Effectiveness of Combined Mucosal Advancement Flap with Autologous Platelet-Rich Plasma in the Management of Complex Anal Fistula: A Pilot Randomized Controlled Trial

Original Article

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ABSTRACT

Background: The management of complex anal fistulas often requires advanced techniques, especially when a considerable portion of the anal sphincter is involved. Platelet-rich plasma (PRP) has emerged as a talented adjunctive therapy, enhancing healing rates and reducing recurrence when combined with mucosal advancement flap (MAF) surgery.
Patients and Methods: This study evaluated the effectiveness of MAF with and without locally applied PRP in patients with complex anal fistulas. Primary outcomes included healing rate, with secondary outcomes assessing pain, continence, and quality of life (QoL).
Results: This pilot randomized-controlled trial involved 82 patients with comparable demographics and fistula characteristics across groups. PRP significantly reduced healing time (4.2 vs. 4.5 weeks, *P*= 0.0081) and improved postoperative QoL scores at 1, 3, and 6 months. While initial postoperative pain levels were similar, PRP led to complete pain resolution by 3 months (*P*= 0.0359). Complication and recurrence rates were comparable between groups, with minor wound infections and incontinence resolving in most cases.
Conclusion: The findings indicate that locally applied PRP significantly accelerates healing and enhances QoL for patients undergoing MAF for complex anal fistulas. Although recurrence and complication rates were similar, PRP seems to be a safe and effective adjunctive therapy.

Key Words: Anal fistula, Autologous platelet-rich plasma, Healing rate, Mucosal advancement flap, Postoperative pain, Quality of life, Recurrence.

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INTRODUCTION

An anal fistula is an abnormal tract connecting the anal canal to the skin around the anus, often caused by the rupture of an anorectal abscess. This condition frequently results in persistent purulent discharge or periodic swelling and tenderness, making it one of the most common anorectal disorders, affecting ~1.2–2.8 per 10.000 individuals globally[1,2].

Clinically, the ideal treatment outcome for an anal fistula is complete closure without fecal incontinence. Low anal fistulas that involve a minor ratio of the anal sphincter could often be effectively treated with fistulotomy. However, treating high fistulas or those comprising a considerable ratio of the sphincter muscles is considerably more complex, requiring advanced techniques[3].

A meta-analysis including 1655 patients who underwent different types of advancement flaps for management of anal fistula recorded an overall recurrence rate of 21% following anal fistula surgery. In terms of anal incontinence, the pooled rate was 13.3%. However, full-thickness flaps had a higher incontinence rate at 20.4%, though most symptoms were mild[4].

Platelet-rich plasma (PRP) has emerged as an innovative therapy applied across various medical specialties, including dentistry, surgery, orthopedics, dermatology, and esthetic medicine. PRP preparation systems have received FDA approval for use in bone grafting and orthopedic procedures, and their application in anal fistula treatment is expanding[5].

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PRP is prepared by centrifuging the patient's plasma to concentrate platelets and growth factors. These platelets contain key proteins, such as platelet-derived growth factor, transforming growth factor-beta, interleukin-1, FADP, vascular endothelial growth factor, ECGF, osteocalcin, osteonectin, fibrinogen, fibronectin, and thrombospondin, which play essential roles in tissue repair. After clot formation, platelets begin secreting these proteins and continue to release them for several days, facilitating tissue regeneration until macrophages arrive to support ongoing repair[6].

Compared to other biomaterials, PRP offers benefits such as a reduced risk of rejection, lower cost, and strong anti-inflammatory and regenerative effects, capturing the interest of many anorectal surgeons. Studies indicate that PRP treatment for anal fistulas can reduce complications like urinary incontinence and other adverse effects[7].

A recent meta-analysis included six case-control studies and three randomized-controlled trials involving 289 patients, revealing an overall cure rate of 65% and a recurrence rate of 12% across all studies[8].

A study of 25 patients with high anal fistulas treated with a mucosal advancement flap (MAF) and PRP achieved an 83% recurrence-free rate at 2 years, with most fistulas closing within three months. Four patients experienced recurrence, and two healed after a second procedure[9]. A more recent study comparing PRP with MAF reported closure rates of 71.4% for PRP and 57.5% for MAF alone, showing no significant differences in overall closure (P= 0.152) and no recurrence in either group[10]. Similarly, a cohort study of 42 patients treated with suture closure or MAF, with or without PRP, achieved successful internal orifice closure in all cases. The PRP group achieved a 75% complete closure rate within 12 months, while the non-PRP group achieved 45.5%[11].

The current study aimed to compare the outcomes of MAF combined with locally applied PRP as an adjunct against MAF alone in the treatment of anal fistulas, with a focus on healing rate, time to healing, recurrence rate, and patient-reported outcome measures.

PATIENTS AND METHODS:

This is a pilot randomized clinical trial comparing MAF combined with locally applied PRP against MAF alone for treating complex anal fistulas. Conducted at the Colorectal Surgery Unit, General Surgery Department, Mansoura University Hospital, from December 2022 to February 2024, it involved 82 patients.

Patients aged 18–65 years with cryptoglandular complex anal fistulas affecting more than 30% of the external anal sphincter were included. Exclusions encompassed simple anal fistulas requiring fistulotomy, associated anorectal conditions, inflammatory bowel diseases, specific infections, diabetes mellitus, recurrent anal fistulas, pregnancy, and use of corticosteroids or immunosuppressants.

Participants were randomly allocated into two groups using a sealed envelope method based on a computer-generated sequence. The PRP group underwent MAF with locally applied PRP, while the control group received MAF alone. Both surgeons and assessors were blinded to group assignments.

A thorough clinical and anorectal examination, including continence assessment using the Wexner Incontinence Score and quality of life (QoL) using the Quality of Life in Anal Fistula Questionnaire, was conducted[12,13]. Magnetic resonance fistulography was performed to evaluate fistula anatomy, and classification was based on Parks' system[14].

Surgical technique

All patients received preoperative bowel preparation. The procedure was conducted in two stages: initial seton placement for drainage when indicated, followed by definitive fistula closure with MAF alone or MAF with PRP. The procedure was conducted in the operating room, typically under sedation or general anesthesia. Patient positioning was based on fistula tract location: the prone position was used for anterior fistulas and the lithotomy position for posterior midline tracts, optimizing surgical access to the internal fistula opening. After drainage with a seton, patients with unresolved drainage or side tracts were excluded from further treatment. For eligible patients, the seton was removed, and hydrogen peroxide was avoided to prevent damage to the tract.

Surgeons exposed the internal fistula opening and made a circular mucosal incision, removing the submucosal tract and crypt-bearing tissue. A cranial inside-out dissection freed the tract, followed by suturing of the sphincter muscle defect with absorbable sutures. A partial thickness flap of mucosa and submucosa, raised and mobilized for tension-free coverage, was sutured to the resection site using multiple polyglactin 3-0-U stitches as shown in Figure (1).

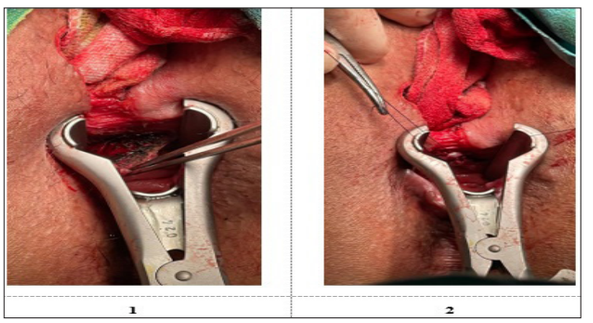

Figure 1: Mucosal advancement flap; (1): creation of the flap through dissection of mucosa; (2): Suturing of the flap to the distal anoderm using U stitches of 3-0 polygalactin suture.

In the PRP group, PRP was applied locally. PRP was prepared from 40ml of peripheral venous blood, collected in the anesthetic room, and processed with 3.8% sodium citrate. The blood was centrifuged at 1800 rpm for 8min, separating plasma and platelets. The upper platelet-rich fraction was mixed with 10% calcium chloride to create a fibrin polymer containing platelets, which served as a source of growth factors[15]. PRP was then injected into the submucosal level of the internal opening and along the fistula tract. A gelatinous plug from the platelet-poor fraction was applied to seal the external opening after tissue debridement, as shown in Figures (2,3).

Figure 2: Application of PRP; (3): Injection into the fistulous tract; (4): Injection into the submucosa; PRP: Platelet-rich plasma.

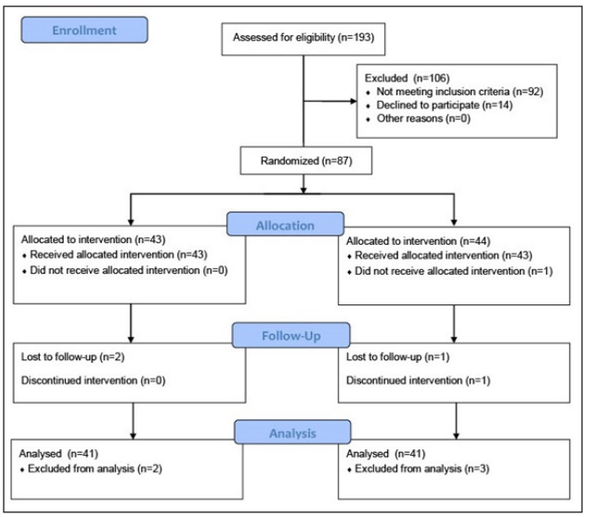

Figure 3: Consort flow chart of patients' allocation.

Postoperative care and follow-up

Postoperative care included pain management, oral antibiotics, and recommendations for diet and hygiene. Patients were followed up weekly in the first month, biweekly in the second month, and at 3 and 6 months postoperatively. Healing progress, recurrence, pain, continence, and QoL were assessed during these visits.

Patients experiencing discomfort or intermittent anal discharge, despite apparent closure of the external fistula opening, underwent magnetic resonance fistulography to rule out recurrence. A patient was considered "cured" when the external fistula opening had closed without any discharge, pain, or perianal swelling. Treatment was considered unsuccessful if there was no closure of the external opening by the 3-month follow-up. Delayed wound healing was defined as healing time > mean±2 SD.

Outcome measures

The primary endpoint was the fistula healing rate. Secondary outcomes included postoperative pain, continence, QoL changes, operation time, healing time, and complications.

Sample size and statistical analysis

The sample size calculation for this pilot randomized trial was based on the primary outcome of healing rate, with prior studies showing a healing rate of 74.6% for MAF alone and 83% with the addition of PRP[9,16,17]. A full-scale trial would require 740 patients for 80% power at a 5% alpha level. For this pilot study, 10% of the full sample size was deemed sufficient, leading to a minimum of 74 patients. To account for a 10% dropout rate, the final sample size was increased to 80, with patients randomly assigned to two groups.

Data analysis was conducted using SPSS, ve rsion 23. Descriptive statistics for continuous variables were presented as mean±SD, while categorical variables were reported as numbers and proportions. The Student *t* test was used for continuous variables, and the Fisher exact or χ^2 test was applied to categorical variables. A *P* value less than 0.05 was considered statistically significant.

RESULTS:

In this pilot randomized-controlled trial, 193 patients were initially assessed, with 113 excluded, resulting in 82 patients included in the study, as shown in Figure (4). The average age in the entire cohort was 44.7±4.4 years, and both groups had a male majority (82.9% in the PRP group and 85.3% in the control group). There were no significant differences between the groups regarding age, sex distribution, symptom duration, or the percentage of patients who underwent first-stage abscess drainage, as shown in Table (1).

Table 1: Basic demographic data.

Variables	PRP group (41 patients)	Control group (41 patients)	*P* value
Age in years, mean±SD	43.7±12.3	45.7±13.2	0.4799
Sex (male/female)	34/7	35/6	1
Duration of symptoms in months, mean±SD	4.9±2	4.9±1.8	1
1st stage abscess drainage, number(%)	24(58.5)	26(63.4)	0.8209

PRP: Platelet-rich plasma.

Table 2: Preoperative fistula characteristics.

Variables	PRP group (41 patients)	Control group (41 patients)	P value
No. of external openings, *n*(%)			
1	33(80.5)	28(68.3)	0.4422
2	7(17.1)	11(26.8)	
3	1(2.4)	2(4.9)	
Parks' classification, *n*(%)			
Intersphincteric	11(26.8)	10(24.4)	
Transsphincteric	26(63.4)	31(75.6)	0.2135
Suprasphincteric	2(4.9)	0	
Extrasphincteric	2(4.9)	0	
Internal Opening, *n*(%)			
I–III o'clock	7(17.1)	10(24.4)	
IV–VI o'clock	17(41.5)	18(43.9)	0.2475
VII–IX o'clock	12(29.3)	5(12.2)	
X–XII o'clock	5(12.2)	8(19.9)	
External opening, *n*(%)			
I–III o'clock	7(17.1)	10(24.4)	
IV–VI o'clock	12(29.3)	19(46.3)	0.0101
VII–IX o'clock	14(34.1)	2(4.9)	
X–XII o'clock	8(19.9)	10(19.9)	
Radial distance in mm, mean±SD	26.6±7	27.2±7	0.6990

PRP: Platelet-rich plasma.

Preoperative analysis of fistula characteristics of both groups showed comparable results regarding the number of external openings (*P*= 0.4422), Park's classification (*P*= 0.2135), the location of external openings (*P*= 0.2475), and radial distance from the anal verge (*P*= 0.6990), as shown in Table (2). However, the distribution of external openings differed significantly (*P*= 0.0101), with the PRP group showing a more even spread, while the control group had higher concentrations in the I–III and IV–VI regions.

The study found no cases of delayed wound healing in either group. Surgery duration was slightly shorter in the PRP group (27.8±4.8min) compared to the control group (29.4±4.3min), though this difference was not significant (*P*= 0.1158). Healing time was significantly shorter in the PRP group, averaging 4.2±0.5 weeks versus 4.5±0.5 weeks in the control group (*P*= 0.0081), indicating a faster recovery with PRP. Preoperative QoL scores were similar between groups.

Postoperatively, both groups showed significant QoL improvements at 1, 3, and 6 months, with the PRP group showing more pronounced improvements at each time point. At 1 month, the PRP group had a QoL score of 19.6±3.2 versus 26.3±4 in the control group (*P*< 0.0001), with similar significant differences at 3 and 6 months as shown in Table (3).

In the early postoperative period, pain levels were comparable between the two groups: at 6 h postoperatively (*P*= 1) with a marked reduction at 1 week (*P*= 0.0583). In the intermediate period (1 month), further pain relief remained similar for both groups (*P*= 1). In the late postoperative period, the PRP group achieved complete pain resolution by 3 months (*P*= 0.0359), and by 6 months, both groups reported no postoperative pain (*P*= 1).

Minor postoperative flatus incontinence was reported in five patients (two in the PRP group and three in the control group), with four resolving spontaneously within 4 weeks. One control group patient required biofeedback retraining and showed full symptom resolution after 12 sessions. No significant difference in incontinence rates was found between groups (*P*= 1). Wound infections occurred in

three PRP patients and four control patients, and were managed conservatively in most cases. One control patient required incision and drainage for a collection under local anesthesia. Complication rates were similar in both groups. Recurrence was reported in one PRP patient at 8 months and in two control patients at 9 and 11 months, with no significant difference between groups. All recurrences were managed surgically with drainage and seton placement.

Table 3: Operative and postoperative outcomes.

Variables	PRP group (41 patients)	Control group (41 patients)	*P* value
Duration of surgery in minutes, mean±SD	27.8±4.8	29.4±4.3	0.1158
Healing duration in weeks, mean±SD	4.2±0.5	4.5±0.5	0.0081
Preoperative QoL AF-Q, median (range)	47.8±8.6	50.1±9	0.2403
Postoperative QoL AF-Q, mean±SD			
1 month	19.6±3.2	26.3±4	<0.0001
3 months	18.8±3.5	24.8±4	<0.0001
6 months	17.5±3.5	22.1±3.9	<0.0001
P value (preoperative vs. postoperative QoL AF-Q at 6 months)	<0.0001	<0.0001	

PRP: Platelet-rich plasma; QoL: Quality of life.

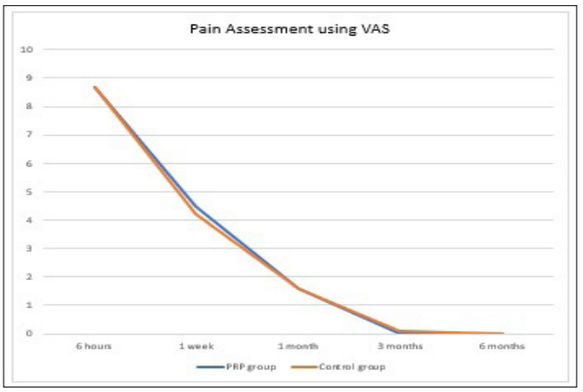

Figure 4: Pain assessment using a visual analog scale in both groups.

DISCUSSION

The MAF is a well-established surgical technique for managing complex anal fistulas, particularly in cases where preserving sphincter integrity is essential. This approach uses healthy rectal mucosa to close the internal fistula opening, effectively minimizing the risk of fecal incontinence and promoting robust healing[18]. MAF is recognized as a prominent sphincter-saving method among various techniques, including seton placement and its modifications, such as EAS-sparing rerouting seton, LIFT, fistula plugs, and VaAFT techniques[19–22].

Despite MAF's proven efficacy, its recurrence rate remains a significant challenge, prompting ongoing research into adjunctive therapies to enhance outcomes. Key obstacles include delayed healing and the risk of fistula recurrence, both of which can negatively impact the overall success of the procedure[23].

PRP has gained interest as a potential adjunctive therapy due to its regenerative capabilities. PRP is an autologous concentrate enriched with growth factors, such as platelet-derived growth factor, vascular endothelial growth factor, and transforming growth factor-beta, which are known to facilitate wound healing and reduce inflammation. Previous studies have demonstrated PRP's efficacy in accelerating healing and decreasing recurrence rates, making it a promising tool for improving patient outcomes[24,25]. This study evaluates the impact of PRP when combined with MAF compared to MAF alone in treating anal fistulas.

Both the PRP and control groups were comparable regarding age, sex distribution, duration of symptoms, and history of abscess drainage. The *P* values for these variables were nonsignificant, confirming a well-balanced randomization process. The study's homogeneity reduces the risk of confounding and strengthens the reliability of the findings, although some variability may still exist due to the natural complexity of anal fistula presentations.

The study revealed that the operative time was marginally shorter in the PRP group compared with the control group, though this difference did not reach statistical significance (P= 0.1158). While one might initially expect that the addition of PRP would prolong the operative time, the reality is that PRP injection is a relatively quick procedure, typically taking less than 2min, and thus has a negligible impact on the overall duration. Moreover, various other factors could influence the operative time beyond the application of PRP. These include the condition of the tissue surrounding the internal opening, such as whether it is healthy or fibrotic, the experience and proficiency of the surgeon, and the elasticity and pliability of the anal tissue, which facilitate better anal dilation

and improved exposure, allowing for more efficient fashioning of MAF.

The more compelling finding in this study is the significantly faster healing time in the PRP group (4.2±0.5 weeks) compared to the control group (4.5±0.5 weeks, *P*= 0.0081). Despite not being reported in previous studies, similar results have been reported regarding wounds other than anal wounds, where PRP application significantly reduced healing times by promoting enhanced tissue repair through growth factor-mediated pathways[26]. The quicker healing observed in the PRP group underscores its potential to accelerate wound closure.

Preoperative QoL scores, assessed using the AF-Q scale, were not significantly different between the groups, indicating a comparable starting point. Postoperatively, however, the PRP group showed significant improvements at all time points, with more favorable scores at 1, 3, and 6 months (*P*< 0.0001 at each interval). By 6 months, the PRP group achieved a mean QoL score of 17.5±3.5 compared to 22.1±3.9 in the control group. These findings support earlier reports by Moreno-Serrano and colleagues, who also documented substantial QoL benefits in patients treated with PRP. However, Moreno-Serrano *et al*.,[27] used SF-36 instead of a more disease-specific and recently developed AF-Q scale.

Disease-specific QoL scales provide a more precise and relevant evaluation of how a particular condition affects a patient's daily life. They are more sensitive to changes in health status or treatment effects compared to generic scales, allowing for improved monitoring of treatment outcomes. By focusing on issues directly related to the disease, these scales enable tailored treatment strategies and enhance patient engagement, ultimately supporting better clinical decision-making and more effective, patient-centered care.

The consistently superior QoL outcomes in the PRP group suggest that PRP may offer sustained benefits beyond faster wound healing. It is plausible that PRP's antibacterial and anti-inflammatory properties, which minimize postoperative discomfort and enhance tissue repair, contribute to these outcomes[28].

Pain levels, measured using the VAS scale, were initially similar between the two groups, with no significant difference at 6 h postoperatively (*P*= 1). By 3 months, however, the PRP group demonstrated complete pain resolution (VAS score of 0), whereas the control group had a slightly higher score of 0.1 (*P*= 0.0359). This finding highlights the potential of PRP to expedite pain relief, likely through its anti-inflammatory and regenerative mechanisms. A study by Cunha[29] has also noted the analgesic benefits of PRP, particularly in surgical settings where inflammation contributes to pain.

Despite these benefits, it is important to note that early postoperative pain levels did not differ significantly, suggesting that PRP's pain-relieving effects may be more pronounced in the intermediate recovery period. This delayed response may be related to the gradual release of growth factors and cytokines from the concentrated platelets, which modulate the inflammatory process and promote tissue healing over time as described in a previous study[30].

The rates of complications, including minor incontinence, infection, and recurrence, did not differ significantly between the groups. Incontinence rates were low and comparable, with no cases of persistent incontinence beyond the short-term recovery period. Infection rates and the requirement for further interventions were similarly low and nonsignificant, corroborating findings from previous studies that demonstrated that PRP does not increase the risk of surgical adverse events[31,32].

The recurrence rate was slightly reduced in the PRP group (2.4%) compared to the control group (4.9%), although this difference was not statistically significant. Larger sample sizes may be needed to detect a meaningful difference in recurrence rates. The potential trend toward fewer recurrences with PRP warrants further exploration, as future larger-scale studies may show that PRP's role in collagen and elastic fibers synthesis and consequent tissue remodeling could theoretically reduce the risk of fistula recurrence.

However, there are limitations to this study. The relatively small sample size and single-center nature of the study limit the generalizability of the findings. Furthermore, the follow-up duration of 6 months, while adequate for short-term outcomes, is insufficient to assess long-term recurrence and chronic complications comprehensively. Future studies should adopt a multicenter approach with larger sample sizes and extended follow-up periods to confirm these results and explore the long-term efficacy of PRP.

CONCLUSION

This study demonstrates that locally applied PRP significantly accelerates healing time and improves the QoL outcomes for patients undergoing MAF surgery for anal fistulas. While recurrence and complication rates were similar between groups, PRP emerges as a promising, safe, and effective adjunctive therapy. Additional studies with larger sample sizes

and extended follow-up are recommended to validate these results and refine PRP application protocols for optimal outcomes.

CONFLICT OF INTEREST

There are no conflicts of interest.

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