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, a 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. 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. 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. 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. 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, but there are more pathways associated with impaired erythropoiesis. Maturation of erythroid progenitor cells was inhibited IL-1, IL-6, IL-8, and transforming growth factor-β in severe trauma. 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. 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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How to cite this article: Kumar M, Bhoi S. 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?. Indian J Crit Care Med 2016;20:207-9.
impaired growth of HPCs and stromal cells following animal and human studies.[9] 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.[43]

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, MGFDF, 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 heptectomy 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.

References


