Intensive Insulin Therapy in Critically ill patients

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Background

- The acute stress response is a hyperadrenergic state
- Characterized by hyperglycemia
- Increased glycogenolysis and gluconeogenesis -> metabolic substrate
- Insulin antagonism:
  - GH, Cortisol, Glucagon, Epinephrine

Background

- Prolonged critical illness is associated with increased mortality and morbidity
- Reduced physiologic reserve
- Hyperglycemia is associated with increased risk of infection
- Infection prolongs critical illness
- Diabetic patients with AMI have better long term outcomes with tight glycemic control

The Question

- Does tight glycemic control in perioperative and critically ill patients improve outcomes?
- Mortality
- Morbity

Design & Setting

- Prospective Randomized Controlled Trial
- Surgical Intensive Care
- Single Center
- 1 year (2000)

Enrollment & Randomization

- All patients admitted to SICU
- 1548 enrolled
- 14 excluded: 5 other trials, 9 DNR or moribund
- Sealed envelopes
- Stratified to nature of critical illness
- Premuted blocks of 10 (balance)

Methodology

- Conventional Therapy Group
  - Insulin Drip started if BG>215mg/dl
  - Level adjusted to maintain BG 180-200
- Intensive Therapy Group
  - Insulin Drip started if BG>110mg/dl
  - Level adjusted to maintain BG 80-110
- Maximal insulin dose 50iu/hour

Methodology

- All patients were given intravenous glucose (feed!) @ 200-300g/24h (equivalent to 200ml/hour D5%) = 800-1200 kcal
- Feeding (preferably enteral) commenced day 2

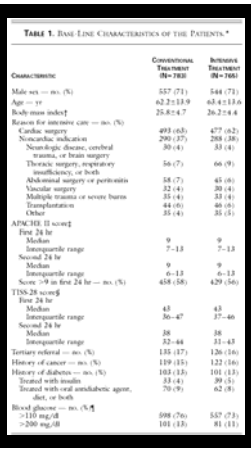


TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	CONVENTIONAL TREATMENT (N=783)	INTENSIVE TREATMENT (N=765)
Male sex — no. (%)	557 (71)	544 (71)
Age — yr	62.2±13.9	63.4±13.6
Body-mass index†	25.8±4.7	26.2±4.4
Reason for intensive care — no. (%)		
Cardiac surgery	493 (63)	477 (62)
Noncardiac indication	290 (37)	288 (38)
Neurologic disease, cerebral trauma, or brain surgery	30 (4)	33 (4)
Thoracic surgery, respiratory insufficiency, or both	56 (7)	66 (9)
Abdominal surgery or peritonitis	58 (7)	45 (6)
Vascular surgery	32 (4)	30 (4)
Multiple trauma or severe burns	35 (4)	33 (4)
Transplantation	44 (6)	46 (6)
Other	35 (4)	35 (5)
APACHE II score‡		
First 24 hr		
Median	9	9
Interquartile range	7–13	7–13
Second 24 hr		
Median	9	9
Interquartile range	6–12	6–13
Score >9 in first 24 hr — no. (%)	458 (58)	429 (56)
TISS-28 score§		
First 24 hr		
Median	43	43
Interquartile range	36–47	37–46
Second 24 hr		
Median	38	38
Interquartile range	32–44	33–43
Tertiary referral — no. (%)	135 (17)	126 (16)
History of cancer — no. (%)	119 (15)	122 (16)
History of diabetes — no. (%)	103 (13)	101 (13)
Treated with insulin	33 (4)	39 (5)
Treated with oral antidiabetic agent, diet, or both	70 (9)	62 (8)
Blood glucose — no. (%)¶		
>110 mg/dl	598 (76)	557 (73)
>200 mg/dl	101 (13)	81 (11)

Standardized Care?

- Clinician dependent
- Blood cultures taken for T >38.5 C
- Weekly EMG
- Death - PM

Type of Patients

Disease/Surgery	Conventional	Intensive
Cardiac Surgery	493	477
Neurologic	30	33
Thoracic /Pulmonary	56	66
Abdominal	58	45
Vascular	32	30
Trauma / Burns	35	33
Transplants	44	46
Other	35	35

Endpoints

- Primary
  - Death
- Secondary
  - In hospital death
  - Number of ICU days
  - ICU > 14 days
  - Readmission
  - Duration of Vent Support
  - Renal Replacement Therapy

Severity of Illness

- Acute Illness Score
  - Apache II
- Resource Consumption
  - TISS-28

Statistical Analysis

- Planned enrollment 2500 patients
- To detect 5% absolute difference in mortality in patients remaining in ICU >5/7, and 2% overall.
- Stopped early at 4th interim analysis
- Baseline data T, X^2, MWU test
- Odds ratios – mv logistic regression analysis
- Outcomes Kaplan Meier analysis, and Mantel-Cox log rank test

Disclaimer

- Supported by local and governmental grants and
- Novo Nordisk

Methodology - Critique

- Were the patients properly randomized?
  - Yes
- Were the groups comparable?
  - Yes
- Was the outcome assessment "blind"?
  - Yes
- Was the study large enough?
  - Yes
- Was the study continued long enough? Was it stopped after an interval evaluation?
  - Yes
- Was the follow up complete – were all the patients who entered the trial accounted for at its conclusion? And were they analyzed in the groups into which they were randomized?
  - Yes

Methodology - Critique

- Administration of dextrose day ? Reason
- Validity of Apache II in this setting
  - Cardiac surgery patients
  - Lead time bias

Results

TABLE 2. INSULIN THERAPY AND CONTROL OF BLOOD GLUCOSE LEVELS.*

VARIABLE	CONVENTIONAL TREATMENT (N=783)	INTENSIVE TREATMENT (N=765)	P VALUE†
Administration of insulin — no. (%)	307 (39.2)	755 (98.7)	<0.001
Insulin dose — IU/day‡			
Median	33	71	
Interquartile range	17–56	48–100	<0.001
Duration of insulin use — % of ICU stay			
Median	67	100	<0.001
Interquartile range	40–100		
Morning blood glucose — mg/dl§			
All patients	153±33	103±19	<0.001
Patients receiving insulin	173±33	103±18	<0.001

*Plus–minus values are means ±SD. ICU denotes intensive care unit.

†P values were determined with the use of Student's t-test, the Mann–Whitney U test, or the chi-square test, as appropriate.

‡Values were calculated only for days on which insulin was given.

§To convert the values for glucose to millimoles per liter, multiply by 0.0555.

Glycemic Control

- Tight control group
  - 103 ± 19 mg/dl (mean)
  - "Almost all" received insulin
- Conventional group
  - 153 ± 33 mg/dl
  - Only 39% received insulin (173 vs 140 mg/dl)

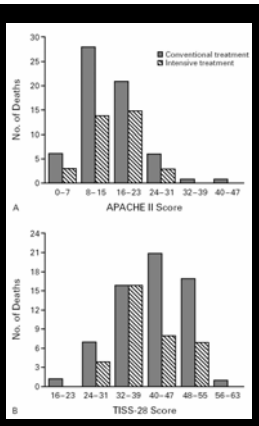
Primary Outcome

- Conventional Group 63 deaths; 8.0
- Intensive Group 35 deaths; 4.6
- P<0.04
- RRR 42% -> 32%*
- ARR 3.4%, NNT 30
- No of deaths similar in first 5 days
- In ICU >5 days 20.2% vs 10.6
- ARR = 9.6%, NNT 10.4
- P = 0.005

TABLE 3. MORTALITY.

VARIABLE	CONVENTIONAL TREATMENT (N=783)	INTENSIVE TREATMENT (N=765)	P VALUE*
Death during intensive care — no./total no. (%)	63/783 (8.0)	35/765 (4.6)	<0.04 (adjusted)
During first 5 days of intensive care	14/783 (1.8)	13/765 (1.7)	0.9
Among patients receiving intensive care for >5 days	49/243 (20.2)	22/208 (10.6)	0.005
Reason for intensive care			
Cardiac surgery	25/493 (5.1)	10/477 (2.1)	
Neurologic disease, cerebral trauma, or brain surgery	7/30 (23.3)	6/33 (18.2)	
Thoracic surgery, respiratory insufficiency, or both	10/56 (17.9)	5/66 (7.6)	
Abdominal surgery or peritonitis	9/58 (15.5)	6/45 (13.3)	
Vascular surgery	2/32 (6.2)	2/30 (6.7)	
Multiple trauma or severe burns	3/35 (8.6)	4/33 (12.1)	
Transplantation	1/44 (2.3)	2/46 (4.4)	
Other	6/35 (17.1)	0/35	
No history of diabetes	57/680 (8.4)	31/664 (4.7)	
No history of diabetes and >5 days of intensive care	45/218 (20.6)	20/187 (10.7)	
History of diabetes	6/103 (5.8)	4/101 (4.0)	
History of diabetes and >5 days of intensive care	4/25 (16.0)	2/21 (9.5)	
Cause of death — no.			0.02
Multiple-organ failure with proven septic focus	33	8	
Multiple-organ failure without detectable septic focus	18	14	
Severe brain damage	5	3	
Acute cardiovascular collapse	7	10	
In-hospital death — no./total no. (%)			
All patients	85/783 (10.9)	55/765 (7.2)	0.01
Patients receiving intensive care for >5 days	64/243 (26.3)	35/208 (16.8)	0.01

*P values were determined with the use of the chi-square test. For the primary outcome variable (death during intensive care), the P value has been corrected for the repeated interim analyses, according to the method of Lan and DeMets[8]; the unadjusted P value is 0.005. Sequential interim analyses were not performed for the other variables, and nominal (unadjusted) P values are given for these comparisons.



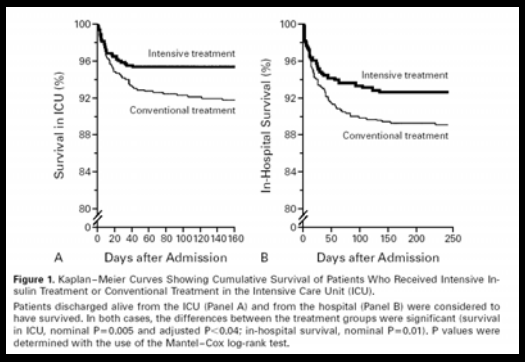


Figure 1. Kaplan–Meier Curves Showing Cumulative Survival of Patients Who Received Intensive Insulin Treatment or Conventional Treatment in the Intensive Care Unit (ICU).

Patients discharged alive from the ICU (Panel A) and from the hospital (Panel B) were considered to have survived. In both cases, the differences between the treatment groups were significant (survival in ICU, nominal P=0.005 and adjusted P<0.04; in-hospital survival, nominal P=0.01). P values were determined with the use of the Mantel–Cox log-rank test.

Primary Endpoint

- Reduced Mortality occurred exclusively in patients admitted to ICU for reasons other than cardiac surgery, with LOS >5 days
- Risk of death
- Higher APACHE II score, increasing age, non cardiac surgery, tertiary referral
- Not diabetes or hyperglycemia on admission

Secondary Endpoints

- Intensive Insulin therapy:
  - Reduced ICU stay, not hospital stay ? cost reductions.
  - Reduced length of vent support, RRT
  - Reduced incidence of hyperbilirubinemia
  - Reduced incidence of sepsis (RRR 46%)
  - Possibly reduced incidence of polyneuropathy
  - Reduced quantity of blood transfused

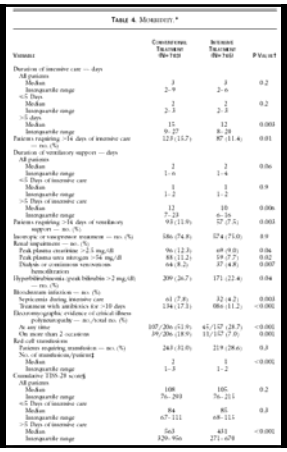


TABLE 4. MORBIDITY.*

VARIABLE	CONVENTIONAL TREATMENT (N=765)	INTENSIVE TREATMENT (N=765)	P VALUE†
Duration of intensive care — days			
All patients			
Median	3	3	0.2
Interquartile range	2–9	2–6	
≤5 Days			
Median	2	2	0.2
Interquartile range	2–3	2–3	
>5 days			
Median	15	12	0.001
Interquartile range	9–27	8–20	
Patients requiring >14 days of intensive care — no. (%)	123 (16.7)	87 (11.4)	0.01
Duration of ventilatory support — days			
All patients			
Median	2	2	0.06
Interquartile range	1–6	1–4	
≤5 Days of intensive care			
Median	1	1	0.9
Interquartile range	1–2	1–2	
>5 Days of intensive care			
Median	12	10	0.006
Interquartile range	7–23	6–16	
Patients requiring >14 days of ventilatory support — no. (%)	93 (11.9)	57 (7.5)	0.002
Inotropic or vasopressor treatment — no. (%)	586 (74.8)	574 (75.0)	0.9
Renal impairment — no. (%)			
Peak plasma creatinine >2.1 mg/dl	96 (12.2)	69 (9.0)	0.04
Peak plasma urea nitrogen >54 mg/dl	88 (11.2)	59 (7.7)	0.02
Diuresis or continuous venovenous hemofiltration	64 (8.2)	37 (4.8)	0.007
Hyperbilirubinemia (peak bilirubin >2 mg/dl) — no. (%)	209 (26.7)	171 (22.4)	0.04
Bloodstream infection — no. (%)			
Septicemia during intensive care	61 (7.8)	32 (4.2)	0.001
Treatment with antibiotics for >10 days	134 (17.1)	086 (11.2)	<0.001
Electromyographic evidence of critical-illness polyneuropathy — no./total no. (%)			
At any time	107/206 (51.9)	45/157 (28.7)	<0.001
On more than 2 occasions	39/206 (18.9)	11/157 (7.0)	0.001
Red-cell transfusion			
Patients requiring transfusion — no. (%)	243 (31.0)	219 (28.6)	0.3
No. of transfusions/patient‖			
Median	2	1	<0.001
Interquartile range	1–3	1–2	
Cumulative TBS-28 score‖			
All patients			
Median	108	105	0.2
Interquartile range	76–293	76–211	
≤5 Days of intensive care			
Median	94	85	0.3
Interquartile range	67–111	68–115	
>5 Days of intensive care			
Median	563	431	<0.001
Interquartile range	320–956	271–678	

Conclusions

- Intensive insulin therapy to maintain blood glucose <110 mg/dl reduces morbidity and mortality in critically ill patients in surgical intensive care

Validity of Results

- Study was not blinded
- Patient population – SCC
- NNT 30 -> 10 to save 1 life compares favorably with ARDSNET study NNT and PROWESS trial (rAPC) NNT
- Simple, inexpensive intervention
- Will change my clinical practice
- Were the cardiac patients protected by beta blockade?