

# Evaluation of the results of platelet-rich plasma (PRP) treatment in the treatment of complex perianal fistula: a prospective study

*Evaluación de los resultados del tratamiento con plasma rico en plaquetas (PRP) en el tratamiento de la fistula perianal compleja: un estudio prospectivo*

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## Abstract

**Background:** Platelet-rich plasma (PRP) has therapeutic effects in accelerating the healing of soft tissue injuries. Due to the side effects of the existing treatment methods in the management of complex anal fistula and the limited research in the field of alternative therapies using new technologies, the present study was conducted to investigate the application of autologous PRP in the treatment of anal fistula.

**Methods:** In this descriptive-prospective study, patients with complex anal fistula were studied. After excision of external orifice and curettage of the tract, PRP was injected into the tract and finally the inside of the tract was filled with PRP material. After surgery, patients underwent 1-week, 1-month, 6-month and 1-year follow-ups to evaluate their recovery status. Outcomes of this study included success rate, recovery time, satisfaction, return to work, readmission, and recurrence.

**Results:** Overall, the results of the study showed that the success rate of PRP treatment in patients with complex anal fistula is 66.7%. In 16.7% of patients, the result was "continuous external discharge" and in 16.7% of patients the result was "abscess formation after healing". Recovery time was 24.29 (8.69) days. Rate of return to work, satisfaction, readmission was 79.2%, 79.2% and 16.37%, respectively. Also, the recurrence rates in the first month, sixth month and first year were 16.37%, 10% and 11.1%, respectively.

**Conclusion:** The present study suggests that PRP treatment is associated with high success rate in the treatment of anal fistula.

**Key words:** Anal fistula, platelet-rich plasma.

## Resumen

**Antecedentes:** El plasma rico en plaquetas (PRP) tiene efectos terapéuticos en la aceleración de la curación de las lesiones de tejidos blandos. Debido a los efectos secundarios de los métodos de tratamiento existentes en el manejo de la fístula anal compleja y a la limitada investigación en el campo de las terapias alternativas con nuevas tecnologías, el presente estudio se realizó para investigar la aplicación del PRP autólogo en el tratamiento de la fístula anal.

**Métodos:** En este estudio descriptivo-prospectivo se estudiaron pacientes con fístula anal compleja. Tras la escisión del orificio externo y el legrado del tracto, se inyectó PRP en el tracto y finalmente se rellenó el interior del tracto con material de PRP. Después de la cirugía, los pacientes se sometieron a seguimientos de 1 semana, 1 mes, 6 meses y 1 año para evaluar su estado de recuperación. Los resultados de este estudio incluyeron la tasa de éxito, el tiempo de recuperación, la satisfacción, la vuelta al trabajo, el reingreso y la recidiva.

**Resultados:** En general, los resultados del estudio mostraron que la tasa de éxito del tratamiento con PRP en pacientes con fístula anal compleja es del 66,7%. En el 16,7% de los pacientes, el resultado fue "secreción externa continua" y en el 16,7% de los pacientes el resultado fue "formación de abscesos después de la curación". El tiempo de recuperación fue de 24,29 (8,69) días. La tasa de retorno al trabajo, satisfacción y readmisión fue del 79,2%, 79,2% y 16,37%, respectivamente. Asimismo, las tasas de recidiva en el primer mes, el sexto mes y el primer año fueron del 16,37%, el 10% y el 11,1%, respectivamente.

**Conclusión:** El presente estudio sugiere que el tratamiento con PRP se asocia con una alta tasa de éxito en el tratamiento de la fístula anal.

**Palabras clave:** Fístula anal; Plasma rico en plaquetas.

## Introduction

Anal sepsis is one of the most common benign anorectal diseases managed by surgeons. Of all patients who present with perianal abscess, up to 65% will develop a chronic or recurrent anal fistula. Operative intervention remains the only effective modality to treat this condition. Although the principal goal of treatment is to eradicate the fistula, it is also important to preserve anal continence, minimize postoperative complications, and decrease risk of recurrence.

Surgical therapy is the main method used to treat anal fistula. The best treatment criterion is to eradicate the infected lesion, ensure sufficient drainage, and promote the closure of the fistula, while minimizing damage to the anal sphincter. The integrity of the internal anal sphincter (IAS) and external anal sphincter (EAS) is the most important guarantee for keeping normal anal function of patients<sup>1,2</sup>.

Anal fistula refers to a duct between the perianal skin and the anorectal canal, a common surgical problem usually occurring after the treatment of perianal abscesses. Continuous discharge of pus, pain, itching, as well as contamination of underwear are among its significant characteristics<sup>1,2</sup>. Fistula treatment options include fistulotomy, fistulectomy (with or without sphincteroplasty surgery), endorectal advancement flap, anocutaneous advancement flap, fistula plug, fibrin glue injection, Fistula-tract Laser Closure (FiLaC) and (LIFT)<sup>3,4</sup>. One of new treatment options in this field is blood-derivatives-based methods. One of the significant blood derivatives of this bioactive substance is Platelet-Rich Plasma (PRP), with more than 20 growth factors and other protein molecules such as binding molecules and chemokines involved in processes like proliferation, differentiation, as well as cell regeneration<sup>5</sup>. The PRP potentials such as its therapeutic ability depend on the amount of growth factors it has. With the addition of certain activating agents like thrombin and calcium chloride that induce and stimulate the growth factors release from granules Alpha's in PRP, the platelets collected in PRP start secreting growth factors<sup>1</sup>. Platelets existing in PRP enhance the level of growth factors in the environment by secreting these factors in this environment<sup>6</sup>. Growth factors perform as a mitogen cell division stimulant in cells like endothelial cells and fibroblast cells, initiating the angiogenesis processes, as well as differentiation and proliferation of fibroblasts. Moreover, growth factors regulate collagen synthesis besides promoting cell proliferation as well as cell differentiation processes<sup>7</sup>. More than 95% of the synthesized growth factors are released in an explosive process during the first hours after activation. Given the impacts of platelet-enriched plasma on acceleration of healing the soft tissue injuries in addition to its autologous nature (prepared from the patient's own blood), the treatment cost is reduced,

and it is time-effective for the surgeon and the patient<sup>8</sup>. Hence, given the complications of therapeutic methods for anal fistula beside the limited research on alternative therapies through new technologies, the current study was performed to investigate the use of autologous PRP in the anal fistula treatment.

## Materials and Methods

### Patient Population

This was a descriptive-prospective study performed on patients with complex anal fistula referring to Shahid Beheshti University of Medical Sciences from 2019 to 2020.

Inclusion criteria were age between 18 and 80 years and diagnosis of high trans sphincteric fistula.

Exclusion criteria were patients with ASA score 4, inflammatory bowel disease, fistula with multiple tracts or active perianal sepsis, lower and middle intrasphincteric fistula, as well as pregnant and lactating patients.

This study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran and registered with the protocol number "IR.SBMU.MSP.REC.1398.566".

After obtaining the patient's consent, preparation of PRP was the first step. In autologous PRP preparation, 30 cc of patient's whole blood was sampled on the day of treatment. Blood coagulation and secretion of platelet granules were controlled by addition of an anticoagulant like dextrose citrate. The whole blood sample was centrifuged (850G) at a constant speed to form three different layers by means of a two-stage centrifuge or by double spin method. The lower layer contained red blood cells; the middle layer has white blood cells, while the upper layer contains plasma-soluble platelets. In the second round of the centrifuge (1200G), the upper and middle layers were then removed and centrifuged. The obtained solution contained pellet platelets. Moreover, the pellet was re-dissolved in plasma in order to reach a volume of 12 cc, with its final volume depended on the volume needed for treatment.

Prior to the operation, the patient was recommended to use four Bisacodyl suppositories the day before surgery. After spinal anesthesia and in lithotomy position anoscopy was performed by colorectal surgeon. After accurate determination of the internal orifice, main tract and the external orifice, the external orifice and a part of the tract at the ischioanal fossa was excised, followed by the curettage of the trans sphincteric tract. The internal orifice was closed by Vicryl suture 2/0. Subsequently, PRP was injected into the tract; and finally the tract was filled with PRP material.

### Outcomes

A questionnaire including age, sex, type of fistula, and treatment methods was data collection tool.

Patients underwent follow-ups of 1 week, 1 month, 6 months, and 1 year after surgery in order to assess their recovery status. The studied outcomes in this review included intensity of pain (based on VAS), success rate, recovery time (days), satisfaction of patient with treatment, return to work, readmission, and recurrence.

### Statistical Analysis

All registered data were analyzed using SPSS software version 20 for Windows (SPSS, Chicago, IL). For descriptive statistics, the Mean ± SD index was used for quantitative variables with normal distribution.

### Sampling

The census method was used as the sampling method and all patients with perianal fistula with an age range of 18-80 years referring to hospitals affiliated to Shahid Beheshti University of Medical Sciences over the years 2019-2020 were investigated considering the exclusion criteria.

### Result

In total, 24 patients with perianal fistula were included in the study and treated with PRP. Among these, (66.7%) 16 patients were male and (33.3%) 8 patients were female. The mean age of the patients was 41.66±11.99

years with a minimum age of 22 and a maximum age of 60 years.

The results of the study on the Mean pain severity one week after surgery, postoperative recovery time (days) are shown in **table I**.

The results of the study on the frequency distribution of response to treatment, return to work, patient satisfaction with treatment, postoperative readmission, recurrence in the first month, sixth month and first year are shown in **table II**.

### Discussion

Several; developments have been occurred in medical sciences, particularly in the management of diseases<sup>9-16</sup>. Fistula surgery remains a matter for colorectal surgeons and an exhausting process for patients with impaired quality of life. Simple fistula is treated usually by fistulotomy, that provides healing for about 90% of patients with low risk of incontinence. The main problem lies in the treatment of complex perianal fistula, as fistulotomy represents an unacceptable risk of incontinence in these patients.

Platelet α-granules contain mitogenic and chemotactic growth factors (GF) and associated healing molecules in an inactive form, important in wound healing, such as platelet-

**Table I:** Mean pain severity one week after surgery & postoperative recovery time in patients.

Variables	Minimum	Maximum	Mean	Standard deviation
Pain severity one week after surgery	2	8	4.7	1.58
Postoperative recovery time(days)	10	40	24.29	8.69

**Table II:** frequency distribution of response to treatment, return to work, patient satisfaction with treatment, postoperative readmission, recurrence in the first month, sixth month and first year.

Variables	Frequency	Percent
<b>Response to treatment</b>		
Improved without abscess formation	16	66.7%
Continuous external discharge	4	16.7%
Abscess formation after healing	4	16.7%
<b>Return to work</b>		
have no	5	20.8%
have	19	79.2%
<b>Patient satisfaction</b>		
have no	5	20.8%
have	19	79.2%
<b>Postoperative readmission</b>		
have	4	16.3%
have no	20	83.3%
<b>Recurrence in the first month</b>		
have	4	16.3%
have no	20	83.3%
<b>Recurrence in the sixth month</b>		
have	2	10%
have no	18	90%
<b>Recurrence in the first year</b>		
have	2	11.1%
have no	16	88.9%

derived growth factor (PDGF), transforming growth factors  $\beta 1$ ,  $\beta 2$ ,  $\beta 3$ , platelet-derived angiogenesis factor, insulin-like growth factor 1, platelet factor 4 (PF-4), epidermal growth factor, epithelial cell growth factor, vascular endothelial cell growth factor (VEGF), basic fibroblast growth factor and others cytokines. During normal wound healing, trapped platelets become activated and degranulate, resulting in releasing of  $\alpha$ -granule content. The secreted growth factors immediately bind to the external surface of cell membranes in the wound via transmembrane receptors in mesenchymal stem cells, osteoblasts, fibroblasts, endothelial cells, and epidermal cells.

This work aimed to evaluate the effect of the use PRP in when it is used as adjunct in the treatment of high perianal fistula.

In 2019, a randomized, double-blind clinical trial was performed by de la Portilla et al. in order to compare the clinical implications of using autologous PRP vs. fibrin glue in treating cryptoglandular anal fistula. Patients were clinically and endoscopically assessed at 1 week, and 3, 6, and 12 months after operation. The main outcome of this study included the rate of fistula recovery (complete, partial, and no improvement) while the secondary outcomes were fistula recurrence, fecal status, quality of life (QoL), and pain. Out of 56 patients enrolled in the present study, 32 were assigned to the PRP group and 24 to the fibrin glue group. The results revealed the overall improvement rate of 71% in the PRP group and 58.3% in the fibrin glue group. In the PRP group, the complete and partial recovery rates were 48.4% and 22.6%, and they were 41.7% and 16.7% in the fibrin glue group. The rate of pain and thus the QoL in the PRP group was significantly better. All complications were minor and no adverse effects were seen in the fecal status<sup>17</sup>. In 2021, Madbouly et al. performed a prospective trial examining the effect of PRP on the treatment of transsphincteric fistula. In the present study, patients with a transsphincteric fistula that involved more than 50% of their anal sphincter were included. They were randomly assigned to two groups of Ligation of Intersphincteric fistula tract (LIFT) with and without PRP. Each group included 49 patients. The complete closure of the fistula and the time needed for recovery were the main outcomes of this study. Forty-two patients in the PRP group and 32 patients in the group without PRP showed complete recovery of fistula, with a significant difference between the two groups. In the PRP group, the mean postoperative recovery time was significantly shorter (15.7 days) compared to that in the group without PRP (21.6 days). Four patients in the

PRP group and three in the group without PRP exhibited one-year recurrence. In the PRP group and on days 1 and 7 after surgery, pain was better, like QoL rate one month after surgery<sup>18</sup>. Moreno-Serrano et al. (2016) investigated the effect of PRP on the recovery of complex anal fistulas. This study was performed from 2011 to 2013. Its outcomes included fistula recovery, treatment complications, as well as QoL. Twenty-three patients (12 men and 11 women) were included in the present study and followed up for at least 12 months, two of whom were excluded from the study. Seventeen out of the remaining 21 patients had low fistulas. In this research, the success rate of treatment was 62%. No patient experienced incontinence after treatment. The QoL improved in all patients except two of them<sup>19</sup>. In 2019, a study was performed by Orban et al. in order to assess the impact of PRP on the treatment of high anal fistula. Their prospective study was conducted on patients with fistula from 2016 to 2019, in which nine males and seven females were included. The success rate was 75%, i.e. twelve patients completely recovered with no recurrence while two patients developed postoperative abscess and two patients experienced continuous discharge from the surgery site<sup>20</sup>.

In our study, we used autologous platelet rich plasma as adjunct in the treatment of high perianal fistula and obtained cure rates of 66/7%. As regard incontinence, our study we had no case develop fecal incontinence.

## Conclusion

Overall, the results of the present study showed that the use of PRP is associated with high success in the treatment of high perianal fistula; without affection of fecal continence. Therefore, the use of this treatment is recommended in the treatment of anal fistula.

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## Conflict of Interest

The authors declare that there is no conflict of interest in the publication of this paper.

## References

1. Buchanan GN, Bartram CI, Phillips RK, Gould SW, Halligan S, Rockall TA, et al. Efficacy of fibrin sealant in the management of complex anal fistula: a prospective trial. *Diseases of the colon and rectum*. 2003;46(9):1167-74.
2. Steele SR, Kumar R, Feingold DL, Rafferty JL, Buie WD. Practice parameters for the management of perianal abscess and fistula-in-ano. *Diseases of the colon and rectum*. 2011;54(12):1465-74.
3. Ritchie RD, Sackier JM, Hodde JP. Incontinence rates after cutting seton treatment for anal fistula. *Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland*. 2009;11(6):564-71.
4. Tozer P, Sala S, Cianci V, Kalmar K, Atkin GK, Rahbour G, et al. Fistulotomy in the tertiary setting can achieve high rates of fistula cure with an acceptable risk of deterioration in continence. *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract*. 2013;17(11):1960-5.
5. van Onkelen RS, Gosselink MP, Schouten WR. Is it possible to improve the outcome of transanal advancement flap repair for high transsphincteric fistulas by additional ligation of the intersphincteric fistula tract? *Diseases of the colon and rectum*. 2012;55(2):163-6.
6. Dhurat R, Sukesh M. Principles and Methods of Preparation of Platelet-Rich Plasma: A Review and Author's Perspective. *Journal of cutaneous and aesthetic surgery*. 2014;7(4):189-97.
7. Sunitha Raja V, Munirathnam Naidu E. Platelet-rich fibrin: evolution of a second-generation platelet concentrate. *Indian journal of dental research: official publication of Indian Society for Dental Research*. 2008;19(1):42-6.
8. Lara FJ, Serrano AM, Moreno JU, Carmona JH, Marquez MF, Pérez LR, et al. Platelet-rich fibrin sealant as a treatment for complex perianal fistulas: a multicentre study. *J Gastrointest Surg*. 2015;19(2):360-8.
9. Dehkordi FS, Saberian S, Momtaz H. Detection and segregation of *Brucella abortus* and *Brucella melitensis* in Aborted Bovine, Ovine, Caprine, Buffaloes and Camelid Fetuses by application of conventional and real-time polymerase chain reaction. *The Thai Journal of Veterinary Medicine*. 2012 Mar 1;42(1):13.
10. Sheikhshahrokh A, Ranjbar R, Saeidi E, Dehkordi FS, Heiat M, Ghasemi-Dehkordi P, Goodarzi H. Frontier therapeutics and vaccine strategies for sars-cov-2 (COVID-19): A review. *Iranian Journal of Public Health*. 2020 Jul 11.
11. Ranjbar R, Seif A, Dehkordi FS. Prevalence of antibiotic resistance and distribution of virulence factors in the shiga toxigenic *Escherichia coli* recovered from hospital food. *Jundishapur Journal of Microbiology*. 2019;12(5):8.
12. Nejat S, Momtaz H, Yadegari M, Nejat S, Safarpour Dehkordi F, Khamesipour F. Seasonal, geographical, age and breed distributions of equine viral arteritis in Iran. *Kafkas Univ Vet Fak Derg*. 2015 Jan 1;21(1):111-6.
13. Rahimi E, Yazdanpour S, Dehkordi FS. Detection of *Toxoplasma gondii* antibodies in various poultry meat samples using enzyme linked immuno sorbent assay and its confirmation by polymerase chain reaction. *J Pure Appl Microbiol*. 2014;8(1):421-7.
14. Dehkordi FS. Prevalence study of Bovine viral diarrhea virus by evaluation of antigen capture ELISA and RT-PCR assay in Bovine, Ovine, Caprine, Buffalo and Camel aborted fetuses in Iran. *AMB express*. 2011 Dec;1(1):1-6.
15. Dehkordi FS, Haghighi N, Momtaz H, Rafsanjani MS, Momeni M. Conventional vs real-time PCR for detection of bovine herpes virus type 1 in aborted bovine, buffalo and camel foetuses. *Bulgarian Journal of Veterinary Medicine*. 2013 Jun 1;16(2).
16. Ranjbar R, Farsani FY, Dehkordi FS. Phenotypic analysis of antibiotic resistance and genotypic study of the *vacA*, *cagA*, *iceA*, *oipA* and *babA* genotypes of the *Helicobacter pylori* strains isolated from raw milk. *Antimicrobial Resistance & Infection Control*. 2018 Dec;7(1):1-4.
17. de la Portilla F, Muñoz-Cruzado MVD, Maestre MV, García-Cabrera AM, Reyes ML, Vázquez-Monchul JM, et al. Platelet-rich plasma (PRP) versus fibrin glue in cryptogenic fistula-in-ano: a phase III single-center, randomized, double-blind trial. *International journal of colorectal disease*. 2019;34(6):1113-9.
18. Madbouly KM, Emile SH, Issa YA, Omar W. Ligation of intersphincteric fistula tract (LIFT) with or without injection of platelet-rich plasma (PRP) in management of high trans-sphincteric fistula-in-ano: Short-term outcomes of a prospective, randomized trial. *Surgery*. 2021;170(1):61-6.
19. Moreno-Serrano A, García-Díaz JJ, Ferrer-Márquez M, Alarcón-Rodríguez R, Álvarez-García A, Reina-Duarte Á. Using autologous platelet-rich plasma for the treatment of complex fistulas. *Revista española de enfermedades digestivas : organo oficial de la Sociedad Espanola de Patología Digestiva*. 2016;108(3):123-8.
20. Yasser A, Orban, Goda A. Effectiveness of autologous platelet rich plasma in the treatment of high perianal fistula. *Int J of Adv Res*. 2019; 7: 59-64.