

Low dose epoetin alfa in critically ill patients

Use of low dose epoetin alfa in the critically ill does not reduce the number of patients requiring blood transfusion, or units of red blood cells transfused. There may be a mortality benefit in trauma patients. Epoetin alfa is associated with an increased risk of thrombotic events.

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

Appraised by: Oona Tanner

Citation: Corwin HL *et al.* Efficacy and safety of epoetin alfa in critically ill patients. *N Engl J Med* 2007;357:965-76.

Lead author: HL Corwin

Three-part clinical question:

Patients: All ICU patients.

Intervention: Low dose epoetin alfa (40,000 IU) or placebo.

Outcome: Percentage of patients receiving blood transfusions, number of units of red cells transfused, change in haemoglobin (Hb) from baseline, mortality, adverse events.

Search terms: erythropoietin, red cell transfusion, critically ill, anaemia, mortality, outcome, randomised controlled trial, EPO Critical Care Trials Group.

The study: Double-blinded, concealed, randomised trial with intention-to-treat analysis.

The study patients: One thousand, four hundred and fifty patients (115 centres) remaining on study ICUs for 48 hours post admission. They were stratified into three admission groups; medical, surgical and trauma.

Inclusion criteria: Eighteen years or older, Hb <12 g/dL, written informed consent (from the patient or assent from a surrogate)

Exclusion criteria: Expected ICU discharge within 48 hours of day 2, acute ischaemic cardiac event during ICU admission, stay >48 hours in the ICU of a transferring hospital, left

ventricular assist device, history of pulmonary embolism, DVT, ischaemic stroke, other arterial or venous thrombosis (excluding superficial thrombosis), chronic hypercoagulable disorder, dialysis, uncontrolled hypertension (systolic BP >200 mm Hg or diastolic >110 mm Hg), new-onset seizures within three months, seizures not controlled on medication, pregnancy or lactation, third degree burns ≥20% body surface area, acute GI bleed, transfusion at time of consideration, treatment with epoetin alfa within last 30 days, unable or unwilling to accept blood products, other study participation, hypersensitivity to epoetin alfa or constituents.

Experimental group (N = 733; 733 analysed): Patients were randomised between 48 and 96 hours post admission to the ICU. Study drug was administered on day 1 of the trial, then weekly; in total three doses were given (days 1,8,15). Follow-up was for 140 days. The study drug was withheld if Hb >12 g/dL during trial.

All patients were given enteral iron (150 mg elemental iron/day) at start of day 1. If there was no response (transferrin saturations <20%, serum ferritin <100 ng/ml), they were converted to parenteral iron.

Blood transfusion requirements were determined on individual clinical grounds, with no set targets. Arbitrary target Hb 7-9 g/dL or haematocrit ≈ 27%.

The evidence (all patients):

Outcome	Time to outcome	CER	EER	RRR	ARR	NNT
Patients receiving blood	29 days	0.483	0.460	5%	2.3%	NS
		95% confidence intervals:		-6% to 15%	NS	NS
Death	29 days	0.114	0.085	25%	2.9%	NS
		95% confidence intervals:		-1% to 52%	NS	NS
Clinically relevant thrombotic vascular event	140 days	0.115	0.165	-43%	-5%	-20
		95% confidence intervals:		-75% to -13%	-8.5 to -1.5%	-68 to -12
Non-event outcomes	Time to outcome/s	Control group	Experimental group	P-value		
Haemoglobin concentration rise	29	1.2±1.8 g/dL	1.6±2.0 g/dL	<0.001		
Absolute haemoglobin concentration	29	10.8±1.7 g/dL	11.2±1.8 g/dL	<0.001		

The evidence (trauma patients, N= 402 intervention / 391 control):

Outcome	Time to outcome	CER	EER	RRR	ARR	NNT
Death	29 days	0.066	0.035	47%	3.1%	32
		95% confidence intervals:		1% to 93%	0.1 to 6.1%	16 to 1887
Death	140 days	0.092	0.060	35%	0.032	NS
		95% confidence intervals:		NS	NS	NS

Control group (N = 727; 727 analysed): Patients treated as experimental group but given placebo instead of epoetin alfa.

EBM comments:

1. *Do the methods allow accurate testing of the hypothesis?* **Yes.** This was a well designed double-blinded, concealed, randomised trial with large patient numbers calculated to achieve statistical power.
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?* **Perhaps.**
 - The authors were correct in stating that there was no benefit for non-trauma patients. However with regards to trauma patients, the authors concluded “we believe that epoetin alfa could benefit trauma patients remaining in an ICU for more than 48 hours and who have haemoglobin concentrations below 12 g/dL and no history of thrombotic disease.” There was a statistically significant mortality benefit at 29 days for trauma patients but in the uncorrected data this was lost by 140 days. Therefore “could” benefit is appropriate. A definite answer for trauma patients can only be derived from a larger study.
 - Sixty per cent of the intervention group received only 1 or 2 doses of epoetin alfa. Therefore, the potential overall effect on haemoglobin concentration may not have been demonstrated in this study. This may explain why a reduction in blood transfusion requirements was not shown.
 - Transfusion triggers were higher than presently recommended (TRICC trial, McIntyre *et al*), especially in the trauma subgroup. Restrictive transfusion in this subgroup was demonstrated to be as safe as liberal.
4. *Did results get omitted, and why?* **No.** All patients, including those lost to follow-up (control:134, epo:115) are included in denominator.
5. *Did they suggest areas of further research?* **Yes.**
 - The mechanism of action responsible for the effects of epoetin alfa, is thought to be non-haematopoietic i.e. anti-apoptotic. Improvement in clinical outcome as represented by decreased mortality and moderate rise in haemoglobin occurred in the absence of a reduction in transfusion requirements as previously found. Is this plausible however in view of the low doses of epoetin alpha administered?
 - Increased thrombotic risk and death.
6. *Did they make any recommendations based on the results and were they appropriate?* **Yes.**
 - Epoetin alfa may be beneficial in trauma patients remaining on ICU ≥ 48 h with a haemoglobin of <12 g/dL and no previous history of thrombotic disease (ie study criteria met). This is only supported by adjusted data at 140 days. In view of this, and the cost and complications, this is unlikely to become routine practice.
 - There is evidence to suggest that epoetin should not be administered before a patient has been in ICU >48 h.
 - The use of epoetin in non-trauma patients is not supported unless they have an approved indication.
 - Concurrent prophylactic heparin should be considered in all patients.
7. *Is the study relevant to my clinical practice?* **Yes.** Although when assessing applicability of the study findings to UK practice one must remember that the case mix was, with $>50\%$ trauma, not typical of the UK.
8. *What level of evidence does this study represent?* **1⁺⁺**
9. *What grade of recommendation can I make on this result alone?* **A**
10. *What grade of recommendation can I make when this study is considered along with other available evidence?* **A**
11. *Should I change my practice because of these results?* **No.** Epoetin is not routinely used in critical care in this clinical setting currently. The exact mechanism of action of epoetin is unclear and there is not sufficient evidence to suggest clinical benefit. The risks currently outweigh the benefits.
12. *Should I audit my current practice because of these results?* **No.** Epoetin alfa is not routinely used in UK ICUs.

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