

Pulsed Electromagnetic Field as a Non-Invasive Alternative or Complementary Treatment in β -Thalassemia

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ABSTRACT

Today, the usual treatment for patients with β -thalassemia is regular blood transfusions and iron chelating therapy. However, iron chelation may be related to undesirable outcomes. Recently, two main therapeutic methods have been performed; the gene therapy and the induction of fetal hemoglobin (HbF). However, de novo production of clinically applicable levels of adult Hb (HbA) is difficult. In consideration of the above, new approaches aiming the treatment of patients with severe β -thalassemia are greatly needed. Due to the fact that transduction with transcription factors such as KLF1 and BCL11A-XL can stimulate β -globin expression and based on the ability of pulsed electromagnetic field (PEMF) to stimulate specific genes transcription and overexpression, we hypothesize that PEMF exposure can activate cell stress signaling pathways that result in β -globin expression which is a cell stress response gene. This considered to be a non-invasive, low-cost and non-cytotoxic treatment approach and represents a small, but significant, step towards this goal

Abbreviations: HbF: Fetal Hemoglobin; PEMF: Pulsed Electromagnetic Field; KLF1: Krueppel-Like Factor 1; BCL11A: B-Cell Lymphoma/Leukemia 11A; HS: Heat-Shock; SCX: Specific Gene Transcription Scleraxis; VEGF: Vascular Endothelial Growth Factor; DPN: Diabetic Peripheral Neuropathy; HBMSCs: Human Bone Marrow Stromal Cells; Ocn: Osteocalcin; MSCs: Mesenchymal Stem Cells; AD: Alzheimer's Disease; PBMCs: Peripheral Blood Mononuclear Cells; TCs: Tendon Cells

Mini Review

β -thalassemia is a monogenic disease that will be caused by β -globin faulty synthesis and represents a global health problem. According to the WHO, the carrier rate of β -thalassemia is around 1.5% of the world population [1]. The usual treatment for patients with β -thalassemia is based on regular blood transfusions and iron chelation therapy. Despite all of the progress made in this field, transfusion therapy is linked with serious complications and requires iron chelation therapy, which causes undesirable effects and scarce compliance. In comparison to traditional methods, therapeutic approaches such as gene therapy have recently drawn more attention for the treatment of β -thalassemia [2]. It was

shown that by increasing the level of transcription factors such as Krueppel-like factor 1 (KLF1) and B-cell lymphoma/leukemia 11A (BCL11A) in K562 cells, a prominent increase in β -globin levels with the resultant level equivalent to that of adult cells can be achieved [3]. Experiments in K562 and KU812 cells also proved that stress signals such as heat-shock (HS), UV- and X-irradiation and osmotic shock can increase γ -globin mRNA and fetal hemoglobin (HbF) levels in differentiating primary human erythroid cells, but only after 3-5 days of treatments [4].

Another stimulant like pulsed electromagnetic field (PEMF), a safer approach compared to other mentioned methods showed

to be a suitable treatment strategy for inflammatory and tissue-specific gene expression related conditions such as Alzheimer, arthritis, bacterial infection and wound healing in diabetic cases and its results demonstrated a significant improvement in the treatment of the patients [5]. The other effects of PEMF are its role in promoting angiogenesis in bone marrow by the overexpression of angiopoietin-2 mRNA [6], and up-regulation of osteogenic factors in human calvarial bone cell cultures which are critical factors in fracture healing [7,8]. It also can increase tendon-specific gene transcription scleraxis (SCX) (+95 %) and type I collagen (COL1A1) (+97 %) in human tendon cells culture model [9]. Angiopoietin-2 up-regulation which caused by PEMF treatment can promote endothelial cell migration by loosening their intercellular contacts, and fibroblast growth factor-2 in the mice bone marrow. These findings suggest that PEMF induces an angiogenesis-prone environment in the bone marrow without having invasive effects including the induction of hypoxic conditions or inflammation [6].

Dose-dependent upregulation in the expression of SCX, and COL1A1 after PEMF treatment of tendon cells (TCs) is particularly important since PEMF stimulates cell proliferation with a consequent positive effect on tendon recovery. The other observation after PEMF treatment is a small, but significant, increase of IL-1 β [9]. IL-1 β induces the production of IL-6, a multifunctional Th2 cytokine which exhibits immunoregulatory functions in tissues and plays an essential role in tissue healing, as it is involved in cell proliferation and survival [9,10]. Thus, the increase of IL-6 correlates with the amount of cell viability and proliferation observed after PEMF treatment. On the other hand, IL-6 also has a stimulatory effect on IL-10 production [9]. IL-10 is not only the most effective anti-inflammatory Th2 cytokine but it also affects connective tissue cells such as fibroblasts and chondrocytes [11]. In tenocytes, upregulation of IL-10 correlates with the healing increase in murine models [12]. The role of IL-10 in tissue repair involves the regeneration of extracellular matrix, especially in elevating elastin [13] and a significant increase in the vascular endothelial growth factor (VEGF). This is in accordance with the observed increase of IL-6, which is the main vascular endothelial growth factor (VEGF) promoter [9].

PEMF promotes angiogenesis in bone marrow, by the overexpression of angiopoietin-2 mRNA [6]. Thus, PEMF positively influences proliferation, tendon-specific marker expression, and the release of anti-inflammatory cytokines and angiogenic factor in a healthy human TCs culture model in a dose-dependent manner [9]. Diabetic peripheral neuropathy (DPN) studies in animal models, demonstrated that the restitution of nerve function induced by PEMF stimulation will lead to down-regulation of VEGF. This down regulation, in turn, causes less damage to peripheral nerve fibers. It is suggested that PEMF might have direct corrective effects in relieving peripheral neuropathic symptoms in diabetic rats with DPN [14]. PEMF stimulation of human bone marrow

stromal cells (HBMSCs), in lumbar spinal fusion, affects cell cycle regulation, cell structure, and growth receptors or kinase pathways. In the differentiation and mineralization stages, PEMF regulated preosteoblast gene expression, the growth factor-beta (TGF- β) transformation signaling pathway and microRNA 21 (miR21) activity are highly regulated.

PEMF can affect bone metabolism by activation of the TGF- β signaling pathway and stimulation of microRNA 21-5p (miR21-5p) expression in human bone marrow stromal cells (HBMSCs) [15]. In the process of bone lesions repair, PEMF stimulation alone is able to motivate the expression of osteogenic genes that can lead to the higher expression levels of the osteocalcin (Ocn) mRNA in mesenchymal stem cells (MSCs) followed by MSCs proliferation. PEMFs also affect the molecular currents and cause a specific transmembrane signaling which will promote osteogenic differentiation [16]. PEMF is able to modulate both microRNA (miRNAs) that functions in RNA silencing and post-transcriptional regulation of gene expression and mRNA that is involved in the Alzheimer's disease (AD) related pathways, which will lead to the rebalancing of the pathways' deregulation occurring in the AD. In an ex vivo human peripheral blood mononuclear cells (PBMCs) study, a quantitative reduction of β -secretase, following by PEMF exposure, confirmed the protective role of the electromagnetic field whose action would counteract the formation of β -amyloid.

Expression values of miR-107 and miR-335-5p that are the negative regulator of enzyme beta-secretase 1 (BACE1) and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, respectively decrease after PEMF exposure, and the same trend can be observed for the expression of miR-26b-5p, which is involved in brain signaling and synaptic plasticity. This possible effect of PEMF exposure confirms the capacity of the electromagnetic field to stimulate both tissue regeneration and brain signaling [17]. According to previous studies, cell stress signals induce γ -globin gene expression and this induction is a part of physiological stress response in erythroid cells [4]. It was shown that K562 cells and erythroid cells from cord blood progenitors in comparison to the adult cells have absent or lower levels of both KLF1 and BCL11A that are essential in the β -globin expression. These types of cells also express predominantly (mainly) γ , with a low level of β -globin. There are increasing data to show that KLF1 also regulates many other erythroid genes and hence plays a critical and central role in erythropoiesis [3].

Since the current conventional drugs and surgical procedures do not have the ideal combination of efficacy, safety, and ease of use, PEMF therapy can be a good choice for complementary treatment in β -Thalassemia because it is a noninvasive, low-cost, non-cytotoxic treatment which causes significantly lower discomfort compared to conventional therapy and there are few known risks associated with the use of PEMF therapy [5]. Regarding the important role of cell stress in γ -globin gene induction and based

on the ability of PEMF to stimulate specific gene transcription and overexpression, we hypothesize that PEMF exposure can activate cell stress signaling pathways that result in β -globin expression which is a cell stress response gene. For proving this hypothesis, at first the PEMF different dosing parameters has to be studied, such as the intensity, the frequency and the burst width/wait, the pulse width/wait, the pulse rise and the fall time, duration of PEMF application and the distance of magnetic surface from targeted cell or tissue. The obtained information can help to optimize and standardize experimental protocol, to increase KLF1 and BCL11A level, effectively. This increase can elevate the β -globin expression and finally might be effective in the β -Thalassemia treatment. Our remark favorites the utility of PEMF as a physical stress to increase β -globin gene expression in erythroid cells for in vitro and or in vivo experiments in the future.

Conclusion

The usual treatment for β -thalassemia that is a combination of blood transfusions and iron chelation therapy has severe side effects that make it necessary for patients to use other medications and procedures like iron chelation therapy. In the pursuit of alternative treatment studies have shown that using heat-shock (HS), UV- and X-irradiation therapy can trigger stress signals that will cause a chain of reaction to activate transcription factors such as KLF1 and BCL11A-XL. These signals can stimulate β -globin production. Other alternatives like pulsed electromagnetic field (PEMF) might provide a better approach. It was shown in multiple studies that PEMF can cause different effects in patients including healing based on promoting angiogenesis in the bone marrow tissue, immunoregulatory functions based on IL-1 β , IL-6, and IL-10 production and up-regulation of osteogenic factors and genes like SCX, COL1A.

It also proves to be effective in restitution of nerve function in DPN studies to relieve peripheral neuropathic symptoms and HBMSCs stimulation via TGF- β signaling pathway and miR21 activity. Other studies also showed promising therapeutic effects of this treatment on both tissue regeneration and brain signaling. Since all of these effects were reported without having side effects such as the induction of hypoxic conditions or inflammation and based on its noninvasive, low-cost, non-cytotoxic nature, we hypothesize to use it for activating cell stress signaling pathways to initiate and increase β -globin expression as a cellular stress response gene. This objective will need future studies to evaluate its effectiveness in thalassemic patients and also provide information to optimize and standardize its experimental protocol.

Conflict of Interest

The authors declare that they have no conflict of interest.

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