Intra-articular platelet-rich plasma for the treatment of osteoarthritis

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Platelet-rich plasma (PRP) is an autologous blood derivative that has been used in different medical fields, ranging from dermatology to ophthalmology and orthopaedic surgery, with the aim of stimulating tissue healing through the local administration of a milieu of platelet-derived growth factors and other bioactive molecules (1). In the orthopaedic practice its main application is in sports medicine (2,3) and in the treatment of degenerative disorders, in particular osteoarthritis (OA) (4). Due to its intrinsic features, PRP is believed to play a beneficial role in joint tissue homeostasis, exerting a positive modulation on all the articular tissues involved in the OA degenerative process, i.e., cartilage, menisci, and synovia (5).

The most common therapeutic approach for PRP application in joint OA consists in intra-articular injections, which can be safely performed in an outpatient setting. PRP intra-articular injection has soon encountered a large success among clinicians, mainly due to the autologous nature of this blood-derived product and due to the attractive perspective of providing a direct stimulus to tissue healing. More than a decade has passed from the very first experiences with intra-articular platelet concentrate (6) but, despite initial enthusiasm and encouraging preliminary results, there is still lack of sounding evidence to recommend it as a first line treatment for the conservative management of OA. The commercial success of PRP has not been backed up by a robust evidence to fully endorse it: in fact, the promising clinical outcomes reported by preliminary case series have not been completely confirmed by high level randomized controlled trials. Just a few double blinded randomised controlled clinical trials (RCTs) are currently available and the overall findings do not allow to assess a clear superiority of PRP over other more traditional approaches. While Patel *et al.* (7) were able to demonstrate that a single PRP injection could provide superior clinical outcome compared to saline solution, Filardo *et al.* (8) failed to document any true, substantial advantage of this blood-derivative compared to viscosupplementation. In particular, the authors could not find any significant inter-group difference at any follow-up evaluation in their trial, which included the strongest study design with the largest cohort of patients currently available in literature. Similar findings were also reported by Battaglia *et al.* (9), who compared PRP to HA in hip OA without showing any superior clinical benefit exerted by growth factors administration.

While a clear superiority compared to other treatments remains to be proven and a powerful placebo effect has been ascribed to PRP (10), its effectiveness is supported by the available literature, with overall positive outcomes in terms of symptomatic relief and functional recovery over time. Single blinded randomized or comparative trials have highlighted better results for PRP compared to saline or HA (11-13).

The main reason beyond these controversial findings, as well as the still inconclusive evidence to support the use of PRP injections in the clinical practice may be due to the great inter-product variability, which is currently the most debated issue in the field of PRP research. From the very beginning of PRP clinical application, several products have been developed and tested, characterized by different preparation methods (blood centrifugation or filtration), different platelet concentration rate, cellular content, activation strategies, storage modalities and also applicative protocols (14,15). Furthermore, PRP has been applied to treat different phases of articular degeneration, ranging from simple chondropathy to severe OA, and

different responses may be ascribed to different disease stages. A superior benefit from PRP application has been hypothesized in lower degrees of cartilage degeneration but the relatively small number of patients included in the current trials has prevented any definitive sub-group analysis. The number of variables to consider is so high that it has been yet impossible to identify the best formulation and therapeutic strategy to fully exploit the potential of PRP and its many biological actions. Despite many attempts to classify different PRP products (16,17), the clinical relevancy of those classifications is questionable, and they are mainly used for research purpose to favour study comparison rather than for guiding clinicians to opt for a particular PRP formulation to address a specific clinical need.

In light of the rising interest towards the application of biologics in the orthopaedic practice, several companies have launched their proprietary formulations on the market and several authors have proposed their particular therapeutic protocols (differing in terms of number of injections and time interval), claiming hypothetical superiority in terms of quality and clinical benefit. *In vitro* and animal studies have been performed in the attempt to shed some light on this controversial field, but even in this case findings have not always been univocal. The paradigmatic example is the role of leukocytes, which is among the most discussed aspects concerning PRP formulation in terms of clinical implications. The presence of leukocytes has been deemed to be detrimental and impair the overall effects of PRP due to the release of metalloproteinases and other lytic enzymes that could interfere with growth factors action and stimulate an early inflammatory response within the joint environment (18,19). Based on the data coming from some *in-vitro* trials (20,21), clinicians argued that leukocyte-poor PRP should be preferred for intra-articular administration. However, the only available clinical trial that compared leukocyte-rich and leukocyte-poor PRP showed no difference in the clinical scores between the two biological approaches, revealing just slightly higher post-injective pain and swelling reaction in the leukocyte-rich PRP group (22). More recently, a systematic review analyzed the adverse events following PRP injection and found a similar safety profile between the different products, suggesting that leukocytes may not be crucial in terms of side effects and overall clinical benefit (23). In light of these recent findings, the role of leukocytes still needs to be fully understood, also taking into account the different leukocytes sub-populations that could exert specific and very different actions in modulating joint homeostasis (24). Therefore, the hunting for the "bad", the "good" and the "ugly" in PRP formulations is still ongoing, and the increasing pre-clinical efforts leave still many unanswered questions. The *in-vitro* setting cannot perfectly mimic the much more complex *in-vivo* scenario, therefore the evidence coming from pre-clinical trials may not be completely mirrored when going into human application, which supports the need for more clinical comparative trials.

PRP technology is still under development and will likely undergo optimization in the future through the identification of factors, related both to the product and to the patient, leading to beneficial effects while avoiding any impairment of joint tissue homeostasis (6). There is still a wide margin to improve this biological treatment approach, and further research efforts are needed to fully exploit the potential of PRP for the treatment of OA.

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Footnote

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