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Platelet-Rich Plasma Injection into the Colorectal Anastomosis Reduces the Anastomotic Leakage Incidence: A Randomized Controlled Trial

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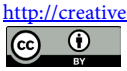

Abstract

Background and Aim: Colorectal anastomosis is a necessary surgical procedure in many medical cases. Anastomosis Leakage (AL) is a serious complication that can lead to severe infections and even the need for additional surgeries. Preventing leakage requires precise techniques and innovative methods to enhance tissue healing and improve surgical outcomes. Using Platelet-Rich Plasma (PRP) is a modern approach aimed at reducing leakage following low anterior resection for rectal cancer. **Materials and Methods:** The sample consisted of 60 patients with a mean age of 60.28 years who underwent open low anterior resection of rectal tumors. Platelet-rich plasma was injected into the anastomotic line in the intervention group, while normal saline (NS) was used in the control group. The results of the two groups were compared in terms of the incidence of anastomotic leakage. **Results**: Leakage occurred in 4 patients, representing 6.7% of the sample. The results showed that PRP injection was statistically significant when compared to the Control group. Leakage did not occur in any of the platelet-rich plasma patients, while it occurred in 4 patients in the control group, representing 13.3%. **Conclusion:** Application of Platelet-Rich Plasma injections into the colorectal anastomosis line reduced the incidence of anastomotic leakage following low anterior resection for rectal cancer from 13.3% to 0%.

Subject Areas

Colorectal Surgery

Keywords

Colorectal Anastomosis, Anastomotic Leakage, Platelet-Rich Plasma, PRP,

Low Anterior Resection

1. Introduction

Anastomotic leakage is defined as an infectious concentration originating from an anastomosis that requires surgical, radiological, or medical management [1]. AL usually occurs in the first week, and often between the fourth and seventh days, when the anastomosis is less strong, and it may occur before that when there is a technical failure in completing the anastomosis. Most reports indicate an incidence ranging from 2% to 20% [2].

In Germany, 26,495 patients undergoing colectomy above the peritoneal fold, the anastomotic leakage rate was documented at 3% [1], for low rectal anastomoses, 3% - 19% [3]. Leakage is associated with high morbidity and mortality rates, as well as significant costs and prolonged hospitalization.

Risk factors for anastomotic leakage have been studied extensively. Several factors have been implicated, including male gender, obesity, diabetes, anemia, hypoalbuminemia, preoperative corticosteroid use, prolonged operative time, and preoperative blood transfusion. Additionally, many studies have highlighted the ASA score and the distance of the anastomosis from the anal verge as contributing factors. There is strong evidence that neoadjuvant chemoradiotherapy for rectal cancer increases the risk of anastomotic leakage [4] [5].

Over time, surgeons have developed various procedures to prevent or reduce anastomotic leakage and mitigate its infectious complications. However, the effectiveness of these approaches has varied, with some carrying additional side effects that may impact recovery and surgical outcomes. Among these procedures, transanal drainage tube placement and diverting stoma are utilized as strategies to decrease intestinal pressure and improve fluid drainage, potentially contributing to a lower leakage rate, but the effectiveness of these procedures remains a topic of debate [6]-[8]. Recently, it has been defined according to the International Study Group of Rectal Cancer (ISREC). Asymptomatic AL (A grade) is the presence of an asymptomatic collection, and no active therapeutic intervention was required. And (B grade), which requires non-surgical interventions. In grade C, a second surgical intervention is required to save the patient, and the clinical picture may deteriorate to death [9].

Thinking at the molecular level about the factors that hinder anastomotic healing and those that accelerate recovery leads us to consider the various growth factors that play a role theoretically.

Platelet-rich plasma (PRP) is characterized by a platelet concentration exceeding the basal level in a plasma sample derived from whole blood [10]. Platelets play a crucial role in hemostasis through aggregation, adhesion, and activation. Their secretory granules release growth factors that facilitate clot formation via fibrin clots. Additionally, platelets release various growth factors and cytokines that promote

angiogenesis, stem cell differentiation, cell proliferation, immune response modulation, and inflammatory processes [11].

The interaction between platelet-rich plasma (PRP) and various biological pathways in the body is highly intricate and largely dependent on the method of PRP preparation. PRP plays a crucial role in modulating the extracellular matrix, contributing to tissue regeneration, and regulating the balance of metabolic proteins essential for healing. Growth factors present in the granules bind to their receptors to stimulate healing [12]. The multiple factors work synergistically to affect. PRP acts slowly, reflecting long-term stimulation of target cells and forming scaffolds that serve as a substrate for promoting cell adhesion [13]. Interest in PRP has significantly increased in dermatology, particularly in applications such as hair restoration, skin rejuvenation, acne scar treatment, scar healing, graft stimulation, and alopecia management, and it has shown positive results in muscle and tendon injuries [14]-[16].

In this randomized clinical trial, we hypothesized that injecting platelet-rich plasma (PRP) into the colorectal anastomosis line would have a clinical benefit in terms of speeding up anastomosis healing and reducing the incidence of leakage so, the primary outcomes was to compare the leakage rate between the PRP and control groups and to prove the effectiveness of PRP injection in reducing the incidence of leakage.

2. Methods

This randomized clinical trial was conducted at the National University Hospital in Damascus between March 2022 and March 2024, by registration decision No. 4005. Written informed consent was obtained from all patients, and ethical approval was obtained from the Ethics Approval Committee at Damascus University. Approval No. MD-301224-381, and it conforms to the provisions of the Declaration of Helsinki. A sample size of 25 patients was calculated for each arm. All operations were performed by the same researcher, and randomization was carried out using a closed-envelope method, on the basis of which either platelet-rich plasma (PRP) or normal saline (NS) injection.

2.1. Inclusion and Exclusion Criteria

All patients eligible for surgery in the normal platelet range, who were diagnosed with a rectal tumor, received preoperative radiotherapy and underwent open low anterior resection using the double-stapling technique (DST). Patients with emergency conditions, such as intestinal obstruction, a history of inflammatory bowel disease, recurrent tumors, and patients who had undergone a transanal intubation or diverting stoma were excluded.

2.2. Intervention

In the intervention group, platelet-rich plasma (PRP) was injected into the colorectal anastomosis line after a fresh sample was prepared in the operating room.

After drawing 10 ml of venous blood, it was mixed in a tube with sodium citrate as an anticoagulant and calcium chloride as a platelet activator. The blood was then centrifuged at 4000 rpm for 5 minutes. The upper layer of PRP and the lower layer of red blood cells were removed, and the middle layer was used to inject the anastomosis line.

In the control group, NS was injected into the colorectal anastomosis line. Except for the stated intervention, all patients received the same pre- and post-operative care.

The diagnosis of anastomotic leak was made when there was fecal drainage from the pelvic drain distinguishing from normal serous drainage after surgery, visual leakage from the wound or vagina, peritonitis, purulent or fecal collection on ultrasound, and elevated septic indicators (leukocyte count, neutrophile percentage, and C-reactive protein).

The following data were collected about the sample: age, sex, body mass index (BMI), medical history (diabetes mellitus DM, hypertension HTN, and preoperative anticoagulant use), habits such as smoking, alcohol consumption, preoperative weight loss, symptomatic or occult hematochezia, anemia, and pre- or post-operative blood transfusion. Data related to laboratory tests were also collected (complete blood count, neutrophil percentage, hemoglobin, albumin, creatinine, and C-reactive protein). The patient was then followed up after surgery, and information related to monitoring the occurrence of anastomotic leakage, such as removing pelvic drain, fecal or purulent discharge, or the occurrence of peri-anastomosis collections, was recorded. The method of managing leakage if it occurs. The endpoint in this trial was considered the occurrence of leakage from the anastomosis.

Statistical Analysis:

Chi-square χ^2 test was used to compare categorical variables between the two groups, and a t-test for quantitative variables.

The comparison of the AL rate in the 2 groups was performed using a χ^2 test and was presented as the relative risk with a 95% CI. All analyses were 2-sided, and $P < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS, version 27.0 (IBM Corp).

3. Results

The study included 60 patients who underwent open surgical resection of the rectum due to tumors, with a low anterior colorectal anastomosis. Total mesorectal excision (TME) with the double stapler technique was performed in all patients. At the end of the procedure, either PRP (50%) or saline serum (50%) was injected.

The median age was 60.28 years, with a standard deviation of 13.4 years, with 50% males and 50% females. Four patients (6.7% of the total sample) were diagnosed with anastomotic leaks, all in the NS group. None occurred in the PRP group. The leakage was classified according to the ISREC classification. The grade A leak occurred in two patients, one a 64-year-old male smoker with no history of disease, and the other a 76-year-old male with anemia, pre- and post-operative

blood transfusions, hypoalbuminemia, and hypertension.

The grade B leak occurred in a 44-year-old female patient with anemia, hematochezia, and preoperative hypoalbuminemia. The grade C leak occurred in a 56-year-old female patient with anemia, pre- and post-operative blood transfusions, and preoperative hypoalbuminemia.

Diabetes mellitus was found in 18.3% of patients, hypertension in 41.7%, and anticoagulants were used in 33.3%. 46.7% of patients were smokers, and 8.3% consumed alcohol.

53.3% of patients presented with significant preoperative weight loss, 51.7% with anemia, and 63.3% with hematochezia. Whole blood transfusions were performed in 26.7% preoperatively and 63.6% postoperatively. The histological tumor grade was distributed to28.3% for grade I, 60% for grade II, and 11.6% for grade III. A double-stapling technique was used in all patients, with 20%, 36.6% and 43.3% using the 32F, 33F, and 34F measurement.

3.1. Studying the Differences between the Two Groups

There were no differences between the two groups in terms of the studied variables, as the differences were statistically insignificant when examining gender, medical history, personal habits, Blood transfusion, tumor grade, and the C-EEA measurement (Table 1). There was no statistically significant difference between the two groups with respect to age and laboratory tests (serum albumin, serum creatinine, and admission hemoglobin as shown in Table 2, indicating the homogeneity of the two groups in terms of influencing factors.

Table 1. Data for the categorical variables.

Variant	Sub Group	PRP	DS	P
Gender	M	16 (53.3%)	14 (46.7%)	0.6
	F	14 (46.7%)	16 (53.3%)	
DM	NO	24 (80%)	25 (83.3%)	0.73
	Yes	6 (20%)	5 (16.7%)	
HNT	NO	18 (60%)	17 (56.7%)	0.79
	Yes	12 (40%)	13 (43.3%)	
Anticoagulants	NO	22 (73.3%)	18 (60%)	0.27
	Yes	8 (26.7%)	12 (40%)	
Smoking	NO	15 (50%)	17 (56.7%)	0.60
	Yes	15 (50%)	13 (43.3%)	
Alcohol	NO	27 (90%)	28 (93.3%)	0.64
	Yes	3 (10%)	2 (6.7%)	
Weight Loss	NO	11 (36.7%)	17 (56.7%)	0.12
	Yes	19 (63.3%)	13 (43.3%)	

Continued

Anemia		NO	12 (40%)	17 (56.7%)	0.19
		Yes	18 (60%)	13 (43.3%)	
Hematochezia		NO	10 (33.3%)	12 (40%)	0.59
		Yes	20 (66.7%)	18 (60%)	
Blood transfusion	Before surgery	NO	23 (76.7%)	0.56	
		Yes	7 (23.3%)	4 (13.3%)	
	After surgery	NO	11 (36.7%)	1	
		Yes	19 (63.3%)	19(63.3%)	
Tumor Grade		G1	7 (23.3%)	10 (33.3%)	
		G2	19 (63.3%)	17 (56.6%)	0.67
		G3	4 (13.3%)	3 (10%)	
Stapler Size		32	5 (16.7%)	7 (23.3%)	
		33	10 (33.3%)	12 (40%)	0.56
		34	15 (50%)	11 (36.7%)	

Table 2. Data for the quantitative variables.

Variants	GROUP	Mean	Std. Deviation	P
AGE	PRP	58.10	11.920	0.21
	NS	62.47	14.734	
ALBUMIN	PRP	4.1433	0.548,15	0.24
	NS	3.9500	0.715,71	
CR	PRP	0.868	0.2752	0.53
	NS	0.830	0.1841	
HB (ADMISSION)	PRP	10.9267	3.037,69	0.81
	NS	11.0833	1.776,88	

3.2. The Relationship between Protection Categories and Leak Incidence

Anastomotic leakage occurred in 4 patients in the NS group, but none of the PRP group in Figure 1. When comparing leak incidence in the two groups in Table 3, we find a statistically significant difference (P = 0.038) between the PRP and NS groups.

4. Discussion

This prospective study evaluated the rate of leakage in a randomized controlled clinical trial, comparing the injection of Platelet-Rich Plasma (PRP) into the anastomotic line with a control group where normal saline (NS) was injected. The trial

was conducted following open low anterior resection of the rectum with colorectal anastomosis using the double-stapling technique.

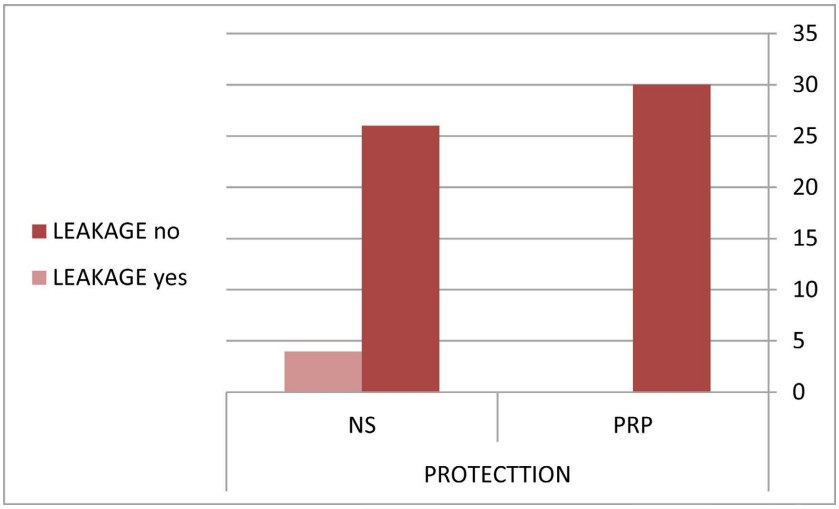

Figure 1. The relationship between protection categories and leak incidence.

Table 3. The relationship between protection categories and leak incidence.

			Leakage			P
			No	Yes	TOTAL	
Protection	PRP	Count	30	0	30	0.038
		% Within	100.00%	0.00%	100.00%	
	NS	Count	26	4	32	
		% Within	86.7.5%	13.3%	100.00%	

Colorectal anastomoses hold significant importance for surgeons due to the high rate of complications associated with them. Anastomotic leakage is one of the most critical concerns because of its severe infectious impact on patient health. AL is associated with increased morbidity and mortality rates [3].

Researchers have studied the factors contributing to leakage under colorectal anastomotic conditions and have identified several potential risk factors [4] [5]. Additionally, they have developed predictive scoring systems based on these risk factors to assist surgeons in taking preventive procedures to protect the anastomosis from leakage [17] [18].

One of these methods is diverting stoma, in which fecal diversion is achieved through a temporary ileostomy until the anastomosis heals. Studies have varied in their assessment of its effectiveness [19], but it has been noted to reduce the risk of infectious complications resulting from leakage. However, it has also been associated with additional morbidity [20].

Also, they have utilized transanal drainage tubes [7], anastomotic reinforcement with sutures [21], and various other techniques to enhance the safety of the

anastomosis.

PRP application to colorectal and intestinal anastomoses has been studied in various animal models across multiple countries. Different forms of PRP have been used, including injections, soaking, spraying, and as platelet-rich fibrin (PRF) in the form of a fibrin membrane or anastomotic coverage. These techniques have been tested in different pathological and normal conditions under controlled environments.

Most studies have agreed on the beneficial effects of PRP in improving anastomotic healing and enhancing burst pressure at varying rates [22]. Although some values lacked strong statistical significance [23], the impact of PRP in strengthening anastomotic resistance to intraluminal pressure cannot be ignored. Additionally, PRP has demonstrated histological benefits in enhancing the inflammatory response and collagen deposition [24].

The type of animal model did not influence the outcomes, nor were there any reported side effects across all studies. However, PRP concentration played a significant role, with low platelet concentration PRP (LOW-PRP) showing improved results compared to (HIGH-PRP). Notably, no residual material effects were observed upon animal sacrifice and abdominal exploration [25].

In our study, we injected PRP into the colorectal anastomosis as a part of a randomized controlled trial and compared the results with the control group, where saline serum was injected at the anastomosis site. The findings were consistent with animal studies in terms of promoting healing and reducing leakage rates. No leakage occurred in the PRP group, whereas the control group experienced a leakage rate of 13.3%.

The results can be explained by the improvement in the local environment of the anastomosis. Activated platelets release a significant amount of growth factors at the anastomotic site, which interact with all three phases of the healing process. Platelet-rich plasma therapy not only supports healing but also amplifies the process of proper repair of injured tissue. The therapeutic benefits lie in stimulating endogenous progenitor cells to promote proliferation and healing. PRP acts as a scaffold and source of growth factors in cell-based therapy and tissue engineering. It improves soft tissue healing by increasing collagen content, enhances early wound strength, and promotes angiogenesis through the migration, proliferation, and differentiation of endothelial cells for oxygen delivery and removal of cellular debris. This is achieved through the synergistic action of VEGF and PDGF-BB and counter-regulation of PF4. Other growth factors carried in platelet granules, inflammatory and anti-inflammatory cytokines, and substances present in other plasma compounds are also considered [26].

PRP injection is considered a cost–effective and easily performed technique. Patients who underwent platelet-rich plasma (PRP) injection reported high levels of postoperative satisfaction, with no recorded side effects related to transfusion reactions. This can be attributed to the autologous nature of the product, which is prepared in a sterile environment and in real time during the procedure, ensuring

its safety, Moreover, patients in this group did not report any discomfort, in contrast to cases where techniques such as transanal drainage tubes or ileostomy are used, which are often associated with additional complications and physical and psychological discomfort.

We want to emphasize that this experiment was conducted at a single center by one surgeon. Given the small sample size, the results cannot be widely generalized. We encourage further expansion of this model's trial. The limitations of this study are that PRP has previously only been used in animal models, so many patients declined to enter the study despite explanations of the potential benefits.

5. Conclusion

The effectiveness of platelet-rich plasma (PRP) in reducing anastomotic leakage in colorectal anastomoses following rectal resection has been tested. PRP was prepared and injected at the anastomotic site, and no leakage occurred in any of the patients. This method is novel and promising, and its clinical application should be expanded.

Conflicts of Interest

The authors declare no conflicts of interest.

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