

Intensive insulin therapy and pentastarch resuscitation in severe sepsis

Neither intensive insulin therapy nor the use of pentastarch as the resuscitation fluid reduces 28-day mortality or morbidity from severe sepsis. Intensive insulin therapy may cause harm because of increased hypoglycaemic episodes. Use of pentastarch increases the need for renal replacement therapy.

Level of evidence: 1* (RCT with a low risk of bias)

Appraised by: Pauline O’Neil

Citation: Brunkhorst FM, Engel C, Bloos F *et al.* Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med* 2008;358:125-39.

Lead author: Konrad Reinhart.

Three-part clinical question:

Patients: Adults with severe sepsis.

Interventions: (i) Intensive insulin therapy (ii) Using 10% pentastarch rather than crystalloid as a resuscitation fluid.

Outcomes: Improved survival or organ dysfunction.

Search terms: Severe sepsis; insulin; pentastarch.

The study: Non-blinded randomised controlled trial with intention-to-treat. Two-by-two factorial design. Co-primary end points of 28-day mortality and mean SOFA score during the intervention.

The study patients: Adult ICU patients with severe sepsis or septic shock (by ACCP/SCCM consensus conference definition). Onset less than 24 hours prior to admission and no

longer than 12 hours after admission to ICU. Baseline characteristics were broadly similar between the groups.

Control group (N=275; 274 analysed): Conventional insulin therapy, with therapy commenced when blood glucose exceeded 200 mg/dL (11.1 mmol/L). Blood glucose maintained between 180-200 mg/dL (10.0-11.1 mmol/L). The resuscitation fluid control group was given Ringer’s lactate to target a CVP >8mmHg during the first 96 hours, following which, fluid resuscitation was left to the discretion of the treating physician (while observing the study assignment)

Experimental group (N=262; 262 analysed): Intensive insulin therapy group commenced therapy when blood glucose exceeded 110 mg/dL (6.1 mmol/L), and maintained blood glucose between 80-110 mg/dL (4.4-6.1 mmol/L). Fluid resuscitation was with 10% pentastarch for the first 96 hours to target a CVP >8 mm Hg, following which, fluid resuscitation was left to the discretion of the treating physician (while observing the study assignment). Both treatments were continued for 21 days or until ICU discharge or death.

The evidence:

Intensive insulin therapy v conventional insulin therapy

Outcome	Time to outcome	CER	EER	RRR	ARR	NNT
Mortality	28 days	0.259	0.247	5%	0.012	83
		95% confidence intervals:		NS	NS	NS
Mortality	90 days	0.352	0.397	-13%	-0.045	NS
		95% confidence intervals:		NS	NS	NS

Non-event outcome	Time to outcome	Control group	Experimental group	P-value
Mean SOFA score	21 days	7.7 (7.3-8.2)	7.8 (7.3-8.3)	NS
Hypoglycaemia (<40 mg/dL(2.2 mmol/L))	21 days	12/290 (4.1%)	42/247 (17.0%)	<0.001

Pentastarch v Ringer’s lactate

Outcome	Time to outcome	CER	EER	RRR	ARR	NNT
Mortality	28 days	0.240	0.267	-11%	-0.027	NS
		95% confidence intervals:		NS	NS	NS
Mortality	90 days	0.338	0.408	-21%	-0.07	NS
		95% confidence intervals:		NS	NS	NS

Non-event outcome	Time to outcome/s	Control group	Experimental group	P-value
Mean SOFA score	21 days	7.5 (7.1-8.0)	8.0 (7.5-8.5)	NS
Renal replacement therapy	21 days	51/272 (18.8%)	81/261 (31.0%)	0.001
Median no. red cell transfusion units	21 days	4 (2-8)	6 (4-12)	<0.001

Comments:

The intensive insulin therapy arm of the study stopped recruiting early on the advice of the Data Monitoring and Safety Committee due to increased hypoglycaemia in the treatment group and so was underpowered.

In this study the use of starch solutions for resuscitation in severe sepsis increased the need for renal replacement therapy, which was a secondary end-point.

EBM comments:

1. *Do the methods allow accurate testing of the hypothesis?* **Yes.** The 2x2 factorial design allowed two non-overlapping interventions to be compared on the same group of patients.
2. *Do the statistical tests correctly test the results to allow differentiation of statistically significant results?* **Yes.**
3. *Are conclusions valid in light of the results?* **Yes.**
4. *Did results get omitted, and why?* **Yes.** There was one patient who was non-assessable for 28-day mortality. For 90-day mortality, two patients were non-assessable. For renal replacement therapy, four patients were not assessable. Reasons for this were not stated.
5. *Did they suggest areas of further research?* **Yes.** Long term studies of the adverse effects of hydroxyethylstarch (HES) solutions in critically ill patients.
6. *Did they make any recommendations based on the results and were they appropriate?*
The authors recommended that "until long term studies with adequate numbers of patients show that a particular HES solution is safe in critically ill patients, HES solutions should be avoided" although they have generalised their results to all starch solutions and to all critically ill patients. This may represent an over-generalisation of the results but could also be said to be a safe conclusion whilst we await further evidence.
7. *Is the study relevant to my clinical practice?* **Yes.** The case mix in this study is similar to Scotland. Intensive insulin therapy is widely used, and it is important that the potential side effects of this therapy are considered. ICUs may decide to opt for less rigid glycaemic control, or alternative regimens to the Leuven protocol in light of this result. We also commonly treat severe sepsis in Scottish ICU and the choice of resuscitation fluid in severe sepsis remains controversial. With the potential increases in the need for renal replacement therapy and 90-day mortality, HES solutions should be avoided when

alternatives are available.

8. *What level of evidence does this study represent?* **1+**
9. *What grade of recommendation can I make on this result alone?* **B**
10. *What grade of recommendation can I make when this study is considered along with other available evidence?* **A.** The results of this study were similar to that of Van den Berghe,¹ which found that intensive insulin therapy did not reduce all-comers mortality in the medical ICU. Both studies also noted an increase in the incidence of hypoglycaemia. In what may be a *post-hoc* analysis, they have suggested that hypoglycaemia is an independent risk factor for death from any cause. The original work demonstrating a mortality benefit with intensive insulin therapy by Van den Berghe was in surgical patients, a different patient population from this study and used a high glucose intake protocol.² Starch solutions have previously been shown to adversely affect renal function in a randomised controlled trial in severe sepsis, which this study has also demonstrate.³
11. *Should I change my practice because of these results?* **Yes.** Starch solutions should be avoided for resuscitation in severe sepsis while awaiting further studies. Perhaps a target for blood glucose of 6.0-8.0 mmol/L would be more appropriate to avoid the potential morbidity and mortality associated with both hyperglycaemia and hypoglycaemia.
12. *Should I audit my current practice because of these results?* **Yes.** An audit of current blood glucose control protocols, with reference to the target blood glucose, actual blood glucose achieved and the incidence of hypoglycaemia would be appropriate. An audit of the type of resuscitation fluids used in severe sepsis would be useful, with a view to producing a guideline as more evidence becomes available.

Appraised by: Pauline O'Neil, 14 January 2008
Intensive Care Unit, Aberdeen Royal Infirmary
Email: paulineoneil@nhs.net

Reviewed by Brian Cuthbertson and Chris Cairns

References

1. 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.
2. Van den Berghe G, Wouters P, Weekers F *et al.* Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001;345:1359-67.
3. Schortgen F, Lacherade JC, Bruneel F *et al.* Effects of hydroxyethylstarch and gelatine on renal function in severe sepsis: a multicentre randomised study. *Lancet* 2001;357:911-16.