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Comparison of platelet rich plasma administration with platelet low plasma for healing incision wounds in cruris of rattus norvegicus rats viewed from histology of collagen tissues

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Abstract

Wound healing is a complicated, multi-step process divided into three major phases: inflammation, proliferation, and scar formation/remodeling. The compartmentalization of this process into discrete stages gives the illusion of simplicity, but in reality, it is much more complicated. For efficient healing to occur, complex interactions between multiple cell types, soluble factors, and extracellular matrix components are required to re-build the tissue; PRP is produced from the blood by centrifugation, which concentrates platelets along with several bioactive factors that can promote various aspects of tissue regeneration and protection. The rationale for using and therapeutic potential of a high concentration of platelets is based on their capacity to supply and release supraphysiologic amounts of essential growth factors and cytokines from their alpha granules to provide a regenerative stimulus that augments healing and promotes repair in tissues. Unlike platelet-rich plasma (PRP), platelet-poor plasma (PPP) does not have many platelets, but PPP has its unique healing properties. This study was an experimental study using the post-test design only control group design in an experimental laboratory. The research subjects were divided into three groups: 10 rats with incision wound at the cruris and given an injection of platelet-rich plasma, then ten white rats with incision wound at the cruris and were given an injection of platelet-poor plasma, and ten rats with incision wound at the cruris for control. The wound area was measured over seven days, the wound was harvested, and histological analysis was performed, including counting collagen finding, and will be analyzed by ANOVA test. The results showed that the amount of collagen between platelet-rich plasma and platelet-poor plasma differs significantly, with a *p*value of 0.000 ($p < 0.05$). The amount of collagen in the healing process of incision wounds in cruris of the rat Rattus norvegicus with the administration of PRP better than the administration of PPP. The use of platelet-rich plasma (PRP) in the process of healing fractures can be studied in humans so that it is expected to be used as a post-operative wound healing therapy.

I. INTRODUCTION

A. Background

Wound is a form of network outages due to anatomical relationship mechanism force. The process of forming generally traumatic injuries in an accident or during surgery. When an injury occurs on a network, there is a wide range of responses hemostasis, inflammation, bleeding and contamination of bacteria to form necrotic tissue with cell death [1, 2].

In the early phase of wound injury, the inflammatory process undergoes a variety of polymorphonuclear and

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macrophage migration. The next stage is the process of proliferation that would trigger a process of re-epitelialisasi, neo-vascularization and granulation tissue formation. In

this phase there is the role of Transforming Growth Factor (TGF-β) released by platelets, macrophages play an important role as a regulator of fibroblast function. TGF-β has several important roles in the formation of the extracellular matrix, which are to increase the movement of epidermal cells, the formation of collagen, proteoglycans and fibronectin, as well as reduction of the production of proteases that destroy the matrix [1, 3]. The final stage is a phase of remodeling that enables new power tissue formed close to the original, during the first 3 weeks after injury, this power is only about 20% of the original, in the remodeling process, there will be the replacement of collagen fibers with fibers of greater accompanied by a stronger crosslinking of each fiber that forms a more robust network [3, 4, 5]. Many factors can delay wound healing significantly. Often, the exact delay mechanism is not well understood and requires further investigation.Wounds that do not heal reportedly affect about 3 to 6 million people in the United States, the age group > 65 years of approximately 85% as well as causing health care costs being very high and long [6, 7].

Therefore, these days there have been various attempts to accelerate the healing of a wound. This is done to reduce the cost of treatment and prevent complications from becoming chronic wounds. The effort is to increase growth and differentiation factors in the area of injury to form a natural healing [8].

Such efforts include the use of PRP and Low Plasma Platelets (PLP). PRP is the result of centrifugation of blood plasma fraction with platelets concentrations 3-5 times above normal [9]. The role of the PRP is associated with the process of platelets in hematopoiesis and factors bioactive are released by platelets that have been activated, particularly of granular alpha form of Platelet-Derived Growth Factor (PDGF), TGF-β , Fibroblast Growth Factor (FGF), Insulin-Like Growth Factor (IGF), Vascular Endothelial Growth Factor (VEGF), Hepatocyte Growth Factor (HGF), Epithelial Growth Factor (EGF), Platelet Factor 4 (PF4), and several others, which in some studies have reported beneficial in healing tissue injury [8, 10].

Meanwhile, PLP is a plasma layer formed after centrifugation of whole blood, consisting of acellular plasma with fibrinogen and growth factors. Some research shows that vascular cells have fibrinogen receptors, which play an important role in building cell-cell interactions after activation of the receptors, as well as inducing angiogenesis directly [11]. Although domestic workers contain fewer numbers of growth factors compared to PRP, several studies have shown significant improvements in wound healing [12].

[7] in his research found that both the Certified Professional Coder (CPC) and PLP can stimulate collagen gel contraction by inducing a significant stimulation on protein content MT1-MMP and TIMP-2. In Type 1 Procollagen Carboxy-Terminal Peptide (PIP) also showed improvement after being given the maximum CPC and PLP. However, the PRP has a stronger effect than PLP [12].

The effects of PKT and PRT can also stimulate the expression of pro-alpha 1 and pro-alpha 2 mRNAs which are part of the Type 1 collagen chain. Type 1 collagen is an important component of collagen in the dermis of the skin. PKT and PRT can also increase the expression of Collagen Type-1 Alpha (COL1A1) and Collagen Type-2 Alpha (COL1A2) proteins. PRP and platelet low plasma can also increase MMP-1 and MMP-3 protein expression. However, there is no significant difference between PRP and PLP [12].

The potential for platelets is explained by [13] where topical hemotherapy with platelet gel can be considered an adjuvant treatment of a multidisciplinary process, which is useful for improving the wound healing process.12 In animal studies, it was reported that the combination of PRP and hydrogel successfully reduced wound size and shortened healing time [14]. [10] also support that various potentially therapeutic growth factors are detected and released from platelets to a significant extent in PRP preparations. Adequate concentration and release of growth factors through autologous platelet gel may be able to accelerate wound healing in various wound applications [15]. Finally, an evaluation of the benefits of PRP on wounds was also explained through the findings of [16] who explained that wound treatment with PRP would accelerate epithelial differentiation and produce tissue with an organized and interrelated collagen bundle [16]. The use of PRP is believed to increase concentration and release growth factors and differentiation in the injured area to augment the natural healing process. Several factors will regulate cellular processes such as mitogenesis, chemotaxis, differentiation and metabolism.

According to some reports and reviews that support the researcher is interested in assessing the comparison between the administration of PRP and PLP on wound healing incision.

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B. Formulation of the Problem

Based on the above background, the problem in this research is "how the PRP was compared with PLP with the amount of collagen in the healing of the incision?"

C. Research Purposes

1) General purpose: Based on the formulation of the problem above, the purpose of this study was to compare the administration of PRP and PPP to the amount of collagen in the healing of the incision.

2) Specific purpose: 1. To determine the role of administration of PRP in the wound healing process is clean.

2. To determine the role of platelets in the provision of low plasma in the wound healing process.

3. To know the advantages and disadvantages of the provision of PRP and PPP in terms of collagen wound clean.

D. Benefits of Research

1) Scientific benefits: There is an increase in the additional information regarding the pharmacological treatment of biomolecular surgical wound healing mechanisms.

E. Practical benefits:

Providing benefits of using PRP and PPP on wound healing can be taken into consideration in the management of the problem.

1) Hypothesis: The provision of PRP is better than the PLP to the acceleration of wound healing incision.

II. RESEARCH METHODS

A. Design

This study is an experimental study using a post-test only control group design. In the experimental group randomly selected and subjected to treatment and in the control group not subjected to treatment, after that, a post-test was conducted. The treatment group in this study were Rattus norvegicus mice with incision wounds in cruris given PRP and a group given platelet low plasma, while the control group was the comparison group of rats with incision wounds in cruris who were not given platelet plasma products.

B. Research Sites

Research was conducted at the Faculty of Veterinary Medicine University of Syiah Kuala Banda Aceh.

C. Research Time

Research was carried out for two months starting from 1 July 2019 to 30 September 2019.

D. Subject and Sample Research

The subject of this research is Rattus norvegicus, male, adult, aged 3-4 months, weighing 200-250 grams, obtained from the Faculty of the Veterinary Medicine University of Syiah Kuala. In this study, subjects were divided into three groups randomly selected study, namely:

1. P0 group = Control group with the incision in cruris and without treatment.
2. Group P1 = The sample group with treated incision wounds in cruris accompanied by injection of PRP.
3. Group P2 = The sample group with treated incision wounds in cruris accompanied by administration of platelet low plasma injection.

1) Inclusion criteria: 1. White male rats Rattus norvegicus.

2. Aged 3-4 months.
3. Weighing between 200 grams and 250 grams.
4. Rats in a healthy state.

2) Exclusion criteria: 1. Animals have abnormalities in the lower extremities.

2. Experimental animals died during the experiment.

E. Conceptual Framework

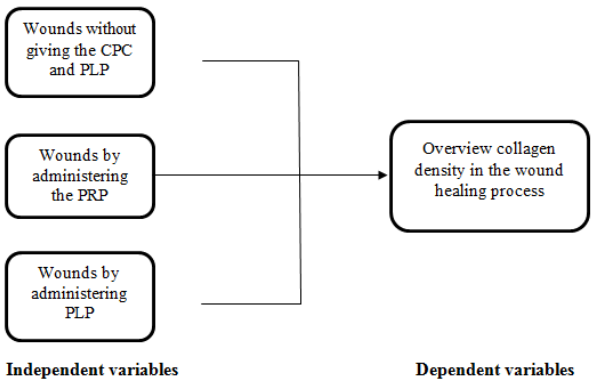

Fig. 1. The conceptual framework

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F. Research Variable

The variables in this study consist of the independent variable, dependent variable and beyond. The following is the elaboration of the study variables:

1. The independent variable or variables in this study a treatment injection of PRP and PPP.
2. The dependent variable or dependent variable in this study a microscopic picture of wound healing (collagen density).
3. Control variables or controlled variables, namely wound, feed, genetics, gender, age, weight, and temperature of the room.

G. Operational Definition

1. Wound healing is the stage of returning the body's wounds to recover starting during the process of inflammation, proliferation to angiogenesis. In the proliferation stage, wound healing will form fibroblasts which stimulate collagen to form stronger fibrotic tissue and replace damaged tissue. In this study wound healing was assessed by assessing collagen tissue density. How to measure with histopathological examination.
2. The PRP is plasma preparations obtained from buffy coat of whole blood centrifuge results which were then conducted at the centrifuge stage kedua [17].
3. PLP is a plasma which is the top layer formed after centrifugation of whole blood [11].

H. Tools and Materials

The tools used for the study include:

1. Treatment facilities rat cage includes a drink and feed.
2. Medicine consists of ketamine, ketorolac and ceftriaxon.
3. 1ml syringe preparation tool blood, blood serology tubes, and centrifuges.
4. Equipment consists of a minor incision wound sets, and sterile gauze.

I. Research Procedure

1) Preparation of experimental animal: Rattus norvegicus, male, adult, 3-4 months old, was obtained from the Faculty of the Veterinary Medicine University of Syiah Kuala as many as 30 individuals. Research sample homogenization was conducted wherein prior to treatment the mice were weighed, measured rectal temperature adaptation has been done made for two weeks to be maintained in the cage. The temperature inside the enclosure is set at room temperature, Every day the mice were fed a pellet as much as 20 grams and drinking water provided ad libitum.

Both the strengths and weaknesses of the experimental animals should be considered in determining whether the mouse is suitable for use in wound healing studies. Table 1 below describes the physiological comparisons between rat and human skin.

2) Making the incision wound: Incision procedures performed minor surgical at wounds, the following stages:

1. Rats in the subcutaneous anesthesia with ketamine 75 mg/kg and xylazine 5 mg/kg.
2. Aseptic technique performed on the right cruris betadin and alcohol use, drapping on the site of the surgery.
3. Incision on the right cruris 2 cm until translucent layers of fascia.

3) Giving mechanical products PRP And PLP: 1. There are three experimental groups, each consisting of 10 animals.

2. After the incision wound, the PRP and PLP were given by injection into the wound with a volume of 0.1 cc using a 1 cc syringe, then sewed and closed with sterile gauze.
3. In the group of control animals, after the incision wound, the wound was then closed with sterile gauze without giving plasma product.

4) Wound healing rate: 1. On day 3, 5th, and 7th after incision and administration of plasma products, the mice will be evaluated under a microscope to study wound healing by assessing the density of collagen.

2. All mice in the experimental group were at termination by breaking her neck, and then performed a biopsy incision at the incision site wounds 8 mm in diameter with a depth of up to subcutaneous. Paraffin blocks were done and painting with Massons trichrome staining.
3. Parameter histopathology score for collagen density was assessed by microscopy at 100X magnification.

- Score 0 if not found collagen fibers (0 collagen finding)
- Score +1 if it looks a bit dens of collagen (1-25 collagens)
- Score +2 if it looks like a moderate amount of collagen density (26-50 collagens)
- Score +3 if the fibers of collagen density looked meetings and many (51-75 collagens)
- Score +4 if the fibers appear solid and very dense (76-100 collagens)

4. Further statistical analysis.

J. Data Analysis

In this study, all data were analyzed using SPSS for Windows version 17.0. Analysis of the data in this study includes:

1. Describing the mean and standard deviation of the variables.
2. Normality test of each group with Shapiro Wilk Test.
3. Variant homogeneity test between groups with Levene Test.
4. ANOVA test performed to assess the effect of plasma

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products on the score for the amount of collagen wound healing.

III. RESULTS AND DISCUSSION

A. Research Result

This is an experimental study using 30 rats Rattus norvegicus aged between 3 and 4 months, sex male, healthy, weighing between 750 and 1000 grams, were divided into three treatment groups: control group of normal mice with the incision, groups of mice with the incision get PRP and mice with the incision gets PLP.

These activities were carried out in three stages, namely the first stage adaptation period of 7 days, aims to familiarize the rats to the environment in research, both conditions cages, food and drink. During the adaptation period mice were given food and drinks which will be used during the research period ad libitum. In the second phase, there was an incision in cruris treatment in mice. Cruris incision was in sharp done using scalpel and fascia incision to pass. The rats were divided into 3 groups: control group of mice with the incision in cruris without giving the CPC and the treatment group of mice with the incision in cruris by the PRP and mouse with the incision in cruris by PLP.

After incision in cruris there was wound closure using sterile gauze and treatment by providing analgesics and antibiotics. Closing the wound using a sterile gauze aims to avoid contaminants from the outside that can lead to complications such as wound infections. Wound closure was considered quite adequate, so that the wound healing process can be run even if the activity of mice as usual. Furthermore, these three groups were kept in cages each - each measuring 60x40x40 cm3 filled with rice hulls, where there are food and drink for the animal. During the study three groups of mice were fed pelleted and drinking at libitum until day 7. The process of making the incision in the PRP cruris and administration as well as domestic workers in mice can be seen in Figures 2 and 3.

Fig. 2. Overview of the process of the incision in cruris

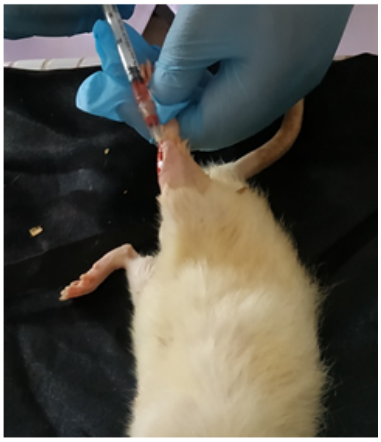
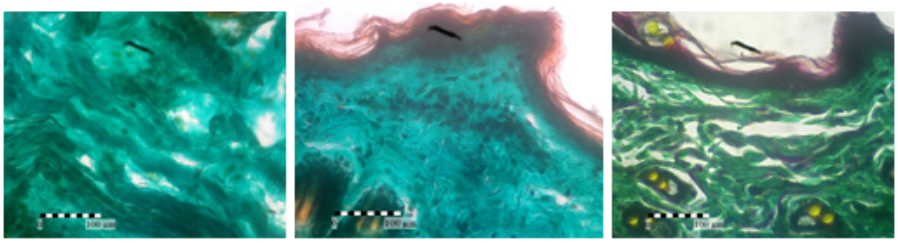


Fig. 3. Image Award PRP and PLP

The third stage is , the stage of making preparations aetanasi and coloring as well as the observations of the amount of collagen. All mice in etanasi used ether to skin tissue sampling to assess the amount of collagen using Mason's trichome staining. The amount of collagen quantitatively assessed visually using an Olympus BX51 light microscope with 400x magnification. Then counted the number of these cells. The sum of all cells that are found then summed and fed as the data (numbers in the table for each animal).

B. Overview Histological collagen Network

The observation of the histological picture of tissue 7 days post incision PRP group (A) PLP group (B) and the control group (C) can be seen in Figure 4.



A B C

Fig. 4. Overview collagen tissue at 7 days after the making of the incision PRP group (A) PLP group (B), and the control group (C)

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From the microscopic observation of the measurement the amounts of collagen after the making of the incision on cruris mice from each group were as follows:

TABLE 1
OVERVIEW AMOUNT OF COLLAGEN

	Treatment		
	Repeat PRP	**PRP**	**PLP Control**
1	40	27	19
2	39	27	19
3	38	25	18
4	36	25	15
5	35	24	15
6	33	24	14
7	31	23	14
8	31	22	14
9	31	22	14
10	29	22	11
amount	343	241	153
Average	34.30	24.10	15:30
SD	3,860	1,911	2,584

To determine whether the data amount of collagen is normally distributed, the data were analyzed by normality using the Shapiro-Wilk test. Normality test results in the amount of collagen are presented in Table 2.

TABLE 2
SHAPIRO-WILK TEST RESULTS THE AMOUNT OF COLLAGEN

Group	**Repeat**	***p* Value**
PRP	10	0,400
PLP	10	.157
Control	10	.117

Description: The p-value was calculated using the Shapiro-Wilk test * $p > 0.05$ (normally distributed data)

The results of the Shapiro-Wilk test showed that the data are normally distributed where the p-value for PRP group, PLP and control is > 0.05, and can then proceed with the next test. The test used is a one-way ANOVA test to see the difference of a research group, but previously done Levence test to assess the homogeneity of the research data presented in Table 3.

TABLE 3
THE TEST RESULTS LEVENCE AMOUNT OF COLLAGEN

Levene Statistics	***p* value/Sig**
Total Collagen	0.025

Description: The p-value was calculated using test Levence * $p > 0.05$ (data not homogeneous)

Significant value for uniformity test and Levence variance test showed 0.025 ($p < 0.05$). This indicates that the data obtained is not homogeneous, then proceed with the analysis of data using one-way ANOVA performed to compare the amount of collagen from the PRP group, PLP, and KN. Here are the results of data analysis using ANOVA test for the amount of collagen.

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TABLE 4
ONE-WAY ANOVA TEST RESULTS COLLAGEN NUMBER

	n	*F*	*p*-value/Sig.
PRP	10	107 493	0,000
PLP	10		
Control	10		

Description: The *p*-value was calculated using one-way ANOVA *p*-value < 0.05 (obtained difference) with *F* table = 107 493

Based on one way ANOVA statistical test that obtained a significant value 0.000 < 0.05, it can be concluded that the results of one way ANOVA statistical test showed a difference ($p < 0.005$) in the study group.

Significant differences between the animal test in assessing the amount of collagen in the skin tissue microscopically are further known to perform advanced analysis of *t*-test.

TABLE 5
ANALYSIS OF ADVANCED T-TEST COMPARISON OF THE AMOUNT OF COLLAGEN BETWEEN GROUPS

	Difference in Average	***p*-value**
PRP vs Control	19.0	< 0.05
PLP vs. Control	8.8	< 0.05
PRP vs PLP	10.2	< 0.05

Description: *p* value of < 0.05 (obtained difference)

Referring to the results of further tests of *t*-test there are differences in the mean difference between the groups with the overall significance level < 0.05.

IV. DISCUSSION

Wound healing is a process that can be divided into three distinct phases (inflammation, proliferation, and remodeling). Each is marked with a specific event that requires a specific component. Wound healing is not always a linear process, can develop forward and backward through a phase of healing depending on a variety of intrinsic and extrinsic factors. Therefore, treatment is effective in improving wound healing may not only involve one or two components. Therefore wound healing indicator used in this study was microscopically performed by making preparations for histological staining and assessment through Masson's trichome excretion amount of collagen in scar tissue preparations at 400x magnification objective lens observed only on day 7 after the making of the incision.

Result Histopathological examination of the MasSon trichome staining using a light microscope with a magnification of 400 times was conducted on day 7 of the amount of collagen density. On day 7, the density of collagen in the treatment group the PRP administration was different from the control group. This is evident from the amount of collagen which is more compared to the control (Figure 4). This indicates that administration of the PRP further enhance the formation of collagen connective tissue in the wound than the control group. These results are consistent with the theory that the proliferative phase took place on day 3 to day 21. The proliferative phase is characterized by the formation of granulation tissue in the wound approximately 12-48 hours after the wound's complete haemostasis. The number of fibroblasts peaked about one week after the injury and is a dominant cell in the first week phase of wound healing [18, 19]

This is also consistent with the theory that the PRP α granules contain 7 major growth factors such as PDGF 3 isomers (PDGF- αα, PDGF-αβ, and PDGF-ββ), 2 isomer TGF-β (TGF-β1 and TGF-β2), VEGF and EGF.9 All these factors are secreted by platelets that have been activated by the wound healing process. PRP can be injected at the wound or applied directly over the wound. The main role of the PRP is able to activate the body's physiological function to meet most of the growth factor in the injury, reducing the potential for infection, pain, and perdarahan [20].

Various studies have reported clinical trials of the effectiveness of the PRP for wound healing, but there is no evidence that clearly demonstrated the efficacy of the PRP. One study reported that the effects of the PRP are weak because it has a short working life and must be used in a certain time period after the time of production. Other studies also show that the PRP will be effective when used repeatedly. However, experimental studies in experimental animals using a combination of the CPC and hydrogel managed to reduce the

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size of the wound and shorten the time penyembuhan.13. This study also assessed the results of a histopathological examination by trichome Masson staining using a light microscope with magnification 400 times performed on day 7 of the amount of collagen density. On the 7th day, collagen density in the treatment group given PRT was different from the control group. This can be seen from the amount of collagen which is higher than the control (Figure 4). This shows that the administration of PRT increased the formation of collagen connective tissue in the wound than the control group. This is in accordance with the theory of PRT containing a lot of fibrinogen, fibronectin, coagulation factor VIII, and prothrombin that can be activated into thrombin by Ca2+ in the process of hemostasis and coagulation. [11]PRT products have higher levels of fibrinogen, which can induce the formation of fibrin clots. This reaction can improve the regulation of collagen synthesis in the extracellular matrix and provide scaffolding for cellular migration and adhesion. Some studies with bone ischemic site samples show that PRT can provide a matrix for cell growth and differentiation and provide a good environment for osteoblastic differentiation, in which cells will invoke fibrin molecules and exhibit cell-to-cell interaction in three dimensions [11]. These results showed that the group with the provision of PRP better than the group of PLP administration is proven by the test value statistical analysis which showed a significant difference consistent with the theory that the PRP nor PLP myofibroblasts stimulate differentiation, cell migration, and production of Enterprise Content Management (ECM) components. Furthermore, both the PRP and the PLP were able to induce the same effects on RhoA activation and the production of MT1-MMP, TIMP-2, a-SMA, FN-EDA, collagen type-I, and periostin. PRP induces stronger effects on cell migration and induction of collagen gel contraction. PLP products contain smaller amounts of growth factors compared with PRP products [12].
In research conducted found that the use of the PRP and the PLP in wound healing showed that the use of PRP accelerates wound healing ($p < 0.005$) [21].

V. CONCLUSION AND SUGGESTIONS

A. Conclusion

The results of the study and discussion can be concluded that the amount of collagen in the healing process of incision wounds in cruris of the rat Rattus norvegicus with the administration of PRP is better than the administration of PPP.

B. Suggestion

The use of PRP in the process of healing fractures can be studied in humans so that it is expected to be used as a postoperative wound healing therapy.

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