

Intensive Insulin Therapy and Pentastarch Resuscitation in Severe Sepsis Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP)

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Background

- The role of intensive insulin therapy in patients with severe sepsis is uncertain.
 - van Den Berghe et al. reported a beneficial effect predominantly in cardiac surgical patients who received high glucose challenges.
 - Follow up study in non-surgical critically ill patients showed no beneficial effect in survival rates and such therapy was associated with an increase in hypoglycemic events.
 - Although it is unknown if outcomes are improved in patients with severe sepsis, intensive insulin therapy is widely advocated.
- Fluid resuscitation improves survival among patients with septic shock, but evidence is lacking to support the choice of either crystalloids or colloids.
 - In animal models, hydroxethyl starch (HES), improves microcirculation during endotoxemia and lessens tissue damage.
 - HES is associated with coagulopathy and acute renal failure.

Hypothesis

1. Intensive insulin therapy improves outcomes during critical illness with severe sepsis.
2. Hydroxethyl starch (HES) improves outcomes in morbidity and mortality in comparison with lactated ringer's crystalloid.

Study Design

Study type: Randomized controlled trial, 2 x 2 factorial, non-blinded, non Placebo

Setting: multidisciplinary ICUs at 18 academic hospitals in Germany

Time period: April 2003- June 2005

Inclusion Criteria:

- severe sepsis or septic shock
- onset less than 24 hours before admission to ICU or less than 12 hours post admission if it developed in the ICU

Exclusion Criteria:

- less than 18 years old, exposure to HES within 24hrs of enrollment, prior renal failure requiring dialysis or Cr_t >3.6, pregnancy, allergy to HES, ICH, NYHA IV CHF, FiO₂ >70%, immunosuppression (chemotherapy, steroids, AIDS), moribund due to co-existing disease, participation in another trial

Treatment Period: 21 days or until discharge from the ICU or death

Randomization: N = 537, randomized into 4 groups.

- Intensive insulin therapy and Ringer's Lactate
- Conventional insulin therapy and Ringer's Lactate
- Intensive insulin therapy and HES
- Conventional insulin therapy and HES

Conventional Insulin therapy: continuous insulin drip started when glucose exceeds 200, adjusted to glucose goal 180-200

Intensive Insulin therapy: continuous insulin drip started when glucose exceeds 110, adjusted to glucose goal 80-110

RL and HES: physician bound to give RL or HES when CVP < 8 mmHg, then it is up to the physician if SVO₂ < 70% or systolic b/p < 90mmHg to give vasopressors or inotropes or more IVF's.

Patient characteristics: Table 1 shows similarities between the two groups, similar APACHE II scores. Besides the insulin regimen and the IV fluids, patients were treated similarly.

Outcomes:

Co-primary: 1. Death from any cause at 28 days. 2. Morbidity measured by the SOFA score.

Secondary: rate of acute renal failure, time to hemodynamic stabilization, frequency of vasopressor therapy, mean SOFA subscores, need for RBC transfusion, duration of mechanical ventilation, length of stay in the ICU, mortality at 90 days

The evidence

	Conventional Insulin Therapy	Intensive Insulin Therapy	Relative Risk (RR)	Relative Risk Reduction (RRR)	Absolute Risk Reduction (ARR)	Number Needed to Treat (NNTT)
28 day mortality	26% (75/289)	24.7% (61/247)	0.95	0.05	1.3%	77
SOFA	32.1% (7.7/24)	32.5% (7.8/24)	1.01	-0.01	-0.4%	-250
Hypoglycemia	4.1% (12/290)	17.0% (42/247)	4.1	-3.1	-12.9%	-7.8
90 day mortality	35.4% (102/288)	38.7% (98/247)	1.09	-0.09	-3.3%	-30.3

	Ringer's Lactate	HES	Relative Risk (RR)	Relative Risk Reduction (RRR)	Absolute Risk Reduction (ARR)	Number Needed to Treat (NNTT)
28 day mortality	24.1% (66/274)	26.7% (70/262)	1.1	-0.1	-2.6%	-38.5
SOFA	7.5 (31.3% of 24)	8.0 33.3% of 24)	1.06	-0.06	-2.0%	-50
Renal Replacement Therapy	18.8% (51/272)	31.0% (81/261)	1.65	-0.65	-12.2%	-8.2
ARF	22.8% (62/272)	34.9% (91/261)	1.53	-0.53	-12.1%	-8.3
90 day mortality	33.9% (93/274)	41.0% (107/261)	1.21	-0.21	-7.1%	-14.1
Coagulation SOFA	2.7% (0.11/4)	11.5% (0.46/4)	4.26	-3.26	-8.8%	-11.4
Pts Transfused RBCs	68.7% (189/275)	76.0% (199/262)	1.11	-0.11	-7.3%	-13.7

Comments

- In this study, intensive insulin therapy resulted in more episodes of hypoglycemia and increased risk of serious adverse events.
- As used here, Pentastarch caused increased renal failure and coagulopathy.
- Though not significant, use of Pentastarch had a trend toward increased 90 day mortality.
- It is unknown how many of the conventional insulin patients were randomized into the HES group and RL group and vice versa. This has potential for confounding.
- It is unknown what antibiotics were used in this study or whether there were differences in the groups. Some antibiotics are prone to cause renal failure.
- The APACHE II score was used pre-study, but the SOFA score was used as an end-point. We also do not have the information as to when the SOFA score was measured.
- There was no pre-study assessment of coagulation.