Editorial

Cytokines, granulocyte-monocyte colony stimulating factor, interleukin-3 and erythropoietin: Can be a therapeutic option for the stimulation of hematopoietic progenitor cells in trauma-hemorrhagic shock?

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Hemorrhagic shock (HS) is the major leading cause of death after trauma,[1] condition with a limited therapeutic option. Fluid, blood, and its component and stopping of bleeders have been the cornerstone of management since many decades. A Recent study showed that recombinant human activated protein C, interleukin-1 (IL-1) receptor antagonist, anti-tumor necrosis factors (TNF) or anti-lipopolysaccharides agents, or tight glycemia control were tested for treatment of HS. However, these treatments were not effective and sometimes dangerous.[1] Finfer *et al*. reported that resuscitation with fluids and blood products induces reperfusion ischemia due to the production of reactive oxygen species and activation of immune cells.[2] The excessive release of inflammatory cytokines contributes to the tissue damage. The present study has shown that HS-induced inflammation leads to drastic changes in active cytokine milieu. Pro- and anti-inflammatory cytokines (TNF-α, IL-6, IL-10, and IL-8) and monocyte chemoattractant protein-1 are thought to be an important role in immune dysfunction resulting multi-organ failure (MOF) and death.[3] It also causes hematopoietic progenitor cells (HPCs: Colony forming unit [CFU-E], burst forming unit [BFU-E], CFU-granulocyte-monocyte/macrophage [CFU-GM]) apoptosis which leads to MOF, following severe injuries and HS in human and animal models.[4,5]

Robinson *et al*. reported that elevated levels of TNF-α bind to the receptor on bone marrow (BM) which activates caspase-8 leading to apoptosis in severe trauma,[5] but there are more pathways associated with impaired erythropoiesis.[6] Maturation of erythroid progenitor cells was inhibited IL-1, IL-6, IL-8, and transforming growth factor-β in severe trauma.[4,5] The previous study showed TNF-α and interferon-γ (IFN-γ) cytokines associated with HPCs apoptosis. Suppressive effects were observed in cultures supplemented with the combination of both cytokines than in cultures treated with IFN-γ or TNF-α alone.[7] Previously study reported that chronic inflammation had a negative impact on the maturation of erythroid progenitors in a mouse model. HPCs apoptosis is a multifactorial process. Previous studies showed that BM failure was associated with

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impaired growth of HPCs and stromal cells following animal and human studies.[8] The previous study has shown that when peripheral blood HPCs were grown in methylcellulose media. It increased in severely injured patients when compared to normal volunteer (15 ± 26 vs. 3 ± 1, <0.05).[4] Impaired HPCs are clinically associated with persistent anemia and are susceptible to infection, sepsis, and MOF.[4,5]

Hematopoietic stem cells (HSCs) are the blood cells derived from mesoderm. Previous studies have demonstrated that HSCs had regeneration capacities and committed to multipotent, oligopotent, and unipotent progenitors. Self-renewal of HSCs is thought to occur in the stem cell niche. HPCs microenvironment is controlled by a complex interplay between intrinsic signals surrounding by BM microenvironment.[5] Liu *et al*. observed that erythropoiesis is physiologically regulated by a balance between apoptosis and proliferation of BM stem cells.[9]

Erythropoietin (EPO) induces erythropoiesis by promoting proliferation and differentiation of HPCs through the CFU-E. A Recent study showed that recombinant human EPO and other erythropoiesis-stimulating agents have been used for a treatment of anemia occurs following critically ill patients.[10] Previous studies reported that IL-3 and GM-colony-stimulating factor (CSF) are also promotes the proliferation and differentiation of HPCs.[11] The Studies have shown EPO act as an anti-apoptosis, neuroprotective, anti-inflammatory, and angiogenesis. HS animal study demonstrated that protection of renal function, liver, and neuromuscular injury in pretreatment group (EPO before day 3 before induction of HS) when compared pretreatment with placebo (phosphate buffer saline before day 3 before induction of HS). In human studies, tibiofibular fractures treatment with EPO helped to accelerate healing. Livingston *et al*. studied the behavior of peripheral and BM HPCs growth at various time intervals. Suppressed HPCs growths were observed without reactivation.[4,12]

Some previous studies suggested that hematopoietic growth factors (EPO, IL-3, and GM-CSF) stimulate the proliferation and differentiation of HSCs in BM. In addition, IL-3 stimulates the proliferation of all cells in the myeloid lineage (GMs, and dendritic cells), in conjunction with other cytokines, EPO, GM-CSF, and IL-6.[13] Wang *et al*. demonstrated that IL-3 and steel cell factor (SCF) have synergistic effect with EPO on the proliferation and differentiation and apoptosis of erythroid progenitor cells in mice model. IL-3, EPO and SCF act as antiapoptotic results inhibit Bcl-2 family such as Bcl-2 and Bcl-xl[14] Previously, studies demonstrated that increased HPCs compartments using a combination of SCF + IL-3 + IL-6 (S36).[15] Combinations of cytokines (FL, MGDF, EPO, and G-CSF), associated with a basic cocktail of S36, to stimulate all hematopoietic compartments.[16] Vassiliou *et al*. demonstrated that administration of EPO with GM-CSF enhanced the liver regeneration after hepatectomy in rats.[17] Lemoli *et al*. demonstrated that combination of IL-11 with SCF, IL-3, or GM-CSF, in the presence of EPO, resulted in a synergistic, or additive increase in the number of CFU cells.[18]

The author feels EPO, GM-CSF, IL-3 may have a therapeutic option for the proliferation and differentiation of HPCs in T/HS. The effect of EPO, GM-CSF, IL-3 alone and conjugation with EG3 (EPO + GM-CSF + IL-3) on HPCs growth in T/HS can be studied.

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