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A novel hypothesis: The application of platelet-rich plasma can promote the clinical healing of white-white meniscal tears

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
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Summary

The white-white tears (meniscus lesion completely in the avascular zone) are without blood supply and theoretically cannot heal. Basal research has demonstrated that menisci are unquestionably important in load bearing, load redistribution, shock absorption, joint lubrication and the stabilization of the knee joint. It has been proven that partial or all-meniscusectomy results in an accelerated degeneration of cartilage and an increased rate of early osteoarthritis. Knee surgeons must face the difficult decision of removing or, if possible, retaining the meniscus; if it is possible to retain the meniscus, surgeons must address the difficulties of meniscal healing. Some preliminary approaches have progressed to improve meniscal healing. However, the problem of promoting meniscal healing in the avascular area has not yet been resolved. The demanding nature of the approach as well as its low utility and efficacy has impeded the progress of these enhancement techniques. Platelet-rich plasma (PRP) is a platelet concentration derived from autologous blood. In recent years, PRP has been used widely in preclinical and clinical applications for bone regeneration and wound healing. Therefore, we hypothesize that the application of platelet-rich plasma for white-white meniscal tears will be a simple and novel technique of high utility in knee surgery.

key words: **platelet-rich plasma • white-white meniscal tear • clinical healing**

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Background

White-white meniscal tear is a difficult problem, and obtaining satisfactory healing of meniscal tears continues to be a major clinical challenge, especially if the tear involves the inner avascular zone. Theoretically, a white-white meniscal tear (in the avascular area) will not heal after a suture repair alone. Trauma is one of the most common etiologies of meniscal tears. For example, 40% to 60% of patients who sustain a rupture of the anterior cruciate ligament also sustain a meniscal tear. Many of these tears extend into the middle-third avascular region. Poor long-term clinical results following partial and total meniscectomy have been reported [1]. It is amenable and important to repair meniscus lesions. However, repairing white-white meniscal tears remains an enigma. Many methods have sought to enhance the healing of white-white meniscal tears until they are provided healing potential (e.g., mechanical trephination, abrasion, exogenous fibrin clot, synovial flaps, high-frequency current, gluing, fascia sheath coverage and fibrin clot, meniscus wrap, technique growth factors, synthetic matrices, and stem cells). Most results are too preliminary to warrant speculation about their potential for clinical use. Some new techniques focus on meniscus tissue engineering such as cell-based therapy and gene therapy, tissue-engineered collagen meniscus implant, or the use of a degradable scaffold for meniscus regeneration. Studies [2,3] are being conducted to find the optimal method, but these have not yet been applied to humans. Thus the controversies about white-white meniscal tears have not ceased. Platelet-rich plasma (PRP) is defined as a biological product for platelet concentration, which is collected from centrifuged whole blood. Through the activation of a reactivator, the accumulated platelets can secrete a large quantity of a preparation rich in growth factors (PRGFs) via the release of intracellular granules. Simultaneously, PRP fragments can polymerize to platelet-rich gel (PRG), which consists of fibrin, fibronectin and vitronectin. In 1998, Dr Robert E. Marx [4] first proposed the use of PRP to enhance the initial phases of bone wound healing. Although the disputes about the increased prevalence of PRP therapy always exist, some authors [5] have claimed a theoretical basis for the prevalence. In the last few years, PRP has been applied as a means to facilitate the healing process in fields such as bone injuries [6–9], chondrogenesis [10], chondral defects [11], reduction of bone resorption [12], cruciate ligament repair [13,14], chronic elbow tendinosis [15], Achilles tendinopathy [16], rotator cuff repair [17,18], jumper's knee [19], chronic soft lesion [20], cardiac disease [21], dentistry, and maxillofacial surgery [22]. Although some studies have shown that platelet-rich plasma intra-articular injections for cartilage degeneration and osteoarthritis can promote osteoarthritic cartilage healing, better results were achieved in younger patients with a low degree of cartilage degeneration [23–25]. So far, no studies have demonstrated that PRP can improve the clinical healing of white-white meniscal tears.

Evidence Supporting the Hypothesis for Healing of White-White Meniscal Tears

The effect of PRP was first introduced by Marx et al. in a 1998 study on bone regeneration for maxillofacial reconstructions. Since then many scholars [26–28] have paid close attention to PRP. Many animal and clinical research efforts have indicated that PRP can promote bone regeneration, wound healing, nerve repair, tendon repair, and burn healing. Some authors combined PRP with a scaffold to repair bone defects, with encouraging results [29]. Kitoh et al. [30] developed a new technique for the transplantation of culture-expanded bone marrow cells (BMC) and PRP in distraction osteogenesis of the long bones in humans. Filardo et al. [23] performed a 12-month follow-up study, and promising results were obtained using intra-articular PRP injections in treating patients with knee degeneration. Using a quantification of cell proliferation, as well as proteoglycan (PG) and collagen synthesis, Akeda et al. [31] reported that PRP isolated from autologous blood may be useful as a source of anabolic growth factors for stimulating chondrocytes to engineer cartilage tissue. Fresno et al. [32] demonstrated that PRP application appeared to increase granulation tissue and fibrosis in pigs, but did not influence anastomotic breaking strength. Kurita et al. [33] concluded that a controlled release system of PRP was effective in inducing angiogenesis for critical ischemia in randomized studies, and vascularization was enhanced in critical limb ischemia rats treated by controlled release of platelet-rich plasma impregnated in biodegradable gelatin hydrogel. Some authors reported that platelet-rich plasma has a good effect on chondrogenic differentiation of human subchondral progenitor cells [34], and inhibition of inflammatory processes in osteoarthritic chondrocytes [35].

The majority of these studies suggest that the receptors of cytokines associated with PRGFs are widely localized on the surfaces of all types of human cells, including meniscus cells. After injury, high levels of these receptors are expressed in the lesion areas. Admittedly, the details of the mechanism involved remains to be clarified, but probably involves receptors on target cells, which in turn are thought to develop high-energy phosphate bonds to internal cytoplasmic signal proteins to initiate specific activity of PDGF, including mitogenesis (increase in the population of healing cells), angiogenesis (endothelial mitoses into functioning capillaries), and macrophage activation (debridement of the wound site and a second phase source of growth factors for continued repair and bone regeneration). How PRP affects human meniscus cells is not known. Notably, animal meniscus cells isolated from the white-on-white zone were cultured at various concentrations of PDGF-AB [36], showing that meniscal cells and, more importantly, cells from the avascular zone are capable of responding favorably to the addition of PDGF-AB. Following stimulation with this growth factor, these cells express their intrinsic potential to proliferate and generate new extracellular matrix.

Hypothesis

On the basis of the above analyses, we propose the hypothesis that PRP and its derivatives have great potential for the treatment of white-white meniscal tears as PRP may provide growth factors that enhance the healing of the meniscus through promoting meniscus cell proliferation and vascularization. We suggest that the mechanism is that activated platelets are a source of growth factors such as platelet-derived growth factor, transforming growth factor beta, fibroblast growth factor, and vascular endothelial growth factor (VEGF). Among them, insulin-like growth factor could regulate meniscus cell proliferation, VEGF could promote meniscus white-white area (avascular area) vascularization, and transforming growth factor beta could attract and activate several types of cells, such as fibroblasts or bone-marrow-derived stem cells in the surrounding tissues to differentiate meniscus cells. These growth factors could engage in a positive feedback during this interaction. PRP gel could be delivered arthroscopically to the avascular area tear after the routine protocol is followed. When PRP is activated to release PRGFs for white-white meniscal tears, PRP could also bridge the lesions as a tissue-engineering scaffold to reconstruct the meniscus. In 1936, King [37] stated that for a meniscal tear to heal, the torn meniscus must communicate with its peripheral blood supply. Therefore, the biggest obstruction to healing in a white-white meniscal tear is the avascular nature of the tissue. By promoting vascularization and cell proliferation, the slow healing and low efficacy of treatment of white-on-white meniscal tears may be solved through autograft PRP in clinical arthroscopy.

Evaluation and Discussion of the Hypothesis

Converging evidence from many areas supports a unifying hypothesis that the application of platelet-rich plasma can bring a breakthrough in the clinical puzzle, and promote the clinical healing of white-on-white meniscal tears. We can further explore the optimal concentration for a white-on-white meniscal tears. Long-term clinical follow-up and evaluation were completed through special physical examination, radiology review, MRI review and Lysholm Knee Scale scores. Meanwhile, the biomechanics changes between meniscus repaired by PRP and non-PRP application should be investigated by second arthroscopy.

PRP has been applied in clinical environments to repair peripheral nerve injury, oral-bone loss, injured tendons or ligaments, and dry eye symptoms, as well as to promote bone regeneration, articular chondrocyte healing, intestinal wound healing, and burn wounding healing. Despite the potential applications in the field of clinical research [38–41], the majority of PRP research has been performed in animal models [42–45]. As for PRP, it is low cost, convenient and does not induce any adverse reaction compared with other growth factors derived from gene-tissue engineering. In addition, the preparation of PRP is convenient, which is beneficial for applications in clinical practice.

However, there are still several issues in the clinical use of PRP. There is no standard regarding the optimal concentration of PRP with which to enhance healing. Moreover, the optimal concentrations for bone regeneration, peripheral nerve injury, articular chondrocyte healing and other domains, such as meniscus lesion, may be different. Few authors suggested that high concentrations of PRP could suppress cell proliferation *in vitro*. Several authors failed to find even a slightly beneficial effect *in vivo* [46–48].Further research will be necessary to determine whether PRP is effective for all types of tissues and cells in animals and humans, as well as the definite mechanism by which PRP affects cell proliferation and tissue healing.

Conclusions

We propose that PRP could become a novel, high efficacy and convenient application for white-white meniscal tears in clinical practice. However, there are still unanswered questions, such as mechanism of action, and optimal concentration needs further investigation.

Conflict of interest statemen

None declared.

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