

# Editorial Commentary: Platelet-Rich Plasma for Knee Osteoarthritis: A “Novel” and Effective Symptomatic Approach



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**Abstract:** Osteoarthritis (OA) constitutes a significant cause of disability, and it is now recognized as a source of increased mortality. Thus, several therapeutic approaches have been reported in the literature in an attempt to mitigate the symptoms of OA with varying degrees of success. Platelet-rich plasma (PRP) is being increasingly accepted as one of the most efficacious approaches for the symptomatic treatment of mild to moderate OA. Several confounding factors can affect the outcome of PRP such as age, grade of OA, PRP processing technique, and number and timing of these injections. However, numerous reports in the literature derived from PRP randomized clinical trials (compared with saline, hyaluronic acid, and other nonsurgical methods) suggest that successful outcomes can be achieved at least at 1-year postinjection with minimal complications.

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Osteoarthritis (OA) can be a devastating disease not only in the elderly but also in a younger and more active population. It is certainly a significant cause of morbidity, and it has been recently recognized as a source of increased mortality.<sup>1</sup> In this regard, a recent systematic review reported that patients with symptomatic hip or knee OA had 55% greater all-cause mortality compared with the general population. Furthermore, a history of walking disability or limitation has been shown to be coupled with all-cause

mortality and mortality due to cardiovascular disease, even after adjustment for age and sex.<sup>2</sup> Notably, as our understanding of this disease becomes more comprehensive (rather than being solely focused on the pain epicenter), we further recognize the potential harmfulness of the cascade of effects derived from OA. This represents a true burden to the economic health care system as OA accounts for almost 1 out of 5 of all health care visits in the United States,<sup>3,4</sup> which translates into an annual cost of nearly \$460 billion to the economy, secondary to lost wages and treatment costs.<sup>5</sup>

In fact, OA is more prevalent than previously reported, and current technology (biomarkers, magnetic resonance imaging [MRI]) has allowed for improved diagnosis at an earlier stage. For instance, the prevalence of OA among asymptomatic uninjured knees (screened with MRI) was up to 43% in adults  $\geq 40$  years.<sup>6</sup> Importantly, we believe that these patients should become our target population to treat, in an attempt to delay disease progression. In this respect, despite technological improvements, as no screening methods are performed in the general population, the majority of the patients will access the health system once the degenerative progress has developed symptoms, with either inflammatory (during early stages of OA) or mechanical signs (late phases of OA).

Despite an exponential growth in the cartilage repair literature, no curative therapies for OA exist, and thus

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health care providers should recognize that management of OA should be directed toward pain control and function optimization. Furthermore, although in vitro studies have shown promising results in growing cartilage when exposed to enriched media, the intra-articular catabolic milieu of osteoarthritic knees could be one of the main obstacles we need to better understand to improve the odds of “true” regeneration. In this regard, the use of orthobiologics for the treatment of cartilage disease emerged as an important tool in the orthopaedic armamentarium due to their minimal invasiveness, potentially disease-modifying properties, and effectiveness.<sup>7-9</sup> These therapies include platelet-rich plasma (PRP), bone marrow aspirate concentrate, and the use of cell-based therapies, among others.

To improve our understanding and assess the real efficacy of these therapies, randomized clinical trials are of utmost importance. The study by Lin, Yang, Hsu, Yeh, and Renn, entitled “Intra-articular Injection of Platelet-Rich Plasma Is Superior to Hyaluronic Acid or Saline in the Treatment of Mild to Moderate Knee Osteoarthritis: A Randomized, Double-Blind, Triple-Paralleled, Placebo-Controlled Clinical Trial,” seeks to compare the effectiveness of platelet-rich plasma (PRP) and hyaluronic acid (HA) with a normal saline (control group) in a randomized (dose-controlled), double-blind, clinical trial for knee osteoarthritis.<sup>10</sup> The authors should be commended on this work as it represents a well-designed randomized clinical trial that helps build the body of literature of an approach that is readily available and that can impact a patient’s quality of life in a positive way.

The authors concluded that intra-articular injections of leukocyte-poor PRP can provide both statistically and clinically significant functional improvement for patients with mild to moderate OA of the knee for at least 1 year. Interestingly, the authors found that only age had a significant effect on outcomes (better outcome for younger patients). Conversely, OA grade and body mass index were not correlated with significant outcome improvements. This study has several strengths such as randomization of 3 different treatment arms (including 1 control group), blindness to the treatment, power calculation, and a comprehensive multivariate analysis. Nevertheless, we have identified some flaws and potential confounding factors in this study such as the presence of unilateral and bilateral pathology treatment, a wide range of OA severity degrees (Ahlback I to III), the use of saline as a control (as it has been previously reported to always produce better outcomes than no treatment),<sup>11</sup> and the lack of objective assessments such as biomarkers of inflammation and/or MRI to assess structural changes if any.

Important discussion points can be raised about the PRP processing methodology in this study. First, although the overall methods are comprehensively

described, not all necessary variables of the PRP processing method are described. It is imperative that future studies report on all these details to compare results from different groups (a recent study reported that only 11.5% of the studies report on every processing variable needed to replicate that study).<sup>12</sup> Remarkably, the platelet increase in this study (1.81 times that of the baseline) is below the arbitrary definition of PRP containing 5 times the amount of baseline platelets.<sup>13</sup> This elevated platelet count in PRP has been suggested as necessary to stimulate targeted injured cells to proliferate in vitro.<sup>14,15</sup> However, it has been recently reported that increased platelet concentration beyond the physiological level did not improve functional graft healing in anterior cruciate ligament<sup>16</sup> and medial collateral ligament animal models.<sup>17</sup> Another controversial topic is the concentration of leukocytes. This study used leukocyte-poor PRP, which has been previously reported to produce more consistent results intra-articularly.<sup>18</sup>

Finally, as stated by the authors in the discussion of their results, recent evidence suggests that PRP provides the greatest point estimate of the treatment effect among 17 treatment modalities.<sup>19</sup> Furthermore, meta-analyses of the available data indicate that, compared with HA and saline, intra-articular PRP injection may have more benefit in pain relief and functional improvement in patients with symptomatic knee OA at 1 year post-injection.<sup>20,21</sup> Therefore, we believe that promising results from methodologically rigorous studies could potentially change the way we practice, as these therapies could also be deemed to be cost effective in the near future.

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