Effect of Low Dose Imipramine in Patients with Nocturnal Enuresis, A Randomized Clinical Trial

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Introduction. Nocturnal enuresis is a condition, which can affect the quality of life in children. The present study was designed to investigate the efficacy of low-dose imipramine combined with desmopressin on treatment of patients with primary nocturnal enuresis who were defined as desmopressin non-responders.
Methods. A randomized clinical trial was carried out on patients with primary nocturnal enuresis. Forty children with enuresis ranging from 5 to 12 years old were randomly divided into the intervention (n = 20) and control groups (n = 20). The subjects in the intervention group were treated with desmopressin combined with 5 mg imipramine at bedtime, and those in the control group were given desmopressin alone. The patients were followed up weekly for one month. The number of wet nights was recorded.
Results. Two individuals in the intervention and three individuals in the control group were excluded from the study. Our findings indicated that the age and gender showed no significant difference. Furthermore, a significant better recovery in the enuresis was observed in 18 of 20 patients who were treated with combination therapy after 1 month ($P < .05$). In addition, the frequency of recovery was significantly higher (83.3%) in the intervention group, compared with the control group (29.4%).
Conclusion. The analysis showed that low-dose imipramine is well tolerated in clinical practice and may represent a good short-term treatment option in combination therapy where desmopressin alone is not efficient enough.

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INTRODUCTION

Involuntary urination during sleep, nocturnal enuresis (NE) or bedwetting, is one of the most common clinical problems in children above the age of five years old and adolescents for whom bladder control must occur.[1,2] Most of these patients are normal in physical and mental functions, without abnormal bladder or dysfunctional voiding.[3]

The prevalence rate of enuresis at the age of 5 years old is 15% to 20% and over 5 years is around 7%. Some studies have demonstrated that enuresis has higher prevalence in boys than girls. Pathogenesis of enuresis is complex and not fully understood, but some remarkable details have recently been revealed.[4] Various factors may affect enuresis incidence such as psychological, social, economic (lower quality of life) factors, sleep cycle abnormalities, genetic predisposition and biological (small functional capacity of bladder) factors.[5,6] Primary enuresis nocturnal (PEN) is the most prevalent type of enuresis. This condition refers to children who have never been dry at

six consecutive months.[7,8] Commonly, PEN is a benign condition, which spontaneously decreases without treatment as children grow-up.[7,9] However, this situation can have a destructive psychosocial impact on children and their parents.[8]

The typical treatment of enuresis is tricyclic antidepressants (TCA), among them, desmopressin acetate (DDAVP), a synthetic analogue of antidiuretic hormone (ADH), is the most often selected option for initial enuresis therapy.[8] Due to high recurrence rate of desmopressin after discontinuation (40%), imipramine (Tofranil) is the most effective management for treatment of enuresis.[10,11] The standard impressive dose of imipramine for enuresis is 10 mg, 25 mg for 5 to 8 years old for three months, and 50 mg tablet for older children.[12] Prescribing lower imipramine doses may be possible to decrease adverse events of this disease. Therefore, we decided to use low-dose imipramine combined with desmopressin for treatment of patients with primary nocturnal enuresis who were defined as desmopressin non-responders.

MATERIALS AND METHODS

Patients and Trial Design

In this clinical trial, 40 patients (26 female and 16 male) with primary nocturnal enuresis were randomly selected according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria,[13] among who were referred to the pediatric clinic of Dr. Sheikh faculty medical hospital in Mashhad, Iran. The participants' age range was 5 to 12 years old. Informed consent was obtained from the parents, with an approval obtained from the Ethics Committee of Mashhad university of medical sciences. The study was also registered with the code IRCT2016082129459N1 in the Iranian Registry of Clinical Trials System.

Exclusion criteria were: drug side effects, diabetes (insipidus or central), urinary tract infection, anatomic abnormality, neurogenic bladder, CNS disorders, and extragenital malformation. Patients were divided into two groups. Twenty patients as intervention group were given the imipramine 5 mg, they also received desmopressin. We selected 20 patients randomly as control group, where this group matched the intervention group according with sex and age. They were administered desmopressin alone. Of the 40 patients enrolled in the study, 2 individuals of the intervention group and 3 patients of the control group refused to continue the study; hence, they were excluded. Besides, during the study, there was no change in the routine and standard drug regimen of the patients in the intervention and control groups. The patients in both groups were followed up for one month.

Statistical Analysis

Demographic and clinical dara of the patients in both intervention and control groups was analyzed using SPSS software version 16 (Inc., Chicago, Il, USA). The Mann-Whitney test was used to compare the effects of the intervention in both groups. Furthermore, the Friedman non-parametric test was used to examine the trend of changes in the indicators during the study time in the intervention and control groups. In all the tests, P value < .05 was considered as significant.

RESULTS

Participants

A total of 40 patients with primary nocturnal enuresis and inadequate response to desmopressin for at least 1 month were enrolled in the study. The basic characteristics and baseline demographics of study subjects are listed in Table. The study included 20 enuresis patients (8 male and 12 female) who received desmopressin combined with imipramine,

Table Characteristics of Subjects in the Control and Intervention Groups at One Month

Characteristic	Intervention n = 20 (18**)	Control n = 20 (17**)	*P*
Gender (Male/Female)	8/12	8/12	P > .05
Daytime Incontinence, n (%)	8 (40)	6 (30)	P > .05
Complete Recovery, n (%)	15 (83.3)	5 (29.4)	P < .05*
Partial Recovery, n (%)	1 (5.6)	4 (23.5)	-
Non-response, n (%)	2 (11.1)	8 (47.1)	-

**P* less than .05 was considered significant.
**Some patients did not complete the follow-up and not counted in recovery.

and 20 controls (8 male and 12 female) who received desmopressin alone. Children's age range was 5 to 12 years. Few patients (intervention group, n = 2 and control group, n = 3) were not available for some of their follow-up appointments. Nobody had received imipramine before enrolling in the study. As expected, no significant difference was observed in the distribution of gender in both intervention and control groups ($P > .05$).

Response to Therapy

Our results revealed a significant difference in complete recovery in intervention group which received imipramine combined with desmopressin, 15 (83.3%) cases, compared to the control group, 5 (29.4%) cases ($P < .05$) after one-month treatment. Furthermore, 6 patients (30%) in the control group and 8 patients (40%) in the intervention group were suffering from daytime incontinence. Nevertheless, no significant difference between the intervention and control groups in terms of daytime incontinence was observed ($P > .05$). Also, we had 2 (5.6%) cases in the intervention group and 8 (23.5%) cases in the control group with no response to treatment. The frequency of patients with partial recovery was 1 (5.6%) in the intervention group and 4 (23.5%) in the control group. No drugs side effects were observed in both groups.

DISCUSSION

Wetting during sleep, irrespective of pathogenetic and mental health problems, is called enuresis. This term is used when wet night occurs at least one time per month.[14] Generally, enuresis has a widespread prevalence among children older than five years old; however, after the age of seven, it is a concern.[15] A study in the north of Iran by Safaei-Asl et al. concluded that the prevalence of enuresis in boys (7.5%) was significantly higher than girls (4.1%).[16] In a similar research by Bakhtiar et al., it was reported that 5.2% of children had primary nocturnal enuresis and 2.8% of them had secondary nocturnal enuresis.[17] They also reported a higher prevalence of nocturnal enuresis in boys (10.7%) in contrast with girls (5.4%), which showed a significant difference ($P < .05$).[17] In contrast, Mahmoodzadeh et al. reported a different gender distribution where the number of girls (51.4%) was higher than boys (48.6%) in 918 children who analyzed.[18]

It has been suggested that various factors are involved with the pathogenesis of enuresis. Hence, different kinds of non-pharmacological and pharmacological treatments are being used for the management of enuresis.[19,20] Among several drugs, desmopressin and imipramine have been given more attention. Evidence from various studies indicates that due to high recurrence rate of desmopressin after discontinuation, a combination therapy can be more effective than mono-therapy by desmopressin.[21,22] Some evidences confirmed that tricyclics have a therapeutic potential for a variety of nocturnal enuresis, in which; imipramine plays a critical role according to epidemiological studies the prevalence of nocturnal enuresis is lower in children who take desmopressin in addition with imipramine.[23]

The present clinical trial was conducted to investigate the effect of low-dose imipramine combined with desmopressin on the treatment and quality of life of the patients with primary nocturnal enuresis who were desmopressin-resistant. Furthermore, our research work focused mainly on patients who failed treatment with desmopressin. The results showed that combination therapy by imipramine significantly improved the signs and symptoms of enuresis in our patients who had not previously received imipramine therapy.

Azarfar et al. in their clinical trial, demonstrated that tolterodine combined with desmopressin regime has a significant performance in the treatment of enuresis compared with desmopressin and oxybutynin regimen.[21] A randomize clinical trial by Seyfhashemi et al. on 92 children with nocturnal enuresis demonstrated that the relapse rate of nocturnal enuresis in monotherapy with desmopressin or imipramine was high.[24] Ravanshad et al. in a group of 59 patients, reported that treatment with combination of desmopressin and oxybutynin was more effective in comparison with monotherapy with desmopressin.[25] In another prospective study by Austin et al. in patients with no response to desmopressin, they reported that a wet episode at night significantly decreased in combination therapy.[26] In a meta-analysis of 64 trials, Caldwell et al. concluded that treatment with tricyclics is more effective, and that imipramine therapy outcome is more effective and stable compared with other treatments.[23] Their results demonstrated that no significant difference

was observed when imipramine combined with desmopressin compared to monotherapy by imipramine. Whereas, combination therapy with imipramine and desmopressin had impressive effects versus monotherapy by desmopressin.[23] Our study confirms these findings. In contrast, Deshpande et al.; who evaluated a total of 40 randomized trials, suggested that imipramine and indomethacin were not as effective as desmopressin and they have a higher chance of harmful side effects.[27]

In the current study, we did not have any side effects. Although the time of trial was one month and was enough for efficacy judgment, the verification of continuous clinical and functional improvement needs a long-term follow up. Further studies with larger sample size and different doses of imipramine are recommended.

CONCLUSION

Regarding the low side effects and excellent tolerability of imipramine, use of this drug in treating various types of enuresis is increasing. Our study on patients with primary nocturnal enuresis who were non-responder to desmopressin within one month showed that administration of desmopressin along with 5 mg imipramine has a significant effect on reducing clinical symptoms.

CONFLICT OF INTEREST

There is no conflict to be reported for this research work.

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