Benefits of platelet rich plasma (PRP) treatment on skin autografts and allografts in a burned patient

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ABSTRACT – REZUMAT

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Wound healing is promoted by a series of growth factors, secreted from the alpha granules of the platelets. Platelet rich plasma (PRP) emerged as a clinical strategy to increase the physiologic concentration of platelets and its clinical use for a large spectrum of disorders is reported, with good results. Extensive burns represent a promising field for PRP use, those patients confronting challenging wound healing and poor long-term results. We present our initial clinical experience represented by a case of a 51-year-old male patient, severely burned, who benefited from sequential surgical treatment of deep burn wound excisions and coverage using autologous and allogenic skin grafts. PRP was added to this patient's therapy in two stages, being injected and externally applied on the autografts in functional areas of the hands and the right upper arm region where both autografts and allografts were placed, with the exciting result of promoting allograft integration, long-term persistence and healing. Several literature data validate successful clinical applications of PRP in various therapies, including treatment of soft tissue injuries and chronic wounds, orthopedic surgery, burns, maxillo-facial surgery and elaboration of tissue-engineered products. Based on our preliminary experience and favourable reports in the literature, we encourage wider use of platelet rich plasma for immunomodulation and tissue-engineered constructs, due to its effects on local inflammatory response and role in enhancing the integration of various types of tissue grafts.

Keywords: *platelet rich plasma (PRP), burns, autograft, allograft, immunomodulation*

Beneficiile tratamentului cu plasmă îmbogățită cu trombocite (PRP) asupra autogrefelor și alogrefelor tegumentare la un pacient ars grav

Vindecarea plăgilor este promovată de o serie de factori de creștere, secretați de la nivelul granulelor alfa ale trombocitelor. Plasma îmbogățită cu trombocite (PRP) este o strategie terapeutică utilă pentru creșterea concentrației fiziologice de trombocite și utilizarea ei clinică a fost raportată pentru un spectru larg de afecțiuni, cu rezultate bune. Un domeniu promițător pentru folosirea PRP este reprezentat de arsurile extensive, pentru pacienții ce se confruntă cu o vindecare precară a plăgii și rezultate nefavorabile pe termen lung. Prezentăm experiența noastră clinică inițială, reprezentată de cazul unui pacient de 51 ani, ars sever, care a beneficiat de tratamentul chirurgical secvențial al arsurilor profunde prin excizia leziunilor și acoperire cu grefe tegumentare autologe și alogrefe. Terapia pacientului a fost suplimentată cu PRP în două etape, fiind atât injectat, cât și aplicat topic pe autogrefele din zonele funcționale ale mâinilor și membrului superior drept, unde au fost folosite atât alogrefe, cât și autogrefe, având un rezultat interesant de promovare a integrării alogrefelor, persistenței pe termen lung și vindecării. Multiple date din literatură validează aplicațiile clinice ale PRP cu succes în tratamentul diverselor patologii, inclusiv tratamentul leziunilor de părți moi și al plăgilor cronice, chirurgie ortopedică, arsuri, chirurgie maxilofacială și utilizarea în domeniul ingineriei tisulare. Pe baza experienței noastre preliminare și a rezultatelor favorabile din literatură, încurajăm folosirea mai largă a plasmei îmbogățite cu trombocite pentru imunomodulare și în asociere cu diverse matrici în ingineria tisulară, datorită efectelor sale asupra răspunsului inflamator local și a rolului în îmbunătățirea integrării grefelor tisulare de diverse tipuri.

Cuvinte-cheie*: plasmă îmbogățită cu trombocite (PRP), arsuri, autogrefă, alogrefă, imunomodulare*

INTRODUCTION

Platelet rich plasma (PRP) represents a fraction of the patient's blood that contains a high density of platelets (3–5 times higher) in comparison with the normal level. PRP is obtained through the centrifugation of the whole blood (harvested through a peripheral venous puncture and maintained in anticoagulant), then each blood component is separated according to its weight, resulting in a high platelet density [1].

In platelets, both cytokines and growth factors are deposited in their incomplete form in the alpha granules. In physiological conditions, activation of the platelets determines the bioactive modification of the growth factors and cytokines, which are actively secreted 10 minutes after the clot formation. This process can be reproduced by activating PRP using thrombin, which leads to the formation of a platelet gel. This gel acts just like a drug-delivery system due to its high platelet count, growth factors and cytokines density, which will stimulate the physiological processes. The result will be the appearance of a constantly repaired and regenerated tissue [2, 3].

The most important growth factors identified in the platelet rich plasma are PDGF (platelet derived growth factor), IL (platelet factor interleukin), TGF-beta1 (beta1 transforming growth factor), VEGF (vascular endothelial growth factor), PDAF (platelet-derived angiogenesis factor), EGF (endothelial growth factor), IGF (insulin-like growth factor) and fibronectin [3, 4].
Various successful clinical applications of PRP therapy were reported: treatment of soft tissue injuries or diseases, orthopedic surgery, burns, oral and maxillo-facial surgery, chronic wounds, tissue engineered products [2, 4, 5]. Burns represent a field where challenging wound healing and poor long-term results motivate researchers to address recently emerging techniques to improve clinical outcome and PRP seems to be a promising tool in this direction [6]. The association of PRP with various tissue grafts may be beneficial in their integration, which is the aim that we wanted to achieve in the case of the patient who is presented in this paper.

CLINICAL CASE PRESENTATION

We present the case of a 51-year-old male patient, a victim of an accidental 3-meter fall at the workplace, who suffered IIA, IIB and III-degree burns produced by steam and hot liquid (water), approximately 30% of total body surface area, involving the facial region, the right humeral region and the dorsal surface of the right upper limb, the dorsal surface of the left radio-carpal joint and hand, the right flank, the antero-postero-lateral right thigh, the antero-lateral right calf surface and foot. Additionally, the patient presented with cranio-cerebral injury, inhalation injury and thoraco-abdominal contusions.
At admission, the CT scan showed the following findings: a right temporal fracture line that extended to the petrous aspect of the temporal bone, a 5 mm right subdural hematoma, a 3 mm left subdural hematoma, bilateral hemorrhagic contusions of the temporal cortex, blood suffusions in the interhemispheric fissure, in the tentorium cerebelli and the peri-mesencephalic cisterns, as well as diffuse cerebral edema.
The initial period was characterized by a severe general status, with marked hemodynamic and respiratory instability, requiring ventilator and vasopressor support (0.2 mg/kg/min norepinephrine), continuous analgesia and sedation and nasogastric tube placement. Thus, the patient was admitted to the Intensive Care Unit, where fluid resuscitation was immediately initiated using the Parkland formula. The patient received blood derivatives as needed, loop diuretics, broad-spectrum antibiotic therapy, mixed enteral and parenteral nutrition and prophylaxis for stress ulcer.
Subsequently, the general status remained extremely severe, with hemodynamic and respiratory instability, the patient being intubated and receiving continuous analgesia and sedation. The lab results showed leukocytosis during the first few days, which then regressed, but the patient persistently presented with anemia and hypoproteinemia with hypoalbuminemia, hence developing systemic and septic complications. Local debridement and sterile dressing in the operating theater were performed daily and deep burns were sequentially excised and covered with antimicrobial dressings and allografts until the patient's general status improved, allowing definitive skin grafting.
The local lesions advanced and deepened. Sterile dressings with antiseptic and antimicrobial topical agents were constantly applied on the wounds, as well as special dressings and skin substituents, including allografts applied on the excised areas as temporary biological dressings. Figure 1 presents the dressings and skin substitutes used for the local treatment of this patient.

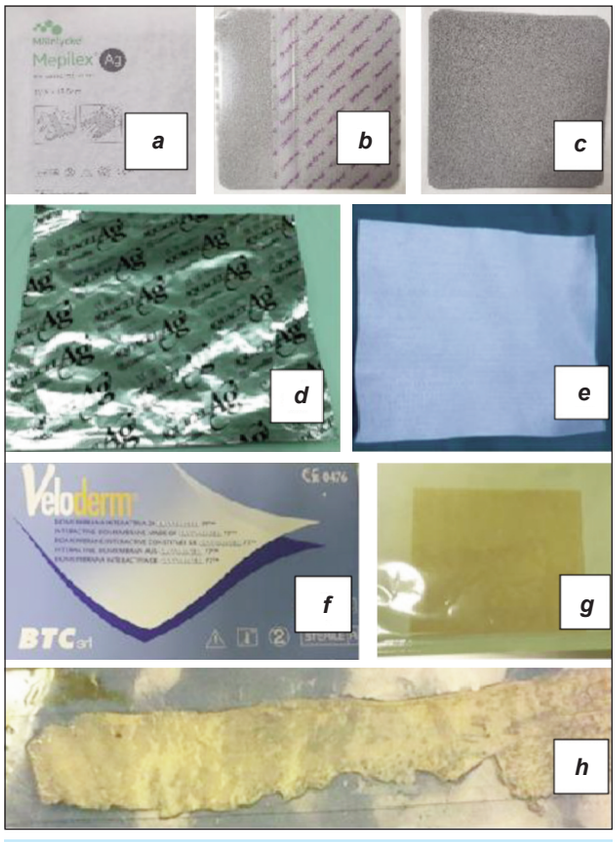

Fig. 1. Dressings and skin substitutes: *a, b* and *c* – Mepilex Ag; *d* and *e* – Aquacel Ag; *f* and *g* – Veloderm, *h* – Human skin allograft

After 2 weeks, the burn injuries stabilized and were completely delimited, allowing the excision of residual burn wounds and coverage with both autografts and allografts, since the wound bed was still not completely adequate for complete autografting.
On the 19th day following the injury, postburn lesions still partially persisted along with granulated wounds in the upper limbs and partially in the right lower limb (previously excised). Surgical intervention was decided and then performed, as follows: excision of the necrotic tissue in the right lower limb, covering the skin defects in the upper limbs with split-thickness autografts harvested from the calves bilaterally and

covering the skin defects of the posterior surface of the right arm and shoulder, right flank and right lower limb with cryopreserved allografts.

Local evolution at 3 weeks is presented in figure 2.

On the 23rd day, PRP treatment was initiated. Laboratory tests taken in the morning preceding the PRP procedure revealed a complete blood count with hemoglobin = 8.5 g/dl, leucocytes = 7700/mmc, and platelets = 294000/mmc.

PRP treatment was further performed for selected areas, as further described. Firstly, PRP was injected in the right arm and forearm and hand bilaterally, but PRP was additionally applied on the dorsal aspect of both hands, topically (figures 3, 4, 5 and 6).

Local evolution revealed almost completely integrated grafts in both upper limbs, with a tendency of lower limb allografts to graft failure. Figure 7 illustrates the dynamic aspect of the autologous and allogenic

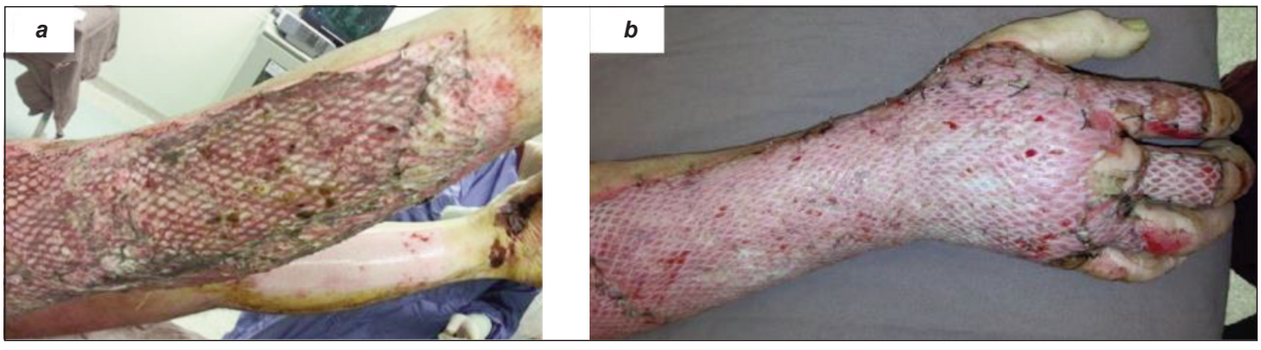

Fig. 2. The allografts: *a* – in the right lower limb, with partial graft failures; *b* – undergoing integration in the forearm and right hand, on the 22nd-day post-burn

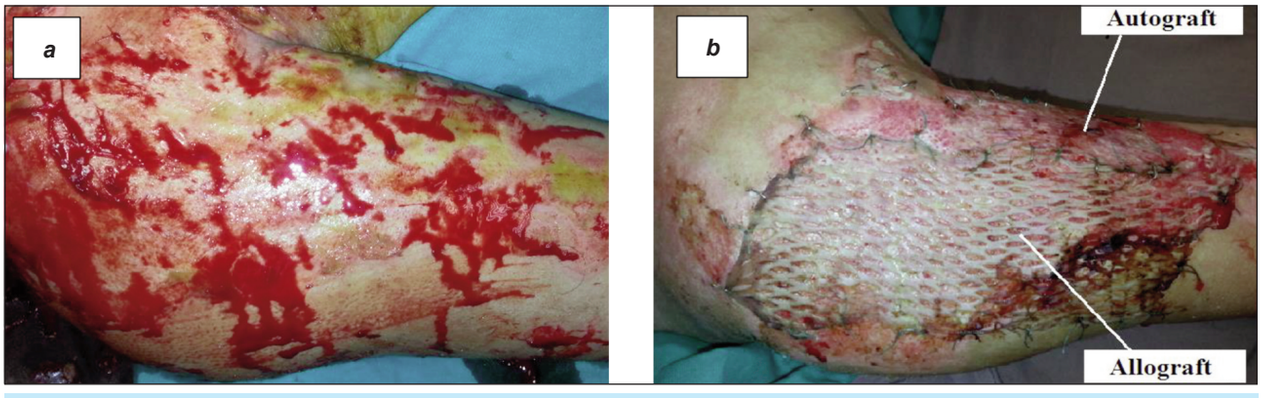

Fig. 3. The aspect of the right brachial region, where we placed both autografts and allografts to highlight their response to the platelet rich plasma therapy: *a* – the aspect of the studied region in the right arm, immediately after excision of the burn; *b* – the aspect of the skin grafts during the PRP treatment, on the 23rd-day post-burn, with the autograft on the antero-external arm and the allograft on the postero-external arm

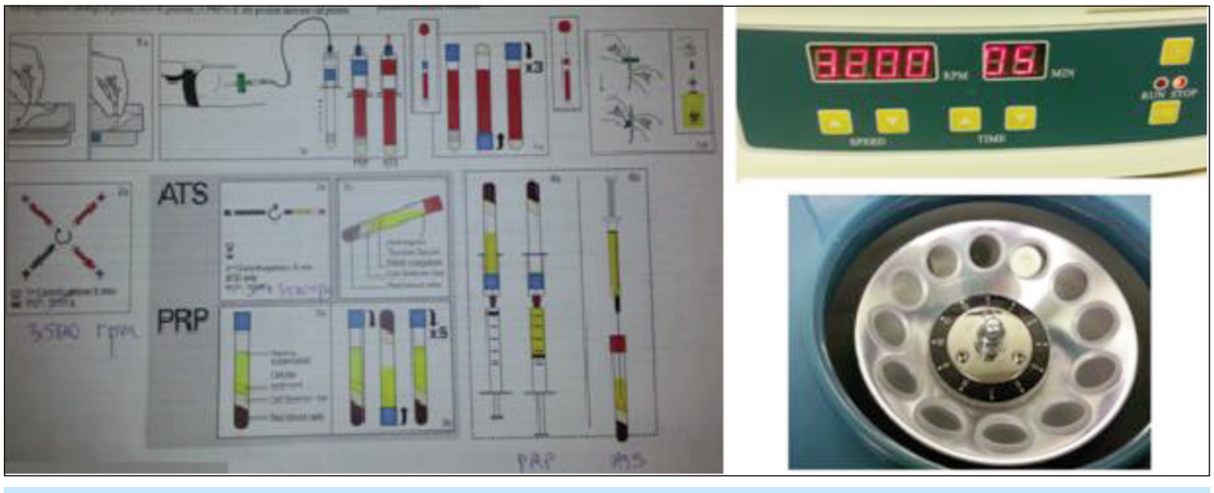

Fig. 4. The kit scheme and the centrifuge used for PRP therapy with 3200 RPM for 5 minutes

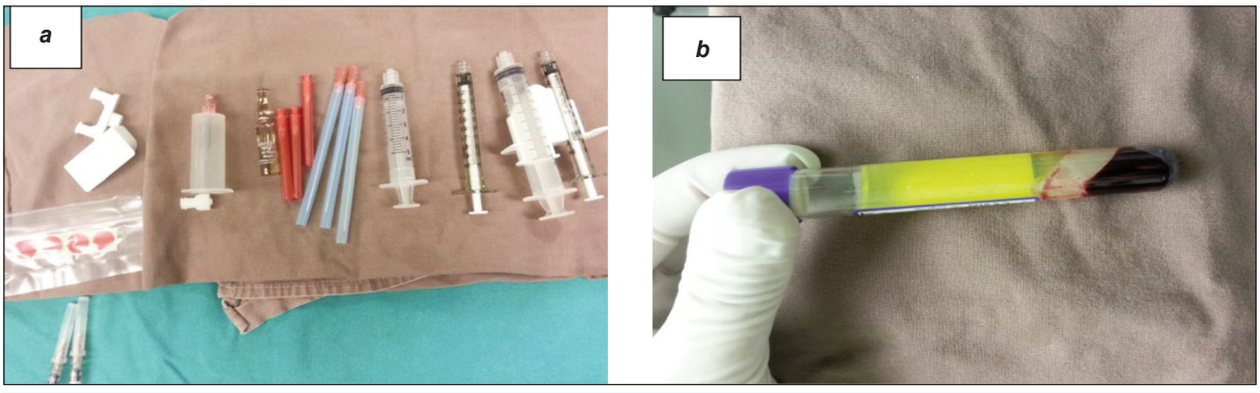

Fig. 5. Photos of: *a* – the devices used for PRP therapy; *b* – the aspect after centrifugation with separated components

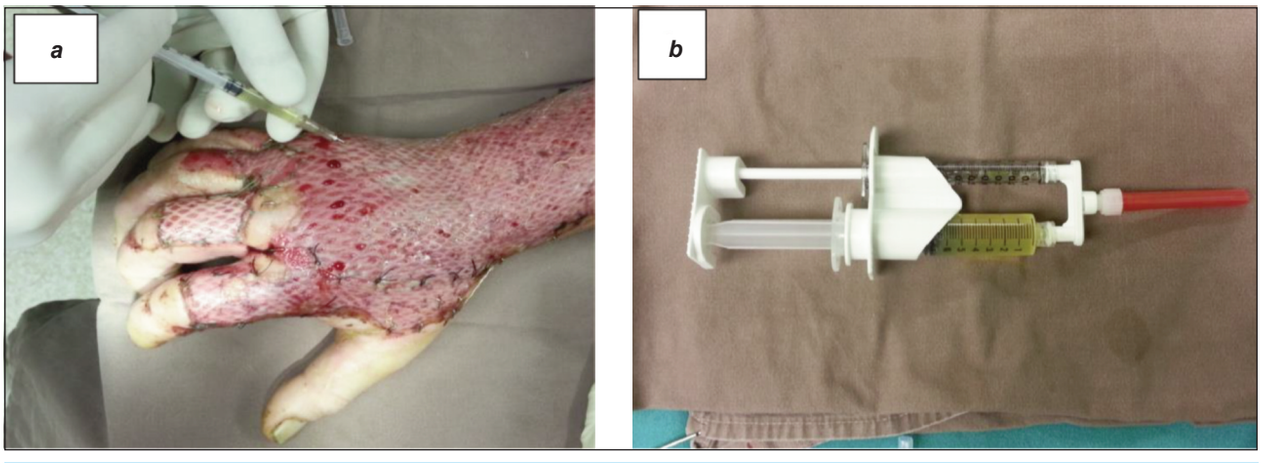

Fig. 6. Technique displayed in the dorsal aspect of the right hand: *a* – local PRP injected; *b* – external application performed with the device

split-thickness skin grafts applied on the right arm after PRP local treatment.

Even though the patient was extubated, the general status remained severe and he developed an embolic complication of the left lower limb, which showed incompletely delimited ischemic lesions of the left foot and areas of dry necrosis at this level.

On the 33rd day post-injury, autologous split-thickness skin grafts harvested from the antero-external region of the left thigh were used to cover the residual defects from the right flank and the right lower limb.

On day 35 of burn evolution, we decided to apply a second PRP treatment in the grafted areas of the upper limbs. Figure 8 displays the aspect of the graft in the right arm and the PRP kit that was used for the procedure.

The appearance of other areas can be observed in figure 9: on one hand, very well-integrated autografts in the right upper limb, with wounds surgically healed; on the other hand, still integrating autografts in the right calf (in the lower limb, the allografts have progressively deteriorated and have been previously removed).

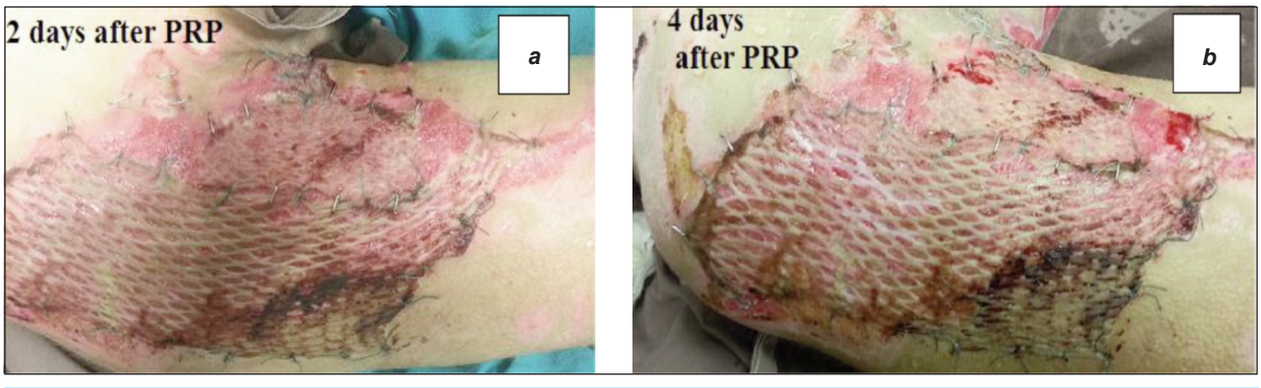

Fig. 7. Autologous and allogenic split-thickness skin grafts: *a* – 2 days; *b* – 4 days after the PRP therapy

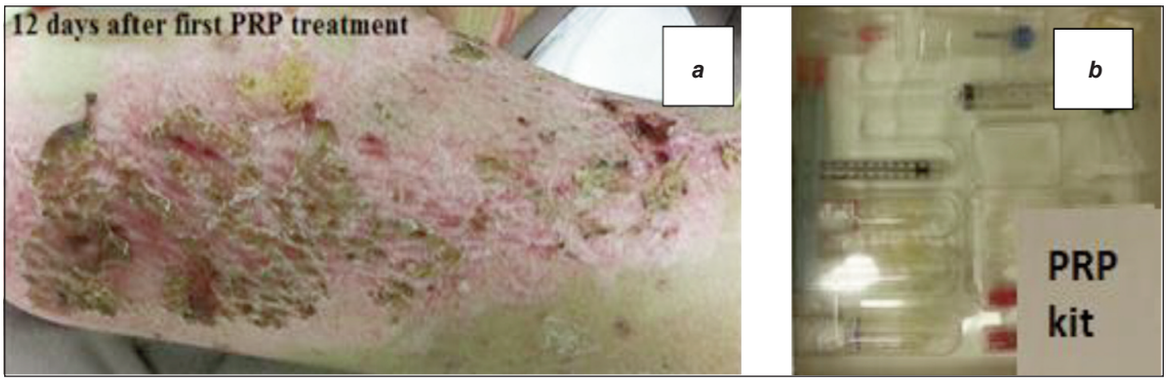

Fig. 8. Photos of: *a* – 12 days after the first PRP treatment on the grafts; *b* – another round of PRP injections

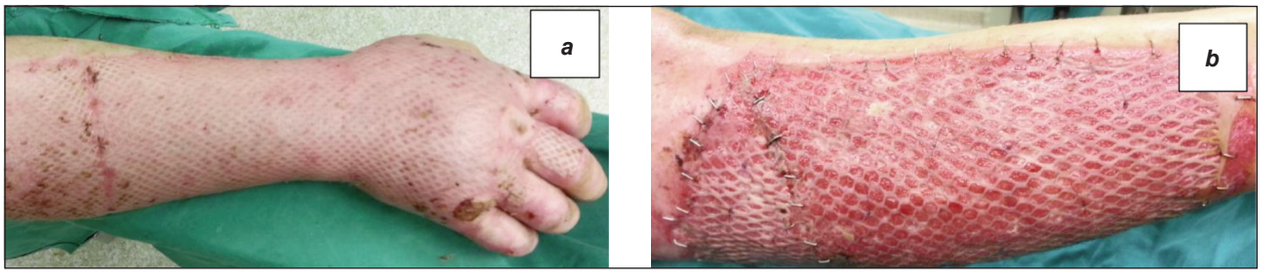

Fig. 9. Photos of: *a* – integrated autografts; *b* – autografts that are still integrating into other areas of the body, without PRP therapy

Figure 10 illustrates the aspect of the observed area in the right arm, 5 days after the second PRP treatment (on day 40 following injury) and we can observe complete integration of the autograft and also a satisfactory integration of the allograft.

However, the local evolution was unfavourable on the left lower limb, with delimited dry necrosis of the foot, requiring the amputation of this segment from the middle third of the left calf, which was performed on the 44th-day post-injury.

The patient then evolved favourably, not only from a general status point of view but also considering the local evolution, with integrated skin grafts, epithelisation of the burn injuries and a supple, surgically healing amputation stump.

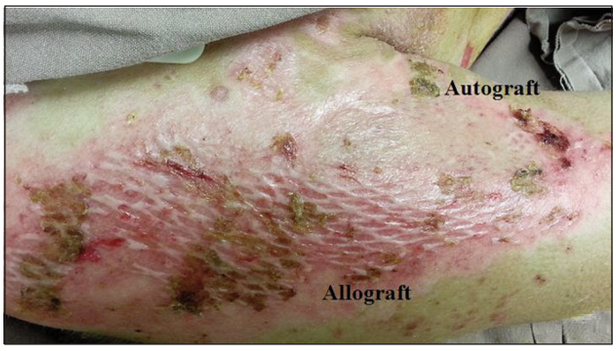

Fig. 10. Autograft and allograft after 5 days from the second round of PRP therapy (the autograft was completely integrated and the allograft showed satisfactory integration in the right arm region)

The patient was discharged from the hospital on day 55 post-burn injury, in good general status, with completely healed burned wounds and he was transferred to the regional hospital for the initiation of the rehabilitation program.

On the day of discharge, the local exam showed healed cervical burn injuries, amputation of the right auricle following deep burned lesions, integrated skin grafts on the right deltoid region, right upper limb, dorsal aspect of the left hand, right flank and right lower limb, with very small areas that were still healing on the posterior side of the right thigh and a supple, surgically-healing amputation stump.

DISCUSSION

The application of platelet rich plasma treatment presented favourable results for various wound treatments. However, there is not a large panel of data regarding the effect of PRP therapy on burn lesions specifically [7].

The case that we presented above illustrates the integration and persistence of the right arm allografts, which received PRP treatment with their viable appearance (complete epithelization) at the time of patient discharge, almost 2 months post-injury. This result of allograft integration could be interpreted as an effect of the long-term immunosuppressive state which is characteristic of severely burned patients, but the particularity of this case is the fact that the rest of the allografts, applied in the other regions of the body and left untreated (without PRP), showed unfavourable evolution with progressive lysis, requiring their removal followed by autografting.

The association of PRP and skin grafts are described in the literature, with good results. The application of autologous platelet rich plasma to split-thickness skin recipient sites provide immediate adherence of the graft to the wound bed, reduces shearing forces, promotes inosculation and reduces healing time in a wound environment enriched in growth factors. [8, 9] PRP also has a benefic role, when applied locally, in reducing donor site pain after split-thickness graft harvesting, improving patient comfort, reducing analgesic usage postoperatively and it may even promote wound healing and angiogenesis in these areas [10–12].

Skin allografts are the best option to cover excised wounds in extensively burned patients when autografts are not available. Homografts represent a temporary solution for wound coverage, due to their high antigenicity, with the rejection process occurring in about two weeks post-grafting. Persistence of the skin allografts was reported in some patients, but the mechanism of those situations is not clear. An increased effort to study the factors influencing allograft longevity is encouraged because these results may improve the outcome of severely burned patients with scarce autologous sources for skin grafting 13, 14].

Adding PRP to burn lesions can, theoretically, stimulate angiogenesis, vascular proliferation, fibroblast proliferation and hemostasis, by facilitating fibrin clot formation. The studies undertaken on animals have revealed a decrease of the inflammatory infiltrate and a speed-up in the healing process for second-degree burns, with the reduction of cells with positive expression of CD31, CD68, CD163, TGF-beta, MPO and an increase of MMP2 cellular expression. However, studies that use PRP as an adjuvant treatment for burns are not standardized yet, which requires additional investigations to reach a complete and correct conclusion [6, 15–19].

PRP also proved to have a promising role in the regeneration of various types of lesions. PRP was used to improve the integration of bone grafts, promoting a faster radiologic maturation process and a higher bone density compared to the control group. An additional decrease in postoperative pain, number of infections, edemas and hematomas after PRP has been noticed. The involved mechanism seems to come from the quantitative expansion of the mesenchymal cells, stromal cells of the bone marrow and also chondrocytes. A key aspect of the integration of bone allografts is represented by early vascular invasion, therefore reducing complications such as delayed and incomplete bone integration. Therefore, PRP represents an important angiogenic inductor through the release of the vascular endothelial growth factor [3, 20–22].

PRP was also tested in association with autologous fat grafts used for contour reconstruction or scar remodelling and it was shown that PRP improves the tridimensional contour and volume maintenance, and speeds up wound healing processes, probably due to its growth factors which stimulate the proliferation of the adipose cells derived from progenitor cells [3, 23, 24].

PRP injection in acute or chronic pathology of the tendons has been followed by different clinical effects, especially regarding pain reduction. In the traumatized tendon, PRP can stimulate the proliferation and mitosis of fibroblasts, and increase TGF-P, followed by an increase in local synthesis of collagen I and II. Chondro-cutaneous grafts previously treated with PRP have benefited from accelerated epithelial and fibroblastic regeneration, inducing neovascularization and decreasing the apoptosis rate. In experimental models on rabbits, PRP administration on these types of autografts resulted in a higher expression of CD31 in blood vessels and also of vascular endothelial growth factor, in comparison with the control group [25–28].

The association of neurorrhaphy techniques with PRP and human mesenchymal stem cells has proven to be more efficient in nervous regeneration, compared to using each technique separately, by increasing angiogenesis and production of neuronal growth factors [1].

All these reports illustrating a wide variety of applications of PRP for wound healing attest to the potential benefits of this therapeutic strategy, but further studies are necessary to elaborate standardized indications and clinical protocols, all while having in mind the safety of the patient and the potential functional benefit [2].

Perspective: PRP and tissue engineering constructs

Tissue engineering is one of the main directions of study in the biomedical field, because of its variety of potential applications, ranging from tissue regeneration to entire organ replacements. To achieve cell proliferation, three components need to be incorporated into the process: stem cells (including various types of adult stem cells), a three-dimensional scaffold that serves as the extracellular matrix and also growth factors and other stimulating molecules [29, 30]. Platelets represent one of the main contributors in the inflammatory reaction, as well as the regeneration processes that arise in the human body, due to the variety of cytokines and growth factors that they release: vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), platelet derived growth factor (PDGF), transforming growth factor (TGF), insulin-like growth factor (IGF), basic fibroblast growth factor (bFGF), to name but a few [31]. These growth factors play important roles not only in processes such as cell proliferation, differentiation or recruitment but also in cell regeneration [32]. Hence, platelet-rich plasma (PRP) has been used as an easily accessible, autologous source of growth factors, providing an alternative to the use of recombinant growth factors, which are not as safe as PRP from an immunological standpoint [33]. Moreover, the fibroblasts in the dermis have an increased expression of type I collagen and matrix metalloproteinase-1 after PRP stimulation [29]. It is regarded to be a type of

advanced therapy for both acute and chronic wounds: chronic ulcers, surgical wounds, and diabetic ulcers [34].

PRP electrospinning is used to obtain scaffolds through which cell proliferation can be promoted. Moreover, it has the capacity to bioactivate scaffolds obtained from other biodegradable polymers, such as poly(ε-caprolactone) (PCL) [33]. The advantages of PRP use in cell regeneration and proliferation are not only related to its safety and abundance of growth factors but also its simplicity and cost-effectiveness as a technique [35]. The activation of PRP is done through freeze-drying, during which the proliferative and adhesive properties of the PRP are conserved since lyophilization does not affect the viability of the growth factors. This contrasts with activating the PRP with thrombin or calcium chloride, forming a PRP gel, which, despite its hemostatic role, has the disadvantage of diminishing these properties [36–38]. However, it has been shown that PRP concentration can influence its effects on mesenchymal stem cell (MSC) proliferation: whilst a low concentration of PRP has a positive effect, with more abundant extracellular matrix production, higher concentrations can suppress cell viability and, thus, proliferation [33, 39]. When it comes to PRP adsorption on biodegradable polymer scaffolds, the same principles apply. According to Diaz-Gomez et. al, freeze-drying not only protects the benefic properties of the PRP, but it also does not affect the PCL scaffolds, preventing the alteration of their nanofibrous structure. The PRP coating can have different densities, depending on both the timespan of scaffold immersion in PRP in advance to freeze-drying and the growth factor concentration. PRP also aids in MSC proliferation through a biodegradable scaffold, which is more efficient than through a non-coated biodegradable scaffold [33]. Animal studies on rodents highlight that hydrogel scaffolds consisting of type I collagen and PRP accelerate wound healing compared to non-PRP coated scaffolds and secondary wound healing, by promoting stem cell recruitment from the dermis. [40] Similar results were seen in studies performed on porcine models [41].

The release pattern of the growth factors from PRP-treated surfaces has been of interest to scientists and clinicians alike. A 2013 study on PRP-coated titanium discs found that VEGF and TGF release is not as sustained as that of PDGF [42]. This finding was seconded by Diaz-Gomez et al., who studied the same patterns of growth factors released on PRP-coated biodegradable scaffolds. They proved that VEGF release showed a burst in the first few hours, reaching nearly complete release after 7 days, as opposed to the PDGF release that had a sustained pattern of release from the coated scaffold. TGF release, on the other hand, showed a progressive pattern, reaching a peak on day 3 [33]. Compared to previous studies using thrombin and calcium chloride for PRP activation, the released growth factor amounts were greater when freeze-thaw cycles were used for this purpose. [36] Recent studies reveal that nanofibrous dressings containing platelet rich fibrin have the same release patterns, with growth factors such as VEGF or PDGF being available for 7 days [43].

The effects of the aforementioned growth factors have been widely studied in the literature. For example, VEGF is known to activate and signal PDGF receptors, leading to cell proliferation. Additionally, PDGF has mitogenic activity and TGF increases MSC proliferation. All these growth factors are released from activated PRP and play important roles in the regeneration process [44].

This combination has been proven to have angiogenic properties, as well, with an increase in the allantoic vessel density of the chicken chorioallantoic membrane (CAM) after PRP-coated scaffold treatment. Moreover, the PRP-coated scaffolds were incorporated in the CAM, which grew around the scaffold, displaying the tissue proliferation properties, as opposed to non-PRP-coated biodegradable scaffolds, which remained as an overlayer on the CAM [33].

Future research is required for developing tissue-engineered constructs able to restore, conserve or improve various affected structures to promote optimal functional recovery and restore the adequate quality of life for patients with various tissular defects.

CONCLUSION

Platelet rich plasma, containing an important amount of growth factors, seems to represent a viable immunomodulatory strategy with effects on local inflammatory response and the ability to improve the success rate of various types of autologous and allogenic tissue grafts. Our clinical case of using PRP in association with skin grafting in a burned patient showed favourable effects of PRP on autologous skin grafts and homografts from the treated anatomical areas, favouring their integration. Future studies should consider PRP as a promising clinical strategy to address a wide range of inflammatory phenomena, including allograft rejection. Through its growth factors, PRP shows also importance in the development of complex tissue engineering constructs in association with recently developed scaffolds and stem cells population.

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