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

Desmopressin Withdrawal Strategy in the Treatment of Children Primary Monosymptomatic Nocturnal Enuresis: A Randomized Controlled Trial

Che-Yu Yang, *Chung-Jing Wang, MD, Mei-Chin Chiang, 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:1553

Running head: Desmopressin and imipramine in the treatment of primary monosymptomatic nocturnal enuresis

Key words: desmopressin, nocturnal enuresis, imipramine, child

Abstract

Objective: to evaluate the relapse rates of structured withdrawal using abrupt cessation and structured withdrawal in a population of children with primary monosymptomatic nocturnal enuresis who were desmopressin responders.

Materials and Methods: This prospectively randomized controlled trial and carried out from January, 2006 to July, 2016. A total of 113 children with primary monosymptomatic nocturnal enuresis completed the study protocol, 59 patients in abrupt cessation group, and 60 patients in structured withdrawal group. Patients were required to visit the outpatient clinic from the first visit, and after 1, 3, 6 and 9 months of treatment. Patient-maintained voiding diaries were used to be evaluated. During follow-up, urinalysis, and serum electrolytes were performed at each visit.

Results: The relapse rate was 20.0% for structured withdrawal group, which was significantly less than 44.68% for abrupt cessation group. There was significant difference observed between groups with regard to the proportion of nocturnal urine volume by total daily urine amount and reduction of nocturnal urine volume.

Conclusions: Structured withdrawal with oral desmopressin mediates decreased relapse rates after 3 months follow-up. Time dependent withdrawal strategy was observed to be effective.

Introduction

Patients with primary monosymptomatic nocturnal enuresis (PMNE) are those without any other lower urinary tract symptoms (nocturia excluded) and without a history of bladder dysfunction.〔1〕 The prevalence of PMNE is reportedly 3.8%, ranging from 0.5% to 1% in adolescence to 10% in early childhood.〔2-5〕

In addition to being highly prevalent, the effect of enuresis on the psychology and social status of children and their parents makes this an important health problem whose definitive treatment is important.〔6〕Treatment alternatives include pharmacological and psychological/behavioral therapeutic modalities. Desmopressin is the first-line medication for patients with monosymptomatic nocturnal enuresis with nocturnal polyuria and normal bladder function.〔7〕 Patients respond well and rapidly to desmopressin therapy. However, relapse after treatment is an important problem that affects up to 83% of patients.〔8〕For this reason, structured withdrawal of desmopressin tablets as reported by Marschall-Kehrel and Harms has been widely accepted.〔9〕

There is only one current study comparing abrupt cessation and a structured withdrawal program (60 mcg daily for 15 days, and then 60 mcg every second evening for another 15 days) in 47 patients, without a placebo group.〔10〕

We compared the relapse rates of two different withdrawal programs consisting of structured withdrawal and abrupt cessation. To our knowledge, this is the first prospective, randomized, controlled trial comparing two different structured

withdrawal protocols of desmopressin cessation.

Materials and Methods

This study was approved (STM No. 02B-011) and its related work undertaken in Chiayi City; the research was overseen by our institutional review board at St. Martin De Porres Hospital in Chiayi City. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and in compliance with the Declaration of Helsinki (1964) 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 was carried out from January 2006 to July 2016. A sample size of 55 patients was required in order to detect a 30% difference in the proportions of the trial parameters (i.e., relapse rate and reduction in nocturnal urine volume) in the treatment groups at a significance level of 0.05 and a power of 80%.

Children 7-12 years of age who had 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 two months preceding the study. Children with clinically significant endocrine, metabolic, hepatic, psychiatric, neurological, musculoskeletal, cardiovascular, hematological, renal, or genitourinary disease were excluded from the trial.

The patients who achieved full response were prospectively randomized into abrupt cessation and structured withdrawal groups using a random numbers table. The abrupt cessation group was to discontinue desmopressin 0.1 mg orally after six months of successful treatment. The cessation programs of the structured withdrawal

group applied for three months (0.1 mg every other day for two weeks, 0.1 mg per three days for two week, 0.1 mg per four days for two weeks, 0.1 mg per five days for two weeks, 0.1 mg per six days for two weeks, and 0.1 mg per week for two weeks), and patients were evaluated for relapse after nine months. During the six months of treatment, all patients received desmopressin 0.1 mg orally at bedtime. During the study, patients were advised to urinate just before going to bed and not drink more than sufficient to satisfy thirst beginning from an hour before bedtime until eight 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 their outpatient clinic after the first visit and after one, three, six, and nine months of treatment. Patient-maintained voiding diaries were used to record the following throughout the study: bedtime, time of rising, 24-hour fluid intake and urine recording, time and volume of nocturnal voids, and time of tablet intake. During follow-ups, urinalysis and serum electrolyte tests were performed at each visit.

Relapse was defined as bedwetting occurring more than three nights weekly. The primary outcome measure of the study was to determine the relapse rates after cessation of desmopressin in the different groups. The secondary outcome measure was to evaluate the nocturnal urine volume and nighttime/24-hour urine volume (≦ 30%), the effect of age and gender on relapse rates, and the safety of long-term interventions. The assessments were based on data in the patients' diaries, and endpoints were derived for the nine-month double-blind study. Safety was evaluated from reported adverse events and laboratory data, with emphasis on serum sodium levels.

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.

Results

A total of 153 patients were eligible and prospectively randomized into two groups before they entered the trial. A total of 25 patients were not recruited in the trial, 12 patients did not meet the inclusion criteria, 6 patients were unwilling to be randomized, and 7 patients declined to participate. A total of 63 patients were allocated into the abrupt cessation group. Among the 63 patients, 4 patients were excluded due to lost follow-up. In all, a total of 59 patients were enrolled and placed into the abrupt cessation group. A total of 65 patients were allocated for the structured withdrawal group. Among the 65 patients, 5 patients were excluded due to lost follow-up. In all, a total of 60 patients were enrolled in the structured withdrawal group. Thus, analysis was done with 59 and 60 patients as the denominator in each randomization arm (Figure 1).

No significant statistical differences were observed in patient age, gender distribution, body mass index, or adverse effects after the trial (Table 1). However, hyponatremia without clinical symptoms was frequently noted in the structured withdrawal group.

The relapse rate was 44.68% of children in the abrupt cessation group after six months of successful treatment. The relapse rate was 20.0% of children in the structured withdrawal group after six months of successful treatment. This set of data revealed a significant difference between groups (Table 2). A significant difference was observed between groups regarding the proportion of nocturnal urine volume by total daily urine amount and reduction of nocturnal urine volume (Table 3).

Discussion

Desmopressin is the first-line treatment for patients with PMNE and has high efficacy rates, although relapse after cessation of treatment is a major concern. In the present study, the relapse rates of abrupt cessation and withdrawal in two different structured methods were evaluated in comparison to placebo. Relapse rates were significantly lower in the structured withdrawal groups.

There have been studies published previously on structured withdrawal of desmopressin. Structured withdrawal programs can be grouped as time-dependent, i.e., approaches that maintain constant doses of medication with increasing time intervals, 〔11,12〕 and dose-dependent, i.e., approaches that decrease the doses of desmopressin after certain time intervals.〔13〕 Our study was based on time dependency. In our study, structured withdrawal programs were associated with lower relapse rates compared
to abrupt cessation ($p < 0.001$). In the study by Marschall-Kehrel and Harms, 0.2 and 0.4 mg tablets of desmopressin were given daily, and structured withdrawal was observed to result in lower relapse rates.〔9〕 This multicenter study offers strong evidence in favor of structured withdrawal. In a review of 13 studies and 1,457 children, Alloussi et al. reported lower relapse rates with time-dependent (mean 6.3%, range 3.7% to 17.6%) and dose-dependent (16.8%, 10.7% to 21.0%) structured withdrawal programs compared to abrupt cessation (56.9%, 10.8% to 90.0%).〔14〕 However, based on these series, no conclusion regarding preference for time- or dose-dependent approaches can be reached, as a direct comparison of two different approaches has not been performed.

Our secondary outcome measure was to identify factors associated with increased relapse rates. The number of wet nights per weel is associated with greater nocturnal urine output, which explains the association with relapse rates after cessation of desmopressin.

PMNE is a common problem seen by 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 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 PMNE. Studies should be performed on children with various cultural and socioeconomic backgrounds and different family circumstances and should take into account the individual characteristics of every child. This will help clinicians to determine which treatment best suits which children.

Conclusions

Structured withdrawal with oral desmopressin mediates decreased relapse rates after a three-month follow-up. A time-dependent withdrawal strategy was observed to be effective. Additional placebo controlled studies for comparison of different methods of withdrawal should be conducted to define the best method of structured withdrawal.

Acknowledgments

The contributing authors declare that there is no existence of financial support in the manuscript.

Conflict of Interest

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

References

1. Nevéus T, von Gontard A, Hoebeke P, Hjälmås K, Bauer S 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. Neveus T (2011) Nocturnal enuresis--theoretic background and practical guidelines. Pediatr Nephrol 26: 1207-1214.
3. Glazener CM and Evans JH (2002) Desmopressin for nocturnal enuresis in children. Cochrane Database Syst Rev 3: CD002112.
4. Deshpande AV, Caldwell PH and Sureshkumar P (2012) Drugs for nocturnal enuresis in children (other than desmopressin and tricyclics). Cochrane Database Syst Rev 12: CD002238.
5. Chiozza ML, Bernardinelli L, Caione P et al. (1998) An Italian epidemiological multicentre study of nocturnal enuresis. Br J Urol 81: 86-89.
6. Ücer O and Gümüs B (2014) Quantifying subjective assessment of sleep quality, quality of life and depressed mood in children with enuresis. World J Urol 32: 239-243.
7. National Institute for Health and Care Excellence: Nocturnal enuresis the management of bedwetting in children and young people. NICE Clinical Guidelines (CG111) 2010. Available at http://publications.nice.org.uk/nocturnal-enuresiscg111. Accessed December 19, 2013.
8. Monda JM and Husmann DA (1995) Primary nocturnal enuresis: a comparison among observation, imipramine, desmopressin acetate and bedwetting alarm systems. J Urol 154: 745-748.

9. Marschall-Kehrel D and Harms TW (2009) Structured desmopressin withdrawal improves response and treatment outcome for monosymptomatic enuretic children. J Urol, suppl., 182: 2022-2026.
10. Ferrara P, Romano V, Cortina I et al. (2014) Oral desmopressin lyophilisate (MELT) for monosymptomatic enuresis: structured versus abrupt withdrawal. J Pediatr Urol 10: 52-55.
11. Marschall-Kehrel AD, Murtz G, Kramer G et al. (2004) A suggested treatment algorithm in nocturnal enuresis with emphasis on partial responders. Urologe A 43: 795-802.
12. Butler RJ, Holland P and Robinson J (2001) Examination of the structured withdrawal program to prevent relapse of nocturnal enuresis. J Urol 166: 2463-2466.
13. Riccabona M, Oswald J and Glauninger P (1998) Long-term use and tapered dose reduction of intranasal desmopressin in the treatment of enuretic children. Br J Urol, suppl., 81:24-25.
14. Alloussi SH, Murtz G, Lang C et al. (2011) Desmopressin treatment regimens in monosymptomatic and nonmonosymptomatic enuresis: a review from a clinical perspective. J Pediatr Urol 7: 10-20.

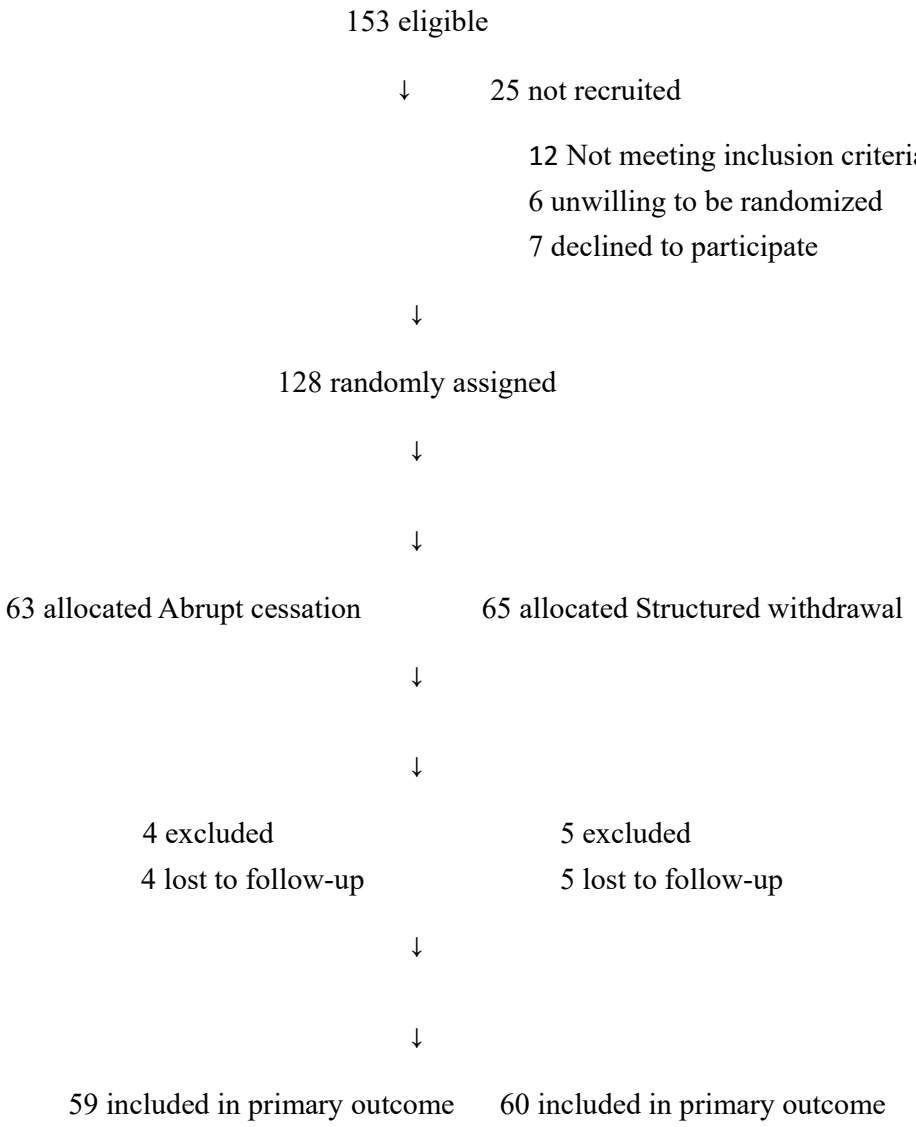

Figure 1: Summary of study disposition

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

Table 1 Patients Characteristics

Characteristic	Abrupt cessation	Structured withdrawal	*P* Value
Patients(n)	59	60	
Age(yr)[a]			
mean	8.11±1.47	73.56±7.71	0.967
range	7-12	7-12	
Gender[b]			0.847
male	42(71.2%)	42(70.0%)	
Female	17(28.8%)	18(30.0%)	
Body mass index[a]	22.37±2.15	22.34±1.73	0923
Total adverse events	4(6.78%)	7(11.67%)	0.857
Oral dryness	1	2	
Dizziness	2	1	
Nausea	1	1	
Hyponatremia without clinical symptoms	0	3	

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

[a] Independent t test

[b] Chi-square test

Table 2 Voiding diary and relapse rates after cessation of desmopressin

	Baseline	9 month	*P* Value
Nocturnal urine volume[a]			<0.01
Abrupt cessation	471.53±42.98	315.76±68.74	
Structured withdrawal	469.00±72.10	304.17±67.53	
Nocturnal volume≦30% of daily total urine volume[b]			<0.01
Abrupt cessation		40 (67.8%)	
Structured withdrawal		48 (80.0%)	
Night wetting/week[a]			<0.01
Abrupt cessation		2.31±1.96	
Structured withdrawal		1.43±1.61	
Relapse rate[b]			<0.01

Abrupt cessation	24 (44.68%)
Structured withdrawal	12 (20.0%)

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

[a] Independent t test

[b] Chi-square test

Table 3 Patient response and voiding diary (Baseline vs Treatment)

	Baseline	1 month	3 month	6 month	*P* value
Nocturnal urine volume[a]					0.953
Abrupt cessation	471.52 ± 42.98	275.76 ± 44.88	276.44 ± 35.80	266.78 ± 35.98	
Structured withdrawal	469.00 ± 72.17	286.17 ± 53.81	283.83 ± 44.96	273.50 ± 40.24	
Nocturnal volume ≧ 30% of daily total urine volume [b]					
Abrupt cessation	59 (100%)	0	0	0	
Structured withdrawal	60 (100%)	0	0	0	
Daily total urine volume (mL/D)[a]					0.873

Abrupt cessation	17.47 ± 1.40	17.91 ± 1.49	17.71± 1.32	17.62 ± 1.11	
Structured withdrawal	18.25 ± 2.22	18.15 ± 1.82	17.79 ± 1.36	17.65 ± 1.31	
Night wetting/week [a]					0.964
Abrupt cessation	6.66 ± 0.67	3.83 ± 2.20	3.91 ± 2.24	4.02 ± 2.36	
Structured withdrawal	6.67 ± 0.64	1.24 ± 1.45	1.39 ± 1.48	1.27 ± 1.45	
Serum sodium [a]					0854
Abrupt cessation	140.25 ± 3.84	139.77 ± 3.73	139.47 ± 3.81	136.91 ± 3.27	
Structured withdrawal	140.15 ± 3.57	135.24 ± 7.83	137.28 ± 5.98	137.57 ± 5.67	
Response rate[a]					0967
Abrupt cessation		59 (100%)	59 (100%)	59 (100%)	
Structured withdrawal		60 (100%)	60 (100%)	60 (100%)	

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

[a] Repeated measures ANOVA

[b] Cochran's Q test