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Efficacy and Safety of Integrative and Complementary Therapy (ICT) based on Cucurbita Maxima in the Treatment of Patients with Overactive Bladder: A Multicentre Prospective Observational Study

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Abstract

Objective: The aim of this study was to assess the effectiveness and safety of an Integrative Complementary Therapy (ICT) based on cucurbita maxima in the improvement of Overactive Bladder (OAB) symptoms in women.

Materials and Methods: Two hundred thirty-eight patients received ICT two tablet orally/daily for 12 weeks. Primary endpoint was changes in the total number of voids/24 h, urgent micturition's/24 h, urinary incontinence events/24 h, nocturia events after 12 weeks of treatment. Secondary endpoints included the assessment of the quality of life through the use of the OAB-Q symptom and HRQL scale, UDI-6 and SF-36 questionnaires. The satisfaction was evaluated by PGI-I.

Results: After 12-weeks the reduction in the mean number of voids (9.87 ± 2.45 *vs*. 7.63 ± 1.22, p=0.01), urgent micturition (4.71 ± 1.28 *vs*. 2.53 ± 1.22, p<0.0001), nocturia episodes (2.75 ± 0.85 *vs*. 1.14 ± 1.15, p=0.02) and urinary incontinence (0.68 ± 0.91 *vs*. 0.41 ± 0.69, p=0.08) was observed. No significant adverse effects were reported. The UDI-6, OAB-Q symptoms, OAB-Q (HRQL) and the SF-36 scores were significantly changed after 12 weeks and the patients showed a good satisfaction after treatment at PGI-I questionnaire.

Conclusion: ICT based on cucurbita maxima is an effective and safe potential therapy for women with OAB improving quality of life.

Keywords: Complementary medicine; Cucurbita maxima; Overactive bladder; Quality of life; Resveratrol; urge urinary incontinence

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Introduction

Overactive Bladder Syndrome (OAB) is a chronic disease characterized by urinary urgency with or without urge incontinence, frequency and nocturia [1]. The overall prevalence of OAB in women is 16.9%; however the prevalence increases with age, reaching 30.9% in women over 65 years of age [2]. The quality-of-life impact is significantly compromised. Pathophysiology is still unknown, even if it is known that neuropathic alteration and the impairment of nerve afference can compromise bladder function and the detrusor contractility [3]. The international guidelines categorize the management of OAB from the least invasive treatment up to the most invasive one. The 1st line treatment is the conservative management; 2nd line treatments the pharmacologic therapy and the peripherical tibial nerve stimulation; 3rd line treatments the Intradetrusor onabotulinumtoxin A injections or sacral neuromodulation; 4th line treatments complex surgical interventions [4]. Pharmacological therapy is considered the standard treatment. Antimuscarinic and beta-3 agonists agents represent the first-

line pharmacological therapy recommended for OAB treatment [5], but cause common adverse events and the adherence rate is extremely low [6]. A conservative approach includes: lifestyle, behavioural modification, pelvic floor muscle training and bladder training. This approach may also include the use of food supplements that contain molecules that modify bladder contractility [7]. In fact, it could be useful to start the treatment in patients with OAB and urgency with Integrative Complementary Therapy (ICT) to try to minimize the side effects of the drugs. The pumpkin seeds extract of the cucurbita maxima showed direct relaxing effect on the detrusor muscle [8]. The pumpkin seeds yield approximately 50% oil, (mostly linoleic and oleic acid and tocopherol), but the main active constituents are sterols (avenasterol, spinasterol) and sterol (sitosterol, stigmasterol). The advantage of pumpkin seeds treatment arises from its tonic influence on the bladder and sphincter relaxation [9]. Pumpkin seed extract has beneficial activity in two ways: One on the hormonal level by inhibiting 5-alpha reductase an enzyme involved in hormone metabolism, resulting in anabolic and muscle strengthening effects; and a direct muscle relaxing effect resulting in a decreased urinary urgency and frequency [10]. The aim of this study is to demonstrate the efficacy and safety of supplementation with a product based on cucurbita maxima, Capsicum annum (Chili pepper), Polygonum cuspidatum (Resveratrol) Vitamin C and Vitamin D in the initial treatment in women with OAB.

Materials and Methods

From January 2016 to January 2019, 312 consecutive patients affected by OAB syndrome, with or without coexisting urinary incontinence were referred to our department and were considered for the study. Of these, 52 (16.7%) refused treatment, 22 (7%) underwent treatment but were lost to follow up. The remaining 238 patients (76.3%) were enrolled for this study. All data collected were evaluated from a prospectively collected urogynecological internal database. The Institutional Review Board approved the study. The inclusion criteria were as follows: signed informed consent; symptoms of OAB for at least 12 weeks. OAB diagnosis was assessed clinically with following anamnestic criteria: Urgency, frequent urination (equal or more than 8 times in the daytime and 2 times at night) and/or urgent urinary incontinence in absence of pathologic or metabolic conditions that may cause or mimic OAB, no previous administration of other drugs for OAB.

The exclusion criteria were as follows: Stress urinary incontinence or mixed urinary incontinence (mainly stress incontinence) confirmed by urodynamic testing; neurogenic bladder; gynecological tumours; urological tumours; clinical evidence of a urinary tract infection or chronic inflammation; history of pelvic radiotherapy; pelvic organ prolapse ≥ grade 3 (according to POP-Q classification); interstitial cystitis; bladder pain syndrome; urinary retention, neurologic abnormalities and confirmed or suspected allergy to lactose. The pre-treatment evaluation consisted of clinical exam and the 3-day voiding diary. The Urogenital Distress Inventory (UDI-6) was administered to assess the lower urinary tract symptoms impact on quality of life and symptom distress for urinary incontinence in women [11]. The OAB-Q a symptom bothers and HRQL scale was administered to measure the subjective degree of OAB symptoms and impact on quality of life. We used a validated shorter version (OAB-Q SF) [12]. The Short Form (36) Health Survey it was used to assess the impact on the overall quality of life [13].

Physical examination and the 3-day voiding diary took place at the start and at the end of treatment. At baseline and at 12 weeks, patients completed the OAB-Q SF to assess symptom bother and the impact of OAB on HRQL; UDI-6 and SF-36 questionnaires were completed.

Patient impression of global improvement (PGI-I) after 12 weeks of treatment was assessed to evaluate the patient satisfaction [14].

All patients received the Integrative Complementary Therapy (ICT) (Kubiker®, Naturneed srl, *Via* Giosuè Carducci, 12, 62100 Macerata MC, Italy) two tablets orally/daily for 12 weeks; to be taken after meals, swallowing with water without breaking or chewing. Each tablet contains: 10 mg of pumpkin seed extract, 265 mg of vitamin C, 200 mg of L-Glutamine, 10 mg of Resveratrol, 10 mg of peppers extract and 10 mcg of vitamin D.

Primary endpoint was changes in the total number of voids/24 h, urgent micturition's/24 h, urinary incontinence events/24 h, nocturia events after 12 weeks of treatment. Secondary endpoints included improvement in OAB symptoms bother (measured by the OAB-Q SF), improvement in OAB Health-Related Quality of Life (HRQL) (measured by OAB-Q), UDI-6 after 12 weeks and the overall quality of life with the measured by the SF-36 questionnaire. Statistical analysis was carried out with Wilcoxon matched pairs test for the continuous variables χ-square test for the frequency data. Quantitative data were expressed as mean ± SD (standard deviation) in tables. To demonstrate the differences, Student-t and Mann-Whitney U test was used. Matched t-test was applied to determine the change in OABSS values. All analyses were conducted using the Statistical Package for the Social Sciences (SPSS) 22.0 for Mac (SSPS, Chicago, IL, USA). Significance was set at a p-value of <0.05.

Results

Two hundred thirty-eight patients were enrolled in the study. The baseline demographic and clinical characteristics of the patients are shown in Table 1. The mean age was 60.34 ± 8.23 and the menopausal patients were 143 (60.1%). After 12 weeks, the reduction in the mean number in 24 h of voids (9.87 ± 2.45 *vs.* 7.63 ± 1.22, p=0.01) with a mean reduction of (-3.24 ± 2.35), urgent micturition episodes/24 h (4.71±1.28 *vs.* 2.53 ± 1.22, p<0.0001) with a mean reduction of (-2.18 ± 1.48), nocturia episodes (2.75 ± 0.85 *vs.* 1.14±1.15, p<0.02) with a mean reduction of (-1.61 ± 1.11) urinary incontinence episodes/24 h (0.68±0.91 *vs.* 0.41±0.69, p=0.08) with a mean reduction of (-0.29 ± 0.79), was observed (Table 2). No significant adverse effects were reported during and after treatment; 5 (2.1%) patients reported nausea in the first week. The UDI-6, OAB-Q symptoms, OAB-Q (HRQL) scores were 8.71 ± 0.91 *vs.* 5.57 ± 1.53; 60.12 ± 13.29 *vs.* 23.32 ± 11.76 and 22.76 ± 7.65 *vs.* 77.73 ± 11.87 (p<0.001) before and after 12 weeks. SF-36 changed from 52.86 ± 9.21 *vs.* 83.43 ± 10.76 after

Table 1: Demographic and clinical characteristics of 238 patients.

Variables	n
Age, y (mean ± SD)	60.34 ± 8.23
BMI (mean ± SD)	25.89 ± 2.39
Menopausal patients (%)	143 (60.1)
Hormonal Replacement Therapy (%)[a]	42 (29.4)
Parity (range)	2 (0-3)
Smoke (%)	75 (31.5)
Previous pelvic surgery (%)	88 (37)

Abbreviation: SD: Standard Deviation; BMI: Body Mass Index
[a]: the percentage is calculated on menopausal patients

Table 2: Comparison of voiding diary, quality of life questionnaires, before and after treatment (12-weeks follow-up).

Variables	Baseline	12-weeks FU	*p value*
Mean number of voids (24 h)	9.87 ± 2.45	7.63 ± 1.22	0.01
Mean number of urgent micturition events (24 h)	4.71 ± 1.28	2.53 ± 1.22	<0.0001
Mean number of urinary incontinence events (24 h)	0.68 ± 0.91	0.41 ± 0.69	0.08
Mean number of nocturia events	2.75 ± 0.85	1.14 ± 1.15	0.02
UDI 6	8.71 ± 0.91	5.57 ± 1.53	<0.0001
OAB-Q symptoms	60.12 ± 13.29	23.32 ± 11.76	<0.0001
OAB-Q (HRQL)	22.76 ± 7.65	77.73 ± 11.87	<0.0001
SF-36	52.86 ± 9.21	83.43 ± 10.76	<0.0001

Table 3: Patient impression of global improvement (PGI-I) after 12 weeks of treatment in 238 patients.

Variables	n (%)
1: Very much better (%)	181 (76.1)
2: Much better (%)	28 (11.8)
3: A little better (%)	12 (5)
4: No improvement (%)	15 (6.3)
5: A little worse (%)	2 (0.8)
6: Much worse (%)	0
7: Very much worse (%)	0
Success (%)	209 (87.8)

treatment (Table 2). PGI-I evaluation showed a total satisfaction of 87.8% (very much better + much better) (Table 3). Two hundred two (84.5%) patients wanted to continue therapy after 12 weeks of treatment.

Discussion

The study supports the efficacy and the safety of the integrative therapy based on cucurbita maxima in the OAB treatment in woman. After 12 weeks, the objective reduction in micturition/24 h, urgent micturition episodes/24 h, nocturia episodes and urinary incontinence episodes/24 h was observed. The guidelines recommend a stepwise treatment and initial conservative treatment must be offered [4]. If the lifestyle change is not effective the most used treatment is the pelvic floor rehabilitation. It is based on the combination of different rehabilitation approaches and electrical stimulation, showing, an improvement that can go up to 60% to 70% but with a significant recurrence rate [15].

The main treatment in patients with OAB is drug therapy which is essentially based on two families of drugs: antimuscarinics and beta-3-agonists [16]. While, demonstrating efficacy in 70% to 80% of patients with a significant reduction in the number of voids/24 h and urgent episodes, the discontinuity rate of therapy is extremely high. In fact, only 14% to 35% of patients continue therapy after the first cycle and this depends on the side effects, the ineffectiveness and for the high cost [17,18]. Moreover, these are often elderly patients who have different comorbidities and therefore drugs may be contraindicated [16]. Therefore, before proposing drug therapy or more invasive methods, such as injection of botulinum toxin A or sacral neuromodulation, nutraceutical integrative complementary therapy can be prescribed [19]. Diet significantly influences urinary functions and the lack of certain substances can compromise bladder compliance [20]. Several studies have shown the impact of some natural molecules on the pathophysiology of OAB. In particular, there is a possible dietary association with OAB in terms of food groups and individual food items and showed that lower intakes of three food groups (vegetables, chicken and breads) are independently associated with increased risks of OAB onset [21]. Taking nutraceutical food supplements can also help menopausal women who show an increased risk of OAB due to estrogen deprivation. In fact, it has been shown by several studies that local estrogen therapy or the use of oral Ospemifene improve the urinary symptoms in patients with genitourinary syndrome; but not all women want or can take hormonal treatment [22-25]. Therefore, the use of ICT, can improve the quality of life of patients. The ICT is composed of several components that mediate a different action. Cucurbita maxima through its relaxing action on the detrusor muscle and anti-inflammatory activity reduces the symptoms of OAB; and is also effective against benign prostatic hypertrophy in the male, reducing prostate weight after treatment [26].

Furthermore, pumpkin extracts showed a positive activity towards bacterial and fungal infections. In menopausal women with genitourinary syndrome is useful because the risk of urinary tract infections is greater [27]. Our data showed the effectiveness of ICT in improving bladder capacity and in decreasing the frequency. The improvement of urinary symptoms positively affects the quality of life. The other product components also support therapy, through other specific functions. Resveratrol may have the potential to improve urinary function in patients with OAB or other dysfunctions. In several prospective studies Resveratrol increase maximum bladder capacity and reduce the detrusor pressure in rats with Chronic Prostatitis (CP). The protein expression of Stem Cell Factor (SCF) and c-Kit in bladder of rats was examined to investigate the resveratrol mechanism. The results of western blot analysis, immunohistochemical staining and immunofluorescence labelling demonstrate that Resveratrol may reduce the expression of c-Kit by downregulating SCF expression, which improves OAB in rats with CP [28]. Vitamin C was inversely associated with progression of daytime urinary storage symptoms in men or urgency symptoms in women. Although the experiments suggested that the stimulatory effect of ascorbic and citric acid on bladder smooth muscle was possibly by enhancing Ca2þ influx, it was difficult to specify the pathway of Ca2þ influx [29]. However, ascorbic acid slightly inhibited the response to muscarinic receptor activation with carbachol, indicating a possible intracellular action, which requires further investigation.

Finally, vitamin D is also important for the urinary tract function. Urinary incontinence, particularly OAB were associated with diminished plasma vitamin D levels in geriatric patients. This can be explained by the importance of intracellular calcium concentration on regulation of smooth muscle contractions. Vitamin D and its analogs were shown to cause calcium desensitization

there by relaxing smooth muscles [30]. Therefore, ICT containing different molecules that perform different functions. Furthermore, no major adverse events occurred. Patients were satisfied after 12 weeks of treatment and more than 80% of them wanted to continue taking ICT. Contrariwise, patients taking standard drugs show a higher discontinuity rate complaining of a high rate of side effects that negatively impact the quality of life [18]. In this study, this ICT proposed in the therapy of OAB syndrome, was an effective and well tolerated treatment. The strength of the study is the fairly large number of patients examined; however, the non-randomized design without a placebo control group prevents us from drawing definitive conclusions. Further randomized prospective studies on a greater number of patients are needed to confirm these findings and any possible combination treatment that can synergize with each other and increase effectiveness.

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