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Early versus delayed erythropoietin for the anaemia of end-stage kidney disease (Review)

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TABLE OF CONTENTS

[Intervention Review]

Early versus delayed erythropoietin for the anaemia of end-stage kidney disease

Jorge Coronado Daza[1], Arturo J Martí-Carvajal[2], Amaury Ariza García[1], Joaquín Rodelo Ceballos[3], Nancy Yomayusa González[4], Carol Páez-Canro[5], César Loza Munárriz[6], Gerard Urrútia[7]

[1]Facultad de Medicina, Departamento Médico, Grupo de Investigación Alta Tensión, Universidad de Cartagena, Cartagena, Colombia. [2]Iberoamerican Cochrane Network, Valencia, Venezuela. [3]Hospital Universitario San Vicente Fundacion, Servicio de Nefrologia, University of Antioquia, Medellin, Colombia. [4]Clínica Colsanitas. Grupo de Investigación Traslacional, Universidad Sanitas, Bogotá, Bogota, Colombia. [5]Instituto de Investigaciones Clínicas, Facultad de Medicina, Universidad Nacional de Colombia, Bogota, Colombia. [6]Department of Nephrology, Universidad Peruana Cayetano Heredia, Lima, Peru. [7]Iberoamerican Cochrane Centre - Biomedical Research Institute Sant Pau (IIB Sant Pau), CIBER Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain

Contact: Jorge Coronado Daza, Facultad de Medicina, Departamento Médico, Grupo de Investigación Alta Tensión, Universidad de Cartagena, Sede Zaragocilla, Campus de la Salud, Cartagena, Bolivar, 130015, Colombia. jocodada@yahoo.es.

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ABSTRACT

Background

Anaemia is a common complication in people with chronic kidney disease (CKD) and mainly develops as a consequence of relative erythropoietin (EPO) deficiency. Anaemia develops early in the course of disease and peaks among people with end-stage kidney disease (ESKD). Many types of EPO - also called erythropoiesis-stimulating agents (ESAs) - are used to treat anaemia in people with ESKD.

ESAs have changed treatment of severe anaemia among people with CKD by relieving symptoms and avoiding complications associated with blood transfusion. However, no benefits have been found in relation to mortality rates and non-cardiac fatal events, except quality of life. Moreover, a relationship between ESA use and increased cardiovascular morbidity and mortality in patients with CKD has been reported in studies with fully correcting anaemia comparing with partial anaemia correction. Until 2012, guidelines recommended commencing ESA treatment when haemoglobin was less than 11 g/dL; the current recommendation is EPO commencement when haemoglobin is between 9 and 10 g/dL. However, advantages in commencing therapy when haemoglobin levels are greater than 10 g/dL but less than 11 g/dL remain unknown, especially among older people whose life expectancy is limited, but in whom EPO therapy may improve quality of life.

Objectives

To assess the clinical benefits and harms of early versus delayed EPO for anaemia in patients with ESKD undergoing haemodialysis or peritoneal dialysis

Search methods

We searched the Cochrane Kidney and Transplant Specialised Register to 22 May 2017 through contact with the Information Specialist using search terms relevant to this review.

Selection criteria

We planned to include randomised controlled trials (RCTs) and quasi-RCTs evaluating at the clinical benefits and harms of early versus delayed EPO for anaemia in patients with ESKD undergoing haemodialysis or peritoneal dialysis. Studies comparing EPO with another EPO, placebo or no treatment were eligible for inclusion.

Data collection and analysis

It was planned that two authors would independently extract data from included studies and assess risk of bias using the Cochrane risk of bias tool. For dichotomous outcomes (all-cause mortality, cardiovascular mortality, overall myocardial infarction, overall stroke, vascular access thrombosis, adverse effects of treatment, transfusion), we planned to use the risk ratio (RR) with 95% confidence intervals (CI). We planned to calculate the mean difference (MD) and CI 95% for continuous data (haemoglobin level) and the standardised mean difference (SMD) with CI 95% for quality of life if different scales had been used.

Main results

Literature searches yielded 1910 records, of these 1534 were screened after duplicates removed, of which 1376 were excluded following title and abstract assessment. We assessed 158 full text records and identified 18 studies (66 records) that were potentially eligible for inclusion. However, none matched our inclusion criteria and were excluded.

Authors' conclusions

We found no evidence to assess the benefits and harms of early versus delayed EPO for the anaemia of ESKD.

PLAIN LANGUAGE SUMMARY

Early versus delayed erythropoietin for the anaemia of end-stage kidney disease

Anaemia (low haemoglobin) is a common complication among people with end-stage kidney disease (ESKD) receiving dialysis treatment. Dialysis treatment removes toxic waste products from the blood when kidneys no longer function. Anaemia treatment is based on the use of manufactured erythropoietin (EPO, a hormone that increases haemoglobin), to improve fatigue and breathlessness which are common symptoms of severe anaemia. It is widely accepted that EPO treatment should be initiated when haemoglobin levels are less than or equal to 10 g/dL (delayed onset). However, it remains unknown if there are clinical benefits or harms when EPO treatment is commenced when haemoglobin levels are greater than 10 g/dL but less than 11 g/dL (early onset).

We conducted this review to try to determine if there are clinical benefits and harms associated with early versus delayed EPO.

We searched the literature to 8 July 2015 but found no studies that investigated early versus delayed EPO for ESKD-related anaemia. Benefits and harms of early versus delayed EPO remain unknown.

BACKGROUND

Description of the condition

Anaemia has been defined by the World Health Organization (WHO) as a haemoglobin concentration less than 13.0 g/dL and 12.0 g/dL respectively for males and non-pregnant females aged 15 years or over (WHO 2008). This definition is widely accepted for people with anaemia caused by CKD (KDIGO 2012).

Anaemia is a common complication in people with CKD and develops early in the course of the disease. Anaemia increases in frequency with a corresponding decline in kidney function, and peaks in incidence among people with ESKD (Astor 2002). Kidney-related anaemia develops mainly as a consequence of relative EPO deficiency in relation to haemoglobin levels; EPO levels are 10 to 100 times higher among anaemic patients with normal kidney function (Artunc 2007; Ly 2004; McGonigle 1984).

Description of the intervention

EPO is an essential growth factor for the recruitment, differentiation, maintenance and survival of erythroid progenitor cells. EPO is produced by hepatocytes in the foetal stage, and after birth is synthesised mainly by the kidneys in response to hypoxia (Glaspy 2009; Jelkmann 2011). After cloning the EPO gene in 1983, recombinant human technology enabled development and production of the first erythropoietin - epoetin-α - which was approved for clinical use in 1989 (Eschbach 1988; Eschbach 1989). Since then, many EPO types - also called erythropoiesis-stimulating agents (ESAs) - have been produced. According to their action time, they are classified as short-acting and long-acting (Horl 2013).

Short-acting ESAs have a half-life from six to eight hours intravenously and from 19 to 24 hours subcutaneously; most are administered two to three times weekly (Halstenson 1991). Short-acting ESAs are more effective when administered subcutaneously. Alfa and beta are the most widely used short-acting ESAs. Epoetin-α biosimilars are used in Europe (Schellekens 2008).

Long-acting ESAs have improved pharmacokinetic and pharmacodynamic characteristics. Dose requirements do not differ according to the route of administration. The combination of a significantly increased half-life and lower binding affinity for the EPO receptor explains why long-acting ESAs stimulate erythropoiesis for longer periods. Long-acting ESAs used for the treatment of kidney-related anaemia are darbepoetin-α and the continuous EPO receptor activator (CERA). One darbepoetin dose is given every one or two weeks (Macdougall 1999; Padhi 2006) and CERA is administered biweekly or monthly (Macdougall 2006).

EPO therapy improves cognitive function and quality of life (Astor 2002; Drueke 2006; Pfeffer 2009; Ross 2002) and helps regression of left ventricular hypertrophy (Levin 2002; Parfrey 2009). However, EPO is not free of complications which are mainly hypertensive reactions, thrombosis of arteriovenous fistula in patients on haemodialysis, increased risk of stroke and faster tumour growth; appearance of severe anaemia as part of pure red cell aplasia, and seizures (Del Vecchio 2010; Rizzo 2010; Zhu 2006).

How the intervention might work

EPO acts as an essential growth factor. It regulates erythropoiesis, maintaining the survival of erythroid progenitors, stimulating their proliferation and differentiation in the bone marrow (Jelkmann 2011). EPO production is markedly up-regulated by hypoxia via a negative feedback loop; hypoxia induces an increase in EPO hormone production in the kidneys, increasing the mass of circulating red blood cells, thereby increasing the oxygen-carrying capacity of blood and suppressing further expression of EPO (Bunn 2013). Specifically, EPO binds to the EPO receptor through the high affinity isoform EPO, which is responsible for the erythropoietic effects by activation of several pathways (hypoxia-inducible factor 1, 2 and 3, Janus kinase-2, phosphatidylinositol 3-kinase, protein kinase C, anti-apoptotic protein) stimulating differentiation of erythroid precursor cells and inhibiting apoptosis of erythroid progenitors (Elliott 2008; Sinclair 2013).

Recombinant human EPO and human EPO have similar biological activity. Increase in red blood cell mass is dependent on the exposure time of the level of EPO; therefore, subcutaneous administration of short-acting ESAs is more effective (Kaufman 1998). The response to administration of EPO may vary from patient to patient. The dose should be adjusted to reach a haemoglobin monthly increase between 1 and 2 g/dL. If the increase is less than expected, the dose is increased by 25%; if higher, it is decreased by 25%. After reaching the target haemoglobin level, the maintenance dose of EPO is adjusted according to monthly haemoglobin readings (Del Vecchio 2010; KDOQI 2006; KDIGO 2012).

Why it is important to do this review

The importance of this systematic review is based on the following premises.

1. Many of the clinical manifestations of CKD may be epiphenomena of anaemia, which is associated with the worsening of cognitive functions, exercise capacity, mental acuity, quality of life; depression and fatigue (Finkelstein 2009; Gerson 2004; Weisbord 2008). Increased risk of cardiovascular morbidity and mortality may also be present (Astor 2006; Glassock 2009; Locatelli 2004).
2. ESAs have changed treatment of kidney-related anaemia by improving the signs and symptoms of severe anaemia, avoiding the complications of iron overload, transmission of viral diseases and sensitisation for future kidney transplants (Del Vecchio 2010). However, no benefits have been found in RCTs and meta-analyses when correcting anaemia with regard to patients' mortality and non-cardiac fatal events, except for quality of life (Drueke 2006; Johansen 2010; Johansen 2012; Pfeffer 2009). Notwithstanding, a relationship between the use of ESAs and an increased cardiovascular morbidity and mortality in patients with CKD has been reported in studies with fully correcting anaemia comparing with partial anaemia correction (Palmer 2010; Phrommintikul 2007; Singh 2006). Patients with cancer also experience increased cardiovascular morbidity and mortality associated with ESA use (Rizzo 2010; Tonia 2012).
3. From 2000 to 2009 clinical guidelines from the United States and Europe recommended commencing ESA treatment when haemoglobin was less than 11 g/dL (EBPG 2004; ERBP 2009; ERBP 2010; KDOQI 2000; KDOQI 2006; KDOQI 2007; KDIGO 2008). The 2012 Anaemia Work Group of Kidney Disease Improving Global Outcomes (KDIGO) guidelines suggested starting treatment in dialysis patients when haemoglobin is

between 9 to 10 g/dL (Grade 2B), and in some cases, starting treatment when haemoglobin is greater than 10 g/dL (not graded), primarily in older people among whom life expectancy is limited, being more relevant to improve quality of life (KDIGO 2012). The European Renal Best Practice (ERBP) Advisory Board and Canadian Society of Nephrology guidelines agree with KDIGO about whether and when to start ESA therapy in dialysis patients (ERBP 2013; Moist 2013).

Several systematic reviews have investigated ESA treatment for anaemia in patients with CKD and ESKD evaluating haemoglobin level, energy and physical function, fatigue, left ventricular mass index and mortality (Johansen 2010; Johansen 2012; Palmer 2010; Parfrey 2009; Vinhas 2012), but to date, a systematic review on the benefits and harms of early (haemoglobin < 11 g/dL but > 10 g/dL) versus delayed (haemoglobin ≤ 10 g/dL) ESA treatment for anaemia in dialysis patients with ESKD has not been published.

OBJECTIVES

To assess the clinical benefits and harms of early versus delayed EPO for anaemia in patients with ESKD undergoing haemodialysis or peritoneal dialysis.

METHODS

Criteria for considering studies for this review

Types of studies

This review included all RCTs and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, the use of alternate medical records, date of birth or other predictable methods) looking at EPO in people with ESKD on dialysis with anaemia. Studies were considered without language restriction. Studies of at least 12 weeks follow-up were to be included.

Types of participants

Inclusion criteria

Dialysis patients with anaemia due to ESKD irrespective of gender or age were eligible for inclusion. We planned to accept any definition of anaemia provided in individual studies.

Exclusion criteria

We excluded studies involving patients with functional or absolute iron deficiency.

Types of interventions

This review included studies of early (haemoglobin between 10 and 11 g/dL) versus delayed (haemoglobin ≤ 10 g/dL) treatment with any EPO or EPO against placebo/no treatment, by any route (subcutaneous or intravenous) or dose. The following comparisons were considered for inclusion.

- EPO versus placebo/no treatment
- EPO versus EPO

Types of outcome measures

We planned to evaluate all-cause mortality and cardiovascular mortality according to end-of-study reports. We also planned to assess outcomes on mortality at the short (< 6 months), medium (from 6 to 12 months) and long term (> 12 months). We planned to evaluate numbers of adverse and cardiovascular events according to their occurrence during study follow-up.

Primary outcomes

1. All-cause mortality
2. Cardiovascular mortality
3. Quality of life (end of treatment scores obtained using validated tools such as the Kidney Disease Quality of Life tool or others as mentioned in the studies).

Secondary outcomes

1. Adverse events: hypertension (one or more hypertensive events requiring additional antihypertensive medication or as defined by the investigators); seizure ≥ 1 event)
2. Myocardial infarction (fatal or non-fatal)
3. Stroke (ischaemic or haemorrhagic, either fatal or non-fatal)
4. Thrombotic events (deep venous thrombosis, peripheral arterial thrombotic events, and dialysis vascular access thrombosis)
5. Blood transfusions requirements (number of individuals requiring one or more packed red blood cell transfusion)
6. Haemoglobin level reached at end of study.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Kidney and Transplant Specialised Register up to 22 May 2017 through contact with the Information Specialist using search terms relevant to this review. The Specialised Register contains studies identified from the following sources:

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of kidney-related journals and the proceedings of major kidney conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney and transplant journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Specialised Register are identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of these strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available in the Specialised Register section of information about Cochrane Kidney and Transplant.

See Appendix 1 for search terms used in strategies for this review.

Searching other resources

1. Reference lists of review articles, relevant studies and clinical practice guidelines.
2. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.

Data collection and analysis

Selection of studies

Titles and abstracts were screened independently by two authors who discarded studies that were clearly not eligible and assessed the full text of potentially eligible studies to determine which satisfied inclusion criteria. Disagreements were to be resolved through discussion, with a third author if necessary.

Data extraction and management

Data extraction was to be carried out independently by two authors using standard forms. Studies reported in non-English language journals were to be translated before assessment. Where more than one publication of one study existed, reports were to be grouped together and the publication with the most complete data used in the analyses. Where relevant outcomes were only published in earlier versions these data were to be used. Any discrepancies between published versions were to be highlighted.

Assessment of risk of bias in included studies

We planned to assess risk of bias using the Cochrane risk of bias assessment tool (Higgins 2011) (Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study?
  - Participants and personnel (performance bias)
  - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

For dichotomous outcomes (all-cause mortality, cardiovascular mortality, overall myocardial infarction, overall stroke, vascular access thrombosis, adverse effects of treatment, transfusion), we planned to use the risk ratio (RR) with 95% confidence intervals (CI). We planned to calculate the mean difference (MD) and CI 95% for continuous data (haemoglobin level) and the standardised mean difference (SMD) with CI 95% for quality of life if different scales had been used.

Dealing with missing data

We planned to request any further information required from the original author in writing and to include any relevant information obtained in the review.

Assessment of heterogeneity

We planned to analyse heterogeneity using a Chi^2 test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance, and the I^2 statistic (Higgins 2003).

Assessment of reporting biases

We planned to construct funnel plots to provide visual assessment of whether treatment estimates were associated with study size.

Data synthesis

We planned to pool data using the random-effects model and to use the fixed-effect model to ensure the robustness of the model chosen and the susceptibility to outliers.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was planned to explore possible sources of heterogeneity (e.g. participants, interventions and study quality). Heterogeneity among participants could be related to age and dialysis modality. Heterogeneity in treatments could be related to dose, type (short versus long acting) and duration of ESA treatment. Quality of life parameters were to be assessed based on the Kidney Disease Quality of Life tool, or as reported in studies (Hays 1997). We planned to perform the following subgroup analyses:

- Patients on haemodialysis versus peritoneal dialysis
- Paediatric versus adult participants
- Use of EPO higher doses versus lower dose
- EPO short-acting versus long-acting
- Use the Kidney Disease Quality of Life tool versus others as mentioned in the studies.

Sensitivity analysis

We planned to perform sensitivity analysis to explore the influence of the following factors on the effect on size.

- Repeating the analysis excluding unpublished studies
- Repeating the analysis taking into account risk of bias
- Repeating the analysis excluding any very long or large studies to establish how much they dominate the results
- Repeating the analysis excluding quasi-RCTs.

'Summary of findings' tables

We were not able to assess quality evidence associated with primary outcomes (all-cause mortality, cardiovascular mortality, quality of life, cardiovascular events, adverse events, haemoglobin level reached at the end of the study, and blood transfusions requirements) with the GRADE system (Guyatt 2008).

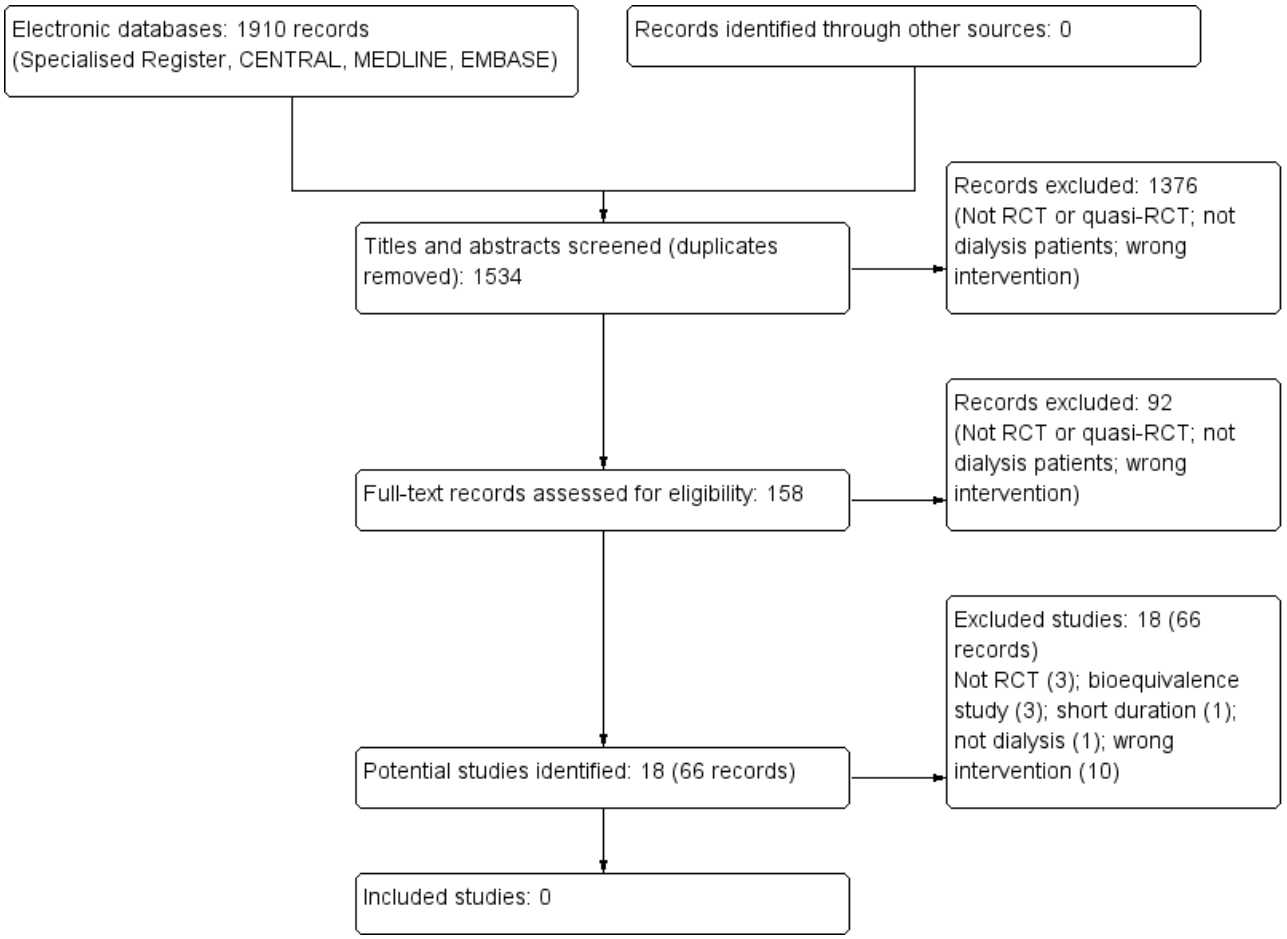
RESULTS

Description of studies

Results of the search

We searched the literature to 8 July 2015 and identified 1910 potentially relevant records (Figure 1). We excluded duplicate records, and assessed titles and abstracts of 1534 records. Of these, 1376 were excluded (not RCT or quasi-RCT; wrong population; wrong intervention). We obtained the full text of 158 papers for assessment, and excluded 92. We identified 18 potential studies (66 records) none of which met our inclusion criteria.

Figure 1. Study flow diagram



Excluded studies

We excluded 18 studies (66 records)

- Three studies were not randomised (Besarab 1998; Linde 2001; Tareeva 1992)
- Three were bioequivalence studies (Krivoshiev 2008; Krivoshiev 2010; Wizemann 2008).
- Suzuki 1989 was short duration (8 weeks)
- Teehan 1990 studied pre-dialysis patients
- Ten studies did not compare early versus delayed EPO for the anaemia of ESKD (Bahlmann 1991; Bennett 1991; Canadian EPO Study 1990; Foley 2000; Morris 1993; Muirhead 1992; Nissenson 1995; Parfrey 2005; Park 2014; Trembecki 1995a).

See Characteristics of excluded studies.

Risk of bias in included studies

Risk of bias assessment could not be conducted.

Effects of interventions

No studies met our inclusion criteria.

DISCUSSION

Summary of main results

This Cochrane Review identified no studies assessing benefits or harms of early or delayed EPO to treat anaemia in patients on dialysis. Early versus delayed EPO for the treatment of anaemia among people with ESKD has unknown either benefits or harms.

Potential biases in the review process

We have been unable to identify evidence from RCTs supporting the use of early or delayed erythropoietin for treating anaemia of ESKD. The main limitation of this Cochrane Review is the paucity of evidence of the use of early or delayed erythropoietin for treating anaemia of ESKD.

Agreements and disagreements with other studies or reviews

We found no studies assessing early versus delayed EPO for anaemia associated with ESKD.

AUTHORS' CONCLUSIONS

Implications for practice

We found no studies assessing early versus delayed EPO for ESKD-related anaemia. Benefits and harms remain unknown.

Implications for research

This Cochrane Review has highlighted a need for well-designed, high-quality RCTs to assess the benefits and harms of early versus delayed erythropoietin for the anaemia of end-stage kidney disease. The potential study should include main clinical outcomes (patients-oriented outcomes) such as all-cause mortality, cardiovascular mortality, quality of life, adverse events and cardiovascular events according to their occurrence during study follow-up.

The study should be reported according to the Consolidated standards of reporting trials (CONSORT) statement for improving the quality of reporting of efficacy and to get better reports of harms in clinical research (Ioannidis 2004; Moher 2010; Turner 2012). Future studies should be planned according to the recommendations of Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) (Chan 2013a; Chan 2013b) and the Foundation of Patient-Centered Outcomes Research (Gabriel 2012; PCORI 2012).

Future studies should be conducted by independent researchers and reported according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines (Ioannidis 2004; Moher 2010) and using the Foundation of Patient-Centered Outcomes Research recommendations (Gabriel 2012; PCORI 2012).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bahlmann 1991	RCT; did not compare early versus delayed EPO for the anaemia of ESKD
Bennett 1991	Quasi-RCT; did not compare early versus delayed EPO for the anaemia of ESKD
Besarab 1998	Open-label study investigating EPO alfa to achieve normal or low haematocrit
Canadian EPO Study 1990	RCT; did not compare early versus delayed EPO for the anaemia of ESKD
Foley 2000	RCT; did not compare early versus delayed EPO for the anaemia of ESKD
Krivoshiev 2008	RCT. Bioequivalence study comparing IV EPO zeta and EPO alfa

Study	Reason for exclusion
Krivoshiev 2010	RCT. Bioequivalence study comparing SC EPO zeta and EPO alfa
Linde 2001	Open-label study investigated EPO alfa to reach normal haemoglobin or subnormal haemoglobin
Morris 1993	Did not compare early versus delayed EPO for the anaemia of ESKD
Muirhead 1992	Quasi-RCT; did not compare early versus delayed EPO for the anaemia of ESKD
Nissenson 1995	RCT; did not compare early versus delayed EPO for the anaemia of ESKD
Parfrey 2005	RCT; did not compare early versus delayed EPO for the anaemia of ESKD
Park 2014	RCT; did not compare early versus delayed EPO for the anaemia of ESKD
Suzuki 1989	RCT; was short duration (8 weeks).
Trembecki 1995a	RCT; did not compare early versus delayed EPO for the anaemia of ESKD
Wizemann 2008	Bioequivalence study of IV erythropoietin zeta and erythropoietin alfa

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. "renal replacement therapy":ti,ab,kw 2. h*emodialysis:ti,ab,kw 3. h*emodiafiltration:ti,ab,kw 4. dialysis:ti,ab,kw 5. (CAPD or CCPD or APD):ti,ab,kw 6. ("endstage kidney" or "endstage renal" or "end-stage kidney" or "end-stage renal"):ti,ab,kw 7. (ESKD or ESKF or ESRD or ESRF):ti,ab,kw 8. ("chronic kidney" or "chronic renal"):ti,ab,kw 9. {or #1-#8} 10.an*emi*:ti,ab,kw 11.{and #9-#10} 12.erythropoie*:ti,ab,kw 13.epo?etin:ti,ab,kw 14.darbepoetin:ti,ab,kw 15.EPO:ti,ab,kw 16.rhEPO:ti,ab,kw 17.CERA:ti,ab,kw 18.Mircera:ti,ab,kw 19.(Epogen or Eprex or Procrit or Epoyet):ti,ab,kw 20.(Binacrit or Retacrit or Eporatio):ti,ab,kw 21.Aranesp:ti,ab,kw 22.{or #12-#21}

(Continued)

	23.{and #11, #22} 24.(early or delay* or defer* or late):ti,ab,kw 25.{and #11, #24} 26.{or #23, #25}
MEDLINE	1. exp Renal Dialysis/ 2. exp Hemofiltration/ 3. Kidney Failure, Chronic/ 4. dialysis.tw. 5. (hemodialysis or haemodialysis).tw. 6. (hemodiafiltration or haemodiafiltration).tw. 7. (CAPD or CCPD or APD).tw. 8. (end-stage kidney or end-stage renal or endstage kidney or endstage renal).tw. 9. (ESKD or ESKF or ESRD or ESRF).tw. 10.or/1-9 11.Anemia/ 12.exp Anemia, Hypochromic/ 13.an?emi*.tw. 14.or/11-13 15.and/10,14 16.exp Erythropoietin/ 17.erythropoie*.tw. 18.epo?etin.tw. 19.darbepoetin.tw. 20.EPO.tw. 21.rhEPO.tw. 22.CERA.tw. 23.Mircera.tw. 24.(Epogen or Eprex or Procrit or Epoyet).tw. 25.(Binacrit or Retacrit or Eporatio).tw. 26.Aranesp.tw. 27.or/16-26 28.and/15,27 29.(early or delay* or defer* or late).tw. 30.and/15,29 31.or/28,30
EMBASE	1. exp Renal Replacement Therapy/ 2. (hemodialysis or haemodialysis).tw. 3. (hemodiafiltration or haemodiafiltration).tw. 4. dialysis.tw. 5. (CAPD or CCPD or APD).tw. 6. Chronic Kidney Disease/ 7. Kidney Failure/ 8. Chronic Kidney Failure/ 9. (end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw. 10.(ESRF or ESKF or ESRD or ESKD).tw. 11.or/1-10 12.Anemia/ 13.Iron deficiency anemia/ 14.an?emi*.tw. 15.or/12-14

(Continued)

16.and/11,15
17.erythropoietin/
18.recombinant erythropoietin/
19.novel erythropoiesis stimulating protein/
20.erythropoie*.tw.
21.epo?etin.tw.
22.darbepoetin.tw.
23.EPO.tw.
24.rhEPO.tw.
25.CERA.tw.
26.Mircera.tw.
27.(Epogen or Eprex or Procrit or Epoyet).tw.
28.(Binacrit or Retacrit or Eporatio).tw.
29.Aranesp.tw.
30.or/17-29
31.and/16,30
32.Early intervention/
33.(early or delay* or defer* or late).tw.
34.or/32-33
35.and/16,34
36.or/31,35

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random).
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.
	Unclear: Insufficient information about the sequence generation process to permit judgement.
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear: Randomisation stated but no information on method used is available.

(Continued)

Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data.	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.

(Continued)

	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

Appendix 3. Glossary

Epoetin Biosimilars: a biological medicinal product referring to an existing one and submitted to regulatory authorities for marketing authorization by an independent applicant after the existing agents' protection expires. Biosimilars can resemble the agents on which they are modelled but cannot fully copy their properties (Horl 2013; Schellekens 2008).

Erythropoiesis-stimulating agents: an agent similar to the cytokine (erythropoietin) that stimulates red blood cell production, commonly abbreviated ESAs (Horl 2013).

Erythropoietin high dose: subcutaneous doses > 120 UI/kg/wk, or intravenous doses > 240 UI/kg/wk of epoetin alfa or beta or biosimilars; darbepoetin alfa corrected weekly ESAs doses can be calculated multiplying by 200; and the continuous erythropoietin receptor activator can be calculated as per the pharmacological equivalence (Kainz 2010; Tolman 2005).

European Best Practice Guidelines (EBPG): The first EBPG for the Management of Anaemia in Patients with Chronic Renal Failure were created to fulfil the need for recommendations that reflected current European clinical practice and experience. They were presented at the ERA-EDTA Congress in Madrid in 1999. They were prompted from the need to analyse the huge volume of published data on anaemia management (Zoccali 2008).

European Renal Best Practice (ERBP): The ERA-EDTA in 2008 opted to change the name EBPG to European Renal Best Practice (ERBP) as a means of acknowledging that, especially in nephrology, it is difficult to generate real 'guidelines' because of the lack of sufficient evidence (Zoccali 2008).

KDIGO: Kidney Disease Improving Global Outcomes (KDIGO) was established in 2003 as an independently incorporated non-profit foundation governed by an international Board. The Mission is to improve the care and outcomes of kidney disease patients worldwide through the development and implementation of global clinical practice guidelines. KDIGO is led by an international Board comprised of approximately 50 members. The majority of the Board members are practicing nephrologists, but it also includes patient representatives, professionals from other medical specialties and disciplines – nephrology nurses, dieticians and social workers (KDIGO 2003).

KDOQI: In 1995, the National Kidney Foundation (NKF) began the development of what would become the first broadly accepted clinical practice guidelines in nephrology, now known as KDOQI—Kidney Disease Outcomes Quality Initiative. The first guidelines were published in 1997, and today there are 13 guidelines, which have made a major difference in the quality of care for kidney patients in the United States and worldwide (KDOQI 2014).

Long-acting erythropoiesis-stimulating agent: an agent with a half-life from 24 to 134 hours when given intravenously and from 54 to 134 hours when given subcutaneously. It is administered once every two to four weeks to maintain haemoglobin levels (Horl 2013).

Short-acting erythropoiesis-stimulating agent: an agent with a half-life from six to eight hours when given intravenously and from 19 to 24 hours when given subcutaneously. It is administered twice or three times weekly to maintain haemoglobin levels (Horl 2013).

WHAT'S NEW

Date	Event	Description
1 June 2017	Review declared as stable	New search undertaken in May 2017 - no studies identified

CONTRIBUTIONS OF AUTHORS

1. Draft the review: JC, AMC, JR, NY, GU, AA, CL, CP
2. Study selection: JC, AA
3. Extract data from studies: JC, AA

4. Enter data into RevMan: JC, AMC, GU, CL
5. Carry out the analysis: JC, AA, JR, CL, NY, CP
6. Interpret the analysis: JC, AA, JR, CL, NY, CP
7. Draft the final review: JC, AMC, GU, CL
8. Disagreement resolution: JR
9. Update the review: JC, AMC

DECLARATIONS OF INTEREST

- Jorge Coronado Daza: none known
- Arturo Martí-Carvajal: none known
- Amaury Ariza García: none known
- Joaquín Rodelo Ceballos: none known
- Nancy Yomayusa González: none known
- Carol Páez-Canro: none known
- César Loza Munárriz: none known
- Gerard Urrútia: none known

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Cartagena, University, Colombia.

  Full time professor salary

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There were no differences between the protocol and the review.

NOTES

New search undertaken in May 2017 - no studies identified.

INDEX TERMS

Medical Subject Headings (MeSH)

Anemia [*drug therapy] [etiology]; Erythropoietin [*therapeutic use]; Hematinics [therapeutic use]; Kidney Failure, Chronic [*complications] [therapy]; Renal Dialysis

MeSH check words

Humans