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Journal of Urology and Research

Case Report

Microfractured and Purified Adipose Tissue (Lipogems™ system) Injections for Treatment of Atrophic Vaginitis

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Submitted: 18 August 2016

Accepted: 24 October 2016

Published: 26 October 2016

ISSN: 2379-951X

Keywords
- Vaginal atrophy
- Adipose tissue
- Mesenchymal stem cells
- Lipogems™ system
- Stromal vascular niche

Abstract

It is estimated that 10-40% of post-menopausal women experience local symptoms related to vaginal atrophy; current treatments focus on symptom management. To mitigate these degenerative changes and associated symptoms, patients may benefit from novel treatment involving adipose-derived mesenchymal stem cells, both as a native tissue bulking agent and for the regenerative, trophic environment stimulated by these cells. This case reports details the first known case of treatment for atrophic vaginitis with mesenchymal stem cells, with promising early and late improvement in symptoms (dryness, dyspareunia). Cell-based and regenerative medicine therapies represent promising novel treatments for atrophic vaginitis and additional studies are warranted to determine clinical efficacy and long-term effect.

ABBREVIATIONS

MSC: Mesenchymal Stem Cells; cGMP: Current Good Manufacturing Practices (cGMP); FSFI: Female Sexual Function Index

INTRODUCTION

The urogenital symptoms that result from decreased estrogen levels in post-menopausal women carry significant implications for quality of life. It is estimated that 10-40% of post-menopausal women experience local symptoms related to vaginal atrophy and with an aging, active population, the prevalence of these symptoms continues to increase[1]. Broadly, these symptoms can be categorized into vaginal, urinary and sexual function symptoms, often with patients experiencing symptoms from more than one category [1]. Vaginal symptoms associated with vaginal atrophy include dryness, pruritus, bleeding, thinning and restructuring of tissues. Urinary symptoms include dysuria, irritative urinary symptoms and increased risk of developing recurrent urinary tract infections. Finally, this collective of urogenital symptoms and anatomical changes can impact sexual function, with dyspareunia being common. Clinicians should inquire regarding these symptoms as they are often underreported [2]. Urologists encounter many patients who present for work up of recurrent urinary tract infections and urinary symptoms that can be secondary to vaginal atrophy. Currently, treatment options for symptomatic vaginal atrophy include both hormonal and non-hormonal therapies. In both cases, treatment involves local administration of topical lubricants, creams or estrogen therapy, which helps to stimulate estrogen-sensitive tissues to promote a pre-menopausal vaginal environment and thus mitigate bothersome symptoms [1]. However, these treatments require ongoing therapy to maintain effectiveness and there is limited data regarding safe use of hormonal therapy in certain populations, particularly women with hormone-sensitive breast cancer. To mitigate the degenerative changes associated with menopause and aging vaginal tissues, patients with symptomatic vaginal atrophy may benefit from the promising new research involving regenerative medicine and cell therapy. In this case report, we present the use of auto logous micro fractured fat tissue product harboring mesenchymal stem cells (MSCs) and pericytes within a preserved stromal vascular niche, harvested and processed in a non-enzymatic fashion for the purpose of revitalizing atrophic vaginal tissues and improving sexual function.

Cell therapy continues to be an exciting frontier with a multitude of experimental applications in regenerative medicine. However, concerns regarding regulation and safety have resulted in strict current Good Manufacturing Practices (cGMP), a necessary but significant barrier to further development and practical clinical application[3]. Fortunately, developments in cell therapy, particularly the discovery of additional stem cell niches in numerous tissues throughout the body, as well as alternative processing methods, have increased access to more practical

and readily available sources of stem cells for clinical use [3]. Additionally, improved understanding of cell signaling holds promise for a great variety of clinical applications [3].

Recently, autologous MSC have been investigated in a number of regenerative and reconstructive fields with promising early results [4-6]. MSC represent a class of multi-potent stromal stem cells, with the potential to differentiate into a number of cell types as well as the ability to promote a regenerative environment through the use of cell signaling [7]. Previous studies demonstrated the trophic effects promoted by MSC, including angiogenic, anti-apoptotic and anti-fibrotic responses stimulated in the recipient tissues [3]. As such, MSCs have been referred to as "Medicinal Signaling Cells" by Dr. Caplan [8]. It is believed that these auto- and paracrine functions of the MSC lend additional therapeutic benefit, making them uniquely suited for clinical application in regenerative medicine [3]. Additionally, these cells can be readily obtained from adipose tissue with minimal harvesting morbidity, in a fashion similar to current lipo aspiration techniques. Thus, MSC represent an available and accessible resource that can be easily recruited for regenerative and cell-based therapies. Early studies required extensive harvesting, processing and culturing of these cells to achieve sufficient quantity for demonstrable clinical effect in other fields [6]. This significantly limited practical application. The pre-requisite *in vitro* culturing also introduced risk for infection or contamination, development of mutation in cell lines during culturing and human error [6]. However new developments in harvesting and processing, as with the minimal manipulation Lipogems™ system, presents a practical and convenient method to utilize this valuable native resource for patients.

The Lipogems™ system was initially designed to facilitate harvesting of fat graft for lipo filling as is used in classic fat grafting for reconstruction [5]. It is a closed system, using gentle mechanical forces to micro fracture harvested fat with minimal trauma to cells and with preservation of the stromal vascular niche [5]. The procedure includes two phases; lipo aspiration (harvesting) and processing. The donor site, lower or lateral abdomen, is prepared and using the Lipogems™ system disposable cannula (19cm 18G), the area injected with local anesthetic and diluted adrenaline for vasoconstriction [5]. After infiltration, the adipose tissue is harvested using standard liposuction techniques, again utilizing the Lipogems™ system disposable aspiration cannula. The aspiration cannula, 19cm 13G, is blunted to prevent additional trauma to cells during the aspiration process [5]. The substrate is then transferred to the closed processing unit, passing through a series of reduction filters after gentle mechanical manipulation to emulsify the lipoaspirate and remove oils and debris [5]. After processing, the lipoaspirate is immediately available for clinical application; the entire process takes between 15-20 minutes.

CASE PRESENTATION

In this case report, we present the first known use of MSC-based therapy for treatment of vaginal atrophy with the goal to improve sexual function and atrophic vaginitis symptoms. GB is a 50year old female who initially presented with local vaginal symptoms and sexual dysfunction, primarily citing intermittent dryness, dyspareunia and anorgasmia as her most bothersome symptoms. Clinical history was significant for three prior vaginal deliveries, including two episiotomies and subsequent development of stress urinary incontinence; she ultimately underwent hysterectomy for benign reasons and she eventually underwent mid urethral vaginal sling for stress urinary incontinence. Despite pelvic floor therapy and local medical therapy for her symptoms she had no improvement of the presenting symptoms. In hopes of addressing these issues, she agreed to undergo autologous fat grafting for treatment of atrophic vaginitis. After counseling and evaluation, the patient signed informed consent for lipofilling technique using Lipogems™ system.

Utilizing the Lipogems™ system, donor adipose tissue was aspirated from the abdominal flanks (45 cc of adipose tissue mixed with tumescent fluid) and processed, resulting in 12 cc of autologous micro-fractured lipoaspirate (Lipogems™ system). The substrate was then injected at the anterior and posterior vaginal canal, lateral walls and circumferentially around the introitus.

GB's symptoms were followed clinically via self-reported responses to the validate questionnaire, Female Sexual Function Index (FSFI). Responses were collected prior to treatment and then again at 4-weeks, 8-weeks and 10-months after treatment. The patient experienced the greatest improvement in her symptoms regarding orgasm. In response to FSFI Question 12 ("Over the past 4 weeks, when you had sexual stimulation or intercourse, how difficult was it for you to reach orgasm?"), GB's pre-treatment baseline was 1 ("Extremely difficult") and improved to 3 ("Difficult") at ten months post-treatment. Similarly, her baseline response to Question 13 ("Over the past 4 weeks, how satisfied were you with your ability to reach orgasm during sexual activity or intercourse") was 1 ("Extremely difficult") and this measure also improved to 3 ("Equally satisfied and dissatisfied") at ten months post-treatment.

While the most striking symptom improvement involved the patient's ability to achieve satisfactory orgasm, she also demonstrated improvement in lubrication and dyspareunia, Responding to FSFI Question 17 ("Over the last 4 weeks, how often did you experience discomfort or pain during vaginal penetration?"), GB's pre-treatment baseline was a score of 3 ("Sometimes"), which improved to 4 ("A few times") for all subsequent assessments (four weeks, eight weeks and ten months post treatment). Similarly, in response to FSFI Question 18 ("Over the past 4 weeks, how often did you experience discomfort or pain following vaginal penetration"), GB's pretreatment baseline was a score of 4 ("A few times"), which improved to 5 ("Never") at both four-weeks and ten months post-treatment. Regarding lubrication (Question 7: "Over the past 4 weeks, how often did you become lubricated during sexual activity or intercourse"), GB's initial pre-treatment response was a 3 ("Sometimes"), which improved to a 4 ("Most times") at both four weeks and ten months post-treatment. Overall, GB experience improvement in all identified bothersome symptoms, anorgasmia, dyspareunia and lubrication.

DISCUSSION

Vaginal atrophy in post-menopausal women may include vaginal, urinary and sexual function symptoms that can

significantly impact quality of life. Currently, treatment options available are very limited and in some cases contraindicated in some patients (hormonal treatments). Utilization of autologous MSC fat graft may represent a novel treatment for these symptoms. It is hypothesized that the therapeutic effect of this treatment is multi factorial. Patients may benefit from the immediate bulking effect of the lipoaspirate in a manner similar to autologous fat grafting for reconstructive procedures. In contrast to synthetic agents administered for urethral bulking, autologous tissue grafting represents a non-foreign body bulking agent [9]. While laser vaginal rejuvenation (Mona Lisa Touch®) purports a rejuvenation of vaginal tissues for the purpose of collagen production, previous studies focusing on the trophic effects of MSC suggest that these cells play a multi-faceted role in stromal tissue repair, revascularization and anti-fibrotic recipient tumor response [3,9]. This suggests a regenerative aspect to this MSC therapy that may positively extend the duration of clinical efficacy as atrophic tissues undergo cell-directed revitalization.

This first case report of the use of autologous MSC via lipoaspiration for the treatment of vaginal atrophy and sexual dysfunction holds promising results and future studies will further investigate objective measurements and longer-term follow-up in addition to subjective reporting to determine treatment efficacy. It will be important to evaluate treatment with objective measures, such as vaginal pH and cytologic studies of the vaginal epithelium via the Papanicolau method as objective measures of local impact on the cellular level, as well as clinical images, which have been used in other similar studies [5,10]. While more in depth studies are pending, treatment of vaginal atrophy with the Lipogems™ system preparation of MSC remains an intriguing option. As a method, it is both convenient and practical, allowing for immediate injection of the autologous prepared substrate. Employing the natural regenerative properties of the MSC and preserved stromal vascular nicheholds promise for revitalizing atrophic vaginal tissues and thus decreasing the impact of vaginal atrophy on patient quality of life.

ACKNOWLEDGEMENTS

Dr. Carlo Tremolada, MD for his expert opinion and techniques

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Cite this article

Fantasia J, Chen H, Santos Cortes JA (2016) Microfractured and Purified Adipose Tissue (Lipogems™ system) Injections for Treatment of Atrophic Vaginitis. J Urol Res 3(7): 1073.