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General Information

Key Personnel (in addition to PI): **First Name:** Howard
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Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.

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Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.
Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

Associated Trial(s): NCT00091910 - A Randomized, Double-Blind, Placebo-Controlled Study to Determine the Efficacy and Safety of Epoetin Alfa in Critically Ill Subjects
Efficacy in the rHuEPO (Epoetin Alfa) in the Critically Ill Patient: A Randomized, Double Blind, Placebo-Controlled trial
What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Individual patient data meta-analysis of four multicenter, randomized, controlled trials evaluating epoetin alfa in critically ill trauma patients.

Narrative Summary:
Erythropoietin (EPO), a hormone that stimulates the body to produce red blood cells, has been used for the last 25 years to treat anemia in a number of clinical conditions. Over the last decade several large multi-center studies have suggested that EPO may also improve mortality in trauma patients. We propose to combine the data from four large studies that evaluated the effects of EPO to evaluate if the combined data suggests that EPO improves mortality in trauma patients. We plan to use this data to design a future trial determine if EPO treatment improves outcome in trauma patients.

Scientific Abstract:
Background: Erythropoietin (EPO) has been used for the treatment of anemia in a number of clinical settings, however it is now clear that EPO has a number of non-hematologic effects. Several large randomized clinical trials have suggested that EPO may improve mortality in critically ill trauma patients independent of any transfusion effect (1-4).
Objective: Examine the effect of epoetin alfa as compared to placebo on all-cause mortality after adjustment for important baseline covariates.
Study Design: Individual patient data meta-analysis of four identified multicenter, randomized, controlled trials evaluating EPO in critically ill trauma patients at low or intermediate risk of bias that have been identified by systematic review of the literature.
Participants: Trauma patients from four identified randomized controlled trials comparing individual receiving EPO versus placebo (1-4).
Main Outcome Measured: Primary outcome is 28-day all-cause mortality in patients receiving EPO versus placebo. Secondary outcomes include 90-day all cause mortality, functional neurologic outcome, and length of stay
Statistical Analysis: Individual patient data meta-analysis will be performed using one stage, multi-level (patients nested in sites nested in trials), mixed modeling. Heterogeneity between trials will be determined by fitting a fixed interaction term between treatment and trial, while overall treatment effect will be reported with trial treated as a fixed effect and site treated as a random effect. A secondary analysis will adjust for important baseline covariates.

Brief Project Background and Statement of Project Significance:
Erythropoietin (EPO) is a pleiotropic hormone with non-hematopoietic biological effects in many non-hematopoietic tissues.1 EPO is a cytokine with anti-apoptotic activity and has been demonstrated in preclinical and small clinical studies to protect cells from hypoxemia/ischemia.2,3 There is increasing evidence that EPO and its receptor function as a paracrine/autocrine system to mediate the protection of tissues subjected to metabolic stress.4 Results from multiple studies suggest that endogenous EPO signaling contributes to wound healing responses, physiological and pathological angiogenesis, and the body’s innate response to injury in the brain and heart.5 These “non-hematopoetic” activities of are locally mediated through tissue protector receptors and modulate the actions of pro-inflammatory cytokines.
The mortality benefit of EPO in the trauma subgroup was initially suggested in a post-hoc analysis of a large clinical trial.6 The finding was subsequently confirmed in a prospective analysis of a second large clinical trial in which the population was stratified by admission subgroup (trauma, surgery non-trauma, medicine).7 Trauma patients treated with EPO had a significantly reduced mortality at day 29 (adjusted hazard ratio 0.36; 95% CI 0.18-0.74), day 42 (adjusted hazard ratio 0.35; 95% CI 0.18-0.68) and day140 (adjusted hazard ratio, 0.40; 95% CI, 0.23 to 0.69). This mortality reduction was independent of baseline trauma specific variables and was greatest in patients with high ISS on admission (ISS ? 25, mortality 9.4% placebo vs. 5.0% epoetin alpha). In contrast to the trauma cohort, mortality was not significantly decreased in either medicine or surgery (non-trauma) patients receiving EPO. Taken together, the two trials, with a study cohort of 1433 trauma patients, provide strong evidence in support of a mortality benefit for EPOin trauma patients. Similar findings have been observed in critically ill patients with traumatic brain injury (TBI).8,9 EPO therapy in the critically ill (all patients) was associated with an increase in thrombotic events (hazard ratio, 1.41; 95% CI, 1.06 to 1.86). In a recent meta-analysis of ESA in critically ill patients, while no increase in adverse events in general there was a significant increase in thrombotic vascular events noted.10
Trauma is a leading cause of mortality and morbidity, particularly for those trauma patients requiring intensive care.11 The potential for EPO to increase survival in trauma patients remains an open question. The strength of the subgroup findings across the two largest studies as well as findings with TBI suggest a potential benefit of EPO treatment for trauma patients admitted to the ICU for more than 48 hours and meeting the other study criteria.6,7 However, while intriguing, any recommendation for routine treatment of trauma patients in the ICU with EPO awaits further confirmatory study. The results of the proposed individual patient data meta-analysis, if positive, would

provide support for proceeding with a confirmatory trial as well as help to design future trial of EPO in trauma patients.

Specific Aims of the Project:
The aim of the individual patient data meta-analysis is to assess the effects of EPO as compared with placebo in critically ill trauma patients. Specifically we will investigate whether when administered to adult trauma patients EPO influences mortality, neurological outcome, renal outcomes, and adverse events.

1. Primary objective
Compare the effect of EPO with placebo on all-cause mortality
2. Secondary objectives
i) Compare the effect of EPO with placebo on all-cause mortality after adjustment for important baseline covariates
ii) Compare the effect of EPO with placebo on secondary/intermediate outcomes including functional neurological outcome
iii) Compare the effect of EPO with placebo in pre-determined, clinically important subgroups: isolated TBI; isolated diffuse TBI; isolated TBI with an intracranial mass lesion; multi-trauma with TBI; multi-trauma with diffuse TBI; and multi-trauma without TBI.

What is the purpose of the analysis being proposed? Please select all that apply. Participant-level data meta-analysis
Participant-level data meta-analysis will pool data from YODA Project with other additional data sources

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:
The PRISMA-IPD methodologies were used to report the findings of a systematic review from RCTs. The systematic review identified 4 RCTs of EPO in critically ill trauma pts at low/moderate risk of bias. Included were studies randomizing trauma pts to EPO. Studies included refs 6 and 7 (requested from YODA) and refs 8 and 9 (data already available to investigators).
Inclusion criteria:
•RCT
•Pts ? 15 years
•Pts treated in hospital or prehospital clinical setting
•?1 intervention group randomized to receive EPO within 96 hrs of injury
•?1 intervention group randomized to receive placebo
•Study reports ?1 of these outcomes: mortality; functional neurological outcome
Exclusion criteria:
-Studies with exclusively pediatric pts (<15 years)
-Studies enrolling only healthy volunteers
-Non RCTs, observational & case control studies, case studies, case series, letters, abstracts & reviews
-Study assessed as being at high risk of bias in any one of the key Cochrane domains. Standard methods from Cochrane used to assess the risk of bias in the following domains:
-Low: method of reducing bias identified & described in detail
-Unclear: risk not addressed
-High: no method stated

Main Outcome Measure and how it will be categorized/defined for your study:
Compare the effect of EPO with placebo on all-cause mortality at 28 days.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:
Intervention: EPO (type, dose, route of administration, frequency, and duration of therapy). Comparator: No ESA.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:
? Mortality
o ICU, where recorded
o Hospital, where recorded

o End-of-follow-up, where recorded
o Other time points (e.g. 30d, 90d)
? Length of Stay
o ICU
o Hospital
? Functional Neurological Outcome
o Extended Glasgow Outcome Scale
o Proportional odds model
o Sliding dichotomy
o Midpoint dichotomization
? Adverse Events
• Thrombotic events
o Proximal deep venous thrombosis/pulmonary embolism
o Cardiac Arrest
o Thromboembolic stroke
o Acute Myocardial Infarction
o Upper limb venous thrombosis
• Seizures
• Hypertension

Statistical Analysis Plan:
IPDMA will be performed using one stage, multi-level (patients nested in sites nested in trials), mixed modeling. Heterogeneity will be determined by fitting a fixed interaction term between treatment and trial, while overall treatment effect will be reported with trial treated as a fixed effect and site treated as a random effect. A secondary analysis will adjust for baseline covariates, including but not limited to: age; sex; APACHE II score; and AIS score.
Primary outcome: 28-day all-cause mortality - logistic, mixed modeling, with terms for trial and site.
Secondary/intermediate outcomes: hospital (censored at 60 days) and six-month mortality - binomial, mixed modeling reported.
Survival analysis: Cox proportional hazards regression if proportionality assumption holds.
Duration of stay (ICU and hospital) will be assessed for normality, appropriate transformation reported as ratios of geometric means, accounting for impact of survivorship.
Subgroup analyses on pre-specified patient groups: isolated TBI, isolated diffuse TBI, isolated TBI with an intracranial mass lesion, multi-trauma with TBI with an intracranial mass lesion, multi-trauma with diffuse TBI, multi-trauma without TBI. To determine if the relationship between treatment and the primary outcome differs between subgroups, fixed interaction terms between treatment and subgroup will be reported. To further ascertain if the treatment-subgroup interaction varied between trials, a three-way fixed interaction between trial, treatment and subgroup will be reported.

Project Timeline:
Project Start: March/April 2016
Analysis Completion: July/August 2016
Manuscript Draft: October 2016
Manuscript Submission: December 2016
Report to Yoda Project: January 2016

Dissemination Plan:
Treatment of trauma patients in the ICU with EPO awaits remains an open question. The results of the proposed individual patient data meta-analysis, if positive, would provide support for obtaining support for a confirmatory trial. It will also provide data that can help to design a trial of EPO in trauma patients The target audiences for the project are trauma and critical care physicians. Suitable journals for submission of the completed project include: JAMA, Critical Care Medicine, Journal of Trauma and Acute Care Surgery, and Lancet.

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