Scholars Journal of Applied Medical Sciences
Abbreviated Key Title: Sch J App Med Sci
ISSN 2347-954X (Print) | ISSN 2320-6691 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Urology

A Comparative Study of Imipramine and Tolterodine for the Treatment of Children with Primary Nocturnal Enuresis

Dr. Md. Nazmul Haque[1*], Dr. Samia Nargis[2], Dr. Md. Abul Kalam Azad[3], Dr. Md. Tazrul Islam[4], Dr. Arif Mohammad[5]

[1]Associate Professor, Department of Urology, Khulna Medical College, Khulna, Bangladesh
[2]Jr. Consultant, Department of Anesthesiology, 250 Bed General Hospital, Khulna, Bangladesh
[3]Assistant Professor, Department of Urology, Khulna Medical College, Khulna, Bangladesh
[4]Medical Officer, Department of Urology, Khulna Medical College Hospital, Khulna, Bangladesh
[5]Assistant Registrar, Department of Urology, Khulna Specialized Hospital, Khulna, Bangladesh

DOI: https://doi.org/10.36347/sjams.2024.v12i11.034 | **Received:** 18.10.2024 | **Accepted:** 23.11.2024 | **Published:** 25.11.2024

***Corresponding author:** Dr. Md. Nazmul Haque
Associate Professor, Department of Urology, Khulna Medical College, Khulna, Bangladesh

Abstract **Original Research Article**

Background: Nocturnal enuresis (NE), or bed-wetting, affects children aged ≥5 years after ruling out organic causes. The ICCS defines NE as intermittent urinary incontinence during sleep, categorized into monosymptomatic (MNE) and non-monosymptomatic (NMNE) forms. NE is also classified by onset: primary (no dry period) and secondary (bed-wetting after a dry period). Contributing factors include sleep disorders, stress, hereditary predisposition, and delayed bladder development. Management involves behavioral and pharmacological treatments, with desmopressin and anticholinergic drugs being common options. ***Aim of the study:*** This study aims to find out an alternate effective and safe drug for the treatment of primary nocturnal enuresis. ***Methods:*** This study was conducted at the Department of Urology(outdoor), Shahid Sk. Abu Naser Specialized Hospital, Khulna, Bangladesh from January 2020 to December 2021. After excluding 12 patient's pre-randomizations for non-cooperation, 60 patients were split into two groups: Group A received 25mg of imipramine before bedtime, while Group B took 1mg of tolterodine tartrate twice daily evaluated efficacy over 6 months, including a 2-week behavioral modification baseline and follow-ups at 3 and 6 months. Data were analyzed using SPSS 26, employing various statistical tests with significance set at $p < 0.05$. ***Result:*** The study involved 60 children (mean age 10.0±3.1 years, 55% male), assessing bed-wetting patterns and treatment outcomes. The majority (80%) had unsatisfactory behavioral modifications, with 35% having a family history of enuresis. Both groups (A and B) showed no significant difference in bed-wetting episodes at baseline or after 3 months of treatment. Complications were more common in Group A, including dry mouth, nausea, and insomnia. Imipramine led to a higher proportion of patients with fewer than 50 dry nights after drug withdrawal, while Tolterodine showed better results at month 3 but a higher decrease in dry nights by month 6. ***Conclusion:*** The study concluded that neither imipramine nor tolterodine effectively treated primary nocturnal enuresis. While tolterodine showed slightly better efficacy, the difference was not statistically significant. Imipramine was effective but caused more adverse effects, whereas tolterodine had fewer side effects despite its limited efficacy.

Keywords: Imipramine, Tolterodine and Nocturnal Enuresis.

INTRODUCTION

Nocturnal enuresis (NE), commonly referred to as bed-wetting in children aged ≥5 years, is diagnosed after ruling out any organic causes [1,2]. The International Children's Continence Society (ICCS) defines NE as intermittent urinary incontinence during sleep, which is synonymous with nocturnal incontinence. This term is applied regardless of the presence of other lower urinary tract symptoms [3]. NE is further categorized into monosymptomatic nocturnal enuresis (MNE), where no other lower urinary tract symptoms are present, and non-monosymptomatic nocturnal enuresis (NMNE), which is associated with symptoms such as urgency or daytime incontinence [4]. Enuresis can also be classified based on its onset: primary enuresis, where the child has never achieved a dry period for six months, and secondary enuresis, where the child experiences bed-wetting after a dry period of at least six months [5,6]. Among children with enuresis, 85% exhibit the primary form, while secondary enuresis is less common [5]. The prevalence of NE varies with age. Globally, around 10-15% of five-year-old children are affected by NE, with the rate decreasing to approximately 1% by the age of 15

years [7]. In children aged eight years, the prevalence is estimated at 4%. Among affected children, 65% are male, and a familial history is noted in 50% of cases [8]. Approximately 61% of parents report NE as their primary concern, leading to punitive measures in some cases [9]. The etiology of NE is multifactorial and remains incompletely understood. Contributing factors include sleep disorders, emotional stress, a hereditary predisposition, and delayed bladder development. Organic causes, such as urinary tract infections or structural anomalies, may also play a role, but in most cases of primary enuresis, a developmental delay in bladder function is implicated [10]. NE is considered benign, often resolving spontaneously with age, with an annual spontaneous recovery rate of 15% [5]. However, its psychological, emotional, and social implications necessitate effective management strategies [11]. Treatment modalities for NE include both behavioral and pharmacological approaches. Behavioral therapies, such as enuresis alarms, aim to condition the child to awaken in response to bladder fullness [12]. Pharmacological treatments include desmopressin, imipramine, and anticholinergic agents such as oxybutynin and tolterodine [13]. Desmopressin, widely used as a first-line treatment, reduces nocturnal polyuria by mimicking the action of vasopressin. However, its high relapse rate of 60-80% remains a challenge [14]. Anticholinergic drugs target detrusor overactivity, addressing bladder capacity limitations and uninhibited contractions that contribute to NE. Oxybutynin and tolterodine are notable examples, with tolterodine offering similar efficacy to oxybutynin but with fewer side effects [15]. Imipramine, a tricyclic antidepressant, has been shown to be effective in several studies but is now used cautiously due to its potential cardiotoxic effects [16]. Thus, this study aims to find out an alternate effective and safe drug for the treatment of primary nocturnal enuresis.

METHODOLOGY & MATERIALS

A total of 100 cases were selected randomly according to selection criteria from the patients attending at the Department of Urology(outdoor), Shahid Sk. Abu Naser Specialized Hospital, Khulna, Bangladesh from January 2020 to December 2021 with a history suggestive of primary nocturnal enuresis. Among them, 12 patients were withdrawn before randomization due to non-cooperation. After duly taking written informed consent, rest 60 patients were randomly divided into two groups (Group A and Group B).

Group-A (N=30): Group-A was given a single dose of imipramine 25mg half an hour before bedtime

Group-B (N=30): Group-B was given tolterodine tartrate tablet 1mg twice daily.

Inclusion criteria:

- Both male and female children and adolescents of 7 or more years of age had a diagnosis of primary nocturnal enuresis.
- Both parents and patients were cooperative.
- Patients with a supportive family environment.

Exclusion criteria:

- Secondary nocturnal enuresis (SNE).
- Diurnal enuresis - daytime incontinence.
- Patients <7 years old.
- Non-cooperative parents and children.
- Patients with psychological problems.
- Organic lesion present for enuresis.
- Abnormality in ultrasound of KUB.
- Large post-void residual urine.
- History of febrile UTI.
- Cardiovascular, hepatic, renal, gastrointestinal and haematologic disorders.
- Diabetes insipidus.
- Any condition that was a contraindication to tolterodine or imipramine.

During the study period, in Group A, ten patients showed poor compliance, and six did not attend at follow-up schedule. Similarly, in Group B, 8 patients showed poor compliance, and another four did not attend at follow-up. So, they were excluded, leaving 30 patients in each group total of sixty, for the final study. Written informed consent was taken from all parents. The same protocol evaluated all children. A detailed data sheet was completed, and this included a particular patient history. Results of physical examinations and relevant investigations. At history, information regarding the patient's age, sex, address, name of parents, telephone number etc, severity of enuresis, history regarding voiding pattern, and previous therapy was asked. The physical examination included general, abdominal, genital, urologic and neurologic assessments to look for evidence of distended bladder, spinal lesions, epispadias etc. The laboratory investigations included urinalysis, urine culture and sensitivity, and ultrasonography of the KUB region to exclude obstructive uropathy. Routine radiological and urodynamic investigations are not done.

Data Collection:

The clinical history, physical findings, relevant investigations and treatment results were recorded in a preformed data sheet. Parents were explained well about the possible adverse effects of drugs. Initially, patients were observed for two weeks with behavioral modifications such as time voiding, evening fluid restriction, bladder control exercise etc, to determine their enuretic frequency (bed-wetting nights/week), which was regarded as a baseline study. Then the drugs started. Efficacy was evaluated in each group after serial follow-up at 3 months and six months. After 3 months, the drug in both groups stopped, and their enuretic frequency was observed to see the relapse rate. In the first

follow-up, a number of bed wetting/week, and adverse effects of the drug were noted, and in 2nd follow-up, a number of bed wetting/week was noted.

Data Analysis:

Data were analyzed using SPSS (Statistical Package for Social Sciences) version 26. Data presented on a categorical scale were expressed as frequency and corresponding percentages, and those presented on a quantitative scale were expressed as mean ± SD. Categorical data were compared between groups using Chi-square (x^2) or Fisher's Exact Probability Test. In contrast, quantitative data were compared with the help of Student's t-test, Paired t-test and Repeated Measure ANOVA. For each analytical test, the level of significance was set at 0.05, and $p < 0.05$ was considered significant.

RESULT

A total of 60 children participated in the study, with an age range from less than 8 years to 11 years or older, and a mean age of 10.0 ± 3.1 years. The majority of children were male (55%), and 80% had unsatisfactory behavioral modifications. Family history of enuresis was reported in 35% of the children. The frequency of bed-wetting was highest in children with 4-5 episodes per week (55%), followed by 2-3 episodes per week (28.33%) (Table 1). The children were divided into two groups (Group A and Group B), each containing 30 participants. At baseline, both groups had similar bed-wetting episodes, 4.20±1.24 nights per week in group A and 4.37±1.25 nights per week in group B, with no statistically significant difference (p=0.606). At month 3, bed-wetting episodes decreased in both groups, but this change was also not statistically significant. Three months after drug discontinuation, no significant differences were observed between the two groups (Table 2). Complications were compared between the two groups, revealing some notable differences. Group A reported a higher incidence of dry mouth (23.3%), nausea (16.7%), palpitation and constipation both (16.7%) compared to Group B. Additionally, insomnia (6.7%) and nervousness (13.3%) were more common in Group A. However, headaches (23.3%) and fever (3.3%) were observed exclusively in Group B. Statistically significant differences were found for nausea, constipation, and headaches (Table 3). Regarding drug effects on bed-wetting episodes, the Imipramine and Tolterodine groups showed different outcomes. Imipramine led to a higher proportion of patients with 50-90 dry nights per week at month 3, while Tolterodine had a higher percentage of patients reporting more than 90 dry nights per week (Figure 1). After drug withdrawal, the Imipramine group showed a higher proportion of patients (60%) with fewer than 50 dry nights per week compared to the Tolterodine group (Figure 2). At month 3, the percentage of dry nights per week was significantly higher in the Imipramine group (68.42±18.28%) compared to the Tolterodine group (68.70±20.33%), with both groups showing a decrease at month 6. Imipramine's percentage decreased to 55.95±20.24%, while Tolterodine's percentage decreased to 63.38±21.68%, with both changes being statistically significant (Table 4).

Table 1: Demographical characteristics of the study children (N=60)

Variables	Frequency (n)	Percentage (%)
Age (years)		
<8	16	26.67
8-9	14	23.33
9-10	7	11.67
10-11	9	15.00
≥11	14	23.33
Mean ± SD	10.0 ± 3.1	
Sex		
Male	33	55.00
Female	27	45.00
Behavioral modification		
Improved	12	20.00
Unsatisfactory	48	80.00
Family history of enuresis		
Present	21	35.00
Absent	39	65.00
No. of bed wetting (nights/week)		
2-3	17	28.33
4-5	33	55.00
6-7	10	16.67

Table 2: Comparison of bed wetting between groups

No. of bed wetting	Group A (N=30)	Group B (N=30)	p-value
At baseline	4.20±1.24	4.37±1.25	0.606
At the end of month 3	2.17±1.18	2.37±1.38	0.548
3 months after discontinuation of drugs	3.13±1.33	2.63±1.43	0.166

Table 3: Comparison of complications in the both groups

Complications	Group A (N=30)		Group B (N=30)		P-Value
	n	%	n	%	
Dry mouth	7	23.3	3	10.0	0.166
Anxiety	4	13.3	3	10.0	0.5
Insomnia	2	6.7	00	00	0.246
Nausea	5	16.7	00	00	0.026
Tiredness	4	13.3	00	00	0.056
Nervousness	4	13.3	00	00	0.056
Palpitation	5	16.7	2	6.7	0.212
Constipation	5	16.7	00	0.00	0.026
Hesitancy	00	00	3	10.0	0.119
Headache	00	00	7	23.3	0.005
Fever	00	00	1	3.3	0.5
Lethargy	1	3.3	00	0.00	0.5

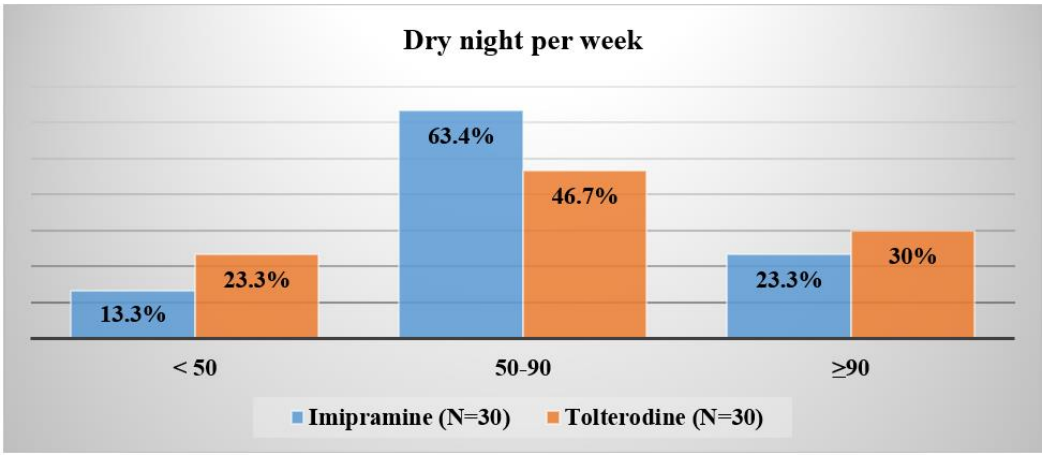

Figure 1: Comparison of outcome between groups at month 3

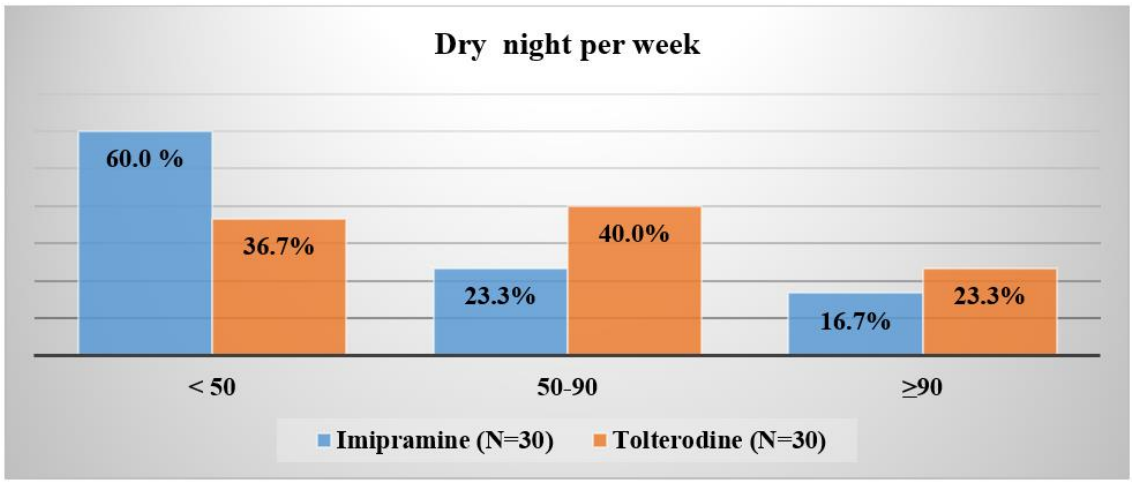

Figure 2: Comparison of outcome between groups after withdrawal of drugs

Table 4: Changes in outcome after withdrawal of drugs

Drug used	% of Dry nights/week		p-value
	At month 3 (n = 30)	At month 6 (n = 30)	
Imipramine	68.42 ± 18.28	55.95±20.24	< 0.001
Tolterodine	68.70±20.33	63.38 ± 21.68	0.005

DISCUSSION

Imipramine has gained widespread acceptance for the treatment of primary nocturnal enuresis. Tolterodine tartrate, a newer anti-cholinergic agent, has proven effective and safe drug treatment for children with voiding dysfunction. The primary objective of the drug treatment of primary nocturnal enuresis is to control bed-wetting by reducing the sufferings of the parents and children. In this study, the number of wetting nights per week, adverse effects of the drugs and relapse rate were used as variables to assess the effectiveness and safety of the drugs. In this study, Impramine, 25mg tablet half an hour before bedtime and tolterodine 1mg tablet twice daily were used in 27-year patients in two separate groups for 3 months. Then, the efficacy and adverse effects are noted after 3 months from a voiding diary, which the parents or patients were asked to maintain. Then, all patients were told to stop the drug. At the end of the next 3 months, after discontinuation of the drugs again, the enuretic frequency was noted from the same voiding diary. In this study, all cases were randomly selected from the outpatient department of urology, DMCH, with ages ranging from 7-16 years, who had been suffering from primary nocturnal enuresis. The age range in a separate study done in 2017 was 5-14 years, and had a diagnosis of voiding dysfunction [17]. Initially, all the patients were observed for two weeks without any drug but with behavioral modifications such as time voiding. fluid restriction in the evening and bladder control exercise and their baseline enuretic frequency observed in terms of bed wetting night per week. By behavioral modification, the majority (80%) of the subjects did not show satisfactory results following 2 weeks, while 20% showed improvement to some extent. In another study, it was found that 6-month observation along with fluid restriction and time voiding, only 16% became continent [18]. Among 60 patients, 55% were male, 45% were female, and the ratio was 11:9. In 35% of patients, there were positive family histories, and in another 65%, it was none. Before starting drug therapy, 55% of patients had 4-5 bed-wetting nights/week, 28.3% had 2-3 bed-wetting nights/week, and 16.7% had 6-7 bed-wetting nights/week. In the Imipramine group, before starting the drug, the mean enuretic frequency was 4.20±1.24 SD, and in the tolterodine group, it was 4.37±1.25 SD. The difference was not significant. After 3 months of drug treatment, these mean enuretic frequencies dropped to 2.17±18 SD in the Imipramine group and 2.37±1.38 SD in the tolterodine group (bed wetting night/week). This improvement is not statistically significant. After 3 months of discontinuation of the drugs, again, these mean values rise to 3.13±1.33 SD in imipramine and 2.63±1.43 SD in the tolterodine group. This finding is almost similar to another study, which showed that imipramine causes significant Improvement of nocturnal enuresis, but withdrawal causes relapse in a significant number of patients [18]. In another study, 12-week treatment with tolterodine significantly reduces the mean urgency rating, urinary frequency and total number of voids in 24-hour continent patients with overactive bladder and nocturia [19]. In this study, standard definitions determined by the International Children's Continence Society were adopted to designate final treatment outcomes on medication as cured- >90% reduction in wetting episodes, improved - >50% reduction or failed - <50% reduction [20]. At the end of 3 months of drug treatment, it was found that in imipramine group cured in 23.3%, improved in 63.4% and failed in 13.3%. But after the next 3 months of discontinuation of the imipramine, these values became 16.7%, 23.3% and 60%, respectively. Which was nearly their pretreatment status. This result is consistent with another study where the cure rate was 36% at 6 months with imipramine on medication, and it was only 16% at 12 months off medication [21]. This result was also supported by several other studies where they found imipramine cured in patients with primary nocturnal enuresis during the treatment period, and after discontinuation of therapy, it caused relapse in significant cases [22-24]. On the other hand, in the tolterodine group 3 months after therapy, 30% improved by 46.7% and failed 23.3%. At the end of the next 3 months after discontinuation of the tolterodine, these values were 23.3%, 40% and 36.7%, respectively. This study is consistent with another study in primary nocturnal enuresis done with anticholinergic-oxybutynin and showed a 30% therapeutic benefit [25]. In another study, tolterodine in children with voiding dysfunction cases. 40% and failed in another 27% Cases [20]. In another study, 3-month treatment by tolterodine in children with voiding dysfunction significantly improved the dysfunctional voiding symptoms score, and they recommended it as a first-line treatment before invasive evaluation. In the imipramine group, nausea and constipation were significantly higher. Headache was most common in the tolterodine group. Tiredness and nervousness were absent in the tolterodine group compared to 13.3% in the imipramine group. No other adverse effects were found to any significant difference. This finding is consistent with another study with tolterodine, where the dry mouth was 31%, and the headache was 4% [26]. In another study of tolterodine in children with overactive bladder, headache was the most common adverse effect, and one patient showed palpitation [27]. In another study in children with

primary nocturnal enuresis by imipramine, adverse effects were anxiety, dry mouth, insomnia, and nausea, which is consistent with this study [25].

Limitations of the study:

This study has several limitations. It was a short-term, single-center study with a small sample size, and it lacked a placebo control group. Additionally, the outcome values were baseline-dependent, which may affect the accuracy of the final results. The study also did not include separate trials for Imipramine and Tolterodine, meaning the individual efficacy of these agents was not assessed independently. These factors may limit the generalizability and reliability of the findings.

CONCLUSION AND RECOMMENDATIONS

This study inferred that both imipramine and tolterodine were not so effective in treating primary nocturnal enuresis. Though the efficacy of tolterodine is more than that of imipramine, this is not statistically significant. Imipramine is also effective but has more adverse effects than tolterodine. Though tolterodine has no high efficacy, it has fewer adverse effects.

Funding: *No funding sources*

Conflict of interest: *None declared*

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