



# The Effect of Platelet Rich Plasma on Wound Healing in the Repair of Experimental Penile Fractures

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## ABSTRACT

**Background:** Penile fractures are caused by the rupture of the tunica albuginea and the underlying layers of corpus cavernosum as a result of the exposure of the erect penis to blunt trauma. Although conservative treatment methods have been recommended in former studies, recent studies favor early surgical options. Platelet-rich plasma (PRP) is a blood product rich in cytokines and several growth factors, obtained from the patient's own blood commonly used to stimulate healing in acute and chronic wound treatments. The efficiency of homologous PRP treatment in rats with penile fractures have been assessed in terms of clinical manifestation and histopathological findings in the present study.

**Methods:** Thirty-five rats were randomly divided into five groups, each containing seven rats as follows: 1. Conservative group: Following the formation of penile fracture, medical interventions were not initiated on fracture area and the wound was left for secondary healing. 2. Bandage group: Following the formation of penile fracture, self-adherent elastic bandage (3 M Coban) was applied to the fracture area for three days. 3. Primary repair group: Following the formation of a penile fracture, the lacerated area was repaired with 7/0 vicryl primary sutures. 4. Primary repair + Homologous Platelet Rich Plasma group: Before the operation, 10 cc of blood was taken from one rat under general anesthesia by intracardiac puncture and PRP material was prepared from this blood. Homologous PRP was topically administered on the wound in the fracture area and then the penile fracture was repaired with 7/0 vicryl as simple separate stitches. 5. Non-operative control group: Surgical procedures were not applied to this group; it was used as the control group.

**Result:** The effect of the PRP treatments on the surgical repair options in the rats with penile fractures was investigated. The present findings revealed that following the repair with conservative treatments, the fracture format persisted and various complications like infection, oedema, excessive fibrosis and hyperemia were encountered. On the other hand, the best healing was achieved in primary repair + PRP group in terms of clinical manifestation and histopathological findings.

**Key words:** Penile fracture, Platelet-rich plasma, Rat.

## INTRODUCTION

Penile fracture is induced by the rupture of tunica albuginea and underlying corpus cavernosum layers through exposure of the erect penis to blunt trauma (Eke, 2002). Fractures are generally encountered as a result of aggressive sexual intercourse, masturbation, falling onto an erect penis or the sadistic mechanical and physical traumas inflicted by humans on this organ of animals (Eke, 2002; Fergany *et al.* 1999; Jack *et al.* 2004).

A penile fracture is a urological condition characterized by an audible popping or cracking sound induced by sudden trauma applied to an erect penis that causes severe pain followed by deformity, detumescence and the discoloration of the penis (Eke, 2002; Fergany *et al.* 1999). Penile fractures are described as wound-induced sudden loss of erection, severe pain and swelling. Although the majority of the cases are diagnosed by anamnesis and regular physical examination, radiographic examinations including retrograde urethrography and corporal cavernosography can aid in the diagnosis of penile fracture cases complicated with urethral rupture manifested by dysuria, urethrorrhagia or blood in meatus (Eke, 2002; Jack *et al.* 2004).

The first penile fracture case was reported in literature in 1924. Although it was accepted initially as a rarely encountered injury, penile fracture has become a more frequently reported genitourinary trauma (Jack *et al.* 2004).

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From the past to the present, various treatment options have been proposed for the treatment of penile fracture. In previous studies, while cold compresses, urethra characterization, anti-inflammatory drug prescriptions and suppression of erection were recommended as conservative treatments, these treatments were followed with complaints of

penile deformities, painful erection, urethral fistula and erectile dysfunction after recovery (Eke, 2002; Jack *et al.* 2004).

Subsequently, early surgical options minimizing fracture complications were proposed with the intent of early surgical intervention right after the trauma to repair the corpus cavernosum. Currently, various medical treatments are used in penile fracture cases in addition to emergency surgical treatment. Such treatments include fibrin glue, virgin olive oil and Ankaferd Blood Stopper treatments on the fractured penile area, wrapping with a Coban Bandage, bonding with Cyanoacrylic glue and so on (Taşdemir *et al.* 2011; Güneş *et al.* 2015; Eslahi *et al.* 2020).

Platelet rich plasma (PRP) treatment, discovered as an advanced treatment option, has been used to stimulate acute and chronic wound healing for more than twenty years. Autologous plasma is a blood product obtained from the blood of the patient and contains cytokines and several growth factors [Platelet derived growth factor (PDGF), transforming growth factor - B (TGF-B), insulin-like growth factor - I (IGF-I), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF) and basic fibroblast growth factor (BFGF)]. Among these factors, transforming growth factors- $\beta$  (TGF- $\beta$ 1) and platelet-derived growth factor (PDGF) play a key role in wound healing (Carter *et al.* 2003; Anitua *et al.* 2004). TGF- $\beta$ 1 supports chemoattractions of monocyte and macrophages and both attract fibroblasts to the area resulting in fibroblast proliferation (Carter *et al.* 2003; Theoret, 2005).

It is known that local applications of growth factors to chronic injuries generate a synergic effect in wound healing and have a significant therapeutic potential. Similarly, it has been reported in several clinical studies that growth factors play a key role in the repair of hard and soft tissue, thus topical treatments facilitate wound healing in normal tissue and heal persistent non-healing wounds (Debus *et al.* 2000; Tahir *et al.*, 2018). They are also efficiently used in skin lesions, urology, orthopedics and plastic surgery, ophthalmology, dental surgery and the repair of various tissues (Parafioriti *et al.*, 2011; Chung *et al.*, 2015; Roshini *et al.*, 2019; Sardari *et al.*, 2011; Carter *et al.*, 2011).

In PRP treatments, basically autologous plasma is used, but Homologous PRP obtained from donor's blood or Heterologous PRP obtained from other species are also used in small animals (birds, rats, squirrel and similar exotic animals) and in humans and animals when their general condition does not allow transfusion (Abegao *et al.* 2015; Shan *et al.* 2013).

The efficiency of homologous PRP treatment in rats with penile fractures was assessed in terms of clinical manifestation and histopathology in the present study.

## MATERIALS AND METHODS

### Experimental conditions

This study was conducted with the approval of the Animal Experiments Local Ethical Committee of Van Yüzüncü Yıl University number 07 dated 26.07.2019. The trial was carried out with 35 male wistar albino rats aged 3 months and with

250-320 g live weight. The rats were kept in cages in groups of 2-3 animals in a closed room at 50-60% relative humidity, 20- 23°C temperature and 12:12 light:dark photoperiods (12 hours light (06:00-18:00) and 12 hours dark). The rats were supplied ad libitum with water and pellet feed (18% protein (min), 2.5% oil (min), 4% fiber (max), 5.5% ash (max), 57.0% nitrogen-free substance (max), 2650 kcal/kg metabolic energy (min), 13% water (max) and amino acid, vitamins, minerals).

### PRP preparation

Three drops (0.05 ml as one drop) covering the entire wound surface of penile fracture area of each rat, were planned to use. A total of 1,05 ml of PRP was required for seven rats in this group. For this purpose, 10 cc of blood was collected by intracardiac puncture from a healthy rat under general anesthesia (ketamine hydrochloride 40 mg/kg, Xylazine 5mg/kg intra peritoneally) and placed into a blood collection tube supplemented with Sodium Citrate as anticoagulant. The PRP preparation was standardized as suggested by Mahmoud *et al.* (2019). Three layers formed in the centrifuged blood tube based on density: the lower layer included red blood cells; the middle layer was composed of platelets and leukocytes and included PRP; the upper layer included platelet-poor plasma. Following the separation of red blood cells and re-centrifuging of the tubes, the clot around 1.2 ml remaining in the lowest 1/3 section of the tube was separated as PRP.

### Penile fracture

Following the shaving of the genital area of the rats under general anesthesia (ketamine hydrochloride 40 mg/kg, Xylazine 5 mg/kg intra peritoneal), antisepsis was ensured with 10% Povidone iodine, a 24 Gauge branule was placed from the ostium urethra externum up to 2 cm mid-penile level and a penile rupture was instigated in accordance with the method specified by Taşdemir *et al* (2011) through a 3-4 mm laceration applied perpendicularly to the penile axis on the Tunica albuginea and corpus cavernosum layer on the dorsal of the corpus penis of the rats. All the surgical procedures were performed using a surgical loop (2.5x).

### Experimental groups

Thirty-five rats were randomly divided into five groups, each containing seven rats as follows:

#### Conservative group

No medical interventions were carried out on the fracture area following the formation of the penile fracture and the wound was left for secondary healing.

#### Bandage group

Self-adherent elastic bandage (3M Coban) was applied to the fracture area for three days following the formation of the penile fracture.

#### Primary repair group

The lacerated area was repaired with 7/0 vicryl as primary suturing following the formation of the penile fracture.

### Primary repair + Homologous platelet rich plasma group

Three drops of homologous PRP was topically administered on the wound for each rat (approximately equal to 0.15 ml) and then the penile fracture was repaired with 7/0 vicryl as simple interrupted sutures.

### Non-operative control group

Surgical procedures were not applied to this group; it was used as the control group.

### Histopathological analysis

At the end of the 14<sup>th</sup> day, a penectomy was performed on the rats under Ketamine + Xylazine general anesthesia. The penectomy materials were kept in 10% formalin solution for 48 hours for histopathological assessment. Following the routine tissue monitoring processes, they were embedded into paraffin blocks. Subsequently, 4 µm thick sections were taken. The preparates prepared for histopathological analysis were stained with hematoxylin-eosin (HE) and examined under a light microscope (Leica DM 1000, Germany) with blinded tests by an expert pathologist. The groups were compared according to edema, hyperemia, fibrosis and inflammation parameters.

Sections were scored in accordance with the modified method of Tasdemir *et al.* (2011) based on histopathological findings as: absent (-), slight (+), moderate (++) and extensive (+++).

### Statistical analysis

The semi-quantitative data of histopathological assessments was carried out by using the Kruskal-Wallis test, a non-parametric test, was used for analysis of differences between the groups while the Mann Whitney U test was used for pairwise comparisons of the groups. SPSS 13.0 software was used for statistical analyses.

## RESULTS AND DISCUSSION

### Clinical findings

#### Conservative group

On the 14<sup>th</sup> post-operative day, 4 rats had relatively good and significant healing while 3 rats had more oedema and preserved their fracture formation.

#### Bandage group

The bandages were opened on the 3<sup>rd</sup> post-operative day. Two rats manifested a necrotic appearance and bandages fell off spontaneously while the penile tissues of two rats appeared to be well. The penile tissues of three rats had oedema in the bandaged cases when the bandages were opened. Both rats with necrotic penile tissue died on the 5<sup>th</sup> day of the post-operative period. On the 14<sup>th</sup> day of the post-operative period, 2 of 5 cases had excessive infection and a purulent appearance, 2 had a partially infected appearance and 1 looked well.

#### Primary repair group

On the 14<sup>th</sup> day of the post-operative period, visible infection

symptoms and oedema were not encountered in any of the 5 surviving cases while slight infection and oedema were encountered in 2 cases. Findings of wound parameters in early days except bandage group were at normal appearance.

### Primary repair + PRP group

On the 14<sup>th</sup> day of the post-operative period, visible infection symptoms and oedema were not encountered in any of the 7 surviving cases (Fig 1).

### Non-operative control group

Operative processes were not applied to the rats in this group.

### Histopathological findings

#### Conservative group

In the histopathological analyses of the penile tissues, prevalent fibrosis was encountered in the corpus cavernosum layer and resultant depressions in cavernous tissues, moderate oedema and mononuclear cell infiltration were encountered in cavernous tissues and prevalent hyperemia was diagnosed in vessels (Fig 2, 3).

#### Bandage group

The histopathological analyses of the penile tissues of this rat group revealed prevalent fibrosis and polymorph cell infiltrations composed especially of neutrophil leukocytes which were encountered in the corpus cavernosum layer while prevalent dilatation and hyperemia were encountered in vessels (Fig 4).

#### Primary repair group

In the histopathological analyses of the penile tissues of this rat group, moderate fibrosis was encountered in the corpus cavernosum layer, a moderate level of hyperemia was encountered in vessels, prevalent oedema and slight mononuclear cell infiltration were encountered between the corpus cavernosum and tunica albuginea layers (Fig 5, 6).

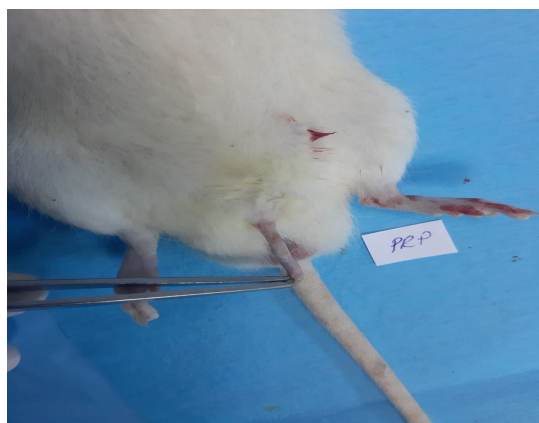
#### Primary repair + PRP group

The histopathological analyses of the penile tissues of this rat group indicated slight oedema between the corpus cavernosum and tunica albuginea layers; slight fibrosis, mature collagen tissue and slight mononuclear cell infiltration were encountered in the corpus cavernosum layer and slight hyperemia was encountered in the vessels (Fig 7, 8). Compared to the conservative group, the differences were not found to be significant ( $p < 0.05$ ).

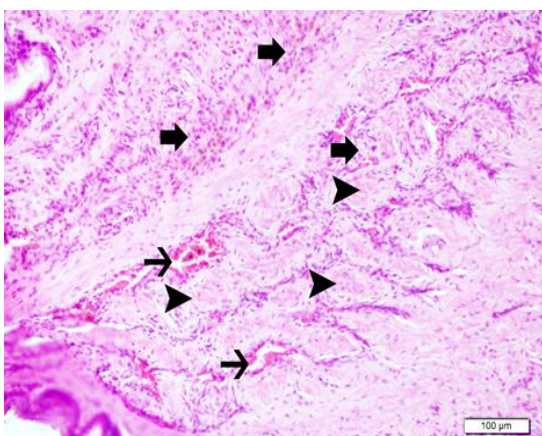
### Non-operative control group

The histopathological analysis of the penile tissues of this group had a normal appearance (Fig 9,10).

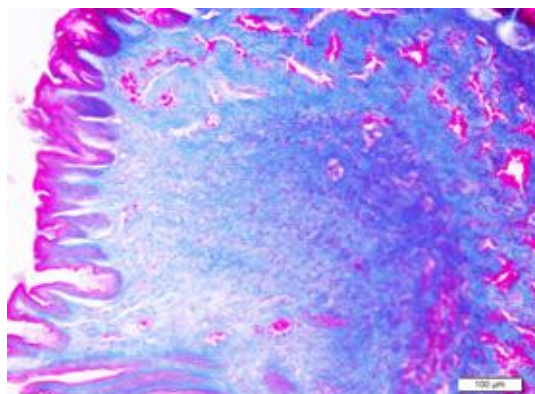
Penile fracture is a traumatic rupture in the corpus cavernosum layer. The tunica albuginea layer has quite a high tensile strength, but it is torn at pressures above 1500 mm Hg (De Rose *et al.* 2001). Among the current treatment



**Fig 1:** The 14<sup>th</sup> day clinical manifestation of Primary repair + PRP group.

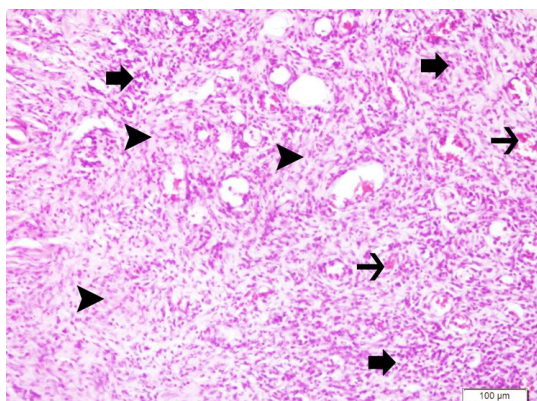


**Fig 2:** Penile tissue, conservative group, severe fibrosis in the corpus cavernosum layer (arrow heads), hyperemia in vessels (thin arrows), mononuclear cell infiltration (bold arrows), H&E, Bar: 100 µm.

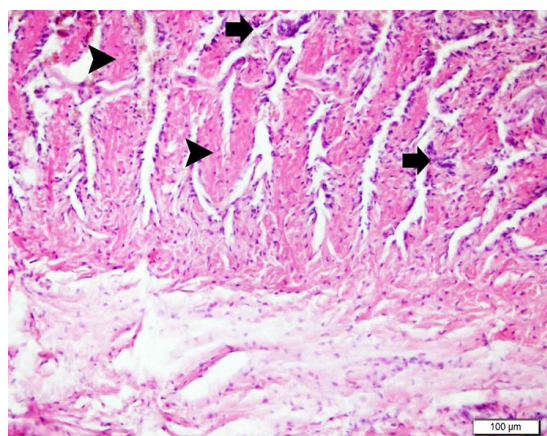


**Fig 3:** Penile tissue, conservative group, severe fibrosis in the corpus cavernosum layer, Masson trichrome, Bar: 100 µm.

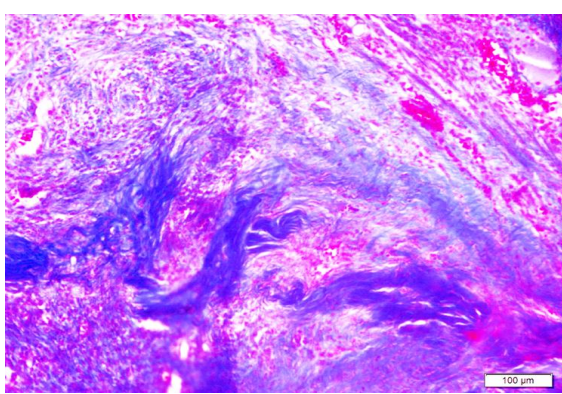
options for penile fracture cases, surgery is accepted as the most efficient method of treatment with minimum complications (Ishikawa *et al.* 2003). The objective of emergency surgical repair is to preserve the integrity of the tunica albuginea, essential for erection and prevent penile curvature, penile deformity, fibrosis and sexual dysfunction-like complications incurred by the conservative method.



**Fig 4:** Penile tissue, Bandage group, severe fibrosis in the corpus cavernosum layer (arrow heads), hyperemia in vessels (thin arrows), mononuclear cell infiltration (bold arrows), H&E, Bar: 100 µm.

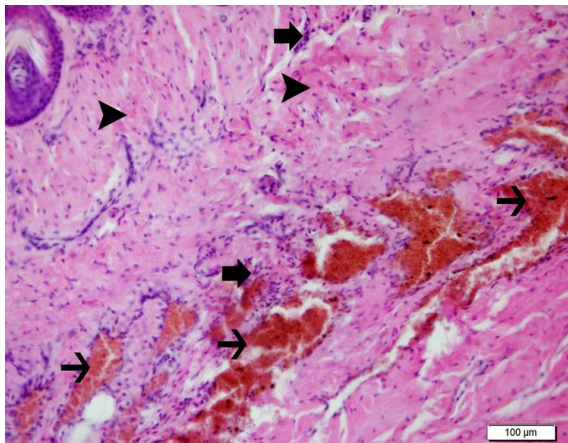


**Fig 5:** Penile tissue, Primary repair group, moderate fibrosis in the corpus cavernosum layer (arrow heads), hyperemia in vessels (thin arrows), mononuclear cell infiltration (bold arrows), H&E, Bar: 100 µm.

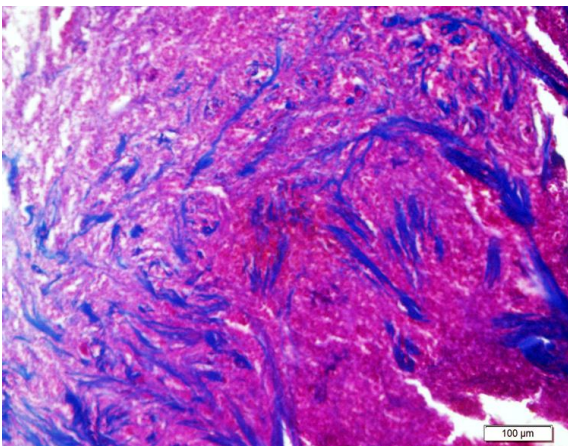


**Fig 6:** Penile tissue, Primary repair group, moderate fibrosis in the corpus cavernosum layer, Masson trichrome, Bar: 100 µm.

Wound healing process is induced by a series of peptides, also known as cytokines or growth factors and some cells. Following an injury, growth factors secreted from platelets and macrophages initiate inflammation and the healing process (Frykberg *et al.* 2010; Reese, 2010; Theoret, 2005). Growth factors also regulate the transcription of extracellular matrix proteins, namely fibronectin, collagen



**Fig 7:** Penile tissue, PRP group, slight fibrosis in the corpus cavernosum layer (arrow heads), hyperemia in vessels (thin arrows), mononuclear cell infiltration (bold arrows), H&E, Bar: 100 µm.

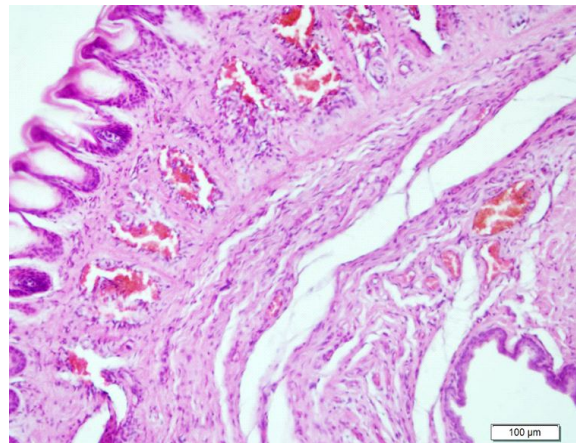


**Fig 8:** Penile tissue, PRP group, slight fibrosis in the corpus cavernosum layer, Masson trichrome, Bar: 100 µm.

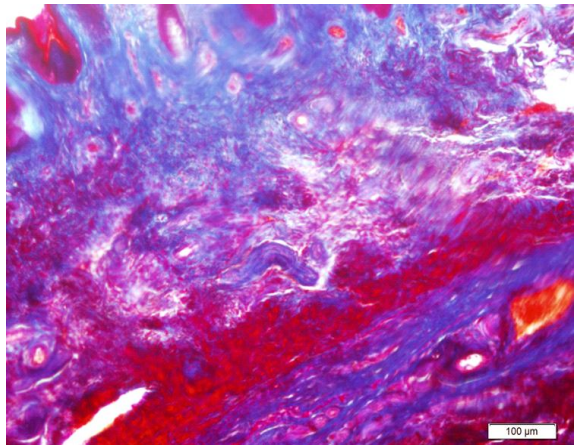
and glycosaminoglycans, organize wound healing-related cellular processes, attract the cells to the wound, stimulate their proliferation and provide significant contributions to extracellular matrix deposition (Theoret, 2005; Declare, 1999; Nishimoto *et al.* 2007).

The objective of the present study was to investigate if the topical application of homologous Platelet-Rich Plasma on the rupture area had positive impacts on wound healing in the emergency surgical repair of penile ruptures. As can be seen in Table 1, histopathological analyses revealed moderate (++) and prevalent (+++) oedema between the layers in the conservative group, bandage group and primary repair group, but slight (+) oedema in the primary repair + PRP group, which can be assessed as a positive effect of PRP on healing (Fig 2,4,7).

The histopathological analysis revealed that while prevalent hyperemia was encountered in vessels in the conservative group, bandage group and primary repair groups, a moderate level of hyperemia was encountered in the primary repair + PRP group which can also be assessed as a positive effect of PRP on healing (Fig 2,4,7).



**Fig 9:** Penile tissue, Non-operative group, corpus cavernosum, normal appearance H&E, Bar: 100 µm.



**Fig 10:** Penile tissue, Non-operative group, corpus cavernosum layer with normal histological appearance, Masson trichrome, Bar: 50 µm.

In a retrospective study, Gedik *et al.* (2011) applied surgical repair to 101 patients and did not encounter post-operative complications in any one of them, but reported penile curvature formation in 6 patients to whom conservative treatment was applied. Similarly, in this study, persistence of the fracture in addition to oedema and infection symptoms was observed in two cases in the conservative group for which no treatment was applied. Furthermore, all the rats in the second group in which bandages were applied, manifested excessive oedema and infection and penile necrosis was encountered in two rats. On the other hand, no serious postoperative complications were encountered in the third and fourth groups in which surgical repair was performed.

Right after acute injuries, platelets in the blood rush to the wound area to provide hemostasis instantly on the one hand by releasing cytokines and messenger molecules, so called growth factors and being responsible for the initiation of inflammation and wound healing on the other hand (Carter *et al.* 2003; Anitua *et al.* 2004). PDGF is one of the most important molecules of healing. Fibroblasts in the wound

**Table 1:** Scoring of histopathological findings observed in penile tissue (14<sup>th</sup> day).

	Conservative group	Bandage group	Primary repair group	Primary repair + PRP group	Non-operative group
Edema between the layers	++	++	+++	+	-
Hyperemia in vessels	+++	+++	+++	++	-
Fibrosis in corpus cavernosum	+++	+++	++	+	-
Inflammation	+++	+++	++	++	-

section, stimulated by PDGF and the other growth factors, produce and propagate extracellular matrix, an important component of granulation tissue (Sardari *et al.* 2011). Histopathological analyses of the cases in the present Primary repair + PRP group revealed that when compared to conservative group, slight fibrosis and mature collagen tissue were encountered in the corpus cavernosum layer and it was remarkable that such differences were not found to be significant ( $p < 0.05$ ).

Histopathological analyses of the penile tissues of the rats in the bandage group and conservative group revealed severe granulation tissue and severe fibrosis in the corpus cavernosum layer, resultant constriction in cavernous tissues, polymorph cell infiltration mostly composed of neutrophil leukocytes, severe dilatation and hyperemia in vessels (Fig 2, 3, 4), on the other hand, similar outcomes in the primary repair group (Fig 5, 6) were at moderate levels and the Primary repair + PRP group (Fig 7, 8) displayed slight levels. All these findings put forth the efficiency of PRP in healing.

Several clinical studies have reported that PRP has sufficient efficiency in stimulating healing in persistent wounds. It has also been reported in both chronic and acute injury studies that full wound closure is achieved in a shorter time with PRP treatments, PRP reduced infection rates as well as pain and constituted an alternative of advanced wound treatment in diabetic foot-like chronic and persistent wounds (Carter *et al.* 2011; Eryilmaz *et al.* 2020; Martinez-Zapata *et al.* 2009; Villela and Santos, 2010A; Villela and Santos, 2010B; Donohue and Falanga, 2003; Dougherty, 2008; Krull, 1985). In the histopathological analysis of penile tissues of the cases in the primary repair group in the present study, severe oedema, hyperemia and mononuclear cell infiltration were encountered between the corpus cavernosum and tunica albuginea layers while slight oedema, slight fibrosis and mature collagen tissue were encountered in the primary repair + PRP group (Fig 7). Such findings comply with the findings of previous researchers asserting that PRP both reduced wound infection rates and had positive effects on wound healing.

In addition to autologous PRP, although the use of homologous and heterologous PRP brings along some disadvantages especially in terms of antigenicity, successful outcomes have recently been reported in the use of homologous and heterologous PRP in diabetic wounds in the lower extremities of diabetic individuals, in the cornea and skin lesions of rabbits (Chung *et al.* 2015; Abegao *et al.* 2015; Shan *et al.* 2013; Kaffashi *et al.* 2012). In the present study, Allogenic-homologous PRP obtained from the blood

of a single rat was used. Similarly to the findings of Chung *et al.* (2015); Abegao *et al.* (2015); Shan *et al.* (2013); Kaffashi *et al.* (2012); Rezende *et al.* (2011); Gemignani *et al.* (2017); Chung *et al.* (2015); Shan *et al.* (2013); Márcia Uchôa de Rezende *et al.* (2011); Gemignani *et al.* (2017) an allergic reaction was not encountered in the operational wounds of rats treated with Primary repair + PRP.

## CONCLUSION

The effect of PRP treatments on the surgical repair options for rats with penile fractures were examined in the current study. The present findings reveal that following repair with conservative treatments, fracture format persisted and various complications like infection, oedema, excessive fibrosis and hyperemia were encountered. On the other hand, in terms of clinical manifestation and histopathological findings, the best healing was achieved in the primary repair + PRP group.

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