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Can local Erythropoietin administration enhance bone regeneration in osteonecrosis of femoral head?

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**Abstract**

Osteonecrosis of the femoral head (ONFH) is a challenging disease. Regardless of underlying causes, the ultimate result in all cases is disruption of femoral head blood supply. Once the disease starts, it is progressive in 80% of cases. Since the majority of the affected individuals are young, every effort should be focused on preserving the patients own femoral head. These years, the role of angiogenic growth factors has been investigated with promising results in animal models of ONFH. Erythropoietin (EPO) is a well known hormone that has been used in treatment of chronic anemia for many years with few side effects. Considering the angiogenic properties of EPO, we hypothesize that local delivery of recombinant human EPO during core decompression will enhance bone regeneration in ONFH. In this way we also can avoid systemic side effects of EPO.

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**Introduction**

Osteonecrosis of the femoral head (ONFH) is a debilitating and relatively common disease. Annually 10,000–20,000 new cases are diagnosed in the United States [1]. This disease is more common in the third and fourth decade of life [2] and affects predominately men [3]. The disease can be idiopathic or secondary to an underlying systemic disease. Some well known secondary etiologic factors are trauma, steroid intake, excessive alcohol use, systemic lupus erythematosus, hemoglobinopathies and dysbarism [4]. The pathophysiology of the ONFH has not yet been discovered precisely; however, it has been suggested that the pathophysiology of the disease is multifactorial [5]. This means that in addition to environmental factors, genetic predisposition may also play a role in pathophysiology of the ONFH. Whatever be the cause, disruption of the femoral head blood supply occurs in all cases with ONFH [6]. Occlusion of the femoral head microvasculature occurs secondary to either intravascular thrombi or extravascular compression [7]. Consequent ischemia will result in of the femoral head necrosis [8]. Once the process begins, it will progress in 80% of cases [9] and femoral head collapse and hip osteoarthritis will eventually occur in the majority of cases [1]. In this stage, the only definitive treatment is joint replacement. Since most of the patients are young individuals, a considerable number of these patients will need revision surgeries in future. Even if the disease is diagnosed in early stages, few options with limited efficacy are available to prevent progression of the ONFH [5].

The most common surgical procedure which is performed in early stages of disease is core decompression [5]. The goal of the procedure is restoration of blood supply to the femoral head via reducing intraosseous pressure [10]. The outcome of core decompression in small, precollapse lesions is better than larger, more advanced ones [5]. In order to increase the likelihood of success, some surgeons combine core decompression with nonvascularized [11] or vascularized [12] bone grafts.

In recent years, angiogenic factors have been used in experimental models of ONFH with promising results [13]. Angiogenic factors that have been mostly studied are vascular endothelial growth factor (VEGF) [14], fibroblast growth factors (FGFs) [15], and hepatocyte growth factor (HGF) [16].

VEGF is a potent angiogenic factor that has a critical role in bone formation and bone healing [17]. In addition to angiogenesis, it attracts mesenchymal stem cells to the bone repair site. It also has shown that VEGF helps osteoblast differentiation [18]. FGFs are another group of polypeptides that have an essential role in angiogenesis and bone formation [15]. In an animal study using adult rabbits, Kuroda et al. have shown that a single injection of recombinant human FGF-2 microspheres into femoral head promotes regeneration of the necrotic bone [19]. HGF is also a very potent angiogenic factor. Wen et al. suggested that the combination of core decompression and transplantation of HGF transgenic autologous bone marrow stromal stem cells improves angiogenesis and bone regeneration in an animal model of the ONFH [16].

Although the clinical application of these angiogenic factors seems appealing, they are not without complications [20]. It has been shown that VEGF increases vascular permeability [21] and
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thus theoretically worsens the intrasosseous pressure [16]. FGF also leads to vascular smooth muscle proliferation which may cause arterial obliteration [16].

Hypothesis

Erythropoietin is a hormone that has been used in the treatment of anemia, especially in end stage renal disease, for more than two decades and its angiogenic effects have been well demonstrated [22].

Given the role of angiogenic growth factors in bone regeneration, we hypothesize that local administration of recombinant human erythropoietin (rEPO) along with core decompression surgery will enhance angiogenesis and bone regeneration in the early stages of ONFH.

Evaluation of the hypothesis

The kidney secretes EPO and its main role is to stimulate the production of red blood cells [23]. Recent studies have found other roles for erythropoietin such as cytoprotective effects on non-erythroid cells [24]. In addition, it has been suggested that EPO has angiogenesis properties [22,25]. EPO can induce angiogenesis either directly or via VEGF [26]. It has been shown that EPO has an important role in all stages of neovascularization including migration and proliferation of endothelial cells and vascular tube formation [27]. Del Peso et al. have shown that EPO treatment in peritoneal dialysis patients results in elevated serum level of VEGF which is a potent angiogenic growth factor [28]. The angiogenesis role of EPO has been investigated in several tissues.

Intracardiac injection of EPO in a rat myocardial infarction model reduced infarct size and increased capillary density [29]. Galeano et al. demonstrated that systemic EPO administration promotes burn wound repair by enhancing angiogenesis [30]. In another study by Hamed et al. it was suggested that topical administration of EPO cream accelerates wound healing in diabetic rats [31]. They proposed that EPO enhances angiogenesis, VEGF and collagen synthesis, and inhibits apoptosis.

Additionally, it has been shown that EPO has bone regeneration/formation properties [32]. Holstein et al. studied the effects of intraperitoneal erythropoietin injection on femoral fracture healing in mice. They reported that callus formed in erythropoietin group was more resistant against torsional forces [33]. In another study by Holstein et al. using a femoral segmental defect model in mice, it was demonstrated that EPO stimulates bone formation, cell proliferation, and VEGF-mediated angiogenesis [34]. The callus density in EPO-treated animals was higher 2 weeks after fracture.

As mentioned before, occlusion of microvasculature of the femoral head contributes to pathogenesis of ONFH [6]. On the other hand, systemic administration of EPO induces erythropoiesis and consequently increases RBC mass and blood viscosity which will deteriorate further blood supply to the femoral head [35]. Moreover, systemic administration of EPO is associated with other serious side effects such as hypertension and thromboembolic events [36]. In order to decrease the incidence of these side effects, local delivery of EPO has been suggested [37]. Kobayashi et al. utilized an EPO-gelatin hydrogel drug delivery system to the surface of the infarcted area of the rabbit heart [38]. They reported that the infarct size was decreased in EPO-delivered animals while no systemic side effects were observed.

Consequences of the hypothesis and discussion

ONFH is responsible for 5–18% of all total hip arthroplasties (THA) annually performed in the United States [1]. However, THA is not an ideal treatment for young individuals who consist of the majority of ONFH cases [39]. Early diagnosis of ONFH will give the opportunity for performing core decompression; however, in a considerable number of cases, the outcome of this procedure is unpredictable. Combining the core decompression procedure with modalities that improve angiogenesis and osteogenesis may increase the success rate of core decompression [8,40]. Among the long list of angiogenic agents, EPO may be distinguished from other agents because it has both potent osteogenic and angiogenic properties. Therefore, local delivery of EPO during core decompression in patients with early stage ONFH may increase success rate of the procedure. To prove this hypothesis, an animal model of ONFH should be used in which EPO drug delivery devices implemented in femoral head during the core decompression surgery.

Conflict of interest statement

None.

References


