

Assessment of recurrent anal fistulas treatment with platelet-rich plasma

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ABSTRACT – Background – Surgical treatment of recurrent anal fistulas can lead to numerous complications, including fecal incontinence. Therefore, sphincter preserving techniques are gaining more popularity. **Objective** – The aim of the study was to assess effectiveness of platelet-rich plasma (PRP) therapy in the patients with recurrent cryptoglandular anal fistulas. **Methods** – A cohort of 18 patients with anal fistulas was enrolled into a preliminary and prospective trial. They were divided into two groups consisting of eight and ten patients respectively. PRP was injected locally in all patients, however in the group II it was applied after 7 days drainage of fistulas with polyurethane foam or negative pressure wound therapy. On average, three doses of PRP were administered, but with the opportunity to double the number of applications if it was clinically justified. The patients were evaluated in an out-patient department after fortnight and then in 1, 6, and 12 months following the last PRP application. **Results** – Anal fistulas were closed in 4 (50%) patients from the group I and in 7 (70%) patients from the group II. Although, the difference between both groups was not statistically significant, PRP therapy should be preceded with fistulous tract drainage in all patients. Summarizing, that successful result was achieved in 11 (60%) patients from the entire group of 18 participants. **Conclusion** – The rate of recurrent cryptoglandular anal fistulas closure reaching 60%, after topical treatment with PRP, exceeds the results of other sphincter-saving methods of treatment. Therefore, it might become a novel method of anal fistulas therapy.

Keywords – Platelet-rich plasma; anal fistula; polyurethane foam.

INTRODUCTION

Anal fistulas treatment still poses a challenge to the surgeons due to a high rate of recurrences exceeding 50% regardless of the surgical method^(1,2). What is more, multiple operations may result in damage to the anal sphincters due to inflammation and fibrosis of the tissues surrounding the anal canal in the form of so called “woody anus” with subsequent fecal incontinence, exceeding 60%^(3,4). Therefore, traditional surgery in those patients should be replaced with more conservative methods⁽⁵⁾. There are sphincter preserving techniques which have been recently introduced such as ligation of intersphincteric fistula tract (LIFT), video-assisted anal fistula treatment (VAAFT), over the scope clip (OTSC®), or even less invasive e.g. fibrins and plugs, however with higher risk of recurrences⁽⁶⁻⁹⁾.

Local application of platelet-rich plasma (PRP), or platelet rich fibrin (PRF), might have become alternatives to aforementioned methods. The ability of enriched plasma to provide the soft tissues in vicinity of fistulous tracts with high concentration of platelet-derived growth factors with following acceleration of fistulas healing have been mentioned in few experimental reports, including application in complex and Crohn’s anal fistulas⁽¹⁰⁻¹²⁾. Several technical aspects e.g. enriched plasma acquisition, volume of solution, number of applications remain to be determined. The aim of the study was to assess the local application of PRP in recurrent crypto-glandular anal fistulas.

METHODS

The study designed as a preliminary, prospective and a randomized trial to evaluate effectiveness of topical PRP was carried out from 2017 to 2019 at the Department of General, Endocrinological Surgery and Gastroenterological Oncology, Poznan University of Medical Sciences. The study group included 18 patients diagnosed with recurrent cryptoglandular anal fistula after at least one cutting procedure and with one or at most two active channels.

All investigated patients underwent digital rectal examination and probing under anesthesia supplemented by transrectal ultrasound (TRUS). Additional magnetic resonance imaging (MRI) was performed to diagnose the fistulas with more than one orifice for whom physical examination was not adequate. A total of nine patients required this assessment, three patients with transsphincteric fistulas from the group I, four patients from the second group and both patients with suprasphincteric fistulas. Patients with non crypto-glandular fistulas e.g. Crohn’s, post-radiation, cancerous anal fistulas or fistulas to other pelvic organs were excluded from this study.

The procedure was preceded by enema the evening before. Next, curettage of fistulous tracts to remove the epithelium and infected granulation tissue was routinely performed. The patients were then divided into two groups. In the first group, consisted of eight patients, PRP was administered topically just immediately after fistulous tracts debridement whereas in 10 individuals from

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the group II, application of the plasma was followed after 7 days of fistulas continuous drainage. For this purpose a polyurethane foam (Wound Pad, Schulke, Germany) or vacuum dressing was inserted into the fistula tract (FIGURE 1). The negative pressure wound therapy (NPWT) was indicated for fistulas with a diameter greater than 10 mm with concurrent abundant discharge, and it took the form of a nasogastric catheter wrapped with a polyurethane foam (Vivano, Hartmann, Germany), and inserted into a fistula through the external opening (FIGURE 2). As far as the dressing was considered, it was necessary to change the foam soaked with pus every second day in most cases, whereas negative pressure drainage was changed twice a week. Throughout the treatment, a stable negative pressure of 40–60 mm Hg was maintained. Antibiotic prophylaxis was not routinely used either before curettage or injection of PRP. Although, both NPWT and PRP are approved for medical therapy, the novelty was the use of PRP for the treatment of anal fistulas. Therefore, the study protocol was approved by the Ethics Committee of the author's institution. Statistical analysis of all data obtained throughout the study was processed with the Statistica (Statsoft version 6.0). for Windows software.

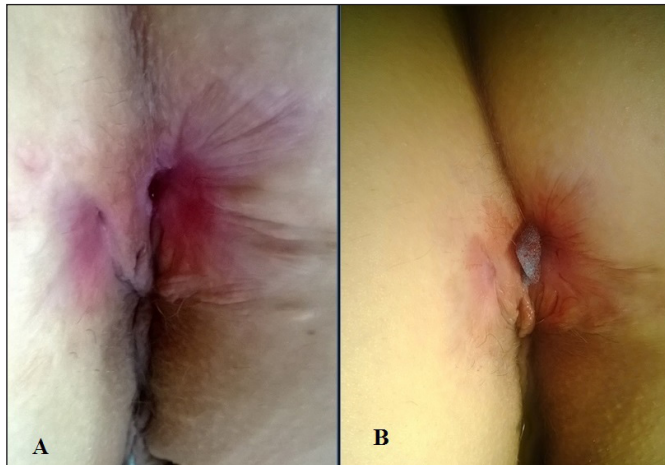


FIGURE 1. Anal fistula (A) with the tract filled with polyurethane foam (B).

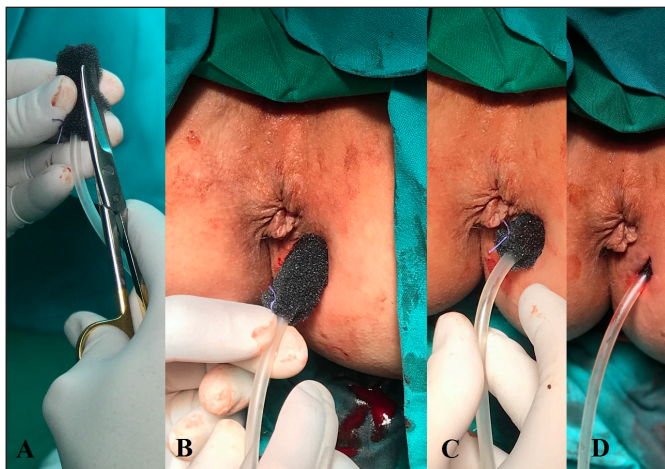


FIGURE 2. Debridement the fistula with the use of negative pressure wound therapy. Preparation of a vacuum dressing (A) and next steps of introducing the dressing into the fistula (B-D).

PRP

The volume of 1 mL of PRP with concentration of 10^6 of platelets, was acquired from 15 mL of whole venous blood, through the process of gradient density centrifugation with speed of 1776 g using a commercial kit (Xerthra PRP Kit, Biovico, Poland). The concentrate in the volume of 1.5 mL was administered into the tissues surrounding fistulous tracts, beginning from the internal orifice towards the external one. The penetration depth was controlled with an index inserted into the anal canal or under TRUS (FIGURE 3).

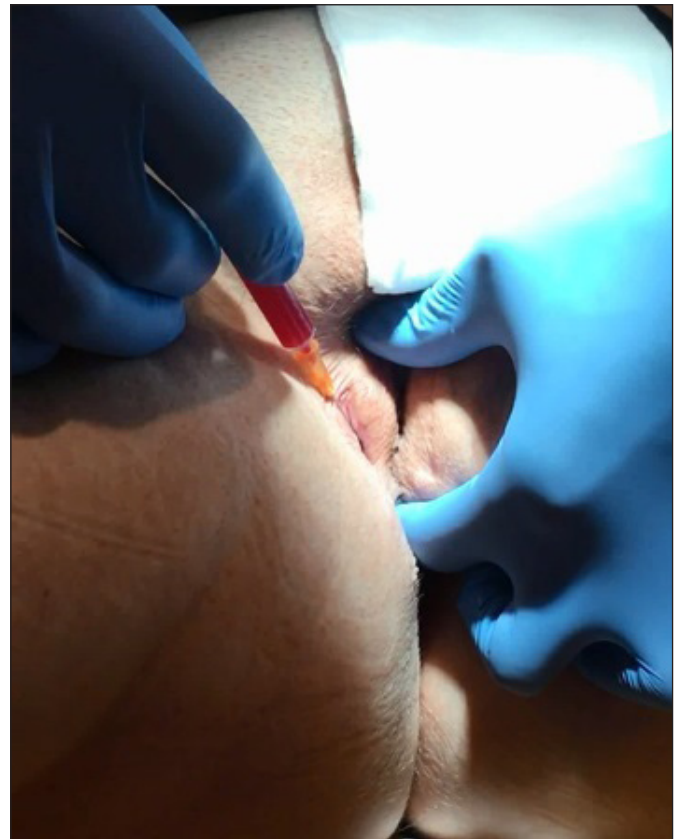


FIGURE 3. Local injection of platelet rich plasma into the tissues surrounding the fistulous tract.

According to the protocol the procedures could be repeated three times every fortnight until therapeutic effect was achieved with the opportunity to double the number of applications if it was clinically justified. If a patient did not respond to the treatment within 6 months from the last injection, an exceptional application was considered after individual evaluation based on the patients complaints and digital rectal examination. First dose of PRP was administered after admission to hospital, whereas subsequent injections were done in most cases on the basis of a proctologic clinic.

Follow-up

The patients were evaluated in an out-patient department after fortnight and then in 1, 6, and 12 months following final PRP application. That evaluation consisted of digital rectal examination, TRUS, and completion of Wexner questionnaire. In several questionable cases that examination was supplemented by MRI.

RESULTS

The investigated group consisted of 18 patients with eight males and ten females, mean age 41 years (range: 22–67years). Recurrent transsphincteric anal fistula was diagnosed in 13 patients, whereas suprasphincteric in two and intersphincteric in three. patients. The number of previous operations in all patients ranged from three through seven, mean four, and everyone underwent at least one cutting as well as one non-cutting procedure. Mild form of faecal incontinence for gases was recognized in three patients with the Wexner score between nine and 11. There was no significant deference between both groups regarding demographics, type of fistula, and number or method of operation (TABLE 1).

TABLE 1. Characteristics of both groups of patients before surgery.

n	Group I	Group II
	8	10
Men/female	4/4	4/5
Age (years)	46.5 (32–61)	38.7 (22–67)
Total nuber of previous procedures	4 (3–5)	4 (3–6)
Cutting procedures	2 (1–3)	2 (2–3)
Non-cutting procedures	3 (2–4)	2 (1–4)
Type of fistula		
Intersphincteric	1	2
Transsphincteric	6	7
Suprashincteric	1	1

Discharge as well as gas passage through fistulous tracts were reduced in all patients from the group I after first application of PRP. In turn, fistula was closed in one patient following second injection, whereas sporadic passage of gases remained in five patients. Two patients failed to respond to PRP. Third injection of the concentrate was performed in five patients with sporadic evacuation of gases with following complete fistula closure within two through four weeks. Afterwards, fistula recurred in three of those patients in 6 to 9 weeks after the last application. Therefore, fourth and fifth injection was performed, which resulted in fistula closure in one patient. Finally, 4 (50%) patients from the group I closed fistula in 12 months from the beginning of therapy.

Fistulas in the group II were healed in seven patients after two injections of PRP (FIGURE 4). The procedure was repeated in remaining three patients due to preserved, however reduced discharge. They were given another successful dosage of PRP. Recurrence was diagnosed in 1 to 4 months after the last injection in three patients with two injections, and in two after three procedures. All five patients with recurrence underwent additional application of PRP with fistula closure in two of them (FIGURE 5). Finally, fistulas were healed in 7 (70%) patients form the group II. To sum up, the rate of fistula healing was not statistically significant between both groups, and it was achieved in 11 (60%) patients from the entire group of 18 patients (FIGURE 6).



FIGURE 4. Anal fistula after removal of polyurethane foam dressing and before platelet-rich plasma (PRP) treatment (A). Complete closure of the fistula after 2 PRP injections and after another 6 weeks following final PRP application (B).

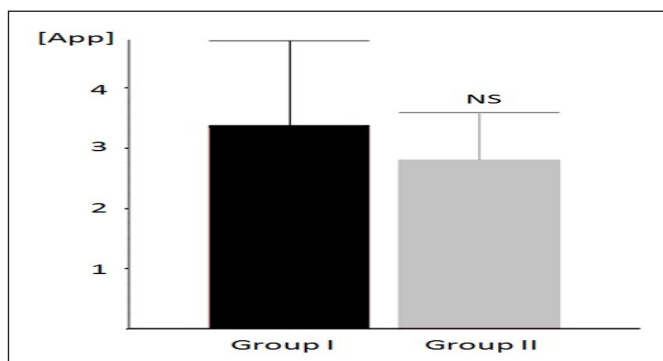


FIGURE 5. The average number of platelet-rich plasma applications [App] in patients from both groups.

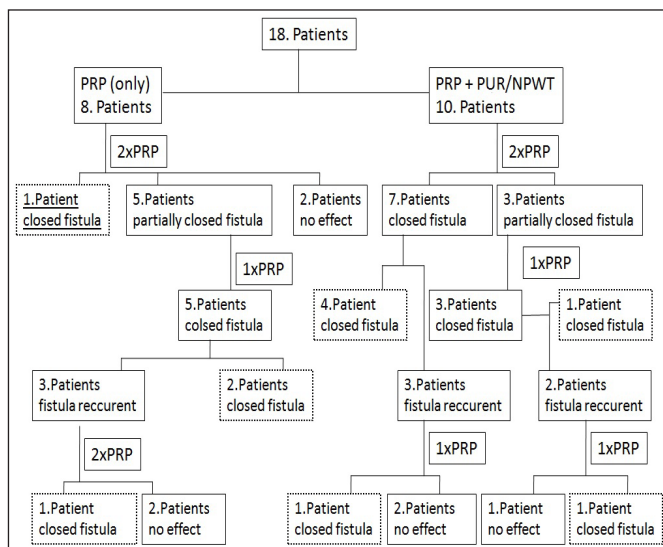


FIGURE 6. Treatment flow chart including the number of platelet-rich plasma (PRP) applications in both groups of patients.

DISCUSSION

The main difficulties in the treatment of recurrent anal fistulas are postoperative scars and tissue fibrosis involving the anal sphincter. Fistulous canal is composed of dense, amorphous, and poorly vascularized connective tissue, and it is an essential factor preventing fistula from healing. Although the rate of recurrences after primary operations for anal fistulas is high and ranges from 30% through 65%, there is scarce of reports regarding secondary interventions^(6,13). There are also no guidelines based on randomized, multicentre trials recommending surgical treatment for recurrent anal fistulas, and the existing experience is based on a small number of the investigated groups of patients, and that primary as well as secondary interventions took place in the same center. For example, MAF was used by Podetta et al., in primary operations as well as for secondary ones, regardless of similar rate of recurrences reaching 26.4% and 21.9% after both interventions respectively⁽¹⁴⁾. In turn, Wright et al., identified 20 (37.7%) patients with recurrence among 53 after primary LIFT, who then underwent loose-seton placement with following either MAF or fistulotomy, resulting in fistula closure in 10 (50%) patients⁽¹⁵⁾.

Because repeated operations for recurrent anal fistulas may result in damage to the anal sphincters with following faecal incontinence, those patients require sphincter-saving methods such as LIFT, VAAFT, OTSC[®] or less invasive e.g. fibrins, cyanoacrylate glue, pastes or plugs. Efficacy of fibrins is estimated on 0 to 86%, and it decreases with time⁽⁶⁾. For example, closure of anal fistulas after application of fibrin sealant Tisseel was estimated on 33–69%^(16,17). The rate of fistula healing was achieved by Basillari et al., in 71.4% and 90.2% of patients, after primary and secondary application of Cyanoacrylate glue (N-butyl-2-cyanoacrylate and methacryloxy sulfolane) respectively⁽¹⁸⁾. In turn, Moreno-Serrano et al., reported successful over-sewing of internal orifice combined with PRF in 69% of patients. That result was confirmed on MRI in 42.9% of cases⁽¹¹⁾. Even though these techniques have a higher rate of recurrences, all of them may be applied several times if failures are to occur. What is more, during those procedures preparation of lower value tissues within recurrent anal fistulas is not necessary. In addition, bio-products build a scaffold to promote formation of a fresh granulation tissue and finally scar within fistulous tracts^(19,20). On the other hand the impaction of the tract with fibrins or plugs may result in infiltration of neutrophils of the tissues surrounding fistulous canal. In the aftermath, outpour of cytotoxic and cytotoxic enzymes together with oxygen free radicals cause tissue necrosis with following anal fistula recurrence⁵. Hence, despite initial enthusiasm, those methods require further investigation to assess their efficacy⁽⁷⁾.

In turn, PRP is an autologous product derived from whole blood and therefore with no risk of transmitting infections, allergies, and rejections. Various cytokines freed from platelets granularities such as PDGF, TGF- β , FGF, VEGF, and IGF are responsible for creating a fibrin clot which works as a scaffolding for granulocytes, endothelial cells, and fibroblasts with following formation of well vascularized fresh granulation tissue, and finally fistula healing. The platelet concentrate was applied into the tissues surrounding fistulous tract due to its fluid consistency, slightly larger than plasma. Hence, mechanical compression of internal orifice as well as fistulous canal by edematous tissues soaked with PRP is one mode of action. On the other hand, it promotes fistula healing due to a high concentration of platelet-derived growth factors^(21,22).

Local injection of PRP is a novel sphincter preserving method of treatment for the patients with recurrent anal fistulas. It is a conservative method of therapy with the opportunity to repeat the procedure as often as necessary if failures or recurrences are to occur, with low rate of morbidity. The treatment requires patience from the patients' side, as well as the doctors', because it is extended in time to repeat applications of the plasma as often as necessary. However, PRP is accepted by the patients, because it is frequently a last resort therapy.

CONCLUSION

The rate of recurrent crypto-glandular anal fistulas closure reaching 60%, after topical treatment with PRP, exceeds the results of other sphincter-saving methods of treatment. Therefore, it might become a novel method of anal fistulas therapy.

Authors' contribution

All authors contributed equally to this work and approved the last version of the manuscript. Cwalinski J principal investigator responsible for the conception and partially for design of the study, acquisition of data and liable for article drafting. Hermann J prepared English language editing and reviewed the images. Paszkowski J contributed critical revision of the article for important intellectual content. Banasiewicz T drafted the concepts and designed the study.

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RESUMO – Contexto – O tratamento cirúrgico de fistulas anais recorrentes pode levar a inúmeras complicações, incluindo incontinência fecal. Portanto, as técnicas de preservação do esfíncter estão ganhando mais popularidade. **Objetivo** – O objetivo do estudo foi avaliar a eficácia da terapia de plasma rico em plaquetas (PRP) nos pacientes com fistulas anais criptoglandulares recorrentes. **Métodos** – Uma coorte de 18 pacientes com fistulas anais foi inscrita em ensaio preliminar e prospectivo. Eles foram divididos em dois grupos compostos por 8 e 10 pacientes, respectivamente. PRP foi injetado localmente em todos os pacientes, porém no grupo II foi aplicado espuma de poliuretano ou terapia de feridas por pressão negativa após 7 dias de drenagem de fistulas. Em média, foram administradas três doses de PRP, mas com a oportunidade de dobrar o número de aplicações se fosse clinicamente justificado. Os pacientes foram avaliados em ambulatório após quinze dias e depois em 1, 6 e 12 meses após a última aplicação do PRP. **Resultados** – As fistulas anais foram fechadas em 4 (50%) pacientes do grupo I e em 7 (70%) pacientes do grupo II. Embora a diferença entre ambos os grupos não tenha sido estatisticamente significativa, a terapia PRP deve ser precedida de drenagem do trato fistuloso em todos os pacientes. Resumindo, esse resultado bem-sucedido foi alcançado em 11 (60%) pacientes de todo o grupo de 18 participantes. **Conclusão** – A taxa de fechamento recorrente de fistulas anais criptoglandulares chegando a 60%, após tratamento tópico com PRP, excede os resultados de outros métodos de tratamento que preservam o esfíncter. Portanto, pode se tornar um novo método de terapia das fistulas anais.

Palavras-chave – Plasma rico em plaquetas; fistula anal; espuma de poliuretano.

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