Exokine and the Youth-Boosting Treatment Based on One’s Own Serum: Wheat and Chaff

Philippe Magistretti, MD1 Dario Bertossi, MD2 Ali Pirayesh, MD3 Alessandra Magistretti, MS4 Salvatore Chirumbolo, PhD5

1 Summit Clinic Crans Montana, Switzerland 2 Department of Surgery, Dentistry, Paediatrics and Gynaecology and Head of Maxillofacial Plastic Surgery Unit, University of Verona, Italy 3 Amsterdam Plastic Surgery, Amsterdam, The Netherlands 4 School of Medicine, University of Verona, Italy 5 Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Italy

Address for correspondence Salvatore Chirumbolo, PhD, Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Strada Le Grazie 9 37134 Verona, Italy (e-mail: salvatore.chirumbolo@univr.it).

Facial Plast Surg

Abstract

Within the field of skin rejuvenation, clinicians have broadened the application of proven therapies toward antiaging medicine. Specifically, both platelet-rich plasma (PRP) and autologous-conditioned serum (ACS) have received great consideration among experts for novel indications. While the medical research focused on ACS is strengthened in their evidence and supported by promising outcomes, much more debates exist regarding the efficacy of PRP. Despite limited supporting literature to date, physicians and surgeons should be encouraged to explore the use of these approaches and in shedding further light on their potential benefits by contributing new evidence from basic and clinical scientific investigation.

Keywords

platelet-rich plasma  
autologous serum  
rejuvenation  
PRP  
aesthetic medicine

Within the field of skin rejuvenation, current strategies have endowed clinicians with novel opportunities of application for these proven tools. Specifically, both platelet-rich plasma (PRP) and autologous-conditioned serum (ACS) have received great consideration among experts for the use in antiaging regimens. So far, worldwide information about aesthetics is claiming the existence of a new promising way to reverse the aging process on skin through focused therapy directed at and the effects of thinning. Specifically, the simple use of one’s own incubated serum or PRP is a proposed method for achieving antiaging benefits. This attempt might simply be described, therefore, as the use of an autologous blood extract, for example, PRP or ACS, which are both particularly enriched in biomolecules and growth factors and adapted for skin rejuvenation and musculoskeletal disorders.1 Briefly speaking, the idea is particularly encouraging and appealing; however, given the limited supporting literature, it must be determined if we are dealing with a myth or a real opportunity.1

Actually, skin rejuvenation by using PRP is highly controversial, as it seems that the majority of clinical case studies are scientifically inconsistent and unreliable, with respect to the more rigorous open randomized clinical trials.1 A possible reason is the puzzling complexity of actions associated with autologous PRP, which renders any good experimental and scientific attempt an empirical approach.2,3 Yet, Lei et al, in a systematic review on a total of 108 articles, reported that PRP should play a major role in tissue rejuvenation.4 Despite some encouraging evidence, further research is needed, however, as contradictory evidence was also reported.5–7 As a matter of fact, the term Exokine (or Exokine-Serum) is a commercial translation of autologous transfer of plasma or serum, which is used in numerous healthcare structures, held for aesthetics purposes to get skin rejuvenation. Examples of Exokine application are shown in ►Figs. 1 to 3 in this article.

To explain the biological role of PRP in tissue rejuvenation, plasma or serum should be finely characterized in their
In this sense, plasma and serum metabolomes were recently reported and obviously they depend on an individual’s and populations’ genetics. Furthermore, the process of aging dramatically changes the presence of at least 100 different major metabolites over 300 unique substances recently reported in plasma metabolomics. This evidence compels experts in the field to standardize PRP on the basis of its outcome on patients, not of its biological nature, an issue that leaves to PRP a certain degree of empiricism. Despite this, Banihashemi et al reported a mild-to-excellent amelioration in nasolabial fold, periorbital dark circles, skin rigidity, and periorbital wrinkles by using pure PRP facial injection in 30 female subjects. Positive outcomes in periorbital dark circles by using periorbital dark circles were reported also by other authors, who described the achievement of an increasing satisfaction score in treated patients. Actually, current literature seems to support the use of PRP in the periorbital region, including crow’s feet wrinkles. Notwithstanding, the majority of PRP applications, as a therapeutic approach, can be retrieved on musculoskeletal disorders. The application of the Exokine Serum methodology includes therefore a wide umbrella of autologous transfer of blood derived products to ameliorate a plethora of illnesses or discomforts regarding skin, bone, or connective tissues.

Before expanding this issue further on, it is of the utmost importance to review and detail the biological nature and composition of PRP and ACS.

**PRP Composition and Its Impact in Rejuvenation Medicine**

A great deal of research has gone into the characterization of components present in PRP and ACS. So far, the spotlight was principally pointed onto the numerous growth factors present in PRP, such as epidermal growth factor (EGF), insulin-like growth factor 1 (IGF-1), hepatocyte growth factor (HGF), transforming growth factor β (TGF-β) vascular endothelium growth factor (VEGF), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF), most of which are indeed complex families of growth factors, more than single components. A more recent renewed interest was yet devoted to exosomes present in PRP. PRP exosomes (PRP-exos) are nanovesicles carrying a great deal of molecular factors, including biomolecules, microRNAs, transcripts, and proteins, and in this sense they play a major role in modulating plastic rejuvenation and tissue turnover. This evidence suggests that the bioactivity of PRP is particularly complicated by the existence of a plethora of factors, each with complex interactions and functions. For example, FGFs, which have a major role in tissue rejuvenation, are represented by a complex family of growth factors, usually known as heparin-binding growth factors, because linking heparin, which include acidic FGF (FGF-1), basic FGF (FGF-2), int-2 (FGF-3), hst/KS3 (FGF-4), FGF-5, FGF-6, keratinocyte growth factor (FGF-7), androgen induced growth factor (FGF-8), glia activating factor (FGF-9), and at least 23...
different members of FGFs. Discriminating the single activity of each FGF component in such complex milieu to follow the subsequent biomolecular and cellular events leading to skin rejuvenation is particularly burdensome, for obvious practical reasons.

However, the presence of skin microenvironments, epidermal, dermal, subdermal, or musculoskeletal, may differentiate actions depending on the depth of delivery of the active principles. This practically prompts up possible strategies as different procedures and devices, activating skin rejuvenation at different depths. Usually, the quality of a PRP is evaluated via its total platelet amount (at least 4 times higher respect to the physiological content in whole blood) and platelet viability and functionality, measured by analyzing platelet aggregometry, thromboelastography, and flow cytometry. Platelet α-granules produce fundamental growth factors such as PDGF, VEGF, TGF-β, and EGF. The amount and composition in growth factors of a PRP have been recently reported and may account on simple enzyme-linked immunosorbent assay. The role of these growth factors for tissue rejuvenation is of major importance. The regenerative effect of PDGF-BB has been reported on the dentin–pulp complex, bone regeneration, skin rejuvenation, and wound healing. and even as a topical direct treatment. The widespread idea about PRP quality is that its potential depends on the “proper” cocktail of growth factors components, most of which produced by platelets themselves. What we would like to assess is that the use of PRP is an example of “autologous orthobiologics,” a biological way used in medicine and surgery to renew and recover damaged or functionally impaired tissues accounting on the regenerative potential of autologous tissue transfer, such as haemoderivatives. Hemoderivatives, for example, PRP, are functionally promising agents also in musculoskeletal disorders such as tendinitophathy, involving an anatomical district where is particularly effective also ACS.

PRP is enriched with growth factors by using a cavitation process (via sonication or ultrasonication) able to allow the release from platelets of the major growth factors with rejuvenation properties (Fig. 4). In this context, a wide plethora of different technological approaches can be retrieved from literature, which are able to produce PRP with commercial purposes. The concentration of the different GF is lower in PRP samples compared with ACS. This is likely due to the fact that platelets in the former sample have not had the time to produce them. This circumstance represents the major shortcoming of PRP versus ACS as the uncertainty to the destiny of the platelets after the injection cannot be verified.

**Autologous-Conditioned Serum: Wheat and Chaff**

ACS is a type of autologous serum enriched with IL-1-ra (interleukin 1-receptor antagonist) and is particularly used in rheumatic, osteoarthritic, and musculoskeletal disorders. The usual content of ACS is its enrichment in IL-1ra, IL-10, TGF-β, associated with the presence of IL-6, tumor necrosis factor-α, oncostatin M, and IL-1β. Conventional ACS (CCS) was successfully treated chronic Achilles tendinopathy with ACS. These authors conducted a retrospective study with 50 patients undergoing only eccentric training who exhibited better VISA-A-G (Victorian Institute of Sport Assessment–Achilles questionnaire—German) following treatment with ACS, an indication of an improvement in their tendon functionality. ACS therapy for tendinopathy works also in farm animals. The biological activity of ACS, in that ACS is able to modulate the stem cell property of mesenchymal progenitors in the tissue, is of the utmost importance for the use of ACS in rejuvenation biomedicine. ACS is a kind of topically applied autologous serum deprived of cells (cell-free) and treated on glass spheres. Therefore, both Exokine and Orthokine are patented formulas, usually identifying a PRP or an ACS, used often for tissue regeneration (skin) the former and musculoskeletal disorders the latter. Actually, the use of ACS in veterinary science can account also on different technologies to produce them. Typically, any rupture of the Achilles tendon can lead to slow rescue its full functionality and often incompletely recovery. Heisterbach et al, in Sprague-Dawley rat models, assessed that tendon healing was fundamentally exerted by BMP-12 and TGF-β1, besides ACS, an experience of tendon healing reported also by others.

At least in chronic knee osteoarthritis, ACS reported promising outcomes with respect to PRP. Shirokova et al treated 123 patients suffering from osteoarthritis (Kellgren and Lawrence grade I to II) with PRP and ACS, reporting that at the 3-month follow-up ACS showed higher efficacy than PRP. Wright-Carpenter et al used ACS in sport athletes with muscle strain and reported a shorter recovery time in comparison to the control group by approximately 6 months.

The evaluation of ACS in skin rejuvenation was recently considered. These authors wondered if a novel developed antiaging ACS, produced by using a particular syringe-like device which is able to expose autologous blood to medical-grade glass spheres, arranged in a closed system, was effective for skin rejuvenation. Actually, the use of topical injected ACS gradually replaced also further approaches, such as directly topical application of growth factors.
The role of ACS in tissue rejuvenation and wound healing appears undisputable, yet, are there concerns about the use of ACS in dermatology and skin rejuvenation? The Orthoskin trial recently assessed that cell-free conditioned autologous serum in knee osteoarthritis and lumbar radiculitis on 21 female subjects ensured a significant improvement in cutaneous elasticity and skin firmness, reporting therefore an outcome in skin rejuvenation.54 The effect of ACS, likewise PRP, depends on the way by which ACS is produced.55 For example, efficiency in producing high-quality ACS depends on glass spheres or beads diameters (usually used altogether 2.0, 2.5, 3.5, and 4.0 mm diameters) and/or polished or coated with chromium sulfate, a way that allows blood-derived ACS to be enriched in IL-1-ra following 24 hours incubation with glass beads.53 The commercial way with Exokine-Serum and Orthokine-Serum may provide the simplest solution to offering autologous hemoderivatives for tissue rejuvenation, and ultimately endowing surgeons with the proper technology.

Conclusions
What kind of message can we retrieve from this very short tale about PRP and ACS? The continuous development of new approaches to improve skin health, reduced aging-associated discomforts and damages, ensuring skin rejuvenation and tissue remodeling nowadays is referring to novel practices using autologous blood-derived products. Repair and rescue your health from yourself; this seems a very attracting message. While for ACS medical research seems much more strengthened in their evidence, supported by promising outcomes, much more debates are being arranged about the usefulness of PRP. Despite the possible criticisms raised around these products, physicians and surgeons should take advantage in their jobs by the use of these approaches and therefore they would be particularly encouraged in shedding further light on their use and development by adding new evidence from basic and clinical scientific investigation.

Authors’ Contributions
DB and PM were involved in substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work. SC and DB were involved in drafting the work or revising it critically for important intellectual content. PM, DB, AM, AP, and SC gave final approval of the version to be published. PM, DB, AM, AP, and SC agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding
None.

Conflict of Interests
None declared.

References
32 Dos Santos RG, Santos GS, Alkass N, et al. The regenerative mechanisms of platelet-rich plasma: a review. Cytokine 2021; 144:155560
33 Wagner RJ, Zach KN. Platelet-rich plasma injection for quadriceps tendinopathy: a case report. WMJ 2021;120(01):78–81
52 Kerscher M. Cell-free autologous conditioned serum (ACS) improved skin elasticity: results of an investigator initiated clinical trial. Orthoskin I JADD 2017;76(06) Suppl 1:AB63