

EDITORIAL

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Platelet rich plasma (PRP) and similar products derived from peripheral blood are now widely used in clinical medicine, and especially in orthopaedics, for supporting the tissue regeneration and reparation after trauma or surgery. The increase of the PRP use and, consequently, of the current scientific literature deserves a specific review of basic, research and clinical aspects of its introduction as an adjuvant therapy in clinical medicine.

Categorization of different phases of PRP preparation, the quality of the final product, the real composition of the product, the application techniques are crucial for obtaining correct and valid data and for judging the efficacy of such a therapy.

We collected in the present Supplement a series of papers properly describing the various aspects of PRP therapy.

The content of platelets collected in the enriched plasma, the lipidomic of these particles, and the anti-inflammatory potential of the released substances from activated particles are described in some papers. In additional articles, the use of PRP in sports medicine, maxillo-facial surgery, and in orthopaedics is reviewed, showing pros and cons of the treatment and the efficacy on some specific inflammatory and(or) degenerative processes. A paper is also devoted to the antimicrobial properties of the procedure, which is a new and very interesting insight for using platelets concentrates.

We hope that this Supplement could be useful for the readers of the Journal and could focus the attention of the academic and professional world on scientific aspects of this widely accepted treatment.

GROWTH FACTOR CONTENT IN PLATELET RICH PLASMA AND THEIR APPLICABILITY IN MEDICINE

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This paper reviews available reports on the advantages and possibilities of clinical use of platelet-rich plasma preparations, with particular emphasis on platelet growth factors.

Platelets, an important reservoir of growth factors in the body, play an important role in many processes such as coagulation, immune response, angiogenesis and the healing of damaged tissues. Numerous proteins are contained in the α -granules of platelets: platelet-derived growth factor (PDGF), transforming growth factor (TGF), platelet factor interleukin (IL), platelet-derived angiogenesis factor (PDAF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), insulin-like growth factor IGF and fibronectin.

The development of methods and systems for blood and cell sorting (e.g. CAPSS - compact advanced platelet sequestration system Elektromedics 500, PCCS - platelet concentrate collection system Curasan) have made it possible to obtain significant concentrations of platelets (even by 338%) and high concentrations of growth factors, in a form of sterile mass that can be used immediately for clinical purposes. Platelet-rich plasma (PRP; autologous platelet-rich plasma - APRP) are platelet concentrates made of autogenous blood with a high number of platelets in a small volume of plasma. The clinical efficacy of platelet concentrates depends mainly on the number of platelets and the concentration of their growth factors, which act as transmitters in most processes in tissues, particularly in healing where they are responsible for proliferation, differentiation, chemotaxis and tissue morphogenesis. They operate as part of autocrine, paracrine and endocrine mechanisms.

Growth factors derived from centrifuged blood were first used in patients with chronic skin ulcers. The clinical use of PRP for a wide variety of applications has been reported mostly in oral and maxillo-facial surgery, orthopedic surgery, treatment of soft tissue diseases and injuries, treatment of burns, hard-to-heal wounds, tissue engineering and implantology.

PLATELET LIPIDOMIC

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Lipids account for 16-19% dry platelets' matter and includes 65% phospholipids, 25% neutral lipids and about 8% glycosphingolipids. The cell membrane that surrounds platelets is a bilayer that contains different types phospholipids symmetrically distributed in resting platelets, such as phosphatidylserine (PS), phosphatidylethanolamine (PE), phosphatidylcholine, and sphingomyelin. The collapse of lipid asymmetry is exposure of phosphatidylserine in the external leaflet of the plasma bilayer, where it is known to serve at least two major functions: providing a platform for development of the blood coagulation cascade and presenting the signal that induces phagocytosis of apoptotic cells. During activation, this asymmetrical distribution becomes disrupted, and PS and PE become exposed on the cell surface. The transbilayer movement of phosphatidylserine is responsible for the platelet procoagulant activity. Exposure of phosphatidylserine is a flag for macrophage recognition and clearance from the circulation. Platelets, stored at room temperature for transfusion for more than 5 days, undergo changes collectively known as platelet storage lesions. Thus, the platelet lipid composition and its possible modifications over time are crucial for efficacy of platelet rich plasma therapy. Moreover, a number of substances derived from lipids are contained into platelets. Eicosanoids are lipid signaling mediators generated by the action of lipoxygenase and include prostaglandins, thromboxane A₂, 12-hydroxyeicosatetraenoic acid. Isoprostanes have a chemical structure similar to this of prostanoids, but are differently produced into the particle, and are ligands for prostaglandins receptors, exhibiting biological activity like thromboxane A₂. Endocannabinoids are derivatives from arachidonic acid which could reduce local pain. Phospholipids growth factors (sphingolipids, lysophosphatidic acid, platelet-activating factor) are involved in tissue regenerating process. Finally, a warning concerning the atherogenic role of platelets, although it should not be exerted in a local therapy, is mentioned. The lipid content of platelets must be taken into account when these particles are concentrated and used for a local therapy, while the different categories of lipid derivatives could improve or affect the quality of the product

PLATELET RICH PLASMA THERAPY: INFLAMMATORY MOLECULES INVOLVED IN TISSUE HEALING

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Inflammation represents a fundamental aspect of the healing process. Besides their primary role in hemostasis, platelets play an active role in the immunological and inflammatory aspect of tissue healing. Indeed, they can be directly involved in the inflammatory response by the production and release of several inflammatory mediators, including a variety of cytokines, such as TGF- β , IL-1 β , CD40L, and chemokines, such as CXCL7, CXCL4, CXCL4L1, CCL5, CXCL1, CXCL8, CXCL5, CXCL12, CCL2, CCL3. Platelets are not only a source of several chemokines involved in the inflammatory response and tissue healing, but they also express chemokine receptors, in particular CCR1, CCR3, CCR4 and CXCR4, thus being able to regulate the inflammatory response associated to the healing process. However, this local inflammation must be taken under control, and platelets can prevent the excess of leukocyte recruitment by anti-inflammatory cytokines, such as TGF- β . For these biological properties of platelets, platelet rich plasma therapy (PRP) is considered an innovative and promising approach that has been extended to many fields of medicine, ranging from non-union defects, bone fractures, spinal fusion, bone implant and osteointegration, joint arthroplasty, to the treatment of several traumatic or degenerative pathologies of tendons, cartilage and ligaments.

MICROBICIDAL PROPERTIES OF LEUKOCYTE- AND PLATELET-RICH PLASMA/FIBRIN (L-PRP/L-PRF): NEW PERSPECTIVES.

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Platelets, as main actors of the first stage of the healing process, play an important role in tissue repair. Their granules contain many active substances, particularly over 30 growth factors with significant effects on the resident cells at the site of injury, such as mesenchymal stem cells, chondrocytes, fibroblasts, osteoblasts. This potential may be increased by the concentration of the platelets, using platelet-rich plasma/fibrin products. In the four families of platelet concentrates, 2 families contain also significant concentrations of leukocytes: L-PRP (Leukocyte- and Platelet-Rich Plasma) and L-PRF (Leukocyte- and Platelet-Rich Fibrin). Inductive properties of platelet concentrates were widely described. However, they present also antimicrobial effects. The antibacterial effects of L-PRP were highlighted in only a few in vitro studies. Strong activity comparable to gentamicin and oxacillin for L-PRP against methicillin susceptible *Staphylococcus aureus* (MSSA) was already demonstrated. L-PRP also inhibited the growth of methicillin resistant *Staphylococcus aureus* (MRSA) and *Escherichia coli*. Some authors also reported clinical observations about the reduction of infections and the induction of healing processes after the use of platelet concentrates in cardiac, orthopaedic, oral and maxillofacial surgery. However, very little is yet known about the antibacterial effects of these concentrates. In this manuscript, the current data about the antimicrobial agents and cells present in the platelet-rich plasma/fibrin are highlighted and discussed, in order to introduce this new key chapter of the platelet concentrate technology history.

APPLICATIONS AND LIMITS OF PLATELET-RICH PLASMA IN SPORTS RELATED INJURIES

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Platelet-rich plasma (PRP) is a promising alternative approach based on the efficacy of autologous growth factors to accelerate tissue healing, allowing a fast recovery after muscles, ligaments, tendon or cartilage lesions. This literature review begins focusing on the role of platelets growth factors' in these tissue healing and on the available preparation methods for PRP. Moreover we consider the in vitro and in vivo study on PRP, some of the most important therapeutic applications and limitations. Although several preclinical studies show promising results, clinical studies still show controversial results. Further studies are required to define the efficacy and to specify the way of using PRP in the orthopaedic practice.

**THE USE OF AUTOLOGOUS PLATELET AND PLASMA PRODUCTS IN SALVAGE NECK
DISSECTIONS: A PROSPECTIVE CLINICAL STUDY EVALUATING EARLY
AND LATE WOUND HEALING**

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Objectives: To evaluate the effect of autologous platelet and plasma adhesives (APA) on postoperative drainage and soft-tissue fibrosis following neck dissections. **Design:** This was a blinded comparative prospective cohort study done as two parts: part one evaluated early post-surgical outcomes and part two evaluated late tissue fibrosis. **Method:** Salvage neck dissections were stratified into two groups based on severity of prior treatment. High risk patients were defined as those who had previously undergone chemoradiation therapy and autologous platelet adhesives were administered to the surgical wound intraoperatively. The low risk group consisted of patients undergoing salvage neck dissections following radiation only and acted as controls. Part one evaluated postsurgical wound drainage as the primary outcome as well as length of hospital stay and complications. Part two evaluated late postoperative tissue fibrosis by comparing neck skin using the Cutometer. R2 and F0 were the specific Cutometer parameters for quantifying the viscoelastic properties of the skin. **Results:** Postoperative wound drainage was significantly less (253.7 vs. 345.8) in the autologous platelet adhesive group as compared to the control group ($p < 0.03$). Length of stay in the APA group versus the control group was 3.13 and 3.86 days respectively ($p < 0.004$). Both R2 and F0 measurements showed improved viscoelastic properties of the skin in the APA group (R2 $p < 0.05$, F0 $p < 0.05$). **Conclusions:** APA application following salvage neck dissections may reduce early postoperative wound drainage and improve long-term skin quality

TREATMENT OF KNEE CHONDROPATHY WITH PLATELET RICH PLASMA. PRELIMINARY RESULTS AT 6 MONTHS OF FOLLOW-UP WITH ONLY ONE INJECTION

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Application of new biological treatments in orthopaedics is controversial nowadays. Surgeons and practitioners know how difficult can be to choose a solution for chondral injuries. Joint damages are from little contusions, osteochondral fractures, avascular necrosis, osteochondritis and degenerative processes like osteoarthritis and rheumatisms. All mentioned have a common problem: the lack of regenerating hyaline cartilage by themselves. Recently, PRP have been used to treat early moderate chondropathies. Here we show the preliminary results of 30 patients affected by chondropathy of the knee after 6 months treated with a single intrarticular injection of PRP. Thirty patients, 18-65 years old, with a diagnosis of I to III Outerbridge chondropathy in the knee, pain for more than 3 months following conservative treatment and no bone axial defect, were treated with one intraarticular injection of PRP (GPS mini set, BIOMET[®]), after written consent and Ethic and Legal Committee approval. VAS and KOOS scores were evaluated before PRP injection and at 1, 3 and 6 months after the treatment. ANOVA with repeated measures using the SPSS[®] showed significantly better results in term of KOOS and VAS scores at 1, 3 and 6 months respect to the pre-injection value ($p < 0,05$) We think that PRP treatment is a promising alternative for the treatment of knee chondropathy; however its efficacy has to be demonstrated with more clinical works, with longer follow up and with greater number of patients, even with controlled and randomized trials. In our study only one injection of PRP has been able to allow a clinical improvement, suggesting the possibility to avoid multiple injections protocols, and consequently reducing the health expenses. Until the efficacy of PRP will not be definitely demonstrated, surgeons should be very prudent in indications.