http://dx.doi.org/10.4314/ajtcam.v10i2.16

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED CROSSOVER STUDY OF CAPPRA® FOR THE TREATMENT OF MILD OR MILD TO MODERATE ERECTILE DYSFUNCTION IN THAI MALE

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Abstract

Erectile dysfunction (ED) is one of the major health concerns affects the quality of life among Thai male. The treatment of ED by the first-line drugs is limited to a certain group of patients due to their side effects and costs. Alternative medicine can be beneficial for the treatment of ED. This is a randomized, double-blind, placebo-controlled, crossover study aimed to assess the efficacy and safety of Cappra®, a traditional herbal medicine which was used in Thailand for decades, for the treatment of mild and mild to moderate ED in Thai patients. A total of 63 patients with mild or mild to moderate ED were randomized to receive Cappra® or placebo for two weeks in the first period, followed by one week washout period. The patients were switched to the alternative treatment in the second period. The efficacy was assessed by the International Index of Erectile Function (IIEF) questionnaire and adverse events. Sixty one patients completed the study. There was an improvement of IIEF score for all domains in Cappra® group compared with placebo group. The mean change of IIEF score from baseline for erectile function domain of Cappra® was significantly higher than placebo (4.87 vs 3.44, p = 0.032). The most common adverse events were dizziness (13.3% Cappra®, 9.6% placebo), face numbness (1.6% Cappra®, 0% placebo), and tachycardia (1.6% Cappra®, 0% placebo). The results from this study demonstrated that Cappra® is effective and well-tolerated and can be used as alternative therapy for mild and mild to moderate ED.

Key words: Erectile dysfunction, herbal medicine, International Index of Erectile Function, IIEF

Introduction

Erectile dysfunction (ED), the inability to get and maintain an erection that is sufficient for satisfactory sexual intercourse (Lue, Giuliano et al. 2004), is estimated to affect up to 37.5% of Thai male age 40-70 years according to Thailand Erectile Dysfunction Epidemiology Study in 2000 (Anonymous 2000). The prevalence of erectile dysfunction in Thai male has been increasing with an estimated prevalence of 42.18% in 2008 (Permpongkosol, Kongkakand et al. 2008). Several factors have been shown to be associated with the ED including age, comorbid diseases, socioeconomic status, and life style factors (Kupelian, Araujo et al.; Kongkanand 2000; Doumas, Tsakiris et al. 2006). The ED is a major health concern affecting physiological, psychological, and quality of life among sufferers, their partners, and families (Feldman, Goldstein et al. 1994).

Phosphodiesterase-5 inhibitors (PDE5-Is); sildenafil, tadalafil, and vardenafil are recommended to be used as first-line drug therapy for ED. Even though previous studies demonstrated the efficacy of drugs in this group, serious side effects are commonly found and sometimes cause drug cessation (Harrington, Campbell et al.; Goldstein, Lue et al. 1998). Common adverse events of PED5-Is include headache (10-16%), nasal congestion (1-10%), and dyspepsia (4-12%) (Hatzimouratidis and Hatzichristou 2005). There are risks of drug interactions that are life-threatening. The use of drugs in this group with nitrates is contraindicated due to the occurrence of unpredictable hypotension. Additionally, the high cost of drugs is often bearing financial burden. As ED is associated with socioeconomic status, drug cost is one of the concerns (Permpongkosol, Kongkakand et al. 2008). Due to these reasons, the treatment options for ED patients are limited. Alternative therapies including acupuncture and herbal medicines would be beneficial for this group of patients. However, evidence of their efficacy is scarce and further evaluation of their efficacy with well-designed clinical studies are needed (Crimmel, Conner et al. 2001).

Alternative and herbal medicines have been increasingly popular among patients worldwide, unfortunately the studies evaluating its efficacy is limited. Even though, most of the herbal medicines have long been used, its efficacy and safety has not necessarily been confirmed (Bansal, Hota et al. 2010). The appropriate clinical studies of herbal medicine are therefore encouraged to conduct to provide useful information and support the proper use of herbal medicine. Cappra® is herbal medicine consisted of 13 Chinese herbs including Suoyang (Cynomorium Stem), Yinyanghuo (Epimedium Herb), Lurong (Hairy Deer Horn or Cervus Nippon Temminck), Honghua (Safflower), Shanyao (Common Yam Rhizome), Gougizi (Wolfberry Fruit), Chushizi (Papermulberry Fruit), Jiucaizi (Fragrant-flowered Garlic Seed), Bajitian (Morinda Root), Gouguye (Chinese Holly Leaf), Shanzhuyu (Dogwood Fruit), Roucongrong (Cistanche Stem), and Fengmi (honey). Cappra® has been widely used for a long period of time as a tonic agent in Thailand. Tonic herbs are generally used to strengthen the

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body, increase immunity, and improve overall health status (Bensky, Clavey et al. 2004). The ingredients of the product also exert their pharmacological properties that could be beneficial for the treatment of ED, nevertheless its efficacy and safety when used in ED patients has not been investigated. This study aimed to determine the efficacy and safety of Cappra® for the treatment of ED in Thai male with mild and mild to moderate ED

Materials and Methods

Cappra® (Zun Seng Heng Medical Factory Ltd., Part, Bangkok, Thailand, Thai FDA registration number G 587/53) in 8,220 grams composed mainly of Cervus Nippon Temminck 150 grams, Epimedium Drevicornum Maxim 120 grams, Cynomorium Songaricum Rupr. 844 grams, Carthamus Tinctorius 138 grams and Cistanche Deserticola 150 grams.

Patients and treatment

This was a randomized, double-blind, placebo-controlled crossover study. Patients aged 18 years or older with mild or mild to moderate ED identified by the simplified International Index of Erectile Function (IIEF-5) (Rosen, Cappelleri et al. 1999) who were able to have sexual intercourse at least 3 times within 2 weeks were eligible to be included in the study. Exclusion criteria were poorly controlled diabetes or hypertension; renal or hepatic abnormality; active upper gastrointestinal bleeding; allergy to sulfonamides or honey; use of drugs or other natural products that may interfere erectile function; use of drugs that may interact with Cappra® including warfarin, antiplatelets, potassium sparing diuretics, monoamine oxidase inhibitors (MAOI), selective serotonin reuptake inhibitors (SSRI). The patients who were unable to verbally communicate were excluded from the study. The study was approved by the Joint Research Ethics Committees (JREC), Bangkok, Thailand. Informed consents were obtained from all patients participated in the study.

Eligible patients were randomized to receive Cappra® or identical-looking placebo using blocked randomization with block size 2. The patients randomized to receive Cappra® in the first period were switched to placebo in the second period (group 1) and vice versa for the other group (group 2). There was a one week washout between the two 2-weeks treatment periods. The patients were received 3 tablets of Cappra® or placebo according to their randomization and they were instructed to take Cappra® or placebo 1 tablet approximately 1 hour before planned sexual activity. The patients were required to take a minimum of 3 tablets of Cappra® or placebo during the 2-weeks treatment period. Figure 1 represents the schematic diagram of the study design of this study.

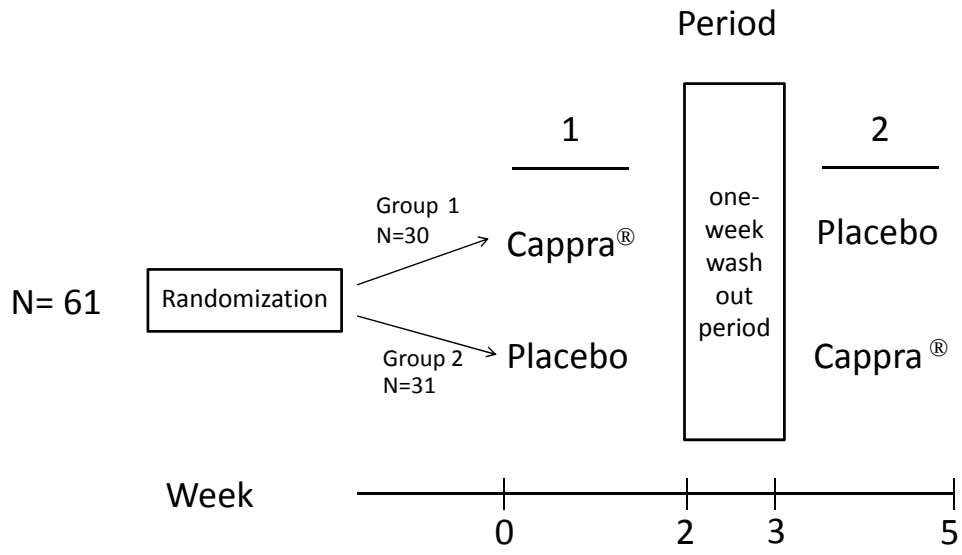

Figure 1: The schematic diagram of the study design

Efficacy and safety assessment

The efficacy of Cappra® was assessed by the response to the 15 questions of the International Index of Erectile Function (IIEF) which is a self-administered questionnaire used for evaluating the principle aspects of ED including erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction. Each item of the questions was

http://dx.doi.org/10.4314/ajtcam.v10i2.16

rated from a scale of 1 ("never") to 5 ("almost always/always"). The IIEF scores were obtained at baseline and at the end of each treatment period. The primary endpoint was the change of the erectile function domain score at the end of the treatment period from baseline. The secondary endpoint was the change of other domain score at the end of the treatment period from baseline. Standard laboratory tests and physical examination were performed at baseline and at the end of each treatment period. Any adverse effects developed during the study were recorded by the investigators.

Statistical analysis

The number of patients required for the study was determined by the change of erectile function domain score. A total of 62 patients were required to detect a beneficial effect of Cappra® assuming an increase of erectile function domain score of 0.25 from baseline with 80% power and an estimate of 10% drop-out. A mean change of each IIEF domain score at the end of the treatment period was compared by Paired-t-test or Wilcoxon signed-rank test where appropriate. Statistical analysis was performed using SPSS software (version 17, SPSS Thailand Co., Ltd, Bangkok, Thailand). The analysis was performed on an intention-to-treat basis. The significance level of 0.05 was used for all analysis.

Results

Baseline characteristics

A total of 63 patients participated in this study. Among them, 61 patients completed the study. Two patients lost follow-up since randomization with no known reasons. Thirty patients were randomized to receive Cappra® in the first period and switch to placebo in the second period (group 1), and vise versa for 31 patients (group 2). No significant difference of the patient characteristics was observed between the two allocation sequences (Table 1). The patients were between the ages of 35 and 61 years. None of the patients had diabetes and 3 patients had cardiovascular disease. The IIEF scores for all domains at baseline were similar between the two groups.

Table1: Summary of baseline characteristics

Characteristic	Mean (SD)		
	Cappra first (N=30)	**Placebo first (N=31)**	***p*-value***
Age (years)	45 (7.14)	44 (6.7)	0.58
Weight (kg)	72.5 (14.28)	69 (9.8)	0.25
Alanine transaminase (ALT) (U/L)	31.3 (15.26)	34.48 (24.8)	0.55
Aspartate transaminase (AST) (U/L)	40.5 (21.61)	43.1 (24.27)	0.66
Blood urea nitrogen (BUN) (mg/dL)	11.7 (2.38)	13 (4.30)	0.15
Serum creatinine (Scr) (mg/dL)	1.05 (0.13)	1.07 (0.13)	0.5
Fasting blood sugar (FBS) (mg/dL)	110 (33.1)	100 (15.5)	0.16
IIEF domain scores			
- Erectile function	20.1 (5.9)	19.2 (5.4)	0.52
- Orgasmic function	7.4 (2.3)	8 (2.5)	0.33
- Sexual desire	6.6 (1.3)	6.7 (1.5)	0.9
- Intercourse satisfaction	8.3 (2.3)	7.9 (2.5)	0.5
- Overall satisfaction	6.9 (1.8)	7.2 (1.6)	0.46
	Frequency (%)		
History of cardiovascular disease	1 (3.3)	2 (6.5)	0.57
Smoking	14 (46.7)	17 (54.8)	0.52
Alcohol consumption	21 (70)	15 (48.4)	0.086
Comedications	-	1 (3.2)	NA
- Enalapril			
- Atenolol	-	1 (3.2)	NA

* Student's t-test for mean comparison, Chi-square test for proportion comparison
NA: Not applicable

Efficacy and side effects

At the end of the treatment period, Cappra® showed a higher improvement of the IIEF score for all domains compared with placebo. The mean changes of IIEF score from baseline for the erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction domain in patients received Cappra® and placebo were 4.87 vs 3.44, 1.15 vs 0.81, 0.75 vs 0.52, 2.3 vs 1.82, and 1.49 vs 1.13, respectively (Figure 2). The mean change of erectile function domain score of Cappra® was significantly higher than the placebo group (4.87 vs 3.44, p = 0.032). With the mean improvement of erectile function domain score of approximately 5 points in Cappra® group, this corresponds to a moderate improvement of erectile function. However, the mean changes of IIEF score for the remaining domains were not statistically significant. During the study, Cappra® was shown to be generally well tolerated. Four patients in Cappra® group (13.3%) and 3 patients in placebo group (9.6%) reported dizziness after taking medications. One patient reported face numbness and

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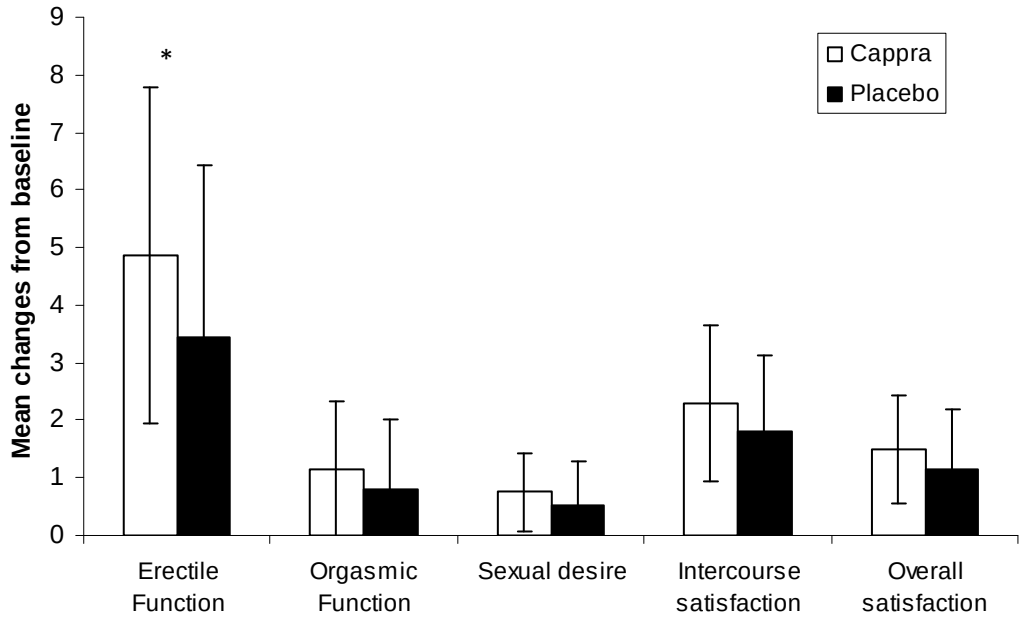
another patient reported tachycardia after the administration of Cappra®. However, these side effects were mild and did not cause the discontinuation of medication. The standard laboratory tests at baseline and after the treatment with Cappra® and placebo were presented in Table 2. The results showed that the standard laboratory tests performed after the treatment were not different from baseline and were found to be similar between Cappra® and placebo group, except for serum creatinine. The serum creatinine measured after the treatment with Cappra® was significantly higher than baseline value (1.12 vs 1.06, $p = 0.036$), but it was not significantly different from the value measured after the treatment of placebo (1.12 vs 1.11, $p > 0.05$).



* indicates significant difference between Cappra® and placebo ($p < 0.05$)

Figure 2: Mean changes of IIEF domain scores

Table 2: Standard laboratory tests at baseline and after 2 weeks of the treatment with Cappra® and placebo

Laboratory tests	Baseline Mean (SD)	Cappra® Mean (SD)	Placebo Mean (SD)
Hemoglobin (Hgb) (gm/dL)	14.7 (1.0)	14.4 (1.2)	14.5 (1.0)
Hematocrit (Hct) (%)	43.5 (3.0)	43.2 (3.3)	43.5 (3.1)
Platelet count (PLT) ($x10^3/mm^3$)	238.5 (55.8)	244.8 (55.5)	247.7 (57.5)
Alanine transaminase (ALT) (U/L)	41.9 (22.8)	42 (27.0)	40 (22.4)
Aspartate transaminase (AST) (U/L)	32.9 (20.6)	32.9 (22.9)	31.8 (16.1)
Alkaline phosphatase (ALP) (U/L)	65.4 (19.8)	62.3 (16.5)	63.2 (15.2)
Blood urea nitrogen (BUN) (mg/dL)	12.4 (3.5)	14 (13.2)	12 (3.6)
Serum creatinine (Scr) (mg/dL)	1.1 (0.13)	1.1 (0.15)*	1.1 (0.12)
Fasting blood sugar (FBS) (mg/dL)	105.6 (25.9)	105.6 (26.3)	101.6 (23.5)

* $p < 0.05$ vs placebo, SD: standard deviation

Discussion

The incidence of ED is increasing, thus it leads to a growing demand of clinical services and medications. However, the choice of ED treatment is limited because of cost and side effects of the first-line drug. Therefore, alternative medicines including Chinese herbal formulas for the treatment of ED could be an important option for many patients. A fundamental concept of traditional Chinese medicine is based on a balance of the two forces; Yin (representing cold and consolidate) and Yang (representing heat and activity). These two forces are believed to control all natural phenomena in human. Chinese herbal formulas commonly consist of a wide variety of ingredients, which works in harmony to balance Yin and Yang. Previous studies have investigated the efficacy and safety of Chinese herbal products and alternative medicine for the treatment of ED and infertility. There was a study demonstrated a significant improvement of sperm quality i.e., sperm

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density and sperm motility of Sheng Jing, a Chinese herbal formula, among male with infertility (Chen and Wen 1995). Moreover, previous studies demonstrated a beneficial effect of ginseng, ginger, and Astragalus membranaceus on sperm density and motility (Liu 1990; Li, Li et al. 1995; Hsu 1997). Besides the Chinese herbal products, acupuncture has grown public acceptance for the treatment of ED and infertility. Previous studies reported a successful improvement of sexual intercourse and satisfactory after the use of acupuncture (Yaman, Kilic et al. 1994; Kho, Sweep et al. 1999). However, most of these studies were not adequately controlled and well designed. The well-controlled clinical studies to evaluate the efficacy of the Chinese herbal products and alternative medicines are required to establish the confidence in using these treatments in ED patients. This study aimed to investigate the efficacy and safety of Cappra®, a Chinese herbal product consisted of herbal ingredients intended to be used for the treatment of ED.

In this study, the IIEF-5 was used as diagnostic tool to identify patients with ED. The possible scores range from 1 to 25 with a higher score refers to a better sexual function (Rosen, Cappelleri et al. 1999). The efficacy of the product was assessed by the IIEF questionnaire which measures the relevant domains of male sexual function. The IIEF demonstrates a high sensitivity and specificity for detecting changes of sexual function in male ED and has been accepted as the "gold standard" for assessing treatment-related changes in ED clinical trial studies (Rosen, Riley et al. 1997).

The results from this study demonstrated the efficacy and safety of Cappra® in the treatment of ED. There was a moderate improvement of erectile function based on the increase of erectile function domain score of approximately 5 points in patients using Cappra® compared with placebo. Even though, the mean changes of score in other domains in Cappra® group were higher than those in placebo group, these differences were not statistically significant. These results are not surprised as the IIEF mainly focuses on erectile function, whereas it provides a superficial assessment of other sexual functioning including sexual desire and orgasmic function (Rosen, Cappelleri et al. 2002). Interestingly, it should be pointed out that the IIEF score was increased for all domains in patients using placebo which could be due to placebo responses. These results are not surprised as it was shown that placebo effect in erectile dysfunction studies could be as high as 50% (de Araujo, da Silva et al. 2009).

Cappra® contains a wide variety of Chinese herbs that has been proved to be beneficial for erectile function and male sexuality. Previous study showed a significant improvement of erectile function among patients with impotence who were receiving Lurong (Chen, Chen et al. 2001). There is evidence that the administration of Yinyanghuo can increase sperm production, sexual desire, and increase a secretion of endogenous hormones such as testosterone, cortisol, and corticosterone (Chen, Chen et al. 2001). Additionally, a clinical study found an increase of sperm count and sexual activity after 1 month of the administration of Gouqizi 15 mg every night in men with low sperm count and poor sperm motility (Chen, Chen et al. 2001). In this study, the combination of these herbal medicines was proved to be effective for the treatment of ED.

The results from this study confirmed that Cappra® is well tolerated when it was used for the treatment of ED. No treatment-related serious side effect was reported. The most common side effect found in patients using Cappra® were mild dizziness, however the incidence was not different from the placebo group. Cappra® consisted of Lurong that exert vasodilation effect and decrease blood pressure (Chen, Chen et al. 2001). Therefore, the occurrence of dizziness in patients receiving Cappra® could be a consequence of the pharmacological effect of Lurong.

This study has some limitations. First, as the IIEF mainly focus on erectile function, the effect of the product on other domains needs to be further investigated with other appropriate instruments. Moreover, this study investigated the efficacy of Cappra® for the treatment of mild or mild to moderate ED, therefore its efficacy in patients with moderate and severe ED requires further studies. Finally, there is evidence that some herbal ingredients of Cappra® can increase sperm quantity and quality, thus Cappra® could be beneficial for the treatment of male infertility. However, the measurement of sperm quantity and quality was not performed in this study. Its efficacy for the treatment of infertility required further investigation. Regardless of these limitations, the results from our study confirm the efficacy and safety of Cappra® for the treatment of patients with mild or mild to moderate ED.

Conclusion

The results of a randomized, double-blind, placebo-controlled, crossover study for Cappra®, a traditional herbal medicine which was used in Thailand composed mainly of Cervus Nippon Temminck, Epimedium Drevicornum Maxim, Cynomorium Songaricum Rupr, Carthamus Tinctorius and Cistanche Deserticola, indicated that Cappra® can improve erectile function in patients with mild and mild to moderate ED without serious side-effects. Therefore, it has the potential to be used as alternative therapy in this group of patients.

Acknowledgments

This research was supported with grants from C.A.P.P. Innovation Research and Development Center, Thailand.

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