Erythropoiesis Stimulating Agents in Critically Ill Trauma Patients:

a systematic review and meta-analysis

Craig J French¹,³: craig.french@wh.org.au
Neil Glassford²,³: neil.glassford@austin.org.au
Dashiel Gantner¹,³: dashiell.gantner@wh.org.au
Alisa Higgins³: lisa.higgins@monash.edu
D James Cooper³,⁴ jamie.cooper@monash.edu
Alistair Nichol³,⁵: alistair.nichol@monash.edu
Markus Skrifvars³ markus.skrifvars@hus.fi
Georgina Imberger¹ gumberger@gmail.com
Jeffrey Presneill³,⁶ intensive@fastmail.com.au
Michael Bailey³ michael.bailey@monash.edu.au
Rinaldo Bellomo²,³ rinaldo.bellomo@austin.org.au

1. Department of Intensive Care, Western Health, Gordon Street, Footscray, Melbourne, Australia
2. Department of Intensive Care, Austin Hospital, 145 Studley Rd, Heidelberg, Melbourne, Australia.
3. Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia.
4. Department of Intensive Care, The Alfred, Commercial Road, Melbourne, Australia.
5. St Vincent’s University Hospital, Dublin, Ireland.
6. Royal Brisbane and Women’s Hospital, Brisbane, Australia.
Corresponding author:

Dr Craig French

Department of Intensive Care, Western Health, Gordon Street, Footscray, VIC, 3011 Australia.

Tel.:+61-3-83456639; Fax: +61-3-83456572
CONTRIBUTIONS OF AUTHORS

CF, NG, will be responsible for: developing PICO question and search strategy, conducting search, screening of abstracts, data extraction, data synthesis, data analysis, bias estimation including meta-bias, and preparation of the first draft of manuscript

MB and JP will be responsible for data analysis

GI will be responsible for Trial Sequential Analysis

DG and LH will be responsible for review of the search strategy and protocol, screening of abstracts, data extraction, data analysis and bias estimation, and preparation of first draft of manuscript

JC, AN, JP MS, and RB will be responsible for review of the search strategy, protocol, and draft manuscript.

Guarantor of the review: Dr Craig French

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ORGANISATIONAL AFFILIATIONS

Department of Intensive Care, Western Health, Gordon Street, Footscray, VIC, 3011 Australia

Department of Intensive Care, Austin Hospital, 145 Studley Rd, Heidelberg, Melbourne, VIC 3084, Australia
Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, Prahran, VIC 3004, Australia

ANTICIPATED OR ACTUAL START DATE
September 2015

ANTICIPATED COMPLETION DATE
January 2016

SUBJECT INDEXING TERMS
Erythropoietin, Trauma, Injury, Mortality, Neurological Outcome, Renal Replacement Therapy.
CONDITION OR DOMAIN BEING STUDIED

Trauma is a major public health issue for all jurisdictions; the consequences for individuals and societies are significant.\(^1\) Erythropoiesis stimulating agents (ESAs) are glycoproteins that stimulate erythropoiesis\(^2\); they also have pleotropic cytokine like effects that may be both neuroprotective\(^3\) and anti-inflammatory\(^4\). Large multicentre, double-blind, randomized trials of the ESA epoietin alfa as a transfusion sparing agent in critically ill patients\(^5,\,6\) have suggested that it may reduce mortality in trauma patients. Similar findings have been observed in critically ill patients with traumatic brain injury.\(^7,\,8\)

Systematic reviews and meta-analyses evaluating the non-haemopoietic effects of ESAs have been conducted in non-trauma populations\(^9-11\). To our knowledge there are no previous systematic reviews and meta-analyses of the published literature of the effects of ESAs on patient centred outcomes in trauma patients.
References:


REVIEW QUESTION

The main aim of this systematic review and meta-analysis is to summarize the available evidence evaluating the effect of erythropoietin in trauma patients.

Specifically we will investigate whether when administered to adult (≥ 15 years) trauma patients erythropoietin effects on mortality, neurological outcome, renal outcomes, and adverse events.

SEARCHES

- We will use the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement methodologies to report the findings of the systematic review from RCTs.
- We will electronically search OVID Medline, OVID Medline in process and other non-indexed citations, OVID EMBASE and Cochrane CENTRAL databases for original articles published in peer-reviewed journals.
- We will not set any limitations on year of publication.
- The search will not be limited by language of publication.
- We will use a variety of key words relating to ESAs, trauma, and critical illness in adult patients.
  - ESAs, erythropoietin, epoetin, darbepoietin
  - injury, trauma, wound, accident
  - critical care, intensive care, critical illness
• Related articles and reference lists will be manually searched to avoid omissions. We will search clinical trial registries to identify ongoing or completed but not yet published studies.

• Once the searches have been conducted, two independent reviewers (DG, NG or CF) will independently assess titles and abstracts for potential relevance and identify the manuscript as included, excluded or requiring further assessment.

• The full text of potentially relevant articles will then be examined

• Any articles causing a discrepancy between reviewers will then be independently assessed by author (LH) and resolved through consensus

• If a paper requires further assessment, we will contact the study lead investigator by e-mail and/or telephone with a request for any necessary additional information.

**Inclusion Criteria**

Studies will be included if they meet all the following criteria

• Randomized controlled trial

• Patients ≥ 15 years

• Patients were treated in a hospital or pre hospital clinical setting

• At least one intervention group was randomized to receive erythropoietin

• At least one intervention group was randomized to receive placebo.

• The study reports at least one of the following three outcomes: mortality; functional neurological outcome; need for renal replacement therapy
Exclusion Criteria

- Studies exclusively paediatric patients (<15 years) will be excluded.
- Non randomized controlled trials, observational and case control studies, case studies, case series, letters, abstracts and reviews will be excluded.
- Studies enrolling only healthy volunteers will be excluded
Research (PICO) Question

- **Population**
  - We will include studies relating to adult (≥ 15 years) critically ill trauma patients.

- **Intervention and Comparison**
  - We will include all articles randomizing trauma patients to an ESA. Studies reporting the administration of ESAs to trauma patients within larger cohorts of critically ill patients will be included. If an outcome is not reported we contact the authors.

- **Outcomes**
  - We will include articles that report the following outcomes of interest.
    - Primary
      - Mortality
        - ICU, where recorded
        - Hospital, where recorded
        - End-of-follow-up, where recorded
        - Other time points (e.g. 28d, 30d, 90d)
      - Functional Neurological Outcome
        - Extended Glasgow Outcome Scale
        - Other measures of this outcome include Glasgow Coma Score, Functional Assessment Measure (FAM)
Disability Rating Scale, Functional status examination, quality of life assessment. The search will not be limited to these measures; they are provided as examples.

- Renal
  - Need for renal replacement therapy
- Adverse Events
  - Thrombotic events
    - Proximal deep venous thrombosis
    - Cardiac Arrest
    - Thromboembolic stroke
    - Acute Myocardial Infarction
    - Upper limb venous thrombosis
  - Seizures
  - Hypertension

Data extraction

We will use Covidence (www.covidence.org) to facilitate title and abstract screening, full text review, conflict resolution, quality assessment and data extraction.
We will extract and record the following study features:

Publication information: source, study ID (created by review author), report ID (created by review author to uniquely identify study), review author ID (created by review author), author, article title, citation, country of origin, source of funding, eligibility: confirm eligibility for review, reason for exclusion. Study characteristics: setting, location, relevant dates, aim/objectives of the study, study design, recruitment procedures used (e.g. details of randomization, blinding), total study duration, sequence generation, allocation sequence concealment, blinding.

Participant and setting characteristics: characteristics of participants at the beginning of the study (e.g. total number, setting, age, gender, ethnicity, socio-economic status, disease characteristics including Glasgow Coma Scale and TBI severity (mild, moderate or severe), co-morbidities, Acute physiology and Chronic Health Examination (APACHE) III score, Abbreviated Injury Score, Injury Severity Score, number of participants in each characteristic category for intervention and control group(s), Red Cell Transfusion (incidence and volume)

Intervention: ESA (type, dose, route of administration, frequency, and duration of therapy)

Comparator: No ESA

Outcome data/results: number of participants allocated to each intervention group, for each outcome of interest, sample size, unit of assessment/analysis,
statistical techniques used for each pre-specified outcome: definition used in study, measurement tool or method used, length of follow-up, for all intervention group(s) and control group(s): number of participants enrolled, number of participants included in analysis, number of withdrawals, exclusions, and lost to follow-up.

**Risk of bias (quality) assessment**

Two review authors (LH and DG) will independently conduct risk of bias assessments for the included studies. Where there are disagreements in classifications, additional authors (NG and CF) and an experienced Cochrane review author will be consulted until a consensus could be reached.

We will use standard methods from the Cochrane Collaboration to assess the risk of bias in included randomized studies in the following domains:

- Low risk: method of reducing bias identified and described in detail
- Unclear: risk of bias not addressed
- High: no method stated or used


The risk of selection bias associated with the described method will be categorised as

- i) low risk: random method such as computer generation or random numbers table.
- ii) high risk: non-random method such as alternating allocation or allocation based on date of birth or hospital record number.
iii) unclear risk: no specified method.

2. *Allocation concealment.*

The risk of selection bias associated with the described method will be categorised as

i) low risk: allocations were adequately concealed such that participants and investigators enrolling participants could not foresee assignment (examples include sealed opaque envelopes or centralised allocations).

ii) high risk: participants and investigators enrolling participants could foresee assignment (examples include alternate allocation or transparent envelopes).

iii) unclear risk: no specified method

3. *Blinding of participants.*

The risk of performance bias associated with the described method was categorised as

i) low risk: participants were blinded to the intervention.

ii) high risk: participants were not blinded to the intervention.

iii) unclear risk: it was unclear whether participants were blinded to the intervention.

4. *Blinding of outcome assessment.*

The risk of detection bias associated with the described method was categorised as
i) low risk: blinding of outcome measurement ensured; or, no blinding, but outcome measurement unlikely to be influenced by inadequate blinding (e.g. death, demonstrable ICU-length of stay).

ii) high risk: no blinding, incomplete blinding or broken blinding.

iii) unclear risk: it was unclear whether outcome assessors were blinded to the intervention, or if inadequate blinding was likely to influence the outcome.

Where outcomes were explicit in nature (mortality), or explicitly defined (ICU-length of stay), then blinding of the outcome assessors is unlikely to introduce significant bias.

It is acknowledged that length of hospital/ICU stay and assessment of adverse effects could possibly be influenced if blinding is not ensured.

5. **Incomplete outcome data.** The risk of attrition bias associated with the described method will be categorised as

   i) *low risk:* intention to treat (ITT analysis) or per protocol analysis with <10% missing data and missing data balanced across intervention groups and unlikely to have significant effect on reported outcomes. When a study was missing outcome data, reasons were explicitly stated and were assessed as being unlikely to introduce bias.

   ii) *high risk:* per protocol analysis with >10% missing data or with data not balanced across intervention groups, likely to significantly impact on reported outcomes or if missing data imputed with inappropriate methods.
iii) unclear risk: ITT or per protocol analysis methods not clearly described; proportion of missing data and/or imputation methods for missing data unclear.

7. Selective reporting.

The risk of reporting bias associated with the described method will be categorised as

i) low risk: the study protocol was available and all stated outcomes were reported in the pre-specified manner. Where the protocol was not available, all expected outcomes were presented and it is clear that they were reported in the pre-specified manner.

ii) high risk: pre-specified outcomes were not reported or were reported in insufficient detail; or the absence of reporting of any outcome which would be expected to have been analysed.

iii) unclear risk: insufficient information reported to permit a definitive judgement of high or low risk.

- Trials with high risk of bias for one or more key domains will be considered at high risk of bias.
- Trials with low risk of bias for all key domains will be considered at low risk of bias.
- Otherwise, they will be considered at unclear risk of bias.
- Risk of bias will be assessed at both the outcome and the study level. It will be used to describe the robustness of findings.

Strategy for data synthesis
• All data reported by eligible randomised controlled trials will be used.
• Before the analysis, the data will be standardized into equivalent units.
• For dichotomous variables will be expressed as RR and 95% CI.
• For continuous variable, MD and 95% CI will be calculated for each study.
• Heterogeneity will be evaluated using the Cochrane Q test and the $I^2$ statistic to assess the degree of inter-study variation.
  o $I^2$ values of 0 to 24.9%, 25 to 49.9%, 50 to 74.9%, and 75 to 100% will be considered as having no, mild, moderate, and significant thresholds for statistical heterogeneity.
• A random-effects model using restricted maximum likelihood (REML) will be performed to provide more conservative estimates of effect in the presence of known or unknown heterogeneity.
• We will use fixed effect model in the following situations:
  (a) A large dominant Trial with estimates in opposite direction compared to other small studies.
  (b) Less than three studies in a single analysis
• Sensitivity analysis will be conducted by sequentially omitting a single study each time in an attempt to identify the potential influence of an individual study.
• Subgroup Analysis: $\chi^2$ test (p-interaction) will be used to assess subgroup difference
• Publication bias: we will assess publication bias visually using funnel plot, or statistically using Egger test, if 10 or more RCTs are included
• Data analysis will be performed using Review Manager 5.3. software (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014)
• Trial Sequential Analysis will be performed using TSA software (version 0.9 Copenhagen Trial Unit, Copenhagen, Denmark.)

**Analysis of subgroups or subsets**

• Subgroup analyses will be conducted based on the following pre-specified patient groups: isolated TBI, isolated diffuse TBI, isolated TBI with an intracranial mass lesion, multi-trauma with TBI (intracranial mass lesion), multi-trauma with diffuse TBI, multi-trauma without TBI.

• Meta-regression will be carried out if appropriate using plausible confounding variables.

**Contact details for further information**

Craig French  
Department of Intensive Care  
Western Health  
Gordon Street  
Footscray 3011  
Australia  
Craig.French@wh.org.au
Tel: +61 3 83456639  
Fax: +61 3 83456572
Proposed Search Strategies

**Medline (and Medline in process) Ovid SP**

1. exp Erythropoietin/
2. (esa or esas).tw.
3. (epoetin adj (alpha or alfa or beta)).tw.
4. (EPO or darbepoetin$ or epoietin or erythropoietin).tw.
5. or/1-4
6. exp wounds/
7. exp injuries/
8. exp injury/
9. (wound* or trauma* or injur* or accident*).mp.
10. or/6-9
11. exp critical care
12. exp Intensive Care, Neonatal/
13. 11 not 12/
14. exp critical illness/
15. 13 and 14
16. ((intensive or critical) adj (treatment or care or illness)).mp.
17. 15 and 16
18. 10 or 17
19. 5 and 18
20. exp animals/ not humans.sh.
21. 19 not 20
Embase (Ovid SP)

1. exp Injury/
2. (wound* or trauma* or injur* or accident*).mp.
3. 1 or 2
4. (critical care or critical illness).mp.
5. (intensive care or intensive care units).mp.
6. 4 or 5
7. exp Intensive Care, Neonatal
8. 6 not 7
9. exp recombinant erythropoietin/
10. (EPO or darbepoetin$ or epoietin or erythropoietin or erythropoietin).tw.
11. 9 or 10
12. 3 or 8
13. 12 and 11
14. exp animal/ not (exp human/ and exp animal/)
15. 13 not 14
Central

#1 MeSH descriptor Erythropoietin explode all trees
#2 MeSH descriptor Erythropoiesis Stimulating Agents explode all trees
#3 Erythropo* or epoieti* or darbepoieti*
#4 (#1 OR #2 OR #3)
#5 MeSH descriptor Trauma explode all trees
#6 MeSH descriptor critical illness explode all trees
#7 (# 5 OR 6)
#8 (#4 AND #7)