium risk of bias. We identified eight groups of patients in which intensive insulin treatment has been compared to less intensive insulin therapy. Mortality rates varied by patient population with rates of < 10% in predominantly surgical patients with mixed conditions to nearly 75% in neurosurgical patients. Overall, mortality rates ranged from 4% to 74% but the overall level of evidence for mortality was inconclusive. Hyperglycemia rates ranged from 5% to 94% and the overall level of evidence for hyperglycemia was borderline.

Interpretation:

The evidence is insufficient for determining the effect of intensive insulin treatment compared to less intensive treatment in adult ICUs hyperglycemic patients. The evidence does not justify guideline recommendations for specific glycemic target ranges for critical care populations. Further research is needed, but should be carefully planned with attention to trial bias, populations, type of insulin protocols used, adherence, co-interventions, and frequency of blood glucose testing to avoid the heterogeneity and bias present in currently available research.

LITERATURE SEARCH STRATEGY

MEDLINE (March 1, 2008-September 17, 2008, updating our search on December 30, 2009), the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews (March 2008 – December 2009).

Search terms and text words using the Boolean operator OR:
- "critical care OR ICU OR critical care OR Intensive Care OR Intensive Care Unit OR Critical Care Unit OR Critical Care Unit OR Intensive Care Unit OR Intensive Care Unit" OR "OR postoperative care with text words intensive care OR ICU OR critical care OR CCU OR coronary care OR recovery room OR post anesthetic recovery OR critical care OR burn unit OR critically ill OR cardiac care OR ANH (insulin OR blood glucose OR hypoglycemia agents with text words intensive insulin OR glycemic control OR blood glucose OR insulin.

Grading System for Studies:

Each included study was graded using a proprietary and validated checklist (an expanded list of the Cochrane Collaboration Tool for assessing risk of bias) compared to less intensive insulin treatment in hyperglycemic ICU patients.

Grading System for Quality of Evidence: Domains recently selected by the Agency for Healthcare Research and Quality (AHRQ) and the Effective Health Care Program (EHCP) group were used for the documentation of the overall quality of evidence. The AHRQ EHCP approach assesses four attributes/domains for each outcome of interest utilized by each study rating the quality of evidence for mortality and hypoglycemia outcomes with evidence grades B-D or higher were included in the final review. Because of the high risk of bias, studies rated U were excluded.

Grading System for Level of evidence (LOE): For each outcome of interest utilized by the AHRQ and EHCP group includes three grades:

1. High: Further research is unlikely to change confidence in the estimate of effect.
2. Moderate: Interpretation: Evidence is unavailable or does not permit a conclusion.
3. Inconclusive: Evidence is unavailable or does not permit a conclusion.
4. Borderline: For this review, we modified this grading system for overall LOE by adding a fourth category — "borderline" — to increase clarity as we believe that "moderate" is not precise enough to address evidence of borderline usefulness.

Overall Scores: We graded the overall LOE for mortality and hyperglycemia as High: ≥ grade B (valid and possibly useful) study reporting consistent results Moderate: At least one grade B study Borderline: At least two grade B-U (possibly to uncertain validity and usefulness) studies with consistent findings and Inconclusive: single grade B-U studies or studies with conflicting results or only grade U studies (uncertain usefulness or validity).

RESULTS

We included a total of 17 clinical trials with 12,345 patients met criteria for analysis. All included trials were rated as being at medium risk of bias. We identified eight groups of patients in which intensive insulin treatment has been compared to less intensive insulin therapy. Mortality rates varied by patient population with rates of < 10% in predominantly surgical patients with mixed conditions to nearly 75% in neurosurgical patients. Overall, mortality rates ranged from 4% to 74% but the overall level of evidence for mortality was inconclusive. Hyperglycemia rates ranged from 5% to 94% and the overall level of evidence for hyperglycemia was borderline.

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CONCLUSIONS

The evidence is inconclusive regarding the effect of Intensive Insulin Therapy compared to less intensive insulin therapy on ICU mortality, hospital mortality, 28 day mortality and 90 day mortality.

Although intensive insulin therapy may be associated with an increased in the risk of hypoglycemia, it is unclear if this increase in risk is due to differences in frequency of BG testing, differences in study populations or adherence to protocol and it is also not known if the increased risk of hypoglycemia results in clinically meaningful adverse outcomes.

Because of the unknown benefit-risk ratio of intensive insulin therapy, the evidence does not justify guidelines recommendations for specific glycemic target ranges for adult ICU patients.

Until higher quality, reliable evidence becomes available, local experience should be relied upon for determining glycemic ranges for ICU patients.