Intensive insulin therapy during cardiac surgery did not reduce mortality or morbidity but increased risk for stroke

Gandhi GY, Nuttall GA, Abel MD, et al. **Intensive intraoperative insulin therapy versus conventional glucose management during cardiac surgery: a randomized trial.** Ann Intern Med. 2007;146:233-43.

Clinical impact ratings: Cardiology ★★★★★☆☆ Endocrinology ★★★★★★☆

QUESTION

In patients having cardiac surgery, does intraoperative intensive insulin therapy (IIT) reduce morbidity and mortality?

METHODS

Design: Randomized controlled trial (RCT).
Allocation: Concealed.*
Blinding: Blinded (outcome assessors).*
Follow-up period: 30 days.
Setting: A tertiary care teaching hospital in Rochester, Minnesota, USA.
Patients: 400 patients (mean age 63 y, 68% men, 96% white) who were having elective cardiac surgery. Patients having off-pump cardiopulmonary bypass procedures were excluded.
Intervention: IIT (n = 199) or conventional insulin therapy (n = 201) during surgery. IIT consisted of continuous intravenous (IV) insulin infusion when blood glucose levels were > 5.6 mmol/L (> 100 mg/dL) and then adjustment to maintain intraoperative glucose levels at 4.4 (80 mg/dL) to 5.6 mmol/L (100 mg/dL). The conventional-therapy group was given insulin during surgery only when glucose levels were ≥ 11.1 mmol/L (≥ 200 mg/dL). After surgery, both groups received IV insulin infusion to maintain normal blood glucose levels.
Outcomes: A composite endpoint of death, sternal infections, prolonged (> 24 h) pulmonary ventilation, new-onset atrial fibrillation, heart block requiring permanent pacemaker, cardiac arrest, stroke, or acute renal failure within 30 days of surgery. Secondary outcomes were length of stay in the intensive care unit (ICU) and hospital. The study had 90% power to detect a 40% decrease in the composite endpoint.
Patient follow-up: 93% (intention-to-treat analysis).

MAIN RESULTS

Groups did not differ for the primary composite endpoint (Table) or for ICU or hospital length of stay. The IIT group had a higher incidence of stroke and nonsignificant increases in the incidences of death and heart block requiring pacemaker than did the conventional-therapy group (Table).

CONCLUSION

Intensive insulin therapy during cardiac surgery did not reduce morbidity and mortality but increased risk for stroke more than conventional insulin therapy.

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For correspondence: Dr. G.Y. Gandhi, Mayo Clinic College of Medicine, Rochester, MN, USA. E-mail gandhi.gunjan@mayo.edu.

*See Glossary.

Intensive insulin vs conventional insulin therapy during cardiac surgery at 30 days†

Outcomes	Intensive insulin	Conventional therapy	RRR (95% CI)	NNT
Composite endpoint‡	44% (82/185)	46% (86/186)	4.1% (–20 to 23)	Not significant
			RRI (CI)	NNH (CI)
Stroke	4.3% (8/185)	0.54% (1/186)	704% (33 to 4832)	27 (13 to 120)
Death	2.2% (4/185)	0% (0/186)	—	Not significant
Heart block requiring pacemaker	2.7% (5/185)	0.54% (1/186)	403% (–21 to 3131)	Not significant

†Abbreviations defined in Glossary. RRR, RRI, NNT, NNH, and CI calculated from data in article.
‡Death, sternal infections (3.2% vs 3.8%), pulmonary ventilation for > 24 hours (19% vs 20%), new-onset atrial fibrillation (29% vs 32%), heart block requiring pacemaker, cardiac arrest (0.54% vs 0%), stroke, or acute renal failure (3.2% vs 2.2%).

COMMENTARY

The landmark study by Van den Berghe and colleagues showed that postoperative IIT reduced mortality and morbidity in patients in the surgical ICU (1). In another study, patients in the medical ICU treated with IIT had reduced morbidity, and a subgroup of patients in the ICU ≥ 3 days had reduced morbidity and mortality (2).

It is tempting to extrapolate results from these trials to other settings. Because intraoperative hyperglycemia was found to be a marker for complications in a previous observational study (3), it was hypothesized that maintaining intraoperative normoglycemia could reduce complications. Surprisingly, the RCT by Gandhi and colleagues failed to show any benefit.

There are several potential explanations. First, if there is a benefit to intraoperative IIT, it may be < 40% of the difference the study was powered to detect. Second, it is possible that the benefit of intensive glycemic control is realized after prolonged postoperative insulin therapy and not after a few hours of intraoperative insulin. Third, although the probability is relatively small, the findings might have occurred by chance. The unexpected potential harms, an increased risk for stroke and a trend toward increased death in the IIT group, are of concern. If the risk is real, the mechanism is unclear, as episodes of hypoglycemia did not differ between groups.

For internists and endocrinologists, the study by Gandhi and colleagues does not affect practice. For cardiothoracic surgeons and anesthesiologists, given the lack of supporting data and extensive resources required to implement IIT protocols during surgery, intraoperative IIT is not ready for current use.

Meera Jain, MD
Elizabeth Stephens, MD
Providence Portland Medical Center
Portland, Oregon, USA

References

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