



Novel Sphincter-preserving Therapies for Recurrent Anal Fistulas

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ABSTRACT

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Aim: There is still a need for more effective methods of treatment for the patients with recurrent, crypto-glandular anal fistulas due to a high rate of recurrences with threatening risk of fecal incontinence. The aim of this study was to compare the rate of fistula healing after application of either Platelet-Rich Plasma - PRP or Porcine-Derived Paste - PDP.

Methods: Medical records of 50 patients with anal fistulas were retrospectively evaluated. The patients were divided into two groups. Group I, treated with PRP, consisted of 25 patients, whereas the group II, supplied with PDP consisted also of 25 patients. Fistula closure evaluated clinically was the primary endpoint of the study.

Results: Closure of anal fistulas was achieved in 16 (64%) patients from the group I, and in 9 (36%) from the group II and that difference was statistically significant ($p=0.048$). There was no significant difference between both groups regarding demographic characteristics except for higher mean age of the patients within the group I ($p=0.010$).

Conclusion: Preliminary results of PRP application in the patients with recurrent, crypto-glandular anal fistulas showed a higher rate of fistulas closure compared to the treatment with PDP.

Keywords: Crypto-glandular anal fistula, Platelet-Rich Plasma, Porcine-Derived Paste

Introduction

Anal fistulas continue to be a challenge to surgeons due to a high rate of recurrences [1]. Refractory course of the disease might prompt multiple surgical interventions with possible risk of damage to the anal sphincters with subsequent fecal incontinence. Therefore, the patients should be treated in a conservative manner [2]. Consequently, they are offered today several sphincter-saving methods e.g. Mucosal Advancement Flap-MAF, Ligation of Intersphincteric Fistula Tract-LIFT, or less invasive such as Video-Assisted Anal Fistula Treatment-VAAFT, Negative Pressure Wound Therapy-NPWT, setons, fibrins, and plugs however with a higher risk of recurrence. An attempt to close the internal opening without jeopardizing function of the sphincter is a major advantage of those methods [3]. Application of Platelet-Rich Plasma - PRP or Porcine-Derived Paste - PDP have appeared recently in the

field of anal fistula therapy. PRP is an autologous product obtained from the whole blood. The value of that plasma lies on its ability to soak the adjacent soft tissues relative to fistulous tract with high concentration of platelet-derived growth factors to accelerate the healing process [4]. In turn, PDP consists of collagen retrieved from porcine dermis which becomes a scaffold promoting formation of a fresh granulation tissue with following fistula closure [5]. The aim of this study was to assess preliminary results of recurrent anal fistulas treatments with PRP compared to PDP.

Materials and Methods

Medical records of 50 patients with primary or recurrent high anal fistulas of crypto-glandular origin treated between 2017 and 2020 were retrospectively evaluated. The patients were divided into two groups. Group I, treated with PRP, consisted of 25 patients with 13(52%) males and 12(48%)

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Received/Geliş Tarihi: 26.01.2021 Accepted/Kabul Tarihi: 02.03.2021

females, median age 32 years (IQR: 29-39 years). Group II, supplied with PDP consisted of 25 patients including 14 (56%) males and 11 (44%) females, median age 38 years (IQR: 32-41 years). Previous anal operations such as excision, fistulotomy, MAF, LIFT were performed in most of the investigated patients that is in 19 (76%) patients from the group I, and in 18 (72%) from the group II [Table 1]. The patients underwent digital rectal examination and probing and/or dyeing of fistulous tracts under anesthesia. High transsphincteric fistulas were diagnosed, if more than lower one-third of the anal sphincter was involved [2]. Application of either PRP or PDP was preceded with loose seton pretreatment in all patients with purulent discharge. Next, application of the bio-products was preferred for the patients with a relatively long, and narrow fistulous tract, and with a small bore internal orifice, especially if application of PDP was considered. It was a surgeon's choice to use PRP or PDP in a certain case of anal fistula. The length of fistulous tract, as well as diameter of internal opening were assessed after digital rectal examination. Curettage and cauterization of fistulous tracts to remove the epithelium and infected granulation tissue with following irrigation of those canals, trimming of external orifices, and simple closure of the internal orifice were performed in all patients. That procedure was accomplished with application of PRP in the first group and PDP in the latter. The volume of 15 ml of the whole blood was centrifuged just before the procedure to obtain 1 ml of PRP, using a commercial kit (Xerthra PRP Kit, Biovico, Poland). The concentrate was administered into the adjacent tissues surrounding

fistulous tracts, beginning from the internal orifice towards the external one. The penetration depth was controlled with the index inserted into the anal canal or TRUS. The procedure was repeated 3 times every fortnight according to the protocol until therapeutic effect was achieved with the opportunity to double the number of applications if it was clinically justified. In turn, a fistulous canal was filled with the paste - Permacol (Covidien, Mansfield, MA) during one procedure. External orifices were left open in all patients. Fistula closure was defined as absence of discharge after gentle finger compression of an external orifice and of perianal tissues. The closure was confirmed by TRUS [6]. The patients were evaluated in an out-patient department in 1, 6, and 12 months following final PRP or PDP application. That evaluation consisted of digital rectal examination, TRUS, and completion of the Wexner questionnaire [7]. Patients with non crypto-glandular fistulas e.g. Crohn's, post-radiation, and cancerous anal fistulas were excluded from this investigation. Analyzed data were presented as medians with range or interquartile range (IQR). Categorical data were presented as percentages. Differences in components of demographic characteristics among two groups were detected by Mann-Whitney U-tests or Chi-square test. The Chi-square test was also used to examine the significance of the fistula closure rate between the groups. The changes of Wexner score in groups and between groups were identified by Wilcoxon signed-rank tests or Mann-Whitney U-tests, respectively. AP value less than 0.05 was considered statistically significant. All analyses were performed with the statistical package STATISTICA v. 13.1 (Stat Soft. Inc.,

Table 1. Characteristics of patients

Patients and methods		Group I (n=25) PRP	Percent	Group II (n=25) PDP	Percent	Significance
Gender	Male	13	52%	14	56%	0.777
	Female	12	48%	11	44%	
Age (in years)		Me=31 (Range: 29-39)		Me=38 (Range: 32-41)		0.010
Previous anal surgery		19		18		
	Excision	10		10		
	Fistulotomy	6		3		
	MAF	2		3		
	LIFT	1		2		
Fistula type						
	Trans-sphincteric	24		23		
	Supra- sphincteric	1		2		

PRP: Platelet-Rich Plasma, PDP: Porcine-Derived Paste, MAF: Mucosal Advancement Flap, LIFT: Ligation of Intersphincteric Fistula Tract

Tulsa, OK, USA). The application of Platelet-Rich Plasma (PRP) as well as of a porcine-derived acellular dermal paste (PDP) in anal fistulas was approved by the Bioethics Committee at the University. All participants/patients signed an informed consent before this study.

Results

Complete closure of anal fistulas was achieved in 16(64%) patients from the group I compared to 9(36%) from the group II, and that difference was statistically significant ($p=0.048$). The healing time was ranging from 4 to 8 weeks in the former group with application of PRP repeated from 3 to 5 times. Closure of anal fistulas in the latter group occurred in the period of 4 through 12 weeks. Anal fistula remained closed in 19 patients in 6th month from the group I, and in 16 patients in 12th month, whereas it was healed in 11, and 9 patients from the group II, respectively. There was no significant difference between both groups regarding demographic characteristics except for higher mean age of the patients within the group I ($p=0.010$). Mild to moderate form of fecal incontinence that is for gases or liquid stools was recognized in half of the patients from both groups before therapy, and the change of Wexner score after the treatment was not statistically significant (Group I: $p=0.120$, Group II: $p=0.065$).

Discussion

Conservative surgery is indicated for most complex and recurrent anal fistulas due to the high rate recurrences, and to avoid damage to the sphincters with following fecal incontinence. Several sphincter-saving methods such as MAF, LIFT, VAAFT, NPWT, fibrins, and plugs have been introduced recently [3]. All aforementioned methods, except for MAF with efficacy approaching 50%, requires further clinical investigation, since representative, randomized trials have not yet been available [8]. As far as LIFT is considered, it relies on identification of the space between the internal and external sphincters, and on mobilization and partial excision of fistulous tract within that space. Efficacy of that method is estimated below 50% [9]. Next, advantage of VAAFT is an accurate debridement of fistulous tracts under sight control, and closure of the internal opening. Equipment costs are major disadvantages of that method. However, preliminary results of VAAFT are encouraging with more than half of fistulas closure [10]. Vacuum therapy shows its potential for the management of anal fistulas. NPWT can be defined as a sphincter-saving procedure, because the anal sphincter is left intact. What is more, it is a kind of surgical drainage, which is more effective compared to e.g. loose setons [11]. As far as fibrins

are concerned, fistulous tract is sealed with fibrin glue, starting from the external opening. A major advantage of that method is an opportunity to repeat it several times if necessary. Low efficacy of fibrins estimated on 14 to 60% is a major drawback [12]. In turn, a plug is a bio absorbable prosthesis made from porcine intestinal submucosa. It serves as a scaffolding for host cell proliferation. A major advantage of that method is the opportunity to repeat it. However, efficacy is estimated around 30% due to frequent rejections [13]. The porcine-derived acellular dermal paste (PDP) consists of collagen type I and elastin fibers retrieved from porcine dermis. During the manufacturing process the cells are removed to reduce immunological response against foreign antigens. The collagen also undergoes cross-linking, which results in increased resistance to degradation, reduction of tissue antigenicity, higher durability and greater strength. It is important to mention, that the paste is a slowly-absorbable material and the collagen becomes a scaffold which enables cellular infiltration and neovascularization. The process of dissolution takes on average a few months after which the paste is replaced with the own patient's dense and strong scar tissue. If compare to synthetic pastes, the biological one induces milder inflammatory response, and more orderly collagen deposition. Apart from that, the cross-linked materials showed greater resistance to collagenase digestion. The major drawback is a relatively low efficacy of that method mainly due to a frequent leakage of the paste from a fistulous tract before cellular infiltration and neovascularization occurs [5, 14]. Platelet-Rich Plasma is an autologous product obtained from whole blood through the process of gradient density centrifugation. The results achieved after application of PRP, in the investigated group of patients, were better compared to PDP and other aforementioned conservative methods. The plasma works not only as a fibrin tissue adhesive, and a scaffold for cellular infiltration, but it promotes wound healing by increasing cellular proliferation, angiogenesis, and collagen synthesis due to a high concentration of platelet-derived growth factors within the soft tissues in vicinity of fistulous tracts. Mechanical compression of fistulous tract by the plasma, injected into the adjacent tissues to anal fistulas is another PRP mode of action. Finally, it carries no risk of allergies and transmitting infections, since it is an autologous product [4]. There are several limitations of this study such as a retrospective nature of this series, and a small sample size. However, the study might be considered in further meta analyses.

Conclusion

Preliminary results of local PRP application in the patients with recurrent, crypto-glandular anal fistulas showed a

higher rate of fistulas closure compared to the treatment with PDP. However, application of either PRP or PDP might be repeated several times if recurrences are to occur. Both methods could be combined with other conservative, sphincter-saving methods of surgery in a selected group of patients mainly with recurrent high cryptoglandular anal fistulas. Those methods might be recommended as novel sphincter-saving procedures for recurrent anal fistulas.

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