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Comparison of the Efficacy of Fluvoxamine and Desmopressin-Oxybutynin Combination in the Treatment of Nocturnal Enuresis: A Clinical Trial

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Abstract

Background: Primary nocturnal enuresis (PNE), with a prevalence of 5-30%, is a common and important disease in children. We aimed to investigate the efficacy of fluvoxamine in the treatment of refractory PNE and to compare it with standard desmopressin-oxybutynin treatment.

Materials and Methods: In this pilot clinical trial study, children with PNE referred to the Dr. Sheikh Hospital (Mashhad, Iran, 2019) who were resistant to the first line of behavioral and drug treatment and did not have any other psychological disorders were enrolled in the present pilot clinical trial. Patients were randomly divided into fluvoxamine (25 mg at bedtime for one month), combination therapy (desmopressin, 10µg intranasal), and oxybutynin (0.1 mg/kg for one month). The recovery status of patients in the two groups was investigated and compared based on the number of wet nights during one month.

Results: 30 patients with PNE were included in this study. Three patients of the treatment group were excluded from the study due to lack of referral and follow-up. At the end of follow-up in the fluvoxamine treatment group, full recovery was observed in 8 patients (66.7%), partial recovery in 2 patients (16.7%), and no recovery in 2 patients (16.7%). Also, the desmopressin-oxybutynin treatment resulted in full recovery in 7 patients (46.7%), partial recovery in 4 patients (26.7%), and no recovery in 4 patients (26.7%), but there was no significant difference between the two groups in terms of therapeutic results (P> 0.05).

Conclusion: Based on the results, there was no difference between the two groups of fluvoxamine and desmopressin-oxybutynin combination in the treatment of nocturnal enuresis.

Key Words: Children, Fluvoxamine, Nocturnal Enuresis, Oxybutynin, Desmopressin.

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1- INTRODUCTION

Normally, children gain daytime bladder control earlier than nighttime bladder control and during sleep. A cohort study showed that children gained gain daytime and nighttime bladder control at 3.5 and 4 years of age, on average, respectively (1). Generally, enuresis refers to the wetting of clothing or beds by involuntary emptying of the bladder during the day or night (2). However, enuresis usually means nocturnal enuresis. Nocturnal enuresis is defined as wetting of clothing or bed by urination for at least 3 consecutive months in children over 5 years of age (3). The prevalence of nocturnal enuresis (NE) at the age of 5 is estimated to be 5-30% (4). Also, a study reported that the prevalence of NE was 6.8% in Iranian children aged 5-18 years (5). A study in the UK revealed that the prevalence of NE was 30% among 5-year-old children and 9.5% in 10-year-old children (6). Spontaneous recovery of NE is estimated at 1۵% per year (7).

However, 7% of children who had NE at age 7 do not recover until adulthood (8) so that 0.5% of adults aged 18-64 years have NE (9). A positive family history is reported in many patients. One study showed that the children of people who had NE during childhood suffer from it in 77% of cases, and the odds ratio for NE was 44% in children whose parents had NE as compared with 15% in other children (10). Other risk factors of enuresis include the greater number of siblings, the birth order of the child, the economic and social status of the family, the male sex, constipation, and a history of urinary tract infection (11). Although several hypotheses have been made about the cause of NE, the root cause has not been well determined. Different factors seem to be involved in this regard; in other words, NE is a multifactorial disease (12). Increased nocturnal urinary output (13), decreased bladder capacity (14, 15), or detrusor over activity, and arousal disorder are the three main factors in NE physiopathology (16, 17). NE can lead to psychosocial developmental disorders as well as impaired self-confidence development and socializability in children. NE has been shown to reduce a child's sense of self-worth and self-esteem, and enuresis treatment can improve a child's mental state (18). Enuresis can also lead to feelings of embracement, harassment in school and the unwillingness to participate in school camps and can have a significant impact on the quality of life of the children and their family (19). Enuresis can also continue until adulthood in 7% of children, which indicates the importance of early treatment of the disease (8). Non-pharmacological and behavioral therapies aimed at correcting urinary excretion habits, such as taking the child to bathroom before bed, or waking him or her to pass urine at night, are the basis of enuresis therapy (20). It has also been recommended to reduce fluid intake during the day, especially diuretic fluids, such as caffeinated beverages, although their efficacy has not been proved yet (21).

Constipation can lead to unsuccessful treatment of NE, so timely diagnosis and treatment of constipation is very important in these patients (22). The use of alarm therapy is another method of enuresis treatment. This treatment focuses on child's education and conditioning and thus helps the child to wake up before occurrence of NE (23), and its success rate is reported to be 65-75% (24). Pharmacotherapy using desmopressin, a vasopressin analogue, is another treatment for NE. In most children with NE, nocturnal polyuria is seen due to disruption of the vasopressin secretion cycle (25). One study found that nocturnal urine volume in vasopressin-treated children with NE was significantly lower on dry nights than on wet nights when they

underwent no treatment (26). Desmopressin is used in the form of pills or nasal sprays. The most important side effects of desmopressin include headache, nasal congestion, nosebleeds, abdominal pain, water poisoning, allergic reactions, hyponatremia, anorexia, nausea, bad taste in the mouth, and vision problems (27). Response to desmopressin treatment was reported to be about 60-70%, but the recurrence rate after discontinuation of the treatment was estimated to be 50-90% (28). In children who do not respond to behavioral therapy, alarm therapy, desmopressin, or a combination thereof, it is recommended to add an anticholinergic such as oxybutynin, which inhibits the detrusor muscle. One study showed that adding oxybutynin to desmopressin increased response to treatment and reduced recurrence rate (29). The rate of response to oxybutynin treatment alone was reported to be 47-71% (30).

The use of tricyclic antidepressants is another drug used for enuresis treatment (31). The most common tricyclic antidepressant used for enuresis treatment is imipramine (32). Imipramine is the oldest pharmacological treatment for NE, but its use is very limited due to its many side effects, including its adverse effects on the heart, as well as the presence of better alternative drugs (31). Although there are the many therapies for enuresis, the efficacy of these treatments is limited and children are resistant to treatment in more than 50% of cases (19). Therefore, it is important to identify new and effective treatments. The aim of the present clinical trial was to compare the efficacy of fluvoxamine and the desmopressin-oxybutynin in children with refractory PNE.

2- MATERIALS AND METHODS

2-1. Study design and population

This clinical trial was performed to compare the therapeutic effect of fluvoxamine and desmopressin-oxybutynin combination in children with refractory PNE in Pediatric Nephrology Clinic of Dr. Sheikh Hospital, Mashhad, Iran in 2019. Considering the fact that this study was performed for the first time, this pilot clinical trial was carried out on 30 patients based on the opinion of a statistician. After being examined for inclusion and exclusion criteria, a total of 30 patients with refractory PNE who referred to the Nephrology Clinic of Dr. Sheikh Hospital entered the study. Patients were randomly divided into fluvoxamine (fluvoxamine recipients) group or combination treatment (desmopressin-oxybutynin) group. After evaluating the baseline variables, patients were followed up for one month. During the follow-up, 3 patients in the treatment group were excluded from the study due to lack of referral and follow-up. At the end of the follow-up using number of wet nights, the main result of the present study was recorded as full recovery, partial recovery, and no recovery and the results of the two groups were compared.

2-2. Inclusion criteria

1. The patient has PNE and has never had a period of nocturnal urinary control for at least 6 consecutive months during his/her lifetime.

2. The patient should be resistant to the first line of pharmacological and behavioral therapy.

3. Considering the fact that the use of fluvoxamine in children over 8 years of age has been approved, patients should be within 8-14 years of age.

2-3. Exclusion Criteria

1. The presence of clinical and laboratory evidence indicating the presence of other diseases of the renal-urinary system.

2. Suffering from psychiatric illnesses defined in Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5),

including major depressive disorder, anxiety disorder, and ADHD.

3. Side effects of fluvoxamine, including unusual behavioral changes, irritability, impulsivity, and insomnia.

2-4. Intervention

Fluvoxamine (25 mg at bedtime) was administrated to the fluvoxamine group for 1 month. The combination of desmopressin (10 µg intranasal) and oxybutynin (0.1 mg/kg) for 1 month was also prescribed for the combination group. In addition to drug therapy, both groups of patients received behavioral therapy recommendations (such as taking the child to the toilet before bed, or waking him/her up to pass urine at night). The recovery status of patients was considered as the main outcome of the present study based on the number of wet nights (nights when the patient suffers from NE) for one month and based on the patient's and parents' own statements. Full recovery was defined as the number of wet nights less than 2 nights per month and partial recovery as more than 50% reduction in wet nights. Demographic characteristics (gender and age), constipation, family history of EN, and patients' ultrasound status were also assessed as intervening variables. Patients' ultrasound status was defined as both normal and abnormal and based on the latest ultrasound report of patients' kidneys and urinary tract.

2-5. Ethical Considerations

The ethical considerations of the present study were confirmed by the Ethics Committee (IR.MUMS.sm.REC.1396412) of Mashhad University of Medical Sciences. To participate in this study, the details of the study were explained to the parents of all participants in the study, and an informed written consent was obtained from them. Participants' information was kept confidential and none of their personal information was entered into the data. The current study has been registered in the Iranian registry of clinical trials (IRCT20171112037417N1)

2-6. Statistical Analysis

Statistical analysis was performed using SPSS ver. 16.0. Descriptive statistics included the frequency and percentage of different values of qualitative variables and mean and standard deviation of quantitative variables in all patients of the two groups. The homogeneity of the two groups was investigated by comparing the intervening variables between the two groups. Qualitative and quantitative variables were evaluated in this study using appropriate statistical tests such as Student's independent t-test, chi-square, and Mann–Whitney U test. The treatment outcomes were compared between the two groups using Chi-square or Fischer's exact test. P-value<0.05 was considered as the significant level in all tests.

3- RESULTS

3-1. Baseline Characteristics

A total of 30 patients with PNE were enrolled in this study based on inclusion and exclusion criteria. Three patients in the treatment group were excluded due to lack of follow-up and follow-up during the follow-up period. Therefore, 12 patients (44.4%) received fluvoxamine treatment and 15 patients (55.6%) underwent desmopressin-oxybutynin treatment. The mean age (standard deviation) of the patients was 8.5 years (0.9). The mean age in the fluvoxamine and desmopressin-oxybutynin-treated groups was 8.7 ± 0.7 and 8.3± 1.0 years, respectively (P>0.05). Thirteen patients (48.1%) were boys and fourteen (51.9%) were girls (P = 0.86) (**Table.1**).

Table-1: Baseline characteristics of patients

Variables	Fluvoxamine group, n=12	Desmopressin-oxybutynin group, n=15	P-value
Age	8.7+ 0.7	8.3+1.0	0.8*
Gender/ boy	50%	46.7%	0.86**

*Mann-Whitney, ** Chi-Square test.

3-2. Clinical Specifications

In total, 11 patients (40.7%) had constipation at the same time. This rate was 41.7% in the intervention group and 40% in the control group (P = 0.93). Relatives of 14 patients (51.9%) had a family history of NE. This rate was 50.0% in the intervention group and 53.3% in the control group (P = 0.86). Abnormal findings were reported in the last ultrasound of 5 patients (18.5%), two of whom were in the intervention group and three in the control group. There was no significant difference between the two groups in terms of frequency of abnormal ultrasound findings (P = 0.61) (**Table.2**).

Table-2: Clinical Specifications of patients.

Variables	Fluvoxamine group, n=12, %	Desmopressin-oxybutynin group, n=15, %	P-value
Constipation	41.7	40	0.93
Family history	50	53.3	0.86
Abnormal ultrasound	16.7	20	0.61

* Chi-Square test, - - Fischer's exact.

3-3. Comparison of the efficacy of fluvoxamine and desmopressin-oxybutynin

At the end of treatment, a total of 15 patients (55.6%) had full recovery and 6 patients (22.2%) had partial recovery, but 6 patients (22.2%) had no significant recovery. The recovery status in the fluvoxamine group was as follows: full recovery (n=8 patients, 66.7%), partial recovery (n=2 patients, 16.7%), and no recovery (n=2 patients, 16.7%). Also, desmopressin-oxybutynin treatment yielded the following recovery status: full recovery (n= 7 patients, 46.7%), partial recovery (n= 4 patients, 26.7%), and no recovery (n=4 patients, 26.7%). Although the crude recovery rate in the intervention group was higher than the control group, Fischer's exact test showed that this difference was not statistically significant (P = 0.663) (**Table.3**).

Table-3: Comparison of patient outcomes in two groups of fluvoxamine and combination.

Variables	Fluvoxamine group, n=12	Desmopressin-oxybutynin group, n=15	P-value
Constipation	66.7%	46.7%	0.663
Family history	16.7%	26.7%	
Abnormal ultrasound	16.7%	26.7%	

* Fischer's exact.

4- DISCUSSION

The aim of the present study was to compare the efficacy of fluvoxamine and the desmopressin-oxybutynin combination in children with refractory PNE. This pilot clinical trial was conducted on 27 children with refractory PNE that was resistant to the first line of drug and behavioral therapy. The results showed that although one-month fluvoxamine treatment led to full recovery in 66.7% and partial recovery in 16.7% of patients, the treatment outcomes of patients undergoing this treatment did not differ significantly from the treatment outcomes of patients receiving routine desmopressin-oxybutynin treatment. Mesaros (1993) first reported the effect of fluoxetine in the treatment of PNE in a 15-year-old teenager who had the disease since the age of five and had NE six nights a week (33).

Similarly, Murray (1997) reported that paroxetine was effective in treating PNE in a 16-year-old teenager (34). In the same year (1997), Sprenger reported that sertraline improved enuresis in a 13-year-old adolescent with PNE who had undergone treatment for mood disorders (35). Toren et al. (2001) conducted a pilot clinical study aimed at investigating the effect of fluvoxamine on enuresis in children and adolescents for the first time (36). The above non-controlled study was performed on only nine children with PNE aged 9-14 years, and the results showed no significant difference in the number of wet nights in fluvoxamine recipients after at least five weeks of treatment and no significant difference was observed in the frequency of NE four weeks after discontinuation of this treatment.

After a more detailed investigation, the authors of this study reported that the fluvoxamine treatment had a relative effect in three cases, had no effect in two cases, and led to an exacerbation of enuresis in four cases. In contrast, this non-controlled study was performed on a smaller number of patients and examined the effect of the drug by pre-and post-design. Five patients included in this study were also treated with fluvoxamine due to psychological problems such as obsessive-compulsive disorder (OCD), and its effect on enuresis was investigated only as a sub-phenomenon and different doses of fluvoxamine were used in patients.

Although these limitations were eliminated in the present study, we achieved results similar to the study of Toren et al. (36) that showed fluvoxamine had no effect on improving enuresis symptoms. In another study, Kano et al. (2003) examined 40 children with PNE and 7 children with secondary nocturnal enuresis (SNE). They showed that 35% of children with PNE experienced full recovery, and 45% experienced partial recovery, and only 20% of patients did not respond to treatment after fluvoxamine treatment (25 mg, daily) for 3 months. Similarly, fluvoxamine treatment in children with SNE resulted in full recovery in 43% and partial recovery in 43% of patients. They also showed that response to fluvoxamine treatment was directly related to stress biomarkers, and that patients with elevated stress biomarkers showed a better response to treatment (37).

In a prospective study by Mahdavi-Zafarghandi (2013), 25 adolescents PNE resistant to desmopressin treatment underwent sertraline therapy (50 mg, daily) for three months. This study showed that the number of wet nights decreased significantly after treatment. In the above study, a total of 72% of patients showed a full or partial response to treatment, of whom 48% had full response and 24% had partial response to treatment (38). Lundmark et al. (2016) also investigated the effect of another antidepressant called reboxetine, a reuptake inhibitor of norepinephrine, in patients with PNE. The results showed that reboxetine alone or in combination with desmopressin had a

significantly better efficacy than placebo (39). A systematic review, by Caldwell et al. (2016) examined the effect of imipramine and tetracyclic antidepressants on NE in general. The results showed that imipramine significantly reduced a wet night per week compared to placebo and increased the odds ratio of full dryness by 35% for two consecutive weeks.

On the other hand, a very high recurrence rate of 96% was reported with imipramine discontinuation. The above systematic review also showed that imipramine was less effective than alarm therapy, but the treatment efficacy will be increased if it administrated along with desmopressin (40). Although the present study showed that the outcomes of fluvoxamine treatment did not differ significantly from those of the desmopressin-oxybutynin treatment, the drug led to full or partial recovery of enuresis in 83% of patients.

It seems that fluvoxamine and other selective serotonin reuptake inhibitors (SSRIs) can be effective in controlling enuresis through several mechanisms. First, previous studies have shown that serotonin is directly involved in urine control and excretion through brain and spinal processes. Serotonin inhibits urinary tract movements and urinary excretion by affecting 5-HT3 receptors on spinal neurons, and inhibits bladder activity by acting on 5-HT1A presynaptic receptors in the brain (41, 42). Therefore, SSRIs can directly improve bladder control and urination by increasing the level of serotonin in the inter-synaptic space.

It is important to note that although fluvoxamine has led to varying degrees of recovery in patient with enuresis in most cases, it has been ineffective in some cases. Also, previous studies revealed that the use of SSRIs has even led to the development or worsening of NE in some cases (36, 43, 44). Different factors can be effective in patients' response to treatment with SSRIs. A study was carried out on patients with obsessive–compulsive disorder (OCD) treated with fluvoxamine and results showed that the lower severity of the disease, the shorter duration of the disease; the family history of mental illness, and the female sex were related with a greater response to treatment (45). It seems that genetic factors may also be involved in the response to fluvoxamine. Results of a clinical trial study on children with autism showed that the level of serotonin transporter gene promoter polymorphism was effective in the response to fluvoxamine treatment (46).

4-1. Study Limitations

One of the most important limitations of the present pilot study is the low sample size. Also, in this study, the long-term effects of treatment as well as the rate of recurrence after discontinuation of treatment were not investigated due to the short follow-up period. Besides, the frequency of side effects was not accurately assessed, although none of the patients had a serious side effect. Also, the study population was limited to patients who did not respond to the first line of treatment considering ethical considerations, which limits the generalizability of the results.

Other limitations of the present study include the qualitative investigation of the treatment outcomes, the lack of a placebo recipient group, the lack of randomization, and the lack of double-blind design. Compared to the studies of Toren et al., and Kano et al., that investigated the effect of fluvoxamine on PNE before the present study, the current study compared the effect of this drug with standard desmopressin-oxybutynin treatment for the first time (36, 37). The non-homogeneity of the study population was also lower in the present study than previous studies and hence the results are more generalizable.

5- CONCLUSION

The present pilot clinical trial was carried out on 27 children aged above 8 years with refractory PNE, and the results showed that outcomes of both fluvoxamine treatment (25 mg per night for one month), and standard desmopressin-oxybutynin treatment are equivalent and increase treatment response significantly. Therefore, it is recommended to use it as an alternative treatment in cases of refractory PNE after carrying out further studies and confirming the efficacy of this treatment. Fluvoxamine is a CNS-effective drug that has far fewer and less dangerous side effects than imipramine, the most common CNS-effective drug used in enuresis, and could be a good alternative.

6- CONFLICT OF INTEREST: None.

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