Intensive Insulin Therapy for The Treatment of Hyperglycemia in Critically Ill Adults:
A Qualitative Systematic Review and Critical Appraisal of the Evidence

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ABSTRACT

Background: Hyperglycemia in intensive care patients is associated with high mortality, but optimal management of this population with insulin therapy is controversial as are current guidelines for glycemic targets.

Methods: We utilized the extensive search from a recent published meta-analysis and conducted an updated search using MEDLINE (2008-2009), the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews. We assessed bias of trials using a detailed checklist to document the overall quality of the evidence for mortality and hypoglycemia 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 < 16% 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. Hypoglycemia rates ranged from 0% to 94% and the overall level of evidence for hypoglycemia was borderline.

Interpretation: The evidence is insufficient for determining the effect of intensive insulin treatment compared to less intensive treatment in acutely ill hyperglycemic patients. The evidence does not justify guideline recommendations for specific glycemic target ranges for adults being treated in intensive care units. 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.

BACKGROUND

Inpatient hyperglycemia particularly in the Intensive Care settings is associated with increased morbidity and mortality 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 glycemic targets for critically ill patients with hyperglycemia based on their review of published literature including Randomized Controlled Trials (RCT's), meta-analysis and Systematic reviews. Many meta-analysis however use the Jadad Scale for assessing quality of included RCT's 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 concealment of allocation, a large number of drop outs, 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.

If valid evidence supporting specific targets lacking, implementation of guidelines may not result in improved care. Our concern about heterogeneity in recently published meta-analyses 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 morality and hypoglycemia in acutely ill, hospitalized ICU adults to determine if results would be altered by the exclusion of trials at high risk of bias.

PURPOSE

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 the evidence sufficient to conclude that reported hypoglycemia occurring with intensive insulin therapy results in clinically meaningful adverse outcomes in any critically ill population?

LITERATURE SEARCH STRATEGY

Literature Search Strategy:
MEDLINE (March 1, 2008-September 17, 2009, 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),

PubMed methodological filters, "randomized controlled trials" and "systematic reviews"

MeSH terms and text words using the Boolean operator OR: "critical care OR intensive care OR intensive care units OR cardiac care facilities OR critical illness 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 illness OR burn unit OR critically ill OR cardiac care) AND (insulin OR blood glucose OR hypoglycemic agents with text words intensive insulin OR glycemic control OR blood glucose OR insulin."

Study Selection:
Inclusion Criteria:
RCT's involving hyperglycemic patients receiving intensive Insulin treatment (IIT) in the ICU. Trials that evaluated mortality and hypoglycemia were analyzed for both. Trials that analyzed only mortality were evaluated only for that outcome.
Exclusion Criteria:
Abstract only publications
Unpublished (presentation at meetings)
Trials with less than 25 subjects in each study arm
Trials focused only on intra-operative comparisons
Trials that excluded 20% or more subjects from analysis
Trials that did not report mortality.

Grouping of Studies: Studies were grouped as following
A. Mortality:
1. Surgical/Predominantly Surgical ICU patients with Mixed conditions
2. Surgical /Predominantly Surgical ICU patients with Single Conditions (SAH/Traumatic Brain Injury/Cardiac Surgery)
3. Combined Medical and Surgical ICU patients
4. Medical ICU patients with mixed conditions
5. Medical ICU patients with Single Conditions

B. Hypoglycemia with Insulin therapy in ICU patients

QUALITY ASSESSMENT FOR INCLUDED STUDIES

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) by two reviewers independently assessing the methodological quality, performance, attrition and assessment bias of the included studies and given one of the following evidence grades:
Grade A: Valid and Useful for Informing Decisions
Grade B: Possibly Valid and Useful
Grade B-U: Possible to uncertain validity and usefulness
Grade U: Uncertain validity and/or usefulness
Only studies with mortality and hypoglycemia outcomes with evidence grades B-U or higher were included in the final review. Because of the high risk of bias, studies graded U were excluded.

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 or comparison of interest (mortality and hypoglycemia in this analysis):
1. **Bias** is scored as low, medium, or high risk of bias. Each study is scored based on study design and conduct, and the aggregate of studies is scored for an overall "risk of bias" score.
2. **Consistency** (the degree of similarity of effect sizes of included studies) is scored as consistent, inconsistent, or unknown/not applicable.
3. **Directness** is the linkage between the intervention and health outcomes scored as direct or indirect (meaning intermediate or surrogate outcome measures).
4. **Precision** concerns the ability to draw a clinically useful conclusion from the confidence intervals. An imprecise estimate, for example, is one for which the confidence interval is wide enough to include clinically distinct conclusions (e.g., favoring both the interventions being compared).

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**
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 hypoglycemia as
High: >1 grade B (valid and possibly useful) study reporting consistent results
Moderate: At least one grade B study
Borderline: At least two grade B-U (possible 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

- 17 clinical trials with 12,345 patients met criteria for analysis.

- AHRQ aggregate **results for evidence for Mortality** with IIT compared to less intensive insulin treatment in hyperglycemic ICU patients
  - Risk of Bias: Medium
  - Consistency of results: Inconsistent
  - Directness: Direct
  - Precision: Imprecise
- **Overall level of Evidence** (Confidence that evidence represents a true effect on mortality by Intensive Insulin Therapy): **INCONCLUSIVE**

- AHRQ aggregate **results for Hypoglycemia** with IIT compared to less intensive treatment in hyperglycemic ICU patients
  - Risk of Bias: Medium
  - Consistency of results: Inconsistent
  - Directness: Indirect
  - Precision: Imprecise
- **Overall level of Evidence** (Confidence that evidence represents a true effect that IIT results in more hypoglycemia compared to less intensive Insulin Therapy): **INCONCLUSIVE**

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 increase 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 guideline 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.