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Mini Review

Synergistic Effects of Hyperbaric Oxygen Combining with Platelet Rich Plasma on Bone Defects Repair: A Mini-Review

Chen TL[1]*, Wang SF[2]*, Zhang XH[1], Chen J[1] and Liu J[1]

[1]Department of Periodontal, Oral Center of PLA, Affiliated Changhai Hospital, Second Military Medical University, Shanghai, China

[2]Department of Diving Medicine, Naval Medical Center, Second Military Medical University, Shanghai, China

***Co-first author. Corresponding author:** Tie-Lou Chen, Department of Periodontal, Oral Center of PLA, Affiliated Changhai Hospital, Second Military Medical University, Shanghai, China, E-mail: chentielou2010@163.com (Chen TL)

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Abstract

Platelet-Rich Plasma (PRP) is an autologous concentration of platelets in a small volume of plasma. Most of growth factors released while PRP activated. The majority of publications showed a significant enhancement of tissue damage healing when PRP used. Hyperbaric Oxygen (HBO) therapy can increase collagen synthesis, improve bone defect repair. However, the really effects and the detailed mechanism of HBO combining with PRP on bone regeneration is unclear. Therefore, we write the mini-review manuscript to study the effects and mechanism of HBO combing with PRP to induce bone regeneration for repairing bone defects to provide evidence for clinical application.

Keywords: Hyperbaric oxygen; Platelet rich plasma; Growth factors; Bone regeneration; Mechanism; Wound healing

Introduction

Periodontal bone defect and maxillofacial defects are the most common condition. And it is still a difficult problem to be solved in clinic. Although there are many treatments for bone defects, including bone grafts and implants of different biomaterials, but none has proven to be fully satisfactory. Therefore, it is of great significance to study the techniques and methods of bone defect repair. Platelet Rich Plasma (PRP) is an autologous concentration of platelets in a small volume of plasma, and literature report a significant enhancement of bone healing when PRP is used. Hyperbaric Oxygen (HBO) consists of intermittent inhalation of 100% oxygen under a pressure higher than 1.5 atmospheres absolute, HBO can accelerate bone regeneration and collagen synthesis to improve bone defect repair. Moreover, HBO has a certain effect on bone injury caused by decompression sickness. While the use of PRP combined HBO in bone defects has been reported in a literature [1], the detailed effects and mechanisms remain unclear. Therefore, it is very important to investigate the projects how does HBO combing with PRP to improve bone regeneration.

Effects of PRP on bone regeneration

While tissue damaged, the platelet activated to secrete growth factors to play prominent role in wound healing. Newly formed bone densities were found to be higher in PRP group, and PRP can improve newly bone formation and bone healing of rabbit critical-size bone defects [2]. Belli E, et al [3] showed that combination PRP and bovine derived hydroxyapatite xenograft can improve the remineralization rates in the region of bony defect. The graft viability and blood perfusion was higher, and the number of CD31+ blood vessels and Vascular Endothelial Growth Factor (VEGF) expression were significantly increased in PRP group. PRP enhanced revascularization, graft survival and blood flow of the graft [4].

During the early phases in wound healing, platelets participate in initiating repair by forming a provisional fibrin scaffold that allows cell migration to the tissue defects. In later phases, platelets support the recruitment, differentiation, and cross-talk of cells by releasing bioactive factors [5]. Normally, surgeons activated platelets with thrombin and/or calcium to induce the immediate and full release factors to play biological effects [6]. When PRP activated, more than 70% of preserved growth factors released within 10 minutes [7]. Chen TL [8] showed that PRP increased the amount of mitochondria and rough endoplasmic reticulum in osteoblasts, and increased concentration of alkaline phosphatase.

The mechanism of PRP on bone regeneration is not clear. When PRP activated, the platelets released growth factors into the extracellular matrix, which interact with surface receptors on the target cells, activating an intracellular metabolic pathway to induce transcription of the proteins. Platelet derived growth factor has a chemotactic activity for fibroblasts to promote collagen and protein synthesis [9]. In addition, the expression of platelet glycoprotein Ib and proteinase-activated receptors regulates the balance of pro- and antiangiogenic growth factors from platelets [10].

Effects of HBO on bone regeneration

HBO can accelerate tissue repair, and increase collagen synthesis and the mobilization of Endothelial Progenitor Cells (EPC) from the bone marrow into peripheral blood [11]. HBO accelerated the rate of osteoblast differentiation, and increased alkaline phosphatase activity and expression of type I collagen and Runx-2 mRNA during the early stages of culture. HBO augmented bone nodule formation in hypoxic conditions, and induced bone reconstruction [12]. HBO significantly increased the mineral apposition and bone formation rates and alkaline phosphatase mRNA expression. The fracture callus was significantly larger, and the femur stiffness and maximum load were higher in HBO group. HBO enhanced bone anabolism, accelerated fracture healing and improved bone repair process without causing oxidative DNA damage and disruption of plasma calcium homeostasis

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[13]. HBO treatment accelerated the initial events of bone healing, improved bone neoformation, and increased expression of Runx2, reduced inflammation [14]. HBO significantly increased the mast cell population and improved early bone regeneration in diabetic rats, and reduced the effect of diabetes on bone regeneration [15]. Liao J, et al. [16] showed that the mean values of bone ingrowth fraction and the percentage of bone area were higher. Bone tissue around the implant in HBO group has more osteoblasts, and many irregular marrow cavities and Haversian bone plates in the new bone tissue [17].

HBO is used to treat or prevent tissue necrosis in patients undergoing irradiation. The defects treated with HBO exhibited greater numbers of cells positive for the CD31, up-regulated gene expression of osteogenic markers, and down-regulated expression of pro-inflammatory cytokines. HBO stimulated vascularization and bone formation and exhibited a higher percentage of radiopacities than normobaric controls in rat calvarial defects [18]. Jan A, et al. [19] showed HBO treatment reduced the amount of fibrous tissue in biphasic calcium phosphate filled defects, and increased new bone. The residual graft volume significant reduced in the HBO group. HBO enhanced bony healing in ungrafted rabbit calvarial defects [20]. There was no significant difference between the percentage of new bone forming in the 15-mm and 18-mm HBO-treated defects. HBO is effective in enhancing bony healing of critical sized as well as supraecritical-sized defects in the rabbit calvarial model [21]. HBO increased the diameter of the rabbit critical-sized calvarial defect to more than 18 mm, and had a beneficial effect on irradiated mandible [22].

Okubo Y [23] showed that the local tissue alkaline phosphatase activity and calcium content in the HBO group were significantly greater. HBO accelerated the activity and rate of osteoinduction by rhBMP-2, and HBO treatment once a day can accelerate bone repair and vessel ingrowth, but the HBO treatment twice a day can slow the process [24]. The new bone area was higher and the residual material area decreased in the HBO group. HBO combined with PTH can improve radiation-induced bone injury [25]. HBO improved kinetics of blood count recovery of the patients undergoing Umbilical Cord Blood (UCB) transplantation. Mucositis incidence was significantly lower in the HBO group [26]. HBO improved crosslink maturation and increased maximum strength and stiffness in the femur diabetes animals [27].

The mechanism of HBO on bone regeneration is unclear. According to the current data, HBO contributes to wound healing by increasing fibroblasts proliferation, collagen synthesis, and production of growth factors, inducing angiogenesis and inhibiting antimicrobial activity. Sunkari VG [28] showed that HBO activated hypoxia-inducible factor 1 (HIF-1) α by increasing both HIF-1α stability and activity, and activated HIF-1 can increase cellular proliferation. The CD34+ cell population contained 2 to 3-fold higher levels of HIF-1, -2 and -3, as well as thioredoxin-1 when HBO used in neuropathic ulcers. HBO is known to mobilize bone marrow stem cells by stimulating Nitric Oxide Synthase (NOS) and NOS increased in platelets following HBO and remains for 20 hours. HBO increased nitric oxide levels through activating NOS to improve EPC mobilization from bone marrow to the peripheral blood to stimulate vessel healing [29]. Benincasa JC [30] showed that the endothelial NOS expression increased after HBO treatment, and intercellular cell adhesion molecule expression and reactive oxygen species production decreased. HBO decreased the inflammatory response in endothelial cells mediated by TNF-alpha to promote vascular recovery after injury, and enhanced biomineralization with an increase in bone nodule formation, calcium deposition, and alkaline phosphatase activity. The HBO exposure on osteoblasts enhanced the differentiation to provide cellular evidence for HBO in fracture healing [31].

Shyu WC [32] showed that HBO can increase the Prion Protein (PrP) and heat shock protein 70 (Hsp70) in a mouse neuroblastoma cell in a time- and dose-dependent, with a concomitant upregulation of c-Jun N-terminal kinase (JNK). And HBO regulated PrP and Hsp70 through the activation of JNK, the activated heat shock transcriptional factor 1, phosphorylated by JNK interacted with heat shock element in the promoter of PrP resulted in increased gene expression. And HBO decreased the nuclear translocation of nuclear factor-kB; down regulated the phosphorylation of mitogen-activated protein kinase to decrease the secretion of matrix metalloproteases. HBO enhanced cartilage repair and the area stained positive for high mobility group box 1 (HMGB-1) and inducible NOS tended to be lower. HBO inhibited the HMGB1/RAGE signaling pathway by upregulating MicroRNA-107 expression in human osteoarthritic chondrocytes [33].

Pretreating irradiated mice with HBO prior to UCB CD34+ cell graft can decrease host erythropoietin and improve UCB CD34+ cell homing [34]. Liu ZJ [35] showed that hyperoxia can enhance the mobilization of EPC from the bone marrow into peripheral blood. Exogenous stromal cell derived factor1α (SDF-1α) into wounds reversed the EPC homing impairment, with hyperoxia synergistically enhanced EPC mobilization, homing, neovascularization, and wound healing. In our previous study, we found that HBO can reduce prostaglandin in gingiva and alveolar bone and inhibit alveolar bone resorption in experimental periodontitis [36].

Synergistic effects combining HBO and PRP on bone regeneration

PRP and HBO had the synergistic effects on neovascularization and bone regeneration enhancing the osteoinductive capacity of sole application of either method [1]. Shaw et al exposed human platelets to HBO induced an increase in platelet aggregation and protein release. Release of nitric oxide by platelets was unaffected following exposure to HBO, as was platelet activation as measured by surface expression of PECAM-1, CD62P and the activated form of αIIB βIIIa [37]. The percentage of collagen increased and the lesion thickness decreased in combing autologous platelet concentrates (APC) with HBO group compared to APC group, or HBO group. The bone healing increased in osteotomy sites of rabbit fibulae in APC+HBO group. The combination therapy was successful in terms of the activity of osteoblasts, osteocytes and collagen. APC and HBO applied together were superior in greater quantity of new bone compared with the APC or HBO treatments [38]. Yumun G showed that the number of active ulcers in the combined therapy group was fewer than that in the control group. And the amount of fibrous collagen in combined therapy groups was greater than that in

control group. The combination therapy and separate therapies had effects in terms of angiogenesis and new collagen fiber regeneration, but the combination therapy was more successful in wound closing, and resulted in a decrease in the wound area and an increase in the amount of granulation [39].

Conclusion

There is evidence that PRP and HBO alone can promote new bone formation and tissue wound healing, but few reports on the effects of and mechanism of combing HBO with PRP therapy on bone regeneration. Therefore, it is necessary to study in depth to elucidate the detailed mechanism.

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