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AN EARLY-EXERCISE-RELATED ADVERSE REACTION FOLLOWING PLATELET-RICH PLASMA THERAPY: A CASE REPORT

CASE REPORT

ABSTRACT

Purpose: Platelet Rich Plasma (PRP) is a well-established autologous therapy with several indications in the musculoskeletal spectrum with a few reported complications. PRP pathophysiologic mechanism remains unclear so cause-effect relationships are difficult to be established. To our knowledge, acute inflammatory reactions associated with intra-articular PRP injection have never been reported. We herein present a rare case of adverse reaction in a patient who exercised after only 16 hours from PRP therapy.

Methods: She was admitted to hospital with sensation of fever, pain and inflammation of the knee 8 hours after the training session and 24 hours after last PRP injection.

Results: Laboratory studies did not reveal any infection sign. Once the clinical picture was resolved, the patient was able to resume previous activity level.

Conclusion: In this case, early exercise-related adverse reaction following PRP therapy may have played a role via mediating stimulus as a causative factor.

Key Words: Growth factor, Adverse Effect, Knee joint, Exercise.

TROMBOSİTTEN ZENGİN PLAZMA TEDAVİSİNİ TAKİBEN ERKEN EGZERSİZLE İLİŞKİLİ YAN ETKİ: VAKA RAPORU

VAKA RAPORU

ÖZ

Amaç: Trombositlen Zengin Plazma Tedavisi (PRP), bildirilen birkaç komplikasyonla birlikte kas-iskelet sistemi spektrumunda çeşitli endikasyonları olan köklü bir otolog tedavidir. PRP'nin patofizyolojik mekanizması belirsizliğini korumaktadır, bu nedenle neden-sonuç ilişkilerinin kurulması zordur. Bildiğimiz kadarıyla, eklem içi PRP enjeksiyonu ile ilişkili akut inflamatuvar reaksiyonlar hiç bildirilmemiştir. Bu çalışmada PRP tedavisinden sadece 16 saat sonra egzersiz yapan bir hastada nadir görülen bir advers reaksiyon vakası sunulmaktadır.

Yöntem: Eğitim seansından 8 saat sonra ve son PRP enjeksiyonundan 24 saat sonra ateş, ağrı ve dizde iltihaplanma hissi ile hastaneye başvuru.

Sonuçlar: Laboratuvar çalışmaları herhangi bir enfeksiyon belirtisi göstermedi. Klinik tablo düzeldiğinde, hasta önceki aktivite seviyesine devam edebildi.

Tartışma: Bu durumda, erken bir egzersiz aracılı uyaran nedensel bir faktör olarak rol oynamış olabilir. PRP tedavisini takiben erken egzersizle ilişkili advers reaksiyon, uyarana aracılık etme yoluyla nedensel bir faktör olarak rol oynamış olabilir.

Anahtar Kelimeler: Büyüme faktörü, Yan Etki, Diz Eklemi, Egzersiz

INTRODUCTION

Platelet Rich Plasma (PRP) has been used for different purposes in orthopedics, both in conservative and invasive proposals in the management of cartilage, tendon, or muscle injuries, with positive outcomes (1). Evidence for its effectiveness has been related to a specific indication and highly dependent to managing protocols. This same evidence highlights PRP as a decidedly safe therapy due to its autologous nature, even in cancer patients (2). However, despite encouraging clinical and functional reports, the safety of this approach has been occasionally questioned in surgical contexts, where several variables are known to play a role beyond PRP product (3). Less invasive procedures performed on patellar tendon can promote various forms of adverse reaction (4,5). Classical undesirable effects related to PRP administration include those involving infiltration, such as local infections, nerve damage, pain around the injection site, and tissue damage. Scarce literature has been published on the adverse effects of autologous PRP, and it has been mostly related with the procedure rather than PRP component itself (3). In addition, to our knowledge adverse reactions derived from intra-articular PRP injection followed by early exercise stimulus have never been described.

CASE REPORT

A 47-year-old Caucasian female with a 6 week-history of right knee pain was selected for PRP intra-articular injection. There were no records of previous or present systemic illnesses. She worked as a bank manager and practiced yoga on daily basis three times a week for a total of 4.5 hours. Her right knee was painful and experienced snapping and temporary locking following a twisting movement during yoga practice. The patient presented to our facilities with medial knee pain -7 out of 10 on a Numeric Rating Pain Scale (NPRS) (0, no pain; 10, maximal pain) (6), and limited range of motion (ROM). Manual muscle testing, based on Kendall et al, (7) revealed slight weakness of the quadriceps femoris and hamstring muscles on the involved side probably due to slight inhibition, with a rating of 4-/5 on the right versus 5/5 on the left. Physical examination revealed focal swelling and medial joint line tenderness, and McMurray/Apley

Grind test provoked pain with external rotation. Subsequent Magnetic Resonance Imaging (MRI) of the knee demonstrated myxoid degeneration of the posterior horn of the medial meniscus with no clear signs of rupture. Based upon the clinical examination and after imaging confirmation, she was proposed to undergo PRP injection series to treat the meniscal injury.

A 45 mL peripheral whole blood was withdrawn from the patient antecubital vein and collected on 5 mL tubes containing 3.8% (w/v) trisodium citrate, and then centrifuged in the gravitational platelet separation system (Auxilab, Nahita Blue, FugelabGB10, Navarra, Spain). With the patient in supine and her knee bent to 90° using an infrapatellar and percutaneous approaches the knee was injected. After careful disinfection using povidone-iodine, the intraarticular injection of 6 mL of PRP (with no red or white blood cells) was administered. Additional 1.5 mL of PRP were periarticularly administered in loco dolenti, at the body and/or horn and according to previously described approaches (8). All injections were performed under ultrasound-guidance and no local anesthetic was employed. The whole procedure was uneventful. Patient was instructed to rest from all sporting activity during 48 hours and to locally apply ice along with lower limb elevation.

A PRP injection regime consisting of 3 PRP applications separated by 1 week between infiltrations was conducted. Pain and neuromuscular inhibition had already normalized right before the third and last injection series, with a rating of 0/10 on NPRS and 5/5 on Kendall's scale, respectively. However, twenty-four hours after last PRP injection the patient referred sensation of fever, pain (NPRS 9/10) and a positive right knee ballottement test with local increase of temperature. She described a moderate workout session around 16 hours after the last injection, which may have altered the recommended 48-hour resting period. The reported session consisted of aerobic exercise series (bike), and yoga postures combined with breathing techniques. Details are summarized in Table 1.

She was admitted to hospital with the symptoms referred and a fever of 39°C. The knee was aspirated with a return of 20 mL of dark, cloudy sy-

Table 2. Workout Completed Right After The Third PRP-Injection.

Practice	Description	Position	Duration	
Aerobic Exercise - Warm Up	Stationary biking	Sitting on a bike	3 rounds of 15 minutes each, 60W	
	Balasana - Child's pose	Kneeling	5 rounds of 30s each, with a 2-minute rest period	
	Marjaryasana/Bitilasana - Cat/Cow poses	Dynamic Quadruped	5 rounds of 30s each, with a 2-minute rest period	
	Uttanasana - Rag Doll pose	Bipedal Stance	5 rounds of 30s each, with a 2-minute rest period	
	Baddha Konasana - Seated cobblers pose	Sitting	5 rounds of 30s each, with a 2-minute rest period	
	Paschimottanasana - Seated forward fold	Sitting	5 rounds of 30s each, with a 2-minute rest period	
	Yoga Practice	Viparita Karani - Legs up the wall pose	Supine	5 rounds of 30s each, with a 2-minute rest period
		Tadasana - Mountain pose	Bipedal Stance	5 rounds of 30s each, with a 2-minute rest period
		Nauksana - Boat pose	Sitting, balance	5 rounds of 30s each, with a 2-minute rest period
		Bananasana - Banana pose	Supine, lateral	5 rounds of 30s each, with a 2-minute rest period
Vrksasana - Tree pose		Unipedal Stance	5 rounds of 30s each, with a 2-minute rest period	
Meditation	Dhyana and Pranayama – deep breathing for anxiety/rajasic depression	Sitting	15 minutes each	

novial fluid with low viscosity. She was then hospitalized to rule out iatrogenic septic arthritis, or inflammatory arthritis acutely worsened by early exercise stimulus, until synovial fluid analysis and cultures could be performed. Biochemistry study of synovial liquid showed high level of proteins and glucose over normal range and Gram stain demonstrated no organisms' presence. All these findings were compatible with inflammatory arthritis (Table 2). Five days after being admitted to hospital patient's signs and symptoms disappeared and she was discharged. The patient returned to the hospital for follow-up assessment 7 days later showing consistent improvement. Pain only appeared at the

posteromedial aspect beyond 130° of knee flexion and during full squat. A progressive lower limb balance and strengthening program based on previously reported proposals was prescribed (9,10), along with restoration of full yoga activity. She reported complete resolution of her knee symptoms at her 2-month follow-up Table 2..

This case report was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The current study was conducted upon Institutional Ethics Committee approval (n. 1-2020-H). The patient provided verbal and written consent for participation.

Table 2. Synovial Fluid Characteristics 24 hours and 72 hours after third PRP injection.

Parameter	24 Hours After Injection	72 Hours After Injection
Colour, aspect	Dark Cloudy Yellow	Light yellow
Red blood cell count	3000 cells/ μ l	5425 cells/ μ l
White blood cell count	6304 cells/ μ l 70.9 / PMN	1048 cells/ μ l 41.8 / PMN
Proteins	3.73 g/dL	3.60 g/dL
Glucose	82.70 mg/dL	70.70 mg/dL
Culture	Negative	Negative

DISCUSSION

Adverse events from PRP inoculation are equivalent to those inherently related to any form of injection, and may include infection, scar tissue formation, pain at the injection site, and neurovascular injury leading to numbness and tingling or ecchymosis at best. To our knowledge, no robust preclinical nor clinical studies reporting systemic effects following local PRP injections exist in scientific literature. Uniquely development of antibodies against clotting Factor V leading to life threatening maladies has been associated to bovine thrombin as activating substance, rather than PRP product itself (1,2). PRP complications are also related to the anatomical region being treated or the involved tissue. Redler et al. questioned the efficacy and safety of PRP in severe degenerative tendinopathies by presenting a case of a 40-year-old male soccer player who sustained a patellar tendon rupture after a 4-PRP-injection series. Surgical findings demonstrated a complete rupture of the patellar tendon, with severe degenerative changes of the tendon tissue. However, a clear cause-effect relationship is not documented as they recognized those severe degenerative changes themselves might have led to that rupture. An exuberant inflammatory reaction affecting the same region has been reported in a type 1 diabetic patient suffering from jumper's knee after 1 injection of PRP. These authors exposed a reasonable doubt when using this product and highlighted the diabetes factor[5]. Regarding our presented case, no side effects have been reported in the literature following intraarticular injection of PRP in any type of condition. Only significant synovitis has been described after subacromial decompression combined with PRP injection. In this case the authors admitted that an unequivocal PRP implication in the development of the hypertrophic synovitis could not be assumed, as both procedures were developed during the same surgery time[12]. In our case the patient did not develop an intraarticular inflammatory reaction immediately but 24 hours after the third PRP injection. We hypothesize that this joint inflammation was probably initiated by an early exercise program assumed by the patient in the context of initial phase of GFs release, whose action was too broad for a recently injected joint.

There are multiple factors that may influence the efficacy of PRP procedures. These include, but are not limited to centrifugation protocol, platelet concentration, white cells inclusion, pH of the injected product, type of activator employed, total number of administrations, or ultrasound guidance, being the subject of much debate. Beyond these parameters, a wide variety of post procedure recommendations and rehabilitation interventions have been proposed, and little consensus exists to date on when and how to exercise after PRP injection (1). Important aspects in early post-intervention requiring validation include the need for immobilization following the injection and the best time to introduce joint load activities as well as the specific variables regarding return to play. Most of available research has been focused on tendinopathies and include small samples with short-term follow-up periods (13). Post-injection exercise-based protocols after intraarticular applications are lacking and should be addressed in future investigations.

Specially in sports medicine where early exercise prescription is vital, the mechanical stimulus whether associated to physiotherapy or exertion, plays an important role in cellular differentiation and tissue repair. Consequently it may act synergically with the PRP treatment in the healing process of musculoskeletal tissues (14). A general recommendation of a 48 hours resting period is accepted. In the acute phase patients are recommended to rest with ice and limb elevation after injection as well as avoiding NSAIDs for two weeks following the application[1]. In this case we identified the absence of resting period after the last infiltration as the probable cause of inflammatory arthritis. Due to her initial response the patient became confident and decided not to rest after the last injection. When interviewed she wanted to test her knee as she was starting to feel much better. She did not wait the time recommended and shortly after 16 hours of PRP application she began her activity of yoga after 45-minute bike warm-up.

According to its nature, this case report is accompanied by several limitations. First, the data herein presented permit less clinical generalizability than that provided by case series or randomized studies with larger sample sizes. Second, since multiple variables may have influenced the reported clinical

adverse reaction, no cause-effect relationship can be solidly established as it is hard to distinguish the amount of contribution of each to the eventual outcome. Third, our work is also limited by its lack of objective data (e.g., dynamometry rather than manual muscle testing) and patient-reported outcome measures. Finally, inherent limitations such as danger of over-interpretation, publication bias, or retrospective design are common to this type of scientific report and consequently affect to this paper.

Although a defined complication occurred in this particular patient, the causality between the early-exercise stimulus and the joint reaction cannot be determined by a single case report. This case report also cannot determine whether the PRP procedure itself may have played a role in the reported reaction. Further studies are required to answer all of these questions. PRP is a well-established autologous therapy with several indications in the musculoskeletal spectrum with a few reported complications. The pathophysiologic mechanism in those cases remains unclear but might be related to the procedure itself rather than the inoculated product. The present case involved a joint inflammatory reaction in response to intraarticular administration of PRP followed by early-exercise stimulus. Post-injection, exercise-associated reactions are rare but significant events, and clinicians prescribing and treating joint pathologies with PRP preparations should be aware of this potential reaction.

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