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Early High-Dose Erythropoietin Therapy After Out-of-Hospital Cardiac Arrest

A Multicenter, Randomized Controlled Trial

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ABSTRACT

BACKGROUND Preliminary data suggested a clinical benefit in treating out-of-hospital cardiac arrest (OHCA) patients with a high dose of erythropoietin (Epo) analogs.

OBJECTIVES The authors aimed to evaluate the efficacy of epoetin alfa treatment on the outcome of OHCA patients in a phase 3 trial.

METHODS The authors performed a multicenter, single-blind, randomized controlled trial. Patients still comatose after a witnessed OHCA of presumed cardiac origin were eligible. In the intervention group, patients received 5 intravenous injections spaced 12 h apart during the first 48 h (40,000 units each, resulting in a maximal dose of 200,000 total units), started as soon as possible after resuscitation. In the control group, patients received standard care without Epo. The main endpoint was the proportion of patients in each group reaching level 1 on the Cerebral Performance Category (CPC) scale (survival with no or minor neurological sequelae) at day 60. Secondary endpoints included all-cause mortality rate, distribution of patients in CPC levels at different time points, and side effects.

RESULTS In total, 476 patients were included in the primary analysis. Baseline characteristics were similar in the 2 groups. At day 60, 32.4% of patients (76 of 234) in the intervention group reached a CPC 1 level, as compared with 32.1% of patients (78 of 242) in the control group (odds ratio: 1.01; 95% confidence interval: 0.68 to 1.48). The mortality rate and proportion of patients in each CPC level did not differ at any time points. Serious adverse events were more frequent in Epo-treated patients as compared with controls (22.6% vs. 14.9%; $p = 0.03$), particularly thrombotic complications (12.4% vs. 5.8%; $p = 0.01$).

CONCLUSIONS In patients resuscitated from an OHCA of presumed cardiac cause, early administration of erythropoietin plus standard therapy did not confer a benefit, and was associated with a higher complication rate. (High Dose of Erythropoietin Analogue After Cardiac Arrest [Epo-ACR-02]; NCT00999583) (J Am Coll Cardiol 2016;68:40–9)

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Cardiac arrest patients frequently have post-anoxic brain damage, even when the initial resuscitation is successful. This brain injury is either transient or definitive, and represents the major cause of death in these patients (1). Of importance, this brain injury continues even after restoration of cerebral perfusion and oxygenation, in a process known as reperfusion injury. In recent years, evidence of further cerebral damage occurring during this reperfusion phase encouraged intense research aiming to limit the worsening of these neurological lesions. To date, despite numerous attempts, no drug has demonstrated its ability to reduce the consequences of cerebral anoxo-ischemia after out-of-hospital cardiac arrest (OHCA) (2–4). Currently, apart from targeted temperature management, no other treatment is recommended to mitigate the consequences of cerebral ischemia-reperfusion due to cardiac arrest.

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The main role of erythropoietin (Epo) is to support erythropoiesis, leading to the use of analogs of this hormone for many years to prevent anemia in different pathological conditions. However, the biological activity of Epo is not restricted to regulation of erythropoiesis. The survival and proliferative activities of Epo that are required for red blood cell formation appear to extend to other Epo receptor–expressing tissues, resulting in Epo protective activity associated with stress or ischemia in nonhematopoietic tissue, such as heart and brain (5). Numerous pre-clinical data suggested a tissue protective effect of Epo and analogs in various experimental models, particularly after brain and myocardial damage related to ischemia-reperfusion stress (6,7). Nevertheless, results obtained in humans, in both acute myocardial infarction and stroke, were disappointing (8,9). In the setting of whole-body ischemia due to cardiac arrest, experimental research showed promising results, and a pilot clinical study showed that early treatment with a high dose of an Epo analog was feasible in conjunction with mild hypothermia (10).

We hypothesized that early administration of a high dose of epoetin alfa, an Epo analog, could improve the neurological outcome of post-cardiac arrest patients still comatose after resuscitation in comparison with standard treatment.

ABBREVIATIONS AND ACRONYMS

AMI = acute myocardial infarction

CPC = Cerebral Performance Category

CSF = cerebrospinal fluid

Epo = erythropoietin

ICU = intensive care unit

OHCA = out-of-hospital cardiac arrest

PCI = percutaneous coronary intervention

ROSC = return of spontaneous circulation

SAE = serious adverse event

METHODS

The EPO-ACR-02 (High Dose of Erythropoietin Analogue After Cardiac Arrest) trial was a multicenter, phase 3, randomized, single-blind, controlled trial that evaluated the safety and efficacy of a high dose of Epo in patients resuscitated from a cardiac arrest. The study was performed between October 2009 and July 2013 in 20 French hospitals. In all participating centers, an emergency team (with at least 1 emergency physician) performed out-of-hospital resuscitation, and patients were then referred to a corresponding hospital with all of the facilities required to manage post-cardiac arrest patients. The study received ethics committee approval by CPP Ile de France III, Paris-Tarnier Cochin, Paris (France). The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practices, and adhered to French regulatory requirements. When possible, written informed consent was obtained from patient surrogates before study enrollment. According to French law, in the case of impaired decision-making capacity without any surrogate at the time of inclusion, the patient's written informed consent could be obtained after enrollment.

ELIGIBILITY CRITERIA, RANDOMIZATION, AND STUDY MEDICATION. Patients who achieved a sustainable return of spontaneous circulation (ROSC) were screened for participation in the study. The following

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