The following article discusses the advantages and risks of using platelet-rich plasma for bone healing.

Platelet-rich plasma for bone healing—to use or not to use?

Introduction  At the beginning of the 21st century, the clinical application of platelet-rich plasma (PRP) was considered a breakthrough in the stimulation and acceleration of bone and soft tissue healing. Since then, its use has been predominantly in maxillofacial surgery as an autologous additive to bone grafts and soft tissue transplants, although other indications such as chronic diabetic ulcers and some standard orthopedic procedures have been suggested. This article will clarify the rationale behind the clinical application of PRP by reviewing the literature and outlining some of our own observations in basic research.

Platelets and the growth factors they release are essential for regulating the cellular events that follow tissue damage. They adhere, aggregate, form a fibrin mesh, and subsequently release a large variety of growth factors and cytokines. At least 15 different factors are known to be contained within platelets [1–3], including platelet derived growth factor (PDGF-bb, -ab und -aa isoforms), transforming growth factor-beta (TGF-beta, -beta1 and -beta2 isoforms), platelet factor 4 (PF4), interleukin 1 (IL-1), platelet-derived angiogenesis factor (PDAF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), platelet-derived endothelial growth factor (PDEGF), epithelial cell growth factor (ECGF), insulin-like growth factor (IGF), osteocalcin (Oc), osteonectin (On), fibrinogen (Fg), vitronectin (Vn), fibronectin (Fn) und thrombospondin-1 (TSP-1). The impact on bone and tissue regeneration of most of these factors has been recognized by many authors [4–13]. As opposed to an artificial composition of recombinant proteins, PRP maintains the natural concentrations within a cocktail of growth factors acting on multiple pathways [14]. Furthermore, artificial recombinant growth factors require further synthetic or animal proteins as carriers. PRP in contrast serves as a natural carrier itself [15]. Thereby PRP can mimic the highly efficient in vivo situation much more closely than a custom designed protein preparation.

As platelet concentrates can be prepared from whole blood within a short time using relatively simple methods, they have the potential to be an immunogenically inert additive to promote rapid healing and tissue regeneration. Preparation of platelet concentrates usually requires a two step centrifugation procedure [16]. In the first step full blood is divided into a platelet-containing and a cell-containing fraction [17]. During the second step, which is high speed centrifugation, platelets can be sedimented and rediluted to the desired volume of plasma (usually 1/10 of the initial blood volume) yielding platelet concentrations of more than 1,000,000 platelets/μl [15, 17]. To release the growth factors and cytokines, platelets need to be activated. In vivo this happens through platelet agonists like thrombin, collagen, ADP, serotonin, and thromboxane A2. For experimental purposes, bovine thrombin and CaCl2 are the most commonly used agents. In our own studies
we have demonstrated equal efficacy for freeze-thaw-activation of PRP [18]. In clinical practice PRP is used as a liquid, made from 50–100ml of full blood that quickly forms a gel when applied with thrombin. Several companies have developed kits and devices for automatic preparation during surgical procedures. Although the general concept seems plausible, controversy remains about whether PRP and other platelet preparations meet the high expectations set by the clinical demands. For the practitioner it appears very difficult to obtain information on the actions and the possible risks of using platelet concentrates.

**Clinical safety considerations** Clearly an autologous preparation does not bear the risks of transmissible diseases nor of immunogenic reactions. If commercially available devices are used, FDA approval will usually ensure that the preparation process is carried out in a sterile and pyrogen free manner. We are not currently aware of any serious adverse effects that have occurred when PRP was used for wound healing and bone grafting. Still, a possible risk arises from bovine thrombin that is used to activate PRP. Coagulopathies due to antibody formation against thrombin, Factor V, and Factor XI have been reported after cardiac surgery [19, 20].

**Basic research—*in vitro and in vivo effects of autologous platelet concentrates*** While there are numerous case studies and small clinical trials on the clinical applications, knowledge about the underlying effects at the cellular level is limited. Nevertheless, PRP has been shown to stimulate cell proliferation of osteoblasts and fibroblasts and to upregulate osteocalcin in these cells [21, 22]. In a recent study by our own group we demonstrated the differentiation of mesenchymal stem cells (MSC) into bone forming cells in the presence

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### Table 1  Application in bone healing

<table>
<thead>
<tr>
<th>Application</th>
<th>Type of study</th>
<th>Study design</th>
<th>Conclusion</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of intra-bony defects</td>
<td>Comparative controlled clinical study</td>
<td>70 interproximal intra-bony osseous defects were treated with PRP and a ceramic porous hydroxyapatite (HA) scaffold or HA and saline</td>
<td>Treatment with PRP and HA led to significantly more clinical improvement than HA and saline</td>
<td>[32]</td>
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<tr>
<td>Treatment of intra-bony defects</td>
<td>Randomized clinical trial (split mouth, double masked)</td>
<td>Bilateral periodontal intra-bony defects were matched in 13 individuals and treated only with a bovine xenograft or with PRP</td>
<td>PRP significantly increased the clinical periodontal response of lesions treated with xenogenic bone grafts</td>
<td>[33]</td>
</tr>
<tr>
<td>Treatment of infrabony defects</td>
<td>Prospective case series</td>
<td>Five similar bilateral paired infrabony defects were treated with autologous platelet concentrate (APC) or a biodegradable barrier membrane (MEM)</td>
<td>Similar gain in clinical attachment level and probing depths in APC and MEM treated groups</td>
<td>[34]</td>
</tr>
<tr>
<td>Lumbar spine fusion</td>
<td>Prospective review compared to historical results</td>
<td>23 individuals underwent transforaminal lumbar interbody spinal fusion (TLIF) with PRP compared to historical results</td>
<td>2-year minimum follow-up showed faster healing in the PRP group, but no significant difference in the pseudarthrosis rate was observed</td>
<td>[35]</td>
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<tr>
<td>Total ankle replacement</td>
<td>Comparative Study</td>
<td>114 and 66 Agility total ankle replacements were performed without and with autologous concentrated growth factors for distal syndesmosis fusion</td>
<td>Autologous concentrated growth factors appeared to make a significant positive difference in the syndesmosis union rate in total ankle replacements</td>
<td>[36]</td>
</tr>
<tr>
<td>Treatment of mandibular continuity defects in tumor cases</td>
<td>Prospective study</td>
<td>44 individuals were treated with bone graft and PRP and bone graft alone</td>
<td>Maturity index of bone grafts with PRP was higher than in bone grafts alone</td>
<td>[37]</td>
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</table>
of PRP [18]. An increase in growth and differentiation of PRP-treated periodontal ligament cells has been shown by two groups [10, 23]. Further investigation revealed stimulation of the mitogenic (ie, transforming) response to PRP in human trabecular and rat bone marrow cells [24, 25]. Additionally, we were able to demonstrate a strong effect on the expansion of endothelial progenitor cells by platelet-released growth factors [26].

In vivo studies do not support the positive actions of PRP. In fact, in one of the most recent investigations PRP decreased the osteoinductivity of demineralized bone matrix in nude mice [27]. Other researchers performed trials on various animals and reported no beneficial effect of using PRP for bone healing [28] or suggest a low regenerative potential for its use in combination with xenogenic bone grafts [29]. Some studies also show effective augmentation of porous biomaterial in rats [30] and sheep [31]. Careful analysis of these studies reveals that none are scientifically comparable. Therefore, we cannot draw an overall scientific conclusion of PRP actions in animal models.

Clinical trials and case studies Case reports and small clinical trials have been reported in craniomaxillofacial surgery as in other specialties. Table 1 and Table 2 display a selection of such studies which overall support the beneficial effect of PRP and other platelet concentrates. As previously mentioned, in animal studies the two main factors making it almost impossible to compare any two of the studies published are the lack of a standardized PRP preparation protocol (Table 3) and the lack of commonly accepted evaluation criteria.

### Table 2 Other applications

<table>
<thead>
<tr>
<th>Application</th>
<th>Type of study</th>
<th>Study design</th>
<th>Conclusion</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Treatment of chronic elbow tendinosis</td>
<td>Cohort study</td>
<td>Out of a cohort of 150 patients with chronic elbow tendinosis, 15 were given one injection of PRP, and 5 were given one injection of bupivacaine</td>
<td>Pain was reduced in patients treated with PRP compared to the control group in this pilot study</td>
<td>[38]</td>
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<tr>
<td>Treatment of diabetic foot ulcers</td>
<td>Prospective randomized controlled trial</td>
<td>40 individuals were randomized into a PRP- and saline-gel group and followed up for 12 weeks</td>
<td>Significantly more ulcers healed in the PRP group</td>
<td>[39]</td>
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<tr>
<td>Treatment of diabetic foot ulcers</td>
<td>Meta-analysis</td>
<td>More than 25,000 cases of diabetic foot ulcers were treated with and without platelets</td>
<td>Ulcers treated with platelet concentrate were significantly more likely to heal</td>
<td>[40]</td>
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</table>

### Table 3 Commercially available preparation systems

<table>
<thead>
<tr>
<th>Device</th>
<th>Preparation time</th>
<th>Platelet yield (whole blood) as stated by manufacturer</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>GPS (gravitational platelet separation)</td>
<td>12 min</td>
<td>Up to 8</td>
<td>Cell Factor Technologies</td>
</tr>
<tr>
<td>PCCS (platelet concentrate collection system)</td>
<td>20 min</td>
<td>Up to 7</td>
<td>Implant Innovations</td>
</tr>
<tr>
<td>Symphony II</td>
<td>15 min</td>
<td>Up to 6</td>
<td>DePuy</td>
</tr>
<tr>
<td>SmartPReP</td>
<td>15 min</td>
<td>Up to 9</td>
<td>Harvest Technologies Corp</td>
</tr>
<tr>
<td>Magellan</td>
<td>15 min</td>
<td>Up to 10</td>
<td>Medtronic</td>
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</table>
Summary and conclusions  PRP preparation provides a fairly simple method to deliver a variety of natural growth factors to the patient. High concentrations of proteins acting in concert through different pathways can be achieved by commercially available systems that can be used in the operating room. The risks of contamination and immunogenic response are considerably low when using FDA approved systems. The remaining risk of coagulopathies could be minimized by using alternative activation methods to standard bovine thrombin. On the whole, the beneficial effects of PRP in clinical application remain doubtful. No appropriate clinical investigations that meet all modern quality criteria have been conducted up to now.

Based on our own and other groups’ in vitro findings, one could hypothesize that PRP can be supportive of the healing processes if used in the right manner. The appropriate use of PRP has yet to be determined by larger randomized controlled trials. Additional basic investigations on the mechanisms of action could elucidate under which conditions PRP can act as a tissue healing additive.

Bibliography


