

10.4 Strategies to Optimize Parenteral Nutrition: Intensive Insulin Therapy

June 28th, 2005

Recommendation:

Based on 2 level 2 studies, in surgical critically ill patients receiving nutrition support, intensive insulin therapy to tightly control blood sugars between 4.4-6.6 mmol/L should be considered. There are insufficient data to make a recommendation regarding intensive insulin therapy in other critically ill patients.

Discussion: The committee noted the strong effect size seen with narrow confidence intervals and high internal validity in the one large study (n = 1548) of surgical ICU patients, predominantly elective cardiovascular surgery (Van Den Berghe 2001). The committee noted that in this trial, patients had a relatively low APACHE II score (mean of 9), received high amounts of IV dextrose within 24 hours and then a significant proportion received PN (~60 %). This limits the applicability of the results from this trial to other ICU's where patients are sicker, do not receive high amounts of parenteral glucose early on and where the use PN is not excessive. The study by Grey et al was noted to have a weak study design. The safety, cost and feasibility of intensive insulin therapy were reasonable. The committee raised concerns regarding the tight range of blood sugars (4.4-6.6 mmol/L) and realized that most ICUs would aim for a more moderate range of blood sugar control. It was agreed that the recommendation for tight control should be specific to surgical critically ill patients.

Values	definition	Score : +, ++, +++
Effect size	magnitude of the absolute risk reduction attributable to the intervention listed--a higher score indicates a larger effect size	3+
Confidence interval	95% confidence interval around the point estimate of the absolute risk reduction, or the pooled estimate (if more than one trial)--a higher score indicates a smaller confidence interval	3+
Validity	refers to internal validity of the study (or studies) as measured by the presence of concealed randomization, blinded outcome adjudication, an intention to treat analysis, and an explicit definition of outcomes--a higher score indicates presence of more of these features in the trials appraised	3+
Homogeneity	similar direction of findings among trials--a higher score indicates greater similarity of direction of findings among trials	1+
Safe	estimated probability of avoiding any significant harm that may be associated with the intervention listed--a higher score indicates a lower probability of harm	2+
Feasible	ease of implementing the intervention listed--a higher score indicates greater ease of implementing the intervention in an average ICU	2+
Cost	estimated cost of implementing the intervention listed--a higher score indicates a lower cost to implement the intervention in an average ICU	3+

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Question: Does tight blood sugar control result in better outcomes in the critically ill adult patient?

Summary of evidence: There were 2 level 2 studies reviewed. Van den Berghe et al compared intensive insulin therapy vs. conventional treatment in critically ill patients receiving nutrition support. Patients were started on a glucose load (200-300 gms per day) and then advanced to either PN, combined PN/EN or EN after 24 hrs of admission. Grey et al compared strict insulin therapy (target blood sugar range between 4.4 to 6.6 mmol/L) vs. standard insulin therapy (target blood sugar range between 10-12 mmol/L) in patients requiring treatment for hyperglycemia (blood sugars > 7.7 mmol/L).

Mortality: When the data from the 2 trials was aggregated, intensive insulin was associated with a significant reduction in hospital mortality, (RR 0.65, 95 %CI 0.48, 0.89, $p = 0.007$). ICU mortality was only reported in the Van den Berghe trial and was also significantly reduced in the experimental group ($p < 0.04$).

Infections: When the data from the 2 trials was aggregated, intensive insulin therapy was associated with a trend towards a reduction in infectious complications compared to conventional insulin therapy (RR = 0.68, 95% CI 0.41, 1.11, $p = 0.12$).

LOS: No significant difference in ICU LOS was found between the intensive and conventional insulin groups ($p = 0.2$ Van den Berghe, $p = 0.52$ Grey).

Ventilator days: There was a trend towards a reduction in ventilator days in the intensive insulin group compared to the conventional insulin group ($p = 0.06$ Van den Berghe).

Conclusions:

- 1) Intensive insulin therapy is associated with a significant reduction in mortality and a trend towards reduced infections in surgical critically ill patients.
- 2) Intensive insulin therapy maybe associated with a reduction in ventilated days in surgical critically ill patients

Level 1 study: if all of the following are fulfilled: concealed randomization, blinded outcome adjudication and an intention to treat analysis.

Level 2 study: If any one of the above characteristics are unfulfilled.

Table 1. Randomized studies evaluating intensive insulin therapy in critically ill patients

Study	Population	Methods (score)	Intervention	Mortality # (%)		RR (CI)**	Infections # (%)‡		RR (CI)**
				Intensive insulin	Conventional		Intensive insulin	Conventional	
Van Den Berghe 2001	ICU ventilated (mainly surgical) N=1548	C.Random: yes ITT: yes Blinding: no (11)	Intensive insulin (blood sugar range between 4.4 – 6.1 mmol/L) vs. conventional (blood sugar range between 10-11.1 mmol/L)	35/765 (5) ICU	63/783 (8) ICU	0.57 (0.38-0.85) 0.66 (0.48-0.92)	32/765 (4)	61/783 (8)	0.54 (0.35-0.81)
				55/765 (7) hospital	85/783 (11) hospital				
Grey 2004	Surgical ICU needing treatment for hyperglycemia N = 61	C.Random: no ITT: no Blinding: no (4)	Strict insulin therapy (blood sugar range between 4.4 to 6.6 mmol/L) vs. conventional (blood sugar range between 10-12 mmol/L) in patients requiring treatment for hyperglycemia (blood sugars > 7.7 mmol/L).	4/34 (11)	6/27 (27)	0.42 (0.25-0.7)	21/34 (26)	20/27 (38)	0.83 (0.59,1.18)

Study	LOS days		Ventilator days		Cost		Other	
	Intensive insulin	Conventional	Intensive insulin	Conventional	Intensive insulin	Conventional	Intensive insulin	Conventional
Van Den Berghe 2001	3 (2-6) ICU	3 (2-9) ICU	2 (1-4)	2 (1-6)	NA	NA	Hypoglycemia 39/765 (5) 6/783 (<1)	
Grey 2004	33.4 ± 68.3 ICU	24.5 ± 19.4 ICU	NA	NA	NA	NA	Intensive insulin Conventional Hypoglycemia 32% 74%	

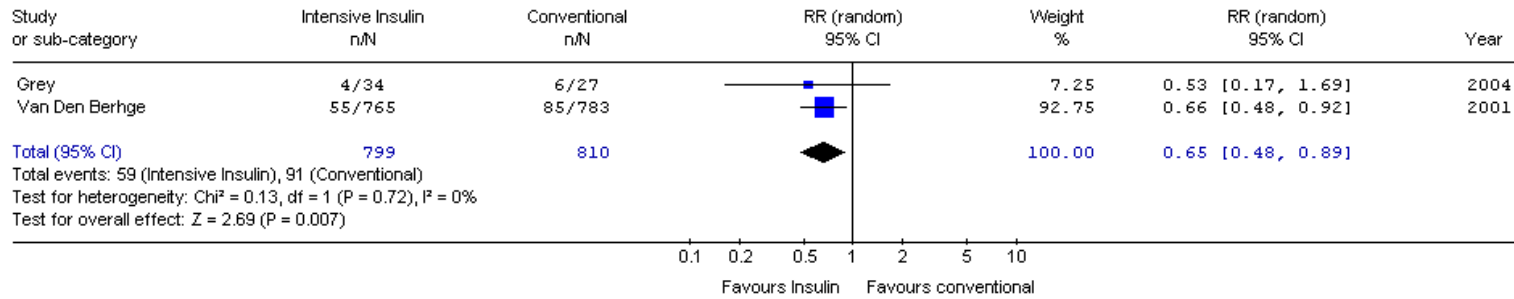
C.Random: concealed randomization
ITT: intent to treat; NA: not available

‡ refers to the # of patients with infections unless specified
** RR= relative risk, CI= Confidence intervals

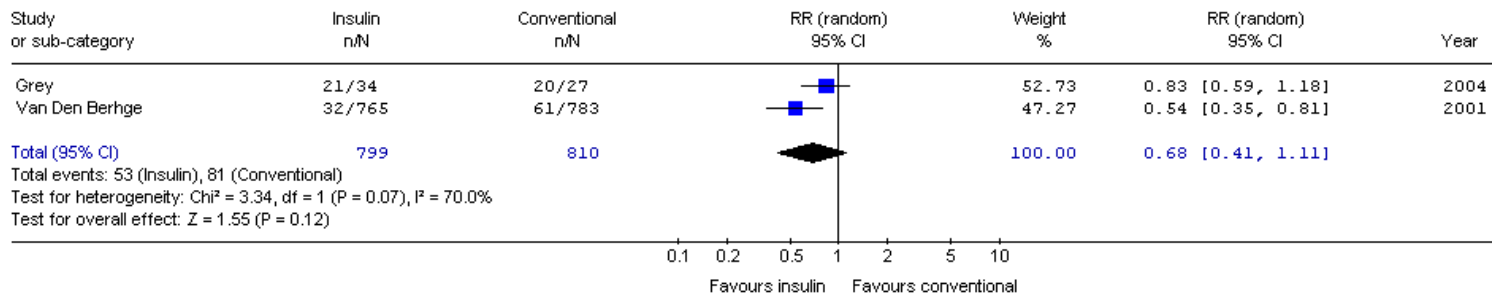
TNA: Total Nutrient Admixtures
() : mean ± Standard deviation (number)

(-): median (range)

Review: Intensive insulin therapy
 Comparison: 01 Intensive Insulin vs. Conventional
 Outcome: 01 Mortality



Review: Intensive insulin therapy
 Comparison: 01 Intensive Insulin vs. Conventional
 Outcome: 02 Infections



TOPIC: Optimizing PN (Intensive Insulin Therapy)
 (Reviewers: *Carmen Christman and Dominique Michaud*)

Article inclusion log

Criteria for study selection

Type of study: RCT or Meta-analysis
Population: critically ill human patients (no elective sx.)
Intervention :TPN and /or EN
Outcomes: mortality, LOS, QOL, functional recovery, complications, cost. Exclude studies with only biochemical, metabolic or nutritional outcomes.

ID #		Author	Journal	I	E	why rejected
67.	1.	Van den Berghe	NEJM 2001		√	
	2.	Grey	Endocrine Practice 2004		√	
	3.	Christiansen	Int Care Med 2004			√ Not RCT
	4.	Zimmerman	Annals Pharm 2004			√ Not RCT
	5.	Finney	JAMA 2003			√ Not RCT
	6.	Lewis	Annals Pharm 2004			√ Not RCT
	7.	Lazar	Circulation 2004			√ Elective sx patients
	8.	Kanji	Inten Care Med 2004			√ Not RCT

I = included, E = excluded