

# ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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## Should Autologous Platelet-Rich Plasma Be Used in Patients With Hematologic Disease?



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### H&O What is autologous platelet-rich plasma, and how is it prepared?

**AMC** More than 30 years ago, Knighton and colleagues studied 49 patients with chronic, nonhealing cutaneous ulcers—including venous ulcers and arterial insufficiency ulcers—and reported that autologous platelet-derived wound-healing factors promoted healing.<sup>1</sup> From this finding came the development of autologous

Platelet growth factors promote ulcer repair by complex biological processes, including activation of angiogenesis, collagen synthesis, and re-epithelialization and stimulation of fibroblasts.

platelet-rich plasma (aPRP), a platelet concentrate in which the platelet count is 5 times the baseline count,<sup>2</sup> or 1 million platelets per microliter in 5 mL of plasma.<sup>3</sup> The components of aPRP have bioactive functions that affect musculoskeletal tissue regeneration and healing.<sup>4</sup>

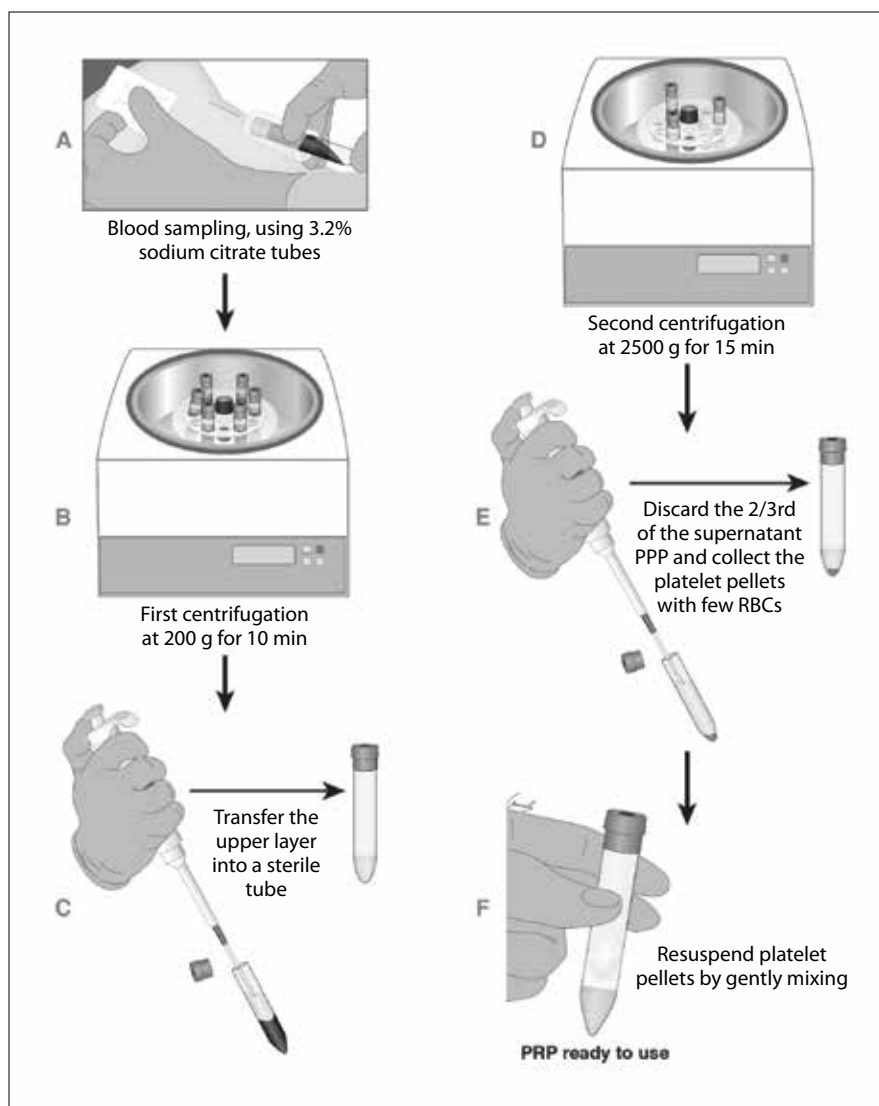
Several steps are required to reach the required concentration of platelets in aPRP (Figure).<sup>2</sup> First, 30 mL

of blood is collected in a tube that has been treated with the anticoagulant sodium citrate. Second, the blood is placed in a centrifuge and spun at 200 to 600 g (ie, 200 to 600 times Earth's gravitational force) for 10 minutes, a process that generates 3 layers. The upper layer is referred to as platelet-poor plasma, and contains plasma and a low number of platelets; the middle layer is referred to as buffy coat, and is rich in white blood cells and plasma; and the bottom layer contains red blood cells. The top 2 layers are removed from the red blood cell layer and centrifuged a second time at 700 to 2500 g for 15 minutes to concentrate the platelets.<sup>2</sup> The bottom third of this mixture, which contains the highest concentration of platelets, is used as aPRP. To date, at least 40 commercial devices are available to create aPRP from autologous whole blood.<sup>5</sup>

There are 4 main categories of aPRP, each containing a different quantity of white blood cells and fibrin<sup>5-8</sup>:

1. Pure platelet-rich plasma with few or no white blood cells;
2. Platelet-rich plasma with white blood cells;
3. Pure platelet-rich fibrin with few or no white blood cells,
4. Platelet-rich fibrin with white blood cells. This is also called Choukroun's platelet-rich fibrin (PRF) in honor of Dr Joseph Choukroun, who simplified the procedure for preparing PRF and improved the efficiency of handling without the use of animal-derived factors.<sup>7</sup>

Although controversy continues about the best way to prepare aPRP,<sup>9,10</sup> the agent is used extensively in regenerative medicine.<sup>11</sup>



**Figure.** Preparation of autologous platelet-rich plasma. (A) Blood sampling with 3.2% sodium citrate tubes. (B) First centrifugation, at 200 g for 10 minutes. (C) Transfer the upper layer into a sterile tube. (D) Second centrifugation, at 2500 g for 15 minutes. (E) Discard two-thirds of the supernatant platelet-poor plasma and collect the platelet pellets with a few red blood cells. (F) Resuspend the platelet pellets by gently mixing. PPP, platelet-poor plasma; PRP, platelet-rich plasma; RBCs, red blood cells. From Piccin A, Di Pierro AM, Canzian L, et al. Platelet gel: a new therapeutic tool with great potential. *Blood Transfus.* 2017;15(4):333-340. Republished with permission.

**H&O** What are the potential applications of aPRP in hematologic diseases, such as leg ulcers in sickle cell disease? What about other types of chronic wounds?

**AMC** Although the properties of aPRP would seem to make it useful for the treatment of leg ulcers in sickle cell disease (SCD), a Cochrane systematic review found no randomized clinical trials of aPRP for that use.<sup>12</sup> Furthermore, neither ClinicalTrials.gov nor the World Health Organization International Clinical Trials Registry Platform lists any ongoing trials to assess the use of aPRP in patients with leg ulcers related to SCD.

Regarding the use of aPRP to treat chronic wounds, another Cochrane systematic review that included 101 patients concluded that the evidence regarding the healing

of venous leg ulcers was uncertain (relative risk, 1.02; 95% CI, 0.81-1.27;  $P=0\%$ ).<sup>13</sup>

The use of aPRP to treat sternal ulcers following radiotherapy for Hodgkin disease has been reported.<sup>14</sup> Another case report was published on the use of aPRP to treat chemotherapy extravasation injuries in a patient with multiple myeloma who was undergoing high-dose chemotherapy and autologous stem cell transplant.<sup>15</sup> Finally, a case series examined the use of aPRP for mucocutaneous lesions related to graft-versus-host disease following allogeneic hematopoietic stem cell transplant.<sup>16</sup> The fact that these examples are from case reports and case series dramatically limits their value, however.

Velier and colleagues published results supporting the feasibility of using aPRP gel in elderly patients with nonhealing chronic wounds who were receiving

antiplatelet agents or anticoagulants. These researchers compared aPRP gel derived from elderly people (75-92 years old) who were taking antithrombotic drugs with gel derived from healthy volunteers (23-37 years old). They found “no significant difference” between the volume, composition, and functionality of platelets in the 2 aPRP gels, the single exception being a higher expression of adenosine diphosphate–induced P-selectin in the gel from healthy donors than in the gel from elderly patients. The characteristics of autologous thrombin were similar in the 2 groups, and the PRP gel formation time and final composition were not significantly modified.<sup>17</sup>

### **H&O** How is aPRP believed to help heal these ulcers?

**AMC** Platelets are versatile anucleated cells<sup>18</sup> that contain 3 types of secretory granules—dense, alpha, and lysosomal granules.<sup>19</sup> The alpha secretory granules have numerous types of proteins with different functions: adhesive glycoproteins, proteoglycans, mitogens, protease inhibitors, coagulation factors, and membrane.<sup>19,20</sup> These proteins are what enable platelets to play a fundamental role in various physiologic and pathophysiologic processes, such as inflammation, hemostasis, thrombosis, antimicrobial host defense, tumor biology, maintenance and regulation of vascular flow, and tissue repair and development.<sup>2,19,21,22</sup>

When aPRP is added to thrombin, platelet activation occurs, with the subsequent release of growth factors. For wound repair, the fundamental proteins are those with mitogenic capacity—insulin-like growth factor 1, platelet-derived growth factor, vascular endothelial growth factor, basic fibroblastic growth factor, epidermal growth factor, transforming growth factor beta, and connective tissue growth factor.<sup>19,23</sup> Together with growth factors of nonplatelet origin and cells such as macrophages, neutrophils, and fibroblasts, platelets release cytokine molecules—including tumor necrosis factor alpha and interleukins. These platelet growth factors promote ulcer repair by complex biological processes, including activation of angiogenesis, collagen synthesis, and re-epithelialization and stimulation of fibroblasts.<sup>24-26</sup>

### **H&O** What are the potential side effects and disadvantages of aPRP?

**AMC** Because the patient is the source of the aPRP, the risk for contracting a blood-transmitted disease is avoided, and the risk for an immune reaction is minimal.<sup>27</sup> In addition, a study found that aPRP reduces the cost of treating hemophilic arthropathy by reducing the need for coagulations factors.<sup>28</sup>

Ziyadeh and colleagues conducted a matched cohort study to study the risk for cancer in users of becaplermin (Regranex, Smith & Nephew), a recombinant preparation of platelet-derived growth factor.<sup>29</sup> Although this study concluded that becaplermin did not appear to increase the risk for cancer or cancer mortality overall, the risk for cancer was elevated among patients who received 3 or more tubes of becaplermin.<sup>29</sup> As a result, the European Medicines Agency has banned the agent,<sup>30</sup> and the US Food and Drug Administration requires a black box warning.<sup>31</sup> A Cochrane systematic review for assessing the clinical benefits and harms of growth factors for treating diabetic foot ulcers found that safety data were poorly reported, and adverse events may have been underestimated.<sup>32</sup>

### **H&O** Is aPRP a good option to treat hemophilic arthropathy?

**AMC** Hemophilic arthropathy (HA) is a complication of hemophilia that produces severe pain and has a dramatic adverse effect on quality of life.<sup>33,34</sup> Our understanding of the pathophysiology and treatment of HA has undergone major changes in recent years,<sup>35-38</sup> and treatment of this painful condition is another potential use of aPRP.<sup>39</sup>

No randomized clinical trials have examined the use of aPRP for the treatment of HA, although 2 case series suggest that aPRP is safe, effective, and inexpensive for this use.<sup>28,40</sup> One small randomized trial compared a single intra-articular injection of 2 mL of aPRP vs 5 weekly intra-articular injections of 2.5 mL of hyaluronate sodium, but the results have not yet been published.<sup>41</sup> Therefore, the evidence is insufficient to either reject or support the use of aPRP for treating HA.

### **H&O** What direction should future research take?

**AMC** There is a major need for adequately powered randomized controlled trials to assess the clinical benefit of aPRP for leg ulcers associated with SCD and for the pain of HA. Such trials should be planned, conducted, and reported according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials)<sup>42</sup> and CONSORT (Consolidated Standards of Reporting Trials)<sup>43</sup> statements. Trial authors should include outcomes according to PCORI (Patient-Centered Outcomes Research Institute) recommendations.<sup>44</sup>

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*Dr Martí-Carvajal has no disclosures to report.*

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