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Review

Platelet-rich plasma in burns

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ABSTRACT

Platelet-rich plasma stimulates angiogenesis, promoting vascular in-growth and fibroblast proliferation. In addition, PRP functions as haemostatic by forming a fibrin clot. Also application of PRP enhances wound-healing in both soft and hard tissue. A survey of the literature to assess the current clinical experience and the possible effects of platelet-rich plasma (PRP) on wound-healing in burn cases yields only few reports. The application of PRP is not currently standardized and the effects in wound-healing are poorly understood. The use of PRP as an analog to fibrin sealant is also only seldomly reported.

The value of PRP application in burns remains unclear. A definitive assessment as to the application of PRP in burn treatment will require further studies. Theoretically the effects of PRP in burn wounds could be beneficial, however the interaction in tissue repair and regeneration must be better understood.

Contents

1. Introduction

Impaired wound-healing and a long treatment course in severe burns as well as secondary complications originating from uncovered wounds motivate research to accelerate the wound-healing process and speed up re-epithelialization in burn patients. Application of autologous platelet-rich plasma (PRP) has been reported to facilitate wound-healing in several fields of surgery [1], raising the question whether there is scientific evidence to justify the application of PRP in burns.

Platelets play a key role in haemostasis and wound-healing after tissue damage [2]. Immediately after the trauma they activate fibrinogen and form a fibrin clot, thus acting haemostatic and as a tissue sealant. They also play an important role in the following stages of tissue repair. These longer lasting effects of platelet activation are caused by the expression of more than 30 growth factors [3]. Platelets are chemotactic and induce the proliferation of fibroblasts, endothelial cells and progenitor cells [4], regulating the process of wound-healing. The released growth factors include platelet-derived growth factor (PDGF), transforming

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Table 1 – Factors which platelets or subpopulations have been shown to express.

bFGF (FGF-2) [13]
BMP-2 [14]
BMP-6 [14]
EGF [15]
GM-CSF (CSF-2) [16]
IL1 [17]
IL1-alpha [18]
IL1-beta [19]
IL7 [20]
IL8 [21]
IGF [22]
MMP-2 (gelatinase A) [23]
MMP-9 (gelatinase B) [24]
PDGF [25]
PF4 [26]
SCF [stem cell factor] [27]
TGF-β [25]
TGF-β1 [28]
TIMP-1 [23]
TIMP-2 [29]
TIMP-4 [23]
Tissue factor [30]
TNF-α [31]
VEGF [32]

growth factor-β1 (TGF-β1), platelet-derived epidermal growth factor (EGF), platelet-derived angiogenesis factor platelet factor 4 (PF4) and platelet-activating factor (PAF) (Table 1). In addition, platelets express proteinases which trigger the release of proteolytic enzymes by other cell types playing a part in the degradation of basement membrane and extracellular matrix [5].

Autologous platelet-rich plasma (PRP) is plasma with a higher concentration of platelets than baseline. No definition exists as to that absolute number required, generally they are increased up to 3–5 times [6]. PRP can be applied externally, added to implanted material (e.g. bonemarrow) or injected directly into a lesion as a matrix for regeneration. As an immediate effect, PRP will provide more rapid haemostasis and tissue adhesion by forming a fibrin clot, similar to fibrin glue. As the amount of released factors increases with the total number of platelets delivered to a site of injury, application of PRP increases the physiologic response to a trauma emulating and surpassing the ''normal'' deposition of growth factors and proteins in trauma. Advocates of PRP therapy therefore claim benefits include increased tissue regeneration and a lower rate of infection, pain and blood loss [7].

PRP is obtained by centrifugation of anti-coagulated blood. After centrifugation, the separated buffy coat layer, consisting of platelets and white blood cells, forms the PRP. Originally a full unit of blood was needed for the preparation, however nowadays preparations from smaller volumes of blood are possible. Obtaining PRP has been simplified in recent years, making its use not only available in the operating theatre but also in the doctor's office (Fig. 1). Several commercially distributed systems for in-office preparation of PRP are on the market.

After preparation, anti-coagulated PRP is stable for approximately 8 h [8]. As in normal platelet deposition, degranulation of the alpha granules in the platelets releases the pre-packaged growth factors. The active secretion of these

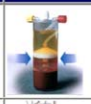
Device Name	Device Image	Technology Summary	Total Process Time	Disposable Compatibility	Disposable List Price (1 kit)	Hardware List Price	Increase Above Baseline	% Platelet Recovery
Biomet GPS™		Floating Buoy	27 min	Druker 755 VES Centrifuge	$ 700	$16,000	3.2 x	70%
Cell Saver Based Systems		Standard Centrifugation	20 min	Machine Specific	$ 75-175	$10,000	4-6x	75%
Sorin Angel		Computer Aided System	25 min	Sorin Centrifuge	$ 495	$10,950	4.3x	76%
AutoloGel System		Standard Centrifugation	1-2 min	Cytomedix Centrifuge	$ 325	$5000	1x	78%
GenesisCS		Direct Siphoning	16 min	Druker 755 VES Centrifuge	$ 1550	$11,500	10 ± 3 (4ml)*	68 ± 17.1
Harvest® SmartPrep2 BMAC™		Floating Shelf	16 min	Harvest Centrifuge	$ 395	$9950	4.0x	72.0 ± 10
Depuy Symphony II		Floating Shelf	16 min	Harvest Centrifuge	$ 395	$9950	4.0x	72.0 ± 10
Arteriocyte Medical Magellan™		Computer Aided System	17 min	Machine Specific	$ 350-495	$9950	5.1x	70%
Secquire		Direct Aspiration	20 min	Centra CL2 Centrifuge	$ 395	$6000	1.6x	31 ± 15

Fig. 1 – Increase above baseline is based on a collection volume of 50–60 ml (except for the cell saver device at 450 ml) whole blood with a single pass. PRP collection volumes (in ml) vary between the devices listed. The results above have been obtained from the manufacturer's product literature. Perfusion.com, Inc. does not warranty the accuracy or validity of the above data, as pricing is subject to change and individual test results may vary significantly. Origin: http://www.perfusion.com/Perfusion/prpdevicesummary.asp.

cytokines is triggered by the clotting cascade of blood and starts within 10 min after aggregation. In PRP this induction is triggered by addition of calcium chloride (CaCl) and thrombin. In the initial burst within the first hour, about 95% of the pre-synthesised growth factors are released. In the remaining seven days of their viability, the platelets synthesise and secrete additional growth factors. Macrophages are attracted by chemotaxis and brought to the zone of injury by the vascular in-growth also stimulated by the platelets. Here they continue regulation of the wound-healing by secreting additional growth factors, such as tumour necrosis factor-α (TNF-α) and basic fibroblast growth factor (bFGF).

PRP has been reported to facilitate wound-healing for burns [9], radio-therapy burns, cosmetic surgery [10], plastic surgery [11], dental surgery [12–15], orthopaedic surgery [16] and cardio-thoracic surgery [17]. To evaluate the use PRP in burn

therapy the two effects of PRP must be considered: an immediate haemostatic and tissue adherent effect and a long term regulation of wound-healing.

2. Review of the literature

A search for the literature up to and including February 2009 was performed in Ovid MEDLINE and Entrez-PubMed (Table 2). No language restrictions were placed on the search. The searchkeys were ''burns'' + ''platelet-rich plasma'' and ''burns'' and ''fibrin sealant''. Also a search was carried out for platelet-rich plasma'' and ''scar''. The various search keys yielded only few results connected to burn therapy. Also the recent literature for PRP in wound-healing was reviewed. Relevant documents were retrieved and evaluated for their relevance towards burn therapy.

Very few studies related to the use of PRP in burns were found. Only three investigate the influence of PRP on wound-healing in burns.

Marquez-De-Aracena et al. [18] found significant differences in the outcomes of the cases of 10 patients suffering from ocular burns. PRP application resulted in faster epithelialization of the cornea and the eye. Subconjunctival injection of autologous blood has been shown to achieve a significant reduction in the conjunctival cicatrisation time in grade III burn cases.

Kazakos investigated PRP gel in the management of acute wounds, including friction burns. They found PRP was an effective aid in the management of acute wounds [19]. In a study of five pigs, Henderson [20] showed that autologous platelet gel (a concentration of platelet-rich plasma) influences wound-healing by stimulating an intense inflammatory response. A significant increase in the production of extracellular matrix and granulation tissue occurs, with vascular in-growth, fibroblastic proliferation, and collagen production also accelerated. Contrary to this, re-epithelialization was not enhanced.

A number of clinical studies showed the application of PRP to soft and hard tissue wounds and found encouraging results. Martinez-Zapata presented a metaanalysis of 20 clinical studies on PRP. With regard to skin ulcers they conclude inconclusive data, selected applications in oromaxillar surgery show advantageous results. The authors also identify several methodological limitations and call for future well designed random controlled trials [21].

For mandibular defects, enhanced bone deposition through PRP-treated grafts has been described by Marx et al. [8,22]. Simman showed that PRP accelerates bone fracture healing via modulation of TGF-1 and BMP-2 [23].

The mechanism of action for PRP in chronic and acute wounds is controversial. Knighton et al. and Ganio et al. have shown enhanced re-epithelialization of chronic lower extremity ulcers [24,25]. The wounds were treated using the platelet releasate suspended on a collagen base (platelet-derived wound-healing factor) for 8–10 weeks. As stated above, Henderson [20] did not find re-epithelialization to be enhanced. Vermeulen showed in a porcine model that PRP serves as a biomatrix, organises ECM, promotes angiogenesis and accelerates re-epithelialization [26].

In a porcine study, Blanton saw advantages in wound-healing by PRP and adipose tissue stem cell combinations, regarding cosmesis and microvessel density, but not in re-epithelialization [27]. In an emerging clinical application, Cervelli demonstrated advantageous results of combined PRP and AFT for lower leg ulcers [28].

Reports of the use of fibrin sealant in burns are almost exclusively related to the application of fibrin glue to split thickness skin grafts (STSG), comparing take rate and patient comfort. For example, Gibran [29] and Mittermayer [30] compared fibrin glue to staples in sheet grafts for partial or full-thickness burns. Fibrin glue proved ''similar or better''. Patient comfort was increased because no removal of staples was necessary. Also Foster describes efficacy and safety of fibrin glue for STSG in burn wounds with similar results [31]. The same author describes the use of fibrin glue in burn surgery for efficient control of blood loss [32].

The use of tissue sealant in wounds has been frequently reported with controversial results. In 1990, the first application of fibrin glue (Tisseel) to achieve haemostasis and adherence of skin flaps in aesthetic facial applications was reported [10]. In 2005 Marchac [33] in a prospective study of 30 patients, found minimal differences between bound and unbound sides regarding bruising, oedema and the incidence of haematoma. After his enthusiastic initial report in 1994, this author revised his opinion and concluded that the theoretical benefit of fibrin in facelifts was not as great as previously thought. This is in agreement with Jones et al. who obtained similar haematoma rates for fibrin glue as compared with dressings, drains or the use of tumescence [34]. One report about the combined use of PRP and fibrin gel in wounds was found. Man et al. have presented a clinical study of 20 patients [11]. The use of autologous fibrin glue and platelet gel in flaps, face and neck lifts, breast reductions and augmentations provided advantages, such as the elimination of drains, a reduction in postoperative pain and oedema, and also faster wound-healing.

The effect of PRP on scarring in burns patients or wounds in general has not been evaluated yet.

Table 2 – Search of bibliographies.

Potentially relevant articles	$n = 433$
Complete texts retrieved	$n = 48$
Papers not meeting the criteria and excluded	$n = 7$
Articles included	$n = 41$

3. Discussion

A number of reports have indicated that the application of autologous platelet-rich plasma accelerates the regeneration of tissue defects. At the same time, controlled and scientifically proven clinical studies remain to be published.

Up to the present, the relevance of PRP to burn surgery remains unclear. PRP has shown to induce an intensive inflammatory response manifesting as the production of granulation tissue [20]. In an animal study, this inflammatory phase occurred much earlier in the treated burn areas than in

the control burns. This increased inflammatory phase can stimulate the formation of hypertrophic scarring, and thus needs to be avoided on superficial partial-thickness defects. At the same time, autologous PRP might play a role in the treatment of deep partial-thickness to full-thickness burns. A highly vascularised bed of granulation tissue might promote the take of skin grafts.

The influence on re-epithelialization is controversial: Knighton et al. and Ganio et al. have shown enhanced re-epithelialization of chronic lower extremity ulcers [24,25]. PRP resulted in faster epithelialization on the eye surface after burn, yet Henderson did not find a faster re-epithelialization. As the eye is not a comparable anatomic structure to the skin, the findings of Marquez-De-Aracena et al. [18] must be carefully evaluated.

Evidence of advantageous use of PRP tissue sealant properties in burns is scarce. As the immediate haemostasis can be beneficial but can also be attained by other methods fibrin sealant application as skin graft fixation has shown little quantifiable advantage.

The influence of PRP in scarring has not been evaluated, but as there are indications that increased scarring might occur, careful indication is advised.

However, assessment of the value of the application of PRP in treating burns will require further investigation. Several points should be kept in mind.

Unlike in other indications for PRP application, burn patients undergo many changes during the course of the treatment with effect on wound-healing, skin regeneration and immune response. Many of the factors released by PRP have been identified in the burn response, e.g. TNF-α or PAF. Therefore the timing of the PRP application needs investigation. Theoretically the application of PRP could be beneficial at some times and have a negative effect at other times.

Normally preparation of the PRP is recommended before surgery, to have as many ''healthy'' platelets as possible. Naturally that is not possible in burn injury. Also, as the preparation only increases the relative percentage of platelets in plasma, the absolute number might be considerable lower in a patient who has undergone entensive surgery or suffered a trauma. To compare studies between burn patients and other indications, the evaluation of PRP use must be adjusted to the absolute number of platelets and their functionality. Also a patient with severe burns will have an impaired endocrine and immune status compared to a patient with a chronic ulcer or a patient undergoing a facelift procedure.

As already mentioned, the required tissue regeneration depends on the burn depth and the previous surgical treatment. Tangentially excised deep dermal wounds will benefit from dermal regeneration and neo-vascularisation of the wound bed, while in superficial burns, faster re-epithelialization is required. Autologous platelet gel could help to create a vascularised matrix, aiding the success of skin grafting in patients with deep partial-thickness and full-thickness burns. Also PRP might provide a better in-growth in dermal replacement materials, as already demonstrated by enhancing in-growth of bony replacement material.

With regard to scarring, the question if and at what time in the treatment course the application of PRP leads to inflammation or re-epithelialization is an important topic as it is known that prolonged inflammation induces hypertrophic scarring. However, reconstructive surgery of burn patients might benefit from PRP. As scar reconstruction can be improved with fat transfer, the combination of PRP and lipotransfer might offer promising results.

The theoretical benefits of PRP treatment are considerable. The benefits of autologous substances to improve tissue regeneration have been demonstrated before. Autologous serum facilitates epithelial regeneration and healing [4], because it provides growth factors and fat grafting also has beneficial effects by transferring growth factors. Thus autologous platelet-rich plasma could be a valuable addition in burn treatment.

4. Conclusions

Identification of the conditions under which the application of PRP in burns is beneficial will require more controlled clinical studies. Currently, PRP application seems to offer a certain degree of efficacy in some acute and chronic wounds. In the treatment of burns, PRP could, by stimulating dermal regeneration, increase the take rate after skin grafting or speed up re-epithelialization. To achieve this, the mechanism of plasma-rich platelet effect must be further elucidated in order to adjust the released factors to the needs of the burn wound.

Conflict of interest statement

The authors would like to make clear that that any conflict of interest, including any that could arise from financial or personal relationships with other people or organisations and inappropriately bias their work, is fully excluded.

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