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Clinical Applications of Plasma Growth Factors

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Abstract

The use of plasma rich in growth factors has become a technique increasingly used in various fields of medicine. Since its inception in use in sports medicine and dental implants in the mid-80s, gradually it has expanded its field of use in clinical specialties. The power cell tropism for certain tissues, attributed to growth factors, has currently talked of a new medical discipline as Regenerative Medicine. Not only has experienced an ever increasing boom in various medical specialties, but simultaneously has increased exponentially types and methodology for obtaining application forms even for the same pathology. So much so that now its use has exceeded the capacity to produce scientific evidence for successful clinical application.

Keywords: plasma growth factors, medicine regenerative, platelet rich plasma

1. Introduction

The use of plasma rich in platelet growth factors has become a technique increasingly used in various fields of medicine. Since its inception in use in sports medicine and dental implants in the mid-80s, gradually it has expanded its field of use in clinical specialties as diverse as otolaryngology, plastic surgery and dermatology, general surgery, ophthalmology, obstetrics and gynecology or neurosurgery between other. The power cell tropism for certain tissues, attributed to growth factors, has currently talked of a new medical discipline as regenerative medicine. Not only has experienced an ever increasing boom in various medical specialties, but simultaneously has increased exponentially types and methodology for obtaining application forms even for the same pathology. So much so that now its use has exceeded the capacity to produce scientific evidence for successful clinical application. The objective of this

work is to review the clinical applications where there has been more scientific evidence and those where although still lack solid scientific basis are interesting from the point of view of clinical and preclinical.

2. Fields of application of platelet RICH plasma

They are numerous and ever growing fields where PRP is being implemented and its various fractions. Let us review for specialty applications where there seems to be more consensus, emphasizing those where there is scientific evidence of greater support; furthermore task not without difficulty given the controversy in the medical community even for the same clinical application and the absence of scientific studies weight as properly designed clinical trials for this purpose; although as will most indications are based on case series and even isolated clinical cases difficult to reproduce by the authors as to design more scientific studies force.

2.1. Rheumatology, traumatology or sports medicine

This is certainly the field of greatest projection in the use of PRP, far surpassing even the existing clinical evidence. In vitro PRP shown to regulate cytokine processes involved in neo-vascularization, proliferation of tenocytes, fibroblasts, myocytes and chondrocytes, and the recruitment of inflammatory cells with inhibitory effect of proinflammatory cytokines (IL-1) with anti-inflammatory and regenerative activity (**Tables 1 and 2**).

2.1.1. Epicondylitis

Epicondylitis is a tendinopathy limiting, with a clear tendency to become chronic and random partial response to conventional therapy with steroid injections and rehabilitation. Studies using PRP in these patients as single infiltration resulted in significant functional improvement in analgesic and 85% of them without imparting any adverse effect. Further deepening is necessary anyway, since existing studies contained small numbers of patients [1, 2].

2.1.2. Plantar fasciitis

As in the rest of tendinopathy with a tendency to become chronic, has reviewed a study of a case series of patients with plantar fasciitis refractory to treatment with NSAIDs, immobilization, physical therapy and corticosteroid infiltration, who are PRP infiltrated with a significant functional improvement and pain in 90% of them. Also in this case more studies are needed to objectify the benefit in this pathology [3, 18].

2.1.3. Knee osteoarthritis

A relatively new application that is currently bringing together most of the current clinical research. Case series studies of patients compared with single infiltration of hyaluronic acid,

Area	Clinical applications	Scientific evidence
<ul style="list-style-type: none">Skeletal muscle pathologies	<ul style="list-style-type: none">TendinopathiesMeniscopathyLigament injuriesBone fracturesFasciitisMuscle tearsOsteoarthritis	<ul style="list-style-type: none">Preclinical and clinical Studies (cases-control)
<ul style="list-style-type: none">Surgical wounds	<ul style="list-style-type: none">Gynecological surgery (abdominal)Cardiovascular surgery (sternal and vascular access)Plastic surgery (skin flap)	<ul style="list-style-type: none">Clinical studies (case series).
<ul style="list-style-type: none">Burns	<ul style="list-style-type: none">Skin and corneal	<ul style="list-style-type: none">Clinical studies (clinical isolates).
<ul style="list-style-type: none">Chronic ulcers	<ul style="list-style-type: none">DiabeticVascularFor pressure	<ul style="list-style-type: none">Clinical Studies (Case-control)
<ul style="list-style-type: none">Ophthalmology	<ul style="list-style-type: none">Corneal ulcersDry eye	<ul style="list-style-type: none">Preclinical and clinical studies (case series)
<ul style="list-style-type: none">Otolaryngology	<ul style="list-style-type: none">Tympanoplasty	<ul style="list-style-type: none">Preclinical and clinical studies (case series)
<ul style="list-style-type: none">Cosmetic surgery and dermatology	<ul style="list-style-type: none">Facial expression linesHair Implants	<ul style="list-style-type: none">Preclinical and clinical studies (case series).
<ul style="list-style-type: none">Neurology and neurosurgery	<ul style="list-style-type: none">Suture of peripheral nerves and neurorehabilitation	<ul style="list-style-type: none">Preclinical and clinical studies (clinical isolates)

Table 1. Applications of PRP in different fields of medicine and scientific evidence.

document up to 35% of respondents to the PRP infiltrate, compared with 10% hyaluronic acid. While these studies collect causística few patients, the importance is that for the first time the concentrations of growth factors contained in PRP infiltrated specified, stressing the importance of leukocyte fraction not potentiate the proinflammatory effect of the final product obtained. In recent years most extensive series of clinical cases have reported their success in implementing PRP injections; perhaps the largest series the Spanish belonging to a group that included the treatment of 261 patients with 3 injections of PRP 15 days set apart from each other, with a follow up of 1 year, with a functional improvement in 67% of them, on especially those younger patients and those with a more incipient development of the disease [4–6, 11, 15, 16].

Study		Results	Authors
• Tendinopathy chronicle	• Injury chronic more than 6 weeks.	• 97% good results	• Gandia and col.
	• Refractory epicondylitis	• 8% poor results.	• Edwards y Calandruccio.
	• Chronic pain lateral epicondyle.	• 79% success rate.	• Mishard and Pavelko.
	• Achilles tendinopathy.	• 60% improvement at 8 weeks, 81% at 6 months and 93% at 12 months.	• Sanchez and col.
	• Progress of a patient with Achilles rupture.	• PRP did not generate damage and faster recovery.	• Filardo and col.
	• PRP vs. saline infiltration.	• Regeneration and faster return to activity.	• De Vos and col.
	• Chronic refractory tendinitis: PRP vs. saline infiltration.	• Same results though less inconvenience.	• De Jonge and col.
		• No significant differences.	
• Patellar tendinitis	• Animal study.	• Greater immunogenic response without abnormal marcadores.	• Taylor and col.
	• Plasma in rat patellar tendon.	• Increased levels of collagen I and II.	• Kajikawa and col.
	• 20 athletes with chronic patellar tendinitis (three injections of PRP).	• 70% complete recovery at 6 months, the rest 80% with decreased pain.	• Kon and col.
	• Patellar tendon in 31 patients during 6 months.	• Better results and better quality.	• Filardo and col.
	• PRP vs. Others treatments.	• PRP more effective in degenerative conditions	• Van Ark and col.
• Elbow tendinitis	• Corticosteroid injections vs. PRP.	• 79% good results with PRP vs. 51% with corticosteroids.	• Gosens and Perbons.
	• Using PRP in epicondylitis.	• Increased angiogenesis, wound healing and accelerates higher histological grade.	• Lyras and col.
	• PRP Injections vs. corticosteroids infiltrations.	• Long-term benefits.	• Coombes and col.
• Plantar fasciitis	• Cronica.	• 6/9 symptomatic relief als 8 weeks and 77.9% complete resolution of symptoms a year.	• Barret and Erredge.
	• PRP vs. another treatments.	• Best treatment to avoid relapses.	• Glazer and col.
	• Chronic plantar fasciitis.	• Ecure method and reduces pain.	• Martinelli y col.
• Ligament acute injury	• ACL reconstruction.	• Shortening the return to activity by 27%.	• Samspsn and col.
	• ACL reconstruction.	• There is no consensus, faster transformation of LCA with PRP.	• Ventura and col.

Study	Results	Authors
<ul style="list-style-type: none">• Muscle injuries	<ul style="list-style-type: none">• 11 elite athletes with muscle tears.• 20 professional athletes.• 8 football players and 6 of basketball.• PRP in animals.	<ul style="list-style-type: none">• Return to the fastest competition and 30% shortens recovery• Good results.• Faster return to competition.• It shortens the recovery period of the muscle.
		<ul style="list-style-type: none">• Wright-Carpenter.• Sanchez and col.• Cugat and col.• Hammond and col.

Table 2. Applications PRP in trauma and orthopaedic surgery.

2.1.4. Other applications

It has been seen that the PRP is useful in chronic Achilles tendinopathy especially when infiltrations Ozone [8, 9, 10], patellar tendinopathy [5, 6, 11], previously used in repairing cuff rotators [12, 13, 14], repair the anterior cruciate ligament [11] or with plasty erector or tibial bone-tendon graft-bone, meniscal repair the knee joint [5, 6], in the reconstruction of the glenoid labrum or hip and ultimately partial and total muscle injury made here open repair and strengthening PRP later [7, 19].

2.2. Chiropody

In most cases, the goal of medical research is not only to extend the patient’s life, but to improve the quality of the patient. Growth factor rich plasma is a novel and relatively recent technique applicable to tissue repair. It consists of a simple system for obtaining platelet and autologous plasma proteins from a patient’s blood sample. In the field of podiatry the application of PRGF allows to improve the evolution of patients with regenerative needs in lower limbs such as: accelerate ossification postoperatively, shorten the resolution time in diabetic ulcers or improve scarring among many others. Several studies on the application of growth factors have shown excellent results in different medical specialties among which podiatry is found; therefore it is considered a technique of high effectiveness and clinical interest for its contribution to the scientific community [17].

2.3. Dentistry and maxillofacial surgery

Maybe another field where the PRP has seen a more visible development. However there is a strong controversy and debate as to the usefulness of the PRP in the recovery of dental alveolar bed with lyophilized bone plasty, objectifying alveolar increased, improving the healing of the soft tissues and facilitating greater cohesiveness particulate graft, which would useful in dental implantology. Others are more pessimistic when it comes to reproduce these results, due to the large differences in growth factors present in the PRP, according to the method of obtaining the final product applied [20–23]. This led to think that the higher the concentration of these factors would be more effective regeneration, promoting the use of systems that got a

higher concentration of growth factors, systems that were approved and used without thinking of the concentration obtained product end. Far from achieving the desired effect, in vitro otherwise completely it observed when the concentration factor exceeds a certain level. Hence the strong controversy arose in its use in many cases fueled by the lack of systematic obtaining PRP that may be incorrect.

2.3.1. *Aggressive periodontitis*

Platelet-rich plasma has emerged as an alternative in periodontal therapy. PRP appears to increase the speed of the healing process since it is biologically possible that a higher concentration of platelets can assist in wound healing due to the higher concentration of platelets and initiate a faster cellular response than the normal blood clot [6, 7]. Today we have an evidence-based learning curve that shows us a first stage where it was used as a cementing biomaterial and as a stimulant for the regeneration of bone tissue. In a second stage, it is applied for the healing of soft tissue wounds based on biological evidence, which has generated great expectations in several medical specialties, among which is dentistry. The clinician today increasingly understands the need to make decisions based on scientific evidence. Until now, we know that biologically it is possible that a higher concentration of platelets can aid in healing.

2.3.2. *Dental implants*

In the field of Implantology, we report the use of PRP in the preparation of maxillary bone for placement of implants; thus it is described that in the alveoli to which PRP are placed they show a greater buccolingual/palatal bone width, accompanied by a higher bone density and a faster tissue coverage compared to patients in whom this compound was not used [33]. Probably, the benefits of PRP on implants may be related to the type of bone on which they act, since most of the studies that show better clinical indices correspond to sites without grafts or autologous grafts where factors such as vascularization may play an important role. In a radiographic clinical study of 11 patients who were implanted in the posterior mandibular area without grafting, no implant failure was observed, and it was shown that the use of PRP may lead to early bone apposition around the implant, and that improves soft tissue healing. Previous in vitro studies have demonstrated a PRP stimulatory effect on osteoblast proliferation that appears to begin in vivo at the second week, increase from the third week, and is maintained during the fourth week, so the local application of PRP would increase the amount of newly formed bone around the implant and bone density. In studies on canines, it has been observed that the application of PRP significantly increases the contact between bone and implant ($P = 0.028$). B15. In the dental area, most studies have focused on bone regeneration. With respect to the use of plasma in sinus elevation and increased alveolar ridge published a study that determined the advantages of its use in conjunction with lyophilized bone, but also indicate that it is necessary to have more studies that support this method. With regard to repair of bone defects and use of PRP in a study with 10 patients with diagnosis of periodontitis we used bone graft associated with PRP in the cases group, and bone graft and serum in the control group. Comparatively a greater reduction of the sacks and better quality of bone was obtained in the patients of

the case group with respect to the control group. Evaluated the use of PRP with tricalcium phosphate compared with the use of alloplastic material only in intraosseous defects. They conclude that the associated use of the materials presents better clinical and radiographic results. Conducted a study in which they evaluated the ability to reduce bone resorption in fractured alveoli, in a case group of 14 people who used PRP compared to 6 people in whom it was not used. It was concluded that the use of PRP decreases bone resorption.

Several clinical procedures have used the PRP observing their qualities in the dental area. Presented platelet gel for use as an adhesive in bone grafts and one that aided the consolidation. The platelet gel is obtained and processed immediately in the operating room. Marx et al. [23] observed that a platelet concentrate obtained by blood centrifugation caused a high concentration of platelets in the graft and with them, the presence of growth factors and that the cells of the spongy bone also possess receptors for these.

It was also described that the use of PRP and PRF offer a new and useful therapeutic tool in the acceleration of healing and bone maturation in maxillofacial and reconstructive surgery. In this regard, Marx et al. and Fennis et al. [29], demonstrated that PRP improves bone regeneration and that platelets can act as local regulators of the healing process; in turn, the application of the PRP and the CFs it contains, increase the microcirculation of the gingival mucosa surrounding the wound. Other studies have shown that with a single 20 pM application of a recombinant factor PDGF-BB type, a significant effect can be achieved in increasing capillary density. A similar effect could be achieved in patients treated with PRP [30]. The characteristics of the PRP suggest that it could be of great use in implant procedures, and generally in procedures involving the preservation of bone and soft tissue. The use of PRP has several advantages such as a safe autogenous preparation, free of worries about communicable diseases such as HIV, hepatitis or Creutzfeldt-Jakob disease; and is convenient for the patient, since the blood is collected in the immediate preoperative. However, although PRP therapy has been used for decades, there is no agreement in the literature as to whether this procedure influences the success of bone integration of an implant. Our observations have shown lower rates of failure with the use of PRP compared to the conventional technique without PRP, although this difference is not statistically significant and, although the calculated risk and treatment measures show a beneficial effect of PRP, it is reduced.

2.3.3. *Periodontics*

In the field of periodontics, the use of PRP has been described as adjuvant of regenerative therapy. Some authors found that there was a significantly greater increase in the periodontal ligament when the injured sites were treated with PRP [31, 32]. Since the beginning of the research with the PRP, studies have been published that showed optimal results in bone regeneration with its application alone or combined with grafting. In general, most of the studies where PRP is applied agree that there is a visible improvement of soft tissue healing and a greater cohesiveness of the particulate grafts, since it facilitates their manipulation and transport to the surgical bed; however, it is important to emphasize that the real role of growth factors is in relation to differentiated cells (preosteoblasts or osteoblasts), promoting their proliferation and differentiation and not on the stem cells of the tissue (able to differentiate

into cells of the bone tissue), which would explain some controversies regarding the main role of these factors in the formation of bone tissue. However, the application of PRP in the specialty of periodontics continues to be of great utility since it behaves as a matrix for particulate grafts in the regeneration of bone defects (GTR) left by periodontal disease and in the area of periodontal cosmetic surgery (for root coverage), where it has been reported that it may be a good alternative to connective tissue grafts in root coverage surgery to promote the formation of lost soft tissues and decrease postoperative inflammatory response, as reported in the studies reviewed.

2.4. Gynecology

Gels have been used for handling PRP surgical wounds in various major surgeries, with positive effects on aspects like reduction in postoperative pain with less conventional analgesic requirement. In a case-control study, application of recombinant PDGF gels in dehiscence abdominal surgery, showed a significantly shorter closure, compared to controls, no significant side effects [24, 25].

Furthermore the PRP has been used in vitro as “plug” in the management of premature rupture of fetal membranes, watertight sealing of defects in biological membranes [26].

However it has not been informed of the effect of PRP in areas such as infection or trans and postoperative bleeding.

2.5. Cardiovascular surgery

While it has been used to promote healing of cardiovascular surgical wounds, especially at the sternal level, but also in wounds caused by peripheral vascular access, several studies have shown that the topical application of PRP decreases the frequency of chest infection, improves hemostasis, postoperative pain, the amount of wound drainage and even decreases the days of postoperative hospital stay. Although studies have not shown a significant effect on the management of these [21, 27].

2.6. Plastic surgery

In a case series, we observed that the application of a skin flap on a surgical bed which was previously applied PRP, qualitatively reduced the volume of capillary bleeding from the surgical bed, decreased need for drainage or compression bandages, as well as a reduction in postoperative pain [28].

On the other hand there are few studies strongly demonstrating the usefulness of PRP in the management of burns. Experimental studies have shown that applying a gel burns PRP stimulates an intense inflammatory response, with a significant increase of extracellular matrix proteins, fibroblast proliferation, collagen and granulation tissue. However it has not documented a real acceleration epithelialization of wounds. On the other hand, a study that applied the subconjunctival injection of PRP in 10 patients with ocular burns showed a significantly

faster epithelialization of the cornea and the conjunctiva [26]. Another study that addressed the use of PRP gel for wound management including friction burns demonstrated a significant improvement in its use [27]. Until now, there are no other studies that support the utility of PRP in burns. However, due to the good experimental results, there is a theoretical possibility that due to the reported increase in inflammatory action this could stimulate the formation of hypertrophic scarring in superficial burns and in deeper burns [27].

Therefore there is still no strong scientific evidence to recommend the PRP in the management of burns. There are variables such as type of scarring, burn extent, thickness thereof, time of application or rate of infection that still require more in-depth study [37].

2.7. General surgery

It has been postulated that the use of PRP as rich fibrin glue for placing meshes in correcting inguinal hernias material improves tolerance, postoperative pain, decreasing the amount of suture material for fixing the same, however even better designed studies are needed to refine this clinical application [31].

On the other hand it seems to be well-founded scientifically use in both diabetic ulcers, how in pressure ulcers, significantly speeding up the closure of the same, decreasing the pain without significant side effects. Several studies, including a meta-analysis, have shown that the application of PRP in chronic diabetic ulcers significantly accelerates their closure, decreases pain and even works in the most severe wounds without significant collateral events reported [28]. A study that analyzed the cost of this therapy over conventional treatment over 5 years showed that the management of PRP improves the quality of life of these patients significantly and significantly reduces the costs of their care [29]. Evidence for the efficacy of platelet-rich plasma in these chronic lesions does not appear to be contradictory, so that PRP treatment in diabetic ulcers is well founded, however it remains unknown whether this overall effect of PRP on chronic wounds, if its beneficial effects are maintained in the long term, decreasing the percentages of amputation or if the outcome may be influenced by other factors of the wound, concomitant treatment or the particular patient. In this sense, a recent study that included 49 patients with chronic wounds of various etiologies (pressure ulcers, venous ulcers, diabetic ulcers, etc.) also demonstrated the degree of improvement (area reduction, wound closure) in 97% of cases regardless of wound origin [29, 30].

2.8. Ophthalmology

Experimental studies in vitro demonstrated that PRP increases the migration of fibroblasts and conjunctival keratinocytes. Similarly, some clinical studies have objectified positive effects of PRP in corneal ulcers and keratoconjunctivitis sicca Sjogren's syndrome, for which there is currently no satisfactory treatment [33, 35].

In the case of eye burns subconjunctival injection of PRP in a number of patients showed significantly more rapid epithelialization of the cornea and conjunctiva, however this has not been demonstrated later [32].

2.9. Otolaryngology

On preclinical and clinical use in type 1 patients with perforated eardrum Tympanoplasty studies could be useful in defect closure, however still required study more scientific evidence to corroborate this fact, not having such studies with controls [34, 36].

2.10. Dermatology

Experimental studies have shown that dermal papilla cells exposed to significantly increase their proliferation PRP, which was associated with increased Akt and ERK signaling and upregulation of fibroblast growth factor 7 and the B-catenin, which are recognized hair growth factors. Even though scientific studies are needed more power, PRP opens a range of possibilities in the treatment of psoriasis, vitiligo, alopecia, lichen planus and other cosmetic applications [28, 39].

2.11. Neurology and neurosurgery

Preclinical experimental studies have shown healing capacity and neuroregeneration with functional recovery in applying jointly PRP and suturing the edges of the injured nerve, due to a significant increase of axons in the distal segment, however these studies are still experimental, although it has documented some isolated case report with positive results. Similarly this opens a door to the possibility of nerve stimulation in patients with neurological hypoxic ischemic tare origin especially following active neurorehabilitation programs. Still needed are appropriately supported in this respect clinical trials to assess the potential clinical benefit that PRP can contribute in this field [38, 40].

2.12. Anesthesiology

Nerve growth factor (NGF) is the founding member of the neurotrophin protein family. It was discovered over half a century ago through its ability to promote sympathetic and sensory neuronal survival and axonal growth during the development of the peripheral nervous system, and are the paradigmatic neurotrophic factor-derived targets underlying the neurotrophic hypothesis. Since that time, NGF has also been shown to play a key role in the generation of acute and chronic pain and in hyperalgesia in various pain states. NGF is expressed at high levels in damaged or inflamed tissues and facilitates the transmission of pain by nociceptive neurons through a variety of mechanisms. Genetic mutations in NGF or its receptor TrkA tyrosine kinase, lead to a lack of congenital sensitivity or a decrease in the ability of humans to perceive pain. B16. In humans, NGF levels are elevated in a variety of acute and chronic pain states including rheumatoid and spondyloarthritis in neurogenic overactive bladder and interstitial cystitis induced cancer pain prostatitis and in patients with degenerative intervertebral disc disease (Lee et al. [38]). The functional link between these increased levels of NGF and pain was determined through a variety of animal and human studies that modulate NGF levels and observe the resulting effects on the level of pain experienced. In humans, intramuscular injections of NGF in one trial resulted in an increase in pain scores and increased pressure pain sensitivity in NGF injected muscle compared to baseline; these effects were resistant

to local muscle anesthesia. NGF also induced localized and long-lasting non-inflammatory mechanical and thermal hypersensitivity in human skin after local injection. Similarly, local injection of NGF into the masseter muscle induced mechanical allodynia and hyperalgesia that persisted for at least 7 days after administration of NGF B16. The results of clinical trials of tanezumab (a monoclonal antibody that sequesters NGF and does not let it act) that are currently underway, particularly those related to the progression of arthritis or osteonecrosis, are the next determinant of if and when realized that potential. In the event that tanezumab is shown to have an acceptable long-term safety profile. The key role of tanezumab in the management of pain in patients with chronic diseases may depend on a greater understanding of their different effects on symptom control (i.e., analgesia) vs. disease modification (chronic pain or persistence) B16.

2.13. Other applications

From the standpoint of experimentation, the scientific evidence regarding the role of PRP in stimulating proliferation of various cell lines both epidermal and mesenchymal, have been used as a support for growing and clonal expansion in vitro of same laboratory.

3. Conclusion

Surely we are facing a new era of treatment in the new field of what is called regenerative medicine with an extraordinary range of possibilities for clinical applications increased, but that requires a process of scientific and medical systematization which allows channel it safely and effectively in applications where there is scientific evidence really enough weight so apply. To do this it is necessary to two things: first the consensus of the authors engaged in the production and application of this therapy in order to standardize procedures for obtaining those more effective and allow adequate traceability and monitoring of the end product, depending clinical application given their intended and secondly the design of clinical trials which management and establish appropriate guidelines to that effect.

Today we are still far from achieve, given that almost all existing clinical applications, the scientific evidence is weak, based on case series or case-control studies in the most positive assumptions. The growing presence of various protocols to obtain, low control over the final product component and variety of clinical applications, difficult first reach some sort of consensus on the process or procedures more reliable and adequate collection and secondly development of appropriate clinical trials to test them in different pathologies susceptible to it.

Revised everything published about the conclusion you reach is that the PRP is well tolerated technique, considered from 2 years as a medicine ago, restricted its use to prescribing physicians, dentists and podiatrists, lacking tab Currently technique, and cannot be considered standard treatment for any medical condition where intended to be used, if it is accepted that it can be used as adjunctive therapy along with conventional therapies to implement clinical and functional improvement of the patient.

They are necessary in the future of basic research and translational medicine to better understand the pathophysiological mechanisms underlying its regenerative effects.

Similarly sheet to establish a sound scientific studies are necessary in the form of clinical trials to standardize the techniques for obtaining both depending on the cellular composition of the final product as a protein obtained and is reproducible by all authors and specific management guidelines for each clinical application where feasible use in regenerative medicine.

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