The Egyptian Journal of Hospital Medicine (January 2023) Vol. 90 (2), Page 2259-2264

Safety and Efficacy of Mirabegron in Treatment of Nocturnal Enuresis in Children

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ABSTRACT

Background: Nocturnal enuresis affects 5% to 10% of in the United States; an estimated to be 5 to 7 million kids. It affects all 7-year-olds, and it is more prevalent in boys. About 15% of cases are spontaneously cured each year, although 2% to 3% of children continue to experience symptoms as adults.

Objective: The aim of the current study was to evaluate the safety and effectiveness of Mirabegron for treatment of NE.

Patients and methods: A one-arm clinical trial was carried out at the Pediatric Unit, Urology Department, Zagazig University Hospital. A total 36 patients with monosymptomatic nocturnal enuresis (MNE) were enrolled in the study. All patients received mirabegron 25mg for 3 months at bedtime, together with some strategies for parents to help children who are wetting the bed.

Results: The age of participants ranged from 7 to 15 with a mean of 9.8 (SD 2.5) years. Sex distribution was 20 (55.2%) males and 16 (44.4%) females. The duration of the study ranged from 6-12 months. There was a significant decrease in the mean bed wet after six months from treatment compared with the mean before treatment ($P<0.05$). After six months of treatment with Mirabegron, 10 (31.3%) parents reported complete response, 13 (40.6%) had partial response, and 9 (28.1%) had no response to treatment. Adverse effects were reported in 5 (13.9%) patients; constipation in 3 (8.3%) patients and dry mouth in 2 (5.5%) patients.

Conclusion: Mirabegron, a brand-new, first-in-class medication, surfaced as a secure and reliable substitute for children with NE. More research including more patients and a longer period of follow-up is needed.

Keywords: Nocturnal enuresis, Bedwetting, Mirabegron**,** Children, Cohort study, Zagazig University**.**

INTRODUCTION

Younger children may experience nocturnal enuresis (NE), sometimes known as "bedwetting," which is a type of nighttime urine incontinence.

In order to be more precise, primary nocturnal enuresis (PNE) is the involuntary flow of urine at night in children and adolescents 5 years of age and older who do not have a congenital or acquired defect of the central nervous system or urinary tract and who have not gone more than 6 months without passing urine. Enuresis is categorized as monosymptomatic enuresis, which means it has neither non-monosymptomatic enuresis, which indicates the presence of other lower urinary tract symptoms, nor any other lower urinary tract symptoms, mostly daytime symptoms **(1).**

An altered antidiuretic hormone profile with nocturnal polyuria, arousal failure, delayed bladder maturation, and nocturnal detrusor overactivity are examples of multifactorial pathophysiological factors, have been implicated in the pathophysiology of NE. Common co-morbidities linked to NE include constipation, diabetes mellitus, developmental attention or learning difficulties, a history of recurrent urinary tract infection (UTI) in males, and pinworm infestation.

NE has been linked to risk factors such as age, male gender, daytime incontinence, encopresis, social anxiety, delayed walking age, positive parental history of enuresis, and sibling history of enuresis **(2).**

The urothelial lining and bladder detrusor muscle both contain 3 different types of adrenoceptors (types 1, 2, and 3), with type 3 being the most prevalent. Detrusor smooth muscle relaxation results from stimulation of the 3 receptors. The therapy of overactive bladder (OAB) has been extensively used and researched with mirabegron, an agonist of the 3 receptor. It has been established that mirabegron is safe, efficient, and well-tolerated. In almost all trials, it produced outcomes that were comparable to placebo in terms of the prevalence of dry mouth **(3)**.

The bladder's detrusor smooth muscle relaxes as a result of the beta-3 adrenergic receptor agonist mirabegron, which also improves bladder capacity. It is recommended for people with overactive bladder who experience urge incontinence, urgency, and frequent urination **(4)**. For the treatment of OAB and neurogenic detrusor overactivity (NDO) in adults, mirabegron has received approval. However, using them on kids (≥3 years) has just just been authorised for NDO patients **(5).**

Mirabegron has a high efficacy and tolerability profile, which may support its incorporation as a primary management technique in a formula programme for children who have just been diagnosed with OAB. It still requires longer-term testing to evaluate its enduring safety, effectiveness, discontinuation rate, and tachyphylaxis **(6).**

The aim of the current study was to evaluate the safety and effectiveness of Mirabegron for treatment of NE.

Received: 20/09/2022
Accepted: 23/11/2022

PATIENTS AND METHODS

A one-arm clinical trial was carried out at the Pediatric Unit, Urology Department, Zagazig University Hospital. A total 36 patients with monosymptomatic nocturnal enuresis (MNE) were enrolled in the study.

Inclusion criteria:

Children (male or female) from 6 to 15 years old, who have newly diagnosis with monosymptomatic NE.

Exclusion criteria:

Patients were excluded from the study if there were monosymptomatic NE. Cardiac, nephrogenic, metabolic endocrinal or neurourologic disease.

Active Urinary tract infection. Previous treatment with desmopressin, Tricyclic antidepressants or anticholinergic medications.

Sex, age, fluid intake, and urological symptoms like frequency, urgency, nocturia, urge incontinence, and holding techniques were all factored into the full history. Every patient underwent a physical examination that included a general assessment of their body composition, a back examination to rule out spina bifida, an abdominal examination to rule out suprapubic fullness, and examinations of their genitalia and perineum to rule out meatal stenosis or any other congenital anomalies.

Laboratory investigations:

1) Complete urine analysis, urine culture, and sensitivity tests were performed in the laboratory to rule out active urinary tract infections.
2) Stool examination.

Pelvic abdominal ultrasonography (U/S) was carried out to assess the kidney's size, the thickness of the parenchyma around it, the thickness of the bladder wall, the degree of echogenicity, and to rule out renal, ureteric, or bladder stones, among other abnormalities.

All patients received mirabegron 25mg for 3 months at bed time, together with some strategies for parents to help children who are wetting the bed.

Follow up:

After initial assessment of all patients, we followed up them every 2 weeks for 3 months by documenting the number of dry and wet nights. The families were actively questioned about side effects at follow up visits.

Ethical approval:

This study was ethically approved by the Institutional Review Board of the Faculty of Medicine, Zagazig University (IRB #:9698-14-8-2022). Written informed consent was obtained from all participants. This study was executed according to the code of ethics of the World Medical Association (Declaration of Helsinki) for studies on humans.

Statistical Analysis

The collected data were introduced and statistically analyzed by utilizing the Statistical Package for Social Sciences (IBM SPSS Statistics for Windows 23.0. Armonk, NY: IBM Corp.). Qualitative data were defined as numbers and percentages. Chi-Square test and Fisher's exact were used for comparison between categorical variables as appropriate.

Quantitative data were tested for normality by Kolmogorov-Smirnov test. Normal distribution of variables was described as mean and standard deviation (SD). The Wilcoxon Signed Ranks Test was used to contrast two non-normally distributed pairs of data. P value ≤ 0.05 was considered to be statistically significant.

RESULTS

Table 1 summarizes the demographic characters, Body mass index of studied patients

Table (1): Demographic characters, Body mass index of studied patients (n. 36).

Variables		
Age (years) Mean ± SD Range	9.8 ± 2.5 7 - 15	
	n.	**%**
Sex Males	20	55.2
Females	16	44.4
BMI		
Mean ± SD Range	15.04 ± 1.3 13 - 18.7	

BMI: Body mass index.

Table 2 indicated that there was decrease mean of bed wet after two, four, six, eight, ten and twelve week from treatment with mean before treatment ($P<0.05$).

Table (2): Efficacy of Mirabegron after two, four, six, eight, ten and twelve weeks in treatment of nocturnal enuresis in children.

Variables			P-value
Bed wet after two week Mean ± SD Range	7.4 ± 2.9 3 - 12		<0.001
Response to Mirabegron after two week	**n.**	**%**	---
Partial response	19	52.8	
No response	17	47.2	
Bed wet after four week Mean ± SD Range	6.7 ± 2.5 3 - 11		<0.001
Response to Mirabegron after four week	**n.**	**%**	---
Partial response	24	68.6	
No response	11	31.4	
Bed wet after six week Mean ± SD Range	5.4 ± 2.6 2 - 10		<0.001
Response to Mirabegron after six week	**N.**	**%**	---
partial response	25	71.4	
No response	10	28.6	
Bed wet after eight week Mean ± SD Range	4.5 ± 3 0.0 - 9		<0.001
Response to Mirabegron after eight week	**N.**	**%**	---
Complete response	5	15.2	
Partial response	20	60.6	
No response	8	24.2	
Bed wet after ten weeks Mean ± SD Range	3.5 ± 2.9 0 - 8		<0.001
Response to Mirabegron after ten weeks	**n.**	**%**	---
Complete response	12	36.4	
Partial response	14	42.4	
No response	7	21.2	
Bed wet after twelve weeks Mean ± SD Range	3.1 ± 2.8 0 - 7		<0.001
Response to Mirabegron after twelve weeks	**N.**	**%**	---
Complete response	14	43.8	
Partial response	13	40.6	
No response	5	15.6	

Wilcoxon Signed Ranks Test, P: compare mean of bed wet after 2, 4, 6, 8, 10 and 12 weeks from treatment with mean before treatment(14 ± 0).

Table 3 indicated that there was decrease mean of bed wet after first, second, and third months from treatment with mean before treatment (P<0.05)**.**

Table (3): Nocturnal enuresis in children after first , second, and third month form stop Mirabegron treatment.

Variable			P-value
Bed wet after four months Mean ± SD Range	8.3 ± 7.6 0 - 20		<0.001
Response to Mirabegron after four months	**N.**	**%**	---
Complete response	12	37.5	
Partial response	14	43.8	
No response	6	18.8	
Bed wet after five months Mean ± SD Range	8.6 ± 8.2 0 - 22		<0.001
Response to Mirabegron after five months	**N.**	**%**	---
Complete response	11	34.4	
Partial response	13	40.6	
No response	7	21.9	
Bed wet after six months Mean ± SD Range	8.1 ± 7.5 0 – 21	<0.001	---
Response to Mirabegron after six months	**N.**	**%**	---
Complete response	10	31.3	
Partial response	13	40.6	
No response	9	28.1	

Wilcoxon Signed Ranks Test, P: Compare mean of bed wet after four, five and six months from treatment with mean before treatment (30 ± 0).

Adverse effects manifested in 5 (13.9%) patients, adverse effects included constipation in 3 (8.3%) patients, dry mouth in 2 (5.5%) patients and hallucination in 0 patients (**Table 4**).

Table (4): Adverse effects of mirabegron treatment.

Variable	N.	%
Adverse effects		
Yes	7	19.4
No	29	80.5
Types of adverse		
Constipation	3	8.3
Dry mouth	2	5.5
Hallucination	0	0

DISCUSSION

The studied group included 36 patients, their ages ranged from 7- 15 with a mean of 9.8 (SD 2.5) years, sex distribution was 20 (55.2%) males and 16(44.4%) females. Body mass index of studied children ranged from 13- 18.7 with a mean of 15.04 (SD 1.3) kg/m^2.

In the study of **Huang *et al.*** [7], the average ages of children with and without NE were 7.21 (SD 1.99) and 8.05 (SD 2.08) years ($t = -6.413$, $P<0.001$). The frequency of NE among children ages 5–12 was 3.99% (262/6568), with a higher prevalence among boys (4.96% vs 2.94%, $\chi2 = 17.356$, $P<0.001$). The prevalence of NE in 5-year-old children was higher than the prevalence at older ages (9.09% for boys and 6.03% for girls). Boys' and girls' NE prevalence rates both showed declining patterns as people aged.

Also, in the study of **Bascom *et al.*** [8], 68 kids agreed to take part in the study, and 61 of them finished the protocol and were used in the analysis. Age on average for the kids in this sample was 9.9 (SD 3.8) years (range 5–17 years) and 13 (21%). Patients have NE in their past. Children with enuresis were younger than those without, with age being the only descriptive variable that varied between groups.

The present study showed that as regard the effectiveness of mirabegron in treating NEin the group under study after 2 weeks; there was decrease mean of bed wet after 2 weeks from treatment with mean before treatment ($P<0.05$). In study children 19 (52.8%) had partial response to Mirabegron after 2 weeks, otherwise 17 (47.2%) were no response to treatment. After 4 weeks, there was decrease mean of bed wet after 4 weeks from treatment with mean before treatment ($P<0.05$). In study children, 24 (68.6%) had partial response to Mirabegron after 4 weeks, otherwise 11 (31.4%) were no response to treatment. After 6 weeks, there was decrease mean of bed wet after 6 weeks from treatment with mean before treatment ($P<0.05$). In study children 25 (71.4 %) had partial response to Mirabegron after 6 week, otherwise 10 (28.6%) were no response to treatment.

After 8 weeks, there was decrease mean of bed wet after 8 week from treatment with mean before treatment ($P<0.05$). In study children 5 (15.2%) reported complete response, 20 (60.6%) had partial response, otherwise 8 (24.2%) were no response to treatment. After 10 weeks, there was decrease mean of bed wet after ten week from treatment with mean before treatment ($P<0.05$). In study children 12 (36.4%) reported complete response, 14 (42.4%) had partial response, otherwise 7 (21.2%) were no response to treatment.

After 12 weeks, there was decrease mean of bed wet after 12 weeks from treatment with mean before treatment ($P<0.05$).

In study children 14 (43.8%) reported complete response, 13 (40.6%) had partial response, 5 (15.6%) had no response.

After 4 months; was decrease mean of bed wet after four months from treatment with mean before treatment; difference statistically significant $p<0.05$. In study children 12 (37.5%) reported complete response, 14 (43.8%) had partial response, otherwise 6 (18.8%) were no response to treatment. This indicated that (18.8%) of patients relapse to be no response. After 5 months; there was decrease mean of bed wet after 5 months from treatment with mean before treatment ($P<0.05$). In study children 11 (34.4%) reported complete response, 13 (40.6%) had partial response, otherwise 7 (21.9%) were no response to treatment. This indicated that 21.9% of patients relapse to be no response. After 6 months, there was decrease mean of bed wet after 6 months from treatment with mean before treatment ($P<0.05$).

In study children 10 (31.3%) reported complete response, 13 (40.6%) had partial response, otherwise 9 (28.1%) were no response to treatment.

Also, **Fryer *et al.*** [9] reviewed the medical files of kids who received mirabegron between February 2014 and November 2018, retrospectively. When other approaches, such as bladder retraining and anticholinergics, have failed to relieve OAB symptoms, as a second or third line of defence, mirabegron 25 mg and 50 mg were suggested. The effectiveness of mirabegron, either alone or in combination with other therapies, was the main outcome evaluated after 6 months of treatment. Improvement in symptoms reported by the patient was used to gauge effectiveness. Frequency, urgency, NE, and daytime incontinence were the symptoms that were examined (DI). Review of cardiovascular monitoring, tolerance evaluation, reasons for stopping treatment, and potential adverse effects were all considered secondary outcomes.

At 6 months, 37 (53%) of the 70 kids were still getting medication; 30 were receiving mirabegron monotherapy and 7, anticholinergic combination therapy (Solifenacin n = 4, Decompressing n = 2, both n = 1).

Monitoring of blood pressure and ECGs were all normal in all patients after 6 months. Patients receiving only one treatment, 6 of 17 (35%) had improvement in NE, 11 of 19 (58%) in DI, 12 of 20 (60%) in frequency, and 8 of 21 (38%) in urgency symptoms.

For patients receiving combination therapy, 2 of 6 (33%) had improvement in NE, 2 of 4 in DI (50%), 2 of 4 (50%) in frequency, and 4 of 6 (67%) had improvement in urgency.

Regarding our study showed that 14 (43.8%) children reported complete response to treatment with Mirabegron, our result compare by study of **Seyfhashemi *et al.*** [10] used

oxybutynin as anticholinergic, Imipramine with Desmopressin Primary Nighttime Urinary Incontinence Treatment 92 participants with enuresis were treated with nasal desmopressin, imipramine, and oxybutynin; 30 of the children received nasal desmopressin. In the 6-week trial, 60 kids who received medication responded well, yielding an average response rate of 65.2%. The oxybutynin group had a somewhat greater percentage (71%) of therapeutic response, according to the study.

Our results were supported by study of **Blais *et al.*** [(11)] in a prospective off-label study examine the efficacy and safety of mirabegron as a treatment for urine incontinence in 58 kids with idiopathic OAB who were resistant to and/or intolerant of antimuscarinics. The major end measurement, which was calculated using voiding diaries, postvoid residuals, urine cultures, electrocardiograms, and vital signs, showed superior reported efficacy than when using previous anticholinergic drugs, while enjoyment, security, and toleration are the secondary objectives.

Following the evaluation, median bladder capacity improved from 150 ml to 200 ml ($P<0.001$). Continence improved in 52 of 58, with 13 being completely dry. Median Patient Perception of Bladder Condition (PPBC) improved from 4.0 to 2.0 ($P<0.001$).

Our results showed that adverse effects manifested in 5 (13.9%) patients, adverse effects included constipation in 3 (8.3%) patients, dry mouth in 2 (5.5%) patients and hallucination in 0 patients.

Moreover, **Morin *et al.*** [(12)]**,** 28 (80%) of the patients in a study using mirabegron to treat children with refractory hyperactive bladder did not submit any S/E reports. of 5 (14%) patients described mild S/E (2 transient constipation, 1 abdominal colic, 1 temporary blurred vision, 1 rhinitis); and 1 (3%) experienced moderate S/E (rhinitis). The compliance to medication was excellent in all but one (>80%). Two patients stopped receiving treatment as a result of S/E (rhinitis) and elevated PVR (50 ml).

CONCLUSION

Mirabegron, a brand-new, first-in-class medication, surfaced as a secure and reliable substitute for children with NE. More research including more patients and a longer period of follow-up is needed.

Sources of funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest: There are no conflicts of interest, according to the authors.

REFERENCES

1. **Ring I, Neveus T, Markstrom A *et al.* (2017)**: Bazargani Nocturnal enuresis impaired children's quality of life and friendships. Acta Paediatr., 106(5):806-11.
2. **Haid B, Tekgul S (2017)**: Primary and Secondary Enuresis: Pathophysiology, Diagnosis, and Treatment. European Urology Focus, 3(2-3):198-206.
3. **Lim I, Sellers J, Chess-Williams R (2022):** Current and emerging pharmacological targets for medical expulsive therapy. Basic and Clinical Pharmacology, and Toxicology, 130:16-22.
4. **Calmasini B, de Oliveira M, Alexandre E *et al.* (2017):** Long-term treatment with the beta-3 adrenoceptor agonist, mirabegron ameliorates detrusor overactivity and restores cyclic adenosine monophosphate (cAMP) levels in obese mice. Neurourology and Urodynamics, 36(6):1511-8.
5. **Kim K, De Jesus J, Lee J *et al.* (2022)**: β3-Adrenoceptor agonist for the treatment of bladder dysfunction in children: a systematic review and meta-analysis. The Journal of Urology, 207(3):524-33.
6. **Soliman G, El-Abd S, El-Gamal M *et al.* (2021)**: Mirabegron versus Solifenacin in Children with Overactive Bladder: Prospective Randomized Single-Blind Controlled Trial. Urologia Internationalis, 105(11-12):1011-7.
7. **Huang M, Wei J, Sharma S *et al.* (2020**): Prevalence and risk factors of nocturnal enuresis among children ages 5–12 years in Xi'an, China: a cross-sectional study. BMC Pediatr., 20:305.
8. **Bascom A, McMaster A, Alexander T *et al.* (2019):** Nocturnal enuresis in children is associated with differences in autonomic control. Sleep, 42(3):zsy239.
9. **Fryer S, Nicoara C, Dobson E *et al.* (2020):** Effectiveness and tolerability of mirabegron in children with overactive bladder: a retrospective pilot study. Journal of Pediatric Surgery, 55(2):316-8.
10. **Seyfhashemi M, Ghorbani R, Zolfaghari A (2015):** Desmopressin, Imipramine, and Oxybutynin in the Treatment of Primary Nocturnal Enuresis: A Randomized Clinical Trial. Iran Red Crescent Med J., 17(7):16174.
11. **Blais S, Nadeau G, Moore K *et al.* (2016):** Prospective pilot study of mirabegron in pediatric patients with overactive bladder. European Urology, 70(1):9-13.
12. **Morin F, Blais S, Nadeau G *et al.* (2017):** Dual therapy for refractory overactive bladder in children: a prospective open-label study. The Journal of Urology, 197(4):1158-63.