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Predictors of Success and Relapse after Desmopressin Monotherapy for Monosymptomatic Nocturnal Enuresis

Hosny Mohammed Ahmed El-Masry[1], Ahmed Abdelhamid Shahat[2], Hosny Abdelkareem Ahmed[1], Omnia Nassar Ibrahim Mohamed[1]

[1]Department of Pediatrics and Neonatology Department faculty of Medicine Al-Al-Azhar University (Assiut), Egypt

[2]Department of Urology, Faculty of Medicine, Assiut University, Assiut, Egypt

***Corresponding author:** Omnia Nassar Ibrahim, **Mobile:** (+20) 01010112054, **E-mail:** omnianassar835@gmail.com

ABSTRACT

Background: Enuresis in children can have serious negative effects, and a doctor must be aware of these effects in order to effectively manage the patient. Enuresis can be divided into two types: monosymptomatic nocturnal enuresis (MNE) and non-monosymptomatic nocturnal enuresis (NMNE).

Objective: This study aimed to assess desmopressin's effectiveness in treating PMNE in children.

Patients and methods: This prospective cohort study included children with primary monosymptomatic nocturnal enuresis (PMNE) aged 7 to 14 years who went to The Pediatric Urology Outpatient Clinic. Desmopressin 0.2 mg was given orally once a day, just before bed, for 3 months. According to the International Children's Continence Society's criteria. Outcomes were classified as full response, partial response, and no response. Desmopressin therapy was discontinued after three months of treatment, and patients were checked again after one month to look for signs of relapse.

Results: The study involved a total of 50 children with PMNE. The results revealed that 20% of patients responded fully, 64% partially, and 16% did not respond at all. Desmopressin treatment resulted in a positive response from the patients, with a mean number of episodes per week considerably decreasing from 5.96 ± 1.32 to 1.92 ± 1.140 (p 0.001). After one month of therapy discontinuation, the mean number of episodes per week increased considerably from 1.92 ± 1.140 to 2.66 ± 2.22 (p value 0.041).

Conclusion: Desmopressin is effective in reducing the number of wet nights each week in children with primary MNE. Although it has the advantage of acting more quickly, it has a high rate of relapse. Therefore, additional studies involving more patients should be considered.

Keywords: Desmopressin – Nocturnal enuresis – Pediatrics.

INTRODUCTION

Nocturnal enuresis (NE) is the involuntary passing of urine while asleep that occurs after the age of ordinary control, which is regarded as a developmental age of five to seven years [1]. About 15.4% of Egyptian primary school students have NE [2]. Children and their families experience distress as a result of NE, which is a prevalent issue. It has a negative effect on behavior and social interactions, lowers self-esteem, and can lead to poor emotional health [3].

NE is divided into MNE, which solely manifests as nighttime urination, and NMNE, which manifests as any additional lower urinary tract symptom, such as urgency, urge incontinence, or frequency [4]. PMNE, defined as the occurrence of enuresis without any other symptoms of the lower urinary tract or a history of bladder disease, can be distinguished from secondary enuresis, which develops following a longer than six-month period of persistent dryness [5].

The cause of enuresis is unknown. However, among school-age children in the Egyptian society, excessive caffeine use, constipation, urinary tract infections, and pinworm infestation are possible reversible risk factors for MNE. Several pathophysiological explanations have been hypothesized, including bladder dysfunction, limited functional bladder capacity, aberrant vasopressin levels, nocturnal polyuria, and unusual sleep patterns [6].

Urotherapy is the mainstay of treatment, together with information and psychoeducation about healthy lower urinary tract function, the underlying etiology of MNE, altered bladder functionality in children with NMNE, and guidelines for therapeutic approaches. Randomized trials have demonstrated the effectiveness of alarm therapy and desmopressin use [7].

The posterior pituitary gland secretes antidiuretic hormone (ADH), which decreases the production of urine by enhancing water reabsorption in the collecting tubules and ducts. Desmopressin is a synthetic analogue of ADH [8].

Desmopressin should be given about an hour before bed. After starting treatment, the effects are frequently felt within a few days. Overall, 70% of kids experience a significant reduction in wet nights, with 30% of kids experiencing completely dry nights. However, 60%-70% of kids will relapse after therapy is stopped. If desmopressin is discontinued gradually as opposed to abruptly, the risk of relapse is greatly reduced [3].

The purpose of this study was to assess desmopressin's effectiveness in treating PMNE in school-age children. Prediction of success and relapse following desmopressin monotherapy for MNE was another goal.

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PATIENTS AND METHODS

Design and setting: A prospective cohort study was performed in children enrolled in the outpatient treatment program for PMNE in our Pediatric Urology Center between 2020 and 2022. Children with PMNE ageed 7 to 14 years old were required for study inclusion.

Exclusion criteria: Patients with lower urinary tract discomfort or incontinence during the day, a urinary tract infection within the previous three months, diabetes, history of post-micturition residual urine greater than 1/3 of the predicted bladder capacity, hypertension, genitourinary abnormalities, neurological disease, and psychological disease.

All children were evaluated before inclusion for their medical history, physical condition, psychological or organic illnesses, family history of similar illnesses, and previous treatments. Additionally, neurological examinations were performed to rule out neurological diseases, particularly neural tube defects, urine analyses to exclude the possibility of diabetes insipidus, glucosuria, and pyuria . A simple X-ray of the spine, if necessary. Abdominal ultrasonography to measure the wall thickness index and bladder volume. The thickened bladder wall was defined as (BVWI%) less than 70.

After enrollment, Desmopressin melt form 0.2 mg 1 tablet was prescribed to be taken sublingually one hour before to bedtime. After receiving treatment for three months, children were monitored. Patients who often skipped more than one dose per week were seen as noncompliant with their medication. Full response was defined as a drop in the NE episode of > 90%, partial response as a decrease in the NE episode of 50–90%, and no response as a decrease in the NE episode of 50%. Desmopressin treatment was discontinued after three months, and patients were followed up with one month later to check for relapses.

Ethical approval: This study was carried out after being approved by The Local Ethics Committee of Faculty of Medicine, Al-Azhar University, Assiut with clinical trials identifier number: NCT06285006. Consent was taken from each patient before including them in the study. Aim of the study and possible risks were explained to the patients. Privacy of the collected data were assured. The Helsinki Declaration was followed throughout the study's conduct.

Statistical analysis

We used SPSS version 21.0 for statistical analysis. The Mann-Whitney U test was used for quantitative variables and Fisher's exact test for categorical variables in the statistical analysis of the parameters linked to relapse following treatment discontinuation and the response to desmopressin. The frequencies and relative percentages used to depict the qualitative data. One can use the X^2-test to determine the difference between two or more qualitative variable groups. The formula for quantitative data was mean ± SD. Statistics were deemed significant if the $P \leq 0.05$.

RESULTS

Fifty children with PMNE were involved in the research; whose ages ranged from 7 to 14 years, with a mean of 10.02 ± 2.14 years (Table 1).

Table (1): Descriptive data of studied patients with monosymptomatic nocturnal enuresis

Age (years)	10.02 ± 2.14
Sex	
Male	37(74)%
Female	13(26)%
Thickened bladder wall	
Yes	12(24)%
No	38(76) %
Spina bifida	
Yes	5(10)%
No	45(90)%
Residency	
Urban	12(24)%
Rural	38(76) %
Age of toilet control	2.84 ± 0.63
Urine specific gravity	1019 ± 6.78
Initial number of enuresis episodes / week	5.96 ± 1.32
Compliance	
Compliant	35 (70)%
Non-compliant	15 (30)%

The majority of complaint patients exhibited full and partial responses with significant (p-value 0.015) responses, according to the descriptive data that was investigated. Nonetheless, no statistically significant correlation was observed between the responsiveness to desmopressin medication and other data of patients with PMNE (Table 2).

Table (2): Relationship between desmopressin therapy response and initial data of individuals with monosymptomatic nocturnal enuresis

Variable	Improvement after treatment		P-value
	No response	Full or partial response	
Age	11(8-13)	9 (7-14)	0.382
Sex Male Female	 5(13.5) 3(23)	 32(86.5) 10(77)	0.413
Residence Urban Rural	 2 (25.0) 6 (75.0)	 10 (23.8) 32 (76.2)	1.000
Age of toilet control	3 (2-4)	3 (2-4)	0.765
Urine specific gravity	1017.50 (1010-1030)	1017.50 (1010-1030)	0.887
Initial number of enuresis episodes per week	4.5 (4-7)	7 (3-7)	0.137
Thickened bladder wall Yes No	 3(25) 5(13)	 9(75) 33(87)	0.379
Spina bifida Yes No	 1(20) 7(15)	 4(80) 38(85)	1.000
Compliance **Yes** **No**	 2 (25.0) 6 (75.0)	 32 (76.2) 10 (23.8)	0.015

Out of the 42 patients that had full or partial response to desmopressin, 15 (35.7%) had relapse within one month after stoppage of treatment. Mean no. of episode per week after one month from stoppage of treatment significantly increased from 1.92 ± 1.140 to 2.66 ± 2.22 with (p value 0.041). However, there was a statistically significant difference between mean no. of episodes per week after stoppage of treatment and the initial mean no. of episodes per week before treatment (p value <0.001). There was no significant relation between studied patients baseline characteristics and relapse as shown in (Table 3).

Table (3): Relation between initial data of patients with primary monosymptomatic nocturnal enuresis and relapse rate

Variable*	Relapse		P-value
	No	Yes	
Age	9 (7-14)	11 (7-13)	0.221
Age of toilet control	3 (2-4)	3 (2-4)	0.388
Urine specific gravity	1020 (1010 -1030)	1015 (1010-1030)	0.378
Initial number of enuresis episodes per week	7 (4-7)	7 (3-7)	0.255
Sex Male Female	 21(66) 6(60)	 11(34) 4(40)	1.000
Residence Urban Rural	 7 (25.9) 20 (74.1)	 3 (20.0) 12 (80.0)	0.957
Thickened bladder wall Yes No	 5 (56) 22 (67)	 4 (44) 11 (33)	0.698
Spina bifida Yes No	 3 (75) 24 (63)	 1 (25) 14 (37)	1.000
Compliance Yes No	 11 (73.3) 4 (26.7)	 21 (77.8) 6 (22.2)	1.000

DISCUSSION

Nocturnal enuresis (NE) is defined as a complete or almost complete micturition in bed during sleep more than twice a week for at least three consecutive months in a healthy child over the age of five. 10-15% of children by the age of five have NE, which is the second most frequent chronic pediatric condition following allergy .The condition often resolves on its own, and the proportion of affected children declines yearly until it reaches 1% in maturity.

Bedwetting negatively affects children's social, academic, and emotional development at a critical juncture in their psychosocial growth [9]. Over 80% of NE in children over the age of five is monosymptomatic nocturnal enuresis (MNE), which is characterized by intermittent, uncontrollably occurring bedwetting during sleep that is not accompanied by any symptoms or signs of lower urinary tract dysfunction. Enuresis has been categorized as MNE and NMNE. Given that nocturnal polyuria (NP) is one of the primary features of MNE, the recommended course of treatment is desmopressin [10]. Numerous research studies have investigated how effectively desmopressin works as a treatment for PMNE [11]**.** The reported response rates show significant variability across studies, which could be explained by patient selection, poor adherence rates, delivery techniques, dosages, and formulations. According to research, about 30% of children with enuresis fully respond to desmopressin, and 40% only partially respond, which agrees with our study's conclusions [12].

In this study we found that among 50 patients with PMNE, with age ranged from 7-14 years, 24% had thickened bladder wall and 10% had spina bifida. From a previous study, the most common underlying cause of MNE in children aged 6 to 18 years was spina bifida (44%) and was followed by obstructive sleep apnea, anorectal malformation, and behavioral issues (12%, 8%, and 8%, respectively) [13].

In this thesis, we showed the effectiveness of desmopressin treatment. Of the patients, 8 (16%) showed no response, 32 (64%) showed partial response, and 10 (20%) showed complete response. This incredibly strong response is consistent with another study that indicated 52% of patients receiving desmopressin responded to treatment, of which 42% were complete responders and 10% were partial responders [14]. Another study showed that the response to desmopressin is unrelated to birth order, the first number of wet nights, body mass index, IQ test, and family. However, they discovered that males responded to desmopressin more frequently than females. Additionally, it was discovered that elderly patients reacted better. This is likely because they were more mature and accounted for the patient's natural recovery [15]. According to the results of the current study, the average number of episodes per week increased significantly (p value 0.041) one month after medication was stopped. However, a statistically significant distinction was observed between the mean weekly number of episodes following treatment cessation and the mean weekly number of episodes before therapy (p value <0.001).

According to previous research, patients who received a break after six months and those who received treatment for a year had significantly different rates of relapse, leading the researchers to assume that treatment should be continued for at least a year to lower recurrence rates [16]. In our study, there were no side effects that led to the cessation of desmopressin medication. We think that the fact that none of the patients reported water intoxication was due to their restriction of drinks, especially in the evening (such as milk, water, and soft drinks).

LIMITATION OF THE STUDY

This study was limited in several ways. The first factor that might have impacted the study's findings was the small sample size of participants. Second, we only looked at the immediate effects of desmopressin therapy over three months, with a one-month follow-up. After this brief period, treatment and follow-up were discontinued, which may have resulted in inefficient treatment or undetected relapses. Thirdly, since there was no control group who did not receive treatment, we can't completely rule out the chance of a spontaneous resolution. Since we were aware of the impact of NE on our patients' psychological well-being, we believed it would be unethical to miss or postpone patient treatment, hence we did not include a non-treatment control group in the trial.

CONCLUSION

Desmopressin is effective and safe in treating PMNE in children. Although it has the advantage of acting more quickly, it has a high rate of relapse. Therefore, additional studies involving more patients should be considered.

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