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Review Article

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Management of Perianal Fistula by Platelet Rich Plasma, Mesenchymal Stem Cells and their Secretome: An Up-to-Date Review

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ABSTRACT

Perianal fistula is a challenging condition, characterized as granulomatous inflammation of fistula around the anal canal, are associated with significant morbidity stemming in a negative impact on quality of life, the disease tends to reoccur, and with current treatment options, a large number of patients are left with active ailment. Unfortunately, even the best therapeutic regimens do not have long-term efficacy and cause a significant number of side effects. Therefore, it is crucial to study new therapeutically options such as the use of mesenchymal stromal cells (MSCs) and their secretum (Exosomes, extracellular vesiculas) and Platelet Rich Plasma (PRP). These therapies promote tissue repair via the induction of immunomodulation. The present review aims to explore the existing updated scientific literature on MSCs and PRP adoption in the treatment of perianal fistula to evaluate its efficacy and safety.

Keywords: Mesenchymal Stem Cells, Platelet Rich Plasma, Perianal Fistula, Inflammation, Stem Cell Therapy

Introduction

Perianal Fistula

The word "perianal" refers to the area immediately surrounding the anus and describes a potentially severe gastrointestinal condition [1] An improper connection that develops between two tissues, organs, or vessels that would not typically connect is known as a fistula: inflammatory and granulation tissues are present in an anal fistula, which is an epithelialized connection between the exterior perianal region and the anal canal [2].

Research suggests that a chronic inflammatory disease or an autoimmune disease like Crohn disease or any disease may act as a mediator to the perianal fistula [3]. In fact, the most prevalent anal disease, with an annual incidence of 1 to 8 per 10,000 people, is perianal fistula and abscess [3]. Fistulas have many different causes; however, the well-known mnemonic "FRIEND" helps with memorization. "F" stands for foreign body, "R" stands for radiation, "I" stands for infection or IBD, "E" stands for epithelialization, "N" stands for neoplasm, and "D" is for distal obstruction [1].

Severe discomfort, purulent discharge, fecal incontinence, fever and sexual dysfunction are reportedly among the symptoms [3]. Many surgical treatment methods are available for perianal fistula, but all of them are constrained by moderate success rates and frequent relapses, not to mention risks of anal fistula surgeries that include fistula recurrence, stoma or flatus incontinence, chronic draining wound Anal tightness and many more [2]. Perianal fistulas need to be treated differently depending on their kind, intricacy, and cause. However, the end result is always the same: promoting total healing while also maintaining anal sphincter function and continence [2,4].

A perianal fistula can be short and naive, involving just the internal anal sphincter (intersphincteric fistula), or long and deep, including both anal sphincters (Tran sphincteric fistula or extra sphincteric fistula). Most of fistulas are low and develop

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in the anal canal. Supralevator fistulas are rare and arise from above the anal canal.

Simple fistulae are those involving between 30-50% of the external anal sphincter in a single tract and Complex fistulae, are those with numerous tracts, that include more than 30-half of the outside sphincter and those include the anterior half of the anus (in women) [2].

Perianal fistulas are classified according to their locations with respect to the anal sphincter muscles since the removal of the fistula may endanger these muscles [5]. There are five types of perianal fistulas: intersphincteric, trans sphincteric, suprasphincteric, extra sphincteric and superficial anal fistula [6].

Intersphincteric anal fistula penetrates the internal anal sphincter muscle and escapes through between the internal and external muscles. However, the fistula that passes through both layers of muscles is referred to as trans sphincteric fistula and the one that passes through the internal sphincter and then moves around the external muscles is defined as suprasphincteric fistula. A rare type is the extra sphincteric fistula in which the fistula goes around both sphincters and usually originates from the rectum instead of the anus which indicates that is doesn't come from an anal gland. And finally, the superficial anal fistula or the submucosal fistula travels through the skin below the anal glands and avoiding the muscles [5].

MSCs and PRP

Researchers are investigating the effectiveness of using both allogeneic and autologous adult mesenchymal stem cells (MSCs) to induce fistula repair in perianal patients [5].

Due to their immunomodulatory and differentiation capabilities, MSCs are considered strong potential therapeutic option in the field of regenerative medicine [7]. MSCs are adult stem cells that are undifferentiated, multipotent, and have the capacity to self-renew, which have the ability to develop into a variety of mesenchymal tissue lineages, such as chondrocytes, osteoblasts, and adipocytes and may also be able to differentiate into other cell types, such as endothelium, cardiomyocytes, and neurons [8]. Furthermore, MSCs reveal a similar morphology to fibroblasts and are devoid from hematopoietic stem cells and due to their high adhesion to conventional culture dishes (plastics) and their pattern of marker expression [9]. They are specifically negative for the hematopoietic markers CD45, CD34, CD79a or CD19, CD14 or CD11b and human leukocyte antigen DR, and usually positive for CD90, CD73, as well as CD105 and they represent a novel therapeutic strategy [8-10].

Having an anti-inflammatory potential, MSCs can activate inflammatory cytokines like IL-10, GF SDF-a1, and transforming growth factor (TGF), and move to the damage site, and control the tissue-regeneration process by releasing a range of helping factors [9]. They also have immunomodulatory potential, which reduces B-cell proliferation by arresting their cell cycle and affects B-cell differentiation; they primarily inhibit CD4 T lymphocyte activation and encourage regulatory T cell development [7]. Additionally, they reduce the toxicity of natural killer cells and suppress the pro-inflammatory activity of dendritic cells, which both inhibit the generation and activation of antibodies [7].

MSCs primarily function through three mechanisms: 1- homing, which allows them to migrate into injured areas; 2- differentiation, which allows them to replace damaged tissues; and 3- paracrine, which allows them to secrete bioactive substances aiding repair various tissue, growth, and wound healing from physiological or pathological causes [11].

Regardless of their tissue of origin, bone marrow (BM)-MSCs, adipose tissue (AD)-MSCs, umbilical cord blood (UC)-MSCs, and peripheral blood (PB), the collection of MSCs does not raise ethical concerns [12]. BMSCS, AD-MSC and UC-MSC are positive for the following cell surface markers SH2, SH3, CD29, CD44, CD49e, CD71, CD73, CD90, CD105, CD106, CD166, CD120a, CD124 and negative for CD34, CD45, CD19, CD3, CD31, CD11b, HLA-DR [13].

Recent researches have demonstrated the efficacy of secretum and/or exosome, or MSC-conditioned medium (CM) in view of therapeutic potential [14]. Exosomes, cytokines, chemokines, growth factors, lipid mediators, hormones, and other protective bioactive substances are secreted by MSCs and are referred to as the secretum. These components play critical paracrine roles in the communication between the cells and surrounding tissues, importantly for tissue repair and regeneration [10-14].

Moreover, MSCs-secretum is known as the "garbage bags" of cells and micro-vesicles and could be used as MSC-based therapy with a superior safety profile. It is a cell-free biological alternative therapy, recognized under novel modalities [15]. They have a potential of stabilizing redox microenvironment, can easily cross barriers, are responsible for tissue repair and scars recovery, modulate host immune response, reduce inflammation and infection load as well as stimulating neurogenesis and angiogenesis. Numerous disorders, including colitis, gastric mucosal damage, osteoarthritis, spinal cord injury, and cardiovascular disease, have shown the efficacy of MSCs-secretum in therapeutic applications [14,15].

Due to their endosomal origin, MSCs-secretum have a unique biogenesis process that involves both the normal Endosomal Sorting Complex Required for Transport (ESCRT)-dependent pathway and a non-canonical mechanism mediated by syntenin and the proteins Alix. They are released into the extracellular environment under the control of a complex network of proteins [16].

Secretomes are extracted from conditioned media, nevertheless, there is currently no standardization in isolation techniques, but so far "ultracentrifugation" is the method that is thought to be the most commonly used [14-16].

Secretum linked with MSCs fit in well with their niche and have a longer paracrine effect after engraftment; moreover, the immunomodulatory capability of stem cell secretum has been identified as responsible for its regenerative effect [14].

One of new treatment options for perianal fistula is blood-derivatives- based methods. One of the blood derivatives of this bioactive substance is Platelets rich plasma (PRP), Platelet-rich plasma (PRP) is a quick, effective, and noninvasive method of collecting a natural concentration of autologous growth factors

that involves centrifuging autologous peripheral blood to isolate and extract the plasma and buffy coat a part of the blood, both of which contain high concentrations of platelets with more than 20 growth factors and other protein molecules such as binding molecules and chemokines involved in processes like proliferation, differentiation, as well as cell regeneration [17]. The PRP potentials such as its therapeutic ability depend on the amount of growth factors it has.PRP has become widely used for the repair of soft tissue injuries and wounds [18]. A quick, effective, and minimally invasive procedure called platelet PRP involves centrifugation of autologous blood to separate the plasma and buffy coat part, which contains a great deal of platelets and GFs such as platelet-derived GF (PDGF) and transforming Growth Factor-β1 (TGF-β1), vascular endothelial GF (VEGF), basic fibroblastic GF (bFGF), and epidermal GF (EGF) and with the potential of antibacterial and fungicidal proteins, coagulation factors, and membrane glycoproteins, which regulate inflammation by triggering the production of chemokines, interleukins involving the tissue healing process, causing the creation of a thick scar tissue and preventing wound infection [18,19].

(PRP) contains various proteinaceous healing factors like RANTESa that stimulate multiple responses such as coagulation, inflammation, angiogenesis, neo-vascularization, and tissue regeneration [19]. Platelets also promote the transfer of different platelet antigens, including CD41, CD61, CD62P, CXCR4, and PAR-1, to hematopoietic stem cell progenitors [18]. In addition, the adhesion-promoting chemicals fibronectin, vitronectin, fibrinogen, and sphingosine-1-phosphate are also present in PRP. PRP are used also in many surgical treatments like bone growth and wound healing [18,19].

In this up-to-date review we will determine the different ways of mesenchymal stem cells from many source administrations and their secretum with PRP in perianal fistulizing disease and comparing between surgical and non-surgical treatment and by showing significant results and how those exciting new treatment affect and play a main role in reducing inflammation and treating the disease.

Surgical Management

Similar to most diseases, perianal fistulas can be treated by surgery. However, depending on the severity of the fistula and whether it passes through the sphincter muscles or not, different surgical applications can be applied to avoid bowel incontinence. Fistulotomy is the most common surgical protocol applied if the fistula does not penetrate the sphincter muscles. In this case, the entire infected area will be removed in addition to the pus and fluids present which will then be stitched and left to heal; for this reason, it cannot be applied when the fistula passes through sphincter muscles [20].

The use of a seton for example, which is a surgical thread, can heal the fistula by allowing it to drain and facilitating its healing [21]. Surgeons place the seton to prevent the formation of abscess which is defined as an infected pocket of fluid causing significant pain by keeping the fistula tract open [22]. Additionally, advancement flap procedure can be applied in case the fistula passes through sphincter muscles which consists of removing a flap of tissue from the rectum to cover the fistula hole where it entered the bowel [23]. This sphincter-preserving procedure may be combined with fistula plug or paste [24]. Another technique used to replace fistulotomy in case the fistula passes through the muscles is the ligation of the intersphincteric fistula tract, also known as LIFT. This procedure involves sealing the fistula on both ends and dividing the tract after performing a cut in the skin above the fistula and moving the sphincter muscles apart [25].

Moreover, endoscopic ablation can be used since there are no serious concerns about its safety [26]. This procedure involves the entry of a fertiloscope along which an electrode will pass, two to three stitches will be performed to isolate the internal opening after which using the electrode material in the fistula will be cauterized from the external to the internal opening [27]. Radially emitting laser fiber treatment which involves the application of a small laser beam to seal the fistula has some uncertainties on how it works but no concerns on its safety [28]. Radial fibers are used to emit laser beams within the lumen of the fistula therefore making this technique "sphincter-saving" [29]. In addition to all that, a bioprosthetic plug which is made of animal tissue can be added to block the internal opening of the fistula [30]. This technique aims to keep the muscles intact knowing that the tract is identified using a probe and the conical plug blocks the internal opening leaving the external opening not completely sealed for drainage to continue [30]. Finally, fibrin glue can be applied allowing thrombin to form fibrin clots therefore encouraging the fistula to heal. These fibrin injections are simple, effective and considered to be a well-tolerated therapy for perianal fistulas [31].

Non-Surgical Treatment

Other conventional non-surgical methods have also been used to treat perianal fistula. Such as, the use of antibiotics like ciprofloxacin, in addition to immunomodulators like tacrolimus which have shown higher rates of clinical improvement and reduced pain and symptoms' severity; unfortunately, these treatments did not show complete closure of the fistula [4].

Starting with antibiotics, metronidazole and ciprofloxacin are mainly used as first-line therapy. An initial study on metronidazole showed that it is effective in inducing fistula closure, however, recurrence rates are high [32]. Brandt et al. showed that in perianal fistulas patients treated with metronidazole, only 28% were able to discontinue therapy without recurrence [33]. However, when comparing the two antibiotics, ciprofloxacin is known to have higher closure rates and response when compared to metronidazole [34]. Moreover, topical antibiotics ointments or cream were investigated, reporting an improvement in pain and drainage from the tract while using metronidazole [35].

Furthermore, different types of immunomodulators are also being studied such as thiopurines, methotrexate, tacrolimus, cyclosporine A, thalidomide and mycophenolate mofetil. Several studies were conducted on azathioprine and 6-mercaptopurine showing either complete fistulas healing or improvement in perianal tenderness and fistulas drainage [36-38]. Few studies only investigated the role of methotrexate in healing perianal fistulas. A study published by Mahadevan et al reported fistulas improvement and closure once methotrexate is being injected intramuscular, however, oral administration would result in fistulas recurrence [39]. Topical tacrolimus which is also an

immunomodulator, was studied by different groups reaching a conclusion that it might be beneficial for easing symptoms but not in inducing complete fistula closure [40,41]. Cyclosporine A, when injected intravenously, is reported to cause complete closure of the fistulas in addition to improvement in patients who relapsed after 6-mercaptopurine and/or azathioprine [41]. It is important to mention that if cyclosporine was to be given orally, a collapse in the disease might occur [43]. An immunomodulator which is highly effective but causes side effects is Thalidomide. Many studies performed on this immunomodulator showed very promising results; however, side effects are noted such as neuropathy and leukopenia [44]. Interestingly, lenalidomide is as an analogue for thalidomide, itis reportedly less toxic but to date no studies were conducted on its use for perianal fistulas [45]. Finally, a less commonly used immunomodulator in perianal fistulas is mycophenolate mofetil that showed promising results with complete fistulas closure [46].

In addition to immunomodulators and antibiotics, other biological agents are also being used and studied such as infliximab, adalimumab, certolizumab pegol, and others. Several studies proved the beneficial use of a monoclonal antibody against tumor necrosis factor alpha (TNFα) known as infliximab for perianal fistulas which is also the first approved biological agent for inflammatory bowel disease. Studies since 1999 were conducted by different groups including Present et al. showing that infliximab was able to completely heal the anal fistulas at a specific serum level for perianal diseases and more specifically fistulas [47-51]. Moreover, adalimumab was also studied with promising results concerning fistula closure documented in different studies [52,56]. On the contrary, Certolizumab pegol apparently needs validation in larger cohort studies for the confirmation or the rejection of its beneficial role in perianal fistulas, since contradictory results were reported by different groups [54-57].

Other therapeutic options can be the use of hyperbaric oxygen therapy or adsorbent carbon. Knowing that the mechanism of action is not fully elucidated, hyperbaric oxygen therapy can play a role in tissue repair and therefore was tested on perianal fistulas. Partial fistulas healing and complete fistulas closure were reported [58,59]. However, even though adsorbent carbon's way of action is clear about where it binds to and eliminates toxic and inflammatory particles, only one study proved its efficacy in treating perianal fistulas. More studies are needed to validate these observations [60,61].

Also, some medications are considered first-line therapy prescribed for perianal fistulas, like calcium channel blockers, topical nitrates, and Onabotulinumtoxin A injections. Due to these medications, a reduction in the anal sphincter tone occurs therefore leading to an increase in Ano dermal blood flow [62].

When it comes to traditional and non-surgical therapies, the use of honey was proven to be beneficial in treating perianal fistula by reducing inflammation, pain and induration of the infected area. Moreover, the study showed that most fistulas were healed after 6 months of applying honey on the affected region [63].

State of Art

MSCs are one of the most studied cells for therapy since they are known for their anti-inflammatory, immunomodulatory, and regenerative characteristics [64]. MSCs are being used for wound healing and regeneration of damaged tissues, in particular in perianal fistula [50].

More than ten clinical trials were conducted in the past three years including different MSC sources, with adipose tissue being the main source. These studies investigated the injection of stromal vascular fraction derived from adipose tissue autologously alone or with the association of endorectal advancement flap technique [65,66].

Furthermore, instead of extracting the adipose tissue from the patient for each treatment, a somatic cell therapy product was being made and is being investigated in several clinical trials [67]. Darvadstrocel is the active compound of Alofisel, a type of medicine that contains cells and tissues mainly stem cells extracted from fat tissues of adult donors [68]. In addition to that, several trials are being done in Takeda, Japan on this drug aiming to check for the long-term effects of the administration of Darvadstrocel and for its side effects and improvement of symptoms in patients using it, as well as if its effect is as beneficial in teenagers and children in closing the perianal fistulas as it is in adults [69-71].

In addition to Alofisel, another use of adipose derived stem cell is being investigated where the cells extracted from the subject's adipose tissues will be seeded into a bioabsorbable plug which will be later on inserted into the patient's fistula

Other sources of stem cells are also being studied for the treatment of perianal fistulas such as cells extracted from umbilical cords. Some clinical trials in China investigating the injection of TH-SC01 cells which are made of allogeneic umbilical cord cells derived MSCs to cure perianal fistulas. A Significant improvement in Perianal Crohn Disease Activity Index, Pelvic MRI-Based Score, Crohn Disease Activity Index, and quality of life score were observed at 24 weeks. No serious adverse events occurred. The probability of recurrence-free was 70% at week 52 [72].

Also, bone marrow derived mesenchymal stem cells (BM-MSCs) are being used in different treatment protocols to cure several diseases. Indeed, a study in the Cleveland Clinic analyzed the role of allogeneic BM-MSC in treating perianal fistulas. They have reported that the systemic infusion of MSC or exosomes derived from BM-MSCs has significantly ameliorated body weight loss, colon shortening, and the Disease Activity Index (DAI) score of colitis and reduced the ratio of the Th17 cells with an increased ratio of Treg cells. Interestingly, administration of exosomes derived from BM-MSC revealed superior improving impacts to colitis [73].

However, the use of cellular therapy may be eliminated or prevented by studying their paracrine activities and the molecules released that lead to their highly beneficial effects in wound healing and tissue regeneration. The secretum released by MSCs are proven to cause the same effects as the presence of MSCs, therefore, the transplantation of cellular products may be replaced by the injection of their active products presenting the same efficacy in tissue regeneration [74]. Direct Biologics are studying the effect of ExoFlo on perianal fistulas, which

is a combination of exosomes isolated from allogeneic human bone marrow MSCs [75,76]. In addition to isolating exosomes or secretum from BM-MSCs, two clinical studies are being conducted at Tehran University of Medical Sciences on isolating exosomes from placenta derived mesenchymal stem cells for the treatment of perianal fistulas [77]. Overall, analyses imply that exosomes administration, particularly, can improve the quality of life of treated patients after local or systemic injection mediated by suppression of acute mucosal inflammation through downregulating the secretion of a broad spectrum of mediators contributing in the local and systemic inflammatory reactions. [78,79].

In addition to all that, a well-known and used technique for tissue regeneration, mainly applied in cosmetic medicine, is platelet-rich plasma (PRP). Due to the promising results of soft tissues healing and due to the high concentration of platelets while using PRP method study were conducted to test for the efficacy of PRP in healing or closing perianal [19]. A recent study performed by Kantonsspital Winterthur KSW in Switzerland involves the combination of PRP with the Stromal Vascular Fraction (SVF) for the treatment of perianal fistulas Wounds closed faster in the SVF + PRP group than in the control group or PRP or SVF alone groups, with less inflammation, prominent signs of re-epithelization, more skin appendages and blood vessels, and a higher rate of hair growth. No infection or rat death occurred during the trial [80].

The following two tables summarize the clinical trials conducted in the past three years concerning the treatments of perianal fistulas whether by the use of stem cells, their secretum, or PRP (Table 1, 2).

Table1: Recent clinical trials on perianal fistulas using cellular therapy [82]

Type of Therapy	NCT number	Study Title	Treatment	Name
Cell Therapy	NCT 04010526	Evaluation of local Co-administration of Autologous Adipose derived stromal vascular fraction with microfat for refractory perianal crohn's fistulas	ADMSC (auto)	Assistance Publique Hospitaux De Marseille
	NCT 04750499	Treatment pf perianal fistulas by endorectal advancement flap associated with adipose tissue injection.	ADMSC + Flap	Hospital Clinic of Barcelona
	NCT 05210309	National project to implement mesenchymal stem cells for the treatment of perianal crohn's fistula (The prime stydy).	Darvadstrocel (Aleofisel)	Universidad de Zaragoza
	NCT 04118088	A study of Darvadstocel in adults with crohn's disease amd complex perianal fistula.		Takeda,Japan
	NCT 04701411	A study of Darvadstocel for treating complex perianal fistulas in children and teenagers with crohn's disease.		
	NCT 05113095	A survey of Darvadstocel in people with crohn's disease.		
	NCT 04847739	Seeded cells on matrix plug treating crohn's perianal fistulas.	ADMSC + Flug	Avobis Blo,LLC
	NCT 05677672	The purpose of this study is to evaluate the safety and efficacy of human TH-SC01 cell injection in the treatment of complex perianal fistula.	TH-SC01 (hUC-MSC)	Jiangsu Topcel-KH Pharmaceutical CO.,Ltd.
	NCT 05626023	A study of human TH-SC01 cell injection for treating perianal fistulas in patients with crohn's disease.		
	NCT 04519671	Mesenchymal stem cells for the treatment of perianal fistulizing crohn's disease (PFCD)	BM-MSC	Amy Lightne,the cleveland clinic

Based on this, in all healing processes, combining MSCs with PRP is more effective in encouraging vascularization, proangiogenic potential, and tissue regeneration. Following PRP therapy, MSCs produce increased VEGF and SDF-1, which promotes endothelial cell migration and substantial vessel development [81].

Table 2: Table summarizing the recent clinical trials for perianal fistulas using noncellular therapy [83,84]

Type of Therapy	NCT Number	Study Title	Treatment	Name
Secretum	NCT 05836883	Study of ExoFlo for the treatment of perianal fistulas.	ExoFlo (Exosomes derived from BM-MSC)	Direct biologics,LLC
	NCT 05402748	Safety and efficacy of injection of human placenta MSC derived exosomes for treatment of complex anal fistula	Exosomes derived from human placenta MSC	Tehran university of medical sciences
	NCT 05499156	Safety of injection of placenta MSC derived exosomes for treatment of resistant perianal fistula in crohn's patients.		
PRP	NCT 05709717	Regenerative therapy with autologous stromal vascular fraction derived MSC and PRP to treat complex perianal diseases.	SVF + PRP	Kantonsspital Winterthur KSW, Switzerland

Conclusion and Future Perspective

This review highlights the promising role of novel therapies, including MSC and PRP therapies, in the setting of perianal fistula. Both treatments are considered exciting new treatment options for patients with complex, treatment-refractory perianal fistulas. It is believed that these treatments will result in reduction in inflammation, decrease symptoms and lower the chance of flare-ups. MSC/PRP therapy is a safe treatment and has a strong immunomodulatory effect. This can reduce negative immune responses in patients with perianal fistula. So far, MSC treatment is showing the highest efficiency when compared to other conventional therapeutic options. This minimally invasive tool also avoids obnoxious side effects related to conventional surgical treatment, along with a reduction in relapses. Even though there are no studies confirming the long-term efficiency of MSC treatment and PRP treatment; however, there were also no signs of MSCs rejection, indicating a potential positive long-term outcome.

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