



Topical Use of *Saussurea costus* (Falc.) Lipsch. (Qost) Oil in Pediatric Nocturnal Enuresis in Comparison with Sesame Oil, A Randomized Double-Blind Clinical Trial

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Abstract

Nocturnal enuresis is one of the most common chronic problems of childhood. It has a significant effect on health and quality of life of children and their families. Despite pharmacological treatments, enuresis in most children relapses after the medication is discontinued. Also available drugs have many side effects that limited their uses. So, we compared the effect of topical use of *Saussurea costus* (Falc.) Lipsch. (Qost) oil as a Persian Medicine product on pediatric nocturnal enuresis in a parallel randomized double blinded study. Eighty-two patients aged 5 to 15 years who were diagnosed as monosymptomatic nocturnal enuresis were allocated to receive costus oil or sesame oil topically below the navel twice a day for 4 weeks. Patients were evaluated prior to and following end of the study in terms of frequency of enuresis and any observed adverse events. The results were evaluated with valid PLUTSS questionnaire. For evaluation, Chi-square and Fisher's exact tests, Mann-Whitney and Wilcoxon tests were used. Significant p value was < 0.05. A significant decrease in mean scores of the questionnaires was noted in both groups. The results before and after the intervention were significantly different in both groups, but there was no statistically significant difference between the intervention and control groups. At the end of the 4th week, the frequency and volume of enuresis showed a 46.2 percent reduction in costus oil group and a 25.5 percent reduction in sesame oil

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tus oil group is 74.5%; while in the sesame oil group is 69%. No drug side effect was noticed in this study. Based on the results of this study, costus oil is effective in children with monosymptomatic nocturnal enuresis; however, there is no significant difference between costus oil and sesame oil.

Keywords: Nocturnal enuresis; Persian medicine; Traditional medicine; *Saussurea costus*; pediatric

Introduction

Nocturnal Enuresis (NE) is a common complaint in childhood. It is defined as intermittent incontinence that occurs exclusively during periods of sleep in a child aged five years or more without any other urinary tract symptoms [1]. Night-time bedwetting must occur at least twice per week for at least 3 months or must have a negative impact on other important functions [2]. There are two types of enuresis. Primary enuresis is incontinence during sleep in a child who has never been dry for > 6 months and secondary enuresis, is incontinence in the child after six months of continuous urinary control [3]. The prevalence of NE is approximately 5-10% at age 6 years, 5% at age 10 years, and 0.5-1% among young adults. It is more common in boys in all age-groups [4]. This disorder has a complex condition of genetic, physiologic, neurologic and psychologic etiology.

Although monosymptomatic enuresis is a benign problem and decreases with age, it could affect psychosocial development and cause stigma, stress and inconvenience in children and also decrease self-esteem and quality of life [5].

The treatments of NE are pharmaceuticals and behavioral methods. Behavioral interven-

tions such as bed alarm, overlearning, scheduled waking, star charts, reward systems are considered first line [6]. Medical treatments include antidiuretics, anticholinergics, smooth muscle relaxants and tricyclic antidepressants. Although these drugs are effective in reducing the number of wet nights, they do not have a sustained effect and most children relapse after stopping treatment or do not tolerate the side effects of them [7]. For this reason, many families are interested to use complementary and integrative approaches. Nowadays different alternative therapies such as acupuncture, hypnosis, herbal remedies, chiropractic manipulation, homeopathy and traditional medicines are being used in most parts of the world [8]. There is a lot of information in Persian medicinal books about medicinal plants that is used by physicians to treat enuresis in children [9]. One of these treatments is *Saussurea costus* (Falc.) Lipsch. (Qost) that has been used for more than two thousand years in various medical schools [10,11]. The oil extracted from the roots of this plant is known as costus oil, which is used in different problems such as enuresis in Medieval Persia [12,13].

In this study, our purpose was to evaluate the effect of costus oil, a product of Persian

Medicine (PM), as one of the schools of complementary and alternative medicine (CAM), on NE in children.

Material and Methods

Trial setting and design

This study was designed as a double-blind, randomized clinical trial and conducted between September 2019 and April 2020 in Mofid Hospital, Tehran, Iran. The trial was registered in Iranian Registry of Clinical Trials with the registration number: IRCT20190722044304N1. It was also approved by the Ethics Committee of Research Center at Shahid Beheshti University of Medical Sciences in accordance with the Declaration of Helsinki (IR.SBMU.REC.1398.012). Design and aims of the study were completely explained to both children and their parents or guardians and written consent was obtained from the patients' parents or guardians.

Participants

The participants were 82 outpatient children (56 boys and 26 girls) aged between 5 and 15 years who were recruited from pediatric nephrology clinic of Mofid Hospital. A child nephrologist confirmed the diagnosis of primary monosymptomatic NE before the participants were recruited into the study.

Inclusion criteria

Five to fifteen years old children with a history of enuresis 2 times a week for 3 consecutive months; no skin problem in areas

intended for drug use; no organ disease associated with enuresis and those whose parents were willing to participate in the research and signed the consent form were recruited into the study. The children should not have had a history of allergy to oily drug products.

Exclusion criteria

Children with other urinary symptoms including urinary tract infection; daily symptoms such as frequent urination, urgency, hesitancy; previous surgery in the urinary tract; any chronic degenerative disease involving the nerve or muscle and spinal cord injuries were excluded from the study. If skin allergies and drug intolerance occurred during the study and parents or patients were not satisfied with the treatment, they would be excluded from the study.

Interventions

The patients included in the study were randomized in a 1:1 ratio using a randomized list to receive either costus oil or sesame oil. The randomized list was generated using Microsoft Excel with a block randomization method, as previously described [14]. Eighty-six patients were randomly assigned using 20 drops topically twice a day (in the morning and before sleep) on the area between the navel and pubic region without massage for 4 weeks. In order to prevent possible allergic skin reaction, parents were advised to apply 4 to 5 drops of oil on the child's arm for the first time. The physicians, researchers, and statisticians were blind to the allocation of

patients. The shape and size of the container of oils in two groups were the same.

Preparation of oils

Dried roots of *Saussurea costus* (qost) were purchased from a local herbal market in Tehran. The plant sample was verified by a botanist at the Traditional medicine & Materia medica research center of Shahid Beheshti University of medical sciences with the voucher number of HMS484. The oil was prepared according to ancient PM texts [13]. Hydroalcoholic extract was made from some plant's root powder in 10 times 70% ethanol for 72 h with continuous shaking. Then the extract was mixed with ten times more cold pressed sesame oil and the mixture was boiled until all water was evaporated. Cold pressed sesame oil was considered for control group.

Outcome measurement

The main outcome was measured using the Pediatric Lower Urinary Tract Scoring System (PLUTSS) questionnaire. We used Persian translated version of this questionnaire which is a valid measurement of screening urinary tract symptoms among Iranian children [15]. This standard questionnaire contains 14 questions for assessment of wetting episodes, voiding frequency and pattern. It is used for screening and evaluation of the response to treatment. Reduction in the scores shows improvement in the condition of the urinary problem. The PLUTSS questionnaire was completed at baseline and 4 weeks after

the intervention. Any side effects of topical oil consumption were assessed by a questionnaire that was prepared based on Common Terminology Criteria for Adverse Events (CTCAE, v4.03, 2010).

Statistical analysis

Chi-square and Fisher's exact tests were used for categorical variables in order to check similarity of the two groups. For statistical analysis of primary characteristics and outcomes in each group and between two groups, the Mann-Whitney test was used for independent variables and the Wilcoxon test was performed for dependent variables. The statistical tests were performed by statistical package for the social sciences (SPSS) software version 24.

The sample size was calculated by a statistician to be 39 patients in each group on the basis of following assumptions: study power of 0.8, population variance of 6.25 based on previous study [15] and an α of 0.05. P value < 0.05 was considered significant.

Results

From September 2019 to April 2020, a total of 100 patients were assessed for eligibility. Twelve of them did not meet the inclusion criteria and finally 86 of them were randomized to receive either costus oil or sesame oil. Four patients withdrew from the study due to parents' lack of collaboration and excluded from the final analysis. Further details have been shown in the CONSORT flow diagram (Figure 1).

In this study, 56 boys (68.3%) and 26 girls (31.7%) participated, in which 24 (62%) boys and 15 (38%) girls were in the case group and 32 (74%) boys and 11 (26%) girls were in the control group. The mean age of the case group was 7.1 ± 2.5 while it was 7.6 ± 3 in the control group. There was no significant difference in age or gender between the two groups.

Based on the analysis, the mean frequency and volume of enuresis has significantly decreased in both groups after treatment compared with the base scores ($p < 0.0001$) (Table 1). There was no significant difference between two groups with regard to PLUTSS

scores, which means both treatment groups exhibited a similar declining trend over the 4-week period (Figure 2 and Table 2). Also, the effect of enuresis on children's quality of life decreased in both group over the time with significant difference ($p < 0.05$). Eventually response rate in costus group was 74.5% vs. 69% in sesame group with no significant difference.

There was no report of any adverse event in both groups. There was no report of anticholinergic, tricyclic antidepressants and antidiuretics drugs side effects that were usually used for NE treatment.

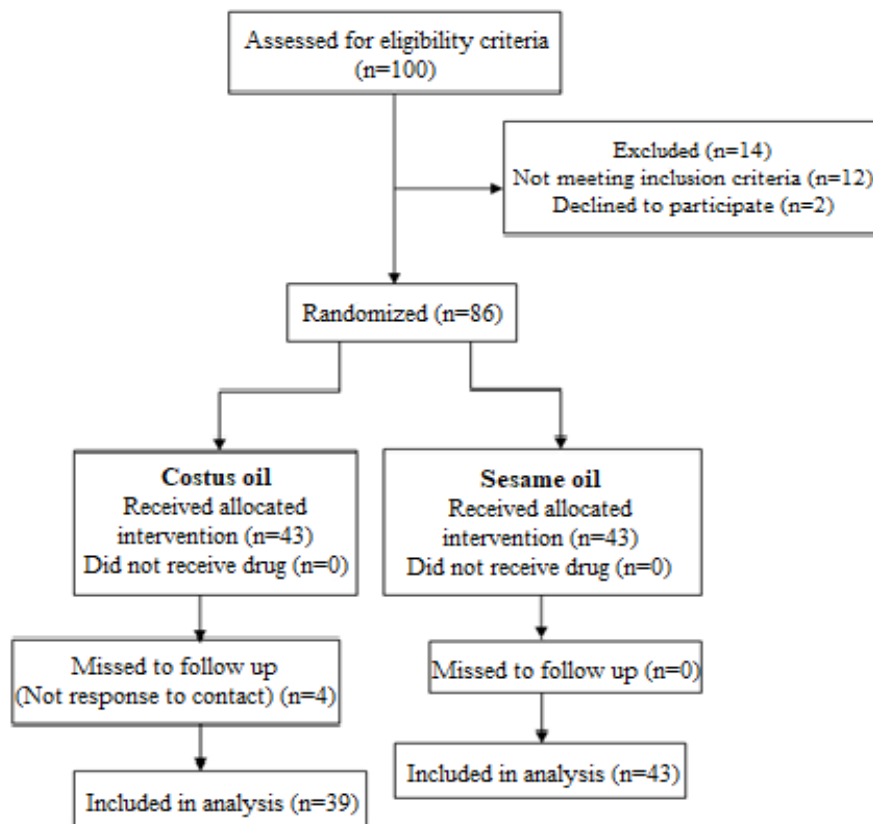


Figure 1. CONSORT flow diagram of the study participants

Table 1. Comparison of the mean frequency and volume of enuresis in the costus and sesame group (Mean ± SEM)

	Group	Before treatment	After treatment	P value
Frequency of enuresis	costus	3.56 ± 0.23	1.66 ± 0.32	< 0.0001
	sesame	4.09 ± 0.22	2.00 ± 0.30	< 0.0001
Volume of enuresis	costus	3.92 ± 0.07	1.92 ± 0.31	< 0.0001
	sesame	3.93 ± 0.06	2.48 ± 0.27	< 0.0001

SEM, standard error of mean

Table 2. Mean PLUTSS scores in the costus and sesame group (Mean ± SEM)

PLUTSS scores	Before treatment	After treatment	P value
costus	12.69 ± 0.53	5.94 ± 0.98	< 0.0001
sesame	13.45 ± 0.62	7.07 ± 0.89	< 0.0001

SEM, standard error of mean

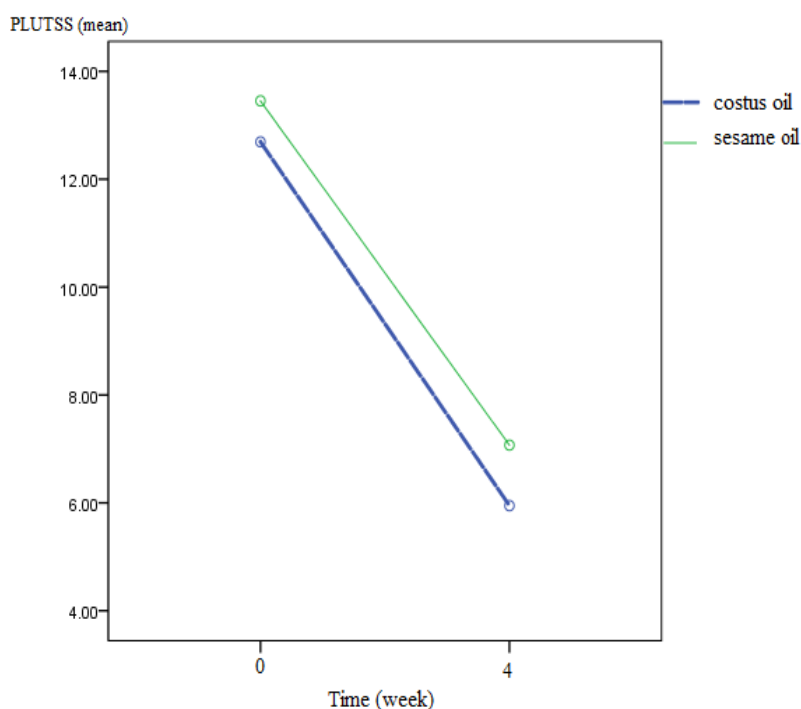


Figure 2. Mean PLUTSS scores before and after intervention

Discussion

This study aimed to evaluate the effectiveness of topical application of *S. costus* oil in

the treatment of NE in children. The standardization document from International Children's Continence Society (ICCS) con-

siders treatment outcome as “Partial Response” when there is improvement of 50 to 99% of the symptom [1]. The response rate in this study based on PLUTSS questionnaire in costus oil group is 74.5%; while in the sesame oil group is 69%, therefore both oils are effective in the treatment of enuresis in children. No significant difference was observed between the two groups at the end of the trial. There is weak evidence to support the use of CAM methods for the treatment of enuresis [16]. There are several herbal remedies that are used in traditional medicine in different countries to treat enuresis. The results of a study by Me et al. in 2017 suggest that *Suo-quan* (a combined Chinese herbal medicine) in combination with desmopressin is effective and has a low relapse rate [17]. A study on the effects of *Yokukansan*, a traditional Japanese medicine, showed that this combination is effective for some children and can be a candidate as a treatment for enuresis [18]. In other trials, three preparations of different medicinal herbs were compared to imipramine and the herbs seemed to be better than imipramine both during and after treatment [16].

PM has its unique theories for concepts of etiology and treatment, being different from that of western medicine. According to the basics of PM, the most common cause of primary enuresis in children is bladder weakness due to coldness of the bladder that decreases the intrinsic natural power of bladder to hold urine during sleep [12]. Another cause is the moisture in the muscle fibers of the external

sphincter that cannot contract strongly on the bladder’s neck [19]. PM suggests simple recommendations for NE which are affordable, available and safe with minimal side effects. One of these recommended treatments is anoint the bladder area with different oils [9]. Herbal oils are easily prepared and their use is convenient and offers several advantages over oral drug therapy [20]. Transdermal therapy has been recently introduced in the medical literature for the treatment of detrusor muscle overactivity [21]. In this regard, the results of a double-blind, randomized clinical trial in 2017 showed that topical use of chamomile oil can decrease the episodes of enuresis in children [22].

To the best of our knowledge, our study is the first trial evaluating the efficacy and safety of costus oil in NE in children, although it has been used in urinary incontinence in adults. The results of this study showed that the topical use of costus oil is effective in treatment of female urinary inconsistency [23]. In a case series study, topical use of costus oil was effective on the primary dysmenorrhea in 13 patients [24].

Costus oil is one of the Persian practitioner’s recommended treatments for NE [12,13]. It is effective in eliminating “cold” and “wet” temperament that affect the bladder wall and relax the bladder sphincter muscle [23]. Avicenna (980-1037 AD), the famous Iranian scientist, in his book “The Canon of Medicine” wrote that the root of costus can be useful for any organ which needs to be warmed up. Also, it can be effective in organs whose

function is impaired due to tissue loosening [12]. Although, the exact mechanism of the effect of this plant root in NE treatment is unknown, the expected function is warming up the bladder and being siccative to remove waste from bladder and being astringent to improve bladder tone and strengthen the kidneys and bladder.

According to our study, the improvement of symptoms in the costus oil group was the same as sesame oil group. There is no significant difference between the two groups, so both drugs are effective in treatment. This could be because of the same mechanism of action of these drugs from the perspective of PM. However, for more precise judgment, further well-designed clinical studies need to be conducted to obtain more reliable evidence.

The safety and no side effect of costus oil in comparison with current drugs can be an important advantage in this study and be a reason for its prescription for NE, alone or as an alternative to the pharmacological treatments.

The most important limitation of our study was the short duration of follow-up and not considering the recurrence rate after discontinuing the treatment. Future studies with higher methodological quality and including follow-up periods of longer duration are suggested. The use of sesame oil as a control group is another limitation. It was also effective and reduced NE in this study but because of the use of this oil as a vehicle of costus oil we selected it for the control group. Further

trials with neutral placebo or in comparison with most commonly used interventions like desmopressin and imipramine is suggested.

Conclusion

NE is a common problem that can impair a child's psychosocial development. The use of medicinal plants has increased considerably because of lower cost and fewer side effects. Due to the convenient method of using oil and low invasion of topical treatment, it can be suitable for NE treatment in children. According to our study, the topical use of costus oil can reduce the frequency and volume of enuresis in children, so it can be effective and safe option in the treatment of NE. Nevertheless, our study is relatively small and further trials with larger sample size, longer treatment and follow-up duration are warranted.

Compliance with Ethical Guidelines

All ethical principles were considered in this article.

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Conflicts of Interest

The authors declared no conflict of interests.

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