

Efficacy of 5-10% Topical Sinecatechins Ointment for Postmenopausal Vestibulodynia

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INTRODUCTION

Most postmenopausal women who experience pain with penetration also have localized provoked vestibulodynia. The majority of these women do not use any hormonal treatments. Of those women who do use hormones, 31% continue to experience vestibulodynia. (1)

Topical green tea, *Camelia sinensis*, ointment has been shown to significantly reduce the severity of pain in the vulvar vestibule of premenopausal women post episiotomy, in some, as early as five days. (2)

15% sinecatechins ointment is a topical FDA approved botanical drug, made from green tea. It is applied to the external genitalia, including the vulvar vestibule, three times daily for its antiproliferative, antiviral effects in the treatment of genital warts. Irritation is a common side effect.

Epigallocatechin gallate, (EGCg) is the major (59%) active catechin component of sinecatechins ointment.

(EGCg), exerts antiproliferative, antitumor effects on breast, endometrial and ovarian cancer cells. (3)

Sensations of sexual pleasure can elevate pain thresholds. (4)

Unmyelinated afferent C-fibers (UACfibers), are polymodal, innervating the vulvar vestibule transmitting both sensations of pain and sexual pleasure, erotic touch. (5,6)

In Persistent Genital Arousal Disorder (PGAD) there is an increase in activity of the UAC-fibers caused by injury or pharmacologic influence. In vestibulodynia, a Genito Pelvic Pain Disorder (GPPD) there is an overgrowth, proliferation of UAC-fibers.

Erotic sensations are also carried by cutaneous UAC-fibers. Both PGAD and GPPD both have been characterized as genito-pelvic dysesthesias in which unpleasant genital conditions are classified according to predominant presenting symptoms (e.g., pain vs arousal) (7).

Vestibulodynia is characterized by a hyperplasia of unmyelinated afferent C-fibers. A local inflammatory renin-angiotensin system drives sensory axonal sprouting of unmyelinated afferent C-fibers (UAC-fibers) in provoked vestibulodynia induced thru activation of angiotensin II Type 2 receptors. (8,9) EGCg blocks both human renin activity (10), human angiotensin converting enzyme (11).

OBJECTIVES

This study was undertaken to:

1. evaluate the efficacy of 5% and 10 % topical sinecatechins ointment to significantly reduce provoked vestibulodynia in sexually active postmenopausal, and
2. demonstrate that sinecatechins ointment, an antiproliferative drug, when applied to the vulvar vestibule had no significant effect on the vaginal mucosa, and
3. note any subjective effects of topical sinecatechins ointment on sexual arousal, lubrication and/or orgasmic response, given that the same UAC-fibers transmit sensations of pain and sexual arousal.

FUNDING AND CONTACT INFORMATION

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MATERIALS AND METHODS

32 postmenopausal sexually active women with a chief complaint of significant to severe secondary provoked vestibulodynia were enrolled into this randomized, double-blind, placebo-controlled clinical trial. Each woman received either placebo, 5% or 10% sinecatechins ointment. Statistical analyses on the pain scores for both the Q-tip test and the Numerical Rating Scale Assessment were performed using a one-way ANOVA analysis.

Vaginal pH and maturation index were done at each of three office visits. All except one patient were not using any hormonal therapeutic for at least one month prior to enrolling in the trial. One woman who was using topical vaginal estrogen cream continued her use for the duration of her participation in the trial.

Localization and severity of pain was documented by standardized Q-Tip testing. To qualify, at least one of seven points on the vulvar vestibule had to have a pain score of 7 or above (significant to severe) to be included. Subjects indicated their overall subjective vulvar vestibular pain on the same 0-10 point Numerical Rating Scale where 0 no pain; (1-3) mild pain; (4-6) moderate pain;(7-9) significant pain; (10) severe pain.

Subject were asked to comment on any subjective sexual sensations.

Subjects applied ½ inch of ointment once daily (5% sinecatechins, 10% sinecatechins or placebo) to the vulvar vestibule, avoiding the urethral introitus. Subjects were asked to immediately report any irritation, and to reduce use to three times per week. Subjects were seen initially and in two subsequent office visits 2 to 3 weeks apart for evaluation of their vestibulodynia.

RESULTS

There was no significant difference in the average vestibular pain between the placebo, 5% and 10% at baseline. Both 5% and 10% active study drug groups showed a progressive decrease in the **one-way ANOVA P-Values** with each visit, indicating a greater degree of pain reduction with continued use of the active study drug.

Based on the Q-tip and NRS Comparison graphs, **Study Group B5** (5% sinecatechins) demonstrated early improvement in pain reduction at Visit 2, while **Study Group B10** (10% sinecatechins) demonstrated pain reduction by final Visit 3, most likely attributed to irritation experienced by several of B10 subjects which was typically resolved by the final visit with decreased frequency of use to no more than 3x/week.

All study groups showed no significant change in vaginal maturation index or vaginal pH between initial and final visits, thereby confirming that the active drug, sinecatechins, an antiproliferative, did not affect the proliferation of the vaginal epithelium.

Clinical Study Findings & Statistical Evaluation

- Standardized Q-Tip Tests and Numerical Rating Scale Assessments were performed in parallel over three office visits to measure subject pain and to cross-validate data quality and accuracy
- Subjects that received the active study drug in **Study Group B5** (5% Sinecatechins) and **Study Group B10** (10% Sinecatechins) indicated a downward trend in average pain scores across both pain assessment methods
- Based on a **one-way ANOVA analysis**, a statistically significant improvement in pain reduction (P-Value < 0.05) is shown in the ANOVA P-Value tables below where a significant improvement can be observed by the **Qtip Test final Visit 3** (P-Value = **0.048**) and by the **NRS Assessment Visit 2** (P-Value= **0.035**) followed by an even greater significant improvement by final Visit 3 (P-Value = **0.0011**)

Analysis of Qtip Averages by Group

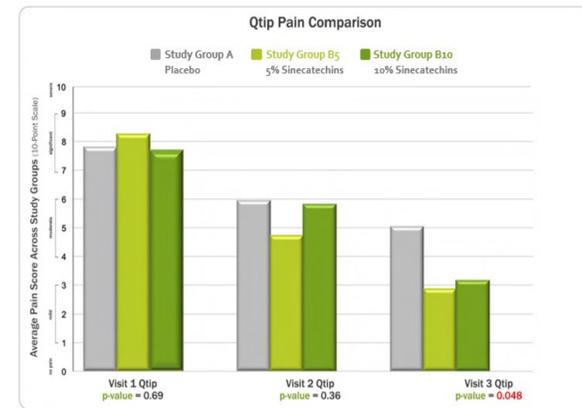
One-Way ANOVA Analysis: Q-Tip Test	Visit 1	Visit 2	Visit 3
Qtip ANOVA P-Value	0.69	0.36	0.048

Analysis of NRS Averages by Group

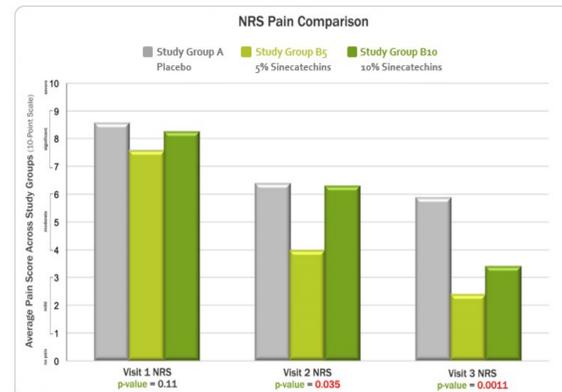
One-Way ANOVA Analysis: NRS Assessment	Visit 1	Visit 2	Visit 3
NRS ANOVA P-Value	0.11	0.035	0.0011

RESULTS

Standardized Q-Tip Test



Numerical Rating Scale (NRS) Assessment



Several subjects using 10% sinecatechins ointment with reduced frequency to three times per week subjectively reported an increase in pleasurable sexual sensations in addition to a significant reduction in their vestibulodynia.

Examples of subjective comments by subjects are:

“increased sexual desire... masturbation was less uncomfortable and more intense [orgasm] and quicker” [Subject qd9]

“It was very helpful... It was easier to have sex. Less painful... It is easier to be aroused.” [Subject 2xj]

The one subject who was using estrogen reported an adjunctive benefit of her use of sinecatechins ointment with estrogen cream: “I’ve continued to use the ointment in conjunction with estrogen cream and it’s helped immensely.” [Subject lw3]

“using ointment 2x/week decrease in irritation, feeling slight genital arousal” and “next day feels increased secretion for 2 days” [Subject ps0]

“less pain, and increase in genital sensations and secretions” [Subject 3pv]

CONCLUSIONS

Topical 5% sinecatechins ointment applied once daily or 10% sinecatechins ointment applied three times a week significantly reduced provoked secondary vestibulodynia in postmenopausal women without having a proliferating effect on the vaginal epithelium, offering a therapeutic alternative for the alleviation of vestibulodynia for women with a history of an estrogen sensitive malignancy, including those on an aromatase inhibitor,

5-10% topical sinecatechins ointment may be used adjunctively to alleviate persistent vulvar vestibular pain in women who are successfully using estrogens to treat vaginal atrophy.

The observed clinical effects of topical sinecatechins ointment on reducing vestibulodynia was dependent on both the concentration of sinecatechins and the frequency of application.

Since 15% sinecatechins ointment applied three times daily to the vulvar vestibule is frequently irritating, the efficacy of sinecatechins ointment as a treatment for vestibulodynia was previously unrecognized.

Although not the primary objective of this clinical trial, several subjects indicated that topical 10% sinecatechins ointment used 3x/week increased sexual arousal, increased lubrication and/or decreased latency to orgasm without causing irritation.

The syndromes of persistent genital arousal disorder, vestibulodynia, restless leg syndrome, and urinary bladder sensitivity are frequently seen in the same women. The peripheral pathophysiological component of each of these is a neuropathy of the small C-unmyelinated sensory fibers.

Both erotic touch sensation and nociceptive pain sensation are transmitted through unmyelinated afferent C fibers..

Given that UAC-fibers transmit both sensations of pain and sexual arousal there is a potential therapeutic use of topical sinecatechins ointment for decreasing provoked vestibulodynia while increasing sexual arousal, lubrication and facilitating orgasm in postmenopausal women. The proposed mechanism, in part, through EGCg’s effect on the local tissue renin angiotensin system.

Future separate clinical trials, for pre- or postmenopausal women with a chief complaints of provoked vestibulodynia, hypoactive sexual arousal and difficulty in achieving an orgasm are needed.

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