Efficacy and safety of the use of autologous plasma rich in platelets for tissue regeneration: a systematic review

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BACKGROUND: Autologous plasma rich in platelets (PRP) is a derived blood product whose application in clinical practice is growing. A systematic review was conducted to evaluate its efficacy and safety.

STUDY DESIGN AND METHODS: A search was performed in electronic databases. Randomized controlled clinical trials (RCTs) in adult patients were included and assessed for methodologic quality. The main outcomes were "tissue regeneration" and "safety." Relative risks (RRs) and standardized mean differences (SMDs) were calculated to show pooled estimates for these outcomes. When the results heterogeneity was more than 50 percent, a sensitivity analysis was performed.

RESULTS: Twenty RCTs were included (11 of oral and maxillofacial surgery, 7 of chronic skin ulcers, and 2 of surgery wounds). Four RCTs evaluated the depth reduction in gingival recession in chronic periodontitis; the SMD was 0.54 (95% confidence interval [CI], 0.16 to 0.92) mm, favorable to PRP. Three RCTs evaluated the clinical attachment level in chronic periodontitis; the SMD was 0.33 (95% CI, –0.71 to 1.37) mm. Six RCTs assessed the complete skin epithelialization in wound ulcers; the RR was 1.40 (95% CI, 0.85 to 2.31). Only 6 RCTs reported adverse effects without differences between groups.

CONCLUSIONS: PRP improves the gingival recession but not the clinical attachment level in chronic periodontitis. In the complete healing process of chronic skin ulcers, the results are inconclusive. There are little data about PRP safety. There are several methodologic limitations and, consequently, future research should focus on strong and well-designed RCTs that assess the efficacy and safety of PRP.

Autologous plasma rich in platelets (PRP) is a product derived from fresh whole blood that contains a high concentration of platelets (PLTs) with healing anti-inflammatory and pro-regenerative properties that permit the body to heal tissue wounds faster and more efficiently. It is obtained from the patient's body through plasmapheresis technique. Although few investigators have quantified the concentration of PLTs obtained, it can be 338 percent more than the normal total blood PLT count.[1]

In recent years, the application of plasmapheresis has been widely extended in diverse medical and surgical procedures,[2] especially in the fields of orthopedic surgery,[3] periodontic surgery,[4] maxillofacial surgery,[1] plastic surgery,[5] thoracic surgery,[6] vascular surgery,[7-9] and ophthalmology.[10]

ABBREVIATIONS: GF(s) = growth factor(s); PRGF = plasma rich in growth factors; PRP = plasma rich in platelets; RCT(s) = randomized controlled trial(s); RR(s) = relative risk(s); SMD(s) = standardized mean difference(s).

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Clinical evidence suggests that PRP could have beneficial therapeutic effects on hard and soft tissue healing, due to the contents of growth factors (GFs) stored in the PLTs. When these GFs are released from the PLTs, they trigger a tissue regeneration process.[7,8] Additionally, PRP contains other intra- and extra-PLT components that also contribute to regeneration. One example is fibrinogen, which creates the fibrin network necessary for cellular implantation and posterior cellular multiplication.[11]

Several commercially available methods to obtain PRP concentrate are currently used in the clinical setting and there are many types of kits, centrifuges, and vials available. The usual methods consist of obtaining less than 100 mL of fresh whole blood from the patient, and separating and concentrating the PLTs by centrifugation. Subsequently, before reinsertion into the patient, the PRP is activated to produce PLT degranulation and clot formation.[12] The substances used in activation are bovine thrombin (which may cause immunologic problems and Factor V deficiencies)[13] or recombinant thrombin or calcium, which have been proven to be safer proactive options.[2]

Despite several in vitro studies published, there are very few clinical studies available on the efficacy of PRP. Although the processing of autologous PRP is highly variable, it is extensively used in different clinical settings. This suggests that there is a need to synthesize current evidence on the subject. Thus, we performed a systematic review to evaluate the efficacy and safety of PRP in tissue regeneration.

MATERIALS AND METHODS

Inclusion and exclusion criteria

We included all randomized controlled trials (RCTs) that assess the efficacy and/or safety of PRP for healing and regeneration of hard and soft tissues in any and all medical and surgical procedures. Split-mouth-design RCTs were included if they were randomized. In this design each patient receives, simultaneously, the active and control treatment in the right or in the left side of the body (for example, of the mouth or the face).[14] Any RCT crossover studies were also included when results regarding the first treatment period were reported.

We considered as relevant outcomes those referring to any kind of "tissue regeneration" after PRP application and/or "safety" related to PRP. Overall, the concept of tissue regeneration referred to an improvement of the functionality or complete tissue healing as specifically defined in the original studies. Different outcomes were assessed, depending on the pathology (i.e., wound healing in chronic skin ulcers, clinical attachment in chronic periodontitis).

Literature search

We performed several computerized literature searches for trials using the following search terms and combining them: autologous plasma, autologous platelet, rich growth factor, plasma rich in growth factors (PRGF), wound, tissue, bone, osseous, heal, and repair implant. This search was filtered with the Cochrane methodologic filter for clinical trials[15] in the following databases: The Cochrane Central Register of Controlled Trials (CENTRAL; The Cochrane Library 2006, issue 1), MEDLINE (accessed via PubMed; 1966-2006), EMBASE (via OVID; 1974-2006), and Science Citation Index (1945-2006). No language restrictions were applied.

Reference lists of the most relevant studies and engines search (http://www.google.com) were checked for possible additional studies. Authors of the identified studies were contacted in some cases.[16]

Data extraction

Papers from the bibliographic search that met the inclusion criteria were reviewed independently by two reviewers and relevant data were extracted using a standardized form.

Data was extracted regarding patient and intervention characteristics, methodological quality and results for each group of participants. The quality of the papers was appraised using the Jadad scale.[17] This scale evaluates whether trials are randomized or double blinded and whether they include a description of dropouts, using a score system. An additional point is given based on whether the method of randomization and double-blinding is appropriate or inappropriate. Based on the resultant score, the studies were classified as "high quality" (score of 4 or 5), "moderate quality" (score of 3), or "low quality" (score < 3). A consensus between reviewers was reached about the methodologic quality of each study.

Statistical analysis

When possible, we pooled data from the included trials as presented in the original publications in a meta-analysis using a random-effects statistical model.[18] We calculated risk ratios for binary outcomes and standardized mean differences (SMDs) for continuous outcomes and their 95 percent confidence intervals (95% CIs).

An analysis of heterogeneity was conducted by an I^2 test considering values of 25, 50, and 75 percent as a sign of low, moderate, and high heterogeneity, respectively.[19] When I^2 values were 50 percent or greater, we conducted a sensitivity analysis to explore the cause of heterogeneity. We anticipated heterogeneity induced by quality of the studies, disease severity, and the PRP processing method.

When an acceptable homogeneity was observed, ($I^2 < 50\%$), the reviewers also estimated measures of clinical effect such as what patients needed to be treated (NNT) to observe a clinical benefit or the number of patients to be treated to detect an adverse event (NNH). The number needed to treat is the estimated number of patients who need to be treated with the new treatment rather than the standard treatment for one additional patient to benefit (NNT) or to harm (NNH). All analyses were undertaken using computer software (Review Manager [RevMan] 4.2, The Nordic Cochrane Centre, Copenhagen).

RESULTS

Overall, 2016 citations were identified, of which 42 were RCTs about PRP. Of these, 22 RCTs[10,16,20-39] were excluded and 20 RCTs[1,4-7,40-55] fulfilled our eligibility criteria (Fig. 1). The reasons of exclusion of RCTs are shown in Table 1. Eleven studies[1,4,40-48] assessed the use of PRP in oral and maxillofacial surgery (Table 2), 7[49-55] in cutaneous ulcers (Table 3), and 2[5,6] in surgical wounds (Table 4).

PRP in oral and maxillofacial surgery

Of the 11 trials assessing the use of PRP in oral and maxillofacial surgery, 5[40,42,44-46] had a parallel design, 1 study[1] did not specify the study design, and 5 studies[4,41,43,47,48] followed a "split-mouth" design. Although all studies were randomized, none explained the process of allocation to treatment as blinded to investigator (e.g., allocation by a central office unaware of subjects' characteristics or sequentially numbered, sealed, opaque envelopes). In the studies with split-mouth design[4,41,43,47,48] the treatment was located in a specific side of the mouth based on a random criterion. Three studies[4,41,46] were double blind and in another 3[43,45,47] the evaluator was blinded to intervention. The other 5 studies[1,40,42,44,48] were not blinded.

The numbers of patients included in each trial was relatively small (n < 100) and no trial reported case sample size calculation. Overall, the quality of five studies[1,40,42,44,48] was low and moderate for the rest.[4,41,43,45-47] Five RCTs[4,41,43,45,46] were conducted in patients with intrabony periodontal defects secondary to chronic periodontitis, three RCTs[42,47,48] were performed with patients that needed sinus floor augmentations with or without implants, two studies[40,44] were conducted in patients with indicated dental extractions, and another study was conducted in patients with maxillary bone grafts in mandibular defects secondary to extirpation of a benign or malign tumor.[1]

The outcomes of each clinical trial are specified in Table 2. It was only possible to combine the results of 4 of 11 RCTs.[4,41,45,46]

Excluding one RCT,[47] all of the non meta-analyzed studies concluded that the PRP group showed better results than the control group. Only two[1,41] of them specified the p value.

The results of four studies[4,43,45,46] were combined to analyze the efficacy of PRP in "depth reduction of gingival recession" (mm) versus a control group in patients suffering from chronic periodontitis. The mean effect showed a greater reduction in patients in the experimental group (153 patients; SMD, 0.54 mm; range, 0.16-0.92 mm; Fig. 2).

Three studies[4,43,46] assessing the "clinical attachment level" (mm) showed nonsignificant differences between the experimental and control groups (126 patients; SMD, 0.33 mm; range, –0.71 to 1.37 mm; Fig. 2), and an important heterogeneity was observed ($I^2 = 86\%$). The heterogeneity was explained by differences in the criteria of disease severity between studies. Results were homogeneous ($I^2 = 0\%$) when only studies[4,46] including patients at severe stages were considered, and were favorable for the experimental group (96 patients; SMD, 0.89 mm; range, 0.47-1.31 mm).

Skin ulcers

Six[49-53,55] of the seven trials on this topic had a parallel design and one[54] a crossover design. Two[50,55] of the seven studies specified the process of random generation sequence by computer numbers and three other studies explained that treatment assignment was by sealed envelopes[49,51] or by a centralized method independent of the investigators.[55] The study by Driver and colleagues[55] explained the method of assignment blinding. Although all studies (except Aguirre et al.[53]) were double-blinded, only one[55] showed the blinding method. RCTs included a relatively small number of patients (n < 100) and only two trials[51,55] reported the sample size calculation. Consequently, three studies[49,50,55] were of high quality, three [51,52,54] were of moderate quality, and one[53] was of low quality.

Four RCTs[49,50,53,54] included patients with chronic ulcers of different etiology, two[51,52] with venous chronic ulcers, and one with diabetic chronic ulcers.[55] It was only possible to combine the results of the RCTs for the outcome "complete ulcer epithelialization." One RCT[53] did not consider that outcome.

Results from six RCTs[49-52,54,55] assessing the efficacy of autologous PRP or PLT factors obtained from autologous PLTs were combined. A total of 122 patients were included in the experimental group and 105 in the control group (Fig. 3).

The results for the "complete ulcer epithelialization" were not significant between the experimental and control groups (relative risk [RR], 1.40; range, 0.85-2.31). However, heterogeneity was found among the studies ($I^2 = 56.8\%$) and consequently a sensitivity analysis was performed. All RCTs had moderate quality except for Knighton and colleagues,[49] Krupski and colleagues,[50] and

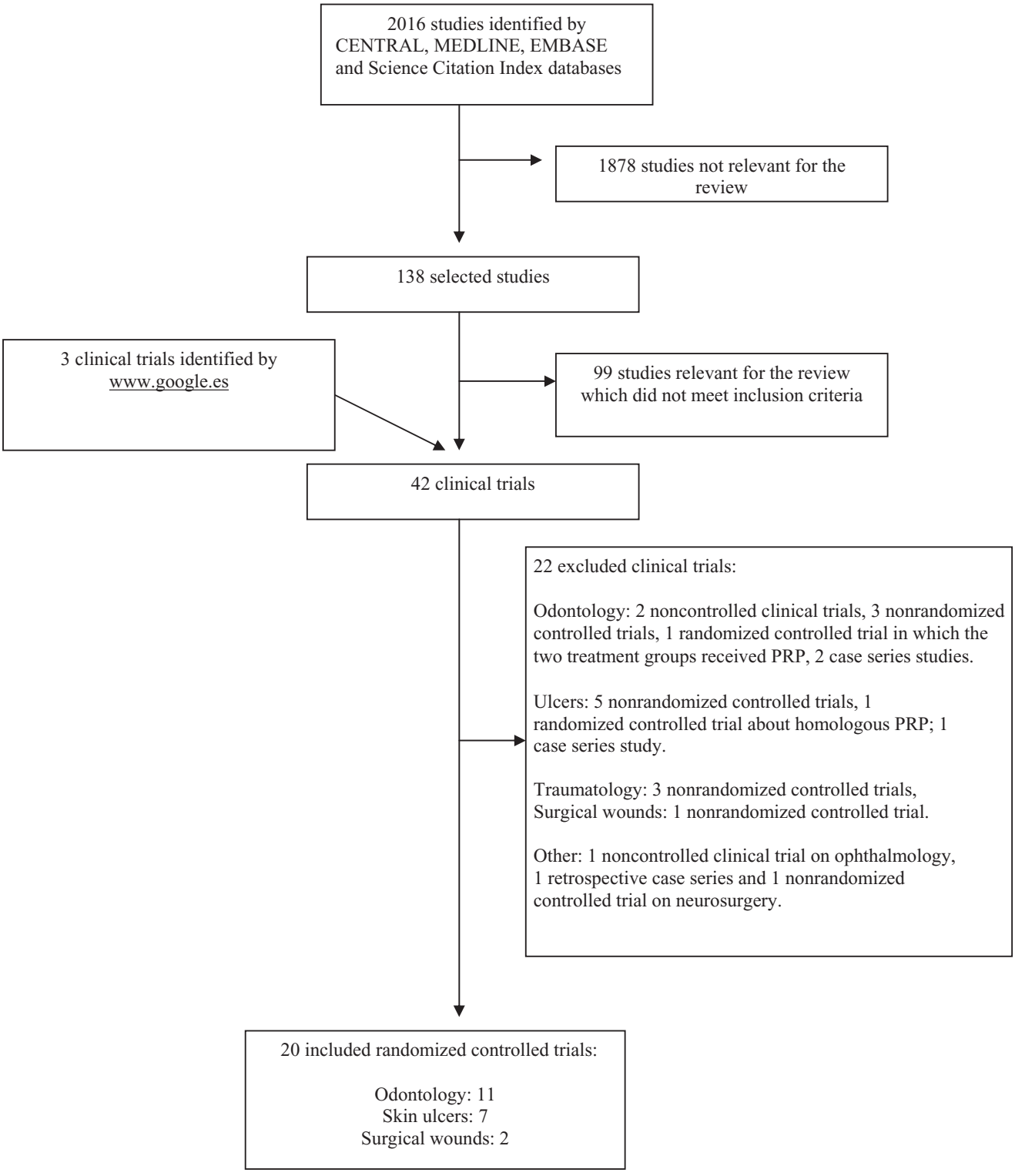

Fig. 1. Trial flow.

Driver and colleagues,[55] studies that had high quality. When only those studies were analyzed, heterogeneity increased to 62.1 percent and the results were significant and favorable to PRP (RR, 1.97; range, 1.19-3.25). When the studies[51,54] that obtained the PRP by applying a PLT lysate were excluded, there was a decrease in the heterogeneity between groups (from $I^2 = 56.8\%$ to $I^2 = 44.9\%$) but the results were similar to the principal analysis (RR, 1.65;

TABLE 1. Excluded studies and reasons of exclusion

Excluded studies (first author, years)	Causes of exclusion
Dentistry/oral and maxillofacial surgery	
Camargo, 2005[20]	Nonrandomized clinical trial
Franchini, 2005[21]	Noncontrolled clinical trial
Froum, 2002[22]	Three case series
Lekovic, 2002[23]	RCTs; both arms receive PRP
Maiorana, 2003[24]	Noncontrolled clinical trial
Monov, 2005[25]	Nonrandomized clinical trial
Robiony, 2002[26]	Five case series
Sammartino, 2005[27]	Nonrandomized clinical trial
Skin ulcers	
Atri, 1990[28]	Nonrandomized sequential clinical trial (a 3-month treatment period first and then a 3-month period with experimental treatment)
Margolis, 2001[29]	Retrospective case series
Mazzuco, 2004[30]	Nonrandomized clinical trial controlled with a retrospective cohort of patients
Reutter, 1999[31]	Nonrandomized clinical trial
Saldamalacchia, 2004[32]	Nonrandomized clinical trial
Steed, 1992[33]	Randomized clinical trial; PRP used is homologous, not autologous
Tarpila, 1998[16]	Nonrandomized clinical trial
Surgical wounds	
Erlich, 2002[34]	Nonrandomized clinical trial
Floryan, 2004[35]	Nonrandomized clinical trial
Mishra, 2006[36]	Nonrandomized clinical trial
Traumatology	
Wright-Carpentier, 2004[37]	Nonrandomized clinical trial
Ophthalmology	
Korobelnik, 1996[10]	Noncontrolled clinical trial
Neurosurgery	
Castro, 2004[38]	Nonrandomized clinical trial
Lowery, 1999[39]	Retrospective case series

range, 0.73-3.70). When the analysis of the RCTs that included ulcers of different etiologies was excluded, the heterogeneity decreased to 10.6 percent and the results were again similar to the principal analysis (RR, 1.23; range, 0.90-1.41).

Surgery wounds

Two RCTs[5,6] assessed the use of PRP in surgery wounds. The number of included patients was smaller (30 patients or less) and none of the studies reported a priori sample size calculation. Both studies were of low quality.

The study by Englert and coworkers[6] used a parallel design and assessed the autologous PRP gel compared with a control group in patients who underwent bypass surgery and had an external incision in the inferior extremity. The experimental group showed better results in chest pain, redness, and swelling. The pain was measured by an ordinal scale that scored from 0 (no pain) to 10 (worst pain). On Day 1, the score was 1.47 ± 0.83 and 4.47 ± 2, for the experimental and control groups, respectively. Similarly, the experimental group had favorable results in comparison with the control group in the outcome of low-extremity pain (1.33 ± 0.72 vs. 3.06 ± 1.62, for the experimental and control groups, respectively). However, neither of the two outcome results showed a significance.

The study by Powell and colleagues[5] used a split-face design. Each patient received both experimental and control treatments in different sides of the face, simultaneously. The autologous PRP gel was compared in patients that underwent face-lifts. This RCT included eight patients. The experimental group showed better results in the outcomes of ecchymosis and edema compared to the control group, although results were not significantly different.

Safety of the treatments

Only 6 of 20 RCTs[4,42,47,50,52,55] reported the treatment-related adverse events. Overall, all studies agreed that there were not treatment-related complications. Two RCTs included the type of adverse event. Driver and coworkers[55] showed an increase in the blood urea nitrogen in the control group, and an increase in either the thrombin time or the activated partial thromboplastin time was observed in both treatment groups (PRP and control). In the study by Senet and colleagues,[52] two patients reported dermatitis (one in each treatment group), one patient developed an infection in an existing ulcer, and one had thrombophlebitis (both in the PRP group).

DISCUSSION

The aim of this systematic review was to evaluate the efficacy and safety of PRP for tissue regeneration. After an exhaustive literature search, 20 RCTs that assessed the efficacy of autologous PRP in oral and maxillofacial applications, chronic skin ulcer, and wound healing after surgery were included.

In oral and maxillofacial surgery, four studies[4,43,45,46] with 153 patients suffering from chronic periodontitis were meta-analyzed. The results of "depth reduction of gingival recession" showed a significant improvement in the group treated with PRP. In the subgroup of patients with more severe stage of the disease the outcome of "clinical attachment level" showed better results than in the subgroup of patients with an incipient illness. These results suggest that patients with more severe chronic periodontitis could benefit from PRP.

In chronic skin ulcers, six studies[49-52,54,55] with 227 patients were included in the meta-analysis. Results

TABLE 2. Characteristics of the included clinical trials in oral and maxillofacial surgery

Study first author, publication year	Inclusion criteria	Intervention	Outcomes	Quality (Jadad score)
Anitua, 1999[2]	Adults of either sex for whom an extraction was indicated because of a nontreatable tooth with vertical fractures or severe periodontal disease and who contemplated an implant and biopsy of the area	Autologous and topically applied PRGF or control group without PRGF	Epithelialization	1
	Number of patients: 20	One-session treatment	Degree of bone regeneration	
Marx, 1998[1]	Elective cellular marrow bone graft reconstructions of mandibular defects 5 cm or greater arising from benign and malignant tumor extirpations without radiotherapy	Cellular bone marrow graft with autologous PRP added during the bone-milling phase of graft preparation and topically applied after bone placement into the defect or cellular bone marrow graft without PRP	Trabecular area of the mineralized bone matrix at 6 months	1
	Number of patients: not specified. 88 Cellular marrow bone graft reconstructions of mandible defects (44 with PRP and 44 without PRP)	One-session treatment	Graft maturity index PLT count Identification of receptors to PDGF and TGF-β in the harvested cellular marrow	
Böhm, 2003[41]	Adults of both sexes, with contralateral, interproximal, and/or intrabony periodontal defects	Synthetic bone material (β-tricalcium phosphate) mixed with autologous PRP versus synthetic bone material (β-tricalcium phosphate)	Early wound healing using the early healing index on a scale from 1 (complete flap closure with no fibrin present) to 5 (necrosis of the overlying tissues)	3
	Number of patients: 8	One-session treatment		
Wiltfang, 2003[42]	Adults of both sexes, needing a sinus floor elevation with a blood concentration of thrombocytes within the normal range and no history of maxillary sinus inflammation	β-Tricalcium phosphate with autologous PRP versus only β-tricalcium phosphate	Percentage of new bone measured in an area of 9 mm^2	1
	Number of patients: 35		Acceleration of the degradation of the ceramic material (β-TCP)	
Cheung, 2004[43]	Adults of both sexes with bilateral gingival recession (Miller Class I or II)	Autologous PLT concentrate graft vs. subepithelial connective tissue graft, both covered by coronally advanced flaps	Vertical recession depth	3
	Number of patients: 18 with 54 treated teeth (29 with subepithelial graft and 25 with PLT concentrate)	One-session treatment	Clinical attachment level Clinical probing depth Keratinized tissue Recession reduction PLT count Postsurgical discomfort level Aesthetic evaluation results Gingival recession reduction	
Hanna, 2004[4]	Adults of both sexes between 35 to 75 years of age with generalized, chronic, severe periodontitis. Teeth with mobility less than Miller's Class III or mobile teeth requiring splinting	Bovine derived xenograft alone or in combination to autologous PRP in the treatment of intrabony defects	Gingival index	3
	Number of patients: 13	One-session treatment	Plaque index Probing depth Recession Clinical attachment level Bleeding on probing	

Huang, 2005[45]	Adults of both sexes with dental defects of Miller's Class I Number of patients: 24	Coronally advanced flap vs. autologous PRP + coronally advanced flap One-session treatment	Recession depth Recession width Gingival thickness Width of keratinized tissue Clinical attachment level Probing depth Plaque index Wound healing index Gingival index	3
Simon, 2004[44]	Adults of both sexes needing treatment for third molar extraction sockets Number of patients: 14	Autologous PRP vs. control group without PRP One-session treatment	Pain on palpation Number of analgesic tablets consumed Swelling Degree of mouth opening margins between the socket and surrounding bone Radiopacity of bone tilling the socket Presence of trabecular bone formation	2
Okuda, 2005[46]	Adults of both sexes with chronic, moderate, or advanced periodontitis Number of patients: 70	PRP combined with a biodegradable ceramic, porous hydroxyapatite (HA) vs. a mixture of HA and saline solution in the treatment of human intrabony defects One-session treatment	Changes at 12 months of: Gingival index Bleeding on probing Probing depth Clinical attachment level Intrabony defect fill Vertical relative attachment gain	3
Raghoebar, 2005[47]	Adults of both sexes, edentulous suffering from insufficient retention of their upper denture related to a severely reabsorbed maxilla, which required augmentation of the maxillary sinus floor Number of patients: 5	Autologous bone graft from the iliac crest versus autologous PRP + autologous bone graft from the iliac crest One-session treatment	Complications during surgery and postoperative healing (inflammation, wound dehiscence, sequestration, and loss of bone particles) TGF-β concentration of PRP and blood were measured Bone biopsies were studied by microradiography and light microscopy	3
Steigman, 2005[48]	Patients who required sinus augmentation with a crestal bone height of approximately 7-9 mm in the posterior maxilla Number of patients: 20	All patients received a graft consisting of Cerasorb (Curasan, Kleinostheim, Germany), β-tricalcium phosphate synthetic material, in one side and only autologous PRP in the contralateral side One-session treatment	Alveolar bone growth at 6 months	1

TABLE 3. Characteristics of the included clinical trials in skin ulcers

Study first author, publication year	Inclusion criteria	Interventions	Outcomes	Quality (Jadad score)
Knighton, 1990[49]	Adults with a chronic skin leg ulcer, an evolution of at least 8 weeks and a normal PLT count	Autologous PLT-derived wound healing formula (Avitene) vs. placebo	Total epithelialization of the wound	4
	Number of patients: 32	Length of treatment: 8 weeks	Time to 100% of epithelialization	
Krupski, 1991[50]	Adult men, with a chronic skin leg ulcer and an evolution of at least 8 weeks	PRP topical solution vs. saline solution every 12 hr	Total epithelialization of the wound	4
	Number of patients: 18	Length of treatment: 12 weeks	Total wound area Wound volume Rate of healing	
Stacey, 2000[51]	Adults of both sexes with chronic venous ulcer	PLTs obtained from autologous PLT lysate vs. placebo	Ulcer healing	3
	Number of patients: 96	Topical application two times a week associated with gauze and pressure dressing	Time to ulcer healing	
		Length of treatment: until ulcer healing or for a 9-month period	PLT growing factor and epidermic growing factor concentrations in the PLT lysate Mitogenic ability of the PLT lysate in a fibroblasts culture	
Senet, 2003[52]	Adults of both sexes with chronic skin venous leg ulcers	Topic use of frozen autologous PLTs gel vs. saline solution	Ulcer healing	3
	Number of patients: 15	In patients under standard and pressure topical treatment	Local expression of the vascular endothelial growing/(growth?) factor	
		Length of treatment: 16 weeks	Local expression of the keratocyte growing factor Local expression of the interleukin-8 Local expression of the metalloproteinase-1 tissular inhibitor	
Aguirre, 2004[53]	Adults of both sexes with chronic skin ulcers	Autologous PRFG vs. conventional treatment (cleansing, debridement, and wet cure with physiologic saline and sterile gauzes)	Recovered surface percentage	1
	Number of patients: 16	Length of treatment: once a week application during 4 weeks.	Lesion area Measures made from photographic records using the Mouseyes software	
Weed, 2004[54]	Adults of both sexes with a chronic skin leg ulcer and an evolution of at least 8 weeks	Autologous PLT lysate combined with collagen vs. poor PLT plasma combined with collagen (placebo group)	Complete healing (100% epithelialization)	3
	Number of patients: 26	Length of treatment: twice a day during 12 weeks.	Rate of wound healing (ulcer surface depending on the duration of the treatment)	
Driver, 2006[55]	Adults of both sexes with diabetes mellitus 1 or 2 and a chronic skin ulcer with an evolution of at least 4 weeks	Autologous PRP gel vs. saline solution.	Changes in the ulcer surface rate	5
	Number of patients: 54	One-session treatment	Volume rate at the end of the study comparing with baseline measure Daily surface reduction rate at the end of the study Healing (100% epithelialization) at the end of study Daily volume reduction rate at the end of the study Safety	

TABLE 4. Characteristics of the included clinical trials in surgical wounds

Study first author, publication year	Inclusion criteria	Interventions	Outcomes	Quality (Jadad score)
Englert, 2005[6]	Adults of both sexes undergoing coronary surgery (bypass) with a sternal incision Number of patients: 30	Autologous PRP gel vs. control group One-session treatment	Thoracic and lower limb pain measured by an ordinal scale (from 0 to 10) Thoracic and lower limb hematoma, PLT index: PLT ADP at the end of the study compared with baseline levels Wound evolution: redness and swelling photograph and measure with a millimeter ruler	1
Powell, 2001[5]	Patients undergoing facial aesthetic surgery (rhytidoplasty) Number of patients: 8	Autologous PLT gel application vs. usual treatment One-session treatment	Edema and ecchymosis (mouth, neck and periauricular), assessed by photography	1

showed nonsignificant differences between experimental and control groups in the complete epithelialization of skin ulcers. The subgroup of RCTs that included chronic ulcers of different etiologies added an important heterogeneity to the analysis. In the subgroup of studies with diabetic ulcers there was a favorable but nonsignificant tendency toward PRP. It is possible that ulcer etiology influenced the efficacy to PRP.

Regarding surgical wounds, two RCTs[5,6] with a total of 38 patients showed no differences between treatment groups. The results may be explained by the smaller sample size, quality of the studies, and the fact that the selected outcomes, edema and ecchymosis, are difficult to measure.

PRP safety has not been properly assessed across the included studies. Only 6 of 20 RCTs reported the frequency of adverse events and none showed a causal relation with the PRP application.

It is certainly difficult to interpret the clinical relevance of these systematic review findings since the CIs were large and study sample sizes were, in general, small. Therefore, the statistical differences warrant caution upon interpretation, as reported by other authors.[56] Well-designed, large RCTs with sample size calculations exclusively based on clinically relevant differences are needed.

Only three RCTs[49,50,55] in chronic skin ulcers were considered to be of high quality. However, primary and secondary outcomes were highly heterogeneous among studies except for the principal outcomes in skin ulcers (complete epithelialization or healing).

Despite these limitations, it was possible to combine several RCTs that had a common endpoint in some of the clinical areas assessed. PRP showed favorable results compared to the control group in chronic periodontitis.

Recently, a systematic review[57] has been published about the effects of PLT-rich plasma on bone regeneration in dentistry. Despite the fact that the search strategy of studies was more limited than ours (pathology, language restriction, and the EMBASE and Science Citation Index databases were not used), there were some differential methodologic questions, and the included studies were not totally coincident, the conclusions were similar. Currently, there are several ongoing trials (http://www.clinicaltrials.gov/ct2/results?term=autologous+PLT) assessing the efficacy of autologous PLT concentrate that can add more evidence of the effects on the pathologies included in our systematic review.

In conclusion PRP has been assessed thought RCTs in several clinical areas. In our systematic review, treatment of skin ulcers with PRP increased the percentage of total recovery but not significantly. In the treatment of chronic periodontitis, there is an improvement in the depth reduction of gingival recession and clinical attachment level at

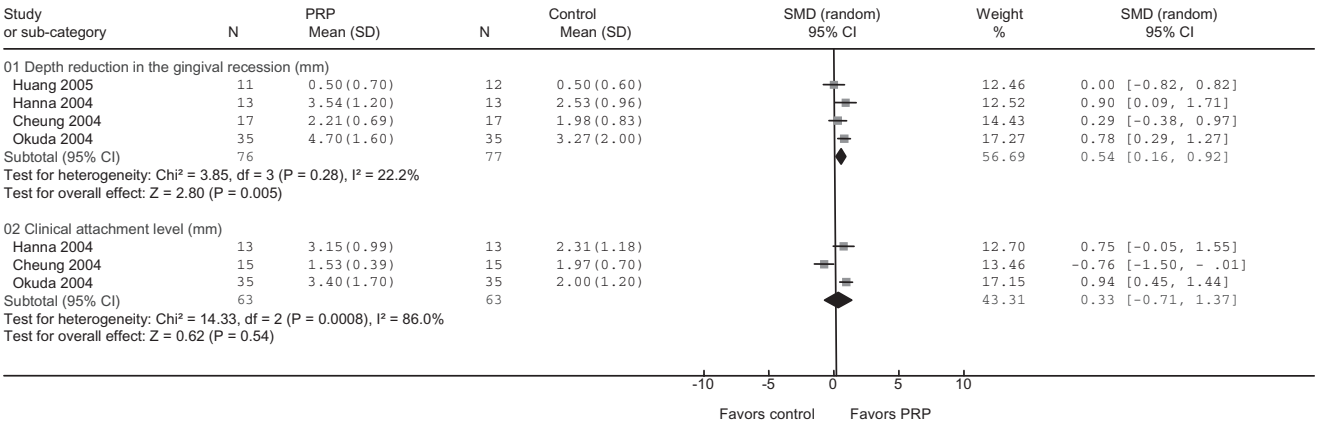

Fig. 2. Efficacy of autologous PRP in chronic periodontitis.

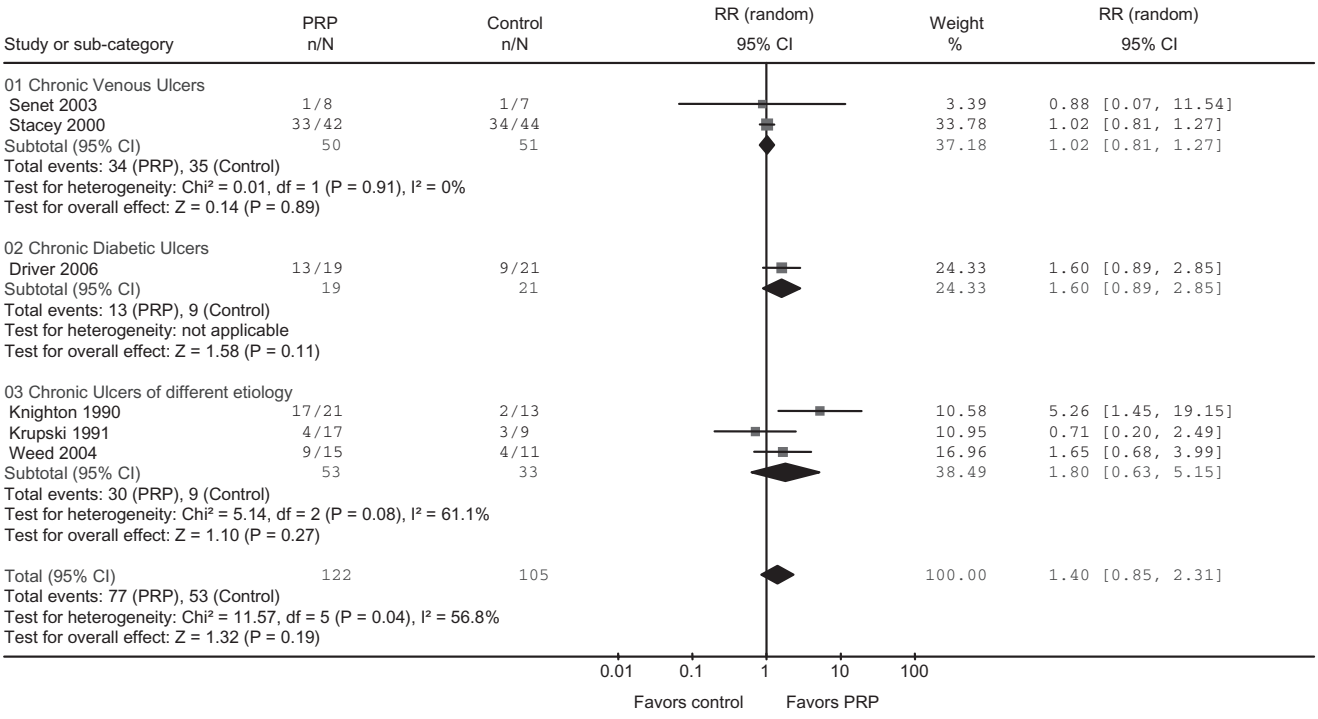

Fig. 3. Efficacy of autologous PRP in chronic skin ulcers.

severe stages. In relation to the PRP for the treatment of surgery wounds, there were not significant differences when compared with a control group. Due to the methodologic limitations of the RCT included in this systematic review, there is a need for further RCTs to determine with certainty the role of PRP for the tissue regeneration.

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