

Chronic anti-platelet therapy: a contraindication for platelet-rich plasma intra-articular injections?

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Abstract. – We report the case of a 50 years-old man who complained persisting knee pain that limited almost completely his sport performance. Since he previously underwent multiple aortocoronaric by-passes, he presented a chronic anti-aggregant therapy. In spite of this clinical history, he was still sport active and able to run long-distance races, until knee symptoms limited his activity level. Conservative treatment approaches proved to be unsuccessful, thus we decided to treat him by 3 Platelet-rich Plasma (PRP) injections even if chronic anti-aggregant therapy is generally regarded as a contra-indication for PRP, since this kind of drugs impairs platelet function and granules' release. Despite these premises, the clinical outcome was very satisfactory and the patient was able to rapidly resume intensive running activity. This experience opens new questions regarding the real potential of PRP in treating degenerative musculo-skeletal disorders, and in particular on its range of biological actions and on its limitations for clinical application.

Key Words:

PRP injections, Chondropathy, Osteoarthritis, PRP contraindications, Anti-aggregant therapy.

Background

Biological products have been recently used to treat a wide range of degenerative disorders, and their application is growing in both clinical and pre-clinical research. In the field of musculo-skeletal pathology, cartilage, tendon, and muscle are the most targeted tissues, especially considering the high prevalence of degenerative lesions affecting these structures¹⁻³. Several different strategies have been tested and, among them, the application of Platelet-rich Plasma (PRP) has emerged as the most exploited way to provide a regenerative stimulus to tissues characterized by a low intrinsic healing potential^{4,5}. The biological rationale is due to the many growth factors (GFs)

and bioactive molecules released by platelet's granules, that could play a beneficial role in modulating tissue homeostasis and healing⁶. After encouraging findings documented in some in-vitro studies and in the animal model⁷⁻¹⁰, PRP has been tested in clinical practice to treat both cartilage¹¹⁻¹³ and tendon pathology¹⁴⁻¹⁶. In the case of intra-articular administration to treat chondropathy or osteoarthritis, satisfactory results were reported: PRP proved to be at least as effective as other traditional approaches such as viscosupplementation¹⁷⁻²¹, thus suggesting that the application of platelet derived GFs might represent a viable treatment option for this specific disease. However, at present moment, clinicians are still looking for a clear clinical indication for this biological approach. Based on the current consensus about PRP application, there are some contraindications to its use^{12,18,20,22,23}. In particular, PRP therapy is not suggested in case of chronic, unstopable anti-platelet therapy. The reason is that anti-aggregant drugs impair platelets' granules secretion and, therefore, the in situ release of GFs and other bioactive molecules²⁴.

Several anti-platelet drugs classes are nowadays applied in clinical practice, with different mechanisms of action: a) Irreversible cyclooxygenase inhibitors; b) Adenosine diphosphate (ADP) receptor inhibitors; c) Phosphodiesterase inhibitors; d) Glycoprotein IIB/IIIA inhibitors; e) Adenosine reuptake inhibitors²⁴. The most used pharmacological agent is aspirin, which is an irreversible cyclo-oxygenase (COX) inhibitor²⁵: it acts as an acetylating agent and it covalently attaches an acetyl group to a serine residue in the active site of the aforementioned enzyme. COX-1 is involved in the arachidonic acid metabolism: its irreversible inhibition blocks the synthesis of prostaglandins and thromboxanes (in particular TX-A₂), which are important mediators that lead to platelet activation and, therefore, to the secretion of granules and their content. Based on these

biochemical premises, clinicians worldwide do not endorse the use of PRP in patients who cannot suspend the use of anti-platelet drugs, since these molecules could negatively affect GFs release and significantly reduce the potential of this biological approach. To the knowledge of the present authors, anti-platelet therapy is commonly regarded as an exclusion criterium for PRP therapy in the clinical trials published up to now, and no study has analyzed the effectiveness of PRP in subjects under this particular pharmacological regimen.

Aim of the present study is to report the clinical results obtained after PRP injective treatment in a patient affected by knee osteoarthritis while undergoing chronic anti-platelet therapy.

Case Presentation

A 52 years old competitive male runner complained about persisting left knee pain since 3 years, associated with a marked functional limitation that obliged him to quit any sport activity for the last 3 months.

The patient was affected by a rare metabolic disorder characterized by high plasmatic level of Lipoprotein(a). This is a LDL-like particle whose high circulating levels are considered a risk factor for cardiovascular diseases. The mechanisms of action are still under investigation but, according to the most accredited theories, lipoprotein(a) is believed to reduce the fibrinolytic potential of plasminogen, to increase the thrombogenesis by stimulating the secretion of plasminogen activator inhibitor-1 and to promote the atherogenic process by carrying cholesterol and other pro-inflammatory molecules^{26,27}. The patient suffered from a severe obstructive coronary disease, that required multiple aorto-coronary by-pass surgery, which was performed when the patient was 43 years old. After the procedure, the patient started a chronic anti-platelet therapy with 160 mg of aspirin on a daily basis, as a prevention to cardiovascular accidents. Other drugs assumed by the patient included Metoprolol, Rosuvastatin, and Niacin. Despite this complex medical history, after the revascularization the patient was able to resume his sport practice under strict surveillance by his cardiologist. He was a long-distance runner, used to train 3-4 times per week and capable of running even marathons with the only condition of keeping his heart rate under the threshold of 120 beats per minute. When the patient asked for our evaluation, his knee functional status was reduced so

that he experienced marked limitation in his physical activity and had to quit running; since the symptom onset, the pain had been worsening over time and also everyday life was affected by some limitations. Clinical examination during our first evaluation revealed a normal alignment of the left knee, moderate swelling, ROM limited to 110°, and diffuse pain at palpation. The patellar tracking was good as a result of a patellar realignment performed 30 years earlier. MRI and X-rays scans revealed signs of advanced pan-compartmental osteoarthritis (Kellgren-Lawrence score: 3) with degenerative changes of both menisci. Based on the clinical and imaging findings, there was no indication for a surgical biological treatment approach to restore the articular surface neither the patient was willing to undergo any resurfacing operation, also considering the high anesthesiological risks.

He previously tried several conservative approaches, such as physical and instrumental therapy (i.e.: magnetotherapy, TENS, etc.) and viscosupplementation (both low and high molecular weight hyaluronic acid), without any substantial clinical benefit. In light of these unsuccessful attempts and the lack of valid alternatives, PRP treatment was applied even if the anti-platelet therapy could not be interrupted, neither aspirin replaced by an anticoagulant drug, as per cardiologist's recommendation. The patient was informed in detail about the lower chance of clinical benefit related to the anti-platelet drug, and agreed to proceed with the injective treatment. Informed consent for treatment and data publication was obtained and the procedure started two weeks after visit. The patient underwent 150 ml autologous venous blood harvesting, and 20 ml of PRP were prepared, according to a previously described method¹², by the Transfusional Medicine Unit of our Institute. Three intra-articular injections of activated PRP were performed one week apart and, after the treatment, physical activity was resumed gradually as tolerated.

The clinical trend was extremely positive: no post-injective swelling was recorded, and 14 days after PRP administration the patient was completely pain-free and started his training, increasing the running distance day by day. His IKDC-subjective score raised from 45.4 to 100 and 35 days after the treatment the patient participated to a running competition, the Bologna City Half-Marathon, which he finished in the time of 1 hour and 58 minutes.

Discussion

The knowledge about the real clinical potential of PRP is still limited and this is due to the many unsolved biological questions about what PRP really is and what are the factors involved in tissue homeostasis and regeneration²⁸. The major role is generally attributed to the platelet-derived GFs but there are also a lot of other important molecules that could exert a beneficial effect. PRP is made of a milieu of several different bioactive substances and further *in vitro* studies are needed to clarify the mechanisms of action of this powerful biological product⁶. Another aspect worth of attention is the fact that there is a large inter-product variability among PRP formulations: several different PRPs have been used in clinical practice, differing in term of preparation methods, cell content, platelet concentration rate, activation methods, applicative protocols and so on. Therefore, each formulation has its own biological properties and peculiarities that could produce different effects according to the specific phase of disease and even to the specific patient treated^{29,30}. Analogously, the knowledge on PRP is limited also with regard to the treatment indications and the limitations for this biological approach.

The main finding of the present case report is that PRP therapy was effective even in a patient who would be commonly considered not suitable for this treatment, due to the daily assumption of an anti-platelet drug. We used a laboratory made, high concentrate, leukocyte-rich PRP which produced good results in a patient under chronic therapy with 160 mg of aspirin daily. Based on the available data it is not possible to assess if these results can be attributed to this particular PRP formulation or if they could be extended to all kinds of platelet concentrates. Moreover, also the patient treated is not representative of the patient population commonly selected for PRP treatment, since he presented a particular metabolic condition, which could be considered a contraindication *per se*. How this metabolic disease could influence articular structures, such as cartilage, meniscus and the surrounding soft tissues, and their responsiveness to biological stimuli, that is another aspect which would require to be better defined.

Since the introduction of this novel class of products in the field of musculo-skeletal medicine, several attempts have been performed to

find the best formula to adopt and the best patient, pathology, and pathology phase to target: a huge amount of variables however must be considered, both related to the blood derivative and the disease considered, which make such attempt particularly challenging. As for each medical treatment, even for this new and largely unknown biological approach, experts tried to suggest some indications and contra-indications that clinicians should take into account before prescribing it. However, for what concerns PRP application, there is still a wide “shadow area” waiting to be brought into light: at present moment we do not know exactly the range of pathologies that could be treated by this approach, we do not know the most effective therapeutic protocols, neither we are aware if there are categories of patients who might respond better to such biological stimulation³⁰. Therefore, the currently proposed “patient selection” criteria are not clearly established and might be reconsidered in the light of new pre-clinical and clinical findings. Anti-platelet therapy has always been considered a major contraindication for PRP therapy^{12,18,20,22,23} since platelet inhibition was seen as an obstacle to the healing potential induced by PRP administration. However, in the present case report we documented encouraging clinical results in a patient under chronic, unstoppable aspirin assumption. Even if a case report lacks the scientific strength to make any general assessment, the rapid and marked response to the treatment suggest that PRP exerted significant intra-articular effects in a patient that would have been commonly considered contra-indicated for such therapy. The hypothesis that PRP could produce its beneficial effects through metabolic pathways not strictly linked to normal granules’ release should be seriously taken into account and stimulate further researches in that sense³¹, with the aim of better understanding what is really effective and who could be definitely considered eligible for this treatment or not. In the present case, authors used PRP as a sort of “salvage procedure” in a patient who had not benefitted from any other previous therapeutic approach and was not candidate for a surgical procedure: the brilliant outcome reported could be a motivation to further inquire about the potentialities of PRP and to put into discussion current established concepts, opening new perspectives for expanding the clinical application of this novel biological treatment.

Conclusions

The clinical application of PRP still needs a careful evaluation to understand its best applicative modalities and treatment indications. The present report suggests that PRP could be effective also in patients currently considered not eligible (i.e.: chronic anti-platelet therapy) for this treatment. Further studies are needed to solve the many still open questions on three different levels: 1) the best PRP formulation to be administered to a specific tissue; 2) the specific disease or disease phase which could benefit the most from this treatment; 3) the profile of the patient who could be safely and successfully treated by this approach, thus determining the proper inclusion and exclusion criteria.

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