Desmopressin and Imipramine in the Treatment of Primary Monosymptomatic Nocturnal Enuresis: A Randomized Controlled Trial

Mei-Chin Chiang, *Chung-Jing Wang, MD, Che-Yu Yang, MD, Hsin-Pao Lai, MD

*Division of Urology, Department of Surgery, Saint Martin De Porres Hospital,

Chiayi, Taiwan, R.O.C.

Department of Pediatrics, Saint Martin De Porres Hospital, Chiayi, Taiwan, R.O.C.

Correspondence and requests for reprints: *Chung-Jing Wang, Division of Urology,

*Department of Surgery, Saint Martin De Porres Hospital, Chiayi, Taiwan, R.O.C.

Telephone:+886 5 2756000 ext: 1013; FAX: +886-5-2788535;

e-mail: jing@stm.org.tw

Manuscript word count:1923

Running head: Desmopressin and imipramine in the treatment of primary

monosymptomatic nocturnal enuresis

Key words: desmopressin, nocturnal enuresis, imipramine, child

International Journal of Scientific Engineering and Applied Science (IJSEAS) – Volume-3, Issue-3, March 2017
ISSN: 2395-3470
www.ijseas.com

Abstract

Objective: To evaluate the effectiveness and safety of oral desmopressin treatment in children with primary monosymptomatic nocturnal enuresis (PMNE).

Materials and Methods: This prospectively randomized controlled trial was carried out from January 2006 to July 2016. In total, 113 children with PMNE completed the study protocol, with 64 patients designated to an imipramine group and 67 to a desmopressin group. Patients were required to visit the outpatient clinic for a first visit, as well as after 1, 3, and 6 months of treatment. Patient-maintained voiding diaries were used for evaluation. During follow up, urinalysis and serum electrolytes were analyzed at each visit.

Results: The response rates were 43.75%, 39.66%, and 32.67% among the children in the imipramine group after 1, 3, and 6 months of treatment, respectively. The response rates were 91.04%, 86.60%, and 86.60% among the children in the desmopressin group after 1, 3, and 6 months of treatment, respectively.

Conclusions: This study shows that oral desmopressin is an effective and well-tolerated treatment for children with PMNE. This study confirms that oral desmopressin may be more effective than oral imipramine in the treatment of children with PMNE.

International Journal of Scientific Engineering and Applied Science (IJSEAS) – Volume-3, Issue-3, March 2017
ISSN: 2395-3470
www.ijseas.com

Introduction

Primary monosymptomatic nocturnal enuresis (PMNE), bedwetting without any other lower urinary tract symptoms (LUTS) [1], is a distressing problem that affects 6–10% of 7-year-old children [2]. It has an annual spontaneous resolution rate of approximately 10–15% [2], but not all cases resolve spontaneously. Nocturnal enuresis persists in up to 3% of adolescents [3] and 1% of untreated adults [2]. Given the huge impact of enuresis on self-esteem, quality of sleep, performance at school, and social and familial life [4, 5], timely and adequate treatment is mandatory. Enuresis is essentially caused by a mismatch between nocturnal bladder capacity and the amount of urine produced during the night in children or adults who do not awake from sleep in response to a full bladder [2]. Nocturnal polyuria (NP), due to insufficient arginine vasopressin hormone release at night, is a major cause of PMNE [6].

There are only two first-line treatments for PMNE available, the enuresis alarm and pharmacological interventions, both of which have level 1 grade A recommendations from the International Consultation on Incontinence [7]. Two drugs used frequently for the treatment of PMNE are imipramine and desmopressin [8, 9]. Desmopressin is a selective vasopressin receptor type 2 agonist that retains the antidiuretic properties of vasopressin without inducing pressor activity. Recent guidelines recommend an individualized treatment based on parameters obtained using a voiding diary to assess important factors, such as whether nocturnal enuresis is monosymptomatic or present with additional LUTS symptoms, as well as whether patients have NP [10]. Amongst those with PMNE with underlying NP, desmopressin is the recommended therapy due to its antidiuretic action [10].

A randomized trial was conducted with its focus being the evaluation of which of

the above pharmacological interventions is more efficacious. We evaluated the outcomes of interventions to determine the rate of initial success, as defined by the reduction in the number of wet nights per week and nocturnal urine volume.

Materials and Methods

The study was approved (STM No. 01B-010), and its related work was undertaken in Chia-Yi city and overseen by our Institutional Review Board at St. Martin De Porres Hospital. All procedures in this study involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and in compliance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. All patients and their caregivers were asked to sign an informed consent form before granting their participation. The study was designed to be a randomized controlled trial and it was carried out from January 2006 to July 2016. A sample size of 60 patients was required to detect a 30% difference in the proportions of the trial parameters (e.g., response rate and reduction in nocturnal urine volume) in the treatment groups at a significance level of 0.05 and a power of 80%.

Children aged 7–12 years who have a history of PMNE with no organic pathology were recruited into the trial. The children all had normal urine concentrating ability, and all patients were free of diurnal problems, such as urgency, frequency (more than seven voids per day) and/or daytime incontinence. None had received any specific treatment for nocturnal enuresis within the 2 months before entering the study. Children with clinically significant endocrine, metabolic, hepatic, psychiatric, neurological, musculoskeletal, cardiovascular, hematological, renal, or genitourinary diseases were excluded from the trial.

The patients were prospectively randomized into an imipramine group and a desmopressin group using a random numbers table. All patients received imipramine 25 mg or desmopressin 0.1 mg orally at bedtime. During the study, patients were advised to urinate just before going to bed and not to drink more than that sufficient to

International Journal of Scientific Engineering and Applied Science (IJSEAS) – Volume-3, Issue-3, March 2017
ISSN: 2395-3470
www.ijseas.com

satisfy thirst starting from the hour before bedtime until 8 hours after drug intake. They were also instructed to avoid drinking liquids with a diuretic effect at night (e.g., caffeine). Patients were required to visit the outpatient clinic for a first visit, as well as after 1, 3, and 6 months of treatment. Patient-maintained voiding diaries were used to record the following throughout the study: bedtime, time of rising, 24-h fluid intake and urine recording, time and volume of nocturnal voids, and time of tablet intake. During follow up, urinalysis and serum electrolytes were analyzed at each visit.

The primary efficacy endpoint was a response rate involving a reduction in the number of wet nights per week in the mean number of wet nights after long-term treatment compared with baseline. Several secondary endpoints were also assessed: nocturnal urine volume and night-time/24-h urine volume ($\leqq 30\%$) and the safety of long-term interventions. The efficacy assessments were based on data in the patients' diaries, and endpoints were derived for a 6-month double-blind study. Safety was evaluated from reported adverse events and laboratory data, with emphasis on serum sodium levels.

A statistical analysis was performed using SPSS® version 14.0.1. The independent t test, chi-square test, repeated measures ANOVA and cochran's Q test were used as appropriate. P values lower than 0.05 were considered significant.

International Journal of Scientific Engineering and Applied Science (IJSEAS) – Volume-3, Issue-3, March 2017
ISSN: 2395-3470
www.ijseas.com

Results

In total, 184 patients were eligible and were prospectively randomized into two groups before they began the trial. As well, 40 patients were not recruited into the trial, 16 patients did not meet the inclusion criteria, 13 patients were unwilling to be randomized, and 11 patients declined to participate in the trial. Therefore, 70 patients in total were allocated for imipramine treatment. Among the 70 patients, six were excluded, two missed the primary outcome, and two lost to follow-up. In all, 64 patients were enrolled and received imipramine treatment. In total, 74 patients were allocated for desmopressin treatment, among which seven were excluded, two missed the primary outcome, and five lost to follow-up. In all, 67 patients were enrolled and received desmopressin treatment. Thus, an analysis was conducted with 64 and 67 patients as the denominators in each randomization arm, respectively (Figure 1).

No significant statistical difference was observed in terms of patient age, gender distribution, body mass index, or adverse effects (Table 1). However, hyponatremia without clinical symptoms was noted significantly in the desmopressin group.

The response rate was achieved in 43.75%, 39.66%, and 32.67% of children in the imipramine group after 1, 3, and 6 months of treatment, respectively. The response rate was achieved in 91.04%, 86.60%, and 86.60% of children in the desmopressin group after 1, 3, and 6 months of treatment, respectively. This set of data noted a significant difference between groups (Table 2) with regard to night wettings per week, the proportion of nocturnal urine volume by total daily urine amount, and a reduction in nocturnal urine volume.

Discussion

Desmopressin is an important treatment available for children with PMNE. Intranasal desmopressin has been shown to produce a statistically significant improvement in PMNE, but intranasal delivery has been associated with a number of clinical problems. Absorption is adversely affected by nasal congestion due to upper respiratory infections and seasonal allergies. Children with other disabilities and poor manual dexterity require additional assistance and supervision to administer desmopressin intranasally. A review of the safety-related problems of intranasal desmopressin revealed epistaxis and nasal stuffiness as relatively common adverse effects. Consequently, an oral route of administration would obviate a number of these problems and be more acceptable to patients.

The study evaluated the treatment outcomes in children with PMNE and compared the success of the responses and the proportion of nocturnal urine volume by total daily urine volume among children treated with two different medications. Our aim was to assess which pharmacological intervention was more efficacious. No serious adverse effects were reported in any group.

The study showed that desmopressin achieved in an 86.60% response rate in children with PMNE after 6 months of therapy, followed by imipramine (32.67% response rate). The reduction in nocturnal urine volume and the decrease in the proportion of nocturnal urine volume by total daily urine volume are significant. However, a noteworthy number of studies has compared the effects of non-pharmacological interventions, desmopressin, antidepressants, or various combination therapies. A review of the literature indicates that oxybutynin has been effective in 47–71% of children and showed a better response if combined with desmopressin [11[. Nasal desmopressin had been efficacious in 60–70% and

International Journal of Scientific Engineering and Applied Science (IJSEAS) – Volume-3, Issue-3, March 2017
ISSN: 2395-3470
www.ijseas.com

imipramine in 40–60% of children [11]. A systematic review based on a meta-analysis from The Cochrane Collaboration stated that desmopressin can result in 1–2 fewer wet nights per week compared with the placebo [12]. Another systematic review showed that imipramine has been associated with a reduction of about one wet night per week during the treatment [13]. There is not enough evidence-based and reliable information supporting oxybutynin as an efficacious treatment for PMNE [14]. Some studies recommended oxybutynin for desmopressin-resistant children or those with PMNE and daytime wetting [11, 15-17]. Several studies stated that oxybutynin is more effective in children who have small bladders, a restricted bladder capacity, a thickened bladder wall, and hyperactive detrusors [15, 18]. In one study, the majority of children being treated for enuresis (88.2%) with inadequate bladder storage function were responsive to the 15 mg daily oxybutynin regime, while in patients with normal bladder function, this medication was generally unsuccessful for enuresis [19]. In a study by Montaldo et al. [15], the combined oxybutynin and desmopressin group showed a higher rate of response (45%) than the desmopressin plus placebo group (17%).

It has been well established that treating enuresis cannot be successful if the child and their parents do not cooperate, and treatment with medication will fail if the family's social construct and home circumstances are not supportive. Previous studies may be partly explained by these dynamics. Other important factors in treatment success include comorbid psychological, behavioral, and emotional problems, as well as the age of the child [14]. A positive family history of enuresis, the child's drinking habits, abnormal deep sleep patterns, and constipation have a strong impact on the response to treatment [20]. Parents who experienced bedwetting may have a more tolerant attitude toward enuresis in their children [20], which can affect positively the

child's response to the medication. Other risk factors of enuresis, including low socioeconomic status of the family, low school success, inappropriate and forced toilet training, and strict or over-protective parents [21], may also influence the response to treatment. Moreover, the various treatment approaches are influenced by the child's environment and by the background and prejudgments of the family. As suggested by the Cochrane Database of systematic reviews, "Not all interventions are suitable for all children" [14].

Nocturnal enuresis is a common problem according to pediatricians and is one of the most common sources of concern for children and their families. Despite many years of research, there are still some uncertainties about the benefit of pharmacological treatment and about the most efficacious interventions. More studies with larger sample sizes and longer durations of treatment and follow up are needed to decide which treatment is the most appropriate for enuresis. Studies should be performed on children with various cultural and socioeconomic backgrounds and with different family circumstances, and they should take into account the individual characteristics of every child. This will help clinicians to determine which treatments best suit which children.

International Journal of Scientific Engineering and Applied Science (IJSEAS) – Volume-3, Issue-3, March 2017
ISSN: 2395-3470
www.ijseas.com

Conclusions

This study demonstrated that oral desmopressin is an effective and well-tolerated treatment for children with PMNE. This study confirms that oral desmopressin may be more effective than oral imipramine in the treatment of children with PMNE. Long-term desmopressin therapy gradually decreased serum sodium, and it might induce asymptomatic hyponatremia. For long-term desmopressin administration, serum sodium should be assessed carefully, at least at 1 month after treatment.

Conflicts of Interest

None of the contributing authors have any conflicts of interest, including specific financial interests or relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

International Journal of Scientific Engineering and Applied Science (IJSEAS) – Volume-3, Issue-3, March 2017
ISSN: 2395-3470
www.ijseas.com

References

1. Nevéus T, von Gontard A, Hoebeke P, Hjälmås K, Bauer S, Bower W, et al.(2006) The standardization of terminology of lower urinary tract function in children and adolescents: report from the Standardisation Committee of the International Children's Continence Society. J Urol ;176:314–324.

2. De Guchtenaere A, Van Herzeele C, Raes A, Dehoorne J, Hoebeke P, Van Laecke E, et al.(2011) Oral lyophylizate formulation of desmopressin: superior pharmacodynamics compared to tablet due to low food interaction. J Urol 185:2308–2313.

3. De Guchtenaere A, Raes A, Vande Walle C, Hoebeke P, Van Laecke E et al. (2009) Evidence of partial anti-enuretic response related to poor pharmacodynamic effects of desmopressin nasal spray. J Urol 181:302–309.

4. Dhondt K, Raes A, Hoebeke P, Van Laecke E, Van Herzeele C, Vande WJ (2009) Abnormal sleep architecture and refractory nocturnal enuresis. J Urol 182(Suppl 4):1961–1965.

5. Theunis M, Van Hoecke E, Paesbrugge S, Hoebeke P, Vande WJ (2002) Self-image and performance in children with nocturnal enuresis. Eur Urol 41:660–667.

6. Rittig S, Schaumburg HL, Siggaard C, Schmidt F, Djurhuus JC (2008) The circadian defect in plasma vasopressin and urine output is related to desmopressin response and enuresis status in children with nocturnal enuresis. J Urol 179:2389–2395.

7. Tekgul S, Nijman R, Hoebeke P, Canning D, Bower W, von Gontard A. Diagnosis and management of urinary incontinence in childhood. Report from the 4th International Consultation on Incontinence.

International Journal of Scientific Engineering and Applied Science (IJSEAS) – Volume-3, Issue-3, March 2017
ISSN: 2395-3470
www.ijseas.com

http://www.icsoffice.org/Publications/ICI_4/filesbook/ Comite-9.pdf.Accessed September 2012

8. Lawless MR, McElderry DH (2001) Nocturnal enuresis: current concepts. Pediatr Rev 22(12):399–407.

9. Ramakrishnan K (2008) Evaluation and treatment of enuresis. Am Fam Physician 78(4):489–96.

10. Vande Walle J, Rittig S, Bauer S, Eggert P, Marschall-Kehrel D et al.(2012) Practical consensus guidelines for the management of enuresis. Eur J Pediatr 171:971–983.

11. Ramakrishnan K Evaluation and treatment of enuresis.(2008) Am Fam Physician 78(4):489–96.

12. Glazener CMA, Evans JHC (2002) Desmopressin for nocturnal enuresis in children. Cochrane Database Syst Rev 3(CD002112).

13. Glazener CMA, Evans JHC, Peto RE, Glazener CMA (2003) Tricyclic and related drugs for nocturnal enuresis in children. Cochrane Database Syst Rev 3:CD002117.

14. Deshpande AV, Caldwell PH, Sureshkumar P(2012) Drugs for nocturnal enuresis in children (other than desmopressin and tricyclics).Cochrane Database Syst Rev 12:CD002238.

15. Montaldo P, Tafuro L, Rea M, Narciso V, Iossa AC et al.(2012) Desmopressin and oxybutynin in monosymptomatic nocturnal enuresis: a randomized, double-blind, placebo-controlled trial and an assessment of predictive factors. BJU Int 110(8 Pt B):381–6.

16. Friedman BC, Friedman B, Goldman RD (2011) Oxybutynin for treatment of nocturnal enuresis in children. Can Fam Physician 57(5):559–61.

International Journal of Scientific Engineering and Applied Science (IJSEAS) – Volume-3, Issue-3, March 2017
ISSN: 2395-3470
www.ijseas.com

17. Radvanska E, Kovacs L, Rittig S (2006) The role of bladder capacity in antidiuretic and anticholinergic treatment for nocturnal enuresis. J Urol 176(2):764–8.

18. Neveus T (2001) Oxybutynin, distance and enuresis. J Urol 166(6):2459–62.

19. Kosar A, Arikan N, Dincel C (1999) Effectiveness of oxybutynin hydrochloride in the treatment of enuresis nocturna--a clinical and urodynamic study. Scand J Urol Nephrol 33(2):115–8.

20. Neveus T, Eggert P, Evans J, Macedo A, Rittig S et al.(2010) Evaluation of and treatment for monosymptomatic enuresis: a standardization document from the International Children's Continence Society. J Urol 183(2):441–7.

21. Ozkan S, Durukan E, Iseri E, Gurocak S, Maral I et al.(2010) Prevalence and risk factors of monosymptomatic nocturnal enuresis in Turkish children. Indian J Urol 26(2):200–5.

184 eligible

↓   40 not recruited

16 Not meeting inclusion criteria

13 unwilling to be randomized

11 declined to participate

↓

144 randomly assigned

↓

↓

70 allocated Imipramine   74 allocated Desmopressin

↓

↓

6 excluded   7 excluded

2 missing primary outcome   2 missing primary outcome

4 lost to follow-up   5 lost to follow-up

↓

↓

64 included in primary outcome   67 included in primary outcome
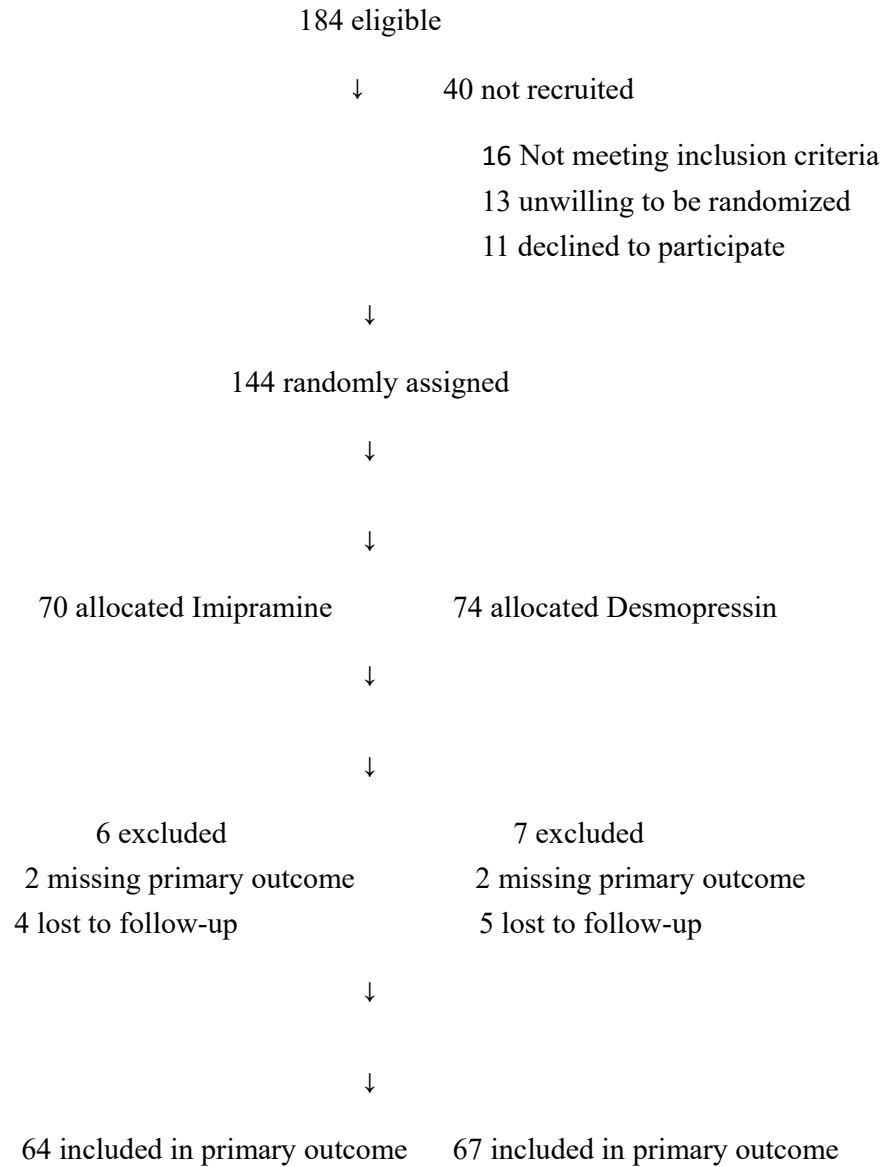
Figure 1: Summary of study disposition

    Numbers of participants declining further follow-up or not responding are cumulative in direction of participant flow.

International Journal of Scientific Engineering and Applied Science (IJSEAS) – Volume-3, Issue-3, March 2017
ISSN: 2395-3470
www.ijseas.com

Table 1   Patients Characteristics

Characteristic	Imipramine	Desmopressin	*P* value
Patients (n)	64	67	
Age (yr) [a]			
Mean	8.11 ± 1.47	8.13 ± 1.41	0.921
Range	6-12	6-12	
Gender [b]			0.837
Male	45 (70.31)	46 (68.66)	
Female	19 (29.69)	21 (31.34)	
Body mass index [a]	22.41 ± 2.09	22.34 ± 1.89	0.857
Total adverse events	9(14.06%)	18(26.87%)	0.972[#]
Oral dryness	4	3	
Dizziness	4	4	
Nausea	1		
Hyponatremia without clinical symptoms	0	11	

Values are presented as mean ± standard deviation or number (%).

[a] Independent t test

[b] Chi-square test

International Journal of Scientific Engineering and Applied Science (IJSEAS) – Volume-3, Issue-3, March 2017
ISSN: 2395-3470
www.ijseas.com

Table 2   Patient response and voiding diary (Baseline vs Treatment)

	Baseline	1 month	3 month	6 month	P valu
Nocturnal urine volume [a]					< 0.0(
Imipramine	470.63 ± 42.16	459.69 ± 38.01	464.84 ± 39.24	464.84 ± 50.33	
Desmopressin	470.45 ± 70.27	284.63 ± 56.20	282.99 ± 44.96	272.09 ± 41.40	
Nocturnal volume ≤ 30% of daily total urine volume [b]					< 0.0(
Imipramine	5 (7.81)	7 (10.94)	9 (14.06)	29 (45.31%)	
Desmopressin	4 (5.97)	66 (98.51)	65 (97.01)	66 (98.51)	
Total urine amount (ml) [a]					< 0.0(
Imipramine	17.44 ± 1.37	17.42 ± 1.34	17.09 ± 1.30	16.65 ± 1.28	
Desmopressin	18.24 ± 2.15	18.11 ± 1.75	17.76 ± 1.30	17.65 ± 1.09	
Daily total volume (mL/D) [a]					< 0.0(
Imipramine	1280.89 ± 172.23	1299.09 ± 174.13	1294.66 ± 199.30	1511.91 ± 178.67	
Desmopressin	1276.61 ± 150.71	1267.73 ± 122.70	1243.07 ± 91.24	1235.34 ± 76.06	
Night wetting/week [a]					< 0.0(
Imipramine	6.66 ± 0.67	3.83 ± 2.20	3.91 ± 2.24	4.02 ± 2.36	
Desmopressin	6.67 ± 0.64	1.24 ± 1.45	1.39 ± 1.48	1.27 ± 1.45	
Serum sodium [a]					0.02:
Imipramine	140.25 ± 3.84	139.77 ± 3.73	139.47 ± 3.81	136.91 ± 3.27	

International Journal of Scientific Engineering and Applied Science (IJSEAS) – Volume-3, Issue-3, March 2017
ISSN: 2395-3470
www.ijseas.com

Desmopressin	140.15 ± 3.57	135.24 ± 7.83	137.28 ± 5.98	137.57 ± 5.67	
Serum chloride [a]					0.78
Imipramine	107.05 ± 2.36	106.94 ± 2.62	107.02 ± 2.92	105.80 ± 2.66	
Desmopressin	107.43 ± 2.22	105.18 ± 6.44	106.70 ± 5.11	106.91 ± 4.13	
Serum potassin [a]					0.12
Imipramine	4.37 ± 0.42	4.32 ± 0.39	4.17 ± 0.52	4.11 ± 0.50	
Desmopressin	4.38 ± 0.53	4.36 ± 0.55	4.34 ± 0.53	4.31 ± 0.53	
Response rate					<0.01
Imipramine		28 (43.75%)	23 (39.66%)	19 (32.67%)	
Desmopressin		61 (91.04%)	58 (86.60%)	58 (86.60%)	

Values are presented as mean ± standard deviation or number (%).

[a] Repeated measures ANOVA

[b] Cochran's Q test

Legends

Figure 1: Summary of study disposition

Numbers of participants declining further follow-up or not responding are cumulative

in direction of participant flow.

Table 1   Patients Characteristics

Table 2   Patient response and voiding diary (Baseline vs Treatment)

Abbreviations

PMNE: Primary monosymptomatic nocturnal enuresis

LUTS: Lower urinary tract symptoms