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Determining if Platelet-rich Plasma is an Effective Treatment of Lichen Sclerosus in Adult Women

Grace McInnes

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Determining if Platelet-rich Plasma is an Effective Treatment of Lichen Sclerosus in Adult Women

Abstract

Background: Lichen sclerosus (LS) is a chronic, inflammatory tissue disease that most commonly affects adult women. The current treatment is long-term topical steroids. Platelet-rich plasma (PRP) has gained much attention as a treatment for multiple tissue disorders due to its rejuvenating qualities. The purpose of this review is to investigate PRP’s effectiveness on treating lichen sclerosus in adult women.

Methods: An Exhaustive literature search was performed using MEDLINE, TRIP, and Google Scholar and the following search terms were used “vaginal atrophy,” "lichen sclerosus,” "vulvovaginal atrophy,” "lichen simplex chronicus,” “platelet.” All studies included were within the last 5 years and of English language.

Results: The search yielded 3 articles that met criteria. All 3 articles were case studies. There was an overall trend in all 3 articles that PRP treatment improves the clinical course of LS as well as improves patients’ symptoms. However, the overall quality of the articles is very low due to limitations and high risk of bias (see Table 1). Future studies are needed to yield a higher grade of research for more definitive conclusions on this topic.

Conclusion: While the studies that investigated the effects of PRP treatment on adult women with LS had an overall positive trend, more research is needed due to the very low quality of evidence. Randomized controlled trials with larger sample sizes, blinding, and adequate follow-up times are needed to better determine the effects of PRP on LS in adult women. Only then will medical professionals have a better idea if PRP can replace topical corticosteroids as the gold standard for treatment.

Keywords: Lichen sclerosus, vaginal atrophy, vulvovaginal atrophy, lichen simplex chronicus, platelet.
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Determining if Platelet-rich Plasma is an Effective Treatment of Lichen Sclerosus in Adult Women

Grace G McInnes

A Clinical Graduate Project Submitted to the Faculty of the
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Faculty Advisor: Dr. Mark Pedemonte
Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

Grace Gontarski McInnes is a native of California. She received her BS in Dietetics from Point Loma Nazarene University and went on to complete her dietetic internship at UCSD in San Diego, CA. She moved back to her hometown of Orangevale as a Registered Dietitian and worked at Whitney Oaks Care Facility for nearly two years before beginning her PA school journey. She enjoys outdoor activities such as running, cycling and playing outside in her free time.
Abstract

**Background:** Lichen sclerosus (LS) is a chronic, inflammatory tissue disease that most commonly affects adult women. The current treatment is long-term topical steroids. Platelet-rich plasma (PRP) has gained much attention as a treatment for multiple tissue disorders due to its rejuvenating qualities. The purpose of this review is to investigate PRP’s effectiveness on treating lichen sclerosus in adult women.

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**Keywords:** *Lichen sclerosus, vaginal atrophy, vulvovaginal atrophy, lichen simplex chronicus, platelet.*
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Table 1: Quality Assessment of Reviewed Studies

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<th>Description</th>
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<td>FSFI</td>
<td>Female Sexual Function Index</td>
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<tr>
<td>ICIQ-VS</td>
<td>International Consultation on Incontinence Questionnaire – Vaginal Symptoms</td>
</tr>
<tr>
<td>LS</td>
<td>Lichen Sclerosus</td>
</tr>
<tr>
<td>PRP</td>
<td>Platelet-rich Plasma</td>
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<td>SCC</td>
<td>Squamous Cell Carcinoma</td>
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Determining if Platelet-rich Plasma is an Effective Treatment of Lichen Sclerosus in Adult Women

BACKGROUND

Lichen sclerosus (LS) is a chronic, immune-mediated skin disease that typically affects the anogenital region.\(^1\) While LS can affect anyone at any age, most cases occur in both prepubertal and postmenopausal women.\(^1,2\) While the exact etiology and pathogenesis is unknown, trauma, chronic irritation, and hormonal changes all seem to contribute as potential causative factors. There is also evidence showing that pre-existing autoimmune-related diseases and/or a family history of LS may also contribute to one developing LS.\(^3,4\) LS may be asymptomatic in some or may cause unpleasant complications such as erosions, atrophy and scarring. These complications are a result from the inflammation the disease causes and may lead to altered fibroblast function and fibrosis of the upper dermis. As the disease progresses, scarring may increase, leading to a loss of the labia minora, sealing of the clitoral hood, and burying of the clitoris.\(^5\) Many women also experience pruritis, dyspareunia, dysuria and genital bleeding which can decrease one’s quality of life, especially sexual satisfaction. These negative side effects are further compounded by the lack of estrogen in postmenopausal women.\(^5\) Furthermore, LS has been known to develop into squamous cell carcinoma (SCC). "There is
a 4% lifetime risk of developing SCC among LS sufferers\textsuperscript{6} and histopathological examination of vulva SCC cases shows that over 60% have a background of LS.”\textsuperscript{7}

Women dealing with LS and the negative side effects that accompany the disease are faced with not only physical ailments, but emotional and psychological issues as well that require extensive counseling and support. Currently, there is no cure for LS, though some few patients have been known to experience spontaneous remission.\textsuperscript{1} The most common existing treatment is topical steroids and these focus merely on symptom relief. Furthermore, they are used long-term and consequently, compliance rates among many patients are low.\textsuperscript{2} There are no universally accepted treatment recommendations based on type and duration of steroid use, however, some studies show success with “Clobetasol propionate (0.05%) twice daily for 2 to 3 months with gradual dose lowering.”\textsuperscript{8} Unfortunately, topical corticosteroids have negative side-effects of their own, especially in long-term use. These can include cutaneous atrophy, adrenal suppression, hypopigmentation and contact sensitivity such as burning, itching, dryness, flaking and maceration. Furthermore, once the patient stops using the topical steroid, their symptoms and disease progression are likely to return and potentially worsen.\textsuperscript{1}
Platelet-rich plasma (PRP) is an “autologous preparation of platelets in concentrated plasma.” It has gained much attention in the medical field due to its regenerating qualities. PRP contains an abundant amount of growth factors, including platelet-derived growth factor (PDGF), transforming growth factor (TGF), vascular endothelial growth factor (VEGF), and insulin-like growth factor (IGF). These factors are pertinent in stem cell migration, differentiation and proliferation. Some hypothesize that PRP may encourage collagen synthesis and other matrix components in the skin by stimulating fibroblasts which are responsible for neovascularization and deposition of new extracellular matrix. PRP treatment has already been successful clinically in tissue regeneration, reconstructive and plastic operations, and surgery, including wound hemostasis, wound sealing, augmentation of bone grafts periodontics, and treatment of tendonitis.

LS could be the next tissue disease that benefits from PRP treatment. This review’s purpose is to look at studies that used PRP injections as treatment for adult women that suffered from topical steroid-resistant LS in hopes that, someday, PRP could become the main treatment for LS.
METHODS

An Exhaustive literature search was performed using MEDLINE, TRIP, and Google Scholar and the following search terms were used; ("vaginal atrophy" OR "lichen sclerosus" OR "vulvovaginal atrophy" OR "lichen simplex chronicus") AND "platelet." Eligibility criteria included studies that used adult women as participants with lichen sclerosus and consented to receive PRP as treatment of their disease. All studies included were within the last 5 years and of English language. Studies were assessed for quality using GRADE criteria.¹⁵
RESULTS

An initial search of MEDLINE using the keywords listed above yielded 11 articles. These were reviewed and 3 articles\(^2,5,16\) met eligibility criteria. All 3 of the studies were case studies. A search of TRIP using the same keywords yielded 19 articles for review. None of the 19 articles met eligibility criteria. Finally, a search of Google Scholar was performed using the same keywords and 739 results appeared. The first 10 pages of articles were reviewed, and 3 articles met eligibility requirements; the same articles that were originally found with MEDLINE. In conclusion, this review analyzes a total of 3 articles.


In this case series,\(^5\) 28 adult women between the ages of 22 to 88 years (M=60) who attended FBW Gynaecology Plus from 2013 to 2016 were enrolled. Twenty-six out of the 28 had confirmed LS on biopsy, yet colposcopy suggested the existence of LS in all 28 patients. All patients’ symptoms were reported as unresponsive to steroids and patients were instructed to cease use of steroids during the study’s course.\(^5\)

Patients had their own blood drawn (10mL) and centrifuged (Regens Lab, New York, N.Y.) on site and injected after being given
local anesthesia. The PRP was injected with a 27 G needle to any affected areas of the women’s external genitalia, including the labia majora, labia minora, clitoris and clitoral hood. The author describes the injection technique as using “a fanning motion to break the scar and fibrotic tissue” and then to inject the PRP in a retrograde fashion into the tissue. Patients received a total of 4 PRP treatments; 3 PRP treatments with 4 to 6 weeks in-between each treatment and then 1 final treatment at 12 months. They were verbally interviewed about their symptoms after each treatment and lesions were evaluated via colposcopy. Patients found to have vulval intraepithelial neoplasia (n=2) were excluded from the study. A verbal scale from 0 to 10 was used after each treatment to measure post-treatment pain and patients were asked to complete the Australian Pelvic Floor Questionnaire 24 at baseline and at 2 to 3 months after the final PRP treatment. This questionnaire measured urinary incontinence, general bladder function, prolapse, and sexual function. “Changes in lesion size, symptoms, and need for topical steroid use were compared from pre- to post-treatment using the Wilcoxon signed-rank test” and “statistical analyses were performed using SPSS Statistics version 21.0 (IBM, Chicago, Ill.).”

Twenty-five of the 28 participants exhibited clinical improvement in the size of their lesions and of those, 8 of the participants’ lesions
disappeared completely. “A Wilcoxon signed-rank test indicated that there was a statistically significant decrease in the number of patients with lesions after the PRP treatment (Z=-4.562; P<0.001).” Before treatments, patients complained of severe itch, soreness, discomfort, and/or dyspareunia. Fifteen of the 28 participants were symptom free after the last treatment at 12 months or more. “A Wilcoxon signed-rank test showed a statistically significant decrease in the presence of symptoms after treatment (Z=-4.768; P<0.001).” After the final treatment of PRP, 82.1% of the patients (n=23) no longer needed to use steroids, and the remaining 17.9% (n=5) reported using them intermittently. “A Wilcoxon signed-rank test showed a statistically significant decrease in steroid use after treatment with PRP (Z=-4.963; P<.001).” The authors noted a trend of declining responses to the Australian Pelvic Floor Questionnaire when comparing pre- and post-treatment scores, however, these were not statistically significant. There were zero cases of infection, bleeding, hematoma or other adverse outcomes. Patients did report minimal to moderate pain during the 24 hours after the procedure: 26 patients (92.9%) reported pain scores of 2 to 3, and the remaining 2 patients reported scores of 5 and 7.

The second study is a case study\(^2\) of a 38-year-old premenopausal woman. She complained of itching, burning, stiffness and pain in her external genital area, and reported impaired sexual activity related to a narrow and thick vaginal introitus. Her condition was refractory to corticosteroid ointment as well as moisturization with emollients. She reported using pH-neutral soaps as well as 2% testosterone gel, all to no avail. To measure her symptoms, she was asked to complete the validated International Consultation on Incontinence Questionnaire – Vaginal Symptoms (ICIQ-VS) instrument rating scale. Her total vaginal symptoms score was 42, her total sexual symptoms score was 42, and her score for quality of life as affected by LS was 8. She also completed the Female Sexual Function Index (FSFI) before and after PRP treatment. This measured desire, arousal, lubrication, orgasm, satisfaction and pain with an initial score of 3.6. Her pretreatment biopsy showed fully developed LS, with epidermal atrophy, hyperkeratosis, subepidermal edema with hyalinization and dilated vessels as well as sparse lymphocytic infiltrates beneath.\(^2\)

The patient’s PRP treatment was prepared from autologous blood from a venous sample using Regenkit®. Anesthetic gel was applied to the vulva and left for 10 minutes before 4mL of PRP was injected
subdermally with a 23 G needle. This same therapy was repeated two months later, in the same fashion, with the exception that two tubes of Cellular Matrix Regenkit were used to attain 8mL of PRP. The patient returned two months after the second treatment for follow-up measurements. Her posttreatment biopsy showed a nearly normal epidermis with restored upper dermal cellularity. She reported feeling comfortable, symptom-free, and stated that her sex drive had returned, and her quality of life had increased significantly. Her posttreatment ICIQ-VS total score improved to 7; her sexual matters score improved to 0; and her quality of life score improved to 0. Her full-scale FSFI score improved to 32.6.²

The author concludes that this case study shows PRP may be a “promising new treatment for female genital LS, as it promotes regeneration and leads to cessation of symptoms, which is generally not achieved with the standard current therapy options.”²

**Goldstein AT, King M, Runels C, Gloth M, Pfau R (2017)**

The final study was a pilot case series¹⁶ that included 15 adult women with biopsy-proven vulvar lichen sclerosus. Each participant received 2 separate treatments of PRP with 6 weeks in-between treatments. Each treatment was comprised of 5mL of autologous PRP, using the Magellan Autologous Platelet Separator System, Arteriocyte Medical Systems. The PRP was injected subdermally and
intradermally. Post-treatment biopsies were taken 6 weeks after the second treatment. Patients were prohibited from using additional medications while the study took place.¹⁶

The primary efficacy variable that the study looked at was change in inflammation between the pre- and post-treatment biopsies. These were measured by 2 masked dermatopathologists. Secondary endpoints were changes from baseline in pruritis and vulvar burning using visual analogue scales (VAS) and change in Investigator’s Global Assessment (IGA) of the severity of the disease, using 0 to 3 scale. Out of the 15 original participants, 12 completed the entire study; 2 patients were lost to follow-up before the second PRP treatment and one refused to have the post-treatment biopsy performed. Results from the biopsies of the 12 remaining participants showed that 7 had decreased inflammation, 3 had no change, and 2 had a “minimal” increase in inflammation. A repeated measures ANOVA showed the results were statistically significant (p=0.024) and a paired-sample t-test comparing the pre- and post-treatment IGA scores showed a statistically significant difference as well: pre-treatment (M=2.67, SD=0.49) and post-treatment (M=1.83, SD=0.83); t(11)=3.4578, p=0.0054. The results showed that changes in subjective VAS scores for pruritis and burning were not statistically significant and no
adverse side effects were reported during the study with the exception of transient discomfort and bruising at biopsy and injection sites.\textsuperscript{16}

The authors conclude, “the statistically significant results suggest that PRP decreased histopathologic inflammation in women with VLS without potential side effects associated with topical or systemic immunomodulators.”\textsuperscript{16}
DISCUSSION

The 3 studies\textsuperscript{2,5,16} show an overall positive trend of injecting PRP as treatment for LS in adult women. The studies’ purposes were to find an alternate treatment for women whose condition failed on topical corticosteroids. In all 3 studies, the majority of women found that their lesions improved or even disappeared completely after the PRP treatments. Additionally, most found a decrease in their accompanying symptoms and therefore an increase in their quality of life. The studies also found minimal side effects with PRP treatment, indicating that the safety of this treatment may be superior over long-term use of corticosteroids. The only side effects reported were minimal pain and bruising at sites of injections and biopsies and Golstein et al’s study found a “minimal” increase of inflammation on two of the participants’ post-treatment biopsies.\textsuperscript{2,5,16} Behnia-Willison et al notes that “the PRP procedure is minimally invasive and safe and may be performed in an office setting under local anesthesia.”\textsuperscript{5}

While the safety of PRP treatment was proven in these studies,\textsuperscript{2,5,16} more research is required on this topic due to the many limitations and risk of bias these studies included. The risk of bias was great in all of the studies since they were not blinded. The Goldstein et al study\textsuperscript{16} does mention a form of blinding to determine the extent of the inflammation on the pre- and post-treatment biopsies as 2
masked dermatopathologists were used. Also, all of the studies were case studies/series, indicating a very low quality of evidence due to their small sample sizes and lack of comparing the therapy to a control group (see Table 1). Behnia-Willison et al\textsuperscript{5} even notes, “it is conceivable that the observed improvements in LS symptoms after PRP treatment were partially or wholly due to the tissue needling involved in the PRP injection process rather than to a simple effect of the PRP in and of itself.” Another flaw in these studies was that there was not sufficient follow-up time with participants. Pugliese et al\textsuperscript{1} noted in their review, corticosteroids may help manage LS when applied in a consistent manner, but when they are stopped, the patient’s symptoms are very likely to return. None of the studies continued to follow-up with participants after the final PRP treatment. Therefore, it is unknown whether or not patients would need to continue to return to clinic for maintenance PRP treatments to keep their LS under control or from returning. Another area of weakness in the studies is their variability in methods. Each study used a different amount of PRP in their injections, different time between treatments, and even different numbers of treatments.

Due to the very low quality of evidence of all 3 of the studies,\textsuperscript{2,5,16} more research is needed before PRP treatment becomes the gold standard of treatment in LS in adult women. Randomized
control trials should be developed and executed with ample population sizes, randomization techniques, double-blinding, control groups and adequate follow-up time. Behnia-Willison et al\textsuperscript{5} states in their study that they “intend to conduct a double-blind RCT in which one group is randomized to a saline injection, with a second group randomized to PRP treatment.” Goldstein is listed as a principle investigator for a “randomized single-blind placebo controlled trial to evaluate the efficacy and safety of autologous Platelet-rich Plasma (PRP) for the treatment of vulvar lichen sclerosus” which just finished up June 2018.\textsuperscript{17}
CONCLUSION

PRP treatment is gaining popularity in tissue diseases due to its regenerative qualities and lichen sclerosus is one of the next diseases that may benefit from it. The studies in this review support the idea that PRP could be an effective treatment and possibly replace topical steroids as the gold standard in treatment of LS in adult women, however, more research is needed due to these studies’ very low quality of evidence. Good news is that there are promising studies currently taking place that will likely bring forth higher quality data in an effort to prove PRP is an effective treatment for adult women with LS.
References


Table I: Quality Assessment of Reviewed Articles

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Downgrade Criteria</th>
<th>Upgrade Criteria</th>
<th>Quality</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Limitations</td>
<td>Indirectness</td>
<td>Inconsistency</td>
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<tr>
<td>Behnia-Willison et al(^5)</td>
<td>Case Series</td>
<td>Serious(^{a,b,c})</td>
<td>Not Serious</td>
<td>Not Serious</td>
</tr>
<tr>
<td>Franic et al(^2)</td>
<td>Case Study</td>
<td>Serious(^{a,b,c})</td>
<td>Not Serious</td>
<td>Not Serious</td>
</tr>
<tr>
<td>Goldstein et al(^16)</td>
<td>Case Series</td>
<td>Serious(^{a,b,c})</td>
<td>Not Serious</td>
<td>Not Serious</td>
</tr>
</tbody>
</table>

\(^a\) Lack of blinding and control group  
\(^b\) Use of subjective questionnaire to determine outcomes  
\(^c\) Inadequate follow-up time  
\(^d\) Small sample size

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