PLATELET-RICH PLASMA – REVIEW OF LITERATURE

Bisera Nikolovska¹, Daniela Miladinova², Sofija Pejкова¹, Andrijana Trajkova¹,
Gordana Georgieva¹, Tomislav Jovanoski¹, Katerina Jovanovska¹

¹ University Clinic for Plastic and Reconstructive Surgery, Skopje, RN Macedonia

² Institute of Pathophysiology and Nuclear Medicine, RN Macedonia

Corresponding author: Bisera Nikolovska, University Clinic for Plastic and Reconstructive Surgery, Skopje, N. Macedonia; e-mail: bisera.nikolovska@yahoo.com

ABSTRACT

Wound healing is a dynamic and physiological process for restoring the normal architecture and functionality of damaged tissue. Platelet-rich plasma (PRP) is an autologous whole blood product that contains a large number of platelets in a small volume of plasma with complete set of coagulation factors, which are in physiological concentrations. PRP has haemostatic, adhesive properties and acts supraphysiologically in the process of wound healing and osteogenesis. Platelets play a very important role in the wound healing process by providing growth factors that enhance the rate and quality of wound healing by many different mechanisms. The aim of this review is to describe: the biology of platelets and their role in the wound healing process, the terminology of platelet rich products, PRP preparation, activation and concentration of PRP, as well as the use of PRP in plastic surgery.

Keywords: platelet-rich plasma, wound healing, plastic surgery

INTRODUCTION

Wound healing is a dynamic and physiological process for restoring the normal architecture and functionality of the damaged tissue. It is a process of regeneration of damaged tissues – an evolutionary trademark of all living tissues. This involves the sequential phases of inflammation, proliferation and remodeling phase. Since the beginning of time and written history there are artefacts of the mastery of wound healing and tissue regeneration and the ultimate goal of medicine: restitutio ad integrum/healing without a scar. Understanding the process of wound healing as well as the factors that contribute to impairment or promotion of wound healing is the pillar of modern medicine in all of its disciplines.

The factors that affect wound healing are divided in two groups: local factors (presence

of foreign bodies in the wound, tissue maceration, ischemia, or infection) and systemic factors (age, chronic inflammatory diseases including diabetes, medication, and malnutrition). These factors may contribute to delayed or impaired wound healing which will affect the physiological mechanisms of tissue regeneration causing abnormal wound healing, chronic wounds, abnormal scarring (hypertrophic, keloid, and atrophic), pain, pruritus, tissue malignancy (Marjolin syndrome), hemorrhage, ulcer, infection, and amputation. Among the optimization of the systemic factors and the standard and advanced principles of local wound care and management, there are several new methods to promote wound repair including synthetic matrices, biological tissue replacement, recombinant growth factors,

and stem cell therapy. The use of growth factors derived from platelet-rich plasma (PRP) to promote tissue regeneration has spread in the past 30 years due to safe and economical properties.

Platelet-rich plasma (PRP) is an autologous whole blood product that contains a large number of platelets in a small volume of plasma with complete set of coagulation factors, which are in physiological concentrations [1]. Platelets contain over 1,100 active substances, including: growth factors, messengers of the immune system, enzymes, enzyme inhibitors and other bioactive substances that are involved in various mechanisms in the wound healing process [2-5].

Autologous platelet concentrates have been used in the fields of dentistry, orthopedics, ophthalmology, neurosurgery, maxillofacial surgery, spinal surgery, cardiovascular surgery, plastic surgery, cosmetology and treatment of acute and chronic wounds [5-7]. Although animal studies and basic medicine studies support the positive effect of growth factors on improving and accelerating wound healing, still, there are different results on the clinical benefits of PRP [1, 8-11]. There is no universal consensus on the production and characterization of the PRP product, therefore, the evaluation of the potential clinical benefit of the PRP is difficult [5].

The objectives of this review paper is to describe the general principles of wound healing, platelet biology and their role in wound healing, terminology, classification, preparation of PRP and application in the field of plastic surgery.

MATERIALS AND METHODS

A search of the NCBI Pub Med literature was made, for the terms: wound healing, thrombocytes, platelet-rich plasma, PRP, platelet concentrate, platelet rich fibrin, platelets and growth factors, limited to the English language over the last 30 years.

RESULTS

Up to date, more than 10,000 papers on PRP and related keywords have been published on NCBI PubMed. More than 1,200 reviews in

the literature and 164 meta-analysis were found and 670 results for randomized controlled clinical trial.

DISCUSSION

General principles of wound healing

Wound healing is a complex cellular and biochemical cascade, that has a predictable course and according to the characteristic cellular populations and biochemical activities, is divided into 3 phases that overlap: hemostasis and inflammation, proliferation and maturation, and remodeling. Several cell lines that produce various bioactive substances participate in the wound healing process (Table 1) [12].

Inflammation is the body's innate initial response to injury, aimed to establish rapid and adequate haemostasis and to initiate the processes of tissue regeneration [12, 13]. When the integrity of the tissue is damaged, blood flows from the injured blood vessels and comes in contact with the extracellular matrix, which activates the coagulation cascade with the final product – fibrin plug. The process will be reviewed in detail in the next section. The fibrin network of the hematoma serves as a temporary matrix to initiate the regeneration process and to provide a platform for cell migration and proliferation, differentiation, and matrix synthesis [12]. The first cells to migrate to the wound are neutrophils that provide rapid protection against infection, kill bacteria and remove cellular debris [13]. The next cell line to migrate are monocytes, which differentiate into macrophages under the action of cytokines. Macrophages play a central role in wound healing by activating and recruiting other cells, through the release of cytokines, growth factors, intercellular communication, and adhesion molecules. They regulate angiogenesis and matrix deposition and remodeling. T-lymphocytes are another cell population that participate in the wound healing process, and their role is not sufficiently known yet [16].

The proliferative phase lasts from the 4th to the 12th day of injury and represents the restoration of tissue integrity. Upon migration into the wound influenced by PDGF fibrocytes proliferate, activate, and begin their function of synthesizing and remodeling the matrix. Endothelial cells located near the injury proliferate and form

Table 1. *Growth factors in wound healing process [13]*

Growth factor	Origin of wound cells	Cellular and biological effects
PDGF	platelets, macrophages, monocytes, smooth muscle cells, endothelial cells	Chemotaxis: fibroblasts, smooth muscle, monocytes, neutrophils.
		Mitogenesis: fibroblasts, smooth cells.
		Stimulation of angiogenesis
		Stimulation of collagen synthesis
FGF	fibroblasts, endothelial cells, smooth muscle cells, chondrocytes	Stimulation of angiogenesis (by stimulating endothelial cell proliferation and migration)
		Mitogenesis: mesoderm and neuroectoderm
		Stimulates fibroblasts, keratinocytes, chondrocytes, myoblasts
Keratinocyte growth factor KGF	keratinocytes, fibroblasts	Significant homology with FGF; stimulates keratinocytes
EGF	platelets, macrophages, monocytes (found in salivary glands, duodenal glands, kidneys, and tear glands)	Stimulates proliferation and migration of all epithelial cell types
TGF α	keratinocytes, platelets, macrophages	Homogeneous with EGF; binds to the EGF receptor
		Mitogenetic and chemotactic for epidermal and endothelial cells
TGF β (three forms $\beta 1$, $\beta 2$, $\beta 3$.)	platelets, T lymphocytes, macrophages, monocytes, neutrophils	Stimulates angiogenesis
		TGF- $\beta 1$ stimulates the production of cell matrix (fibronectin, collagen, GlycosAmylGlycans); regulation of inflammation
		TGF- $\beta 3$ reduces scar formation
Insulin-like growth factor (IGF-I, IGF-II)	platelets (IGF-I in high concentrations in the liver; IGF-II in high concentrations in fetal growth); Most likely a growth hormone effector	Promotes protein / extracellular matrix synthesis, increased membrane glucose transport
Vascular endothelial growth factors	macrophages, fibroblasts, keratinocytes	Similar to PDGF
		Mitogen for endothelial cells (not for fibroblasts)
		Stimulates angiogenesis
Granulocyte-macrophage colony stimulation factor	Macrophages / monocytes, endothelial cells, fibroblasts	Stimulates macrophage differentiation / proliferation

new capillaries (angiogenesis) under the action of cytokines and growth factors such as $\text{TNF}\alpha$, $\text{TNF}\beta$, and VEGF. Mesenchymal cells migrate to the wound and provide a cell line that will be responsible for creating bone, cartilage, connective tissue, blood vessels, and other types of tissue through their cell differentiation [13].

The third and final stage of the wound healing process is characterized by the reorganization of the previously synthesized collagen, into a dynamic process of collagenolysis and collagenosynthesis. The changes that occur in this period are: reduction of the number of cells, reduction of vascularization, removal of excess extracellular matrix, orientation of the collagen fibers towards the forces of tension, remodeling of the bone, etc. This phase lasts from 6 to 12 months [13].

Platelet's biology and role in the processes of wound healing

Platelets are cytoplasmic fragments of megakaryocytes produced in the bone marrow. They have a round or oval shape, and are $2\mu\text{m}$ in diameter. They have no nucleus but have organelles and structures: mitochondria, microtubules and granules (α , δ , γ , λ) [17, 18]. One platelet contains 50 to 80 α -granules, and contains more than 30 bioactive proteins that play a fundamental role in the process of hemostasis and wound healing [18]. Platelets are found intravascularly and are concentrated in the spleen, the normal blood count being between 140,000 and 400,000 per mm^3 of blood. They remain in the circulation for up to 10 days after which they are removed by macrophages in the reticuloendothelial system [14, 17, 18].

After injury, platelets come into contact with the damaged blood vessel, with collagen, the basement membrane of the capillaries, and the subendothelial microfibrils [17]. This interaction activates platelets, they aggregate at the site of injury and release active substances from the α -granules. Other platelet-activating substances are adenosine diphosphate (ADP), thrombin, and adrenaline. The process of α -granule activation, also called degranulation, results in bondage to the cell membrane of platelets where secretory proteins are transformed into a bioactive state by the addition of histones or carbohydrates to the side chains. Platelets participate in several stages of the coagulation process and are located in the final fibrin coagulum which is composed of

a fibrin network, activated platelets and erythrocytes and leukocytes between them. A number of growth factors and other bioactive substances are released from α -granules (secretory proteins below in the text): platelet-derived growth factor PDGF- $\alpha\alpha$, $\beta\beta$ and $\alpha\beta$ isomers, transforming growth factor TGF- β , $\beta 1$ and $\beta 2$ isomers, platelet activating factor, platelet factor 4 (PF4), interleukin (IL)-1, platelet-derived angiogenesis factor (PDAF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), platelet-derived endothelial growth factor (PDEGF), epithelial cell growth factor (ECGF), insulin-like growth factor (IGF), osteocalcin (BGLAP), osteonectin, fibrinogen, vitronectin (VTN), thrombospondin (TSP), fibronectin, serotonin [14, 15].

The secretory proteins contained in α -granules have a strong effect on the wound healing process [14]. Activated proteins are secreted to bind to transmembrane receptors on target cells (mesenchymal stem cells, osteoblasts, fibroblasts, endothelial cells, and epidermal cells). When bound to transmembrane receptors, intracellular signaling proteins activate genes responsible for cell proliferation, matrix formation, osteoid formation, collagen synthesis etc. Platelets begin to actively secrete proteins within 10 minutes of their activation – this process is most active in the first hour. After the initial explosive release of the secretory proteins, the platelets secrete an additional amount of secretory proteins for 5-10 days. As platelet function begins to decline, macrophages that arrive at the site of injury stimulated by platelet-releasing growth factors play a central role in regulating the wound healing process through protein secretion and intercellular communication [13, 14, 17, 18].

The proteins secreted by platelets affect many aspects of wound healing, and Anitua et al. recently gave a detailed overview [19]. Platelet derived growth factor acts chemotactically on macrophages, TGF β , PDGF and IGF help in mitogenesis and chemotaxis of the stem cells, osteoblasts, capillary growth angiogenesis, bone matrix formation, collagen synthesis. TGF β and PDGF help in bone mineralization. Adhesive proteins such as fibrinogen, fibronectin, vitronectin, TSP1 participate in thrombus formation and have mitogenic properties. In chronic wounds, some of the proteins secreted by thrombocytes are absent, further proving their role in wound healing. Sipe et al. recently identified 2 proteins BPM2 and BPM4 that may contribute to bone

formation [20, 21]. In addition to its regenerative action, platelets also release molecules that promote defense against microbes. These include chemokines and cytokines that induce the recruitment and activation of the immune cells, as well as microbicide proteins including kinocidins (e.g., PF4 (CXCL4), CXCL7 (also known as PBP), and CCL5); defensins (e.g., human β -defensin 2 (BD2)); thymosin β 4 (T β 4); and antimicrobial peptides (e.g., fibrinopeptide A or fibrinopeptide B and thrombocidins (which are proteolytic derivatives of CXCL7)) [21].

Platelet-rich plasma

Definition and terminology

Platelet-rich plasma (PRP) is an autologous whole blood product and contains a large number of platelets in a small volume of plasma with complete set of coagulation factors, which are in physiological concentrations [1]. Other terms found in the literature are: platelet concentrate, platelet gel, platelet releasate, platelet-rich fibrin. There is no universal agreement on the definition and terminology and the production of PRP. When platelets are concentrated in a part of the plasma (PRP), the rest of the plasma that is platelet depleted (Platelet Poor Plasma PPP) can serve as tissue glue.

Table 2. Overview of PRP products and names

Platelet-rich plasma (PRP)	non-activated plasma with an amount of platelets larger than normal
Platelet-rich fibrin (PRF)	a product rich in platelets and fibrin with a 3D structure
Platelet concentrate	platelet enriched plasma
Plasma rich in growth factors	type of pure PRP, without leukocytes
Platelet gel	activated PRP
Platelet lysate	Activated PR with lysis, example: freeze-thaw or Triton-X-100
Platelet releasate	Activated PRP from thrombin and calcium chloride

There is a constant debate about the PRP terminology (Table 2). The term PRP is a term first used by transfusiologists. The term is general and does not describe either the content or the structure of the product. Other terms that have been proposed are: pure PRP, PRP with leukocytes, platelet concentrate, growth factors derived from platelets, plasma enriched with platelets, etc. Activated PRP is called platelet gel, leukocyte PRP gel, or PRP releasate. This collection of terms makes the interpretation of the literature difficult. This paper will use the general term PRP [1, 19, 22–24].

Preparation of PRP

Beyond the absence of large randomized trials, another challenge associated with PRP therapies is the lack of consensus on PRP preparation techniques. Currently, there are several manual, automatic, and semiautomatic methods for this purpose [21]. The general methods for preparing PRP include three sequential steps: blood collection, PRP separation and PRP activation. The process of preparing PRP begins with taking blood in a test tube which contains an anticoagulant that binds calcium and thus blocks the blood coagulation cascade. Although there are several anticoagulants, only two have been shown to support the metabolic needs of platelets and allow their separation without damage. These are: citrate dextrose (CDA) and citrate phosphate dextrose (CPDA) [1, 26]. PRP is obtained by centrifugation of whole blood, after which, platelets are separated from erythrocytes with a small amount of plasma. There are many methods for obtaining PRP. It is usually made from autologous blood which has an advantage for safety reasons (disease transmission). The use of heterologous PRP is also possible due to the increased safety in transfusiology and due to the side effect of taking more blood in acute trauma, sepsis, elderly patients, etc [25].

PRP can be prepared: with blood bank technology (cell separators), in a local laboratory or one of the custom-made devices on the market. (Table 3) The methods used to produce PRP can be: by manual method-which is more time consuming and automated devices which are more expensive. In all procedures, after the blood centrifugation, PRP is separated from the erythrocytes, at the bottom of the tube and the platelet-poor plasma is at the surface of the tube. Some systems use the 2-step method, where erythrocytes are removed after the first centrif-

ugation and platelet-depleted plasma is removed after the second centrifugation. Different systems produce different amounts of PRP from different amounts of blood in different ways. (Table

3) Even with one method, the results can vary depending on the amount of platelets count in the blood [27–30].

Table 3. *Commercially available PRP kits [27-30]*

Devices	Volume of blood collection-mL	Anticoagulant	Centrifugation speed/time	Volume of PRP mL	Platelet concentration factor
Selphyl	9	Sodium citrate	1100g/6min	2-3	2-3x
PRGF Endoret	9	Sodium citrate	270g/6min	2-3	2-3x
Cascade	9	Sodium citrate	1100g/6min	4.5	1,3-1,7x
Plateltex	9	ACD	1450g/15min 180g/10min	5	1,5x
Regenkit	9	ACD	1000g/10min 1500g/9min	5-6	1,6x
ACP/Arthrex	15	ACD/NONE	1500rpm/5min	4-7	2-3x
GSP III	30/60	ACD	3200rpm/15min	3/6	2-8
Genesis	30/60	ACD	2400rpm/12min	3-10	7-10x
SmartPrep 2	20/60	ACD	2500rpm/4min 2300rpm/10min	3-10	3-7x
Proteal	20	Sodium citrate	1800rpm/8min	4	2,2x
Magellan	30-60	ACD	Adapted device	7-14	2,8x
Angel	40-180	ACD	Adapted device	6-10	3-4x
Harvest	20-60	ACD	Adapted device	3 or 7-10	3-7x
Vivostat	120	ACD	Adapted device	5	4

ACD- Acid Citrate Dextrose

Activation techniques

Prior to PRP administration, platelets should be activated to release secretory proteins from α -granules. There are several techniques for platelet activation, but the most commonly used technique is the use of thrombin (autologous or bovine) and calcium chloride. Thrombin has strong haemostatic properties and acts mitogenically on fibroblasts. Other methods include: the freezing/thawing method and the Triton X 100 that lysis platelets to release their secretory proteins. Batroxobin is a thrombin-like proteolytic enzyme used to activate platelets by forming a blood clot, which activates platelets more slowly and releases growth factors over time (platelets are not directly sensitive to batroxobin) [31-33]. A novel activation method described as “photo-activated PRP” involves exposing platelets to ultraviolet light (UV) irradiation [21]. These different activation factors result in the release of different amounts of growth factors.

Composition

Leukocytes: Most PRP products contain leukocytes because a “buffy coat” layer is taken from the plasma (a layer of cloudy white pigment in which, after centrifugation of the blood, it contains platelets and leukocytes). The effect of leukocytes on PRP is little known. Leukocytes have antibacterial properties with production of growth factors that participate in the wound healing process [1, 31-33]. Some authors recommend pure platelet PRP, but so far, there hasn't been a solid evidence that leukocytes have side effects, although they theoretically have a catabolic effect that could adversely affect wound healing [11-19].

Fibrin: Platelet-rich plasma may vary in fibrin content. The difference between PRP and PRF (platelet-rich fibrin) is that PRF has fibrin with a three-dimensional network and PRP is liquid. PRF fibrous network looks more natural, so the release of the growth factors is slower [34, 35].

An example of leukocyte PRF is Choukrons PRF, which is made without anticoagulant and activator [35]. Blood is taken in a glass tube and immediately centrifuged for 10 minutes at 3,000 rpm. There is no anticoagulant, so platelets are activated by contact with the glass wall of the test tube and the coagulation process is activated. A clot forms in the middle of the test tube, and theoretically the platelets are stuck in it. An

example of PRF is the Fibrinet platelet rich fibrin matrix (Cascade Medical, Cascade, ID). Although easy to prepare, PRF coagulum is not practical if it is to be administered by injection or when a liquid or gel condition is required.

Fig. 1. Whole blood after centrifugation, schematic representation of the three layers

Platelet concentration and quantification of growth factors: The platelet count in PRP can be increased from 2 to 8.5 times. When analyzing the platelet count in PRP it is necessary to resuspend, because in the suspension the platelets are aggregated and the measurement can give erroneous results. It is not clear whether the method described in the literature uses the method of platelet resuspension, as it is not often explained [19]. There is a consensus on how many platelets are needed in PRP, several authors have suggested that the platelet count should be a minimum of 0.8 to 1 million platelets per milliliter [1, 19, 33]. The idea that more platelets will have a greater effect is wrong because platelets in very high numbers have an inhibitory effect on wound healing [35]. There is a large difference in the content of growth factors in platelets. There are several studies on the quantification of growth factors in PRP and all have concluded that their concentration is variable. The amount of growth factors is influenced by several factors: their concentration in α -granules which can vary, the production technique which can give different platelet concentrations and different degree of their activation or platelet fragmentation [1, 13, 19, 22, 25, 36].

The concentration of leukocytes in PRP also affects the number, as they also produce growth factors. There is no correlation between the platelet count and the growth factor concentration with either age or sex. Despite this variability, quantification of growth factors is the best quality control of PRP [36].

In this system the platelet concentration is measured in platelets per milliliter, and is categorized as follows: T1 less than or equal to the normal number, T2 greater than the normal number up to 750,000, T3 from 750,000 to 1,250,000 and T4

Table 4. PAW classification [37]

	Platelet concentration	Activation	Total WBC count	Neutrophil count
Plasma based systems				
Arthrex/ACP	T2	*	B	β
ConMed-Linvatec/Cascade	T2	*	B	β
BTI/PRGF	T2	*	B	β
Buffy coat based systems [§]				
Biomet GPS	T2-T4	*	A	α
Harvest Smart/DePuy Symphony II	T2-T4	*	A	α
Arteriocyte/Medtronic Magellan	T2-T4	*	A	α
Emcyte Genesis CS/Exactech Accelerate	T4	*	A	α

* All PRP products can be activated by the addition of exogenous materials (CaCl₂, thrombin, etc.) or by contact with endogenous factors (collagen, tissue thromboplastin).

[§] Buffy coat systems typically produce highly variable platelet concentrations.

Classification of PRP

Different PRP production techniques result in a different final product. These products may vary in: blood volume taken, presence or absence of leukocytes, exogenous platelet activation, fibrin matrix formation.

There are currently no universal PRP classification systems. Recently, a PRP classification system has been proposed: PAW (Platelets, Activation, White blood cells) [37]. (Table 4) It is based on 3 components: 1- absolute platelet count-T, 2- mode of platelet activation-A, 3- presence or absence of white blood cells -W.

over 1,250,000. Platelet activation is achieved by endogenous or exogenous factors [37]. (Table 4)

Total leukocyte counts are rated above normal -A and below or normal -B. The A systems are called “buffy-coat systems” and the B systems are called “plasma-based systems” [37].

In addition, with neutrophils present they have the symbol α , and if filtered they have the symbol β . Although the PAW classification can help differentiate PRP production, there is still no evidence-based classification, scheme or recommendation that specifies the optimal application of individual PRP types [37].

More recently, Alsousou and Harrison have postulated a more detailed and complete classification system. This included a combination of numeric and alphabetical characters to identify the class of PRP based on the presence or absence of leukocytes (L or P), the fibrin content (high: PRF; low: PRP), activated or not activated (I or II), platelet concentration (A: $<900 \times 10^3/\mu\text{l}$; B: $900-1700 \times 10^3/\mu\text{l}$; C: $>1700 \times 10^3/\mu\text{l}$), and the preparation category (gravitational platelet sequestration technique; standard cell separators; and autologous selective filtration) [38]. This simple, accurate, and pragmatic system of classification results in a unique term (e.g., L-PRP IB1) that reflects the product properties. This classification system could contribute to clarifying the confusion in the scientific literature and misleading conclusions currently observed regarding these treatments [38, 39].

Use of PRP in Plastic surgery

PRP is used in many surgical specialties and in the wound treatment. In surgical settings, PRP decreases the frequency of intraoperative and postoperative bleeding at donor and recipient sites, accelerates soft-tissue healing, supports the initial stability of grafted tissue at recipient sites as a result of its cohesive and adhesive nature, promotes rapid vascularization of healing tissue by delivering growth factors and, when used in combination with bone replacement materials it induces regeneration [21]. PRP increases lipocyte survival and improves scar appearance by stimulating mesenchymal stem cells [38-42, 57].

Several in vitro studies of PRP and wound healing models that have been published, have shown that PRP stimulates fibroblast proliferation. This function is dependent on the concentration of the activated PRP. Five percent activated PRP significantly increases dermal fibroblast proliferation while 20% activated PRP has no such effect [38, 58]. In clinical settings it is much more difficult to determine the concentration of the activated PRP, therefore there are different results in the clinical studies.

There are several studies where PRP has a positive effect on the healing of acute, chronic and diabetic wounds. In meta-analyses, the rate of infection and pain were reduced in all types of wounds. A review of the literature on the use of PRP in diabetic wounds has shown positive results in speeding the healing and reducing complications [48, 49].

In plastic surgery, PRP is used in: facial surgery, face lifting, blepharoplasty, skin transplantation, flap reconstruction. PRP has a significant positive effect on wound healing, improved cell survival in adipose tissue transplantation, and improved bone graft healing. This claim is based on 15 randomized controlled trials, 25 case/control studies, but these studies also had many limitations: small number of patients, use of different platelet concentrations, different activation module and application [41-49].

There are few studies on the use of PRP in burns. In one study of the effect of PRP on acute wounds, 11 of them (19%) were burns where faster healing was found. In a case study in which a burn patient, with a burn of 34% of the body surface, PRP and PPP were applied, the hemostasis was improved and the wound healing time was reduced without additional complications [50]. Prochazka et al. 2014, were evaluating the effect of Autologous Platelet Concentrate and dermo-epidermal skin graft for treatment of the wounds as a result of debridement of second- and third-degree burns. In this study, 18 patients were enrolled, without a control group. An evaluation of the skin graft survival, complication rate, postoperative pain and scar analysis was done. The authors used clinical examination (digital photography), standardized scales for evaluating pain and scarring, in combination with blood perfusion (laser Doppler imaging), as well as molecular and laboratory analyses. The authors concluded that the use of APC has superior outcomes to the present standard of care and should be embraced widely. Patients treated with skin graft and APC had high quality of healing without evidence of scar hypertrophy or contractures. The intervention markedly benefits patients, the community, and health care in general. They showed that, even though, the length of time for the initial procedure may have been longer, there are significant cost savings in hospital stay and less revisions and usage of orthosis and pain medications. 51

Schade et al. 2008, evaluated the effect of PRP in complex wounds in patients with medical comorbidities in 13 patients. The wounds were skin grafted, 4 of the patients had negative pressure dressing. Wound healing was achieved in 16 days. The authors concluded that the wound healing time is less when PRP is used [52].

Waiker et al. 2015, were comparing mechanical fixation versus fixation with PRP of split thickness skin graft. In this randomized prospective study 200 were enrolled in two groups. The results from this study showed that the incidence of complications is lower in the PRP group. Also, the length of hospital stay and the total cost is lower [53].

Similar studies were done by Dhua et al. in 2019 and Gupta et al. in 2020. They have reproduced the results from the previous study that there is instant adhesion of the skin graft to the surface, less postoperative complications and better cosmesis of the scar at 3 and 6 months [54, 55].

There is an antimicrobial effect of PRP. This property of the PRP is shown in the study of Hersant et al. In their prospective study they used activated PRP on postinfectious soft tissue defects prior to resurfacing with skin grafts. They concluded that in the PRP group there is 50% faster wound healing and no side effects [56].

CONCLUSION

PRP has many potential benefits: improving the wound healing process through the application of autologous growth factors, supporting hemostasis, having antimicrobial action and reducing pain. In this review paper, several aspects of PRP were explained: the differences that exist in its production, PRP content and methods of activation. This diversity makes the comparison and interpretation of the results in the literature difficult. There are many studies where a positive effect has been described when using PRP without complications, so PRP is considered a safe product. Despite the great heterogeneity in PRP products, there is a clear and unequivocal fact – PRP has an increased platelet count which positively affects wound healing by releasing growth factors and cytokines after their activation process.

The technique of producing, platelet count and concentration, plasma factor concentration, exogenous activation, and patient selection should be further defined and investigated.

The effect of PRP on wound healing remains to be proven like Einstein's theory of relativity was for a long time. It is there, it exists but still cannot be calculated even with the fast-

est computer because the wound healing is one of the most complex process in nature with so many chemical reactions happening in fraction of a second.

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Резиме**ПЛАЗМА БОГАТА СО ТРОМБОЦИТИ – РЕВИЈАЛЕН ТРУД**

**Бисера Николовска¹, Даниела Миладинова², Софија Пејкова¹,
Андрејана Трајкова¹, Гордана Георгиева¹, Томислав Јованоски¹, Катерина Јовановска¹**

¹ Универзитетска клиника за пластична и реконструктивна хирургија, Универзитет „Св. Кирил и Методиј“, Медицински Факултет, Скопје, РС Македонија

² Институт за патофизиологија и нуклеарна медицина, Универзитет „Св. Кирил и Методиј“, Медицински Факултет, Скопје, РС Македонија

Заздравувањето на раната е динамичен физиолошки процес, кој има цел да ја врати нормалната архитектура и функција на оштетеното ткиво.

Плазмата богата со тромбоцити (ПРП) е аутологен продукт од полна крв и содржи голем број тромбоцити во мала количина плазма, која има целосен состав на фактори на коагулација што се во физиолошки концентрации.

ПРП има хемостатски, атхезивни својства и влијае супрафизиолошки во процесот на заздравување на раната и на остеогенезата. Тромбоцитите имаат многу важна улога во процесот на заздравување на раната. Факторите на раст што потекнуваат од тромбоцитите го забрзуваат и го подобруваат квалитетот и брзината на заздравување на раната преку различни механизми на дејство.

Во овој ревијален труд ќе бидат опишани: биологијата на тромбоцитите и нивната улога во процесот на заздравување на раната, процесот на правење, поделба, концентрација и активација на ПРП, како и употребата на ПРП во пластичната хирургија.

Клучни зборови: плазма богата со тромбоцити, заздравување на рана, пластична хирургија