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PLATELET-RICH PLASMA ASSOCIATED WITH MICRONEEDLING IN THE TREATMENT OF SKIN SCARS: LITERATURE REVIEW

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ABSTRACT

Abstract: This study aimed to provide a literature review about the association of microneedling and PRP techniques, in terms of improving the final quality of scar tissue from skin lesions. **Methodology:** The search and selection of articles were carried out in the national database ScieloBrasil and in the international database PubMed. **Results:** Microneedling aims to stimulate collagen production without causing total de-epithelialization, in a fast, minimally invasive and effective way, with promising results of the technique being observed in several studies, allowing a transdermal delivery of active agents to the skin through microchannels. Thus, the topical application of PRP helps in the improvement and acceleration of the steps for tissue repair due to its regenerative properties, being an autogenous source of growth factors. **Conclusion:** The association between PRP and microneedling proved to be an effective technique in the treatment of skin lesions, however, more studies are necessary in order to evaluate and adjust it for a possible implementation.

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INTRODUCTION

The skin is responsible for several physiological processes in the body, it performs essential functions such as growth, maintenance and repair of the cells that integrate it (Alves *et al*., 2018). In addition to covering the body surface almost completely. Therefore, any tissue damage that may compromise its continuity and affect its physiology, ends up triggering the healing process, whichaims to return damaged tissue to its integrity and function (Shaw *et al*., 2009). The efficiency and abnormalities of tissue repair represent a phenomenon of great interest to health professionals and researchers (Alves *et al*., 2018). Healing is the process by which injured tissue is replaced by vascularized connective tissue. This process is used to restore tissue homeostasis and therefore, it is necessary to know about such process, so you can interfere in it with the use of auxiliaries (EMING *et al*., 2009).

The course of healing and skin recovery consists of three phases: inflammation, in which there will be an increase in blood flow and leukocyte migration to the injured area; the proliferation of fibroblasts and the deposition of the extracellular matrix and tissue remodeling(Isaac *et al*., 2010; Lima *et al*., 2018). A fast and efficient skin repair is essential in the recovery of the individual, since the faster the process occurs, the shorter the time of exposure of the tissue to different types of pathogens (Shukla *et al*., 2019).Any damage to its structure triggers the healing process, composed of a cascade of complex events between cells-cells and matrix cells, with platelet growth factors, resulting in the replacement of the lesion by fibrous connective tissue, in order to recover the function and the integrity of the injured tissue(EVERTS, 2018). A good tissue repair depends on a biochemical and physiological synchrony involving part of the dermis.However, if the healing involves the complete dermis or extends to the subcutaneous tissue, the scar becomes

noticeable or even unsightly due to an epithelialization only on the margins of the wound, requiring the formation of granulation tissue (Pugliese *et al*., 2018). These scars have a strong psychosocial impact among affected individuals, having been related to impaired quality of life, as they are associated with low self-esteem, anxiety and depression, appearing as one of the most frequent clinical complaints (Figueiredo *et al*., 2011; Montgomery *et al*., 2016; Fernandes *et al*., 2019). These factors open the way for several researches that seek to apply new techniques to improve the process of tissue regeneration and the functionality of scar tissue (Takeo *et al*., 2015). The use of Platelet-Rich Plasma (PRP) associated with microneedling has gained great prominence within human medicine in the treatment of skin lesions. Microneedling is able to stimulate collagen production, quickly and minimally invasive, creating microchannels that facilitate transdermal delivery of active agents such as PRP.

Becoming a combined therapy and autogenous source of growth factors, which helped in the acceleration of response to wound healing (Chawla, 2014; El-domyati *et al*., 2018; Porwal *et al*., 2018; Silva *et al*., 2018). Thus, this work aims, through a literature review, to elucidate the effectiveness of the association between microneedling and PRP techniques, in terms of improving the final quality of scar tissue from skin lesions.

MATERIALS AND METHODS

The present study is a literature review based on evidence about the effectiveness of the association of microneedling and PRP techniques in improving the final quality of tissue in the healing of skin lesions. The search and selection of articles were carried out on August 27, 2019, in the national database ScieloBrasil (Scientifc Eletronic Library Online) and in the

Figure 1. Summary of studies found in the literature

Study identification (authorship)	Study title	Sample	Interventions	Results
Darmawan et al. (2019)	Split-Face Comparative Study of Microneedling with Platelet-Rich Plasma versus Microneedling Alone in Treating Acne Scars.	Man and woman with atrophic acne scars.	Four treatment sessions at 4 consecutive week intervals, each consisting of microneedling followed by application of platelet-rich plasma (PRP) on the right side of the face and microneedling alone on the left.	The man had grade 4 acne scars on both sides of his face, which became grade 2 on the right side and grade 3 on the left side. The woman had grade 4 acne scars on both sides of the face, which decreased to grade 1 on the right side and grade 2 on the left side.
Porwal et al. (2018)	A comparative study of combined dermaroller and platelet-rich plasma versus dermaroller alone in acne scars and assessment of quality of life before and after treatment.	55 patients with atrophic acne scars. Divided into group A: 28 and group B: 27	Group A patients were treated with a dermaroller only, while group B patients were treated with a combination of dermaroller and intradermal PRP injections. Three sessions wereheldata monthlyinterval.	Significant percentage improvement was observed in both groups. However, group B treated with both treatments combined obtained better results when compared to group A.
Ibrahim et al. (2018)	Skin microneedling plus platelet-rich plasma versus skin microneedling alone in the treatment of atrophic post acne scars: a split face comparative study.	35 patients with mild to severe post-acne atrophic scarring.	All patients received four sequential skin microneedling treatments alone on the right side of the face and skin microneedling followed by topical application of platelet-rich plasma (PRP) on the left side of the face with an interval of 3 weeks.	There was a significant improvement in the degree of severity of the scar after treatment on both sides. Regarding the degrees of patient satisfaction, there was a significant improvement after the two treatment modalities, with insignificant differences between the two treatment modalities.
Ibrahim et al. (2017)	Therapeutic effect of microneedling and autologous platelet-rich plasma in the treatment of atrophic scars: A randomized study.	90 patients with atrophic scars and were randomly classified into three groups: I, II and III.	Group I: 28 patients treated with microneedling, one session every 4 weeks; II: 34 patients treated with intradermal injection of platelet-rich plasma, one session every 2 weeks; and III: 28 patients treated with alternative sessions of each microneedling and platelet-rich plasma, 2 weeks between each session, for a maximum of six sessions.	There was a statistically significant improvement in atrophic scars, with a reduction in scores associated with the clinical assessment scale for atrophic scars in all groups, but the improvement was more obvious in group III.
Asif et al. (2016)	Combined autologous platelet-rich plasma with microneedling verses microneedling with distilled water in the treatment of atrophic acne scars: a concurrent split-face study.	50 patients with atrophic acne scars.	Microneedling was performed on both halves of the face. Intradermal injections, as well as topical application of PRP, were administered on the right half of the face, while the left half of the face was treated with intradermal administration of distilled water. Three treatment sessions were carried out with an interval of 1 consecutive month. The quantitative scale and the Goodman quantitative scale were used for the final evaluation of the results.	The right and left halves showed an improvement of 62.20% and 45.84%, respectively, on the Goodman quantitative scale. Goodman's qualitative scale showed excellent response in 20 (40%) patients and good response in 30 (60%) patients on the right half of the face, while the left half of the face showed excellent response in 5 (10%) patients, good response in 42 (6%) patients and poor response in three patients. PRP is effective in treating atrophic acne scars and can be combined with microneedling to improve the final clinical results compared to microneedling alone.

international database PubMed (U.S. National Library of Medicine / NationalInstitutes of Health). The descriptors used in Portuguese were: *Microagulhamento, Plasma Rico em Plaquetas* and the descriptors used in English were: Microneeding AND platelet rich plasma. We included articles written in full, free of charge, published in English and Portuguese, from January 2014 to August 2019, which had contexts related to the treatment of scar tissue from skin lesions using the microneedling associated with PRP. Incomplete and repeated articles that depicted another therapy as treatment were excluded.

RESULTS

After filtering the articles by the inclusion and exclusion criteria, 5 articles were selected, read and recorded in an electronic spreadsheet (Excell-Microsoft Office), as shown in Figure 1.

DISCUSSION

This study aimed to analyze, based on evidence, the association between microneedling and PRP in improving the final quality of scar tissue from skin lesions. The microneedling technique has obtained merit due to its simplicity, cost, effectiveness and safety in all types of skin, in addition to presenting a reduced risk of infection, photosensitivity and post-inflammatory hyperpigmentation (Johnson et al., 2019). The technique proved to be effective in stimulating collagen production, without causing total de-epithelialization, in a fast, minimally invasive and effective way, with promising results observed in the literature (El-domyati et al., 2018; Silva et al., 2018). Such procedure allows the transdermal delivery of active agents to the skin through microchannels, which enhance the effects of topical application of PRP, becoming a combined therapy that helps in the improvement and acceleration of tissue repair due to its regenerative properties, representing an autogenous source of growth factors, which increases the response to wound healing and consequently improves the appearance of scars(Chawla, 2014; El-domyati et al., 2018; Porwal et al., 2018; Silva et al., 2018). The likelihood of a single therapy to be highly effective is low. Therefore, the development of combined therapy approaches for skin treatments become increasingly promising (Montgomery et al., 2016).Thus, new ways in the treatment of cutaneous scar regeneration can be explored with the advent of the microneedling junction to the PRP (Porwal et al., 2018).

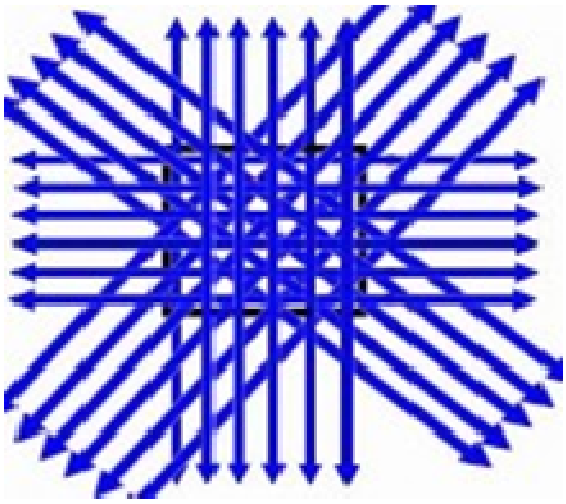
The term microneedling was first described by Orentreich in 1995. In his article the authors speculated that the trauma controlled by a hypodermic needle in the act of subcision, triggers a response to wound healing, production of connective tissue and improvement of depressed skin sites. Since then, research has been conducted on animals and humans to elucidate the mechanism by which microneedling works. It is postulated that it acts by stimulating the wound healing cascade and the release of multiple growth factors, including fibroblast growth factor, platelet-derived growth factor and transforming growth factor (TGF-ß), promoting proliferation and cell migration, neovascularization and neocolagenesis(El-domyati et al 2018). Starting the remodeling process, in which the fibronectin matrix forms and allows the deposition of type III collagen, that will eventually be replaced by type I collagen, result in skin recovery and scar reduction(Silva et al., 2018; Johnson., 2019).

A cylindrical tool with several needles was the first microneedle device described in the literature, it was designed to be rolled up and down the skin until bleeding was obtained (Fernandes, 2005). This device is similar to the current one Dermaroller® (Figure 2).

Source: (AUST, 2010).

Figure 2. Microneedling device

There are several microneedling devices available on the market, varying based on length, number of needles and automation. More superficial devices, with needle lengths up to 0.5 mm, can be purchased for domestic use, while the deeper ones, with needle lengths ranging from 1 mm to 3.5 mm, are designed to be used in medical facilities (Alster et al., 2018). Regardless of the device used, the procedure must be done with clean skin, anesthetized and sanitized with 70% alcohol. The treatment area is divided into zones and treated with a combination of circular movements, horizontal or vertical lines, five times in each location, according to figure 3. The depth of the needle varies depending on the treated location (Khetarpal et al., 2019).



Source: (NEGRAO, 2015)

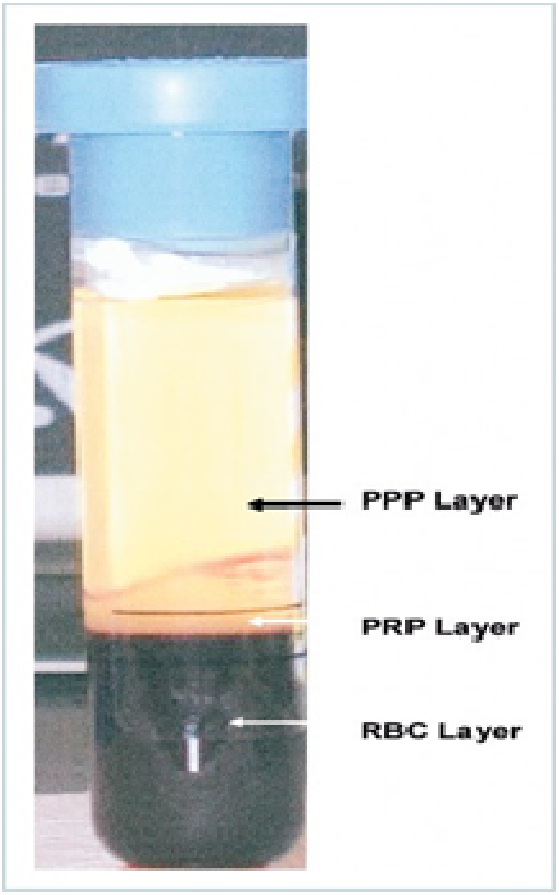
Figure 3. Directions to be followed when performing the microneedling procedure

A lubricant, such as PRP, can be used to allow the device to slide smoothly over the skin, being absorbed by the tiny channels produced by microneedling. In this way, growth factors of both therapies will act together, increasing the

response to wound healing and consequently improving the appearance of scars(Porwal et al., 2018; Johnson et al., 2019).

The description of PRP was created in the area of hematology in the year 1970 as a plasma with a platelet counting above peripheral blood, initially used as a transfusion product in the treatment of patients with thrombocytopenia(Martinez-Zapata et al., 2016). Years later, in the 1990s, it was described as a valuable autologous source of growth factors and started to be used in plastic and maxillofacial surgery, spreading in several areas of dentistry and medicine such as orthopedics, ophthalmology and more recently in dermatology, presenting excellent results in tissue regeneration and wound healing (Asif et al., 2016; Arnulfo et al., 2018; Meza et al., 2019). The theory behind PRP treatment is to decrease the rate of red blood cells, which are less useful in the healing process and concentrate platelets, containing a powerful mix of growth factors (Arnulfo et al., 2018). In a healthy individual, the normal platelet count varies between 150,000 and 450,000 cells per microliter of blood. Platelet concentrations below 1,000 x 10^{6} / ml are unreliable to improve wound healing and very high concentrations did not enhanced the process. The ideal concentration of platelets remains to be defined (Meza et al., 2019). Platelets are small and anucleatedcytoplasmic fragments, derived from bone marrow cells called megakaryocytes. They actively participate in the tissue repair process and are the first cells present at the trauma site. They have hemostatic action thanks to the specific growth factors and chemotactics released that allow the production of cytokines, fundamental in the regulation of the immune-inflammatory response, which can modulate inflammation, angiogenesis, stem cell migration and cell proliferation(Asif et al., 2016; Martinez-Zapata et al., 2016). Platelets can release several types of growth factors, such as platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF); transforming growth factors β (Transforming growth factors - TGF-β); epithelial growth factor (EGF); insulin-like growth factor (Insulin-like growth factor 1); platelet-derived angiogenesis factor (Platelet-derived angiogenesis factor) and platelet factor 4 (Platelet factor 4 - PF-4)(Kobayashi et al., 2016).

PRP is defined with a concentration of platelets above the baseline obtained from a fraction of autologous blood plasma, complemented with clotting factors and enriched by a range of growth factors, chemokines, cytokines and other plasma proteins (Piccin et al., 2017; Shiga et al., 2017; Everts, 2018).As for obtaining it, there is a huge discussion and no consensus regarding the ideal preparation protocol. It is produced through a process called differential centrifugation, in which the acceleration force is adjusted in order to sediment certain cellular constituents based on specific gravity (Alves et al., 2018). There are two techniques for preparing the PRP, the first one is the open technique, in which there is a concern with contamination of the product during microbiological handling, since the product is exposed to the environment of the work area by coming into contact with the materials of its production. The second is the closed technique, the most recommended as it does not expose the product to the environment. It involves the use of commercial devices, including centrifugation equipment and application (Kumaran et al.,2014; Arnulfo et al., 2018). In general, the procedure requires the use of a small amount of blood. Whole blood is obtained by venipuncture in anticoagulated tubes (usually with citrate acid, dextrose or sodium citrate solution). This blood then undergoes single or double spin centrifugation, depending on the device. Soon after, the tube shows 3 basic layers (Figure 4): red blood cells, PRP and low platelet plasma (PPP) which is removed so that the PRP is obtained (Kumaran et al., 2014).



Source: (RUTKOWSKI, 2008)

Figure 4. Anticoagulated whole blood after centrifugation. You can see the 3 separate layers (red blood cells, PRP and PPP)

CONCLUSION

After the literary review, it is concluded that the association of microneedling with platelet-rich plasma has a great potential for treating scarring due to skin lesions.However, additional clinical and histopathological research is needed to assess and adjust for safe implementation.

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