

The impact of topical esterified L-Arginine on female sexual dysfunction

Michael J. Pelekanos M.D., Knox VanDyke Phd., Elizabeth Knepp M.D., B. Bernard Peticca M.D. Mier Sacks Phd.

Pittsburgh Pennsylvania

OBJECTIVE: The aim of this study was to determine whether a patent pending modified topical L-Arginine cream could improve female sexual dysfunction when applied to the clitoral hood prior to intercourse

STUDY DESIGN: A group of 20 women were studied prospectively in a placebo controlled double blind study. Each patient was given 2 identical tubes of cream one active and one placebo and instructed to apply the cream to the clitoral hood at least ten minutes prior to intercourse. The tubes were labeled "A" and "B". After intercourse they filled out the same questionnaire. Comparisons were made with the paired t test p values < .05 were considered significant.

RESULTS: Of the 20 patients recruited 18 completed the study. A positive response was determined from the questionnaires provided. Details on how a positive result was scored are included in the discussion. There was a 50% positive result to the active ingredient with 5.5% positive result to the placebo. The results are statistically significant with a p value of < .05

CONCLUSIONS: Sexual aids have significant placebo responses. Despite the small numbers this prospective placebo controlled double blind study demonstrated a significant improvement in sexual response with the topically applied proprietary modification of L-Arginine

Key words: L-Arginine ethyl ester, clitoral hood, anorgasmia, libido

The incidence of female sexual dysfunction is reported in the literature to be as high as 60%. In one large study of 1767 patients FSD (female sexual dysfunction) was reported to be 43% while the reported incidence in males was reported to be 31%. A unified classification of FSD has been established by the WHO and further categorized by the American Psychiatric association. Despite the magnitude of this problem there are as of yet no FDA approved pharmacologic agents for the treatment of FSD. There are many etiologies for FSD. Medical conditions such as diabetes and multiple sclerosis can decrease genital sensation. Medical treatment with SSRI's has been associated with decreased orgasmic response and varying degrees of genital anesthesia. Because the response to various treatment modalities is subjective and because interventional modalities in FSD have a significant placebo response, it was decided to prospectively study 20 patients using themselves as their own controls.

There are many over the counter preparations that contain L-Arginine and they claim to aid in sexual function. L-Arginine is a zwitter ion and having the properties of a zwitter ion it cannot cross human squamous epithelium to any significant degree. Some of these preparations contain menthol which is an irritant to human skin. By irritating the skin these products will

allow some of the L-Arginine to cross but again not to any significant degree. In order to nullify the charge effect L-Arginine ethyl ester was substituted for standard L-Arginine as there is evidence this compound crosses squamous epithelium to a significant degree. There is good evidence that L-Arginine is a potent vasodilator once it crosses the squamous epithelium. By dilating the vessels and thus increasing blood flow to the clitoris sexual response is enhanced.

The purpose of this study was to show that the proprietary cream containing L-Arginine ethyl ester when topically applied to the clitoral hood would improve sexual response when compared to placebo.

Material and methods.

Study design. Twenty women were enrolled in a prospective double blinded placebo controlled trial with each women serving as her own control. Eighteen of the women completed the trial. The patients ranged from 33 to 62 years of age with a mean age of 45. Each patient was given two identical tubes of cream containing one gram each . One of the tubes contained the vehicle aquaphor ointment available commercially and the second tube contained L-Arginine ethyl ester at a concentration of 40% mixed with the aquaphor. The patients were instructed to apply the cream to the clitoral hood 5 minutes prior to intercourse and to follow the same routine prior to intercourse with each sample. The subjects were required to respond to the same 8 questions after the use of each sample (sample "A" or sample "B") The questions were as follows:

1. Did sample "A" help you get lubricated more than you normally do on your own?
2. Did sample "A" help you maintain your lubrication more than you normally do on your own?
3. If you have had problems with achieving an orgasm did sample "A" help?
4. If you normally achieve orgasms did sample "A" improve the quality or intensity of your orgasm?
5. If you normally do not achieve orgasms did sample "A" improve the quality of your sexual experience?
6. What medications are you currently taking?
7. Prior to using sample "A" did you consume any alcoholic beverages? If so how much?
8. On the reverse side briefly describe in your own words how this sample has changed this sexual encounter for you. Please note any side effects.

The response options for questions 1-5 were as follows: a. Not at all, b. Somewhat, c. Definitely d. Tremendously. If the subject recorded a two letter increase in at least 2 of the first 5 questions a positive response to that particular cream was recorded. The subjective response to question 8 could not alter the response status the subject had to that particular sample.

Results

The table below summarizes the results:

SUBJECT	AGE	DEFICIT	POSITIVE A	POSITIVE B	NO RESPONSE
1	33	ANORGASMIA	DELTA 12		
2	62	AROUSAL DISORDER	DELTA 5		

3	38	NO DEFICIT			DELTA -5
4	43	AROUSAL DISORDER			DELTA 4
5	39	DECREASED LIBIDO			DELTA -4
6	49	NO DEFICIT	DELTA 7		
7	41	ANORGASMIA	DELTA 7		
8	50	DECREASED LIBIDO		DELTA -7	
9	44	HYPO ORGASMIA	DELTA 7		
10	34	NO DEFICIT			DELTA 0
11	51	ANORGASMIA	DELTA 6		
12	62	AROUSAL DISORDER	DELTA 5		
13	38	AROUSAL DISORDER			DELTA -2
14	42	AROUSAL DISORDER			DELTA 0
15	48	ANORGASMIA			DELTA 6
16	50	DECREASED LIBIDO			DELTA -5
17	52	HYPO ORGASMIA	DELTA 7		
18	35	DECREASED LIBIDO	DELTA 9		

Once the responses were returned it was revealed that sample “A” was the active cream containing L-Arginine ethyl ester. With the premise that a positive response to “A” or “B” could only be recorded if there was a two grade improvement in at least 2 of the first 5 questions the results are as follows: 9 of 18 positive for the active cream(50%) with 1 of 18 positive to the placebo(5.5%) and 8 of 18 non responders(44%). Using the paired t- test the response of the active vs the placebo in this small group is statistically significant with a p value <.05. The fact that some of the Deltas in the no response group were similar to the positive responders is explained by the fact that these subjects did not have a two grade improvement in at least 2 of the 5 questions. For instance subject 15 improved with the active cream one grade in 4 of the 5 questions and two letter grades in only one of the five questions hence a no response result.

Comment

The association of L-Arginine as a potent NO donor and subsequently a potent vasodilator is well documented. Oral administration of L-Arginine in significantly large doses(greater than 5 grams) can cause systemic vasodilatation with subsequent drop in blood pressure. Enhanced sexual response and enhanced sensitivity has been linked to increases in clitoral blood flow. Oral administration of L-Arginine is an inefficient method to adequately enhance clitoral blood flow in order to have an impact on sexual response. The only FDA approved aid for female sexual dysfunction is not a drug but a device, the EROS-CTD clitoral suction cup. The efficacy of this device depends on its ability to increase blood flow to the clitoris. Their studies also support the evidence that increasing blood flow to the clitoris will increase sexual responsiveness. The drawback of this device is that it is cumbersome, expensive, and unappealing to those women who do not wish to disclose their use of a sexual aid. There are several over the counter topical L-Arginine preparations that make claims of promoting sexual health (see table below)

PRODUCT	STUDY CREAM	SENSITILLE	LADY-Vi	CLIMATIQUE	VIGEL	VIACREAM
Double blinded clinical results	yes	no	no	no	no	no
Menthol,Mint (irritant)	no	yes	yes	yes	yes	yes
Active Ingredient	L-Arginine ethyl ester	Standard L-Arginine	Standard L-Arginine	Standard L-Arginine	Standard L-Arginine	Standard L-Arginine

To date there are no double blinded published studies with any of these preparations. All the preparations contain menthol except the study cream. Menthol when applied topically is a skin irritant and like other menthol containing creams i.e. Ben Gay™ gives a sensation of warmth without causing vasodilatation. Menthol must be added to these preparations because standard L-Arginine does not cross squamous epithelium for reasons explained above. A local inflammatory response incited by the menthol may facilitate some transfer of standard L-Arginine. This inflammation mediated partial transfer of standard L-Arginine may be the basis of the limited success reported with these products. Even with the small numbers in the study there is no question as to the significance of the positive response of the modified L-Arginine preparation compared to placebo.

The fact that there were nearly as many responders as non responders can be explained by the fact that female sexual dysfunction is complex and multi faceted. Of the eight non responders 3 had arousal disorder, 2 had no deficit, 2 had decreased libido, and 1 had anorgasmia. Arousal disorder is compromised of four subgroups. (see table below)

SUBTYPES OF AROUSAL DISORDER	GENERALIZED FEMALE SEXUAL AROUSAL DISORDER	GENITAL AROUSAL DISORDER	MISSED AROUSAL	DYSPHORIC AROUSAL
MENTAL EXCITEMENT	ABSENT	PRESENT	ABSENT	ABSENT
GENITAL CONGESTION	ABSENT	ABSENT	PRESENT	PRESENT
VASOACTIVE MEDICATION LOGICAL?	NO	YES	NO	NO

Generalized arousal disorder includes women who lack mental excitement but they also have minimal genital engorgement. In missed arousal patients genital engorgement occurs but is ignored or is accompanied with minimal mental attention. Dysphoric arousal patients find genital engorgement uncomfortable and thus the mental excitement is not there. The only subtype that would seem to benefit from a vasoactive agent would be genital arousal disorder. These patients are excited mentally but lack the genital response.

There is good evidence in the literature that libido is androgen driven. At the time of menopause estrogen levels quickly drop over a relatively short period of time. Ovarian androgen production continues for years and the drop in levels is much less acute than seen with estrogen. This is precisely why surgically castrated women are more prone to disorders in libido than women going through natural menopause. The only FDA approved estrogen androgen combination Estratest™ has shown to improve libido significantly more than estrogen alone. There are several androgen receptors in the brain. Clearly there is a CNS role in stimulating libido by androgens. It is entirely possible that patients with libido problems should be treated with androgens instead of vasoactive meds but further confusing this issue is that androgens also increase genital blood flow which has been confirmed by clitoral plethysmography studies.

Summary

L-Arginine's ability to cause vasodilatation is well defined and documented. With the modification of L-Arginine on its ethyl group L-Arginine is now able to cross squamous epithelium. With the ability to cross squamous epithelium new therapeutic modalities are now a possibility. Any medical condition that would benefit from local vasodilatation, like wound healing and circulatory disorders are now a possibility. Female sexual dysfunction is a major problem affecting millions of women. To date there are no FDA approved pharmacologic agents to specifically address this problem. This study has demonstrated that topically applied L-Arginine ethyl ester cream in an aquaphor base does enhance sexual response significantly more than placebo with no reported side effects. The number of non responders could have been decreased by being more selective in our subject recruitment. More detailed questionnaires would be required to select the appropriate subgroups of sexual dysfunction patients that would likely respond to local vasodilatation. More studies need to be done with larger numbers to confirm the findings of this pilot study.

REFERENCES

1. Hallstrom T. Sexuality in the climacteric, *clin obstet gynecol*, 1977;4:227-239.
2. Sarrel PM. Sexuality and menopause. *Obstet Gynecol*. 1990;75:26S-30S.
3. Bachmann G. Sexual dysfunction in postmenopausal women: the role of medical management. *Geriatrics*. 1988;43:79-83.
4. National Center for Health Statistics, Vital Statistics of the United States, 1986, vol 2, Mortality, Parts A&B, DHHS Pub Nos. 88-114, 88-1122, Public Health Service, Washing, DC.
5. Sherwin BB, Gelfand, MM. The role of androgen in the maintenance of sexual functioning in oophorectomized women. *Psychosom Med*. 1987;49:397-409.
6. Willimas JK, Adams MR, Herrington DM, Clarkson, TB. Short-Term administration of estrogen and vascular responses of atherosclerotic coronary arteries. *J Am Coll Cardiol*.
7. Sarrel P, Dobay B, Wiita B. Estrogen and estrogen-androgen replacement in postmenopausal women dissatisfied with estrogen-alone therapy. Sexual behavior and neuroendocrine responses. *J. Reprod Med*. 1998;43:847-856
8. Masters WH, Johnson VE. *Human Sexual Response*. Boston, Ma: Little, Brown and company;1966.
9. Ellison JM. Antidepressant-induced sexual dysfunction: review, classification, and suggestions for treatment. *Harvard Rev Psychiatr*. 1998;6:177-189.
10. Basson R, Berman J, Burnett A, et al. Report of the international consensus development conference on female sexual dysfunction: definitions and classifications. *J Urol*. 2000; 163:888-893.
11. Marwick, C. Survey says patients expect little physician help on sex. *JAM*, 1999;281:2173.
12. Sarrel PM, Giblink L. Helping women function sexually after menopause: a survey to determine women's needs and their positive and negative experiences with health care providers (abstract). *NAMSs Annual Meeting; New York, 1999*.

13. Rhodes JC, Kjerulff KH, Langenberg PW, Guznski GM. Hysterectomy and sexual functioning. *JAMA*. 1999;282:1934-1941.
14. Rosen RC, Taylor JF, Leiblum SR, Bachmann GA. Prevalence of sexual dysfunction in women: results of a survey of 329 women in an outpatient gynecologic clinic. *J Sex Marital Ther*. 1993;19:172-178.
15. Hallstrom T. Sexuality in the climacteric. *Clin Obstet Gynecol*. 1977;4:227-239.
16. Sarrel PM. Sexuality and menopause. *Obstet Gynecol*. 1990;75 (4 suppl):26S-30S.
17. Sarrel PM, Wiita B. Vasodilator effects of estrogen are not diminished by androgen in postmenopausal women. *FertilSteril*. 1997;68:1125-1127.
18. Bachman GA, ed. Role of androgens in the menopause. *OBG Management* 1998; Supplement: 28-29.
19. Sherwin BB, Gelfand MM. the role of androgens in the maintenance of sexual functioning in oophorectomized women. *Psychosom Med*. 1987;49:397-409.
20. Laumann EO, Paik Am, Rosen RC. Sexual dysfunction in the United States. *JAMA*. 1999;281:537-544.
21. Greenblatt RB, Barfield WE, Garner JF et al. Evaluation of an estrogen, androgen and estrogen-androgen combination, and a placebo in the treatment of the menopause. *J Clin Endocrinol Metab*. 1950;10:1547-1558.
22. Zussman L, Zussman S, Sunley R, et al: Sexual response after hysterectomy-oophorectomy: Recent studies and reconsideration of psychogenesis. *Am J Obstet Gynecol* 1981;140:725-729.
23. Sarrel PM, Whitehead MI: Sex and menopause: Defining the issues. *Maturitas* 1985;7:217-224.
24. Davis SR, McCloud P, Strauss B, et al: Testosterone enhances estradiol's effects on postmenopausal bone density and sexuality. *Maturitas* 1995;21:2227-236.
25. Geist SH, Salmon VJ: androgen therapy in gynecology. *JAMA* 1941;1:986-991.
26. Berman, J. R., Berman, L.A. and Goldstein, I, :Evaluation of vasocongestive aspects of the female sexual response in women with arousal disorder and normal age-matched controls. *J. Urol, suppl.*, **163**: 241, abstract 1071, 2000.
27. Berman, J.R., Berman, L.A. Webin, T.J.R., et al: Female sexual dysfunction: anatomy, physiology, evaluation and treatment options. *Curr Opin Urol*, B9: **563**, 1999.