

Clinical use of platelet-rich plasma in orthopaedics

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The increasing use of platelet-rich plasma (PRP) in orthopaedics presents significant opportunities—as well as significant questions—about appropriate clinical applications for this developing therapy.

PRP was initially developed in the 1970s; recent technologic advances have enabled the administration of PRP to move from the hospital setting into outpatient and ambulatory surgical centers...even into physicians' offices.

Although PRP therapy seems quite promising in several areas, it is not appropriate in all cases. A clear understanding of the repair response, the development of PRP therapy, and the variables that may affect the effectiveness of PRP therapy is necessary to make informed clinical judgments on its use.



A centrifuge is used to isolate the platelets, which are rich in growth factors.

The repair response

The repair response of musculoskeletal tissues generally starts with the formation of a blood clot and degranulation of platelets, which releases growth factors and cytokines at the site. This microenvironment results in chemotaxis of inflammatory cells as well as the activation and proliferation of local progenitor cells. In most cases, fibroblastic scar tissue is formed. In some settings, however, such as in a fracture callus, these conditions can also facilitate the formation of new bone tissue.

The following growth factors can be found in the environment of a blood clot:

- transforming growth factor beta (TGF- β)
- platelet-derived growth factor (PDGF)
- insulin-like growth factor (IGF)
- vascular endothelial growth factors (VEGF)
- epidermal growth factor (EGF)
- fibroblast growth factor-2 (FGF-2)

Many of these factors have been shown to enhance one or more phases of osteogenesis. PDGF, EGF, and FGF-2 have been shown to stimulate proliferation of osteoblastic progenitors. TGF- β increases matrix synthesis (eg, type I collagen) in vitro and in vivo. Angiogenic factors, including VEGF and FGF-2, can potentially enhance early angiogenesis and revascularization, as suggested by a recent study examining blood vessel formation in large segmental defects in the tibias of rats treated with platelet-rich plasma (PRP).¹

Enriching a rich environment

The development of PRP focused on enhancing this rich environment. Could concentrated preparations of platelets or of platelet degranulation products increase the growth factors in the blood clot and be used to augment fracture repair or bone grafting sites? Existing technology enabled the isolation and concentration of the patient's own platelets either before or during surgery. The result is an autologous PRP that contains a biologically active mixture of growth factors without the potential for an immune response.

Preclinical and clinical investigations have actively examined the possible usefulness of PRP preparations. Such studies recognize the possibility that the effect of the clot microenvironment or concentrates of PDFGs on fracture repair might be either positive or negative. The nature of this effect, like that of many graft materials, depends on the clinical setting, particularly the graft site's local environment of cells in which PRP or associated factors are placed.

For example, clots also contain bone morphogenetic proteins (BMPs).² Recent in vitro studies suggest that, although components of the platelet releasate stimulate migration and proliferation of osteogenic progenitor cells, they also inhibit the osteogenic action of BMPs.^{3,4}

Because PRP preparations do not provide a source of autogenous osteogenic cells, their effects depend on the presence of a local osteogenic population. In addition to increasing the proliferation of osteoblastic cells and matrix synthesis, the growth factors associated with PRP also promote fibroblastic growth, differentiation, and scar formation. In many cases, they also inhibit later stages of osteoblastic differentiation.

Various methods are now commercially available for preparing PRP and a similar material called "autologous growth factor," which is PRP plus the white blood cell buffy coat obtained during PRP preparation. As a result, assessment of these strategies in clinical orthopaedic practice has accelerated. Studies in the oral and maxillofacial surgery literature⁵ suggest that PRP can be an effective adjunct to some craniofacial bone graft procedures, but it appears to be most useful for soft-tissue applications.

Effectiveness "depends"

The literature on the clinical use of PRP suggests that considerable variability exists in its effectiveness, even in the same clinical setting. Several reasons may account for this variability.

PRP is donor dependent. A recent study examining the effect of PRP in combination with human demineralized bone matrix (DBM) highlighted multiple sources of variation.⁶ Researchers tested PRP from six young male donors with two different batches of human DBM using the nude mouse muscle implantation assay. The results showed that PRP reduced the effectiveness of the DBM in a donor-dependent manner. The effectiveness of the PRP also varied with the quality of the DBM, which is also donor dependent.⁷

The composition of PRP varies with the preparation technique used.⁸ Although all PRP preparations contain a basic set of growth factors, the relative concentration of each factor can differ among preparations. Moreover, the proteases present in the platelet releasate may degrade some of the growth factors,⁹ which reduces the availability of bioactive factors, and changes the composition of the PRP, altering its clinical effectiveness for specific applications.

These factors may help explain the different outcomes that result when PRP is used in orthopaedic applications. Recent studies using PRP to encourage healing after spinal fusion have been disappointing; the addition of PRP to bone graft seems to reduce the spinal fusion rate in animals as well as in humans.^{10,11} In contrast, a different study involving a canine spinal fusion model and the delivery of an enriched population of marrow-derived osteogenic connective tissue progenitors to the graft site found that the addition of a blood clot enhanced fusion and bone formation.^{12,13} Similarly, using the same types of grafts, the addition of PRP in a canine femoral defect model also enhanced bone formation.¹⁴

Use with care

In summary, available data suggest that PRP may be valuable in enhancing soft-tissue repair and in wound healing.¹⁵ However, the clinical role of PRP in bone repair remains controversial. PRP is not uniformly successful as

an adjuvant to bone grafting procedures. PRP may promote or inhibit bone formation, depending on the setting in which it is used and the quality of the PRP.

Significant additional research is needed to define the role of PRP and to determine in which settings it might—or might not—be valuable. This may also involve defining a means of ensuring that a given PRP preparation is biologically active, by determining its critical component(s) and developing assays that can provide this information to the surgeon in a timely manner.

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