Original Article

Desmopressin melt therapy in children with non-monosymptomatic nocturnal enuresis: a prospective study

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Abstract

Objective: The negative consequences of enuresis in children can be far reaching and an understanding of the impact of these is essential for effective treatment by the clinician. Enuresis can be categorized into monosymptomatic nocturnal enuresis (MNE) and non-monosymptomatic nocturnal enuresis (NMNE). There have been several studies in treatment of MNE with lyophilizate desmopressin melt but very limited research into the efficacy of desmopressin melt in treating NMME. The objectives of this study were to measure the efficacy and side effects of desmopressin melt in treating children with NMNE.

Materials and Methods: Children aged 6 to 18 years with NMNE who visited the outpatient department of pediatric urology were included in this prospective study. Any underlying diseases and lower urinary tract symptoms were corrected then their enuresis was treated with 120-240 mcg of desmopressin melt for 6-8 weeks. Outcomes were defined as complete response, partial response, and no-response as defined by the International Children's Continence Society guidelines.

Results: A total of 25 children with NMNE were included in the study. The results showed 44% complete response, 20% partial response, and 36% no-response. The mean volume of nocturnal enuresis decreased from 159.96 to 115.30 ml in the pre and post treatment periods, respectively ($p = 0.012$). The mean frequency of enuresis decreased from 4.36 to 2.84 days per week in pre and post treatment periods, respectively ($p < 0.001$). The mean whole night urine volume decreased from 373.39 to 292.37 ml in pre and post treatment periods ($p = 0.061$). There were no major side effects in the study.

Conclusion: Desmopressin melt is effective and safe in treating NMNE in children. However, to add weight to the findings of this study further research with a larger number of patients should be considered in the near future.

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Introduction

Nocturnal enuresis (NE) is defined as discrete episodes of urinary incontinence during sleep in children older than 5 years of age.[1] In a study of almost 3,500 children in Thailand, the prevalence of enuresis declined with increasing age from 10%, 5.3%, 3%, 1.2% at ages 5, 7, 10 and 12 years, respectively.[2] In two other studies in New Zealand and Belgium, the same pattern was seen, prevalence also declined with increasing age from 15%, 13%, 10%, 7%, 5%, 2-3%, 1-2% at ages 5, 6, 7, 8, 10, 12-14 and 15 years, respectively.[3,4] Enuresis in children frequently has a negative impact on the self-esteem, socializing capacity, [5,6] and intellectual quotient of the children,[7] also impacting on their parents sleep and well-being. The sleep deprivation can seriously affect family life, causing a reduction in patience when dealing with the children, having impact on the working hours of parents,[8] increase household costs of laundry for clothes and sheets[9] and may lead to child abuse or abandonment.[10,11] A previous study reported that the successful treatment of enuresis will improve the personality, behavior and emotions of both children and parents.[12]

NE is categorized into monosymptomatic nocturnal enuresis (MNE) or non-monosymptomatic nocturnal enuresis (NMNE). NE with any daytime lower urinary tract symptoms (LUTS) is defined as NMNE.[13,14] In treatment of primary MNE, there is level 1 evidence to support the use of an enuresis alarm and desmopressin,[15] however, in treatment of NMNE, there are various options available to deal with LUTS. These include clean intermittent catheterization (CIC), anti-muscarinic agents, alpha-blocker agents, behavioral treatment and bowel bladder training. However, no standard approach has been established for these treatments[13]. In our department, there are many underlying diseases associated with NMNE, specifically spina bifida, anorectal malformation, posterior urethral valves, dysfunctional voiding, attention deficit hyperactivity disorder, and obstructive sleep apnea. The most common underlying cause in our outpatient department was found to be spina bifida, which a previous study in our center also had a measurable negative impact on the quality of life.[16]

Anti-diuretic hormone (ADH) is released by the posterior pituitary gland and reduces urine production by increasing water reabsorption in the collecting tubules and ducts. Desmopressin is a synthetic analogue of ADH.[17] There are several forms of this medication, specifically tablet, melt and intranasal spray formulations. It has been shown that the melt formulation of desmopressin demonstrates the same levels of efficacy and safety as the tablet form but at lower dosing levels its bioavailability being almost 60% greater.[18] Several studies have investigated the efficacy of the tablet and intranasal spray formulations of this medication in the treatment of enuresis,[19] but there is limited work into the treatment of NMNE with melt form desmopressin. The aim of this study was to measure the efficacy of melt form of desmopressin in the treatment of NMNE in our center.

Materials and Methods

A prospective study was performed in children enrolled in the outpatient treatment program for NMNE in our pediatric urology center between 2018 and 2020. Criteria for enrollment on the study were assent of parents and children of ages 6 to 18 years with adequate treatment for other LUTS, for example anti-muscarinic agent, and CIC with continued treatment of previous use. Twenty-six children were enrolled onto the study and underlying causes of enuresis and severity of symptoms were varied (Figure 1). One child was subsequently excluded. The exclusion criteria were hyponatremia (defined as serum sodium < 135 mEq/L), chronic kidney stage III to V (defined as estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73m^2) (eGFR was calculated as 0.413 x height [cm] / serum creatinine [mg/dl]), psychiatric underlying disease, symptomatic urinary tract infection at time of enrollment, and moderate to severe mental retardation or encephalopathy. Before inclusion all children were assessed by their medical history, physical examination, evaluation of serum blood urea nitrogen (BUN), serum creatinine and serum electrolytes. If required, urological imaging and/or urodynamic studies were performed to evaluate anatomical and/or neurological abnormalities.

After enrollment, child and parent were requested to record a urine chart for 7 days without the use of desmopressin and directed to not drink water 1 hour before sleep. Details of the urine chart included presence or absence of enuresis each day for 7 days, volume of morning void or

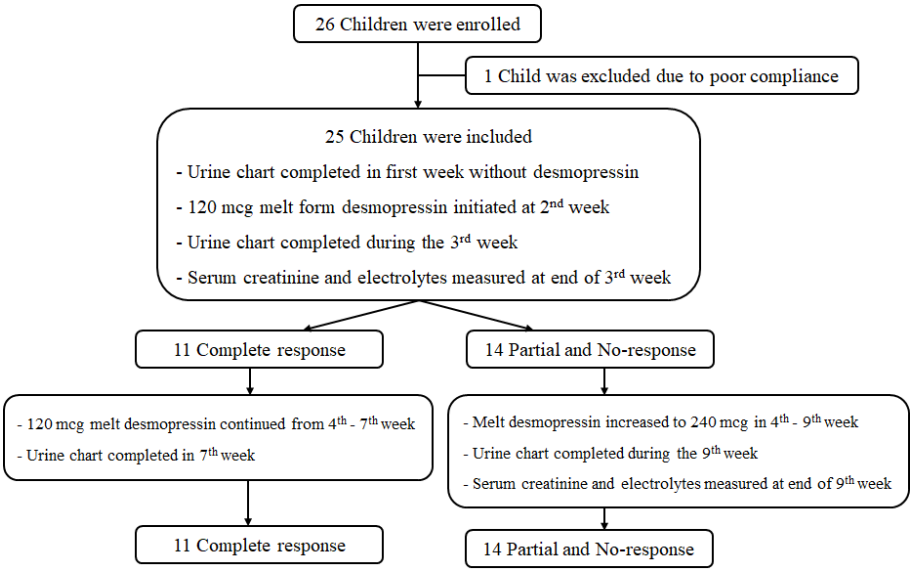

Figure 1. Flow chart of our study.

catheterization, volume of night void, volume of enuresis, and volume of night catheterization during sleep for 3 nights. We used a plastic tumbler with volume scale from Ferring Pharmaceuticals for the measurement of the volume of urine and scales from the same marque to measure the weight of enuresis of each child. After the first 7 days, desmopressin melt form 120 mcg 1 tablet was prescribed to be taken sublingually 1 hour before sleep. The urine chart was completed again on the second week after the start of this medication. After the second week each child was given an appointment to evaluate the incidence of any side effects such as nausea, vomiting, abdominal distension, alteration of consciousness, and seizure and also evaluate serum BUN/creatinine and electrolytes. If there were severe symptom or hyponatremia or the eGFR decreased below 60 the medication was discontinued.

The urine charts were analyzed in accordance with the International Children's Continence Society (ICCS) guidelines: No-response showed a decreased frequency of enuresis < 50%; Partial response showed a decreased frequency of enuresis of 50-99% and Complete response showed a decreased frequency of enuresis 100%.[1] In the complete response group, the child was prescribed 120 mcg desmopressin melt to be taken sublingually 1 hour before sleep for an additional 28 days and asked to complete a urine chart for the last 7 days on this medication. In the no-response and partial response groups, the child was given an increased dose of desmopressin to 240 mcg sublingually 1 hour before sleep for an additional 42 days and was directed to record a urine chart for the last 7 days on this medication and evaluations of serum BUN/creatinine and electrolytes were carried out at the final appointment. The final urine charts were used to analyze the outcome.

A dosage of 120-240 mcg of the melt form of desmopressin was selection following the findings published in a previous study which reported that this melt form dosage of desmopressin can be effective for a period of sleep at night of 7-11 hours.[20]

The Primary outcome was to describe the Complete response. The secondary outcome was to compare the before and after treatment data of average whole night urine volume, average nocturnal enuresis volume and frequency of enuresis.

Statistical analysis

Fisher's exact test and a paired t-test were used to analyze the data using the STATA program. A significance level of $p < 0.05$ was chosen and data were reported as mean ± standard deviation. The study protocol was approved by the Ethical Committee of Chiang Mai University (Research ID: 5323/ Study Code: SUR-2561-05323).

Results

Twenty-six children were enrolled onto the study. One child was excluded because she was unable to keep the appointments. Of the remaining 25, the most frequent underlying disease was

Table 1. Baseline characteristics of the NMNE patients in the study.

Parameters	Patients, n (%)
Gender	
Male	15 (60)
Female	10 (40)
Age, mean (SD)	9.04 (3.22)
Underlying disease	
Spina bifida	11 (44)
Obstructive sleep apnea	3 (12)
Anorectal malformation	2 (8)
Behavioral problem	2 (8)
Brain tumor	1 (4)
Autism	1 (4)
Legg-Clav-Perthes disease	1 (4)
No underlying disease	4 (16)
Other treatment	
Alarm therapy	4 (16)
Clean-intermittent catheterization	4 (16)
Bladder augmentation	1 (4)
Bladder capacity, mean (SD)	277.92 (126.59)

spina bifida (44%) followed by obstructive sleep apnea, anorectal malformation and behavioral problems (12%, 8%, 8%, respectively) (Table 1). The response rate was complete response 44%, partial response 20% and no-response 36% (Table 2). The average volume of nocturnal enuresis decreased significantly from 159.96 to 115.30 ml ($p = 0.012$). The frequency of nocturnal enuresis also decreased significantly from 4.36 to 2.84 days ($p < 0.001$). The average whole night urine did decrease but not significantly from 373.39 to 292.37 ml ($p = 0.061$) (Table 3).

Three children had adverse events leading to discontinuation of the medication, 1 child had allergic symptoms of urticaria to the medication, 1 child had asymptomatic hyponatremia (serum sodium was 134 mEq/L at dose 120 mcg) and 1 child had decreased eGFR from 103.25 to 50.36 ml/min/1.73 m^2 from inadequate CIC. Two children had adverse events, 1 with mild dyspepsia and 1 with mild nausea and dry mouth but following discussion it was decided not to discontinue the medication.

Table 2. Primary outcome in the NMNE patients taking desmopressin melt.

Response of nocturnal enuresis	n (%)
Complete response	11 (44)
Partial response	5 (20)
No-response	9 (36)

Discussion

NE is a common problem in Thailand.[2] It has significant impact on the self-esteem and psychosocial development of children and is also a serious burden for their parents.[5-11] Treatment of enuresis therefore, will patently improve these conditions. Enuresis has been categorized as MNE and NMNE. There are several studies investigating the efficacy of desmopressin in treating MNE with reports of significantly improved symptoms[21], but there are limited studies on the ability of desmopressin to treat NMNE. In the first instance some facets of NMNE which may have impact were addressed including constipation, LUTS, and obvious underlying causes. If the enuresis remained after these were addressed we set out to ascertain if desmopressin melt therapy could help these children.

At our hospital most patients with NE meet the pediatricians first. If NMNE was diagnosed with other underlying causes, the child will then meet our urologist. The most common underlying cause of NMNE in our study is spina bifida. From a previous study it was demonstrated that NMNE was more prevalent in children with spina bifida occulta and had a lower response to behavioral treatment.[22] Therefore these initial treatments may not improve the NMNE.

Table 3. Secondary outcomes in the NMNE patients to desmopressin melt.

Outcomes	Before treatment mean (SD)	After treatment mean (SD)	P-value
Volume of nocturnal enuresis (ml)	159.96 (171.30)	115.30 (244.83)	0.012*
Volume of nocturnal urine (ml)	373.39 (222.06)	292.37 (279.00)	0.061
Nocturnal enuresis (days)	4.36 (2.45)	2.84 (3.20)	< 0.001*

* Denotes statistical significance

In our study there was a complete response rate of 44% with a statistically significant improvement in frequency of enuresis and enuresis urine volume. There was improved whole night urine volume but the data did not reach statistical significance. From a previous study, response of enuresis to melt form 120 mcg desmopressin is lower in spina bifida occulta patients with severe LUTS.[23] That study also treated LUTS daytime with oxybutynin similarly to the treatment given our study. Response of enuresis in children with spina bifida tended to be lower in our study, and also in children with severe enuresis frequency and volume.

Another study demonstrated that the combination of antimuscarinics and desmopressin was more effective than antimuscarinics alone in children with an overactive bladder and enuresis.[24] Similar to our study, after treating daytime LUTS with antimuscarinics, if enuresis persisted we also used desmopressin to control enuresis.

There is an earlier study into children with enuresis. In that study, 82.8% who had NMNE used desmopressin melt form 120 mcg with propiverine 7.5 mg twice per day. The complete response of this study was 87%.[25] This may be higher than our study because they included MNE children in this study.

Our study demonstrated an initial positive response to desmopressin in the treatment of NMNE, but there was limited data for the impact of long-term use. Another study demonstrated that a tapering dose to result in a complete response had a low rate of relapse.[25] It was not possible in our study to continue the medication long term to assess the impact and also to observe the outcome of progressive discontinuation of the drug as the majority of our children could not continue on desmopressin because of financial implications.

There were several limitations to our study. Firstly, the number of the children enrolled onto the study were lower than the population that was required to ensure robust statistical conclusions. Since there were a limited number of previous studies, the minimum population required was 82 children, but only 25 were available because of restrictions of attendance at clinic due to COVID-19. Also, in the Thai culture parents underestimate the problem of enuresis and as a result the whole night urine parameter was not statistically significant. With a higher population this statistic may have reached significance.

Secondly, our study included only a treatment group with no control. This limited our calculation for statistical significance in primary outcome of complete response to bring results for use in treatment. However, as the parameters of enuresis volume and enuresis frequency improved statistically significantly the next randomized controlled trial should to planned to reach statistical significance for this primary outcome. Thirdly, our protocol is only initial short-term outcome, the next study may look for the long-term treatment of NMNE in children. Another limitation might be the method of use of the oral lyophilisate formulation of desmopressin (melt form) which could be ineffective if it was taken the wrong way such as eating or chewing this medication, or drinking a lot of water after taking the medication. The children and parents were advised as to how to use the melt at the time of enrollment but there may have been deviations from the method requested. Lastly, our urine chart only recorded data of urine volume for 3 days and presence or absence of enuresis for 7 days. To calculate a more accurate percentage of volume and frequency, in a future study it may be better to have a longer duration of recorded data. The latter two limitations are a consequence of the culture in our country as in many patients there is a lack of compliance.

Conclusion

Desmopressin melt is effective and safe in treating NMNE in children. A future study with a larger sample size should be considered to further substantiate the findings of this study and add weight to the accumulating body of evidence surrounding the efficacy of this treatment.

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Conflict of Interest

The authors declare no conflict of interest.

References

1. Austin PF, Bauer SB, Bower W, Chase J, Franco I, Hoebeke P, et al. The standardization of terminology of lower urinary tract function in children and adolescents: Update report from the standardization committee of the International Children's Continence Society. Neurourol Urodyn 2016;35:471-81.
2. Hansakunachai T, Ruangdaraganon N, Udomsubpayakul U, Sombuntham T, Kotchabhakdi N. Epidemiology of Enuresis Among School-Age Children in Thailand. J Dev Behav Pediatr 2005;26:356-60.
3. Fergusson DM, Horwood LJ, Shannon FT. Factors Related to the Age of Attainment of Nocturnal Bladder Control: An 8-Year Longitudinal Study. Pediatrics 1986;78:884-90.
4. Bakker E, Sprundel Mv, Auwera JCvd, Gool JDv, Wyndaele JJ. Voiding Habits and Wetting in a Population of 4332 Belgian Schoolchildren Aged Between 10 and 14 Years. Scand J Urol Nephrol 2002;36:354-62.
5. Ertan P, Yilmaz O, Caglayan M, Sogut A, Aslan S, Yuksel H. Relationship of sleep quality and quality of life in children with monosymptomatic enuresis. Child Care Health Dev 2009;35:469-74.
6. Robson WLM. Evaluation and Management of Enuresis. N Engl J Med 2009;360:1429-36.
7. Joinson C, Heron J, Butler R, Von Gontard A, Butler U, Emond A, et al. A United Kingdom Population-Based Study of Intellectual Capacities in Children With and Without Soiling, Daytime Wetting, and Bed-wetting. Pediatrics 2007;120:e308-16.
8. Carskadon MA. Sleep deprivation: health consequences and societal impact. Med Clin North Am 2004;88:767-76.
9. Pugner K, Holmes J. Nocturnal enuresis: economic impacts and self-esteem preliminary research results. Scand J Urol Nephrol Suppl 1997;183:65-9.
10. Butler R, McKenna S. Overcoming parental intolerance in childhood nocturnal enuresis: a survey of professional opinion. BJU Int 2002;89:295-7.
11. Sapi MC, Vasconcelos JS, Silva FG, Damiao R, Silva EA. Assessment of domestic violence against children and adolescents with enuresis. J Pediatr (Rio J). 2009;85:433-7.
12. Schulpen TW. The burden of nocturnal enuresis. Acta Paediatr 1997;86:981-4.
13. Lordelo P, Benevides I, Kerner EG, Teles A, Lordelo M, Barroso U, Jr. Treatment of non-monosymptomatic nocturnal enuresis by transcutaneous parasacral electrical nerve stimulation. J Pediatr Urol 2010;6:486-9.
14. DiBianco JM, Morley C, Al-Omar O. Nocturnal enuresis: A topic review and institution experience. Avicenna J Med 2014;4:77-86.
15. Vande Walle J, Rittig S, Bauer S, Eggert P, Marschall-Kehrel D, Tekgul S, et al. Practical consensus guidelines for the management of enuresis. Eur J Pediatr 2012;171:971-83.
16. Saisaard P, Mahawong P, Boonchooduang N, Chongruksut W. Quality of life in pediatric patients with lumbosacral myelomeningocele compare to normal children. Thai J Urol 2019;39:10-19.
17. Rittig S, Schaumburg HL, Siggaard C, Schmidt F, Djurhuus JC. The Circadian Defect in Plasma Vasopressin and Urine Output is Related to Desmopressin Response and Enuresis Status in Children With Nocturnal Enuresis. J Urol 2008;179:2389-95.
18. Lottmann H, Froeling F, Alloussi S, El-Radhi AS, Rittig S, Riis A, et al. A randomised comparison of oral desmopressin lyophilisate (MELT) and tablet formulations in children and adolescents with primary nocturnal enuresis. Int J Clin Pract 2007;61: 1454-60.
19. Robson WLM, Leung AKC, Norgaard JP. The Comparative Safety of Oral Versus Intranasal Desmopressin for the Treatment of Children With Nocturnal Enuresis. J Urol 2007;178:24-30.
20. Vande Walle JG, Bogaert GA, Mattsson S, Schurmans T, Hoebeke P, Deboe V, et al. A new fast-melting oral formulation of desmopressin: a pharmacodynamic study in children with primary nocturnal enuresis. BJU Int 2006;97:603-9.
21. Alloussi SH, Murtz G, Lang C, Madersbacher H, Strugala G, Seibold J, et al. Desmopressin treatment regimens in monosymptomatic and nonmonosymptomatic enuresis: A review from a clinical perspective. J Pediatr Urol 2011;7:10-20.
22. Kurt O, Yazici CM, Paketci C. Nocturnal enuresis with spina bifida occulta: Does it interfere behavioral management success? Int Urol Nephrol 2015;47:1485-91.
23. Yavuz A, Bayar G, Kilinc MF, Sariogullari U. The Relationship Between Nocturnal Enuresis and Spina Bifida Occulta: A Prospective Controlled Trial. Urology 2018;120:216-21.
24. Im YJ, Lee JK, Park K. Time Course of Treatment for Primary Enuresis With Overactive Bladder. Int Neurourol J 2018;22:107-13.
25. Jabbour M, Abou Zahr R, Boustany M. Primary Nocturnal Enuresis: A Novel Therapeutic Strategy With Higher Efficacy. Urology 2019;124:241-7.