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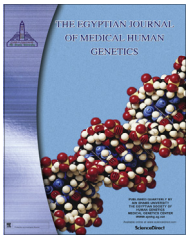

ORIGINAL ARTICLE

Assessment of the efficacy of desmopressin in treatment of Primary Monosymptomatic Nocturnal Enuresis in Egyptian children

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KEYWORDS

Nocturnal enuresis;
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Abstract *Background:* Enuresis is defined as a normal void occurring at an inappropriate social time or place. The treatment approach for enuresis is controversial due to a lack of consensus as to the exact causes of nocturnal enuresis.

Aim: Aim was to assess the efficacy of desmopressin therapy in the treatment of Primary Monosymptomatic Nocturnal Enuresis (PMNE) in Egyptian children.

Method: The study assessed 40 children aged 6–15 years suffering from PMNE. They were divided into 2 groups; Group 1 (20 patients) were on desmopressin tablets (0.2 mg) once daily before bedtime for 8 weeks in addition to behavioral modifications. Group 2 received only behavioral modifications. Both groups were followed up for 8 weeks of treatment, and then another 8 weeks to detect relapse.

Results: The wetting frequency decreased during treatment by 70% in Group 1 and 65% in Group 2. However, this difference was not statistically significantly different. The complete and partial response rates were 45% and 25% respectively in Group 1 and were 35% and 30% respectively in Group 2.

Conclusion: There is a highly significant decrease in wet nights in response to either desmopressin or behavioral therapy. However, the difference is not statistically significant. Also, it was found that relapsers (mainly early relapsers) are significantly more encountered in patients treated by desmopressin.

1. Introduction

Primary Monosymptomatic Nocturnal Enuresis (PMNE) is one of the most common developmental problems in children which affects up to 20% of children at 5 years of age and nearly 1% of young adults [1]. It is defined as involuntary urination while asleep after the age at which bladder control usually occurs [2]. Nocturnal enuresis is essentially benign in a pathological sense but unfortunately it can interfere with normal development because it carries emotional stigmata [3].

Treatment of enuresis is basically on an individual basis and decided, to a reasonable extent, on the basis of the attitude of the child and the parents toward enuresis [3].

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Understanding the different etiological factors sharing in the causation of nocturnal enuresis such as lack of nocturnal vasopressin release, detrusor muscle overactivity at night and lack of arousal from sleep, led to the proposal of various lines of treatment such as behavioral treatment, medical treatment like imipramine, oxybutynin, alarm therapy, hypnosis and acupuncture [4].

Desmopressin is one of the drugs used for the treatment of nocturnal enuresis. It is a synthetic vasopressin (V2) receptor agonist [5].

Based on understanding the presence of lack of nocturnal vasopressin in children with nocturnal enuresis in early 1980s [6], desmopressin was first licensed for the treatment of nocturnal polyuria in 1991 [7].

2. Subjects and methods

This study was a randomized interventional comparative study. It was conducted at the Pediatric Psychiatry Clinic, Pediatric Hospital, Ain Shams University. The study was conducted on 40 patients aged 6–15 years (mean 9.5 ± 2.9) who have Primary Monosymptomatic Nocturnal Enuresis (PMNE). Eligible patients had nocturnal enuresis (non diurnal) and wetting frequency of 3 or more nights per week for at least the last 2 weeks of observation.

Patients with one or more of the following were excluded from the study; Diurnal enuresis, urinary tract infection within the preceding 3 months, polyuric disorders (diabetes mellitus or diabetes insipidus), abnormal urine analysis, urinary tract abnormality, history of renal disease, hypertension or genitourinary abnormality, neurological disease mental retardation or psychological disease.

3. Methodology

100 patients were randomly chosen from the child psychiatry clinic complaining of PMNE, they were stratified according to the modality of treatment they were receiving. 20 patients receiving desmopressin treatment plus behavioral therapy and 20 patients on behavioral therapy only were randomly included in the study. Each patient in this study was subjected to the following; Full history was taken from all patients, including; demographic data, detailed medical history, including the presence of organic or psychological diseases, family history of similar cases, and previous treatment which was received.

Clinical Examination including; body measurements, physical examination, neurological examination to exclude neurological diseases especially neural tube defects and urological examination.

Investigations; urine analysis (for all cases): To exclude the presence of pyuria, glucosuria and diabetes insipidus. Serum creatinine, sodium and potassium, plain X-ray spine and EEG for some cases.

3.1. Scales

3.1.1. Stanford–Binet intelligence scale [8]

An intelligence quotient or IQ is simply the ratio of mental age (MA) to chronological age (CA) multiplied by 100:

$$IQ = MA/CA \times 100$$

The Stanford–Binet intelligence scale consists of 15 subsets. The vocabulary subset is administered first to obtain a basal level for beginning items in all the other subsets. The basal level for each test was established when 2 consecutive items are passed; the ceiling level is established by 4 consecutive failures.

The only timed subset is pattern analysis (subset 5).

The subsets are grouped into 4 broad areas verbal reasoning, abstract/visual reasoning, quantitative reasoning and short term memory and a composite score is derived from the area scores.

The test is designed for ages 2–23 years. Administration requires an average of 60–90 min.

After informed consent was obtained patients were divided according to the modality of treatment they were on into 2 groups. The work has been carried out in accordance with the code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

Group I: Patients on desmopressin tablets 0.2 mg (*Minirin*, Ferring International center, Switzerland) as a treatment for nocturnal enuresis in addition to behavioral instructions.

All children in Group 1 (20 patients) were on desmopressin tablets once daily before bedtime for 2 months after details and instructions about the drug and its use were given to the patients.

Also the parents and the children were also instructed to complete a daily voiding diary and adhere to behavioral instructions which they were given to avoid bedwetting,

Group II: Patients of this group (20 patients) were on the following instructions (behavioral therapy), which they were given to avoid bedwetting, along the entire period of the 16 weeks, also they were instructed to fulfill a star chart to register their voiding diaries.

3.1.2. Recommendations for the use of behavioral therapy [9]

Remove underpants and have child void in toilet at start of every day.

- Encourage child to avoid holding urine.
- Encourage voiding at least once every 2 h, at least several times during school day, and often enough to avoid urgency and incontinence.
- Facilitate easy access to school toilets with a note to the teacher.
- Have child use optimal posture to relax pelvic-floor muscles, facilitating good emptying of bowel.
- Have child drink a liberal amount of water during morning and early afternoon hours, a total of at least 30 ml per kilogram of body weight.
- Minimize intake of fluids and solutes after dinner unless child is participating in evening sports or social activities.
- Encourage a daily bowel movement, preferably after breakfast and before child leaves for school.
- Encourage the child to eat foods that soften stool and to avoid foods that harden stool.
- Encourage the child to engage in physical activity and discourage prolonged sitting in front of television or computer.

Follow up visits for both groups were scheduled every 2 weeks to ensure adherence to the behavioral instructions and

desmopressin therapy, to record any adverse effect, and to analyze the progress of the patients.

The main variable for analysis was the average number of wet nights per week calculated over a defined period of 16 weeks.

3.2. Treatment outcomes were defined as follows [10]

"*Complete responders*" were patients with 1 or less wet night per week in the last 2 weeks of treatment.

"*Partial responders*" were those with more than 1 wet night per week but greater than 50% reduction in the number of wet nights compared with the pretreatment period.

"*Non-responders*" had less than 50% reduction in wetting frequency in the last 2 weeks of treatment. Non-compliant patients and non-responders were considered together as "treatment failure".

Patients were followed for 8 weeks after cessation of treatment. "*Relapsers*" were defined as reappearance of >1 wet night per week for complete responders or >50% of pretreatment wetting frequency for partial responders. "*Early relapsers*" and "*late relapsers*" were defined as those who relapsed in the first 4 weeks and next 4 weeks of the post-treatment observation period, respectively.

4. Statistical analysis

Data were collected, coded, revised, verified and entered into an IBM compatible personal computer. Data were then statistically analyzed using the statistical software package SPSS version 12.0.

Data were summarized and the following statistical tests were used in this study: *Mean and standard deviation* (*SD*) were used to describe qualitative variables. *Percent* was used to describe quantitative variables.

Comparison between quantitative variables was carried out by *paired student T test* of two independent samples, which were expressed in the form of *P*-value. *Chi-square test* (χ^2) was used to compare qualitative variables with each other.

Analysis of variance test (*ANOVA test*) was used for comparison among different times in the same group in quantitative data.

The statistical significance of the results was assessed in the form of *P*-value. Values were considered as follows: *Statistically non significant:* If *P*-value was >0.05, *Statistically significant:* If *P*-value was ⩽0.05, *Statistically highly significant:* If *P*-value was ⩽0.01 and *Statistically extremely significant:* If *P*-value was ⩽0.001.

5. Results

This study was conducted on 40 patients aged 6–15 years (mean age 9.5SD ± 2.9) having Primary Monosymptomatic Nocturnal Enuresis (PMNE). Patients were divided into two equal groups; Group 1 received desmopressin and behavioral therapy and Group 2 was on behavioral therapy only. There was no significant difference regarding the age, gender and IQ level among the two study groups (*P value* > 0.05), i.e. the two samples were homogenous.

On comparing the number of wet nights in the two groups at 8 and 16 weeks in relation to 0 point, it was found that wet nights at 8 and 16 weeks in each individual group has decreased in a highly significant pattern in relation to wet nights at 0 point (the beginning of the study) (Table 1).

When comparing Group 1 versus Group 2 after the treatment period (First 8 weeks) it was found that the total number of responders in the patients of Group 1 was more than that in Group 2. However, these results were not statistically significant (*P value* > 0.05) (Table 2).

The wet nights in both study groups decrease greatly at the second week as shown in Fig. 1 (this drop was more pronounced in Group 1 than in Group 2 (but the difference was not statistically significant), reaching almost a plateau in Group 2 till the end of the study. On the other hand, the wet nights continue to decrease till tenth week in Group 1 (treatment period) and then returned to increase starting from the twelfth week till the end of the study.

On comparing Group 1 patients versus Group 2 patients according to incidence of relapse it was found that (as shown in the Fig. 2), the relapse rate in Group 1 was more than in Group 2; The relapse rate in Group 1 was approximately 64.3%, including 35.7% early relapsers and 28.6% late relapsers, and 35.7% were non relapsers. On the other hand, the relapse rate in Group 2 was 38.5%, including 30.8% early relapsers and 7.7% late relapsers, and 61.5% were non relapsers. However, these differences between the two groups were found to be non significant statistically.

Correlation of desmopressin response with the variables in patients data shows no significant difference in response as regards order of birth and number of wet nights at the beginning of the study and at 16 weeks (*P value* > 0.05). However there was a significant difference in response as regards sex i.e. males were more responders than females (*P value* < 0.05).

Table 1 Comparing the number of wet nights in the two groups at 8 and 16 weeks in relation to 0 point.

Study groups	Time interval (weeks)	Wet nights Mean ± *SD*	*t*	*P* value
Group 1	0	10.3 ± 2.7		
	8	2.67 ± 1.85	10.92	<0.001
	16	3.67 ± 3.29	6.67	<0.001
Group 2	0	12.5 ± 2.59		
	8	4.2 ± 3.85	9.1	<0.001
	16	4.2 ± 3.97	9.19	<0.001

Table 2 Comparing the study groups according to response at the end of the treatment period.

Outcome	Group 1 *n* (%)	Group 2 *n* (%)	χ^2	*P* value
Complete responders	9 (45%)	7 (35%)	3.16	0.37
Partial responders	5 (25%)	6 (30%)		
Non responders	4 (20%)	7 (35%)		
Non complaints	2 (10%)	0 (0%)		

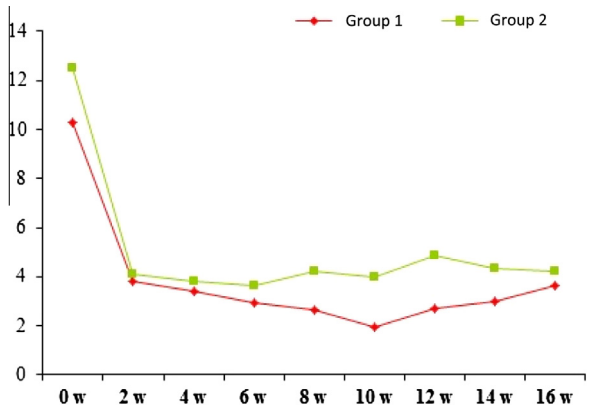

Figure 1 Showing the tracing of wet nights frequency in patients of Group 1 and Group 2 throughout the study (treatment and follow up periods).

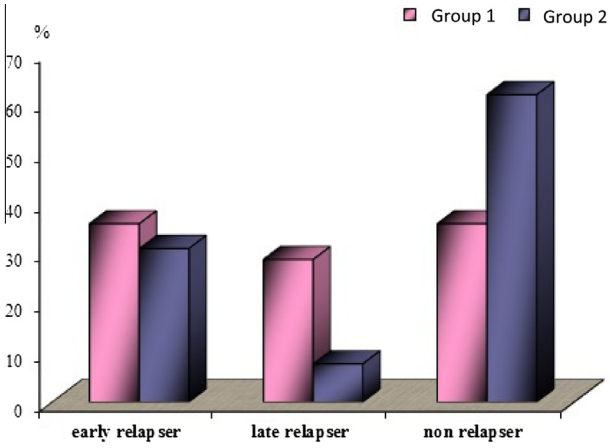

Figure 2 Comparing Group 1 patients versus Group 2 patients according to incidence of relapse.

Also, there was no significant difference in response as regards weight, height, body mass index, and IQ test (*P value* > 0.05), but, there was a significant difference in response as regards age as older patients had a better response (*P value* < 0.05).

Regarding the family history there was no significant difference in response when correlated to the family history (*P value* > 0.05).

6. Discussion

In the early eightieth of the twentieth century, it was found that there was a lack of nocturnal vasopressin in children with nocturnal enuresis and from then on desmopressin became an established treatment for nocturnal enuresis [6].

The main objective of this study was to assess the efficacy of desmopressin in the treatment of PMNE in Egyptian children. As shown in the study, the wet nights decreased in a highly significant pattern in both of the study groups. Also it was shown that the responders in Group 1 (on desmopressin and behavioral therapy) were more than the responders in Group 2 (receiving only behavioral therapy), 70% and 65% respectively, but the difference was statistically non significant. The statistically insignificant result comes in concordance with [11,12].

On the other hand, many studies showed that desmopressin is significantly more effective than placebo in achieving dryness [13,14].

Moffatt et al. [15] reviewed the results of all randomized studies done in the period between 1966 and 1992 to find out the efficacy of desmopressin. They detected 18 randomized controlled trials which included 689 subjects. All studies found decreased mean frequency of wetting nights ranging from 10% to 91%, but only 24.5% of subjects achieved long-term dryness.

Also, another study done in 2012 mentioned that the success rates with desmopressin ranged from 10% to 65% with relapse rate as high as 80% [16]. In most trials a response rate of 60–70% is detected [17]. This is nearly similar to the results of our study showing a response rate of 70% at 8 weeks and 75% at 16 weeks. This highly impressive response comes in concordance with the study done by Cherry and SikNin [10] who found that 70% of patients treated with desmopressin responded to treatment including 31% complete responders and 39% partial responders.

In the current study the responders at 8 weeks (after treatment period) were 70% (45% complete responders and 25% partial responders), however, at 16 weeks (after a short follow up period) the responders became 75% (35% complete responders and 40% partial responders). The decrease in the number of complete responders may be due to relapse of patients and this led them to fall in the category of partial responders (decrease in wet nights >50% from baseline) instead of the category of complete responders (decrease of wet nights to ⩽1).

Most studies found that the number of partial responders is more than that of complete responders, for example, one study states that 30% of responders are complete responders and 40% are partial responders [18], up to in the study done by Matthiesen et al. [19] who found that partial responders were 100% with no complete responders at all. On the other hand, other studies found that complete responders were more than partial responders [20].

Therefore most studies acknowledge the efficacy of desmopressin, but, in some other studies it was shown that long term results have been found to be 23% only of children treated. This 23% is not significantly better than spontaneous resolution [21].

Throughout the study period we traced the frequency of wet nights in the patients, it was found that desmopressin have a more rapid onset of action. However it was associated with relapses starting to occur from the twelfth week till the end of the study. Most studies support the rapid onset action of desmopressin with relatively high relapse rate upon discontinuation [22].

In all studies it became evident that the efficacy of desmopressin continued or improved throughout the treatment period indicating that enuretic patients did not develop tolerance to desmopressin, however, dose and duration of treatment must be tailored for each patient according to symptoms [23].

Concerning the issue of relapse, results of the current study showed that relapse rate was higher with desmopressin use 64.3%, in Group 1 compared to 38.5% in Group 2. These results was in agreement with [22,15] reporting relapse rate

between 80 and 100% after discontinuation of desmopressin treatment. The less relapse recorded in our study may be due to the maintenance of the patients on behavioral therapy.

Another objective of the current study was to correlate the response to desmopressin with the variable patient's data. *When we correlated the response to desmopressin with the age of our patients*, we found that there was a significant positive correlation between age of the patients and their response to desmopressin therapy. This was in agreement with [17]. On the other hand, another study found no significant relation between age and response to desmopressin [24].

As regards the correlation of response to the sex of Group 1 patients, this study found that males were significantly more responsive than females to desmopressin after 16 weeks of treatment and follow up. This comes in contrary with [22]. However, Butler et al. [24] found that there was no significant relation between response and sex.

According to order of birth of the patients, the study found that there was a significant relation between order of birth of the patients and their response to desmopressin therapy after 8 weeks of treatment i.e. patients who were first and second in order of birth had better response than other patients who were later in order of birth, this is probably because they are more responsible. But Butler et al. [24] found that there was no significant relation between response and order of birth.

When we correlated our results with the family history of the patients, the study found that there was no significant relation between family history of the patients and their response to desmopressin therapy.

This comes in concordance with [24]. On the other hand, Kirk et al. [25] found that those patients resistant to desmopressin were more likely to have a first degree relative with a history of nocturnal enuresis. On the contrary, Hogg and Husmann [26] found that responders to desmopressin have family history of enuresis.

Regarding the IQ of the patients, the current study did not find any significant relation between IQ scale of the patients and their response to desmopressin therapy. Unfortunately there is not much data about this issue, but it was mentioned in one study that mentally disabled children should have reached a mental age of 4 years before they are considered enuretic [22].

The correlation between the response and the frequency of wet nights/week of the patients at the beginning of the study, detected that there was no significant relation between baseline wet nights per week of the patients and their response to desmopressin therapy. This is not in agreement with Kruse et al. who found that the best results were obtained in children who do not wet frequently [17].

There were several limitations in this study: firstly, was the relatively small number of the study subjects which may have affected the results of the study.

Secondly, we studied only the short term effect of desmopressin therapy (2 months) with short follow up period (only 2 months). Discontinuation of treatment and follow up after this short time might have led to ineffective treatment or missed relapses.

Thirdly, the lack of non treatment control group, thus we can't definitely exclude the possibility of spontaneous resolution. We didn't include the non treatment control group in the trial because we considered it unethical to exclude or delay patient treatment knowing the effect of NE on the psychological well being of our patients.

Another limitation was that some of patients might have dysfunctional voiding without manifesting with daytime urinary symptoms [27], this would have been spotted if urodynamic studies had been performed.

In conclusion; From this study we can conclude that desmopressin is not superior to behavioral therapy in decreasing wet nights per week in our enuretic Egyptian children. And although it have the advantage of a more rapid onset of action it is associated with an unfortunate higher relapse rates.

Behavioral treatment also proved to be a good monotherapy for nocturnal enuresis, with even less relapse rate, and more efficient if combined with desmopressin.

Conflict of interest

The authors declare no conflict of interest. There is no financial and personal relationship with other people or organizations that could inappropriately influence their work.

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