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Review

Adverse events related to platelet-rich plasma therapy and future issues to be resolved

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ABSTRACT

Platelet-rich plasma (PRP) is the portion of plasma with a platelet concentration above baseline that is recovered through centrifugation of autologous blood. PRP therapy is currently used for wound healing and pain relief in diverse medical fields. Although there have been recent reports of adverse events (AEs) possibly related to PRP treatment, the safety profile of PRP treatment remains unclear. Therefore, this review discusses the risks inherent in PRP therapy and the current issues by surveying reports on AEs associated with PRP treatment within different fields.

PubMed was searched for research articles referring to AEs associated with PRP therapy from inception to January 2024. Literature survey revealed that PRP therapy may involve several AEs, including post-operative infections, blindness, inflammation, allergic reactions, and nodule development. The most commonly reported AE was postoperative infections. Since PRP therapy generally proceeds in the process of blood collection, manufacturing, and administration to patients, it is conjectured that PRP may have been contaminated with microorganisms at some point in this series of processes, leading to bacterial infection. Additionally, because PRP cannot be sterilized like pharmaceuticals, it is important to prevent microbial contamination during each PRP treatment process. However, the specific process that involves the risk of microbial contamination remains unclear. To take measures to prevent microbial contamination of PRP, it may be necessary to elucidate the risk factors for microbial contamination during PRP treatment. It may be important to elucidate the effectiveness and risks of PRP therapy as well as to establish a follow-up system after PRP treatment. Currently, most reports of AEs related to PRP therapy are case reports; therefore, the accumulation of high-quality evidence and detailed verification are necessary to determine the causal relationship between PRP therapy and each AE.

Contents

Abbreviations: PRP, platelet-rich plasma; PRGF, plasma rich in growth factor; CGF, concentrated growth factor; PRF, platelet-rich fibrin; AE, adverse event.

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1. Introduction

The concept of platelet-rich plasma (PRP) began in the field of hematology [1], with PRP being initially used as a transfusion product for treating patients with thrombocytopenia [2]. In the late 1980s, Knighton et al. reported that bioactive molecules released from autologous platelets have a healing effect on damaged tissues, including skin ulcers [3]; subsequently, PRP has been used in regenerative medicine. PRP was initially applied in maxillofacial surgery in the 1990s [4] and in orthopedic and plastic surgeries in the 2000s [5]. Currently, PRP therapy for regenerative medicine is widely practiced in diverse medical fields, including orthopedic surgery [6], dentistry [7], dermatology [8], plastic surgery [9], and sports medicine [10].

PRP is used for a variety of purposes, including wound healing, pain relief, skincare, and anti-aging treatment. Although, the mechanism of action of PRP has not been fully elucidated, it is thought that following activation of the platelets contained in PRP, multiple cytokines and growth factors are released from the α-granules into the injured tissues at supraphysiological concentrations, contributing to anti-inflammatory effects and tissue repair.

PRP is obtained by centrifuging autologous peripheral blood; subsequently, it is injected in liquid form or implanted as a gel into the patient's affected area. Unlike other cellular therapies, PRP preparation is simple and does not require any culturing procedures. Currently, there are numerous commercial PRP preparation systems used in clinical settings. Furthermore, PRP therapy has the advantage of the short period between blood collection and PRP administration as well as its relatively low cost. These advantages with respect to manufacturing, cost, and low burden on patients may have contributed to the widespread use of PRP.

However, although the usefulness of PRP treatment has been demonstrated, there have been recent reports of adverse events (AEs) possibly related to PRP treatment. The causal relationship between PRP therapy and AEs has not been fully elucidated, and AEs associated with PRP treatment range from postoperative infections to severe cases such as blindness. Therefore, this review discusses the risks inherent in PRP therapy and the current issues by surveying reports on AEs associated with PRP treatment within different fields.

2. Overview of PRP therapy

2.1. The biological properties of PRP

PRP is the portion of plasma with a platelet concentration above baseline that is recovered through centrifugation of anticoagulant-added autologous blood. There are various methods for PRP preparation, and there remain no standardized manufacturing method. PRP-related products, including platelet-rich fibrin (PRF) [11], plasma rich in growth factor (PRGF) [4,12], and concentrated growth factor (CGF) [13] have also been used for therapeutic purposes. PRGF is produced by centrifuging the anticoagulant-added blood at a lower speed and for a shorter time than in PRP centrifugation. Similar to PRP, PRGF can be injected in liquid form or implanted as a gel depending on therapeutic purposes. Unlike the method of preparation of PRP, PRF and CGF are manufactured by centrifuging blood using glass tubes without the addition of anticoagulants, and are obtained in the form of a gel.

Platelets are activated by adding calcium chloride, thrombin, and other agents. Following activation of platelets, α-granules release multiple growth factors and cytokines related to the healing of damaged tissue and anti-inflammation [14], including platelet-derived growth factors, transforming growth factors, vascular endothelial growth factor, epidermal growth factor, and fibroblast growth factor. In PRP therapy, supraphysiological concentrations of growth factors and cytokines act on the affected site, repairing damaged tissues and exerting anti-inflammatory effects. However, given the complex properties of PRP, the components responsible for its therapeutic effects remain unclear [15].

2.2. Applications of PRP in diverse disease areas

PRP therapy is currently used in diverse medical fields, including orthopedic surgery, sports medicine, maxillofacial surgery, plastic surgery, dermatology, and ophthalmology. Here, we introduce examples of applications of PRP therapy in particularly relevant fields.

In orthopedic surgery, PRP therapy is used to treat musculoskeletal and other joint diseases, especially knee osteoarthritis. Intra-articular injection of PRP is used to treat symptoms of knee osteoarthritis. A meta-analysis showed that, compared with hyaluronic acid, intra-articular injection of PRP could improve pain and function for up to 12 months in patients with knee osteoarthritis [16]. Multiple clinical studies have shown that PRP is more effective than hyaluronic acid in mild-to-moderate knee osteoarthritis and in younger patients [14,15]. In preclinical studies, activated platelet granule secretions primarily exhibited homeostatic effects with anti-inflammatory and anabolic effects on joint tissues and cells [14].

In the dental field, PRP therapy is used for the regeneration of periodontal tissue lost due to periodontal disease and for wound healing following oral and maxillofacial surgery, including tooth extraction, soft and bone tissue surgery, and implant surgery [7]. For oral and maxillofacial surgery, a PRP gel is generated by adding $CaCl_2$ or another agent to PRP, which is subsequently implanted into the affected area. Further, PRF and CGF have been used for regeneration of periodontal tissues as well as PRP [17]. Numerous studies have demonstrated that PRP gel can significantly reduce postoperative pain and discomfort after tooth extraction and prevent the development of osteitis [18]. However, the clinical implications of PRP in regenerative dentistry remain controversial.

3. Adverse events of PRP therapy

We reviewed reports regarding AEs related to PRP therapy as of January 2024 (Tables 1 and 2). PubMed was searched for research

Table 1
List of adverse effects associated with PRP therapy as of January 2024.

Source	Country	Study design	Target disease	Area treated	Intervention	No. of patients	Adverse events	Whether antibiotics were used during PRP therapy
Dincer D. et al. [19]	Turkey	Case study	Gastrocnemius muscle rupture	Left gastrocnemius muscle	Injection of PRP	1	Local infection with *Staphylococcus aureus*	NR
Beatty N.R. et al. [20]	USA	Case study	Chronic low back pain	L5/S1 disc	Intradiscal injection of PRP	1	Spondylodiscitis due to *Cutibacterium acnes* infection	NR
Toraman N.F. et al. [21]	Turkey	Case study	Knee osteoarthritis	Both knee	Intra-articular injection of L-PRP	1	Septic arthritis in the left knee due to *Streptococcus mitis* infection	NR
Senet P. et al. [25]	France	Placebo-controlled, double-blind RCT	Chronic venous leg ulcers	Leg	1: Topical application of FAP 2: Topical application of saline	1: 7 2: 6	Wound infection, 1: 1 vs 2: 0	NR
Anitua E. et al. [22]	Spain	Open-label RCT (pilot study)	Chronic cutaneous ulcers	Leg or pelvic region	1: Topical application of PRGF 2: Standard care	1: 8 2: 7	Super-infection of the ulcer bed, 1: 1 vs 2: 2	NR
Ghaffarpasand F. et al. [24]	Iran	Placebo-controlled, double-blind RCT	Long bone nonunion fractures	Long bone (femur, tibia, humerus and ulna)	1: PRP 2: Saline	1: 37 2: 38	Infection complications, 1: 5 vs 2: 2	One gram of cefazolin was injected as a prophylaxis just before surgery.
Cervelli V. et al. [23]	Italy	Study with no controls	Vascular, diabetes-correlated, or posttraumatic diseases with ulcers or loss of substance	Lower limbs (fingers, foot, knee, and leg)	Treatment with PRP and autologous fat grafts	30	Infectious complications occurred in two patients.	NR

PRP, platelet-rich plasma; L-PRP, leukocyte-rich PRP; PRGF, plasma rich in growth factor; RCT, randomized clinical trial; FAP, frozen autologous platelets; NR, not reported.

articles referring to AEs associated with PRP therapy from inception to January 2024.

3.1. Post-operative infection

In this literature review, postoperative infection was the most commonly reported AE in PRP therapy. There are a few reported cases in which bacterial species responsible for postoperative infections after PRP injection have been identified. To date, three cases of infection with human skin or oral cavity commensal bacteria following PRP injection have been reported. Among them, there was a case of local infection with *Staphylococcus aureus* in a 27-year-old male professional football player who underwent PRP injection to treat left gastrocnemius muscle rupture [19]. Another one was a 40-year-old woman who developed spondylodiscitis due to *Cutibacterium acnes* infection after receiving an intradiscal PRP injection at the L5/S1 level under fluoroscopic guidance for chronic low back pain [20]. The third one was a 62-year-old woman who received an intra-articular injection of PRP for knee osteoarthritis and developed septic arthritis after three days due to infection with *Streptococcus mitis* [21]. In addition, multiple clinical studies on the efficacy of PRP have confirmed cases of postoperative infection after PRP therapy [22–25]. Given the limited reports regarding postoperative infections related to PRP therapy, the causal relationship between PRP therapy and postoperative infections remains unclear. Although cases of postoperative bacterial infection are rare, physicians should be aware of the risk of infection following PRP administration.

3.2. Inflammation

There have been two reported cases of inflammatory reactions after PRP treatment. A healthy 66-year-old man underwent an initial diagnostic arthroscopy with subacromial decompression for the treatment of impingement syndrome of the dominant right shoulder, followed by PRGF injection into the subacromial space. After PRGF administration, the patient's preoperative pain persisted and progressively worsened. Nine months after PRGF administration, there was no improvement and shoulder arthroscopy revealed no intra-articular lesions; however, dense and exuberant synovitis was observed throughout the subacromial space [26]. In this case, adequate subacromial decompression was performed and other intra-articular pathologies were not identified; however, an unusually thick and adherent synovium was observed. Although it cannot be concluded that PRGF is solely responsible for exuberant synovitis, Mallo et al. speculated that PRGF may be involved in the development of hypertrophic synovitis.

In the other case, a single dose of PRP was administered to treat jumper's knee (patellar tendinitis) in a 35-year-old male patient with type 1 diabetes who developed a severe local inflammatory reaction one week after PRP injection [27]. Although the cause of the inflammatory response to PRP injections remains unclear, Kaux et al. speculated that type 1 diabetes is a likely contributor.

3.3. Blindness

The first case of blindness associated with PRP therapy was reported in the United States in 2017 [28], with similar cases being reported in Venezuela [29] and Malaysia [30]. These cases were attributed to the administration of PRP into the glabellar area or nasolabial folds for anti-aging purposes. All cases, with the exception of that reported by Maslan et al., resulted in irreversible blindness, which is among the most severe AEs associated with PRP therapy. It was speculated that the cause of blindness after PRP

Table 2
List of other adverse effects associated with PRP therapy as of January 2024.

Source	Country	Study design	Target disease/Aim	Area treated	Intervention	No. of patients	Adverse events	Patient's medical history and infection history
Mallo GC. et al. [26]	USA	Case study	Impingement syndrome	Dominant right shoulder	A diagnostic arthroscopy with partial bursectomy, subacromial decompression, and PRGF injection	1	A dense and exuberant synovitis throughout the subacromial space	An otherwise healthy 66 years-old man, nondiabetic and nonsmoker.
Kaux JF. et al. [27]	Belgium	Case study	Patellar tendinitis	Right knee	Intra-tendinous injection of PRP	1	Exuberant local inflammatory reaction at the injection site	A 35-year-old man with type 1 diabetes.
Kalyam K. et al. [28]	USA	Case study	Skin rejuvenation	Glabellar area	PRP injection	1	Irreversible blindness	An otherwise healthy 49-year-old woman.
Karam EZ. et al. [29]	Venezuela	Case study	Skin rejuvenation	Glabellar area or nasolabial fold	PRP injection	4	Irreversible blindness	Four otherwise healthy women aged between 50 and 63 years old.
Maslan N et al. [30]	Malaysia	Case study	Skin rejuvenation	Glabellar area	PRP injection	1	Loss of vision	An otherwise healthy 48-year-old woman.
Latalski M et al. [31]	Poland	Case study	Solitary bone cyst	Distal tibia	Injection with PRP to the bone cyst under image intensifier control	1	Allergic reaction	A 14-year-old boy with no medical history of allergic diseases.
Serizawa et al. [32]	Japan	Case study	Skin rejuvenation	Face	Intradermal injection of PRP	1	Development of multiple slightly reddish nodules at injection sites.	A 68-year-old woman who was suspected of ocular sarcoidosis.
Izhakoff N et al. [34]	USA	Case study	Skin rejuvenation and treatment for a right rotator cuff injury	Face and shoulder	Intradermal injection of PRP	1	Development of nodules at injection sites.	A 62-year-old woman with a medical history of uveitis.
Owczarczyk-Saczonek A et al. [35]	Poland	Case study	Skin rejuvenation	Face and neck	Intradermal injection of PRP	1	Serum sickness disease	A 41-year-old woman with alopecia areata and Meniere's syndrome.
Incel Uysal P and Gunhan O [36]	Turkey	Case study	Skin rejuvenation	Face and neck	Intradermal injection of PRP and autologous fat	1	Development of asymptomatic nodules at injection sites.	The patient infected with COVID-19 3 weeks before the development of the lesions.
Saade S et al. [37]	Lebanon	Case study	Skin rejuvenation	Face and neck	Intradermal injection of PRP	1	Development of cutaneous sarcoidosis at injection sites.	The patient has a history of COVID-19 and has received two vaccinations.
Porter S and Wig S [38]	UK	Case study	Knee osteoarthritis	Left knee	Intra-tendinous injection of PRP	1	Polyarticular gout secondary to PRP injection.	A 57-year-old man with hyperlipidaemia, hypertension, transient ischaemic attack and prediabetes.
Zeineddine et al. [39]	France	Case study	Androgenetic alopecia	Scalp	Injection of PRP into scalp	1	Development of Herpes zoster ophthalmicus with superimposed bacterial infection.	A previously healthy 71-year-old woman.

PubMed was searched for case reports of adverse events associated with PRP therapy from inception to January 2024. PRP platelet-rich plasma, PRGF plasma rich in growth factor.

injection was the inadvertent injection of PRP into the blood vessel, which caused iatrogenic occlusion of the ophthalmic artery.

3.4. Allergic reactions

One case of allergy associated with PRP therapy has been previously reported. A 14-year-old boy with a solitary bone cyst in the distal tibia developed a rash within 24 h of PRP administration under image intensifier control [31]. Since this patient received calcium citrate with PRP administration, an additional calcium citrate test was conducted. The skin prick test result was negative and the intradermal test result was positive. Calcium citrate is formed when citric acid from the anticoagulant citrate dextrose solution A, which is added to venous blood as an anticoagulant during the manufacturing of PRP, chelates the calcium ions in the blood. Latalski et al. speculated that calcium citrate should be considered as the hapten in this case. Since this patient had no medical or family history of allergic disease, Latalski et al. suggested that patients seeking PRP therapy should undergo a skin test before treatment to reduce the risk of side effects.

3.5. Nodules in patients with active sarcoidosis

PRP is often used an anti-aging treatment for the skin and is injected to improve crow's feet, nasolabial folds, and neck wrinkles. Several cases have been reported in which nodules (granulomas) developed at injection sites following PRP injections for anti-aging purposes in patients with sarcoidosis. A 68-year-old Japanese woman with suspected ocular sarcoidosis underwent PRP therapy to treat facial wrinkles and subsequently developed nodules at the injection sites [32]. The appearance of cutaneous sarcoid granulomas is related to the presence of foreign substances such as silicone and hyaluronic acid [33]. According to Serizawa et al., this patient had a history of receiving hyaluronic acid and botulinum toxin injections several years prior to PRP therapy; therefore, it cannot be ruled out that these factors may have played a role in nodule development. Subsequently, another case was reported involving nodules possibly related to PRP injections in a patient without a history of receiving injections of foreign substances. Specifically, a 62-year-old Chilean woman with a history of uveitis received PRP therapy to treat right rotator cuff injury and anti-aging of her face; however, after 4 months, she developed nodules at the injection sites [34]. However, a causal relationship between PRP injections and nodules in patients with active sarcoidosis cannot be established.

3.6. Serum sickness disease in a patient with active autoimmune disease

A 41-year-old female with alopecia areata and Meniere's syndrome received PRP treatment to rejuvenate her facial skin and neck. After 2 weeks, she presented with erythematous wheals with arthralgia, malaise, fatigue, and fever at the PRP injection sites. Accordingly, the patient was diagnosed with serum sickness triggered by PRP injections [35]. The authors suggested that PRP treatment should not be administered to patients with autoimmune diseases in the active phase.

3.7. PRP therapy after infection with COVID-19

There have been two reported cases of AEs following PRP therapy that were related to COVID-19. First, a 39-year-old woman who received PRP and an autologous fat injection in the face and neck for skin rejuvenation developed asymptomatic nodules at the injection sites 2 months after the injection [36]. The patient had contracted a COVID-19 infection 3 weeks before the appearance of skin lesions. It was not indicated whether the patient had been vaccinated. Second, a 41-year-old healthy woman who underwent PRP therapy of the face and neck developed cutaneous sarcoidosis at the injection sites [37]. She had a history of COVID-19 and had received two doses of the COVID-19 vaccine. Systemic sarcoidosis was ruled out in both cases. The patient had received multiple PRP injections before contracting COVID-19 without experiencing any side effects. However, skin lesions developed at the site of PRP injection after the COVID-19 infection. Accordingly, even for patients without COVID-19 infection at the time of PRP administration, subsequent COVID-19 infections may trigger skin lesions. However, the causal relationship between PRP therapy and COVID-19 remains unclear.

3.8. Others

Although the causal relationship to PRP therapy has not been fully elucidated, other AEs related to PRP therapy have been reported. A 57-year-old man at risk of gout received PRP injections in his knee tendon to treat knee osteoarthritis; however, within 24 h, he developed acute pain and swelling and was diagnosed with suspected gout [38]. Porter et al. speculated that uric acid in lysed platelets induces the release of growth factors and cytokines, activating the gout inflammatory response.

A 71-year-old healthy woman developed herpes zoster ophthalmicus (HZO) with a superimposed bacterial infection after receiving PRP injections on her scalp for treatment of androgenetic alopecia [39]. In this case, weakening of the immune system was ruled out. Furthermore, the patient had not received any vaccination before PRP administration; accordingly, PRP injections remained the most likely cause of stress. Zeineddine et al. speculated that HZO was caused by acute stress, which was likely induced by PRP treatment.

4. Discussion

PRP therapy is easy to perform and is offered worldwide for various purposes. Although PRP therapy is considered a relatively low-risk treatment, various AEs can occur. For example, there have been reports of postoperative infections, blindness, inflammation, allergic reactions, and nodule development. These AEs associated with PRP therapy could be related to various factors, including technical problems of the practitioner, problems during PRP manufacturing, and various cytokines and growth factors present in the PRP. Additionally, AEs associated with PRP therapy occur in both healthy and ill patients. Currently, there remains insufficient evidence regarding the AEs of PRP therapy; accordingly, further studies are warranted to prevent AEs associated with PRP therapy. Physicians should carefully consider whether to offer PRP therapy for patients with a history of specific diseases or infections associated with AEs following PRP therapy.

In this literature survey, postoperative infection after PRP administration was the most commonly reported AEs following PRP therapy [19–25]. Since PRP therapy generally proceeds in the process of blood collection, manufacturing, and administration to patients, it is conjectured that PRP may have been contaminated with microorganisms at some point in this series of processes, leading to bacterial infection. Additionally, because PRP cannot be sterilized like pharmaceuticals, it is important to prevent microbial contamination during each PRP treatment process. However, the specific process that involves the risk of microbial contamination remains unclear. To take measures to prevent microbial contamination of PRP, it may be necessary to elucidate the risk factors for microbial contamination during PRP treatment. However, although

PRP therapy is excellent with respect to the short period between blood collection and PRP administration, there remains no rapid microbial test method that is suitable for non-cultured cell products such as PRP and allows cheap and quick evaluation of microbial contamination. Therefore, it is difficult to confirm whether a product is contaminated with microorganisms before the PRP is administered. Elucidation of PRP therapy and appropriate quality assurance methods are warranted in the future.

5. Conclusion

Although PRP therapy is a relatively safe and simple treatment, it involves a risk of several AEs, including postoperative infections. It may be important to elucidate the effectiveness and risks of PRP therapy as well as to establish a follow-up system after PRP treatment. Additionally, if a patient with the specific disease described in this article wishes to undergo PRP therapy, this should be carefully considered. Since PRP treatment is widely administered, it is important to continue collecting information regarding its safety. Currently, most reports of AEs related to PRP therapy are case reports; therefore, the accumulation of high-quality evidence and detailed verification are necessary to determine the causal relationship between PRP therapy and each AE.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Morikuni Tobita reports a relationship with Juntendo University that includes: employment. Anna Arita reports a relationship with Juntendo University that includes: employment.

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