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Original Article

Combined Treatment with Oxybutynin and Imipramine in Enuresis

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Abstract

Background: Primary nocturnal enuresis is a common disorder that often leads to considerable distress in affected children and their family. In many countries pharmacologic therapy is preferred to non-pharmacologic behavioral and conditional alarm therapy. Imipramine, oxybutynin, and desmopressin have been used for enuresis with various efficacies. The aim of the present study was to compare the efficacy of imipramine, oxybutynin, and combined imipramine and oxybutynin in enuretic children aged 6-14 years old.

Methods: In a randomized controlled study 89 primary enuretic children who were otherwise normal were allocated to three groups: group A (imipramine users, n=29), group B (oxybutynin users, n=26), and group C (combined imipramine and oxybutynin users, n=34). The number of wet nights per week during control period (2 weeks prior treatment), and treatment period (1 month) were compared in each group and inter groups. Also the cure rate in the treatment period and the relapse rate in the follow up period (1 month) were compared between the three groups.

Results: The mean ages in groups A, B, and C were 7.9±1.1 years, 8.2±1.6 years, and 8.2±1.4 years respectively. There was no significant difference in the mean ages in the three groups (P=0.53).

In each group the mean number of wet nights per week decreased during treatment period compared with pretreatment period. This reduction was statistically significant (P<0.001 in each group). Efficacy of treatment between the three groups was compared. There was significant difference between them (P<0.001), but there was no significant difference between group A, and group B (P=0.56). The cure rate during treatment period was 13.7%, 23%, and 41% in groups A, B, and C respectively. This difference was statistically significant (P=0.04). The relapse rate during follow up period in groups A, B, and C was 58.6%, 42.3% and 20.5% respectively, revealing statistical significance (P=0.008) No significant adverse effects for the medications were observed.

Conclusion: Our findings suggest that combined imipramine and oxybutynin for primary enuresis is more effective than either drug used alone. The combined therapy is recommended in enuretic children who are non-responsive to imipramine or oxybutynin alone.

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Keywords ● Enuresis ● imipramine ● oxybutynin

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Introduction

Primary enuresis is defined as involuntary urination during sleep, without history of dryness lasting 6 months or more, without any urologic, neurologic, and diurnal wetting problem.[1] It is a common childhood disorder affecting 15-20% of children aged 5 years, 5% of children aged 10 years, and 2-3% of children aged 12-14 years.[2] The spontaneous cure rate is approximately 15%/year.[2] Genetic factors, high arousal threshold, detrusor hyperactivity, low concentrating ability of kidneys, behavioral problems, and delay in maturational development of neurological systems are the proposed important causative factors.[1,3,4] Non-pharmacological treatments include motivated counseling, bladder stretching, self hypnosis, and a conditioning alarm.[5]

Tricyclic antidepressants, anticholinergic agents, and desmopressin have been used in enuretic patients with different efficacies.[1,3,6] To our knowledge there are only two different uncontrolled studies that report the combined treatment using tricyclic antidepressant and an anticholinergic agent in primary enuresis.[7,8] The present randomized controlled study investigated comparative effects of imipramine, oxybutynin, and combined oxybutynin with imipramine in more number of enuretic children.

Material and Methods

This clinical trial included 112 children (69 boys, 43 girls) aged 6-14 years (mean 8.1±1.2 years) with primary nocturnal enuresis that referred to pediatric nephrology clinic of Mashhad University of Medical Sciences between November 2003 and March 2004. This study included only children with primary nocturnal enuresis without any other voiding dysfunction, urologic, and neurologic abnormalities. Primary enuresis was defined as wetting the bed more than two nights per week for at least in the preceding three months with no history of extended dry period for more than 6 months.[5] Exclusion criteria were prior pharmacologic treatment for enuresis in the preceding month, urinary tract infection, diurnal enuresis, secondary enuresis (episodes of dryness lasting 6 months or more), abnormal urinalysis, voiding dysfunction, urological, and neurological abnormalities. During the inclusion period 23 patients (17 boys, 6 girls) were excluded from the study because of no cooperation. Thus, 89 children aged 6-14 years (mean 8.9±1.6) were eligible for enrollment in the study. All patients were evaluated by complete history taking, and physical examination. For the enuretic children overnight fasting urinalysis and urine culture were requested. Kidney and bladder ultrasonography before and after voiding to rule out structural abnormalities and to evaluate post voiding bladder residue was also performed. Verbal informed consents were obtained from all older children and the parents. The children were divided into three groups randomly according to their referral sequence number of the clinic. A diary card was completed by the parents for wet and dry nights during a 2-week period without medication (as baseline data), during a one month treatment period, and then one month follow-up period without medication.

The groups of the children were randomly assigned to treatment protocol for using imipramine, oxybutynin, and combined imipramine with oxybutynin for four weeks after a two week period observation (control period). Imipramine (10mg for patients weighing less than 30kg, 25mg for those weighing more than 30kg), Oxybutynin (3.75 mg for those weighing less than 30 kg, 5mg for children weighing more than 30kg) and combined oxybutynin with imipramine (with the same dosage for the same weights) were used in the three groups of children defined as group A, B, and C respectively.

The children reassessed every 2-4 weeks in the treatment and the follow-up periods for the number of wet nights, compliance with drugs, and any side effects of medications. The determination of efficacy was based on a comparison of wet nights per week during the control period with that of the trial period. During the treatment period, cure was defined as 2 weeks consecutive dry nights. Relapse was defined as two or more wet nights per week during the follow-up period.

Statistical analyses were carried out using the SPSS software version11.5. The mean wet nights per week in the control and the treatment periods in each group and between the three groups of children were compared using paired *t* test for intra group and analysis of variance for inter group findings including the mean ages and the mean wet nights comparison. The chi-square test was used to compare the cure rate and the relapse rate between the three groups. Descriptive values were presented as the mean ± standard deviation. P value less than 0.05 was considered statistically significant.

Results

The data of the 89 children with primary nocturnal enuresis are presented in table 1. In the total 89 patients aged 6-14 years (mean 8.9± 1.6) were evaluated. The mean number of wet nights per week decreased from 5.1±1.1 during the pretreatment period to 2.4±1.9 during the

Table 1: Data of the enuretic children

Patients groups	n=89	Male/Female 52/37	P value=0.53 Age (year) Mean ± SD
Group A (imipramine user)	n=29	19/10	7.9±1.1
Group B (Oxybutynin user)	n=26	14/12	8.2±1.6
Group C (Combined imipramine and oxybutynin user)	n=34	19/15	8.2±1.4

treatment period (P<0.001). The mean reduction rate of wet nights per week during the treatment period was 53%.

The 89 children randomized to three group: imipramine users (n=29), oxybutynin users (n=26) and those used combined imipramine and oxybutynin (n=34). The difference in the mean ages between the three groups was not statistically significant (one way ANOVA, F=0.63, P=0.53). In groups A, B, and C, 22, 21, and 29 children responded favorably to the treatment, respectively.

The mean age of the patients that were non-responsive to the treatment in groups A, B and C was 7.85±0.9, 8.1±0.88, and 7.9±1.1 respectively. In each group the mean age of the patients that were non-responsive to the treatment was not significantly different from those were responsive (group A: t=0.7, P=0.94, group B: t=0.2, P=0.84, group C: t=0.13, P=0.89).

Comparison of mean wet nights per week during pretreatment and along the treatment period in the three groups is shown in table 2.

In the imipramine user group (group A, aged 6-11 years) the mean reduction rate of wet nights per week in the treatment period was 29%. As shown in table 2, the mean number of wet nights per week decreased during the treatment period that is statistically significant (paired *t* test, t=4.43, P<0.001), (mean difference 1.41, CI95%: 0.76 to 2.07).

In the oxybutynin user group (group B, aged 6-14 years) the mean number of wet nights decreased significantly during the treatment period (t=8.35, P<0.001), (mean difference 2.46, CI95%: 1.85 to 3.07). The mean reduction rate of wet nights per week was 50%.

In the group C (combined imipramine and oxybutynin, aged 6-13 years), there was also a significant decrease in the mean wet nights during the treatment period compared with wet nights in the control period that was statistically different (t=13.53, P<0.001), (mean difference 4, CI95%: 3.4 to 4.6). The reduction rate of mean wet nights per week during the treatment period was 74.1%. Comparison of treatment efficacy between the three groups (A, B, and C) by using one way ANOVA test showed statistically significant difference (F=19.3, P<0.001).

Tukey test showed no difference between group A and B (P=0.56, CI95%: -2.11 to 0.22) but there was significant difference between group C and the groups A and B (P<0.001, P=0.002, CI95%: -3.58 to -1.58, CI95%: -2.57 to -0.50 respectively).

The cure rate during the treatment period and the relapse rate during the follow-up period are shown in table 3. There was statistically significant difference in cure rate between the three groups (chi=6.24, P=0.04). Statistically significant difference was noticed in the relapse rates between the three groups (chi=9.62, P=0.008). No significant side effects related to the medications were reported.

Discussion

Despite more than 20 years clinical research on enuretic children, the pathophysiology and the pathogenesis of the disease is still unresolved.[9] The possible etiologies of primary enuresis are genetics, deep sleep, psychologic, neurologic maturational delay, abnormal circadian antidiuretic hormone secretion, and small bladder capacity, or detrusor overactivity.[1,4]

Enuresis may cause emotional and social

Table 2: Comparison of mean wet nights per week during pretreatment and during treatment period in each group

Patients groups	Mean wet nights per week during pretreatment period	Mean wet nights/wk during treatment period	P values
Group A	4.9±1.12	3.5±2	P<0.001
Group B	5±1.1	2.5±1.7	P<0.001
Group C	5.4±1	1.4±1.5	P<0.001

Table 3: The cure rate during the treatment period and the relapse rate during the follow up period in the three groups

Patients groups	Cure rate	Relapse rate
Group A	4: 29 (13.7%)	13: 22 (59%)
Group B	6: 26 (23%)	9: 21 (42%)
Group C	14: 34 (41.1%)	6: 29 (20.6%)
	P=0.04 (between groups)	P=0.008 (between groups)

problems for the children and adolescents, which may result to lack of self confidence.[10] Because of the lack of consensus on the exact causes, the treatment approach is controversial. Thus, the first choice of treatment should be one that will be most accepted by the children and the family.[9] The final goal is to achieve an individual treatment that enables us to give each child the best treatment without unnecessary failures.[3] Treatment strategy varies cross-culturally: Urine alarms (bells) are used more frequently in the United States, United Kingdom, and Scandinavia, but it is used less in other European countries.[9] Despite various modalities of treatment, pharmacotherapy is still preferred by patients and physicians particularly in our country. Although desmopressin is the initial medication that is prescribed for enuresis in many countries,[1,3,11] imipramine is the first and the oldest drug that is prescribed by our physicians. Imipramine is a tricyclic antidepressant. Tricycles antidepressants block presynaptic uptake of amine neurotransmitters and inhibit the detrusor muscle directly.[8,12] The mode of imipramine's action in enuresis is unknown, however the pharmacologic therapeutic effect is not mediated via its antidepressant effect, because the serum level of the drug in enuretic children is 3-5 times less than that required for an optimal antidepressant effect.[8,9] It must be noted there is no linear relationship between the dosage and the serum level. There are many controlled studies confirming the efficacy of tricyclic antidepressants in 40-70% of enuretic patients with a measurable increase in functional bladder capacity.[8,9,13]

Oxybutynin is a drug with both anticholinergic and smooth muscle relaxant properties. It has proven efficacy in detrusor over activity at night, which is a pattern found in 30% or more of enuretic children.[1,11] Anticholinergic agents act at postganglionic parasympathetic cholinergic receptor sites on the detrusor muscle.[12] Although, a double blind study showed ineffectiveness of 10 mg oxybutynin in nocturnal enuresis,[6] the other studies have reported significant efficacy for this drug.[7,13,14] In addition oxybutynin has been increasingly used for the treatment of urge incontinence, uninhibited bladder contraction, and neurogenic bladder.[14] Therefore, it is rationale for its use in enuresis. Desmopressin non-responders often respond favorably to oxybutynin or combined oxybutynin with desmopressin.[3]

Whereas the previous studies have reported imipramine alone or oxybutynin alone was effective in 40-70% and 10-15% of enuretic children respectively,[7,9] the combined imipramine with oxybutynin therapy was effective in more than 90% of the patients.[8]

This controlled prospective study determined efficacy of either imipramine or oxybutynin alone and combined imipramine with oxybutynin in 29%, 50% and 74.1% of patients respectively. This study similar to the previous ones, documented that combined imipramine with oxybutynin therapy was more effective than either drugs used alone.[7,8]

In our study efficacy of imipramine (29%) was less than the previous studies (40-70%).[6,8] The less efficacy of imipramine in our study compared with pervious ones maybe due to lower dosage used in our patients. Oxybutynin was more or less as effective (50%) in comparison with the previous investigations (10-50%).[6,9] Neveus suggested that detrusor hyperactivity should be regarded as a major pathogenic factor in oxybutynin responders.[3] The results of our study further suggest that the more efficacy of combined therapy is due to increasing bladder capacity via different mechanisms. The good response, more cure rate, and less relapse rate of the combined therapy in our study may cause more self confidence and motivation. Self confidence and positive motivations are the most valuable results that may cause improvement in enuretic children. Whereas the relapse rate and cure rate of combined therapy in the other study was about 60% and 28% respectively,[8] in our study they were about 20% and 40% respectively.

The limitations of present study, including the lack of placebo-controlled group and lack of double blind design, should be taken into account, which indicate the need for further research.

The major drawbacks to imipramine are cardiotoxic side effects, personality changes, anorexia, and possibility of overdose. None of such side effects were observed in the present study. This may be due to the low dosage used compared with that mentioned in the literature (25-75mg/day).[1,8]

Dryness of the mouth, flushing of face, and daily urinary retention are side effects of oxybutynin. But the low dose used in the present study compared with 10-15mg/day mentioned in the literature may be the cause for not observing any such side effects in our study. Tolterodine is an antimuscarinic drug with the some clinical efficacy and a lesser frequency of side effects compared with oxybutynin. Although tolterodine has not yet been approved in most countries for children, recent data indicate that it is useful in the pediatric population.[15]

Conclusion

It is proposed that either oxybutynin or imipramine may have effect in control of enuresis by relaxing the detrusor muscle via different

mechanisms. In patients who are not responsive to imipramine or oxybutynin, use of combined treatment is recommended because of more effectiveness. In addition a further comparative controlled study using higher dosage of these medications as single or combined treatment would be worthwhile. Also additional studies are needed to determine the most optimal dosage and duration of treatment.

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