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Original Article

Clinical and physiological efficacy of the application of autologous fat with platelet rich plasma in treating faecal incontinence

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ABSTRACT

Purpose: Faecal incontinence (FI) is a frequent condition that can occur due to different causes; with negative impact on self-esteem and quality of life, secondary morbidity, disability and significant costs. For its treatment there is a wide range of options, being medical treatment, hygienic dietary modifications and biofeedback, the first line of treatment; reserving surgery for patients who do not respond or with severe FI; this with variable success rates and high cost. This study has the primary aim to assess the efficacy and describe the Technique of Application of Autologous Fat with Platelet Rich Plasma (AFPRiP) in patients with faecal incontinence as well as secondary endpoints of quality of life, manometric and ultrasound evaluation, safety of implantation, and complications.

Methods: A single-centre prospective, experimental study, was conducted from January 2017 to February 2018 in Domingo Luciani Hospital. Wexner and FIQL scores were filled preoperative and compared at follow-up at 3, 6 and 12 months as well as anorectal manometry and endoanal ultrasound were performed before and 6 months after surgery.

Results: Twelve patients were operated, mean time 43 min, no major complications. Wexner finding continence improvement from 10.4 pre to 4 in the 3rd month ($p = 0.066$) 4.74 at the 6th month ($p = 0.001$) and 5 at one year ($p = 0.001$); that is, improvement of >50% in 83.4%. FIQL 50.9 prior to 98.6 at 3rd month ($p = 0.001$) 95.5 to 6th month ($p = 0.001$) and 91.3 a year ($p = 0.066$).

Conclusions: We conclude that AFPRiP is innovative, safe and with adequate results.

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Eficácia clínica e fisiológica da aplicação de gordura autóloga com plasma rico em plaquetas no tratamento da incontinência fecal

Palavras-chave:
Incontinência fecal
Gordura autóloga
Plasma rico em plaquetas
Agentes de volume

RESUMO

Objetivo: A incontinência fecal é uma condição frequente que pode ocorrer devido a diferentes causas, com impacto negativo na autoestima e qualidade de vida, morbidade secundária, incapacidade e custos significativos. Existem várias opções para o manejo da incontinência fecal; o tratamento médico, as modificações higiênicas da dieta e o *biofeedback*, são os de primeira linha. A cirurgia é recomendada apenas para pacientes que não respondem ao tratamento de primeira linha ou aqueles com incontinência fecal grave; as taxas de sucesso são variáveis e o custo do tratamento cirúrgico é elevado. Este estudo teve como objetivo principal avaliar a eficácia e descrever a técnica de aplicação de gordura autóloga com plasma rico em plaquetas (AFPRiP) em pacientes com incontinência fecal; o estudo também avaliou parâmetros secundários de qualidade de vida, manométricos e ultrassonográficos, bem como a segurança da implantação e suas complicações.

Métodos: Um estudo experimental prospectivo, de centro único, foi realizado de janeiro de 2017 a fevereiro de 2018 no Hospital Domingo Luciani. A escala de Wexner e o FIQL foram preenchidos no pré-operatório e comparados no seguimento de três, seis e 12 meses; manometria anorretal e ultrassonografia endoanal foram realizadas antes e seis meses após a cirurgia.

Resultados: Doze pacientes foram operados; o tempo médio da cirurgia foi de 43 minutos, sem maiores complicações. Na escala de Wexner, observou-se melhora na continência: de 10,4 pré-operatório a 4 no terceiro mês (p = 0,066), 4,74 no sexto mês (p = 0,001) e 5 em um ano (p = 0,001), uma melhoria de 83,4%. Já o FIQL evoluiu de 50,9 no período pré-operatório para 98,6 no terceiro mês (p = 0,001), 95,5 no sexto mês (p = 0,001) e 91,3 em um ano (p = 0,066).

Conclusões: A AFPRiP é uma técnica inovadora, segura e que apresenta resultados adequados.

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Introduction

The Fecal Incontinence (FI) is a condition with multiple causal agents, situation that turns out to be reflected in the therapeutic options that can be offered to the patient; all with different success rates and major or less grade of acceptance inside the scientific community.[1]

Nowadays is established for the American society of colon and rectal surgeons that Sacral Neuromodulation (SN) is the first treatment line for patient incontinent with or without sphincter injury. Hetzer et al. concluded in its study of 2006 that the cost for the SN, in 5 years of follow-up was over 22.000 euros.[2]

In relation to the bulking agents (BA) for the treatment of the FI it was established that the ideal agent is that what is biocompatible, of small size to facilitate its injection but the sufficiently big as to minimize the migration.[1]

It has been postulated that the mechanism of action of injecting a BA into the submucosal or the intersphincteric space is to increase the anal bearings and, therefore, promote a better seal of the lumen of the anal canal at rest, increase the length of the high pressure zone, alternatively, when the objective of the injection is to fill a significant defect of the anal sphincter, a better seal is achieved by improving the symmetry of the anal canal.[3]

From the first report published in 1993 by Shafik,[4] where it describes the polytetrafluoroethylene injection in 11 patients a big BA variety has been proposed: autologous fat, porcine and synthetic collagen, teflon, silicone, hyaluronic acid, as well as different injection sites and techniques have also been described; all with variable results and short follow-up. Currently, the only BA with longer follow-up (36 months) that has shown reduction of incontinence episodes in 52% of patients is hyaluronic acid stabilized dextranomer.[5] The short follow-up of patients who have been treated with BA, the wide range of agents available, the poor quality of the scientific evidence available means that there is no consensus on these agents so far.[6] In 2019 Sung Hwan Hwang et al[7] published an article where report the effectiveness of the fat graft like a BA in treating FI in 35 patients and discusses satisfaction with the procedure. Symptoms improved in 29 (82.9%), and not improved in 6 (17.1%). In 2 of 6 patients, they felt better than before procedure, although not satisfied. No improvement in 4. Mean Wexner score was 9.5 before procedure and 4.7 after, but only in 6 months of follow-up. There were no serious complications such as inflammation or fat embolism and they concluded that this procedure can be an effective alternative treatment for FI and It is safe, easy to perform and cost effective. To investigate if the association of fat grafts and platelet rich plasma (PRP) improves graft viability in female rats, in 2016 Blumenschein AR et al[8] performed an experimental, ran-

domized and blinded study, which involved 47 rats. Fat was harvested from the inguinal region and grafted to the cranial region. The experimental group consisted of PRP-enriched fat grafts (n = 22) whilst the control group consisted of fat graft only (n = 25). After a 100-day period, the animals were euthanised and the fat grafts were analyzed using scores from 0 (absent) to 4 (abundant), in optical microscopy by two independent and blinded pathologists with the findings that the PRP group scored moderate/abundant in 63% of cases and the fat graft only group scored absent/slight in 72% of cases. The PRP group also presented lower fat necrosis scores when compared to the fat graft only group. In view of the results of these investigations we have combined both products: Autologous fat and platelet rich plasma with the primary aim to assess their efficacy in patients with faecal incontinence and describe the Technique of Application of Autologous Fat with Platelet Rich Plasma (AFPRiP) as well as secondary endpoints of quality of life, manometric and ultrasound evaluation, safety of implantation, and complications.

Methods

A single-centre prospective, experimental study, was conducted at the coloproctology Unit of Domingo Luciani Hospital, Caracas, Venezuela from January 2017 to February 2018. The study protocol was approved by the local ethics research committee (protocol number 00320) and was exempted from an informed consent requirement to the patients.

Inclusion and exclusion criteria

Patients with the following criteria were included: Patients between 18 and 80 years with mild to moderate faecal incontinence without anatomical lesions or with defect no greater than one third of the circumference of the internal or external sphincter, or both; visualized by endoanal ultrasound, who had experienced faecal incontinence for at least 12 months and had failed or with little response to initial treatment that includes dietary hygiene modifications, medical treatment, biofeedback therapy or other failed surgical treatment and were able to consent to participate and attend all scheduled follow-up visits. Exclusion criteria were: Patients with severe faecal incontinence, current diagnosis of cancer; chronic diarrhoea unresponsive to medical treatment; inflammatory bowel disease; acute anorectal sepsis or cryptoglandular fistula; concomitant rectal prolapse; obstructive defaecation syndrome; neurological disease; immunological disease, viral infection spread by blood, previous rectal resection; and sphincter(s) defects of the internal or external anal sphincter, or both, greater than one thrid of anal canal circumference.

Study design

Patients were given two incontinence scales prior to surgery to be filled: the Wexner or Cleveland Clinic Fecal Incontinence Score (CCFIS)[9] and the Faecal Incontinence Quality of Life Scale (FIQL)[10] and these were compared at follow-up at 3, 6 and 12 months as well as high-resolution anorectal manometry (Medical Measurement Systems®) and three-dimensional endoanal ultrasound (BK Medical Pro Focus 2202®) were performed before and 6 months after surgery. Patients visited the outpatient ward at 1, 2 and 4 weeks after the procedure for testing complications such as bleeding, fat leak or anal infections. Then at 3 months after the procedure, the results were evaluated by questioning the patients using scales and it was concluded that it was effective when symptoms of faecal incontinence were reduced by more than 50% compared to baseline. Patients' sex, age, symptom duration, type and severity of fecal incontinence including sphincter(s) defects and past anorectal or pelvic surgery were examined through the review of the medical records (Table 1). The mean maximum resting and squeeze pressure anorectal before and 6 months after the procedure, the amount of autologous fat and PRP at the time of operation, and the persistence of those by ultrasound at 6 months after the procedure, the improvement of faecal incontinence after the operation, and post- operative complications were confirmed. The IBM SPSS Statistics version 22.0 (IBM Co., Armonk, NY, USA) was used for statistical analysis. A value of $p \leq 0.05$ was considered significant.

Table 1 – Baseline patient characteristics.

Characteristics	Value
Age (years)[a]	60.67 (15.4)
Sex ratio (F : M)	11 : 1
Symptom onset (mo)[a]	15.7 (12–31)
CCFIS score preoperative[a]	10.4 (2.55)
Manometric maximum resting pressure preoperative[a]	31.7 (9.32)
Manometric maximum squeeze pressure preoperative[a]	86.6 (55.97)
3D-EAUS features	
Sphincter lesion(s)	6
EAS	6
IAS + EAS	3
IAS	0
No lesion	6
Previous anorectal or pelvic surgery	8
Sphincteroplasties	2
Fistulotomies	2
Hemorrhoidectomy	1
Hysterectomy	3
Previous pelvic radiotherapy	1
Previous deliveries[a]	3.4 (0–9)

[a] values are mean (s.d. or range). FI, faecal incontinence; CCFIS, Cleveland Cleveland Clinic Fecal Incontinence Score; 3D-EAUS, three-dimensional endoanal ultra- sonography; IAS, internal anal sphincter; EAS, external anal sphincter.

Surgical technique

The Technique AFPRiP as BA begins with the administration of prophylactic intravenous antibiotic therapy based on Cefazolin 2 grs and Metronidazole 500 mgs and the consequent harvest of approximately 80–120 cc of fat from the abdominal area or thighs after sedation of the patient, demarcation and antisepsis (Fig. 1). In the next step prior to antisepsis of the

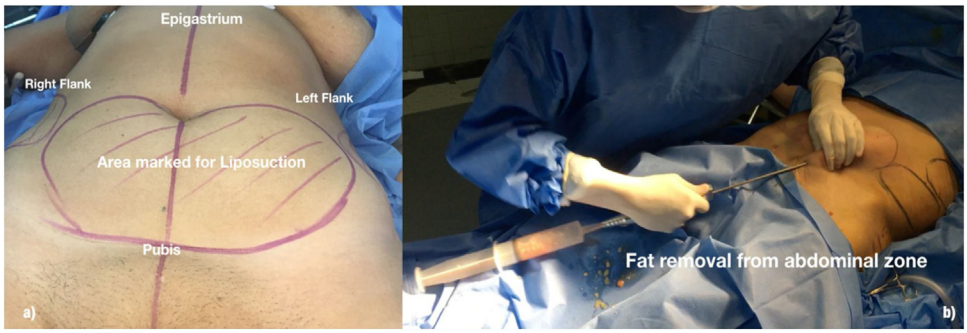

Fig. 1 – a) Demarcation of the area where the fat will be harvested. b) Fat removal from the abdomen using liposuction technique.

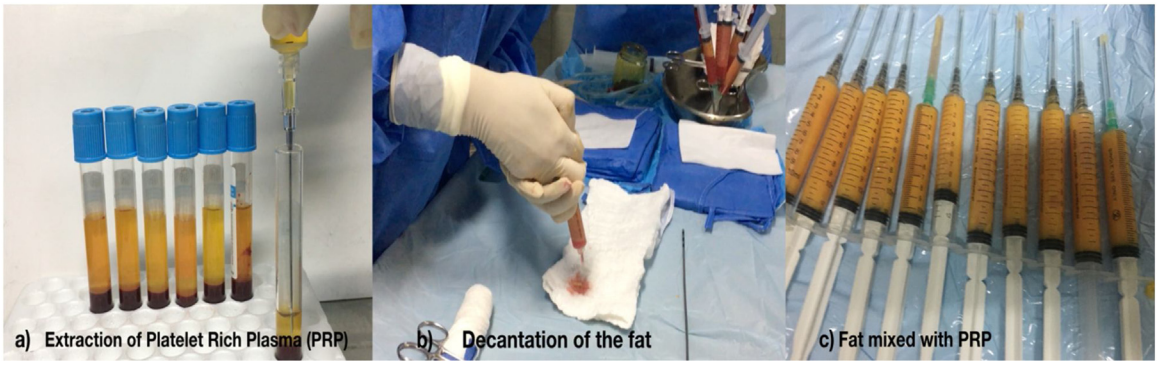

Fig. 2 – a) Separation of the PRP in syringes from other formed elements of the blood. b) Decantation by gravity, washing with serum and preparation of fat. c) Fat mixed with PRP.

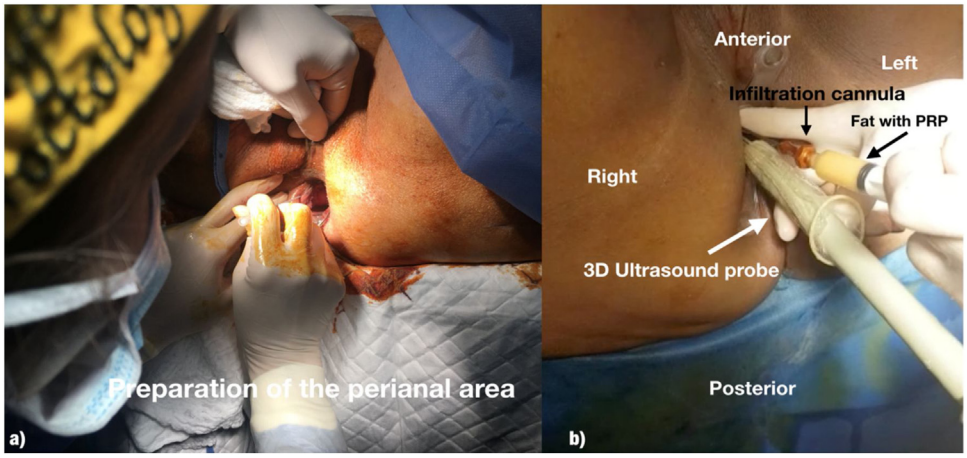

Fig. 3 – a) Preparation of the perianal area. b) Fat placement as appropriate (submucosal or intersphincteric space) under ultrasound vision.

upper limb, 20 ml of blood will be extracted through a peripheral venous line, which will be contained in test tubes with sodium citrate anticoagulant with subsequent centrifugation at 3000 rpm for 5 min, which will allow obtaining approximately 10 ml of Platelet Rich Plasma (PRP) and simultaneously decantation by gravity, washing and preparation of the fat harvested is carried out for subsequent mixing of both (PRP and fat in 10 cc syringes (Fig. 2). With the fat already prepared and mixed with the PRP, it is infiltrated after placing the patient in a lithotomy position, antisepsis of the perianal area and cleaning with an enema 2–3 h before surgery ; using an infiltration cannula of 2 mm in diameter and 7.5 cm long that is introduced through the perianal radialis guided by intraoperative endoanal ultrasound in order to place the product above the dentate line in the submucosal space in an amount of 20 cc (18 cc of fat and 2 cc of PRP) in each quadrant (Hours 12, 3, 6 and 9), total 80 cc (72 cc of fat and 8 cc of PRP) in case of intact anal sphincters and in case of lesions, places in the intersphincteric space in volume of 40 cc (36 cc of fat and 4 cc of PRP) (Fig. 3). Patients are discharged in 3–6 h with paracetamol and ibuprofen every 8 h if necessary, without making physical or sexual efforts for 1 week to ensure the integration of fat in the tissues.

Table 2 – Variation in the Wexner and FIQL scale in patients with fecal incontinence after injection of autologous fat with platelet-rich plasma.

Period	Average	Deviation	95% confidence interval	p-Value	n
Preoperative W	10.4	2.55	8.58–12.22		12
FIQL	50.9	10.05	43.71–58.09		12
Thrid month W	4.0	4.24	0–42.12	0.066	10
FIQL	98.62	11.72	88.82–108.43	0.001	10
Sixth month W	4.75	1.75	3.28–6.22	0.001	10
FIQL	95.5	13.44	29–119	0.001	10
Twelfth month W	5.0	1.26	4.7–6.5	0.001	10
FIQL	91.3	15.18	80.44–102.16	0.066	10

Table 3 – Manometric characteristics in patients with fecal incontinence before and after (6th month) injection of autologous fat with platelet-rich plasma.

Variable	Average Pre n	Deviation	Average 6to mes	Deviation	Confidence Interval 95%	n	p.Value
Resting pressure	31.7 (12)	9.32	42.38	13.74	(30.89, 53.86)	10	0,090
Squeeze pressure	86.6 (12)	55.97	129	51.42	(86.01, 171.99)	10	0,083
Sustained squeeze	88.3(12)	62.33	105.5	39.02	(72.88, 138.12)	10	0,122
Sensitivity	40(12)	12.47	42.5	12.82	(31.78, 53.22)	10	0,672
Capacity	180(12)	63.77	190	35.46	(160.36, 219.64)	10	0,264
Compliance	13.4(12)	9.24	58	70.12	(0,116.62)	10	0,248

Results

Between January 2017 and February 2018, 12 consecutive patients (11 women and 1 man; mean age 60.67 (s.d.) (15.4) (range 44.6–72.5 years). Two patients were lost to follow-up after the first postoperative, leaving 10 for evaluation. Mean follow-up was 14·9 (range 12–20) months. There were 5 patients who had a history of anorectal surgery (2 sphincteroplasties, 2 fistulotomies, 1 hemorrhoidectomy) and 3 patients with hysterectomy. One patient had a history of anal cancer who received chemo-radiotherapy 6 years before, 9 patients had a history of delivery mean 3.4 (range 0–9 deliveries). Six patients by ultrasound had anal sphincter defects. Of these all with external anal sphincter lesion; mean 75.1° (range 27–113°) and 3 with combined defects including internal anal sphincter; mean 71.3° (range 42–114°). The mean duration of symptoms was 15.7 months (range 12–31 months).

Clinical, quality of life and anorectal manometric continence

Twelve patients have undergone this technique with an average operating time of 43 min (31–72 min.). No patient sustained intraoperative complications. Preoperative Wexner and FIQL scales were compared at 3, 6 and 12 months, finding continence improvement from 10.4 pre to 4 in the 3rd month ($p = 0.066$) 4.74 at the 6th month ($p = 0.001$) and 5 at one year ($p = 0.001$); that is, improvement of >50% in 83.4% of the patients, because 2 patients did not accept follow-up due to the non-improvement of their symptoms. Quality of life (FIQL) of 50.9 prior to 98.6 at 3rd month ($p = 0.001$) 95.5 to 6th month ($p = 0.001$) and 91.3 a year ($p = 0.066$) (Table 2) with improvement in all domains evaluated on the scale. In anorectal manometry, improvement in maximum resting and squeeze pressure was obtained from 31.7 to 42.38 ($p = 0.090$) and from 86.6 to 129 ($p = 0.083$) at the 6th month, respectively; the other parameters were not statistically significant (Table 3).

Endoanal ultrasonography findings

A control ultrasound was also performed at the 6th month after surgery to assess the persistence of fat and the percentage of resorption; finding persistence of the infiltrated volume in 80%, that is, a percentage of resorption of 20%.

Complications of procedure

No major complications were reported in our series, only mild to moderate pain that relieves with common analgesic and in one patient, fever 48 h after the procedure without evidence of local infection or rejection of the fat.

Discussion

This study of 12 patients undergoing AFPRiP procedure for faecal incontinence found improved incontinence in the majority of patients during the early postoperative phase and follow-up for 1 year, in mild and moderate faecal incontinence treated with limited or without anal sphincter defects. In 1995, Shafik[11] presented his work on perianal injection of autologous fat as a treatment for FI. To do this, he obtained 60 ml of fat from the abdominal wall and subsequently injected it into the submucosal space at hours 3 and 9. A total of 14 patients, 3 became continent after the first injection, while the rest required a second and third injection to achieve continence in a follow-up period of approximately 18 months. With the appearance of BA, the use of autologous fat was left aside, however, research is currently being resumed on this point considering the available information regarding the high content of stem cells in adipose tissue. Frudinger et al[12]

used Autologous muscle-derived cells for the treatment of FI secondary to obstetric injury. According to their reports, 10 women showed improvement in symptoms after autologous myoblast injection; likewise, they showed improvement in continence and quality of life in the 5-year follow-up. Recently, mesenchymal cells derived from adipose tissue have been used to treat perianal fistulas for Crohn's disease, which has shown beneficial therapeutic effects.[13] Furthermore, adipose tissue has the benefit of having higher rates of mesenchymal stem cells and easier access. The use of PRP combined with fat is for the purpose of improving the cellular quality of fatty tissue infiltrations. The group of Cervelli et al[14] have published studies on the effects of PRP mixed with fat grafts used for skin rejuvenation, evidencing clinically, a higher percentage of maintenance over time of the restored contour and of stereological three-dimensionality when the fat graft it is mixed with PRP. Likewise, it has been evidenced in a series of in vitro studies that PRP increases the survival rate of adipose tissue and the rate of differentiation of stem cells.[15] For all these reasons described above and because autologous fat with PRP is an apparent inert materials and without additional costs, we decided to innovate in a technique that for many had remained in the history of fecal incontinence treatment, but studies that determine their inertia and cost comparatives with other BAs are necessary in the future. This study has some limitations, including a small and heterogeneous sample size made in a single-centre experience and the results should translate to other units. Future larger multicentre trials are required to confirm the efficacy and indications for the AFPRiP.

Conclusion

In conclusion, AFPRiP is safe and outpatient minimal invasive treatment for faecal incontinence, also a technique that donŕ use a sophisticated and expensive equipment, because there are many sites to harvest fat and platelet rich plasma is obtained for the own blood of patients, the procedure could be repeated in failure cases, although in our series it was not done. Procedure has a sequence of steps that must be followed in very well selected patients how we show in our study with intention to avoid complications and subsequent failure and furthermore we recommended its application using endoanal ultrasound.

Conflicts of interest

The authors declare no conflicts of interest.

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