Alternativas A La Transfusión

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Alternativas a la trasfusión

- Substitutos de la sangre
- Tratamiento con hierro
- Ácido Tranexámico
- Eritropoyetina
- Otros:
  - Sistemas de Recuperación de sangre
  - Donación autóloga
  - Hemodilución normovolémica
  - Combinaciones de varios
  - Etc.

Condiciones Para El Empleo De Un Producto

- ¿Responde a una necesidad clínica?
- ¿Es eficaz?
- ¿Es seguro?
- ¿El coste es asumible?
- Comparación con el mejor tratamiento hasta la fecha
- Diferenciar:
  - Lo que se **podría hacer**
  - Lo que se **debe hacer**

Alternativas a la Transfusión:
¿Responde A Una Necesidad Clínica?

- Reducir el número de trasfusiones
- Menos complicaciones
- ***Mejor pronóstico***

Riesgos de las Trasfusiones Alogénicas

Illness	Baseline risk	Range	References
HIV/AIDS	2/1000 000	1·33/1000 000 to 16·7/1000 000	*
Hepatitis B	16/1000 000	5/1000 000 to 300/1000 000	†
Hepatitis C	10/1000 000	9·7/1000 000 to 660/1000 000	‡
Fatal haemolytic reaction	1·67/1000 000	1/1000 000 to 1·67/1000 000	§
Nonfatal haemolytic reaction	52·6/1000 000	52·6/1000 000 to 166·7/1000 000	¶
Febrile reaction	1/100		**

* Schreiber *et al*. (1996), Anon (1997), Krever (1995), Etchason *et al*. (1995), Lackritz *et al*. (1995), Healy *et al*. (1994), Birkmeyer *et al*. (1993), Nelson *et al*. (1992), Murphy *et al*. (1992).
† First six above* plus Anon (1991).
‡ First six above* plus Donahue *et al*. (1992).
§ Linden & Kaplan (1994), Birkmeyer *et al*. (1993).
¶ As above§ plus Walker (1987).
** Walker (1987).

Experience of German Red Cross blood donor services with nucleic acid testing: results of screening more than 30 million blood donations for human immunodeficiency virus-1, hepatitis C virus, and hepatitis B virus

RESULTS: During the observation period, 23 HCV, 7 HIV-1, and 43 HBV NAT-only–positive donations were detected. On the basis of these data and estimated pre-NAT infectious WPs, the residual risk per unit transfused was estimated at 1 in 10.88 million for HCV (95% confidence interval [CI], 7.51-19.72 million), 1 in 4.30 million for HIV-1 (95% CI, 2.39-21.37 million), and 1 in 360,000 for HBV (95% CI, 0.19-3.36 million). Based on observed cases of breakthrough infections, the risk of transfusion-related infections may be even lower.

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CONCLUSION: The risk of a blood recipient becoming infected with HCV, HIV-1, or HBV has reached an extremely low level. Introduction of individual donation testing for HCV and HIV-1 would have a marginal effect on interception of WP donations.

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A MULTICENTER, RANDOMIZED, CONTROLLED CLINICAL TRIAL OF TRANSFUSION REQUIREMENTS IN CRITICAL CARE

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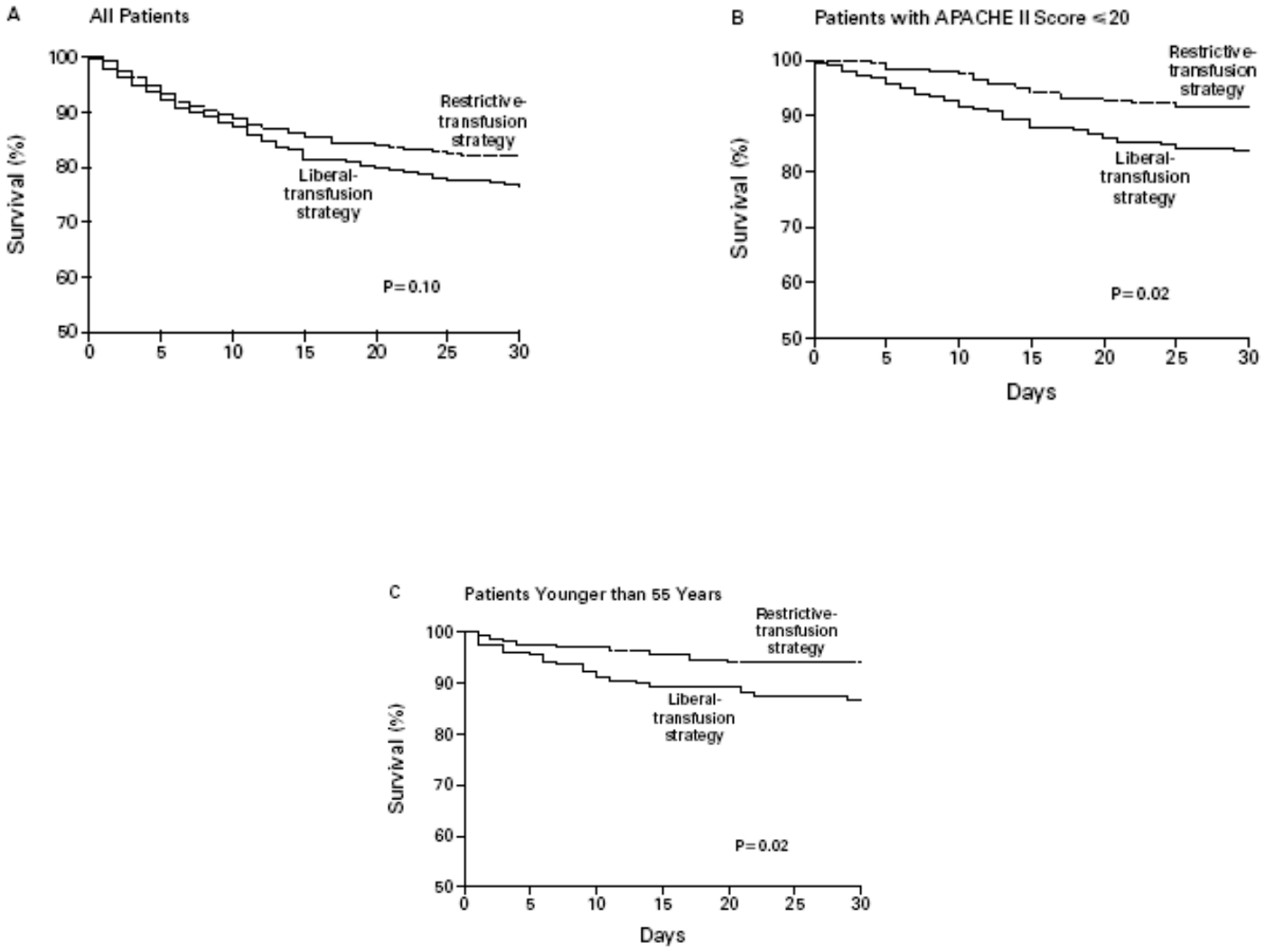
ABSTRACT

Background To determine whether a restrictive strategy of red-cell transfusion and a liberal strategy produced equivalent results in critically ill patients, we compared the rates of death from all causes at 30 days and the severity of organ dysfunction.

Methods We enrolled 838 critically ill patients with euvolemia after initial treatment who had hemoglobin concentrations of less than 9.0 g per deciliter within 72 hours after admission to the intensive care unit and randomly assigned 418 patients to a restrictive strategy of transfusion, in which red cells were transfused if the hemoglobin concentration dropped below 7.0 g per deciliter and hemoglobin concentrations were maintained at 7.0 to 9.0 g per deciliter, and 420 patients to a liberal strategy, in which transfusions were given when the hemoglobin concentration fell below 10.0 g per deciliter and hemoglobin concentrations were maintained at 10.0 to 12.0 g per deciliter.

RED-cell transfusions are a cornerstone of critical care practice,[1] but there are divergent views on the risks of anemia and the benefits of transfusion in this setting. One important concern is that anemia may not be well tolerated by critically ill patients.[2,3] Indeed, two recent studies suggested that anemia increases the risk of death after surgery in patients with cardiac disease[2] and in critically ill patients.[3] Red-cell transfusions are used to augment the delivery of oxygen in the hope of avoiding the deleterious effects of oxygen debt.[4] This view prompted the routine use of transfusion in patients with hemoglobin concentrations that were often more than 10.0 g per deciliter in studies evaluating resuscitation protocols.[5,6]

Critically ill patients may, however, be at increased risk for the immunosuppressive[7,8] and microcirculatory[9,10] complications of red-cell transfusions. In ad-



Hebert PC et al NEJM 1999

Anesthesiology 2008; 108:31–9

Are Blood Transfusions Associated with Greater Mortality Rates?

Results of the Sepsis Occurrence in Acutely Ill Patients Study

Jean-Louis Vincent, M.D., Ph.D., Yasser Sakr, M.B., B.Ch., Ph.D.,† Charles Sprung, M.D.,‡ Svein Harboe, M.D.,§ Pierre Damas, M.D.|| on behalf of the Sepsis Occurrence in Acutely Ill Patients (SOAP) Investigators*

- Relación directa entre el número de trasfusiones y mortalidad

- La trasfusión como tal, no se asociaba a mas mortalidad

- En 821 pares de pacientes (propensity score):
  mejor supervivencia entre los trasfundidos

¿Transfusión?

- Los riesgos conocidos de las transfusiones han inducido a extremar las precauciones
  - Leucodeplección es actualmente la norma (Los leucocitos han sido implicados en gran parte de los efectos adversos: TRALI, Inmunosupresión)
  - Otros
- Balance riesgo/beneficio:
  - Protocolos estrictos: Restricción de trasfusiones
- Tema abierto ¿…?

Cirugía Ortopédica (Cadera y Rodilla)
Evolución de Medidas de ahorro de sangre

Año 2002

- Donación Preop Autóloga: 10%
- EPO: 30%
- Uso Postop. de recuperadores: 11%

Año 2007

- Donación Preop Autóloga: 10%
- EPO: 60%
- Uso Postop. de recuperadores: 50%

Horstmann WG et al. Arch Orthop Trauma Surg. 2009 ,

Sistemas de recuperación de sangre

- Intraoperatorio y postoperatorio
- Se han mostrado eficaces en reducir trasfusiones
- Cirugía limpia

Substitutos de la sangre

Blood Substitutes

- Perfluorocarbon emulsions
- Stroma-Free Hemoglobin
- Polietilenglicol+Hb (Hemospan)
- Artificial blood

Table 3. Investigator-Reported Adverse Events

	As treated (n = 714)			
	PolyHeme (n = 349)		Control (n = 365)	
Event*	n	%	n	%
Adverse events	324	93†	322	88
Serious adverse events	141	40	126	35
Most common SAEs (> 2%)				
Pneumonia	27	8	21	6
Hemorrhagic shock	20	6	16	4
Respiratory failure	21	6	17	5
Hypercoagulable state	18	5	12	3
Coagulopathy	13	4†	4	1
Sepsis	12	3	11	3
Myocardial infarction	10	3†	2	1
Myocardial infarction adverse events‡	11	3†	3	1
Myocardial infarction	7		2	
NSTEMI	3		0	
Non Q wave MI	0		1	
Acute traumatic MI	1		0	
Requiring intervention	1		1	
Death within 30 d	3		1	
Cardiovascular events				
Heart failure/CHF/PE/fluid overload/hypervolemia	20	6	20	5
Cardiac arrest/EMD/V-fibrillation/V-arrhythmia/V-tachycardia	15	4	9	2
CVA/cerebral ischemia/cerebral infarction	3	1	1	1
Multiple organ failure in 30 d (adjudicated)	26	7	20	6
Renal (creatinine > 1.8 mg/dL)	13/26	50	9/20	45
Hepatic (total bilirubin > 2.0 mg/dL)	20/26	77	15/20	75
Cardiac (inotropes)	9/26	35	4/20	20
Pulmonary (PaO_2/FiO_2 < 240)	24/26	92	19/20	95

Cell-Free Hemoglobin-Based Blood Substitutes and Risk of Myocardial Infarction and Death

A Meta-analysis

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THE DEVELOPMENT OF A BLOOD substitute—an infusible liquid that eliminates the need for refrigeration and cross-matching, has a long shelf life, and reduces the risk of iatrogenic infection—would provide a potentially lifesaving option for surgical patients and trauma patients with hemorrhagic shock, especially in rural areas and military settings. To date, a large proportion of blood substitutes in development have been hemoglobin-based products. Yet randomized controlled trials completed as early as 1996[1] have raised questions about the safety of these products and have failed to demonstrate clinical benefit. Nonetheless, at least 1 of these products is approved for use outside the United States and new clinical trials are being conducted or planned worldwide.[2-8]

Context Hemoglobin-based blood substitutes (HBBSs) are infusible oxygen-carrying liquids that have long shelf lives, have no need for refrigeration or cross-matching, and are ideal for treating hemorrhagic shock in remote settings. Some trials of HBBSs during the last decade have reported increased risks without clinical benefit.

Objective To assess the safety of HBBSs in surgical, stroke, and trauma patients.

Data Sources PubMed, EMBASE, and Cochrane Library searches for articles using *hemoglobin* and *blood substitutes* from 1980 through March 25, 2008; reviews of Food and Drug Administration (FDA) advisory committee meeting materials; and Internet searches for company press releases.

Study Selection Randomized controlled trials including patients aged 19 years and older receiving HBBSs therapeutically. The database searches yielded 70 trials of which 13 met these criteria; in addition, data from 2 other trials were reported in 2 press releases, and additional data were included in 1 relevant FDA review.

Data Extraction Data on death and myocardial infarction (MI) as outcome variables.

Results Sixteen trials involving 5 different products and 3711 patients in varied patient populations were identified. A test for heterogeneity of the results of these trials was not significant for either mortality or MI (for both, $I^2=0\%$, $P\geq.60$), and data were combined using a fixed-effects model. Overall, there was a statistically significant increase in the risk of death (164 deaths in the HBBS-treated groups and 123 deaths in the control groups; relative risk [RR], 1.30; 95% confidence interval [CI], 1.05-1.61) and risk of MI (59 MIs in the HBBS-treated groups and 16 MIs in the control groups; RR, 2.71; 95% CI, 1.67-4.40) with these HBBSs. Subgroup analysis of these trials indicated the increased risk was not restricted to a particular HBBS or clinical indication.

Conclusion Based on the available data, use of HBBSs is associated with a significantly increased risk of death and MI.

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Transfusion Medicine, 2008, **18**, 28–39 doi: 10.1111/j.1365-3148.2007.00811.x

ORIGINAL ARTICLE

A randomized, single-blind, increasing dose safety trial of an oxygen-carrying plasma expander (Hemospan®) administered to orthopaedic surgery patients with spinal anaesthesia

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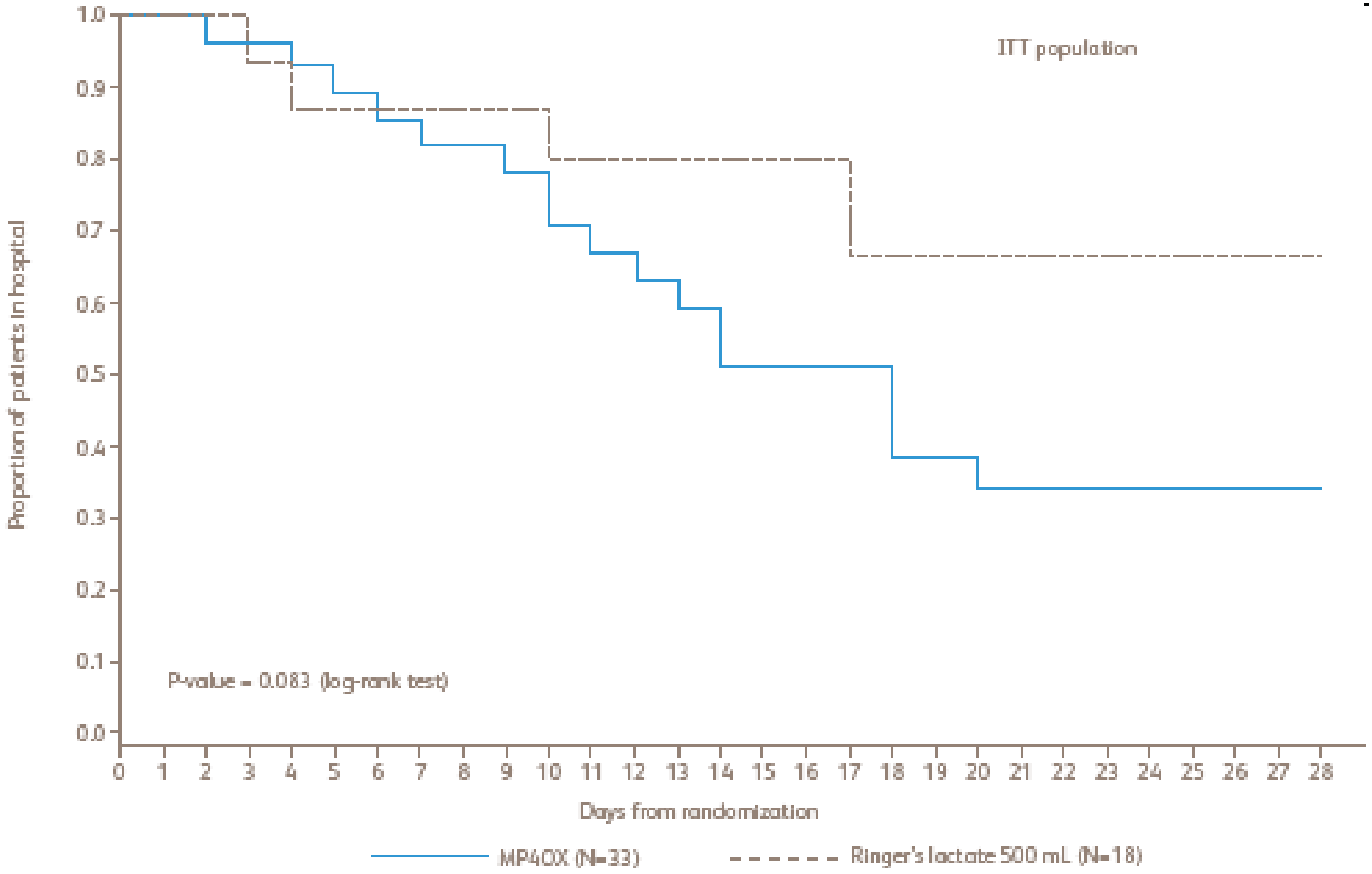
Table 2. Adverse events

MedDRA System Organ Class Term	A	B	C	D	E	Total	RL
Number of patients	4	4	4	4	4	20	10
Blood and lymphatic system disorders		1				1	
Cardiac disorders							1
Gastrointestinal disorders	2	3	2			7	1
General disorders and administration site conditions	3	1		4		8	1
Infections and infestations	1	1	1		1	4	2
Injury, poisoning and procedural complications		1				1	1
Musculoskeletal and connective tissue disorders	1					1	3
Nervous system disorders	1		2	1		4	1
Psychiatric disorders				1		1	1
Respiratory, thoracic and mediastinal disorders					1	1	
Skin and subcutaneous tissue disorders				1		1	2
Vascular disorders				1		1	1
Group Total AEs	8	7	5	8	2	30	14
AEs per patient	2·0	1·8	1·2	2·0	0·5	1·5	1·4

Time from Randomization to Discharge



Substitutos de la sangre

- Por ahora no hay indicación clínica
- Campo de investigación!!
- Sangre artificial
  - (Células Madre de cordón umbilical) disponible para uso militar en 2013 http://www.physorg.com/news198221258.html

Tratamiento Con Hierro

Aporte de Hierro

- Oral
- Intravenoso

Eficaz en Anemia con déficit absoluto de Fe

Ineficaz Anemia con déficit “funcional” de Fe

Tratamiento con Hierro

- Dificultad para el diagnostico de:
  - Anemia por falta de hierro
  - Anemia funcional (Inflamación)
- No se ha mostrado eficaz en pacientes críticos
- Riesgo de infección?

Hierro e infección

- Las bacterias necesitan hierro para multiplicarse
- La administración de hierro iv empeora la función de neutrófilos, macrófagos, linfocitos T, disminuye la eritropoyesis
- La “deprivación” de hierro es un mecanismo de defensa
- El hierro juega un papel crucial en la infección bacteriana (Sideroforas)
- El tratamiento con hierro empeora la evolución de animales infectados
- En humanos (hemodialisis) demuestran asociación entre infección y incremento de ferritina

FCM

Table 3. Adverse events experienced by ≥2% of subjects in either treatment group (safety population)

MedDRA SOC-preferred term, *n* (%)	FCM (*n* = 147)	Oral iron (*n* = 103)	P-value
≥1 adverse event	64 (43.5)	61 (59.2)	0.02
Gastrointestinal disorders	12 (8.2)	40 (38.8)	
Constipation	2 (1.4)	18 (17.5)	<0.001
Diarrhoea	2 (1.4)	4 (3.9)	0.23
Faeces discoloured	0 (0.0)	3 (2.9)	0.07
Gastrointestinal haemorrhage	0 (0.0)	3 (2.9)	0.07
Nausea	2 (1.4)	5 (4.9)	0.13
General disorders and administration site conditions	18 (12.2)	6 (5.8)	
Infusion site reactions	3 (2.0)	0	0.27
Oedema peripheral	9 (6.1)	2 (1.9)	0.13
Infections and infestations	20 (13.6)	8 (7.8)	
Bronchitis	3 (2.0)	0	0.27
Upper respiratory tract infection	2 (1.4)	4 (3.9)	0.23
Urinary tract infection	5 (3.4)	1 (1.0)	0.41
Metabolism and nutrition disorders	10 (6.8)	3 (2.9)	
Hyperkalaemia	6 (4.1)	1 (1.0)	0.25
Nervous system disorders	6 (4.1)	7 (6.8)	
Headache	3 (2.0)	2 (1.9)	1.00
Vascular disorders	9 (6.1)	2 (1.9)	
Hypotension	3 (2.0)	0	0.08

FCM, ferric carboxymaltose; MedDRA, Medical Dictionary for Regulatory Activities; SOC, System Organ Class.

Tratamiento con Hierro (como alternativa a la transfusión)

- Beneficios cuestionables (implicaría controles metabólicos complejos…)
- ¿Riesgos?

Acido Tranexámico

Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial

*CRASH-2 trial collaborators**

Summary

	Tranexamic acid (n=10 060)	Placebo (n=10 067)	RR (95% CI)	p value (two-sided)
Any cause of death	1463 (14·5%)	1613 (16·0%)	0·91 (0·85–0·97)	0·0035
Bleeding	489 (4·9%)	574 (5·7%)	0·85 (0·76–0·96)	0·0077
Vascular occlusion*	33 (0·3%)	48 (0·5%)	0·69 (0·44–1·07)	0·096
Multiorgan failure	209 (2·1%)	233 (2·3%)	0·90 (0·75–1·08)	0·25
Head injury	603 (6·0%)	621 (6·2%)	0·97 (0·87–1·08)	0·60
Other causes	129 (1·3%)	137 (1·4%)	0·94 (0·74–1·20)	0·63

Data are number (%), unless otherwise indicated. RR=relative risk. *Includes myocardial infarction, stroke, and pulmonary embolism.

Table 2: **Death by cause**

EPO

Indicaciones de EPO

- Anemia en IRC
- Anemia en Cáncer tratado con Quimioterapia
- Pacientes anémicos (10<Hb<13 grL) que van a ser intervenidos de cirugía (no cardiaca ni vascular) y que se prevé “sangrante”

EPO En Pacientes Críticos

Efficacy of recombinant human erythropoietin in critically ill patients admitted to a long-term acute care facility: A randomized, double-blind, placebo-controlled trial*

Michael Silver, MD; Michael J. Corwin, MD; Andrea Bazan, MD; Andrew Gettinger, MD; Christopher Enny, BS; Howard L. Corwin, MD

Context: Anemia is common in the critically ill and results in a large number of red blood cell transfusions. Recent data have shown that red blood cell transfusions in critically ill patients can be decreased with recombinant human erythropoietin (rHuEPO) therapy during their intensive care unit stay.

Objective: To assess the efficacy of rHuEPO therapy in decreasing the occurrence of red blood cell transfusions in patients admitted to a long-term acute care facility (LTAC).

Design: A prospective, randomized, double-blind, placebo-controlled, multiple-center trial.

Setting: Two long-term acute care facilities.

Patients: A total of 86 patients who met eligibility criteria were enrolled in the study with 42 randomized to rHuEPO and 44 to placebo.

Interventions: Study drug (rHuEPO 40,000 units) or a placebo was administered by subcutaneous injection before day 7 of long-term acute care facility admission and continued weekly for up to 12 doses.

Main Outcome Measures: The primary efficacy end point was cumulative red blood cell units transfused. Secondary efficacy end points were the percent of patients receiving any red blood cell transfusion; the percent of patients alive and transfusion independent; cumulative mortality; and change in hematologic variables from baseline. Logistic regression was used to adjust the odds ratio for red blood cell transfusion. All end points were assessed at both study day 42 and study day 84.

Results: The baseline hemoglobin level was higher in the rHuEPO group (9.9 ± 1.15 g/dL vs. 9.3 ± 1.41 g/dL, $p = .02$) as was the pretransfusion hemoglobin level (8.0 ± 0.5 g/dL vs. 7.5 ± 0.8 g/dL, $p = .04$). At day 84, patients receiving rHuEPO received fewer red blood cell transfusions (median units per patient 0 vs. 2, $p = .05$), and the ratio of red blood cell transfusion rates per day alive was 0.61 with 95% confidence interval of 0.2, 1.01, indicating a 39% relative reduction in transfusion burden for the rHuEPO group compared with placebo. There was also a trend at day 84 toward a reduction in the total units of red blood cells transfused in the rHuEPO group (113 units of placebo vs. 73 units of rHuEPO). Patients receiving rHuEPO were also less likely to be transfused (64% placebo vs. 41% rHuEPO, $p = .05$; adjusted odds ratio 0.47, 95% confidence interval 0.19, 1.16). Most of the transfusion benefit of rHuEPO occurred by study day 42. Increase in hemoglobin from baseline to final was greater in the rHuEPO group (1.0 ± 2 g/dL vs. 0.4 ± 1.7 g/dL, $p < .001$). Mortality rate (19% rHuEPO, 29.5% placebo, $p = .17$; relative risk, 0.55, 95% confidence interval 0.21–1.43) and serious adverse clinical events (38 % rHuEPO, 32% placebo, $p = .65$) were not significantly different between the two groups.

Conclusions: In patients admitted to a long-term acute care facility, administration of weekly rHuEPO results in a significant reduction in exposure to allogeneic red blood cell transfusion during the initial 42 days of rHuEPO therapy, with little additional benefit achieved with therapy to 84 days. Despite receiving fewer red blood cell transfusions, patients treated with rHuEPO achieve a higher hemoglobin level. (Crit Care Med 2006; 34:2310–2316)

The NEW ENGLAND JOURNAL of MEDICINE

METHODS

In this prospective, randomized, placebo-controlled trial, we enrolled 1460 medical, surgical, or trauma patients between 48 and 96 hours after admission to the intensive care unit. Epoetin alfa (40,000 U) or placebo was administered weekly, for a maximum of 3 weeks; patients were followed for 140 days. The primary end point was the percentage of patients who received a red-cell transfusion. Secondary end points were the number of red-cell units transfused, mortality, and the change in hemoglobin concentration from baseline.

CONCLUSIONS

The use of epoetin alfa does not reduce the incidence of red-cell transfusion among critically ill patients, but it may reduce mortality in patients with trauma. Treatment with epoetin alfa is associated with an increase in the incidence of thromboti events. (ClinicalTrials.gov number, NCT00091910.)

the hemoglobin concentration at day 29 increased more in the epoetin alfa group than in the placebo group (1.6±2.0 g per deciliter vs. 1.2±1.8 g per deciliter, P<0.001). Mortality tended to be lower at day 29 among patients receiving epoetin alfa (adjusted hazard ratio, 0.79; 95% CI, 0.56 to 1.10); this effect was also seen in pre-

Table 3. Mortality at Day 29 and Day 140 in the Intention-to-Treat Population.

Group	Epoetin Alfa	Placebo	Hazard Ratio (95% CI)*	
			Unadjusted	Adjusted
	no./total no. (%)			
Day 29				
All patients	62/733 (8.5)	83/727 (11.4)	0.73 (0.53–1.02)	0.79 (0.56–1.10)
Admission group				
Trauma	14/402 (3.5)	26/391 (6.6)	0.52 (0.27–0.99)	0.37 (0.19–0.72)
Surgical, nontrauma	10/162 (6.2)	14/168 (8.3)	0.73 (0.33–1.65)	0.70 (0.31–1.63)
Medical, nontrauma	38/169 (22.5)	43/168 (25.6)	0.88 (0.57–1.36)	1.04 (0.65–1.67)
Day 140				
All patients	104/733 (14.2)	122/727 (16.8)	0.83 (0.64–1.08)	0.86 (0.65–1.13)
Admission group				
Trauma	24/402 (6.0)	36/391 (9.2)	0.63 (0.38–1.06)	0.40 (0.23–0.69)
Surgical, nontrauma	27/162 (16.7)	27/168 (16.1)	1.02 (0.60–1.74)	0.91 (0.52–1.60)
Medical, nontrauma	53/169 (31.4)	59/168 (35.1)	0.88 (0.60–1.27)	0.99 (0.66–1.49)

The Journal of TRAUMA® Injury, Infection, and Critical Care

Improved Survival of Critically Ill Trauma Patients Treated With Recombinant Human Erythropoietin

Lena M. Napolitano, MD, Timothy C. Fabian, MD, Kathleen M. Kelly, MD, Jeffrey A. Bailey, MD, Ernest F. Block, MD, Wayne Langholff, PhD, Christopher Enny, BS, and Howard L. Corwin, MD

Background: A randomized, double-blind, placebo-controlled, multicenter trial (EPO-2, N = 1,302) in anemic critically ill patients demonstrated a 29-day survival benefit in the trauma subgroup receiving epoetin alfa (mortality 8.9% vs. 4.1%). A second similarly designed trial (EPO-3, N = 1,460) confirmed this survival benefit in the epoetin alfa-treated trauma cohort (mortality 6.7% vs. 3.5%). This analysis presents trauma cohort data from both trials for evaluation of the impact of baseline factors including trauma-specific variables on outcomes.

Methods: Patients received 40,000 U epoetin alfa or placebo weekly, for a total of 4 (EPO-2) or 3 (EPO-3) doses, starting on ICU day 3. Kaplan-Meier survival curves for the two groups were compared using the log-rank test. Univariate and multivariate Cox proportional hazard regression methods were used to evaluate relationship between baseline factors and mortality.

Results: Demographic and trauma variables at baseline were comparable. Mortality was consistently reduced by ≈50% in both studies (EPO-2—day 29 unadjusted HR: 0.46, 95% CI: 0.24–0.89; EPO-3—day 29 unadjusted HR: 0.51, 95% CI: 0.27–0.98.). Adjusting for baseline and trauma variables had minimal effect on hazard ratios for mortality at day 29 (EPO-2—day 29 adjusted HR: 0.50, 95% CI: 0.26–0.97; EPO-3—day 29 adjusted HR: 0.38, 95% CI: 0.19–0.74) and day 140 (EPO-3—adjusted HR: 0.39, 95% CI: 0.21–0.72). In EPO-3, there appeared to be an increase in clinically relevant thrombovascular events in the epoetin alfa treated group (16.4% vs. 12.5%, RR: 1.3, 95% CI: 0.93–1.85) but not in EPO-2 (11.1% vs. 13.3%, RR: 0.84, 95% CI: 0.56–1.28).

Conclusion: Epoetin alfa demonstrated a survival advantage in both of the critically ill trauma patient cohorts of two prospective, randomized clinical trials, which was not affected by baseline factors including trauma-specific variables. A definitive study in trauma subjects is warranted.

Key Words: Trauma, Anemia, Intensive care unit, Epoetin alfa, Mortality, Outcome.

J Trauma. 2008;65:285–299.

application of systems strategies in the community or a tactical approach in the course of patient's care. Specific therapeutic interventions that demonstrate a distinct human survival advantage that are supported by large, randomized controlled trials are rare. For example, in the treatment of sepsis, activated protein C has demonstrated a survival advantage for the most critically ill.[29] That discovery changed the paradigm for the treatment of severe sepsis. Although a secondary endpoint, the significant survival advantage in trauma patients associated with the erythropoietin treatment arm of these two prospective, randomized clinical trials suggests the potential for a similar innovation in the application of therapy in the care of the severely injured.

The survival benefit noted with administration of epoetin alfa in the trauma cohort is not related to a reduction in blood transfusion. The percentage of patients receiving blood transfusion was reduced in EPO-2 and not in EPO-3. Additionally, RBC transfusion was not significant in the Cox step-wise

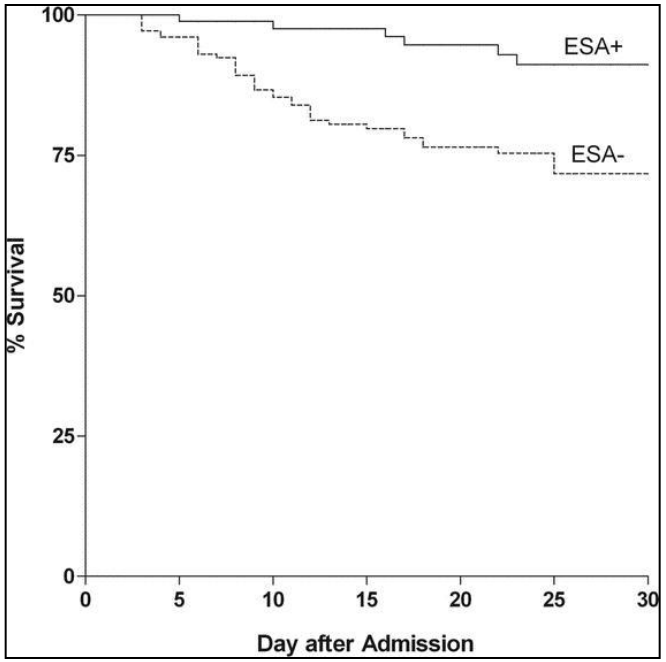
care of the severely injured.

The survival benefit noted with administration of epoetin alfa in the trauma cohort is not related to a reduction in blood transfusion. The percentage of patients receiving blood transfusion was reduced in EPO-2 and not in EPO-3. Additionally,

Erythropoiesis Stimulating Agent Administration Improves Survival After Severe Traumatic Brain Injury: A Matched Case Control Study

Talving, Peep MD, PhD; Lustenberger, Thomas MD; Kobayashi, Leslie MD; Inaba, Kenji MD; Barmparas, Galinos MD; Schnüriger, Beat MD; Lam, Lydia MD; Chan, Linda S. PhD; Demetriades, Demetrios MD, PhD

(Ann Surg 2010)



CONCLUSIONS:

Erythropoiesis stimulating agent administration in sTBI is associated with a significant in-hospital survival advantage without increase in morbidity.

Prospective validation of our findings is warranted

Outcomes with the use of recombinant human erythropoietin in critically ill burn patients.

Lundy JB, Hetz K, Chung KK, Renz EM, White CE, King BT, Huzar T, Wolf SE, Blackbourne LH.

Am Surg. 2010 Sep;76(9):951-6.

No effect was seen for rhEPO treatment on mortality or blood transfusion requirements in the severely burned.

Pharmacokinetics and pharmacodynamics of six epoetin alfa dosing regimens in anemic critically ill patients without acute blood loss

Arroliga, Alejandro C. MD; Guntupalli, Kalpatha K. MD; Beaver, Jessica S. PhD; Langholff, Wayne PhD; Marino, Kimberly MS; Kelly, Kathleen MD, FACS, FCCM

Critical Care Medicine 37(4), April 2009, pp 1299-1307

Conclusions:... The pharmacokinetics of epoetin alfadid not predict pharmacodynamic response in anemic critically ill patients

EPO

- En pacientes críticos: No
- Subgrupo de Trauma ¿…?

SEGURIDAD

Seguridad

- Estudios en Pacientes renales
- Estudios en Pacientes con Cáncer
- Estudios en Cirugía y en Pacientes Críticos
  - Centrados en “disminución de trasfusiones”
  - Poco énfasis en Seguridad

Experiencia con Anemia en Quimioterapia

- Estudios iniciales: Alta eficacia!!
  - Reduce el número de transfusiones
  - ¿Es ese el objetivo?
- Estudios posteriores: Aumento de Mortalidad!!
  - Cancer maxilofacial(Henke et al Lancet 2003)
  - Cancer de mama (Leyland-Jones et al J Clin Oncol 2005)
  - Cancer de pulmón (Wright et al J Clin Oncol 2007),
  - Cancer maxilofacial (Goldberg et al Cancet Letter 2007)
  - Cancer linfoproliferativo y cancer no mieloide (www.fda.gov/ohrms/dockets/ac/07)

¿Causas?

- Aumento de la Hb
- Cambios reológicos secundarios a las variaciones de la Hb
- Efectos tróficos en el endotelio vascular
- Cáncer: Posible incremento del crecimiento del tumor ¿…?

Drug Safety and Availability

Postmarket Drug Safety Information for Patients and Providers

- Index to Drug-Specific Information
- Approved Risk Evaluation and Mitigation Strategies (REMS)
- Postmarketing Safety Evaluation of New Molecular Entities: Final Report
- Drug Safety Communications
- Drug Safety Information for Healthcare Professionals

Drug Safety Communication: Erythropoiesis-Stimulating Agents (ESAs): Procrit, Epogen and Aranesp

Safety Announcement

Additional Information for Patients

Additional Information for Healthcare Professionals and Hospitals: ESA use in cancer

Additional Information for Healthcare Professionals: non-cancer use of ESAs

Table of Key Safety Studies

Safety Announcement

The FDA is requiring all drugs called Erythropoiesis-Stimulating Agents (ESAs) to be prescribed and used under a risk management program, known as a risk evaluation and mitigation strategy (REMS), to ensure the safe use of these drugs. The ESAs that are part of the REMS are marketed under the names Epogen, Procrit, and Aranesp. FDA required Amgen, the manufacturer of these products, to develop a risk management program because studies show that ESAs can increase the risk of tumor growth and shorten survival in patients with cancer who use these products. Studies also show that ESAs can increase the risk of heart attack, heart failure, stroke or blood clots in patients who use these drugs for other conditions.

An Open-Label, Randomized, Parallel-Group Study of Perioperative Epoetin Alfa *Versus* Standard of Care for Blood Conservation in Major Elective Spinal Surgery

Safety Analysis

Christopher P. Stowell, MD, PhD,* Stanley C. Jones, MD,† Christopher Enny, BS,‡ Wayne Langholff, PhD,‡ and Gerhard Leitz, MD‡

Study Design. Prospective, open-label, randomized, parallel-group study at 90 centers.

Objective. To demonstrate there is no clinically important additional risk for deep vein thrombosis with perioperative use of epoetin alfa *versus* standard of care in spine surgery without prophylactic anticoagulation.

Summary of Background Data. Trials of epoetin alfa in orthopedic surgery that demonstrated no additional risk of thrombovascular events included perioperative pharmacologic anticoagulation.

Methods. Subjects received epoetin alfa 600 U/kg subcutaneously once weekly starting 3 weeks before spinal surgery plus standard of care for blood conservation, or standard of care alone. Perioperative anticoagulation therapy was not permitted; mechanical deep vein thrombosis prophylaxis was allowed. Doppler imaging for deep vein thrombosis was done on postoperative day 4 (or day of discharge), or for suspected deep vein thrombosis. Deep vein thrombosis was diagnosed by Doppler result or adverse event report. The criterion for no additional risk of deep vein thrombosis was a 1-sided 97.5% upper confidence limit ≤4% between groups.

Results. Of the 680 subjects analyzed (340 in each treatment group), 16 (4.7%) in the epoetin alfa group and 7 (2.1%) in the standard of care group had a diagnosis of deep vein thrombosis either by Doppler or by adverse event report with normal Doppler. The between-group difference was 2.6% (97.5% upper confidence limit, 5.4%). Deep vein thrombosis confirmed by Doppler (4.1% vs. 2.1%), other clinically relevant thrombovascular events (1.5% vs. 0.9%), and all adverse events combined (76.5% vs. 73.2%) occurred with similar frequency in the 2 treatment groups.

Conclusion. This study documented a higher incidence of deep vein thrombosis and similar rates of other clinically relevant thrombovascular events with epoetin alfa *versus* standard of care for blood conservation in subjects who did not receive prophylactic anticoagulation before spinal surgery. Antithrombotic prophylaxis should be considered when erythropoietin is used in the surgical setting.

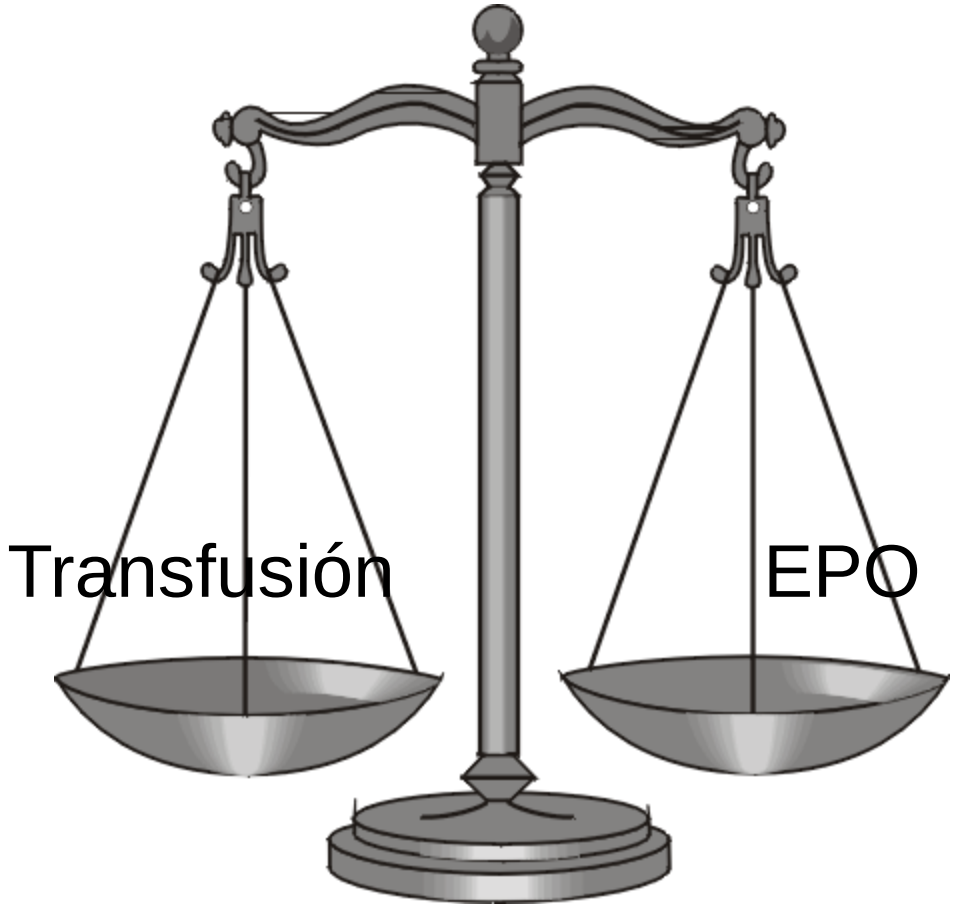
Key words: erythropoietin, epoetin alfa, surgery, deep vein thrombosis, thrombovascular events. **Spine 2009;34: 2479–2485**

Recombinant human erythropoietin (epoetin alfa) is indicated for the reduction of allogeneic blood transfusion in anemic patients with hemoglobin >10 to ≤13 g/dL who are scheduled to undergo elective, noncardiac, nonvascular surgery with significant anticipated blood loss.[1] This indication was established largely on the safety and efficacy findings of 4 orthopedic surgery studies.[2–5] An integrated safety analysis of these clinical trials found the rates of deep vein thrombosis and other thrombovascular events were similar in patients who received epoetin alfa and those who received placebo.[6]

Each of the trials in orthopedic surgery that contributed to the surgical indication for epoetin alfa included perioperative pharmacologic anticoagulation. The primary objective of this study was to demonstrate that there was no clinically important additional risk for deep vein thrombosis in adult spine surgery without prophylactic anticoagulation using a perioperative regimen of epoetin alfa *versus* the standard of care for blood conservation. Spine surgery patients represented an appropriate population to evaluate the risk of deep vein thrombosis because pharmacologic anticoagulation was not used routinely in these patients, and therefore, would not confound the findings from this study.

Sotwell PS et al. Spine, 2009

Riesgo / Beneficio
(Perioperatorio)



¿El coste es asumible?

CME Article

Number needed to treat and cost of recombinant human erythropoietin to avoid one transfusion-related adverse event in critically ill patients*

Kenneth M. Shermock, PharmD; Ed Horn, PharmD, BCPS; Pamela A. Lipsett, MD; Peter J. Pronovost, MD, PhD; Todd Dorman, MD, FCCM

LEARNING OBJECTIVES

On completion of this article, the reader should be able to:

1. Describe the benefits of using erythropoietin.
2. Explain the potential adverse events related to red cell transfusions.
3. Explain the cost of erythropoietin required to avoid one transfusion adverse event.

The authors have disclosed that they have no financial relationships or interests in any commercial companies pertaining to this educational activity. The authors have also disclosed that they will be discussing unlabeled/investigational uses of erythropoietin, a commercial product, and will disclose this to the audience.

Visit the *Critical Care Medicine* Online website (www.ccmjournal.com) for information on obtaining continuing medical education credit.

Objective: To calculate the absolute risk reduction of transfusion-related adverse events, the number of patients needed to treat, and cost to avoid one transfusion-related adverse event by using erythropoietin in critically ill patients

Design: Number needed to treat with sensitivity analysis.

Setting: Teaching hospital

Patients candidates

Interven need for pa

Measur of known t transfusion- ciency virus lination, str frequency c culated the events, the sion-related incidence c

units transfused for all transfusion-related adverse events, 58 per million for serious transfusion-related adverse events, and 21 per million for likely fatal transfusion-related adverse events. The routine use of erythropoietin resulted in an absolute risk reduction of 191 per million for all transfusion-related adverse events, 35 per million for serious transfusion-related adverse events, and 12 per million for such event was 28,785 patients. The cost of EPO to avoid one serious event was $31,001,497. When we factored in the reduced need for transfusions, the total cost to avoid one adverse event in patients treated with EPO was $25,551,929.

he number needed to ated adverse event, adverse event, and erse event. The total elated adverse event, ed adverse event, and ed adverse event. The ensitivity analysis. oidance of adverse an efficient use of l patients. (Crit Care

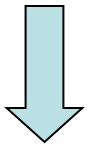
s and cost analysis; alth resources

Condiciones Para Un Producto

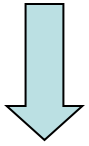
- ¿Responde a una necesidad clínica?
- ¿Es eficaz?
- ¿Es seguro?
- ¿El coste es asumible?
- Comparación con el mejor tratamiento hasta la fecha

Necesidad Clínica (EPO En Pacientes Críticos)

- Reducir el número de trasfusiones



- Menos complicaciones ¿…?



- Mejor pronóstico ¿…?

EPO en Pacientes Críticos: Dilema

- Hay incertidumbre sobre la seguridad
- No hay impacto sobre la supervivencia (¿Trauma?)
- ¿Coste/efectividad?
- Depende de nuestro objetivo:
  - Reducir la Necesidad de transfusión: Hay algún estudio que lo apoya
  - Reducir la Morbi-mortalidad ¿…?

Conclusiones

- Los sistemas de recuperación de sangre, donación preoperatoria… pueden considerarse una alternativa eficaz

- La alternativa mas prometedora es el uso de sangre artificial proveniente de células madre pero por ahora no está disponible.

- Actualmente, la mejor alternativa a la trasfusión es el empleo de un protocolo de trasfusión racional.