Intensive insulin therapy reduced morbidity but not mortality in patients in the medical intensive care unit

Van den Berghe G, Wilmer A, Hermans G, et al. **Intensive insulin therapy in the medical ICU.** N Engl J Med. 2006;354:449-61.

Clinical impact ratings: Hospitalists ★★★★★☆ Endocrinology ★★★★★☆ Critical Care ★★★★★★★

QUESTION

In patients in the medical intensive care unit (ICU) who were assumed to need intensive care for ≥ 3 days, does intensive insulin therapy reduce morbidity and mortality?

METHODS

Design: Randomized controlled trial.
Allocation: {Concealed}†.*
Blinding: Blinded (primary outcome assessors and data analysts).
Follow-up period: Until hospital discharge.
Setting: A medical ICU in Leuven, Belgium.
Patients: 1200 medical patients (mean age 64 y, 62% men) admitted to the medical ICU who were assumed to require at least 3 days of intensive care. Patients were excluded if they were surgical patients, medical patients with do-not-resuscitate orders, or able to receive oral nutrition.
Intervention: Intensive insulin therapy (*n* = 595) or conventional insulin therapy (*n* = 605). For intensive therapy, insulin was given when blood glucose levels were > 110 mg/dL (6.1 mmol/L), and then adjusted to maintain 80 to 110 mg/dL (4.4 to 6.1 mmol/L). For conventional therapy, insulin was given when blood glucose levels were > 215 mg/dL (12 mmol/L), and then adjusted to maintain 180 to 200 mg/dL

(10 to 11 mmol/L). When blood glucose levels fell below 180 mg/dL, the infusion was tapered or stopped.
Outcomes: In-hospital mortality. Secondary outcomes included ICU and 90-day mortality, new kidney injury (serum creatinine level > 2.5 mg/dL [220 µmol/L] or 2 times baseline), days to weaning from mechanical ventilation, duration of ICU and hospital stay, readmission to ICU, presence of bacteremia, and prolonged (> 10 d) antibiotic use.
Patient follow-up: 100% (intention-to-treat analysis).

MAIN RESULTS

Groups did not differ for in-hospital (Table), ICU, or 90-day mortality. The intensive insulin therapy group had fewer new kidney injuries than did the conventional-therapy group (Table). More patients who received intensive insulin therapy had earlier weaning from mechanical ventilation (hazard ratio

[HR] 1.21, 95% CI 1.02 to 1.44) and earlier discharge from the ICU (HR 1.15, CI 1.01 to 1.32) and hospital (HR 1.16, CI 1.00 to 1.35) than did those who received conventional therapy. Groups did not differ for frequency of bacteremia, prolonged antibiotic use, or readmission to ICU.

CONCLUSION

In patients in the medical intensive care unit with intended stay for ≥ 3 days, intensive insulin therapy reduced morbidity but not mortality.

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*See Glossary.
†Information provided by author.

Intensive insulin vs conventional therapy for patients in the medical intensive care unit‡

Outcomes	Intensive insulin	Conventional therapy	RRR (95% CI)	NNT (CI)
In-hospital mortality	37%	40%	6.7% (−7.6 to 19)	Not significant
New kidney injury	5.9%	8.9%	34% (1.0 to 56)	33 (17 to 1281)

‡Abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.

COMMENTARY

The much-anticipated study by Van den Berghe and colleagues follows a previous landmark study (1) in a mostly surgical ICU where intensive insulin therapy using a similar insulin titration guideline (Leuven protocol) showed a 3.4% absolute reduction in mortality. In that previous study, patients who stayed in the surgical ICU for > 5 days had a 48% relative (9.6% absolute) reduction in mortality and reductions in organ dysfunction and length of ICU stay (median 12 to 15 d). Of note, such analysis included subgroups not identified at randomization and is not as valid as the analysis of all patients. A subsequent consecutive, pre–postquality improvement study (2) showed a similar effect size, and many clinicians began to treat hyperglycemia more aggressively during critical illness. The current study supports these efforts, but caution is warranted.

First, while important comorbid conditions were reduced with intensive insulin therapy, mortality was not and hypoglycemia rates were > 3-fold higher in the medical ICU than in the surgical ICU (18.6% vs 5.1%). Lower rates of hypoglycemia have been reported with alternative intensive insulin therapy approaches in other ICUs and in-patient cohorts (2, 3). Second, for the subgroup not identified at the beginning of the trial that stayed in the medical ICU < 3 days, hospital mortality was higher in absolute numbers, possibly because of an adverse treatment effect or an imbalance favoring the control group

(fewer patients in this group had support withdrawn). The possibility of early harm has led some to recommend a delay in strict intensive insulin therapy during the initial stabilization phase of critical illness in medical patients (4).

With these cautions in mind, it is important to note that comorbid conditions were decreased for some clinically important outcomes, and mortality was reduced in the targeted subgroup of patients who stayed in the medical ICU ≥ 3 days (< 43% vs 53%, *P* = 0.009), although this group was difficult to identify at ICU entry. The absolute risk reduction is similar to the longer-stay surgical experience. These effect sizes are large, and until ongoing trials of intensive insulin therapy are completed, most practitioners should continue to explore ways to safely implement intensive insulin therapy for their critically ill patients.

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References
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