

## INVITED ARTICLE

# Critical Analysis of the Use of Platelet-rich Plasma in Orthopedic Clinical Practice: An Evolving Story

<sup>1</sup>Saurabh Singh, <sup>2</sup>Vijay Shetty

## ABSTRACT

Orthobiologics are substances that are believed to help injuries heal more quickly. Orthobiologic agents include products, such as stem cells and platelet-rich plasma (PRP) containing various (good and bad) growth factors. The use of PRP in orthopedic clinical practice and evolution of this treatment in sports medicine, over the last decade or so, is a story of innovation, experimentation, controversies, and matter of huge debate.

**Keywords:** Orthopedics, Platelet-rich plasma, Sports medicine.

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## THE BEGINNING

Way back in 2006, researchers in Milan, Italy, published the possible systemic effects of injecting PRP in professional athletes who were suffering from tendinopathies. The conclusion was that the use of PRP may have systemic effects but local effects are clearly longer and beneficial.<sup>1</sup> This was perhaps one of the earliest reports of the use of PRP in sports-related injuries. Ever since the interest in the use of PRP in orthopedic clinical practice has been growing, given its potential to enhance tendon and muscle healing.<sup>2-4</sup>

## THE JOURNEY

Possibly, the first level II evidence favoring the use of PRP in sports medicine came from Nguyen et al.<sup>5</sup> The authors concluded that PRP can be a potentially efficacious regenerative treatment option for musculoskeletal and sports medicine applications. An animal experimental study by Spang et al<sup>6</sup> in the same year clearly demonstrated that injecting PRP into severed patellar tendons in rats enhances tendon healing. Further, in the same year,

Kon et al<sup>7</sup> concluded after a critical analysis of the literature that the literature shows promising preclinical results but contradictory clinical findings for the treatment of sports-related injuries.

While the researchers agreed that PRP is certainly one emerging strategy to accelerate tissue healing, in a variety of clinical conditions, the major question remained; is PRP or any other orthobiologic product for that matter efficient? For a start, there have been wide variations in agreeing on a definition of PRP.<sup>8</sup> A number of publications started appearing in the literature debating the use of PRP in the early 2010s.<sup>9,10</sup> Besides, PRP received much media attention for being used by many celebrity athletes for injuries.<sup>11,12</sup> At this time, what was missing was robust evidence with level I studies to support the use of PRP, including optimal formulation, dosage, and rehabilitation protocols.

The year 2012 saw the first proposed randomized study protocol on the use of PRP for muscle injuries.<sup>13</sup> The authors targeted “return-to-play” as the main outcome measure. The study was later published in 2014 and concluded that the PRP group did significantly better than the control group.<sup>14</sup> The overall clinical outcomes after using PRP in clinical practice was still not universally accepted, possibly due to the fact that all PRP preparations were not the same. Many authors reported the variations in the volume of blood taken, the platelet recovery efficacy, the final volume of plasma in which the platelets are suspended, and the presence or absence of leukocytes.<sup>15,16</sup>

## INDICATION-SPECIFIC OUTCOMES

Although some case reports suggested benefits of PRP on the healing of ligaments and tendons, indication-specific outcomes (meniscus, ligaments, rotator cuff, muscle injuries, and articular cartilage pathology) on the use of PRP were not forthcoming until late 2013.<sup>17-20</sup>

Muscle injuries and articular cartilage injuries are a common form of sport-related injuries.<sup>21</sup> Although the use of PRP in muscle injuries is validated, in terms of early return to play, through a randomized control study by Hamid et al,<sup>14</sup> there appears to be paucity of data supporting the use of PRP for the management of focal osteochondral defects as suggested by a systematic review by Dold et al.<sup>22</sup> The indications for the use of PRP in sports medicine rather exploded in early 2014. The first double-blind randomized control trial, on the use of PRP for patellar

<sup>1</sup>Clinical and Research Fellow, <sup>2</sup>Consultant Orthopedic Surgeon

<sup>1,2</sup>Department of Orthopedics, Dr L.H. Hiranandani Hospital Mumbai, Maharashtra, India

**Corresponding Author:** Vijay Shetty, Consultant Orthopedic Surgeon, Department of Orthopedics, Dr L.H. Hiranandani Hospital, Mumbai, Maharashtra, India, Phone: +919920707771 e-mail: vijaydshetty@gmail.com

tendinopathy, came from Stanford University, California, in March 2014.<sup>23</sup> The authors concluded that a therapeutic regimen that included the injection of leukocyte-rich PRP accelerated the healing of patellar tendon in the study group. This is an interesting observation, given that there is no previous randomized control trial on the use of PRP in patellar tendinopathy. Going one step further on the use of PRP in sports medicine, researchers in New York studied the use of PRP on tendon-bone-tendon healing, further exploring the opportunities with PRP.<sup>24</sup> However, this study only mentioned about the possibility of PRP augmenting tendon-bone-tendon healing.

## CONTROVERSIES

The use of PRP, in sport-related injuries, is surrounded by controversies and debates. We now have reasonable evidence that PRP works on tennis elbow.<sup>25-27</sup> Although some reports strongly recommended PRP for recalcitrant tennis elbow, a recent systematic review showed strong evidence against PRP use for chronic tennis elbow.<sup>28</sup> This was a very controversial paper when things were going well for tennis elbow with PRP. Muscle injuries are common sports-related injuries and, perhaps, most controversial with PRP treatment. Some authors questioned the use of PRP in muscle injuries, as animal experiments showed no likely benefit of PRP in muscle injuries.<sup>29</sup> Further, a year later, another experimental study<sup>30</sup> concluded that PRP promoted complete tissue restitution between the 7th and 21st days in experimental muscle injuries. To confuse matters further, a randomized control trial in 2015<sup>31</sup> concluded that there is no benefit of PRP in terms of "return to play," clearly contradicting the results of an earlier randomized trial.<sup>14</sup> A recent comparative study further complemented this conclusion.<sup>32</sup> Then again, a most recent randomized control trial<sup>33</sup> concluded that single injection of PRP coupled with rehabilitation program shortened the time to return to sports, suggesting that PRP is recommended for muscle injuries.

## ON THE BALANCE...

Although there is a paucity of data surrounding the use of PRP in sports medicine, some authors believe that PRP can be tried as a therapeutic agent before going under the knife for recalcitrant cases.<sup>34</sup> However, there is a need for continued investigation into the efficacy of PRP and stem cells in sports medicine.<sup>35</sup> A major limitation in the interpretation of current evidence is variability in the preparation of these biologic agents.<sup>36</sup> For the moment, it appears that the use of biological agents in sports medicine is here to stay, as there is no major adverse effect reported so far in the literature.<sup>37</sup> However, care should be taken while using PRP in acute injuries, such as ankle sprains.<sup>38</sup>

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