Published in final edited form as:
Curr Treat Options Neurol. 2013 April ; 15(2): 104–112. doi:10.1007/s11940-013-0222-0.

Erythropoietin in the Neurology ICU

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Opinion statement

Erythropoietin (EPO) is an approved drug that is used in the treatment of chronic anemia associated with chronic renal failure. In the Neuro ICU, there are two potential uses for treatment with EPO. Anemia is common in patients with acute neurological disorders and may be a cause of secondary insults. Studies of EPO to treat anemia associated with critical illness have not conclusively shown a beneficial risk/benefit ratio. The relatively small reduction in transfusion requirement with EPO in critically ill patients is likely due to the 7–10 days required to see an effect of EPO on hematocrit. For these reasons, EPO is not recommended to treat anemia of critical illness. Neuroprotection is the other potential use for EPO in the Neuro ICU. Many experimental studies demonstrate neuroprotective effects with EPO in a variety of acute neurological disorders. To date, no clinical studies have confirmed beneficial effects of EPO on neurological outcome although some studies have suggested a reduction in mortality rate in trauma patients treated with EPO. Additional clinical studies are needed before EPO administration can be recommended for cytoprotection in neurological disorders.

Keywords

Erythropoietin; Stroke; Cerebral ischemia; Subarachnoid hemorrhage; Traumatic brain injury; Intensive care unit; ICU; Anemia

INTRODUCTION

Erythropoietin (EPO) is a 165 amino acid protein belonging to type 1 cytokine family with a molecular mass of 30 kDa, and was first discovered by Carnot and DeFlandre in 1906. EPO as a hematopoietic growth factor is responsible for red blood cell production and is primarily made by kidneys in adults and hepatocytes in fetuses. In 1989, recombinant human erythropoietin was proposed and utilized to treat anemic patients with chronic renal failure [1, 2].

Although EPO production is primarily in response to hypoxia and is genetically promoted by hypoxia inducible factor (HIF) family, there has been a body of evidence supporting local production of EPO in various tissues in response to injury or metabolic stress [3, 4]. Following metabolic stress, apoptosis is induced in injured tissue. Apoptosis stimulates destruction of tissue in the vicinity of injured cells and prevents infection from spreading to

Disclosure No potential conflicts of interest relevant to this article were reported.

the other parts. Although this is a favorable biological response during infection, it may do so at the expense of destruction of potentially salvageable tissue around the site of injury. Locally produced EPO following injury may act as an endogenous cytoprotective agent to counteract these tissue destructive processes. In addition, EPO antagonizes the pro-inflammatory activities post injury. Tissue production of EPO following injury is delayed (by hours) and often suppressed by the inflammatory cytokines [5]. Therefore exogenous administration of erythropoietin can be beneficial in patients following metabolic stress, ischemia, and other tissue injuries.

In 1998, Sakanaka et al. provided evidence that EPO (in a dose-dependent manner) protects rodent neurons from ischemia-induced cell death [6]. Subsequently, a number of experimental studies have shown neuroprotective effects with early and delayed administration of erythropoietin in a variety of neurological disorders [7]. During the past decade, different experimental settings and clinical studies have suggested the possibility of EPO as a neuroprotectant in pathologies such as stroke, cerebral ischemia, traumatic brain injury, spinal cord injury, encephalitis, subarachnoid and intracerebral hemorrhage.

The goal of this review is to discuss the current status of EPO neuroprotection and the potential therapeutic efficacy in treating patients with three major types of acute neurological injury: stroke, subarachnoid hemorrhage, and traumatic brain injury. The current role of EPO in treating anemia of critical illness will also be discussed.

EPO Treatment of Anemia of Critical Illness

Critically ill patients commonly develop anemia during the acute recovery period. Anemia after severe brain trauma or other acute neurological disorders is the result of a complex interaction of bleeding, blunted EPO response to low hemoglobin concentrations, inflammatory mediators, and low iron stores. Anemia requires the injured brain to maintain a higher cerebral blood flow to maintain the same level of oxygen delivery. Cerebrovascular dysfunction caused by the brain injury may prevent an adequate increase in cerebral blood flow, which is the normal compensatory mechanism for a reduced oxygen-carrying capacity. Even if cerebral blood flow does increase to maintain cerebral oxygen delivery, the resulting cerebral vasodilatation required to achieve the increase in cerebral blood flow may result in an increased intracranial pressure. For these reasons, anemia is commonly treated as a potential cause of secondary injury.

Because EPO is effective in treating anemia of chronic illness, the use of EPO in anemia of critical illness has been explored in several large clinical trials. Zarychanski et al. have recently published a meta-analysis of 9 clinical trials of Epo in critically ill patients for the treatment of anemia of critical illness [8]. The total combined number of patients in these trials was 3314. EPO administration, compared with placebo, significantly reduced the risk of a patient receiving at least 1 transfusion (OR 0.73, 95% CI 0.64–0.84, I2 = 54.7%). The mean number of units of blood transfused per patient was decreased by 0.41 units in the EPO group (95% CI 0.10–0.74, I2 = 79.2%). The conclusion of this metaanalysis was that the reduction in requirement for red blood cell transfusions was very small and there was insufficient evidence to determine whether this intervention results in clinical important benefits. One possible reason for the small effect of EPO in this clinical setting is that it takes 7–10 days to see the maximum effect of EPO on erythropoiesis. For an acute illness, this timeframe may not be ideal. Use of EPO for the treatment of anemia of critical illness was not recommended in this meta-analysis.

These studies analyzed included patients with acute neurological disorders, but did not specifically examine this possibly more vulnerable subgroup. As a result, the question about

effectiveness of EPO in the treatment of anemia in critically ill neurological patients remains unanswered.

EPO in Stroke

According to the Center for Disease Control and Prevention, stroke remains to be a leading cause of death and long-term disability in the United States. Ischemic strokes are the more common type of stroke (85% of all strokes), most commonly due to occlusion of middle cerebral artery [9]. Recombinant tissue plasminogen activator (rTPA) has been identified as a thrombolytic agent and can be utilized in treatment of ischemic stroke. However, the short therapeutic window of rTPA (4.5 hours), multiple contraindications, and risk of cerebral hemorrhage have motivated scientists to explore other treatment options [10].

In 2000, experimental studies demonstrated that EPO did cross the blood brain barrier in small amounts and showed neuroprotection in a rat MCA stroke model with EPO given within a clinical relevant time window of 6 hours [11]. In 2001, Siren et al. confirmed over-expression of EPO and EPO receptors in the ischemic tissue and peri-infarct regions of the human brain [12]. A year later Ehrenreich et al. published the results of a pilot trial in stroke patients concluding that EPO is safe and may be a potentially efficacious therapeutic option to treat stroke in humans [13].

The major neuroprotective effects of EPO after stroke have been thought to be on apoptosis and on inflammation. But another potential effect of EPO in treatment of ischemic stroke is mobilization of endothelial progenitor cells (EPC) from the bone marrow. EPCs have the ability to differentiate into endothelial cells and the increased expression of EPCs during the acute phase of stroke has been associated with smaller lesions and improved neurological outcome [14]. In a clinical trial conducted by Yip et al. patients who suffered from ischemic stroke received EPO (5000 IU) or placebo 48 and 72 hours following onset of symptoms. Compared to patients who received placebo, the EPO group had increased levels of EPC on day 21 [15]. Moreover, after 90 days EPO treatment associated with a smaller patient population with NIH Stroke Scale scores higher than 8 and reductions in recurrent incidence of stroke [15].

The phase III randomized trial that followed the encouraging pilot study in 2009, however, did not confirm an improved outcome with EPO administration [16]. The primary outcome of the trial which was the Barthel Index on day 90 was similar in the two treatment groups. Instead, there was a significantly higher mortality rate in the patients who received EPO, and a higher rate of intracerebral hemorrhage with EPO administration. These adverse outcomes were most pronounced in patients who received both EPO and rTPA. In a post-hoc analysis of the patients who did not receive rTPA, the EPO treated patients had a significantly better improvement in the NIH stroke scale between days 1 and 90 post-stroke, compared to the placebo treated patients. A subsequent study of serum biomarker profiles in the patients enrolled in the phase III study showed a significantly lower concentrations of glial markers (S100B and glial fibrillary acid protein) and the neuronal marker ubiquitin C-terminal hydrolase over the first 7 days post-stroke [17]. One interpretation of these studies is that the poor overall outcome in the EPO treated group may have been because of an interaction between rTPA and EPO.

To further understand the potential interaction between rTPA and EPO in the laboratory, Zechariah et al. designed a preclinical study to analyze infarct size, brain edema, and blood-brain barrier integrity following an ischemic injury [18]. In this study mice underwent 90 minutes of induced MCA stroke and upon reperfusion, were treated with normal saline or rTPA (10mg/kg). Animals then received normal saline or EPO (2500 IU/kg) immediately after rTPA treatment and 12 hours later. Mice that were treated with EPO exhibited

decreased brain swelling 24 hours after reperfusion, while combination of EPO and rTPA promoted vascular permeability and extracellular matrix breakdown in blood-brain interface. Neither drug resulted in reduced infarct size.

In a different study, Jia et al. investigated the effect of EPO in combination with rTPA on MCA embolic stroke in rats [8]. The rats were given EPO (5000 units/kg) and rTPA (10 mg/kg) at 2 or 6 hours after ischemic insult. Results indicate that the combination therapy at 6 hours did not reduce the ischemic lesion volume and increased the chance of hemorrhage. The increased risk of hemorrhage with the delayed combination therapy was associated with upregulation of NF-κB, matrix metallpproteinase-9, and interleukin-1. In contrast, the combination therapy 2 hours after MCA occlusion reduced the size of ischemic lesion and did not have a substantial effect on brain hemorrhage. This preclinical study suggested that therapeutic window plays a crucial role in efficacy of EPO and its adverse side effects when utilized in combination with rTPA to treat ischemic stroke.

Regardless of the interpretation of these studies, EPO is not recommended in the treatment of stroke. Different strategies have been proposed to both enhance transport of EPO across the blood brain barrier and also minimize these potential adverse systemic effects of EPO. One strategy that may be useful is to administer the EPO through the intranasal route [19]. Other strategies have been to modify the EPO molecule or to develop EPO-like small molecules, which will be discussed later in the review.

Merelli et al. investigated the effects of intranasal EPO on hypoxia and the behavioral outcome of spontaneous motor activity [20]. Focal brain hypoxia was induced via cortical injection of $CoCl_2$ while other rats were injected with sterile saline solution (equal volume as $CoCl_2$). Hypoxic rats treated with intranasal EPO had significantly better open field test performance than rats treated with saline. In addition, intranasal EPO did not increase reticulocyte counts suggesting that the intranasal route of administration may provide neuroprotection without stimulating erythropoiesis.

EPO in Subarachnoid Hemorrhage

Aneurysmal subarachnoid hemorrhage (SAH) is often followed by episodes of vasospasm. Vasospasm causes vasoconstriction of intracranial blood vessels and can result in death due to impaired autoregulation of cerebral blood flow and delayed cerebral ischemia [21]. Manifestations of vasospasm appear several days after onset of SAH and gives a window for prophylactic treatment of patients to prevent vasospasm or alleviate its adverse effects. Currently the calcium channel blocker nimodipine is used to as the prophylactic drug of choice for SAH [22].

A decade ago Grasso et al. investigated the effect of recombinant EPO (rEPO) on SAH-induced in rabbits. Results suggested that systemic administration of rEPO reduced vasoconstriction of basilar artery and improved delayed ischemic deficits as well as neurological outcomes [23]. Springborg et al. showed in a rat model of SAH that a single dose of EPO normalized pressure autoregulation [24]. These preclinical studies provided promising evidence for rEPO as a SAH treatment option.

A small observational study has suggested improvements in brain tissue oxygenation with EPO administration in patients with severe cerebral vasospasm [25]. The sample size of this study was small and there was no control group making the results of this pilot study difficult to interpret.

Tseng and colleagues designed a phase II clinical trial to investigate the effects of EPO in treating cerebral vasospasm and impaired autoregulation [26]. They recruited 80 patients

with aSAH and randomly treated half with EPO (30000 IU) and the other half with isotonic saline. The second and third doses were given every 48 hours following the first dose for a total of 90,000 IU. All patients received oral Nimodipine 60 mg every 4 hours. Treatment with EPO did not result in fewer incidents of vasospasm assessed by daily transcranial Doppler studies. It however reduced the rate of severe vasospasm from 27.5% to 7.5%. Systemic EPO treatment also reduced the occurrence of delayed ischemic deficit from cerebral infarct (40% to 7.5%) and resulted in shorter periods of impaired autoregulation. No long-term neurological improvement was observed.

A phase III clinical trial was initiated based on these encouraging laboratory studies [27]. However the trial was terminated early because of low enrollment. A total of 73 patients were randomized to either EPO (500 units/kg/day for three days) or placebo. Although the study was too small to draw conclusions, no difference in Glasgow Outcome Score at 6 months, which was the primary outcome, or differences in measures of secondary ischemia were observed. A larger phase III trial of EPO is needed to determine the effects in patients with this disorder.

EPO in Traumatic Brain Injury

Since 2000, with the initial study by Brines et al. which showed significant neuroprotection with EPO in a cortical impact injury model in mice, a number of other experimental studies have reproduced these findings in the laboratory [11, 28–32]. Delayed administration of EPO as long as 24 hours after injury has been shown to improve neurological outcome [33].

Because of the promising neuroprotective effects in laboratory models of TBI, the role of EPO in treating traumatic brain injury (TBI) patients has been the topic of many studies in the past few years. Two large randomized clinical trials of EPO (EPO-2 [34] and EPO-3[35]) in critically ill patients showed a significant reduction in 29 day mortality rate in the subgroup of trauma patients within these two studies. Napolitano et al. reported on the patients with traumatic brain injury within the trauma subgroups of these two studies [36]. Of the total 1423 trauma patients enrolled in the EPO-2 study and the EPO-3 study, most had some degree of brain injury, but 456 (32%) had a severe TBI defined by an admission GCS ≤ 8. Mortality rate in those trauma patients with GCS ≤ 8 was 6.6% (15/229) in the placebo-treated group, and 4% (9/227) in the EPO-treated group. This is a subgroup analysis that was not pre-planned, and the analysis does not give information about long-term outcome which might be more important than mortality for patients with TBI.

Talving and colleagues investigated the role of erythropoiesis-stimulating agents in treating patients with severe TBI [37] in a prospective observational study. They studied 566 patients admitted to the intensive care unit with severe TBI during two years. From these patients, 75 patients received weekly administrations of darbepoietin alpha (0.4μg/kg), a synthetic form of erythropoietin, within the first two weeks of hospitalization. The process of patient selection for darbepoietin administration was not randomized and was at the discretion of the attending physician influenced by patient indications (e.g. low grade anemia or renal failure). For comparison, patients who received darbepoietin were matched with 75 patients from the patients who did not receive darbepoietin. The two groups of patients did not differ in complications, including the occurrence of deep venous thrombosis or pulmonary embolism, and did not differ in neurological status judged by Glasgow Coma Scale at the time of discharge. However, the mortality rate was significantly lower in patients with severe TBI who received ESA compared to those in the control group (9.3% vs. 25.3%).

Two clinical trials of EPO are currently ongoing (NCT00313716 and NCT00987454 in ClinicalTrials.gov). NCT00313716 is a phase II trial in severe TBI patients of erythropoietin 500 IU/kg IV given once a week for 3 doses, with the first dose starting within 6 hours of

injury. NCT00987454 is a phase III trial in moderate and severe TBI patients of erythropoietin 40,000 IU SC given once a week for 3 doses. Both trials use Glasgow Outcome Score at 6 months post-injury as the primary outcome.

EPO Derivatives

Most clinical studies with EPO have reported an increased incidence of deep venous thrombosis, and some have reported an increased incidence of other serious thrombotic complications. EPO increases platelet count, alters platelet activity, and reduces bleeding time [38, 39]. These thrombotic adverse effects are due to the erythropoietic stimulating activities of EPO, which are not necessary for the neuroprotective effects [40]. Two strategies have been used to modify the structure of EPO to minimize the erythropoietic effects. One strategy is to shorten the half-life of EPO, since stimulation of erythropoiesis depends on constant blood levels of EPO. The second strategy is to alter the structure so that it no longer binds to the classical EPO receptor.

Erbayraktar et al. described the neuroprotective effects of asialoerythropoietin, a compound that is the EPO molecule modified by total enzymatic desialylation [41]. Asialoerythropoietin has a very short half-life in circulation and does not increase hematocrit, but has significant neuroprotection in cerebral ischemia, spinal cord injury, and sciatic nerve injury [41].

Leist et al. developed another EPO derivative called carbamylated-EPO (CEPO) that has no affinity to bind to the classical EPO receptor and no hematopoietic effects [42, 43]. CEPO also does not have the adverse effects on platelet count or activity [38, 39]. Neuroprotection was observed with CEPO in models of cerebral ischemia, spinal cord compression, diabetic neuropathy, autoimmune encephalomyelitis, and traumatic brain injury [42, 43]. Pilot trials of CEPO have been completed in patients with stroke (NCT00756249, and NCT00870844 in ClinicalTrials.gov).

The receptor binding to CEPO or other similar EPO derivatives has tissue protection capabilities and is thought to be a heterodimer, consisting of two EPO receptors and two beta common receptors (CD131) disulfide linked to each other [44]. Unlike the classical EPO receptor, the proposed neuroprotective receptor has low affinity for EPO and requires significantly higher concentrations of EPO to activate. However, the neuroprotective receptor only requires transient interaction with EPO to initiate biological activities. Contrary to the classical EPO receptor, small amount of EPO is sufficient to activate downstream biological mechanisms associated with the tissue protective receptor.

With this knowledge of the characteristics of the neuroprotective receptor, a series of small peptides have been developed [45]. One of these peptides, called pyroglutamate helix B surface peptide (pHBSP) or ARA 290, is an 11 amino acid peptide and was designed to mimic the tertiary structure of helix B of EPO. pHBSP has a short half-life in the circulation and demonstrates similar cytoprotective effects to EPO. pHBSP has shown to have neuroprotective effects in the setting of sciatic nerve compression, stroke, TBI, and TBI complicated by hemorrhagic shock [45–47]. A small safety study of this peptide has been completed in patients with neuropathic pain. No adverse effects were observed, and a significant reduction in neuropathic pain was reported [48]. Future studies will be needed to establish the role of these small peptides in neuroprotection.

Acknowledgments

Dr. Robertson has received grant support from the National Institutes of Health.

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