

Can the combined treatment of solifenacin and imipramine has a role in desmopressin refractory monosymptomatic nocturnal enuresis? A prospective double-blind randomized placebo-controlled study

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Abstract

Background: Nocturnal enuresis is a common disease of childhood. It can be classified into monosymptomatic nocturnal enuresis (MNE) or nonmonosymptomatic nocturnal enuresis (NMNE). Imipramine is a tricyclic antidepressant used to treat enuresis with initial success rates are high as 50% but some studies record a high relapse rate and it has a cardiotoxic effect when overdosed. Anticholinergics may be effective in the treatment of children with bladder storage dysfunction, including daytime incontinence. However, anticholinergics monotherapy is not effective in treating MNE. In our study, we used a low dose (25 mg) of imipramine in order to avoid its potential side effects and combined it with the synergistic anticholinergic action of solifenacin. Our objective was to evaluate the efficacy and safety of the combination of solifenacin and imipramine compared with placebo in the treatment of desmopressin refractory MNE.

Methods: One hundred children aged 6 years or more with primary MNE unresponsive to desmopressin treatment were included. The children were randomly divided into two equal groups. Group A received imipramine 25 mg and solifenacin 5–10 mg oral tablets and group B received placebo once 1 h before bedtime for 3 months. The primary end point was to investigate the efficacy of the combined treatment of solifenacin and imipramine and the secondary end point was the safety of the drugs.

Results: Our study showed that the mean post treatment wet nights per month was significantly lesser in the treatment group than placebo group ($p < 0.001$) and cure rate was significantly higher in treatment group than placebo group ($p < 0.001$). The relapse rate was statistically significantly lower in treatment group than placebo group ($p = 0.032$). No significant side effects related to the drugs were reported.

Conclusion: The combination treatment of solifenacin and imipramine is a useful and safe treatment for nocturnal enuresis after failure of everything else.

Keywords

Enuresis, imipramine, solifenacin, antidepressants, anticholinergics

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Introduction

Nocturnal enuresis often has a familial background and is an extremely prevalent disease during childhood. Urine control is achieved by the age of 5.¹ As at this age, the storage capacity of the bladder increases, and the brain centers can inhibit bladder contractions. Nocturnal enuresis is the involuntary leakage of urine during sleep, at least twice per week for three successive months at the age of 5 years

without any congenital or acquired cause, that may be classified into primary or secondary based on presence or absence of a previous bed dryness interval of more than

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6 months.² It is further subdivided into monosymptomatic nocturnal enuresis (MNE) or nonmonosymptomatic nocturnal enuresis (NMNE). MNE is defined as nocturnal enuresis without a history of bladder disorder and without any daytime lower urinary tract symptoms (LUTS).³

As recommended by the International Children's Continence Society (ICCS), combination therapy is indicated in MNE only after the first-line treatment with either desmopressin or enuresis "moisture" alarm has failed. Many studies, however, have shown that monotherapy with desmopressin is less effective in treating patients with bladder storage dysfunction and is associated with high recurrence rates after stoppage of the drug. Furthermore, enuresis alarm is discontinued in about 30% of the patients for many reasons, such as skin irritation, failure to wake the child, and/or sleep disturbances of the other family members.⁴

Imipramine is a tricyclic antidepressant that is postulated to treat nocturnal enuresis via three main mechanisms of action: (1) Arousal and sleep mechanisms change, (2) Sedative action, and (3) Central and peripheral anticholinergic and spasmolytic effects. It may also work by increasing the posterior pituitary secretion of antidiuretic hormone (ADH). Initial success rates reported to be high as 50%. However, some studies document a high relapse rate⁵ and overdose is associated with cardiotoxicity.⁶

Anticholinergics are effective in the treatment of children with bladder storage dysfunction, including daytime UI. However, when anticholinergics are used as a monotherapy, they are not effective in treating MNE.⁴ Many anticholinergics are used as off-label treatment of children with urinary incontinence (UI); however, oxybutynin is the only drug approved by the Food and Drug Administration (FDA).⁷ Trospium chloride is approved for overactive bladder (OAB) patients aged ≥ 12 years while propiverine hydrochloride for those aged ≥ 5 years (Czech Republic, Germany, and Slovakia only). Early treatment discontinuation was reported in many children, due to intolerable side effects (e.g. dry mouth, constipation, headache, behavior change, flushed cheeks, and blurred vision). Furthermore, neurological side effects, especially cognitive impairment, have been documented for oxybutynin.⁸

Solifenacin succinate is a competitive antimuscarinic with better M3 selectivity postulated to reduce side effects compared to oxybutynin, trospium chloride, and tolterodine, approved worldwide at daily doses of 5 and 10 mg for the treatment of urinary frequency, UI, or adult OAB, and has showed good tolerability and efficacy in adult clinical studies.^{7,8} Meanwhile, solifenacin wasn't approved by the FDA to be used in children,⁹ many studies were done suggesting safety and efficacy of solifenacin in pediatric OAB.⁸⁻¹⁰ Until now, there is a limited knowledge on the usage of solifenacin in the treatment of nocturnal enuresis and the optimal dose wasn't determined.

Therefore, we would like to comment on the safety and efficacy of combination therapy of solifenacin and imipramine in children with desmopressin refractory MNE. To

our best of knowledge this is the first study to investigate the effect of combined therapy of solifenacin and imipramine in desmopressin resistant enuretic children.

Methods

This randomized prospective clinical study was carried out at single tertiary care center from March 2019 to January 2020 including children aged 6 years or more with primary MNE (≥ 2 wet nights per week without history of dryness for a more than 6 months) unresponsive to desmopressin oral tablets (properly prescribed for at least 2 months with adequate supervision), in monotherapy and none of them used antimuscarinics before. Children had any LUTS, urologic, or neurologic diseases were excluded. Informed written consents from all families and the approval of the Ethics Committee of our institution were obtained prior to start of the study.

A total of 223 patients with primary MNE refractory to desmopressin were evaluated for eligibility to be included in the study. One hundred and thirteen patients were excluded for different reasons. For not meeting inclusion criteria, 47 patients were excluded while 42 refused to participate and 24 did not enter the study for other reasons as shown in Figure 1. The remaining 100 patients were randomly divided into two groups using computer generated method, each group consisted of 50 patients. Group A received imipramine 25 mg and solifenacin 5–10 mg oral tablets; the higher dosage was given to children older than 10 years of age and group B received placebo once 1 h before bedtime for 3 months. This study was planned as a double-blind study, and both the participants and the outcome assessors were unaware of the received treatment type. Children were assessed every month during the treatment period for the number of wet nights, compliance, and appearance of drugs side effects.

All children were evaluated by history taking and general physical examination. Frequency volume chart, urine analysis, urine culture, random blood sugar, serum creatinine, uroflowmetry, and kidney and bladder ultrasonography with estimation of postvoiding residual urine volume were ordered to exclude NMNE.

The primary end point was to investigate the efficacy of the combined treatment of solifenacin and imipramine in the treatment of nocturnal enuresis and the secondary end point was the safety of the drugs.

Efficacy was determined based on comparing the number of wet nights per month during the pretreatment period (control period), the last month of the treatment period and 1 month follow-up period post treatment. Complete response was defined as no or one wet nights per month, response as a 90% or greater decrease, partial response as a 50% to 89% decrease and nonresponse if the treatment had less to no effect. Relapse if the family reported more than one wet night recurrence during the 1 month follow up period according to the definition of clinical outcome

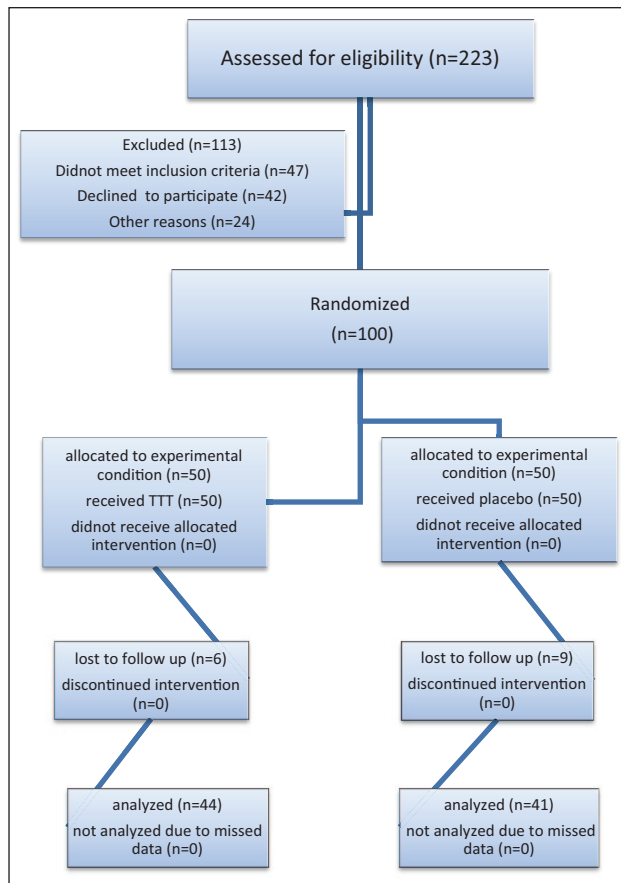


Figure 1. Consort flowchart.

per ICCS.¹¹ For statistical analyses complete cure and response were included in the responder group while partial response and no response in the non-responder group.

Data management and analysis

Quantitative data was expressed as mean and standard deviation. Qualitative data was expressed as frequencies and percent. Independent *t*-test was used to assess the statistical significance of the difference between two study groups mean. Chi square test was used to examine the relationship between qualitative data. The $p < 0.05$ was considered significant in all tests. All statistics were carried out using SPSS version 25 for Windows.

Results

In the total, 85 patients were analyzed divided into 44 patients in the treatment group and 41 patients in the placebo group. Their ages ranged between 6.5 and 15 (mean 10.7 ± 2.3) years including 43 males and 42 females. Both groups had comparable baseline values for age, sex, and mean pretreatment wet nights ($p > 0.05$), as in Table 1.

In the treatment group out of 44 patients, the responders were 31 (70.45%), consisting of 20 children with “complete

Table 1. Baseline data of the patients.

	Group		p-Value
	TTT (N=44)	Placebo (N=41)	
	Mean $\pm$ SD/n (%)	Mean $\pm$ SD/n (%)	
Age	10.48 $\pm$ 2.45	11.08 $\pm$ 2.27	0.24
Sex			
Male	23 (53.5)	20 (46.5)	0.74
Female	21 (50)	21 (50)	
Pretreatment wet nights/month	16.32 $\pm$ 4.328	17.10 $\pm$ 4.7	0.42

Table 2. The clinical outcome in the two groups.

	Group		p-Value
	TTT (N=44)	Placebo (N=41)	
	n (%)	n (%)	
Complete cure	20 (45.4)	2 (4.8)	<0.001
Response	11 (25)	7 (17)	0.37
Partial response	10 (22.7)	13 (31.7)	0.35
No response	3 (6.8)	19 (46.34)	<0.001

cure” and 11 children with “response” while, non-responders were 13 (29.55%) consisting of 10 children with “partial response” and 3 children with “no response”. On the other hand, in the placebo group out of 41 patients, the responders were 9 (21%), consisting of 2 children with “complete cure” and 7 children with “response” while, non-responders were 32 (79%) consisting of 13 children with “partial response” and 19 children with “no response,” as in Table 2.

The mean post treatment wet nights per month was significantly lesser in the treatment group than placebo group ($p < 0.001$) and response rate was significantly higher in treatment group than placebo group ($p < 0.001$). The relapse rate was statistically significantly lower in treatment group than placebo group ($p = 0.032$), as in Table 3. No significant side effects related to the drugs were reported.

Discussion

About 10% of 7-year-old children have nocturnal enuresis.¹² The three main causal mechanisms are poor sleep arousal, nocturnal polyuria, and/or nocturnal detrusor overactivity.³ Many children with enuresis don’t respond to standard treatment (alarm therapy and desmopressin) or suffer from relapse after initial successful treatment.¹³ For NMNE, the ICCS advises to treat the underlying LUTS before addressing the enuresis.¹²

Untreated nocturnal enuresis leads to negative psychological implications. Antimuscarinics have not yet proven the expected success.¹⁴ Another evidence-based therapy of

Table 3. The mean posttreatment wet nights, response, and relapse rates.

	Group		p-Value
	TTT (N=44)	Placebo (N=41)	
	Mean $\pm$ SD/n (%)	Mean $\pm$ SD/n (%)	
Post treatment wet nights/month	5.82 $\pm$ 5.38	16.8 $\pm$ 4.34	<0.001
Response rate	31/44 (70.45)	9/41 (21)	<0.001
Relapse rate	6/31 (19.35)	5/9 (55.5)	0.032

enuresis, the tricyclic antidepressant imipramine is a valid option for some of these patients, but its use has been diminished due to cardiotoxicity with overdose.¹⁵ The search for novel treatment options or the reassessment of old ones is therefore very essential.¹⁶

For therapy resistant enuresis, many drugs have been tried out to treat the condition. Gepertz and Nev us¹⁷ reported that imipramine had a proven benefit when standard treatment else had failed. They used imipramine at a dose of 25–100 mg daily and included 49 children in their study. They found that 64.6% were responders with only 10 children developed mild side effects. The main limitation of their study is that it was a retrospective one.

Nev us and Tullus¹⁶ compared placebo, imipramine 25–50 mg and tolterodine 1–2 mg at bedtime in the treatment of refractory enuresis. They found that imipramine was significantly superior than both tolterodine ($p=0.006$) and placebo ($p=0.001$). The side effects were minor. Nine children on imipramine developed side effects and only one on tolterodine ($p=0.001$). They concluded that tolterodine was not effective treatment option in those enuretic children while, imipramine was effective in some of them.

Lundmark et al.¹⁸ conducted a study using reboxetine which is a selective norepinephrine reuptake inhibitor having similar mechanism of action as imipramine but without serotonergic effect and no cardiotoxicity. They compared reboxetine and placebo, reboxetine and desmopressin, with double placebo treatment including 19 patients in cross-over design. They found that the decrease of wet nights was statically significantly better with both reboxetine alone and combined with desmopressin than with placebo ($p=0.002$). However, complete dryness was achieved in only one patient using monotherapy. Intermediate response was achieved in three patients with monotherapy and five with combination treatment. They explained the low complete cure rate with the low dosage used. The side effects were mild and transient.

Our study like the previous ones used combined imipramine with anticholinergic (oxybutynin), reported that combined therapy was more effective in MNE.^{19,20} We used a low dose (25 mg) of imipramine in order to avoid its

potential side effects and to combine it with the synergistic anticholinergic action of solifenacin. We did not assess the nocturnal urine production to increase patient's compliance. The major limitation of our work was the indirect assessment of the pathogenetic factors, that is, nocturnal polyuria, nocturnal detrusor overactivity and low sleep arousal. So, further studies including larger number of patients are needed to validate our findings. However, our results give a valuable clue to help these patients with desmopressin refractory enuresis.

Conclusion

The combination of solifenacin and imipramine is useful for the management of nocturnal enuresis after failure of the standard therapy without incidence of serious side effects.

Abbreviations

MNE: monosymptomatic nocturnal enuresis, NMNE: nonmonosymptomatic nocturnal enuresis, LUTS: lower urinary tract symptoms, ICCS: International Children's Continence Society, ADH: antidiuretic hormone, UI: urinary incontinence, FDA: Food and Drug Administration, OAB: overactive bladder.

Declaration of conflicting interests

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