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REVIEW

The use of platelet-rich plasma in plastic surgery: A systematic review

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Platelet-rich plasma;
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Summary *Objective:* The study's aim was to evaluate the available evidence regarding the use of platelet-rich plasma in plastic and reconstructive surgery, through implementation of a systematic review of the literature.
Data sources: PubMed and The Cochrane Library were searched using MeSH terms: 'platelet rich plasma' and 'plastic surgery' for all publications up to July 2011. All English, German, French and Dutch papers were included. In addition, the reference lists of relevant articles were searched for potentially appropriate publications.
Study selection: Included studies needed to report on topics related to plastic and reconstructive surgery, mentioning at least one clinical end point. Both *in vivo* and *in vitro* comparative studies, performed in humans or animals, were included. A total of 82 publications were found, of which 40 studies met the inclusion criteria and were relevant to be used in this systematic review.
Data extraction: Data from retrieved studies were reviewed and tabulated according to year of publication, study design, human or animal studies, characteristics of the population, mode of application, outcomes and preparation method.
Data synthesis: A total of 15 randomised controlled trials and 25 case—control studies were found. Thirty-six publications demonstrated favourable outcomes with the use of platelet-rich plasma. The included articles were divided into three topics related to plastic surgery: wound healing, fat grafting and bone grafting.
Conclusions: This systematic review describes a substantially beneficial effect of platelet-rich plasma for several indications, including a better wound healing rate, an increased survival rate of fat grafts and an enhancement of bone graft regeneration.

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Platelet-rich plasma (PRP) is used in several clinical disciplines and is considered to ameliorate tissue regeneration due to the presence of essential cytokines and growth factors (GFs). In early studies, PRP was identified as having a beneficial effect on bone grafting with applications in oral and maxillofacial surgery (e.g., jaw reconstruction surgery and implantology), orthopaedic surgery (e.g., treatment of chronic tendinopathy and cruciate ligament repair) and cardiac surgery (e.g., sternal closure and haemostasis of graft harvest site). More recently, increasing interest is seen in the application of PRP in other areas of tissue regeneration, such as soft-tissue defects and fat grafting. Many trials fail to deliver conclusive evidence of the advantages, while randomised controlled trials (RCTs) are rare.

Marx et al.[1] defined PRP as a portion of the plasma fraction of autologous blood, having a platelet concentration above baseline values. PRP is made by centrifugation of whole blood (drawn from a peripheral vein and stored in an acid citrate dextrose solution A (ACD-A) anticoagulant), which separates the various components of blood by their specific weight and increases the concentration of platelets. At the same time, platelet-poor plasma (PPP) is formed as a by-product, which is transformed into fibrin glue (FG) by activation. In thrombocytes, cytokines and GFs are stored in α-granules in their incomplete form. In physiological conditions, through activation of platelets, these cytokines and GFs are transformed into their bioactive status and actively secreted within 10 min after clotting, with >95% of the pre-synthesised GFs released within 1 h[1] This process can be reproduced in clinical settings through activation of PRP by using an activator, for example, thrombin, resulting in the formation of platelet gel (PG). This gel acts as a drug-delivery system since it comprises a high concentration of platelets and their active cytokines and GFs, which stimulate physiological processes. *In vivo*, following the initial burst, thrombocytes spend the rest of their lives synthesising and secreting additional cytokines and GFs. Of these, (i) platelet-derived GF (PDGF), (ii) transforming GF-beta 1 (TGF-β1), (iii) vascular endothelial GF (VEGF) and (iv) epidermal GF are considered to be the most important (Table 1).[2,3] Subsequently, through stimulation of vascular ingrowth, macrophages arrive and start producing their own cytokines and GFs, some similar to those produced by platelets. This results in a new and continued local tissue repair and re-growth.

This systematic review was performed to collate and evaluate the evidence available to date on the application of PRP within the medical specialisation of plastic and reconstructive surgery. For this purpose, outcomes are evaluated with emphasis upon the efficacy of PRP within the field of wound healing, fat grafting and bone grafting. Furthermore, the process necessary for PRP preparation is evaluated.

Table 1 Growth factors present in platelet-rich plasma and their function.

PDGF	Stimulation of chemotaxis and mitogenesis of fibroblasts, smooth muscle cells, MSC and osteoblasts; stimulation of chemotaxis of monocytes, macrophages and neutrophils; activation of macrophages
TGF-β_1	Matrix synthesis; regulation of keratinocytes proliferation and stimulation of collagen production
VEGF	Stimulation of blood vessel permeability, mitogenesis of endothelial cells and angiogenesis; stimulation of lymfangiogenesis
EGF	Stimulation of chemotaxis of keratinocytes; stimulation of mitogenesis of epithelial-, mesenchymal- and fibroblasts; stimulation of endothelial chemotaxis, mitogenesis and angiogenesis; regulation of the secretion of collagenase

PDGF: platelet-derived growth factor, MSC: mesenchymal stem cells, TGF-β_1: transforming growth factor-beta 1, VEGF: vascular endothelial growth factor, EGF: epidermal growth factor.

Materials and methods

Literature search

The first search of the literature was undertaken by one investigator (C.S.) under supervision of the principal investigator (S.M.), who is a content expert. Following exclusion of non-relevant trials, assessment of eligibility of the remaining publications was performed. The search for potentially relevant studies was undertaken in PubMed and The Cochrane Library for all publications up to July 2011. The following medical subject headings or MeSH terms were used: 'platelet rich plasma' and 'plastic surgery'. No restrictions on publication date or status were made. Several foreign-language publications were found, but only papers written in English, German, French or Dutch were included. In addition, reference lists of relevant trials were searched for other potentially appropriate publications.

Inclusion criteria

Eligible studies needed to report on topics related to plastic and reconstructive surgery and the trial authors needed to report at least one clinical end point. This systematic review only included (i) RCTs which fulfilled the current standard definition for this study design (also named true RCTs), (ii) non-RCTs, (iii) comparative studies and (iv) cohort studies regarding humans or animals.

Data extraction

Data from the retrieved studies were tabulated according to (i) basic study characteristics: year of publication, study type, human or animal studies and population characteristics, manner of application and outcomes, and (ii) method of preparation: origin of whole blood, activation method, whole blood volume, number of spins and platelet concentration.

Results

Using this search filter, 71 articles were found (Figure 1). Eleven articles were found in reference lists and were

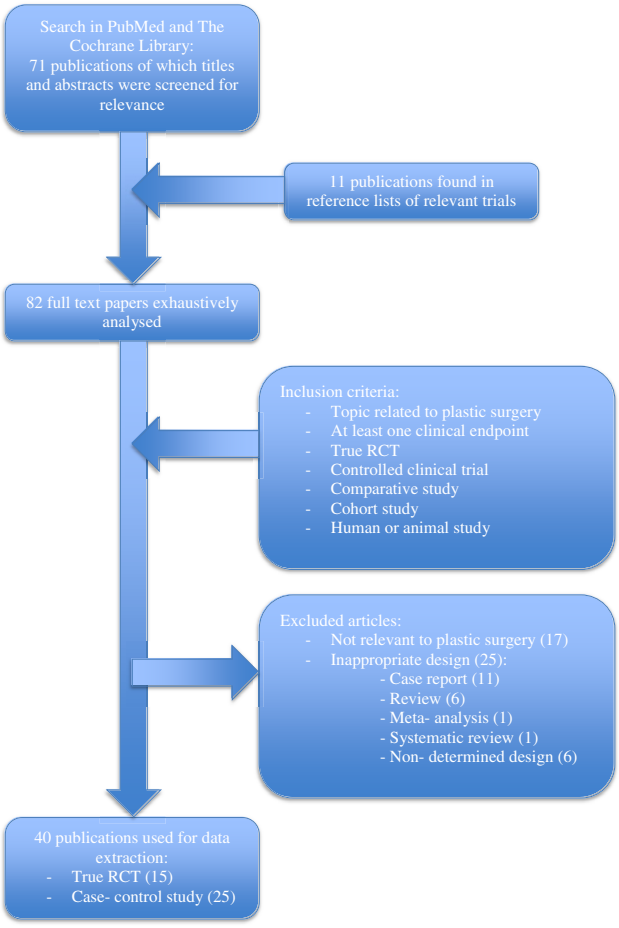

Figure 1 Flowchart of the search.

added to the search results. Seventeen articles were considered not relevant and were excluded. Based on the inclusion criteria, 25 publications could not be included. Fifteen RCTs and 25 case—control studies were found and were analysed thoroughly and used for data extraction. This brought the total of relevant publications dealing with the use of PRP in plastic surgery to 40.

The search retrieved 19 articles conducted in humans (total $n = 4500$), describing 17 trials *in vivo*, one *in vitro* and one trial in both, and 21 on animals (total $n = 446$), describing 15 trials *in vivo*, one *in vitro* and five trials in both.

Division of the articles into topics related to plastic surgery resulted in 14 articles concerning wound healing[3–16] (Table 2), 10 articles about fat grafting[17–26] (Table 3) and 16 articles on bone grafting (Table 4).[1,27–41] Thirty-six articles reported a beneficial effect of PRP (i) when used to promote wound healing of soft tissues,[3–5,7–16] (ii) to enhance survival of fat grafts[17–20,22,24–26] and (iii) to stimulate osteoregeneration.[1,27–39,41] Thirteen of these articles were RCTs.[1,3–5,7,8,12,25,28,29,38,39,41] Of the 40 described publications, four studies could not demonstrate better results when using PRP,[6,21,23,40] two of them were RCTs.[6,40]

The 'method of PRP preparation' was found to be not uniform among the performed studies and several variables needed to be taken into account (Table 5). Autologous blood was used in 30 studies,[1,3–12,18–22,24,25,27–32,34,36,37,39–41] six studies applied human blood in animals,[13–16,23,26] one study processed whole blood from a blood bank,[17] two trials drew blood from one animal and used the resulting PRP for other animals[35,38] and only one study did not mention the origin of PRP.[33] Regarding the number of performed centrifugation rounds, nine studies used a single centrifugation protocol,[3,5,10,18,19,21,22,29,30] in 18 trials a double spin was performed[1,4,7,12,16,17,20,25–28,31,35–40] and in 13 studies the number of centrifugation spins was not reported.[6,8,9,11,13–15,23,24,32–34,41] The obtained platelet concentration in PRP was reported in 21 studies[1,7,10,14,16,17,22–24,28,29,31–35,37–41] and 19 studies[3–6,8,9,11–13,15,18–21,25–27,30,36] did not mention this concentration.

Most commonly, PRP is transformed into PG by adding an 'activator', as was performed in 29 trials. Studies reported the use of thrombin,[3,5,6,34] $CaCl_2$,[18–21,24,29,30,36] a combination of the latter[1,4,7,10,11,17,22,25,26,31,35,38–41] or gelatin molecules.[12] One trial used an activator but did not specify which one.[32] Other authors did not activate the PRP on purpose[13–15,27,37] or did not report this action.[8,9,16,23,28,33] Several studies suspended the produced PRP into a carrier, for example, supernatant plasma,[38,40] FG[27,31,36,39] or other products,[16,18,19] resulting in a more controlled (presumed by the authors) release of cytokines, a longer local availability of cytokines and the possibility to obtain a prior-determined concentration of platelets. To extend the therapeutic shelf life of the platelets in PRP, studies were performed with freeze-dried and fresh-frozen PRP.[13–17]

The 'method of application' of PRP is another variable that needs to be taken into account. To enhance wound healing, the PRP is applied, for the greater part, topically on the wound site,[3–11,13–16] while some studies injected PRP into the wound, with[20] or without[12] a combination of fat grafts. Using PRP to improve survival of fat grafts or bone grafts, it is mixed with the fat or the harvested bone and then injected,[1,20,21,23,26] spread on[18–20,22] or implanted[24,25] (fat grafts) or placed[27–41] (bone grafts) into the defect that needs to be treated.

Wound healing

Humans

The efficacy of PRP to promote wound healing was studied in nine papers.[3–11] Six of them were RCTs,[3–8] of which three[3,4,8] identified a statistically significant improvement by PRP when compared with controls. Wound healing rate,[3–6,9,10] re-epithelialisation[8] and wound closure[11] were used as primary outcomes to assess wound healing. For these outcomes, six studies found a statistically significant difference.[3,4,8–11] Driver et al.[5] did not find any difference in the healing rate between groups, but showed that significantly more wounds in the PRP group healed and Kaplan—Meier time-to-healing significantly differed between groups. A significant shorter time to undergo reconstructive surgery was seen in two studies[3,10]; additionally, the application of PRP resulted in a shorter hospital stay.[10] Furthermore, a significant lower amputation rate,[9] less pain[3] and the ability to reduce the formation of oedema and ecchymosis[7] were attributed to PRP. No treatment-related serious adverse events were seen.[5,9,10]

All reviewed studies reported on the use of autologous and activated PRP. Regarding the number of centrifugations

Table 2 Overview of studies on wound healing.

Authors	Design	n	Comparison	Results in relation to the PRP group
Humans				
Danielsen et al., 2008[6]	RCT	20	PRP vs CT in epithelialisation of donor sites and STGs	No improved epithelial coverage
Driver et al., 2006[5]	RCT	40	PRP vs saline gel in diabetic foot ulcers	Improved healing rate
Glover et al., 1997[9]	C-C	3830	Platelet releasate + CT vs CT in chronic wounds	Overall healing rates: higher[a]; Amputation rates: lower[a]
Hom et al., 2007[11]	C-C	80	PG vs CT in full-thickness skin punch wounds	At 42 days: increased wound closure,[a] higher wound closure velocities,[a] <14 days: greatest effect of healing
Kazakos et al., 2009[3]	RCT	59	PRP vs CT in acute soft tissue wounds of the limb	Faster wound healing,[a] shorter time to surgery[a]
Knighton et al., 1990[8]	RCT	32	Platelet's GFs vs platelet buffer solution in chronic wounds	Increased epithelialisation rate[a]
Mazzucco et al., 2004[10]	C-C	59	PG vs CT in the treatment of nonhealing skin lesions	Improved healing rate, reduced hospital stay,[a] shorter time to surgery,[a] no adverse effects
Powell et al., 2001[7]	RCT	8	PRP vs NT in deep-plane rhytidectomy	Improvement of oedema and ecchymosis (early phase of recovery)
Saad Setta et al., 2011[4]	RCT	24	PRP vs PPP in chronic diabetic ulcers	Faster wound healing[a]
Animals				
Bir et al., 2009[12]	RCT	40	PRP in endothelial cell proliferation (*in vitro*) and PRP in neovascularisation (*in vivo*)	Induction of endothelial cell proliferation and capillary tube formation (*in vitro*), increased perfusion (*in vivo*)[a]
Pietramaggiori et al., 2006[13]	C-C	45	FD PRP vs FF PRP or NT in diabetic wounds	Increased formation of granulation tissue (*in vitro*)[a]
Pietramaggiori et al., 2008[14]	C-C	NR	Different PRP preparations vs spontaneous wound healing in diabetic mice	Improved formation of vascularized wound tissue,[a] increased cell proliferation[a]
Pietramaggiori et al., 2010[15]	C-C	40	Functional status of platelets in diabetic wound healing	Stimulation of angiogenesis, cell proliferation and wound contraction[a]
Takikawa et al., 2011[16]	C-C	NR	PRP + fragmin/protamine microparticles vs controls	Enhancement of neovascularisation (*in vivo*),[a] increased formation of granulation tissue,[a] day 14: Maximal granulation tissue formation, gradually release of GFs (*in vitro*)

RCT: randomised controlled trial, PRP: platelet-rich plasma, CT: conventional treatment.
[a] Significant result, STG: split-thickness skin graft, C-C: case-control study, PG: platelet gel, GF: growth factor, NT: no treatment, PPP: platelet-poor plasma, FD: freeze-dried, FF: fresh-frozen, NR: not reported.

performed, no uniform trend could be identified. Differences in the mode of application were found concerning lower-limb ulcers: Driver et al.[5] and Saad Setta et al.[4] both repeated topical application twice weekly, while Danielsen et al.[6] treated the defect only once. The latter included a wide variation of aetiology of lower-limb ulcers and reported no profit of PRP. The first two studies only included diabetic ulcers and described a beneficial effect of PRP on these wounds.

Animals

Wound closure was analysed in three studies, showing a stimulating effect of PRP in the treated lesions.[13–15] Histological examination was performed, which revealed that, through application of PRP products, the neovascularisation increased significantly[13–16] or at least improved.[12] Furthermore, when compared with controls, PRP significantly enhanced granulation tissue formation, a key element in wound healing.[13,15,16]

Three *in vitro* studies were found.[12,13,16] One demonstrated that PRP induces endothelial cell proliferation and capillary tube formation.[12] Furthermore, it was shown that different preparations of platelet therapeutics have an equal ability to increase fibroblast proliferation when compared with controls.[13] Regarding GFs in modified PRP, Pietramaggiori et al.[13] noted no significant differences in either the total load or the distribution, while Takikawa et al.[16] describe that GFs bound to fragmin/protamine microparticles were gradually diffused and released from this carrier.

In summary, the animal studies on PRP report on the induction of capillary tube formation and the enhancement

Table 3 Overview of studies on fat grafting.

Authors	Design	n	Comparison	Results in relation to the PRP group
Humans				
Cervelli et al., 2009[18]	C-C	43	PRP + fat grafts vs fat grafts in ulcers and facial plastic surgery	More ulcers underwent 100% re-epithelialisation, enhanced maintenance of contour restoring and 3D volume in facial plastic surgery (*in vivo*), increased number of ADSC (*in vitro*)[a]
Cervelli et al., 2009[19]	C-C	30	PRP + fat grafts vs CT in venous chronic ulcers	Decreased time to re-epithelialisation[a]
Cervelli et al., 2011[20]	C-C	20	PRP + fat grafts vs CT or PRP in chronic ulcers	PRP + fat grafts: faster re-epithelialisation[a]
Kakudo et al., 2008[17]	C-C	NR	Different PRP preparations vs controls in proliferation of ADSC and FB	Promotion of proliferation of ADSC and FB[a] (*in vitro*)
Salgarello et al., 2011[21]	C-C	42	PRP + fat grafts vs fat grafts in breast fat grafting	No improvement
Animals				
Blanton et al., 2009[22]	C-C	3	ADSC, with or without PRP, vs saline in full-thickness wounds	ADSC groups: increased microvessel densities,[a] PRP + ADSC: increased wound cosmesis and levels of VEGF (*in vitro*)[a]
Oh et al., 2011[26]	C-C	20	PRP + fat grafts vs fat grafts + saline in fat grafting on the scalp of mice	Higher volume and weight,[a] greater vascularity,[a] fewer cysts,[a] vacuoles[a] and fibrosis[a]
Pires Fraga et al., 2010[25]	RCT	30	PRP + fat grafts vs fat grafts + saline in fat grafting on the ears of rabbits	Higher fat survival weight,[a] increased number of viable adipocytes[a] and blood vessels[a]
Por et al., 2009[23]	C-C	24	PRP + fat grafts vs fat grafts + saline in fat grafting on the scalp of mice	No improvement
Nakamura et al., 2010[24]	C-C	64	PRP + fat grafts vs fat grafts in fat grafting of the limb in rats	Stimulation of angiogenesis[a] and the formation of granulation tissue, less fat resorption

C-C: case-control study, PRP: platelet-rich plasma, ADSC: adipose derived stem cells.
[a] Significant result, CT: conventional treatment, NR: not reported, FB: fibroblasts, VEGF: vascular endothelial growth factor.

of fibroblastic and endothelial cell proliferation. Presumably, the resulting improvement of neo-angiogenesis and the increase in granulation tissue formation are the underlying mechanisms contributing to an improved healing rate as seen in human studies.[3–5,8–11]

Fat grafting

Humans

Five case–control studies concerning the effect of PRP on human fat grafts were found.[17–21] Three used the combination of PRP with the fat grafts, according to the Coleman lipostructure technique, to enhance wound healing.[18–20] These studies demonstrated a decrease in time to full-re-epithelialisation compared with conventional treatment[18,19] or found a statistically significant faster re-epithelialisation in comparison with PRP alone.[20] Regarding the use of fat grafts and PRP in facial surgery, an enhanced maintenance of contour restoring and three-dimensional volume after 1 year was seen, compared to controls treated with fat grafts alone.[18] Recently, a study concerning breast fat grafting was conducted in which no better effect of the combination of PRP with fat grafts was found in comparison with fat grafting alone.[21] Similarly, the use of PRP did not result in a reduction of the number of fat-graft sessions needed but rather in a higher rate of lipo-necrosis.[21]

In vitro studies showed that activated PRP contains large amounts of PDGF-AB and TGF-β_1 and significantly promotes the proliferation of adipose-derived stem cells (ADSCs)[17,18] and dermal fibroblasts.[17] By adding 5% activated PRP to the medium, a maximal promotion of cell proliferation was seen.[17]

All trials concerning wound healing describe use of autologous and activated PRP, which was centrifuged only once (during 10 min) and the level of platelets in the resulting PRP was not reported.[18–20] Salgarello et al.[21] only performed a centrifugation of 5 min at 3500 rpm and did not report the concentration of the thrombocytes in PRP.

Animals

Blanton et al.[22] evaluated the use of PRP for wound-healing purposes: a similar re-epithelialisation was seen in all groups. The combined use of PRP and ADSCs resulted in a significant improvement towards wound cosmesis, when compared with the (PRP only) control group. *In vitro* studies found a sevenfold higher concentration of VEGF in groups with ADSC, compared to PRP and PPP groups without

Table 4 Overview of studies on bone grafting.

Authors	Design	n	Comparison	Results in relation to the PRP group
Humans				
Gentile et al., 2010[30]	C-C	30	PRP + bone vs bone in sinus lifting	Less pain and clinical signs of infection[a]
Lindeboom et al., 2007[28]	RCT	10	PRP + bone vs placebo + bone in oral mucosal wound healing	<10 days: acceleration of the wound healing[a]
Marx et al., 1998[1]	RCT	88	PRP + bone vs bone in mandibular defects	Acceleration of bone formation rate and degree (<6 months)[a]
Oyama et al., 2004[27]	C-C	7	PRP + FG + bone vs FG + bone in alveolar cleft patients	Higher volume ratio of regenerated bone[a]
Torres et al., 2009[29]	RCT	78	PRP + ABB vs ABB in sinus augmentation	Improved bone augmentation[a]
Animals				
Chang et al., 2009[37]	C-C	16	PRP + CH vs CH in bone formation in rabbits	Increased bone formation[a] and in-growth of fibrovascular tissue
Drengk et al., 2009[36]	C-C	NR	Several PRP preparations combined with MSC & CC in sheep	Increased proliferation of MSC & CC (*in vitro*)[a]
Findikcioglu et al., 2009[38]	RCT	32	PRP vs PPP in the healing of critical size calvarial bone defects of rabbits	PRP group: better ossification, PRP and PPP group: no effect on neovascularisation
Gerard et al., 2007[34]	C-C	12	PRP + bone vs bone in mandibular defects in dogs	Higher number of osteoblasts and osteoclasts (1 month)[a]
Hokugo et al., 2007[41]	RCT	12	Several PRP preparations compared in healing of calvarial bone defects in rabbits	PRP + gelatin hydrogel: best enhancement of bone regeneration[a]
Lei et al., 2009[39]	RCT	8	PRP + BMSC vs PPP + BMSC in 3D scaffolds in goats	Enhanced bone regeneration (*in vivo*), stimulation of BMSC proliferation (*in vitro*)[a]
Shayesteh et al., 2010[40]	RCT	12	PRP vs controls in palatal wounds in dogs	No enhancement of early healing
Simman et al., 2008[35]	C-C	48	PRP vs saline in long-bone fractures in rats	Higher callus to cortex width ratio (4 weeks),[a] increased bone strength and enhancement of bone formation
Thorwarth et al., 2006[33]	C-C	24	PRP + bone vs bone in frontal skull defects of pigs	At 14 days: enhancement of bone regeneration[a] and no long-term effects in the mineralisation process
Yamada et al., 2004[32]	C-C	4	PRP + MSC vs PRP or MSC or PCBM or NT in mandibular defects in dogs	PRP + MSC: increased cortical and medullary bone surface area,[a] more mature bone and increased neovascularisation
Yazawa et al., 2004[31]	C-C	12	PRP + FG + bone vs FG + bone in mandibular defects in rabbits	Enhanced bone formation (early postoperative)

C-C: case—control study, PRP: platelet-rich plasma.
[a] Significant result, RCT: randomised controlled trial, FG: fibrin glue, ABB: anorganic bovine bone, CH: collagen/hydroxyapatite beads, NR: not reported, MSC: mesenchymal stem cells, CC: chondrocytes, PPP: platelet-poor plasma, BMSC: bone marrow stromal cells, PCMB: particulate cancellous bone and marrow, NT: no treatment.

ADSC. This higher concentration correlates well with the increased microvessel densities reported in histological examination in these groups.[22]

Survival rate of fat grafts was investigated in four studies.[23–26] The fat grafts' weight, after using PRP and fat grafts, was significantly higher in two studies, in comparison with the use of fat grafts only.[25,26] Histological evaluation showed a significant increase of neo-vascularisation in fat grafts through the application of PRP[24–26] and significant less fibrosis.[25,26] No difference in vascularisation or fibrosis was found by Por et al.[23]

Histological results from Nakamura et al.[24] were in favour of the PRP group, but no significantly different results were reported. Two highly comparable studies concerning free fat survival on the scalp of mice were found, but diverging results were reported.[23,26] Both studies used blood and fat from healthy women. Oh et al.[26] executed a double centrifugation and activated the PRP through injection of thrombin and $CaCl_2$ into the fat, while Por et al.[23] did not mention either of these items.

The rationale for using PRP in combination with fat grafts is the supposed enhancement of neo-angiogenesis, as

Table 5 Preparation methods of platelet-rich plasma.

Authors	V	Aetio	Act	Conc	Centrifugation
Wound healing					
Humans					
Danielsen et al.[6]	120	Auto	T	NR	NR
Driver et al.[5]	<20	Auto	T	NR	1x: 1.5 min
Glover et al.[9]	NR	Auto	NR	NR	NR
Hom et al.[11]	120	Auto	T + C	NR	NR
Kazakos et al.[3]	NR	Auto	T	NR	1x: 20 min (3200 rpm)
Knighton et al.[8]	NR	Auto	NR	NR	NR
Mazzucco et al.[10]	NR	Auto	T + C	1.75×10^6	1x
Powell et al.[7]	450	Auto	T + C	x3 - 6	2x: (5600 rpm) ≥ (2400 rpm)
Saad Setta et al.[4]	10	Auto	T + C	NR	2x: 1007 g ≥ 447.5 g
Animals					
Bir et al.[12]	10	Auto	Gelatin	NR	2x: 10 min (2400 rpm) ≥ 10 min (3600 rpm)
Pietramaggiori et al.[13]	NR	H ≥ A	No	NR	NR
Pietramaggiori et al.[14]	NR	H ≥ A	No	1.2×10^6	NR
Pietramaggiori et al.[15]	NR	H ≥ A	No	NR	NR
Takikawa et al.[16]	40	H ≥ A	NR	x5.43	2x: 15 min (1700 rpm) ≥ 5 min (3000 rpm)
Fat grafting					
Humans					
Cervelli et al.[18]	18	Auto	C	NR	1x: 10 min (1100 g)
Cervelli et al.[19]	13.5	Auto	C	NR	1x: 10 min (1100 g)
Cervelli et al.[20]	18	Auto	C	NR	2x: 10 min (1100 g) ≥ 15 min (1100 g)
Kakudo et al.[17]	NR	H ≥ H	T + C	x7.9	2x: 7 min (1700 rpm) ≥ 5 min (3200 rpm)
Salgarello et al.[21]	18	Auto	C	NR	1x: 5 min (3500 rpm)
Animals					
Blanton et al.[22]	55	Auto	T + C	0.998×10^6	1x: 12 min
Oh et al.[26]	25.5	H ≥ A	T + C	NR	2x: 10 min (160 g) ≥ 10 min (400 g)
Pires Fraga et al.[25]	10	Auto	T + C	NR	2x: 10 min (1450 rpm) ≥ (2100 rpm)
Por et al.[23]	26	H ≥ A	NR	x7	NR
Nakamura et al.[24]	10	Auto	C	x3.18	NR
Bone grafting					
Humans					
Gentile et al.[30]	18	Auto	C	NR	1x: 10 min (1100 g)
Lindeboom et al.[28]	NR	Auto	NR	x4	2x: 10 min (2400 rpm) ≥ 10 min (3600 rpm)
Marx et al.[1]	425	Auto	T + C	x3.38	2x: (5600 rpm) ≥ (2400 rpm)
Oyama et al.[27]	40	Auto	No	NR	2x: 20 min (160 g) ≥ 15 min (400 g)
Torres J et al.[29]	15	Auto	C	x2.97	1x
Animals					
Chang et al.[37]	5	Auto	No	x3.37	2x: 20 min (1500 rpm) ≥ 30 min (3000 rpm)
Drengk et al.[36]	NR	Auto	C	NR	2x: 10 min (2400 rpm) ≥ 10 min (3600 rpm)
Findikcioglu et al.[38]	65	A ≥ A	T + C	x3.9	2x: 20 min (220 g) ≥ 20 min (480 g)
Gerard et al.[34]	20	Auto	T	x3	NR
Hokugo et al.[41]	NR	Auto	T + C	x6.42	NR
Lei et al.[39]	80	Auto	T + C	1×10^6	2x: 20 min (1000 g) ≥ 20 min (3000 g)
Shayesteh et al.[40]	40	Auto	T + C	x6.9	2x: 10 min (2400 rpm) ≥ 15 min (3600 rpm)
Simman et al.[35]	NR	A ≥ A	T + C	x2.46	2x: 10 min (5600 rpm) ≥ 15 min (2400 rpm)
Thorwarth et al.[33]	NR	NR	NR	x5.3	NR
Yamada et al.[32]	NR	Auto	Yes	x4.38	NR
Yazawa et al.[31]	50	Auto	T + C	x4.38	2x: 5 min (1100 rpm) ≥ 5 min (2500 rpm)

V = volume of drawn blood in mL, Aetio: aetiology of used blood, Act: activator, Conc: platelet concentration (x-fold or platelets/μL), Auto: autologous, T: thrombin, NR = not reported, T + C: thrombin and Ca^{2+}, X ≥ Y: first ≥ second centrifugation, 1x: one centrifugation, 2x: two centrifugations, H ≥ A: human blood used in animals, C: Ca^{2+}, H ≥ H: human blood used in other humans, A ≥ A: animal blood used in other animals.

can be concluded from the animal studies. This results in a reduction of the time period (approximately ≤48 h), during which the nutritional supply of the grafted fat depends on diffusion of plasma nutrients.[42] Additionally, PRP creates an optimal micro-environment and stimulates cell growth and cell differentiation (e.g., ADSC).[43–45] Moreover, PRP stimulates chemotaxis of leucocytes, which protects adipocytes against inflammatory processes.

Bone grafting

Humans

Marx et al.[1] were the first to take advantage of the large amount of GFs and cytokines present in PRP to enhance the success of bone grafting. In this study, a faster radiographic maturation rate and a higher bone density were seen when the PRP group was compared with controls. In two other studies, of which one was a prospective RCT,[29] the addition of PRP to bone grafts also resulted in a statistically significant higher bone augmentation, compared with controls.[27,29] Gentile et al.[30] reported a shorter time than the control group, to 100% bone regeneration; they also found significant differences in postoperative pain and the presence of clinical signs of infection, haematoma and oedema for PRP in comparison with controls. Lindeboom et al.[28] mixed PRP with autologous iliac crest bone but did not evaluate the result, as they mainly studied the effect of PRP on the healing of mucosal wounds, which showed a significant increase in capillaries and an acceleration of wound healing during the first week.[28]

All five studies in humans used autologous blood.[1,27–30] One study[28] did not report on activation of the PRP, and Oyama et al.[27] did not activate the PRP. The latter used FG to suspend PRP and used the combination of FG with bone grafts as the control group. A significantly better result for the PRP group was seen, suggesting the additional value of the use of PRP over FG. Three studies[1,27,28] used a double-spin protocol, while two studies[29,30] centrifuged the collected blood once. In both settings, significantly better results for the PRP groups were found. When reported, a 2.97- to 4-fold increase in concentration of the platelets in PRP was identified.

Animals

PRP stimulates the bone formation in animals when compared with FG[31,38,39] and/or with no additional treatment.[33–35,37–39,41] One study integrated PRP into a gelatin hydrogel and reported significantly better bone mineral density values when compared with a treatment of activated PRP.[41] Yamada et al.[32] described a minimal increase of newly formed bone by PRP when used as a scaffold. Additionally, the combination of PRP with *in vitro* expanded mesenchymal stem cells (MSCs) was evaluated and significantly beneficial effects were seen when compared to controls. Their results were confirmed by Drengk et al.[36] who observed a stimulating effect of PRP on the proliferation of MSC and chondrocytes. Furthermore, Lei et al.[39] described a stimulatory effect on the proliferation of bone marrow stromal cells (BMSCs). Regarding neovascularisation, conflicting results were found.[32,38]

Most studies performed in animals used a double centrifugation protocol. Remarkably, some reports described resuspending the PRP in residual plasma[36,40] or in PPP[38,39] following the second centrifugation. In these animals' trials, the concentration of the platelets demonstrated a 2.46- to 6.9-fold increase when compared with baseline values. Shayesteh et al.[40] reported a 6.9-fold increase of platelets and an absence of stimulatory effects of PRP on grafted bone. Not every study used autologous blood, some used allogeneic blood; however, this had no influence on the outcomes.[35,38]

The beneficial effects seen were most distinct in the early stage of bone formation and contributed towards achieving a faster maturation of the bone. Supporting this idea, immunohistochemical analysis of TGF-β_1 and BMP-2 demonstrated modulated GFs associated with acceleration of bone fracture healing.[35] Thorwarth et al.[33] reported the lack of long-term effects of PRP administration in the mineralisation process that occurred during bone grafting.

An explanation for the enhancing effects of PRP on bone grafts could be the fact that the bioactive substances in PRP stimulate the proliferation of MSCs, chondrocytes and BMSCs, eventually leading to improved bone regeneration.

Costs

Regarding the costs of PRP, we received pricing information from manufacturers of PRP showing a price between 290€ and 450€ per set. Furthermore, only one cost-effectiveness analysis[46] was found, comparing the potential economic benefit of PRP to alternative therapies in the treatment of non-healing diabetic foot ulcers. The results demonstrated an improved quality of life and lower cost of care over a 5-year period than other treatment modalities.[46]

Discussion

Clinical applications

Since PRP functions as a vehicle of mitogenic and chemotactic cytokines and GFs, this blood product is highly useful for application in several indications within plastic and reconstructive surgery. The complex interaction of multiple factors and physiological mechanisms contributing to tissue regeneration makes the use of PRP more attractive than the use of a single recombinant GF.

From this systematic review, we report a beneficial influence of PRP on wound healing, with the main contributors being the improved proliferation of endothelial cells and vascularisation and the stimulatory effects on formation of granulation tissue. These advantageous effects are most likely to occur when PRP is repeatedly applied to the wound bed. Not only did more wounds heal when PRP was used, but also the time to healing was notably shorter, leading indirectly to a decrease of sickness-related morbidity and health costs.[3–5,8–11]

As a result, PRP can be used in wound care as an adjuvant therapy to promote wound healing, in addition to conventional methods.

Fat grafting is a technique that is used for several purposes in plastic surgery, which has gained interest in recent years. Nowadays, most indications are found in facial plastic surgery to restore contour and atrophic lesions. We retrieved several studies investigating the effect of PRP on fat grafting, when the latter was used to stimulate wound healing.[18–20] Both substances are considered to have beneficial effects on the healing of soft tissues and their combined use acts in a synergistic way.

In general, studies describing the combined use of PRP and fat grafts suggest an improvement of fat survival and an enhancement of wound healing. Mixing PRP with purified fat results in an intense contact between both substances and leads to stimulatory effects of the cytokines and GFs on the included cells; however, due to different physical

properties of the components, obtaining a homogeneous mixture is difficult which might explain the unequivocal study outcomes. To date, no RCTs concerning this application were performed and the evidence available is based on case–control studies only. Therefore, additional studies are needed to clarify clinical advantages.

In plastic surgery, bone grafts can be used in several clinical settings, for example, reconstruction of mandibular continuity and in cleft palate surgery. For this review, we conclude that PRP significantly enhances bone formation.

Besides the stimulatory effects, PRP is able to reduce oedema, ecchymosis and pain.[7,30] Major disadvantages of the use of PRP have not been reported[5,9,10] and only a few relative contra-indications were formulated such as active infection, the presence of tumour in the wound bed or metastatic disease, patients with platelet dysfunction or blood disorders and patients who cannot endure a blood draft, such as haemodynamically instable patients.[47,48]

The major shortcoming in demonstrating convincing evidence of the beneficial effects of PRP is the lack of true RCTs in humans. Fifteen true RCTs were identified, separated over three major subjects in plastic surgery. However, the available studies had multiple limitations: small sample size, the use of different concentrations of platelets, the use of several different preparation systems and methods as well as different modes of application.

Method of preparation

When comparing the implemented techniques to process whole blood into PRP, no clearly defined single method of preparation was described in studies reporting advantageous effects of PRP. Furthermore, in this systematic review, several trials suspended PRP in a carrier, for example, PPP, or converted the PRP into,for example, fresh-frozen PRP. The main purpose of these latter studies was to optimise the manner of application[7–10] or the preservability[6,11] of the cytokines and GFs; when these results were compared with regular PRP, better results,[5–7,11] some reaching statistical significancy,[10] were found.

Most trials activated the PRP to form PG; in this way, thrombocytes' cytokines and GFs are transformed into their optimal bioactive status and are secreted actively. Conversely, some studies did not activate PRP and still showed good results in its favour. These trials did not involve activating the thrombocytes so that they were able to deliver native platelets, which are thought to provide a more controlled release of PDGFs. Moreover, authors of nonactivated PRP trials suggested that the formed clot only functions as a temporary scaffold for cell ingrowth, lacking in chemical and architectural regenerative abilities.[8] Another reason for using non-activated PRP was the impossibility to inject the PG with a syringe into lesions.[31]

The concentration of the thrombocytes in PRP is mostly described as an x-fold increase compared with base-line values. This leads to difficulties in suggesting a fixed concentration required to demonstrate benefits in using PRP. At this point, 1,000,000 platelets per microlitre is suggested as the minimal therapeutic level.[43] This translates to a four- to fivefold increase in the base-line platelet count of $200{,}000 \pm 75{,}000\ \mu l^{-1}$. We determined the average elevation of base-line values to be 4.7, with no clear evidence that higher or lower concentrations increased or decreased the existing positive effect.

All this demonstrates the necessity of further research in order to identify and qualify an optimal concentration range and preparation method of PRP.

Conclusion

This systematic review strongly suggests that PRP possesses a beneficial effect for different indications within the specialty of plastic and reconstructive surgery. To date, most conclusive evidence supports the use of PRP to improve healing of diabetic lower-limb ulcers and to enhance bone grafting. Regarding fat grafting, there are few medical publications describing this application. Theoretically, the addition of PRP to fat grafts will likely result in an increased survival rate.

In this article we have identified several beneficial effects of PRP and attempted to assess and explain the underlying mechanisms. Nevertheless, there still is a lack of evidence concerning the clinical applications of PRP. In our view this is due to (i) the lack of high-quality RCTs and (ii) the fact that no standard protocol has yet been formulated for the efficacious platelet concentration range and preparation method of PRP, which would serve towards the manufacture of a more homogeneous group of PRP products.

Following the detailed analysis of the available literature, it might seem logical to expect a prosperous future for PRP within the field of plastic and reconstructive surgery. Nevertheless, the widespread adoption of PRP will require clearly defined standardised methods for PRP preparation, and additional comprehensive studies, demonstrating statistical confidence of clinically relevant and validated end points, which may further confirm the potentially high efficacy of this blood product.

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Conflict of interest statement

None of the authors declares any conflict of interest. The authors alone are responsible for the content and writing of this article.

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INVITED COMMENTARY

The use of platelet-rich plasma in plastic surgery remains unproven

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The Ghent group invested a substantial amount of time preparing this review of the literature through July 2011. It would be an injustice to them and an even greater injustice to our patients if we were to take out of context this review's conclusion that:

> "To date, most conclusive evidence supports the use of PRP to improve healing of diabetic lower-limb ulcers and to enhance bone grafting."[1]

Two 2012 Cochrane Collaboration reviews, one for wounds and the other for bones, contradict the claim that there is "conclusive evidence". In addition to finding three human randomized control trials (RCTs) not cited by the Ghent group, the Cochrane Collaboration wound review concluded:

> "Chronic wounds include pressure ulcers, venous leg ulcers, arterial ulcers, neurotrophic ulcers and foot ulcers in people with diabetes. Autologous platelet-rich plasma (PRP) is a potential wound-healing treatment because it contains fibrin and high concentrations of growth factors that are thought to help healing. This review evaluated the effectiveness and safety of PRP and included nine randomised clinical trials, with a total of 325 participants. *There were no differences between the autologous PRP and the control groups in terms of healing.* [Emphasis added] However, these results require confirmation in adequately powered, well conducted RCTs."[2]

The Cochrane Collaboration review of bone healing found but one RCT.[3] This RCT compared allogenic bone graft for tibial osteotomies with and without PRP. It found no difference at one year between the PRP and control groups in patient-reported or clinician-assessed functional outcomes. Furthermore, the Cochrane Collaboration found no data available regarding PRP in the treatment of acute fractures, non-united fractures or large bony defects.

The Ghent group concluded that further research is necessary:

> "The widespread adoption of PRP will require clearly defined standardised methods for PRP preparation, and additional comprehensive studies, demonstrating statistical confidence of clinically relevant and validated end points, which may further confirm the potentially high efficacy of this blood product."

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