Improved Ejacultory Control And Sexual Satisfaction In Pilot Study Of Men Taking Hypericum Perforatum Extract

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Citation

T Cannon-Smith, J Kaufman. *Improved Ejacultory Control And Sexual Satisfaction In Pilot Study Of Men Taking Hypericum Perforatum Extract*. The Internet Journal of Nutrition and Wellness. 2006 Volume 3 Number 2.

Abstract

The most common male sexual dysfunction is premature ejaculation (PE) and yet there are no approved currently effective therapies. Based on research that Hypericum perforatum, a natural supplement has been demonstrated pharmacologically to delay ejaculation in a rat model of PE, we evaluated the effects of hyperforin extract of Hypericum perforatum on the ejaculatory reflex duration by using the intravaginal ejaculatory latency time (IELT) and sexual satisfaction.
Sixteen men who desired longer sexual intercourse and without erectile dysfunction were treated with Hypericum perforatum immediately prior to sexual activity. An intercourse diary was used to document baseline data for 2 weeks and throughout the study period of 4 weeks. Partners were asked to measure IELT using a stopwatch as well as complete a sexual function questionnaire both pre and post treatment.

All 16 subjects completed the study (average age 35.0 ± 4.6 years old). There was a significant increase in mean IELT times from 246±29 to 331±34 seconds ($p<0.002$) in subjects taking hyperforin extract. Fourteen of 16 men (87.5%) reported an improvement in IELT. The increase was seen in both the men who reported PE as bothersome and those who did not feel that PE was a problem for them. There was also significant increase in male satisfaction scores from 3.8±0.27 to 4.25 ±0.21 ($p<0.03$). Female satisfaction scores also showed a significant increase from 4.9±0.27 to 5.2±0.23 ($p<0.04$). This pilot study was limited by the lack of placebo control. No systemic or adverse effects on erectile function or orgasm were reported.
Hyperforin extract of Hypericum perforatum can increase the duration of sexual intercourse and improve sexual satisfaction for men with and without complaints of PE.

BACKGROUND

Premature ejaculation (PE) is a common, embarrassing and significantly undertreated medical condition that affects men and their partners. Approximately one third of sexually active men in the United States report this condition. Though, the prevalence of PE is approximately twice that of erectile dysfunction (ED), many healthcare practitioners have few treatment options for most men with PE [1,2].

The neurotransmitter 5-HT has been implicated in the control of many autonomic and behavioral functions including ejaculation. The link between 5-HT and ejaculation is most likely mediated by the medial preoptic area and paraventricular nucleus of the hypothalamus as these regions have been shown to integrate the sexual responses of men [3,4]. Several lines of evidence suggest that an enhanced synaptic availability of 5-HT in the central nervous system results in an inhibition of ejaculation [5,6,7]. From this perspective, PE is associated with an ejaculation reflex that is genetically "set" at a lower point [8,9].

There are currently no pharmacotherapies specifically approved for the treatment of PE, but a number of selective serotonin reuptake inhibitors (SSRIs) such as paroxetine, sertraline and fluoxetine have been prescribed "off label" as a treatment strategy for PE symptoms [2,10]. Placebo controlled clinical trials have shown fluoxetine, paroxetine, and sertraline increase IELT. A randomized, double-blind, placebo-controlled study found that paroxetine significantly improved PE complaints. After 6 weeks of treatment fluoxetine, paroxetine, and sertraline all significantly increased the mean IELT above the placebo group [10].

Daily treatment with SSRIs can lead to the desired delay in the ejaculation, but their use is associated with side effects that include: nausea, drowsiness, cognitive impairments, anticholinergic and sexual side-effects. Specific unintended sexual effects include abnormal ejaculation, decreased libido, reduced sexual desire, and genital anesthesia [11].

Further drawbacks of SSRIs include the slow onset of action of and relatively long half-life of these agents with the risk of accumulation and an exacerbation of SSRI-related adverse events [1,11]. Side effects with chronic SSRI use to treat PE is otherwise healthy young men with PE would not be generally accept.

A desired treatment for ejaculatory delay would be an oral formulation that is effective from the first dose. It should have a rapid onset of action and pharmacological half-life that commensurate from the beginning of sexual interest through to the conclusion of mutually satisfying sexual intercourse. Although a drug matching this profile is not currently available, there are candidates in development that have the potential to meet these therapeutic requirements. Dapoxetine, a new SSRI, has demonstrated clinical efficacy in phase-III clinical trials when used immediately before intercourse [1]. Dapoxetine is reported to inhibit the reuptake of norepinephrine and dopamine, but to a lesser extent than serotonin. Dapoxetine was found to have more rapid pharmacokinetics than the existing selective SSRI's. Another drug in development is BMS-505130 which has properties similar to dapoxetine. This drug is a short-acting potent SSRI that binds to the serotonin transporter at much lower concentration than the sodium or DA transporters [12].

Hypericum perforatum, a natural supplement has demonstrated pharmacologically to inhibit serotonin reuptake and delay ejaculation in a rat model of PE [13]. The purpose of this study was to evaluate the effects of an oral delivery formulation of the hyperforin extract from Hypericum perforatum on the time to ejaculation in men as well as satisfaction with sexual activity.

METHODS

Men having a desire for a longer duration of sexual intercourse were enrolled in this study. Inclusion criteria included: age 18–65 years, in a steady sexual relationship with one person and willing to have intercourse at least twice weekly. Exclusion criteria included the presence of an organic cause for PE (anatomical abnormality), genital infection, erectile dysfunction, depression or treatment with antidrepressants or any neurological disorder. After a medical and sexual evaluation, participants were instructed to complete a sexual diary. Partners were asked to measure intravaginal ejaculatory latency time (IELT) with a stopwatch for two weeks to capture baseline data and this diary was also used to record IELT throughout the testing period of 4 weeks. Sixteen of the initial 25 men completed the baseline IELT diary and these 16 were then directed to take a rapid dissolving oral tablet formulated with a 20 mg dose of hyperforin at least 15-30 minutes before intercourse over the next four weeks. Extraction of hyperforin from Hypericum perforatum powder was done using the technique of supercritical CO2 extraction (DeLithe Natural Products, Pittsburgh, PA). Material used in the study was extracted using a method reported earlier with slight modifications [14]. The hyperforin content of 20mg in the tablets formulated with extract of Hypericum perforatum was validated by HPLC analysis [15].

Both partners were asked to complete sexual satisfaction questionnaires pre and post treatment. In a three item Likert set of questions, sexual satisfaction in males was assessed along with ejaculatory control and erectile function pre and post treatment. Female partners of subjects were asked to complete the Female Sexual Function Index (FSFI). The Female Sexual Function Index is a brief 19-item self-report questionnaire that assesses sexual function in women in six different domains (desire, arousal, lubrication, orgasm, satisfaction and pain) [16]. This was used to determine a baseline assessment to capture whether female partners were experiencing sexual distress and to assess the levels of satisfaction both pre and post treatment. A Global Assessment Question (1-7 where 1 is not satisfied and 7 is complete satisfied) was also given to males at the end of the study.

Data Analysis: Mean IEFT was compared before and after treatment using the Student t test. The statistical analysis was computed with a Statistical Program (Prism) from GraphPad. A level of $p<0.05$ was considered as significant. Non-parametric statistical tests such as the Rank Sum test for comparing two independent groups, and the Kruskall-Wallis one-way analysis of variance for more than two groups.

RESULTS

Of the 16 subjects completing the study, no adverse effect on sexual function and no systemic side effects were reported by the subjects. The mean age of subjects was 35.0 ± 4.6 years. The mean IELT at baseline was 246 ± 29 seconds. Four men had a mean IELT of < 120 seconds at baseline. None of the men reported change in ability to achieve and maintain erection.

There was a statistically significant increase in mean IELT times from 246±29 to 331±34 seconds ($p<0.002$) after

Hypericum perforatum treatment. Fourteen of 16 men (87.5%) reported an improvement in IELT. The increase was seen in both the men who reported PE as bothersome and those who did not feel that PE was a problem for them. The increase in IELT was seen with the first dose and efficacy was maintained during the study duration of one month (P <0.001, ANOVA).

The distribution of change in IELT (reported as a percent of original) among the 16 subjects was normally distributed as indicated in the normal-quintile and histogram plots. The mean of the distribution individual change in IELT was 34%, and the median was 36%. The p-value associated with this increase is $p < 0.0001$ (confidence range was -13% to 73%).

Subjects with lower initial IELT were more likely to respond to treatment than those with longer initial IELT. Linear regression analysis between initial IELT and change in IELT suggests that approximately 40% of change in IELT variation can be predicted by initial IELT. However, such correlation was not seen for IELT values with treatment, thus indicating that treatment is less likely to have as profound an effect (on a percentage basis) with men of longer initial IELT values.

The overall sexual satisfaction score increased significantly for both the male and female partners after using the hyperforin extract (Table 1). Female satisfaction scores showed a significant increase from 4.9±0.27 to 5.2±0.23 ($p<0.04$). No significant changes were observed in the scoring of the other domains of FSFI (desire, arousal, lubrication, orgasm and pain).

Figure 1

Table 1: Changes in the male and female sexual satisfaction score (N=16 each). P-values change for the sexual satisfaction questions and is derived from the Wilcoxon Matched-Pairs Signed-Ranks Test

Domain	p-value
Male satisfaction	0.0295
Ejaculatory Control	0.1038
Desire	0.2186
Arousal	0.0938
Lubrication	1.00
Orgasm	0.2058
Female Satisfaction Score	0.0366
Pain	0.1876

There was significant increase in male satisfaction scores from 3.8±0.27 to 4.25 ±0.21 ($p<0.03$). None of the male subjects reported any problem in maintenance of erection after penetration. Six participants acknowledged small to medium problem with the ejaculatory control, and they had statistically significant response to treatment ($p< 0.03$). The Global Assessment Question after treatment was 5 on the scale of 1-7 after therapy.

DISCUSSION

This pilot study demonstrated that hyperforin rich extract of Hypericum perforatum delivered in a rapid dissolving formulation can quickly increase the duration of sexual intercourse for men with or without the complaints of PE. Hyperforin, the lipophilic constituent of Hypericum perforatum share the ability of SSRIs to inhibit synaptosomal uptake of several neurotransmitters [17]. Inhibition of neurotransmitter uptake by SSRIs is the underlying rationale for their efficacy in PE [1]. Recent studies show that hyperforin inhibits the synaptosomal uptake of neurotransmitters via activation of nonselective cation channels [18]. Most studies have confirmed the safety of Hypericum perforatum as a treatment for mild to moderate depression and as a nutritional supplement as it is devoid of side effects such as sedation, anticholinergic reactions, gastrointestinal disturbances and sexual dysfunction often found in patients treated with SSRIs [19,20]. The side effect from Hypericum perforatum when used as a nutritional supplement are attributable to its hypericin and to the flavonoid constituents as hypericin is reported to be responsible for the photosensitive reactions [21]. We further improved the safety of hyperforin rich extract of Hypericum perforatum by near complete removal of hypericin from our product by supercritical carbon dioxide extraction which only extracts hyperforin and not hypericin. The efficacy of hyperforin rich extract of Hypericum perforatum in our study to delay ejaculation was improved by formulating it into a rapid dissolving sublingual tablet. This new formulation is not only easy to use but significantly reduces the first pass effect for hyperforin. The time for maximum serum concentration for hyperforin in conventional pills and capsules is around 4hr [22]. Rapid onset of action, ease of use and improved safety makes hyperforin extract of Hypericum perforatum an attractive option for men who wish to increase time to ejaculation during sexual intercourse [23,24].

Patients with PE may have penile hypersensitivity and topical anesthetics have been advocated. It is postulated that when applying local anesthetic cream to the penile skin the

drug would be absorbed, resulting in partial anesthesia of the penis and thus enabling a delay in ejaculation [25,26]. However, the disadvantage of topical desensitizing creams is the unpleasant effect of penile numbness. In addition, in some cases, female partners complain of vaginal or clitoral anesthesia, especially when the man does not use a condom.

The reported assessment of the effectiveness of treatment for PE varies, but prolonging the IELT is an objective measure. However, no consensus has been reached as to how long the IELT should be to define PE or normality [1,27]. In the present study the definition of PE was based on the American Psychiatric Association [27], in which there is no specific time to ejaculate but rather whether the couple is satisfied or not with their sexual life. In this study, hyperforin extract produced rapid onset of action and increased ejaculatory latency time in men with baseline ejaculatory latency of less than or greater than two minutes.

Another frequently used criterion in ejaculatory studies is the self- and partner-reported ratio of sexual satisfaction. Sexual satisfaction responses in both partners in response to treatment were reported with the use of sildenafil citrate [28]. Our study demonstrated a global satisfaction increase by the males and improved sexual satisfaction domain within the FSFI. A limitation of this study was that individual sexual survey questions did not reach statistical significance probably because of the small study size and variability between subjects.

This is the first report of a natural supplement with significant pharmacology SSRIs efficacy for PE. Hyperforin extract may be considered a supplement in men who wish to delay ejaculation. One of the most interesting findings of this study is that hyperforin extract can increase the sexual intercourse time for men with baseline with significant shortened IELT of less than 2 minutes but also for men who would fall into the normal range of sexual intercourse duration. No side effect was reported by the subjects taking Hypericum perforatum in this study. Prospective randomized for Hypericum perforatum are being planned to further evaluation the utility of hyperforin extract to treat premature ejaculation.

The major weakness of this pilot study was that we were limited by the lack of placebo control randomization design. There was also recruitment issue related to the study method requiring the use of a stopwatch to measure IELT. Further controlled studies are recommended.

CONCLUSIONS

This pilot study demonstrated that hyperforin extract of Hypericum perforatum increased the duration of sexual intercourse before ejaculation for men with and without complaints of PE. Sexual satisfaction improved for both the men and his partner after hyperforin use. Rapid onset of action, ease of use and safety make hyperforin extract an attractive option for men who wish to increase time to ejaculation during sexual intercourse.

LIST OF ABBREVIATIONS

Premature ejaculation (PE)
Intravaginal ejaculatory latency time (IELT)
Erectile dysfunction (ED)
Selective serotonin reuptake inhibitors (SSRIs)
Female Sexual Function Index (FSFI)

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